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Abstract: An original two-step organocatalytic synthesis of optically active glutarimides from 2-oxocyclobutane carboxamides is described featuring an isothiourea-catalyzed two-atom ring-expansive rearrangement.

Keywords: Nitrogen heterocycles; Organocatalysis; Rearrangement; Ring expansion; Strained molecules

The glutarimide moiety, that is to say the piperidine-2,6-dione skeleton, can be found in many natural and non-natural products having various biological properties such as antibacterial, antitumoral and anti-inflammatory activities, and several marketed drugs contain a chiral glutarimide unit (Figure 1).[1] While the synthesis of chiral glutarimides in the racemic series is now enabled at the industrial scale, there have been only few enantioselective methods reported to synthesize glutarimides in non-racemic forms.[2] Actually, three approaches have been considered so far, relying either i) on the α-functionalization of preformed glutarimides,[3] ii) on (3 + 3) annulation processes from secondary amides,[4] and more originally iii) on the two-atom ring contraction of eight-membered benzazocinones (Scheme 1).[5] Herein we propose a complementary organocatalytic approach that relies on a base-catalyzed ring rearrangement of 2-oxocyclobutane carboxamides resulting in a two-atom ring expansion (Scheme 1).

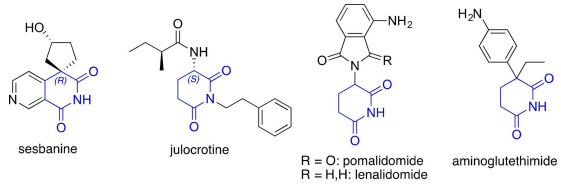
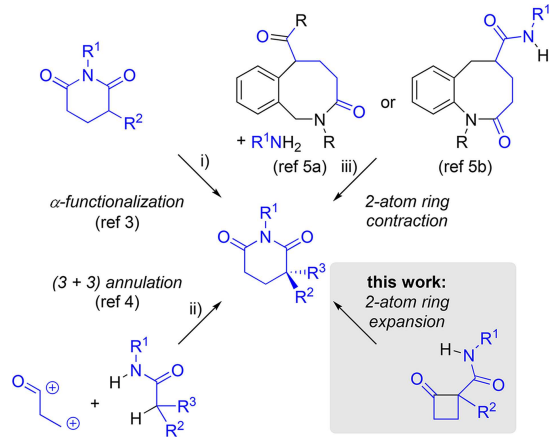
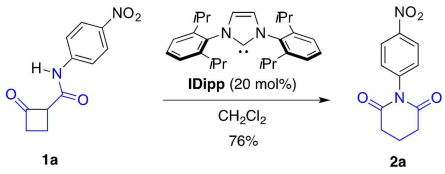


Figure 1. Selected structurally simple natural (left) and non-natural (right) biologically active glutarimides.

In early experiments, it was observed that the 2-oxocyclobutane carboxamide **1 a** could be catalytically rearranged into the corresponding glutarimide **2 a** ensuing a two-atom ring expansion, using the N-heterocyclic carbene (NHC) **IDipp** as the catalyst (Scheme 2). Anecdotally, the four-membered ring substrate **1 a** was conveniently prepared through the ring-contractive Wolff rearrangement of 2-diazo-cyclopentane-1,3-dione in the presence of 4-nitroaniline,[6] and the synthesis of glutarimide **2 a** is thus based on a

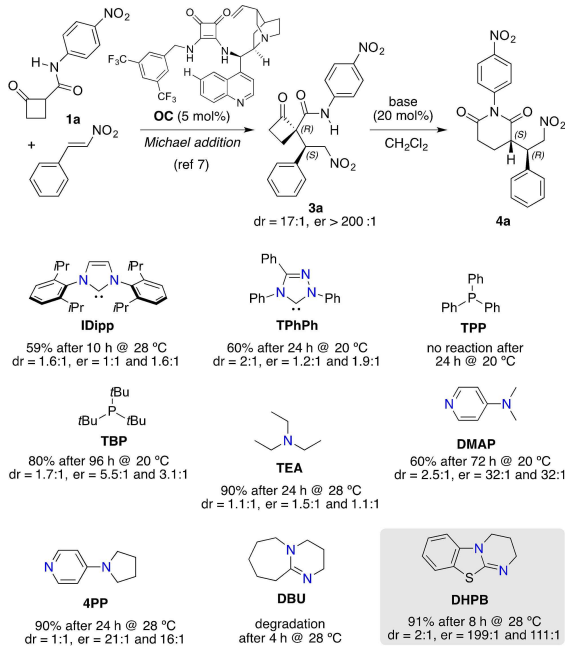


Scheme 1. Enantioselective synthetic approaches to glutarimides.



Scheme 2. Early observation of the base-catalyzed ring rearrangement of the 2-oxocyclobutane carboxamide **1 a** into the glutarimide **2 a**.

one-atom ring contraction/two-atom ring expansion sequence. From there, it was anticipated that a similar ring rearrangement would occur with the more complex and highly enantioenriched 2-oxocyclobutane carboxamide **3 a** derived from the enantioselective organocatalytic Michael addition of cyclobutanone **1 a** to nitrostyrene catalyzed by the bifunctional aminocatalyst **OC**, as described in a previous article.[7] Some representative basic catalysts were screened for the conversion of enantiopure **3 a** (er > 200:1) into the corresponding glutarimide **4 a** (Scheme 3). The NHCs **IDipp** and **TPhPh** afforded encouraging yields of the expected glutarimide product **4 a** as mixtures of the two possible diastereomers, albeit as nearly racemic materials, indicating a rapid racemization under these conditions. Similar observations resulted from the trials

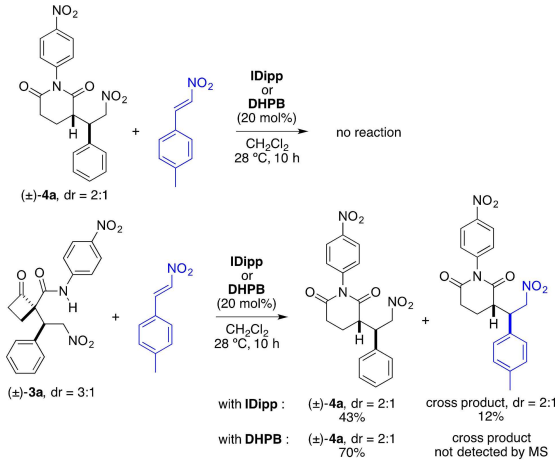


Scheme 3. Screening of basic catalysts for the ring rearrangement of 2-oxocyclobutane carboxamide **3 a**. The major diastereomer of glutarimide **4 a** is depicted.

with tri-*tert*-butylphosphine (**TBP**) and triethylamine (**TEA**). Interestingly, **DMAP** and its analog **4PP** afforded both diastereomers of **4 a** with this time relatively good retentions of optical purity. In contrast, catalytic triphenylphosphine (**TPP**) or **DBU** did not allow the isolation of **4 a**. Finally, it was found that 20 mol% of **DHPB**[8] is optimum to promote this ring rearrangement efficiently, allowing the isolation of **4 a** (dr = 2:1) without significant loss of optical purity, indicating negligible racemization processes in that case. It was briefly explored if the two-step sequence could be performed in one-pot conditions, without isolating the intermediate Michael adduct **3 a**. When 20 mol% **DHPB** were added to the product reaction mixture of the first step, the glutarimide **4 a** (dr = 2.4:1) was produced efficiently (quant. by ^{1}H NMR analysis) after 8 hours at 28 °C but with important racemization (er = 3.3:1 and 8.7:1), showing catalysts incompatibility and a preferred stepwise synthetic sequence.

The stereochemical outcome of the ring rearrangement reaction **3 a**→**4 a** was questioned. The issue of racemization was attributed to catalytic retro-Michael/Michael processes of **3 a** involving the Brønsted base properties of the various achiral catalysts depicted in Scheme 3. This could be confirmed experimentally by a series of cross-experiments in the case of catalyst **IDipp** (Scheme 4).

Indeed, when the racemic glutarimide **4 a** was allowed to react with the nitroolefin having an extra 4-methyl group on the benzene ring in the presence of **IDipp** or **DHPB**, no reaction occurred and **4 a** was recovered quantitatively. This indicates that no retro-Michael/Michael process is occurring on the glutarimide product **4 a** under these conditions. In contrast, when the racemic 2-oxocyclobutane carboxamide **3 a**

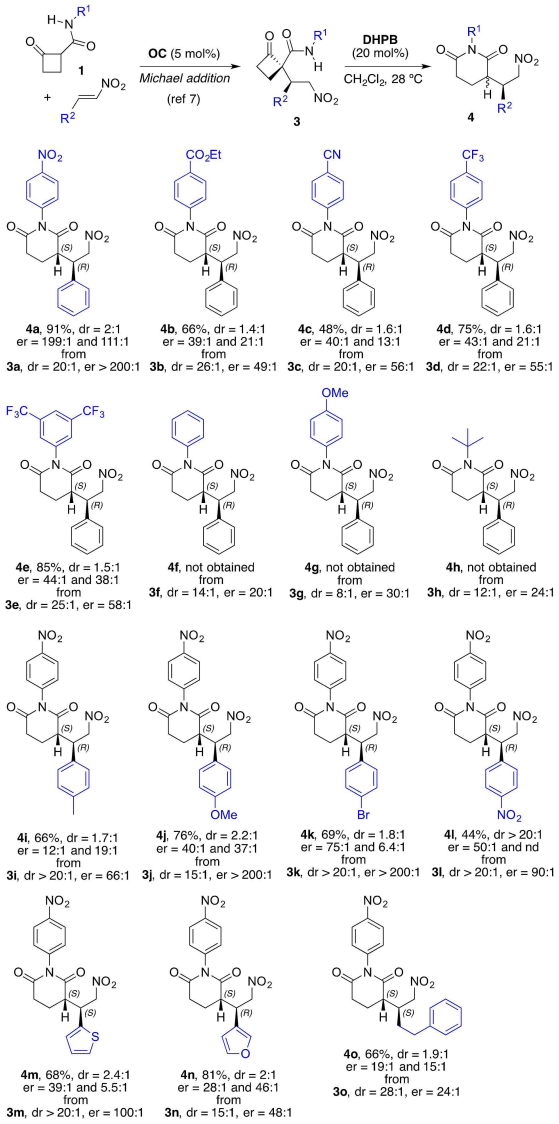


Scheme 4. Cross-experiments probing retro-Michael/Michael racemization processes of **3 a** with **IDipp** and not with **DHPB**. The major diastereomers are depicted.

was employed as the substrate with the **IDipp** catalyst under similar conditions, the glutarimide **4a** (43%) could be obtained together with the cross-product glutarimide incorporating the nitroolefin having an extra 4-methyl group (12%). These experiments demonstrate that **IDipp**-catalyzed retro-Michael/Michael processes occurred prior to the ring rearrangement of **3a**.[9] Similar cross-experiments were performed with **DHPB** instead of **IDipp** and, as expected, no cross-product could be detected in these cases showing that **DHPB** do not catalyze retro-Michael/Michael processes from **3a** at a significant rate. The low diastereoselectivity of the transformation **3a**→**4a** is seemingly governed by thermodynamics due to relatively rapid **DHPB**-catalyzed epimerization at the imide enolizable position in product **4a** as recently observed in closely related cases.[5b,10] Supportive to this hypothesis, the relative Gibbs free energies of (*S*,*R*)-**4a** and its diastereomer (*R*,*R*)-**epi-4a** were calculated using several density functional theory (DFT) methods, indicating that **4a** is the thermodynamic diastereomer, though by only 2.2–3.6 kJ.mol^{-1} corresponding to a 2.4–4.3:1 ratio at equilibrium (see Supporting Information).

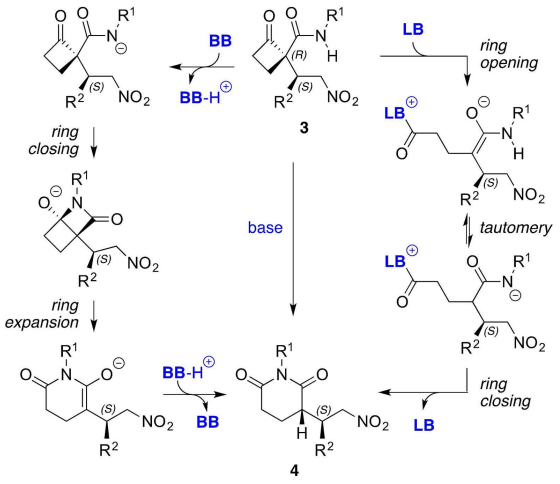
The scope and functional group tolerance of the glutarimides accessible by this approach were explored, first focusing on the electronics of the secondary amide group in cyclobutanones **3** (Scheme 5). It turned out that the two-atom ring-expansive rearrangement is only operative with electron-withdrawing *N*-aryl amide R^1 substituents, affording the glutarimides **4a–e** in good yields and high enantioselectivities. In contrast, cyclobutanones **3f–h** having electron-donating amide substituents were unreactive toward **DHPB**. Then, some representative nitroolefins were screened, which afforded the glutarimides **4i–o** having various aryl, heteroaryl or alkyl R^2 substituents. The observed slight erosions of er in products **4b–e** and **4i–o** were attributed to **DHPB**-catalyzed retro-Michael/Michael processes from the 2-oxocyclobutane carboxamides **3b–e** and **3i–o**, respectively, as demonstrated above for **3a** with **IDipp** (see Scheme 4). Overall, an original enantioselective two-step approach to synthesize optically active glutarimides from 2-oxocyclobutane carboxamides has been discovered based on a two-step Michael/ring rearrangement sequence resulting in a two-atom ring expansion. Using this method, the glutarimide products described herein were generally obtained in good yields and high enantioselectivities, albeit generally as ca. 2:1 mixtures of the two possible diastereomers.

Mechanistically, two distinct scenarios are plausible to account for the observed ring rearrangement **3**→**4**: i) the basic catalyst is acting as a Brønsted base **BB** generating the corresponding amide isothiouronium salt of **3** to trigger an anionic ring closing/ring expansion sequence leading to **4** (Scheme 6, left), or ii)

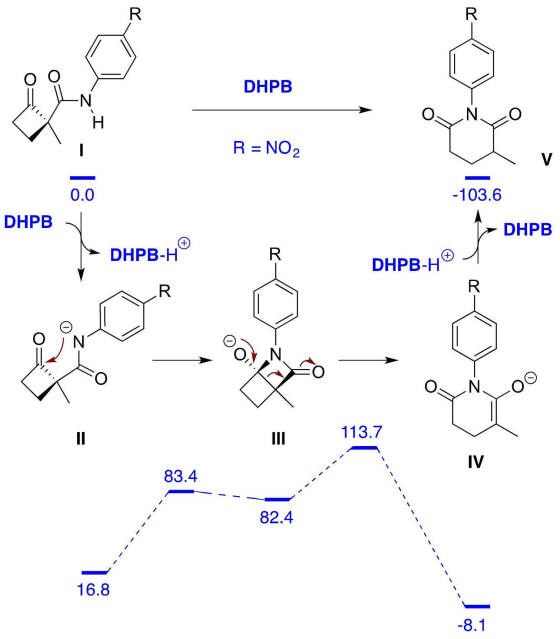


Scheme 5. Scope of the reaction. The major diastereomers are depicted. nd = not determined.

the basic catalyst is acting as a nucleophilic Lewis base **LB** promoting a ring opening/ring closing sequence to give **4** (Scheme 6, right). With the intention to gain insight in the intimate mechanism of this original transformation with **DHPB** as the catalyst, we investigated these two scenarios by computational modelization using DFT methods at an appropriate level of theory (see Supporting Information for details). The model transformations **I**→**V** (R = NO_2 and OMe) were selected for this part of the study, and the mechanism involving **DHPB** as a Brønsted base was first considered (Scheme 7). As it could be anticipated,

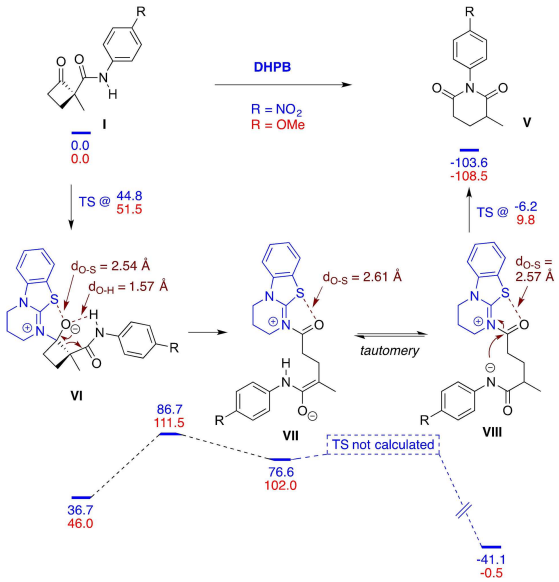


Scheme 6. Plausible mechanistic scenarios with the catalyst acting as a Brønsted base **BB** (left) or a nucleophilic Lewis base **LB** (right).



Scheme 7. Calculated energy profile for the model transformation **I**→**V** (R = NO_2) with **DHPB** employed as a catalytic Brønsted base [DFT, M06-2X-D/6-311 + + G(d,p) including a solvation model for dichloromethane]. Energies are Gibbs free energies expressed in kJ.mol^{-1}.

the ring rearrangement of the anion **II** directly derived from **I** into the anion **IV** precursor of **V** was found a two-step process proceeding via the bicyclic intermediate **III**. The reaction barrier of the overall rearrangement was calculated at + 113.7 kJ.mol^{-1} from the substrate **I** with R = NO_2 (see Supporting Information for details). The alternative mechanism involving **DHPB** as a catalytic nucleophilic Lewis base was then examined (Scheme 8). In this case it was found that the reaction is initiated by the formation of the ephemeral tetrahedral intermediate **VI** resulting from the addition of **DHPB** to the ketone carbonyl group with relatively low barriers. The fragmentation of **VI** into the acyl isothiouronium intermediate **VII** was computed as the rate limiting step in both the R = NO_2 and R = OMe series, with reaction barriers at + 86.7 and + 111.5 kJ.mol^{-1}, respectively. Then, a thermodynamically favored tautomery can afford intermediate **VIII** with this time the negative charge located on the nitrogen atom of the amide group. The relatively important stabilization energies in the zwitterionic intermediates **VIII** (R = NO_2 and OMe) was attributed, at least in part, to strong π donor-acceptor stabilizing interactions between the negatively charged *N*-aryl amide planar moiety and the positively charged acyl isothiouronium planar moiety, with interplanar distances of ca. 3.2 Å for R = NO_2 and 3.4 Å for R = OMe (Figure 2). Finally, intermediate **VIII** can cyclize in an irreversible manner to afford the glutarimide product **V** and regenerate the catalyst. Overall, these calculations with **DHPB** as the catalyst indicate i) that both



Scheme 8. Calculated energy profile for the model transformation **I**→**V** (R = NO_2 and R = OMe) with **DHPB** employed as a catalytic Lewis base [DFT, M06-2X-D/6-311 + + G(d,p) including a solvation model for dichloromethane]. Energies are Gibbs free energies expressed in kJ.mol^{-1}, and significant interactions are highlighted in brown color with inter atomic distances provided for the R = NO_2 series.

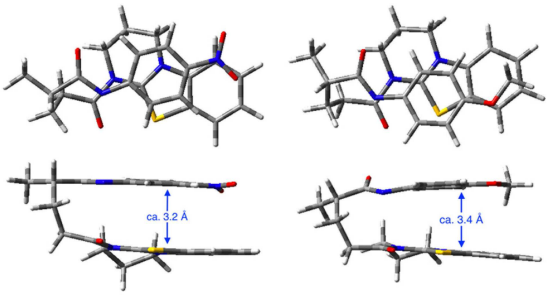


Figure 2. Top and side views of optimized geometries for intermediates **VIII** with R = NO2 (left) and R = OMe (right).

mechanisms are energetically possible, ii) that the mechanism involving the catalyst as a nucleophilic Lewis base is kinetically favored, and iii) that the reaction with R = OMe would proceed at an extremely slow rate under the reaction conditions, which is in perfect agreement with the experimental results (see compound **4 g** not obtained in Scheme 5). In order to confirm this substituent effect, the analog of **1 a** having a OMe substituent in place of the NO_2 group was allowed to react with **DHPB** (20 mol%) in dichloromethane without promoting a detectable reaction after 14 h. Overall, it seems that the ring rearrangement of 2-oxocyclobutane carboxamides into glutarimides catalyzed by **DHPB** described herein proceeded via acyl isothiouronium intermediates of type **VII**/**VIII**.[11] Of course, these conclusions are only valid for **DHPB**, and it cannot be excluded that the other operative catalysts depicted in Scheme 3 behave otherwise.[12]

In summary, an original approach was discovered for the synthesis of optically active glutarimides. It is based on a two-step organocatalytic approach involving an enantioselective Michael addition of 2-oxocyclobutane carboxamides to nitroolefins using a chiral bifunctional aminocatalyst, followed by a two-atom ring-expansive rearrangement catalyzed by an achiral isothiourea catalyst. The glutarimide products prepared by this approach were generally obtained as mixtures of the two possible diastereomers in good yields and high enantioselectivities. Stereochemical outcomes were rationalized, and a computational mechanistic study showed that the ring rearrangement step is seemingly promoted by the nucleophilicity and Lewis basicity of the isothiourea catalyst.

Experimental Section

General Information

See the Supporting Information.

Synthesis of 2-oxocyclobutane Carboxamides 3

The syntheses and characterization data of optically active **3 a**, **3 e**–**h**, and **3 j**–**o** were reported in a previous article.[7] Optically active **3 b**–**d** and **3 i** were prepared following the same procedure and their characterization data are provided below. All racemic 2-oxocyclobutane carboxamides **3 a**–**o** were prepared from the corresponding unsubstituted 2-oxocyclobutane carboxamides **1**[6a] and the corresponding nitroolefins using the polystyrene-supported phosphazene catalyst known as P-BEMP.[13]

Compound 3 b: Following the general procedure,[7] the reaction between the 2-oxocyclobutane carboxamide **1** (R^1 = 4-CO_2Et–C_6H_4, 100 mg, 0.36 mmol) and nitrostyrene (45 mg, 0.30 mmol) in anhydrous dichloromethane (2 mL) with catalyst **OC** (9 mg, 0.015 mmol) for 14 h afforded the 2-oxocyclobutane carboxamide **3 b** (94 mg, 76% yield, dr = 26:1, er = 49:1) as a white solid. R_f = 0.40 (petrol ether/ethyl acetate, 2:1). **Mp** = 182–184 °C (amorphous). $[\alpha]_D^{25} = -153.3$ (c = 1.0, $CHCl_3$). **HRMS** (ESI+) *m/z* calcd for $C_{22}H_{23}N_2O_6^+$ $[M+H]^+$ = 411.1551, found = 411.1551. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.26 (br s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.40–7.31 (m, 3H), 7.30–7.26 (m, 2H), 4.97 (dd, J = 14.0, 10.6 Hz, 1H), 4.86 (dd, J = 14.0, 5.0 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.23 (dd, J = 10.6, 5.0 Hz, 1H), 2.82 (ddd, J = 15.1, 10.2, 4.1 Hz, 1H), 2.63–2.45 (m, 1H), 2.40–2.17 (m, 2H), 1.38 (t, J = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) major diastereomer: δ 208.7 (C), 166.0 (C), 165.7 (C), 140.9 (C), 133.4 (C), 130.9 (2CH), 129.4 (2CH), 129.1 (CH), 128.5 (2CH), 127.0 (C), 119.4 (2CH), 76.2 (C), 74.7 (CH_2), 61.1 (CH_2), 47.0 (CH), 44.5 (CH_2), 17.9 (CH_2), 14.4 (CH_3). **HPLC**: Chiralpak IE eluted with 1:1 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 270 nm, retention times: major enantiomer 7.88 min, minor enantiomer 10.00 min.

Compound 3 c: Following the general procedure,[7] the reaction between the 2-oxocyclobutane carboxamide **1** (R^1 = 4-CN–C_6H_4, 77 mg, 0.36 mmol) and nitrostyrene (45 mg, 0.30 mmol) in anhydrous dichloromethane (2 mL) with catalyst **OC** (9 mg, 0.015 mmol) for 14 h afforded the 2-oxocyclobutane carboxamide **3 c** (72 mg, 66% yield, dr = 20:1, er = 56:1) as a white solid. R_f = 0.51 (petrol ether/ethyl acetate, 2:1). **Mp** = 136-138 °C (amorphous). $[\alpha]_D^{25} = -127.4$ (c = 1.0, $CHCl_3$). **HRMS** (ESI+) *m/z* calcd for $C_{20}H_{18}N_3O_4^+$ $[M+H]^+$ = 364.1292, found = 364.1290. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.32 (br s, 1H), 7.61 (br s, 4H), 7.40–7.32 (m, 3H), 7.29–7.26 (m, 2H), 4.96 (dd, J = 14.0, 10.2 Hz, 1H), 4.85 (dd, J = 14.0, 5.2 Hz, 1H), 4.24 (dd, J = 10.2, 5.2 Hz, 1H), 2.82 (ddd, J = 15.1, 10.2, 4.5 Hz, 1H), 2.63–2.44 (m, 1H), 2.43–2.18 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) major diastereomer: δ 208.5 (C), 165.9 (C), 140.8 (C), 133.3 (2CH), 133.3 (C), 129.4 (2CH), 129.1 (C), 128.4 (2CH), 120.1 (2CH), 118.6 (CH), 108.1 (C), 77.1 (C), 74.6 (CH_2), 46.8 (CH), 44.5 (CH_2), 17.8 (CH_2). **HPLC**: Chiralpak IA eluted with 1:1 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 240 nm, retention times: major enantiomer 6.07 min, minor enantiomer 9.23 min.

Compound 3 d: Following the general procedure,[7] the reaction between the 2-oxocyclobutane carboxamide **1** (R^1 = 4-CF_3–C_6H_4, 93 mg, 0.36 mmol) and nitrostyrene (45 mg, 0.30 mmol) in anhydrous dichloromethane (2 mL) with catalyst

OC (9 mg, 0.015 mmol) for 14 h afforded the 2-oxocyclobutane carboxamide **3d** (100 mg, 82% yield, dr = 22:1, er = 55:1) as a white solid. R_f = 0.60 (petrol ether/ethyl acetate, 2:1). **Mp** = 131-133 °C (amorphous). $[\alpha]_D^{25} = -124.6$ (c = 1.0, $CHCl_3$). **HRMS** (ESI+) *m/z* calcd for $C_{20}H_{18}F_3N_2O_4^+$ $[M+H]^+$ = 407.1213, found = 407.1213. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.25 (br s, 1H), 7.56–7.64 (m, 4H), 7.42–7.32 (m, 3H), 7.28 (dd, J = 7.7, 1.7 Hz, 2H), 4.97 (dd, J = 14.0, 10.4 Hz, 1H), 4.87 (dd, J = 14.0, 5.1 Hz, 1H), 4.24 (dd, J = 10.3, 5.1 Hz, 1H), 2.82 (ddd, J = 15.1, 10.2, 4.1 Hz, 1H), 2.60–2.46 (m, 1H), 2.41–2.19 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) major diastereomer: δ 208.7 (C), 165.9 (C), 139.9 (C), 133.4 (C), 129.4 (2CH), 129.1 (CH), 128.5 (2CH), 126.9 (q, J_{C-F} = 28 Hz, C), 126.4 (q, J_{C-F} = 4 Hz, 2CH), 123.9 (q, J_{C-F} = 270 Hz, C), 120.0 (2CH), 76.1 (C), 74.7 (CH_2), 47.0 (CH), 44.5 (CH_2), 17.9 (CH_2). **^{19}F{^{13}C} NMR** (282 MHz, $CDCl_3$): δ −62.3. **HPLC**: Chiralpak IA eluted with 7:3 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 254 nm, retention times: major enantiomer 6.33 min, minor enantiomer 12.95 min.

Compound 3i: Following the general procedure,[7] the reaction between the 2-oxocyclobutane carboxamide **1** (R^1 = 4-NO_2–C_6H_4, 76 mg, 0.33 mmol) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (45 mg, 0.27 mmol) in anhydrous dichloromethane (2 mL) with catalyst **OC** (8 mg, 0.013 mmol) for 16 h afforded the 2-oxocyclobutane carboxamide **3i** (70 mg, 65% yield, dr > 20:1, er = 66:1) as a white solid. R_f = 0.50 (petrol ether/ethyl acetate, 2:1). **Mp** = 81-83 °C (amorphous). $[\alpha]_D^{25} = -85.5$ (c = 0.5, $CHCl_3$). **HRMS** (ESI+) *m/z* calcd for $C_{20}H_{20}N_3O_6^+$ $[M+H]^+$ = 398.1347, found = 398.1345. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.43 (br s, 1H), 8.24 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 7.23–7.11 (m, 4H), 4.94 (dd, J = 13.9, 10.1 Hz, 1H), 4.84 (dd, J = 13.9, 5.3 Hz, 1H), 4.21 (dd, J = 10.1, 5.3 Hz, 1H), 2.84 (ddd, J = 18.2, 10.1, 4.3 Hz, 1H), 2.61–2.51 (m, 1H), 2.43–2.23 (m, 2H), 2.33 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) major diastereomer: δ 208.9 (C), 166.3 (C), 144.3 (C), 142.6 (C), 139.3 (C), 130.2 (2 CH), 130.1 (C), 128.4 (2CH), 125.3 (2CH), 119.8 (2CH), 76.3 (C), 74.8 (CH_2), 46.7 (CH), 44.7 (CH_2), 21.2 (CH_3), 17.8 (CH_2). **HPLC**: Chiralpak IG eluted with 7:3 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 254 nm, retention times: major enantiomer 11.23 min, minor enantiomer 20.37 min.

General Procedure for the Ring Rearrangement

To a solution of 2-oxocyclobutane carboxamide **3** (ca. 0.2 mmol) in anhydrous dichloromethane (ca. 2 mL) was added the catalyst **DHPB** (20 mol%). The reaction was stirred at 28 °C for the time indicated below with periodical monitoring by TLC analysis, concentrated under vacuum and directly purified by flash chromatography to give the glutarimide product **4**.

Compound 4a: Following the general procedure, **3a** (43 mg, 0.11 mmol, dr = 20:1, er > 200:1) reacted with **DPHB** (4 mg, 0.021 mmol) for 8 h to provide **4a** (39 mg, 91%, dr = 2:1, er = 199:1 and 111:1) as a white solid. R_f = 0.30 (petrol ether/ethyl acetate, 3:1). **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{18}N_3O_6^+$ $[M+H]^+$ = 384.1190, found = 384.1190. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.32 (d, J = 9.0 Hz, 2H), 7.44–7.33 (m, 3H), 7.29–7.21 (m, 3H), 7.17 (d, J = 8.9 Hz, 1H), 5.22 (dd, J = 13.4, 7.6 Hz, 1H), 5.02 (dd, J = 13.3, 7.6 Hz, 1H), 4.06 (ddd, J = 7.6, 7.6, 3.5 Hz, 1H), 3.18 (ddd, J = 12.0, 5.1, 3.6 Hz, 1H), 2.84 (ddd, J = 17.4, 4.2, 4.2 Hz, 1H), 2.79–2.63 (m, 1H), 2.22–2.10 (m, 1H), 2.03 (dd, J = 12.4, 4.7 Hz, 1H); minor diastereomer: δ 8.32 (d, J = 9.0 Hz, 2H), 7.44–7.33 (m, 3H), 7.29–7.21 (m, 3H), 7.17 (d, J = 8.9 Hz, 1H), 5.14 (dd, J = 13.5, 7.4 Hz, 1H), 4.77 (dd, J = 13.5, 7.3 Hz, 1H), 4.17 (ddd, J = 7.5, 7.5, 7.5 Hz, 1H), 3.07 (ddd, J = 8.9, 8.9, 4.9 Hz, 1H), 2.92 (ddd, J = 17.9, 6.8, 4.8 Hz, 1H), 2.79–2.63 (m, 1H), 1.97 (dd, J = 12.7, 4.6 Hz, 1H), 1.71–1.83 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, *d8*-tetrahydrofuran) major diastereomer: δ 172.6 (C), 170.7 (C), 147.5 (C), 142.0 (C), 137.7 (C), 130.1 (2CH), 128.7 (2CH), 128.6 (2CH), 127.7 (CH), 123.6 (2CH), 76.4 (CH_2), 45.9 (CH), 44.7 (CH), 32.2 (CH_2), 20.6 (CH_2); minor diastereomer: δ 172.7 (C), 170.7 (C), 147.5 (C), 142.0 (C), 137.5 (C), 130.1 (2CH), 128.6 (2CH), 127.7 (CH), 123.6 (2CH), 77.6 (CH_2), 44.7 (CH), 43.1 (CH), 31.0 (CH_2), 20.1 (CH_2). **HPLC**: Chiralpak IC eluted with 1:1 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 205 and 230 nm, retention times: major diastereomer 8.10 min (major enantiomer) and 6.38 min (minor enantiomer), minor diastereomer 6.98 min (major enantiomer) and 9.13 min (minor enantiomer).

Compound 4b: Following the general procedure, **3b** (65 mg, 0.16 mmol, dr = 26:1, er = 49:1) reacted with **DPHB** (6 mg, 0.032 mmol) for 48 h to provide **4b** (43 mg, 66%, dr = 1.4:1, er = 39:1 and 21:1) as a white solid. R_f = 0.35 (petrol ether/ethyl acetate, 3:1). **HRMS** (ESI+) *m/z* calcd for $C_{22}H_{23}N_2O_6^+$ $[M+H]^+$ = 411.1551, found = 411.1552. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.14 (d, J = 8.9 Hz, 2H), 7.44–7.20 (m, 5H), 7.05 (d, J = 8.9 Hz, 2H), 5.20 (dd, J = 13.5, 7.1 Hz, 1H), 5.05 (dd, J = 13.5, 8.1 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.02 (ddd, J = 7.6, 7.6, 3.6 Hz, 1H), 3.16 (ddd, J = 12.0, 5.1, 3.7 Hz, 1H), 2.78 (ddd, J = 12.5, 8.4, 4.3 Hz, 1H), 2.74–2.59 (m, 1H), 2.15–1.67 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H); minor diastereomer: δ 8.14 (d, J = 8.9 Hz, 2H), 7.44–7.20 (m, 5H), 7.12 (d, J = 8.9 Hz, 2H), 5.16 (dd, J = 13.3, 6.9 Hz, 1H), 4.78 (dd, J = 13.3, 8.0 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.16 (dd, J = 15.3, 8.0 Hz, 1H), 3.03 (ddd, J = 9.3, 9.3, 4.9 Hz, 1H), 2.88 (ddd, J = 17.9, 6.5, 4.8 Hz, 1H), 2.74–2.59 (m, 1H), 2.15–1.67 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) major diastereomer: δ 172.8 (C), 171.2 (C), 165.7 (C), 139.0 (C), 136.0 (C), 130.9 (C), 130.6 (2CH), 129.2 (2CH), 128.8 (2CH), 128.7 (CH), 128.5 (2CH), 78.1 (CH_2), 61.2 (CH_2), 45.4 (CH), 44.8 (CH_2), 32.3 (CH_2), 21.5, (CH_2) 14.3 (CH_3); minor diastereomer: δ 172.9 (C), 171.2 (C), 165.7 (C), 139.0 (C), 136.3 (C), 130.9 (C), 129.4 (2CH), 128.6 (2CH), 128.7 (CH), 128.6 (2CH), 128.2 (2CH), 77.2 (CH_2), 61.2 (CH_2), 44.8 (CH), 43.7 (CH_2), 31.2 (CH_2), 20.5 (CH_2), 14.3 (CH_3). **HPLC**: Chiralpak IA eluted with 1:1 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 220 nm, retention times: major diastereomer 22.26 min (major enantiomer) and 35.51 min (minor enantiomer), minor diastereomer 41.26 min (major enantiomer) and 32.57 min (minor enantiomer).

Compound 4c: Following the general procedure, **3c** (50 mg, 0.14 mmol, dr = 20:1, er = 56:1) reacted with **DPHB** (5 mg, 0.026 mmol) for 72 h to provide **4c** (24 mg, 48%, dr = 1.6:1, er = 40:1 and 13:1) as a white solid. R_f = 0.28 (petrol ether/ethyl acetate, 3:1). **HRMS** (ESI+) *m/z* calcd for $C_{20}H_{21}N_4O_4^+$ $[M+NH_4]^+$ = 381.1557, found = 381.1556. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 7.74 (d, J = 8.7 Hz, 2H), 7.42–7.32 (m, 3H), 7.26–7.20 (m, 2H), 7.11 (d, J = 8.7 Hz, 2H), 5.20

(dd, J = 13.4, 7.5 Hz, 1H), 5.02 (dd, J = 13.3, 7.7 Hz, 1H), 4.05 (ddd, J = 7.6, 3.6, 3.6 Hz, 1H), 3.16 (ddd, J = 12.0, 5.1, 3.6 Hz, 1H), 2.81 (ddd, J = 17.4, 4.3, 4.3 Hz, 1H), 2.77–2.64 (m, 1H), 2.19–2.09 (m, 1H), 2.06–1.92 (m, 1H); minor diastereomer: δ 7.75 (d, J = 8.7 Hz, 2H), 7.44–7.32 (m, 3H), 7.24–7.20 (m, 2H), 7.18 (d, J = 8.7 Hz, 2H), 5.14 (dd, J = 13.5, 7.3 Hz, 1H), 4.76 (dd, J = 13.5, 7.4 Hz, 1H), 4.16 (ddd, J = 7.5, 7.5, 7.5 Hz, 1H), 3.05 (ddd, J = 8.9, 8.9, 4.9 Hz, 1H), 2.90 (ddd, J = 17.9, 6.8, 4.8 Hz, 1H), 2.77–2.64 (m, 1H), 2.06–1.92 (m, 1H), 1.79–1.70 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) major diastereomer: δ 172.7 (C), 171.1 (C), 139.2 (C), 136.1 (C), 133.2 (2CH), 129.8 (2CH), 129.4 (2CH), 128.9 (CH), 128.8 (2CH), 118.1 (C), 113.0 (C), 77.3 (CH_2), 45.8 (CH), 45.5 (CH), 32.4 (CH_2), 21.5 (CH_2); minor diastereomer: δ 172.9 (C), 171.2 (C), 139.2 (C), 136.3 (C), 133.2 (2CH), 129.8 (2CH), 129.6 (2CH), 128.8 (CH), 128.3 (2CH), 118.2 (C), 113.0 (C), 78.0 (CH_2), 45.0 (CH), 43.6 (CH), 31.1 (CH_2), 20.5 (CH_2). **HPLC**: Chiralpak IC eluted with 7:3 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 220 nm, retention times: major diastereomer 17.05 min (major enantiomer) and 11.83 min (minor enantiomer), minor diastereomer 13.49 min (major enantiomer) and 19.19 min (minor enantiomer).

Compound 4d: Following the general procedure, **3d** (72 mg, 0.18 mmol, dr = 22:1, er = 55:1) reacted with **DPHB** (7 mg, 0.037 mmol) for 72 h to provide **4d** (54 mg, 75%, dr = 1.6:1, er = 43:1 and 21:1) as a white solid. R_f = 0.45 (petrol ether/ethyl acetate, 3:1). **HRMS** (ESI+) *m/z* calcd for $C_{20}H_{18}F_3N_2O_4^+$ $[M+H]^+$ = 407.1213, found = 407.1213. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 7.75 (d, J = 8.7 Hz, 2H), 7.43–7.38 (m, 3H), 7.24–7.33 (m, 2H), 7.14 (d, J = 8.7 Hz, 2H), 5.23 (dd, J = 13.4, 7.3 Hz, 1H), 5.07 (dd, J = 13.4, 7.9 Hz, 1H), 4.05 (ddd, J = 7.6, 7.6, 3.6 Hz, 1H), 3.19 (ddd, J = 12.0, 5.1, 3.6 Hz, 1H), 2.83 (ddd, J = 17.4, 4.3, 4.3 Hz, 1H), 2.76–2.62 (m, 1H), 2.14 (ddd, J = 17.5, 9.1, 5.2 Hz, 1H), 2.06–1.93 (m, 1H); minor diastereomer: δ 7.75 (d, J = 8.7 Hz, 2H), 7.43–7.38 (m, 3H), 7.24–7.33 (m, 2H), 7.21 (d, J = 8.7 Hz, 2H), 5.17 (dd, J = 13.4, 7.1 Hz, 1H), 4.79 (dd, J = 13.4, 7.7 Hz, 1H), 4.19 (dd, J = 15.4, 7.6 Hz, 1H), 3.08 (ddd, J = 9.2, 9.2, 4.9 Hz, 1H), 2.93 (ddd, J = 17.9, 6.7, 4.8 Hz, 1H), 2.76–2.66 (m, 1H), 2.06–1.93 (m, 1H), 1.77 (ddd, J = 14.2, 9.6, 4.7 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) major diastereomer: δ 172.9 (C), 171.2 (C), 138.3 (C), 136.1 (C), 131.1 (q, J_{C-F} = 32.6 Hz, C), 129.4 (2CH), 129.1 (2CH), 128.9 (2CH), 128.8 (CH), 126.6 (q, J_{C-F} = 3.7 Hz, 2CH), 123.8 (q, J_{C-F} = 270 Hz, CF_3), 77.4 (CH_2), 45.9 (CH), 45.5 (CH), 32.4 (CH_2), 21.6 (CH_2); minor diastereomer: δ 173.0 (C), 171.3 (C), 138.2 (C), 136.4 (C), 131.1 (q, J_{C-F} = 32.6 Hz, C), 129.5 (2CH), 129.2 (2CH), 128.7 (CH), 128.3 (2CH), 126.5 (q, J_{C-F} = 3.7 Hz, 2CH), 123.7 (q, J_{C-F} = 270 Hz, CF_3), 78.1 (CH_2), 45.0 (CH), 43.7 (CH), 31.2 (CH_2), 20.6 (CH_2). **^{19}F{^{13}C} NMR** (282 MHz, $CDCl_3$) major diastereomer: δ −62.7; minor diastereomer: δ −62.7. **HPLC**: Chiralpak IC eluted with 8:2 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 235 nm, retention times: major diastereomer 11.67 min (major enantiomer) and 8.25 min (minor enantiomer), minor diastereomer 9.46 min (major enantiomer) and 15.33 min (minor enantiomer).

Compound 4e: Following the general procedure, **3e** (91 mg, 0.19 mmol, dr = 25:1, er = 58:1) reacted with **DPHB** (7 mg, 0.037 mmol) for 24 h to provide **4e** (77 mg, 85%, dr = 1.5:1, er = 44:1 and 38:1) as a colorless oil. R_f = 0.60 (petrol ether/ethyl acetate, 3:1). **HRMS** (ESI+) *m/z* calcd for $C_{21}H_{20}F_6N_3O_4^+$ $[M+NH_4]^+$ = 492.1353, found = 492.1350. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 7.92 (s, 1H), 7.53–7.35 (m, 5H), 7.26–7.19 (m, 2H), 5.21 (dd, J = 13.4, 7.5 Hz, 1H), 5.03 (dd, J = 13.4, 7.8 Hz, 1H), 4.03 (ddd, J = 7.6, 7.6, 3.5 Hz, 1H), 3.18 (ddd, J = 11.9, 5.2, 3.5 Hz, 1H), 2.82 (dd, J = 17.4, 4.2, 4.2 Hz, 1H), 2.77–2.61 (m, 1H), 2.23–2.12 (m, 1H), 2.07–1.90 (m, 1H); minor diastereomer: δ 7.92 (s, 1H), 7.53–7.35 (m, 5H), 7.26–7.19 (m, 2H), 5.14 (dd, J = 13.4, 7.3 Hz, 1H), 4.78 (dd, J = 13.4, 7.6 Hz, 1H), 4.19 (ddd, J = 7.6, 7.6, 7.6 Hz, 1H), 3.06 (ddd, J = 9.7, 8.1, 4.9 Hz, 1H), 2.91 (ddd, J = 17.9, 6.2, 4.7 Hz, 1H), 2.77–2.61 (m, 1H), 2.07–1.90 (m, 1H), 1.77 (dddd, J = 14.4, 10.1, 10.1 4.6 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) major diastereomer: δ 172.8 (C), 171.0 (C), 136.5 (C), 135.8 (C), 132.8 (q, J_{C-F} = 34.3 Hz, $2CF_3$), 129.5 (2CH), 129.3 (2CH), 128.9 (CH), 128.8 (2CH), 122.8 (q, J_{C-F} = 273.7 Hz, $2CF_3$), 122.8 (q, J_{C-F} = 3.7 Hz, CH), 77.2 (CH_2), 45.9 (CH), 45.5 (CH), 32.2 (CH_2), 21.4 (CH_2); minor diastereomer: δ 172.9 (C), 171.1 (C), 136.5 (C), 136.1 (C), 132.8 (q, J_{C-F} = 34.3 Hz, $2CF_3$), 129.4 (2CH), 129.3 (2CH), 128.7 (2CH), 128.7 (CH), 132.7 (q, J_{C-F} = 272.7 Hz, $2CF_3$), 122.8 (q, J_{C-F} = 3.7 Hz, CH), 78.0 (CH_2), 44.9 (CH), 43.7 (CH), 31.3 (CH_2), 20.4 (CH_2). **^{19}F{^{13}C} NMR** (282 MHz, $CDCl_3$) major diastereomer: δ −62.8; minor diastereomer: δ −62.9. **HPLC**: Chiralpak IF eluted with 9:1 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 210 nm, retention times: major diastereomer 13.26 min (major enantiomer) and 6.20 min (minor enantiomer), minor diastereomer 7.38 min (major enantiomer) and 8.19 min (minor enantiomer).

Compound 4i: Following the general procedure, **3i** (65 mg, 0.16 mmol, dr = 26:1, er = 49:1) reacted with **DPHB** (6 mg, 0.032 mmol) for 48 h to provide **4i** (43 mg, 66%, dr = 1.7:1, er = 12:1 and 19:1) as a white solid. R_f = 0.30 (petrol ether/ethyl acetate, 2:1). **HRMS** (ESI+) *m/z* calcd for $C_{20}H_{20}N_3O_6^+$ $[M+H]^+$ = 398.1347, found = 398.1345. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.32 (d, J = 8.7 Hz, 2H), 7.25–7.09 (m, 6H), 5.20 (dd, J = 13.3, 7.6 Hz, 1H), 4.99 (dd, J = 13.3, 7.7 Hz, 1H), 4.00 (ddd, J = 7.7, 7.7, 3.6 Hz, 1H), 3.15 (ddd, J = 11.8, 5.2, 3.5 Hz, 1H), 2.82 (ddd, J = 17.5, 4.4, 4.4 Hz, 1H), 2.72–2.63 (m, 1H), 2.36 (s, 3H), 2.20–2.12 (m, 1H), 2.08–1.94 (m, 1H); minor diastereomer: δ 8.32 (d, J = 8.7 Hz, 2H), 7.25–7.10 (m, 6H), 5.11 (dd, J = 13.4, 7.4 Hz, 1H), 4.74 (dd, J = 13.4, 7.4 Hz, 1H), 4.13 (ddd, J = 7.6, 7.6, 7.6 Hz, 1H), 3.04 (ddd, J = 8.7, 7.6, 4.9 Hz, 1H), 2.91 (ddd, J = 18.0, 7.0, 4.7 Hz, 1H), 2.78–2.72 (m, 1H), 2.36 (s, 3H), 2.08–1.94 (m, 1H), 1.77 (dddd, J = 14.0, 9.3, 9.3, 4.8 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) major diastereomer: δ 173.4 (C), 171.4 (C), 148.2 (C), 142.8 (C), 138.2 (C), 135.3 (C), 130.9 (2CH), 130.0 (2CH), 129.4 (2CH), 124.4 (2CH), 77.4 (CH_2), 46.7 (CH), 45.3 (CH), 32.9 (CH_2), 21.4 (CH_2), 20.9 (CH_3); minor diastereomer: δ 173.5 (C), 171.5 (C), 148.2 (C), 142.8 (C), 138.1 (C), 135.1 (C), 130.9 (2CH), 130.0 (2CH), 129.2 (2CH), 124.4 (2CH), 78.5 (CH_2), 45.5 (CH), 43.6 (CH), 32.6 (CH_2), 20.9 (CH_2), 20.8 (CH_3). **HPLC**: Chiralpak ID eluted with 1:1 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 260 nm, retention time: major diastereomer 17.06 min (major enantiomer) and 9.31 min (minor enantiomer), minor diastereomer 13.02 min (major enantiomer) and 11.14 min (minor enantiomer).

Compound 4j: Following the general procedure, **3j** (50 mg, 0.12 mmol, dr = 15:1, er > 200:1) reacted with **DPHB** (5 mg, 0.026 mmol) for 18 h to provide **4j** (38 mg, 76%, dr = 2.2:1,

er = 40:1 and 37:1) as a white solid. R_f = 0.28 (petrol ether/ethyl acetate, 3:1). **HRMS** (ESI+) *m/z* calcd for $C_{20}H_{20}N_3O_7^+$ $[M+H]^+$ = 414.1296, found = 414.1300. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.31 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.18 (dd, *J* = 13.3, 7.5 Hz, 1H), 5.00 (dd, *J* = 13.3, 7.8 Hz, 1H), 3.97 (ddd, *J* = 7.7, 7.7, 3.6 Hz, 1H), 3.82 (s, 3H), 3.14 (ddd, *J* = 11.8, 5.1, 3.6 Hz, 1H), 2.82 (ddd, *J* = 17.4, 4.3, 4.3 Hz, 1H), 2.72 (dddd, *J* = 12.6, 9.0, 5.8, 5.8 Hz, 1H), 2.22–2.08 (m, 1H), 2.07–1.93 (m, 1H); minor diastereomer: δ 8.31 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.09 (dd, *J* = 13.3, 7.4 Hz, 1H), 4.73 (dd, *J* = 13.3, 7.5 Hz, 1H), 4.13 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 3.81 (s, 3H), 3.02 (ddd, *J* = 9.0, 9.0, 4.9 Hz, 1H), 2.91 (ddd, *J* = 17.9, 6.8, 4.8 Hz, 1H), 2.72 (dddd, *J* = 12.6, 9.0, 5.8, 5.8 Hz, 1H), 2.07–1.93 (m, 1H), 1.77 (dddd, *J* = 14.1, 9.5, 9.0, 4.8 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) major diastereomer: δ 172.8 (C), 171.1 (C), 159.9 (C), 147.8 (C), 140.8 (C), 130.0 (2CH), 129.9 (C), 127.7 (2CH), 124.6 (2CH), 114.7 (2CH), 77.7 (CH_2), 55.5 (CH_3), 45.5 (CH), 45.4 (CH), 32.4 (CH_2), 21.7 (CH_2); minor diastereomer: δ 172.9 (C), 171.2 (C), 159.8 (C), 147.8 (C), 140.8 (C), 130.0 (2 CH), 129.4 (C), 127.9 (2CH), 124.6 (2CH), 114.9 (2CH), 78.1 (CH_2), 55.5 (CH_3), 45.1 (CH), 42.9 (CH), 31.2 (CH_2), 20.4 (CH_2). **HPLC**: Chiralpak IF eluted with 1:1 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 260 and 280 nm, retention time: major diastereomer 31.31 min (major enantiomer) and 16.87 min (minor enantiomer), minor diastereomer 21.34 min (major enantiomer) and 25.29 min (minor enantiomer).

Compound 4k: Following the general procedure, **3k** (54 mg, 0.12 mmol, dr > 20:1, er > 200:1) reacted with **DPHB** (5 mg, 0.026 mmol) for 15 h to provide **4k** (37 mg, 69%, dr = 1.8:1, er = 75:1 and 6.4:1) as a white solid. R_f = 0.30 (petrol ether/ethyl acetate, 3:1). **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{20}BrN_4O_6^+$ $[M+NH_4]^+$ = 479.0561, found = 479.0562. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.32 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 5.17 (dd, *J* = 13.5, 7.2 Hz, 1H), 5.04 (dd, *J* = 13.4, 8.0 Hz, 1H), 4.01 (ddd, *J* = 7.6, 7.6, 3.6 Hz, 1H), 3.16 (ddd, *J* = 12.6, 4.9, 3.7 Hz, 1H), 2.98–2.84 (m, 1H), 2.82–2.68 (m, 1H), 2.18–2.11 (m, 1H), 2.08–1.88 (m, 1H); minor diastereomer: δ 8.32 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 5.12 (dd, *J* = 13.4, 7.3 Hz, 1H), 4.75 (dd, *J* = 13.4, 7.6 Hz, 1H), 4.18 (ddd, *J* = 7.5, 7.5,7.5 Hz, 1H), 3.03 (ddd, *J* = 10.0, 7.8, 4.8 Hz, 1H), 2.98–2.84 (m, 1H), 2.73 (dd, *J* = 12.9, 4.9 Hz, 1H), 2.07–1.90 (m, 1H), 1.76 (dddd, *J* = 14.7, 10.2, 10.2, 4.7 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, *d8*-tetrahydrofuran) major diastereomer: δ 173.3 (C), 171.4 (C), 148.3 (C), 142.7 (C), 137.8 (C), 132.5 (2CH), 131.6 (2CH), 130.9 (2CH), 124.4 (2CH), 122.4 (C), 77.0 (CH_2), 44.6 (CH), 45.0 (CH), 33.0 (CH_2), 21.4 (CH_2); minor diastereomer: δ 173.3 (C), 171.4 (C), 148.3 (C), 142.7 (C), 134.5 (C), 132.5 (2CH), 131.5 (2CH), 130.9 (2CH), 124.4 (2CH), 122.4 (C), 78.0 (CH_2), 45.3 (CH), 43.3 (CH), 32.0 (CH_2), 20.8 (CH_2). **HPLC**: Chiralpak IC eluted with 7:3 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 280 nm, retention times: major diastereomer 12.64 min (major enantiomer) and 9.45 min (minor enantiomer), minor diastereomer 10.38 min (major enantiomer) and 15.81 min (minor enantiomer).

Compound 4l: Following the general procedure, **3l** (50 mg, 0.12 mmol, dr > 20:1, er = 39:1) reacted with **DPHB** (5 mg, 0.026 mmol) for 15 h to provide **4l** (22 mg, 44%, dr > 20:1, er = 50:1) as a white solid. R_f = 0.36 (petrol ether/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = + 21.7 (*c* = 0.5, $CHCl_3$). **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{20}N_5O_8^+$ $[M+NH_4]^+$ = 446.1306, found = 446.1307. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 8.8 Hz, 2H), 8.25 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 5.17 (dd, *J* = 10.8, 3.2 Hz, 1H), 5.14 (dd, *J* = 10.8, 2.8 Hz, 1H), 4.21 (ddd, *J* = 7.4, 3.8, 3.8 Hz, 1H), 3.23 (ddd, *J* = 8.6, 4.6, 4.6 Hz, 1H), 2.97 (ddd, *J* = 17.7, 4.4, 2.9 Hz, 1H), 2.80 (ddd, *J* = 17.7, 13.5, 5.3 Hz, 1H), 2.18 (dddd, *J* = 13.1, 5.1, 5.1, 2.9 Hz, 1H), 1.94 (dddd, *J* = 13.3, 13.3, 13.3, 4.5 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, *d6*-acetone): δ 173.7 (C), 172.2 (C), 148.5 (C), 148.4 (C), 146.7 (C), 143.2 (C), 131.4 (2CH), 131.1 (2CH), 124.8 (2CH), 124.6 (2CH), 77.2 (CH_2), 46.9 (CH), 44.9 (CH), 33.2 (CH_2), 21.1 (CH_2). **HPLC**: Chiralpak IC eluted with 2:2:1 heptane/ethanol/chloroforme at 1 mL/min at 25 °C, UV detection at 254 nm, retention time: major enantiomer 10.63 min, minor enantiomer 8.03 min.

Compound 4m: Following the general procedure, **3m** (60 mg, 0.16 mmol, dr = 28:1, er = 100:1) reacted with **DPHB** (6 mg, 0.032 mmol) for 15 h to provide **4m** (41 mg, 68%, dr = 2.4:1, er = 39:1 and 5.5:1) as a white solid. R_f = 0.30 (petrol ether/ethyl acetate, 3:1). **HRMS** (ESI+) *m/z* calcd for $C_{17}H_{19}N_4O_6S^+$ $[M+NH_4]^+$ = 407.1020, found = 407.1019. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.33 (d, *J* = 8.7 Hz, 2H), 7.33–7.30 (m, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.04–6.94 (m, 2H), 5.23 (dd, *J* = 13.5, 7.3 Hz, 1H), 4.99 (dd, *J* = 13.5, 7.4 Hz, 1H), 4.32 (ddd, *J* = 7.4, 7.4, 3.3 Hz, 1H), 3.20 (ddd, *J* = 12.4, 5.2, 3.3 Hz, 1H), 3.01–2.85 (m, 1H), 2.83–2.73 (m, 1H), 2.22–2.14 (m, 1H), 2.08–2.00 (m, 1H); minor diastereomer: δ 8.32 (d, *J* = 8.7 Hz, 2H), 7.33–7.30 (m, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.04–6.94 (m, 2H), 5.03 (dd, *J* = 13.1, 8.3 Hz, 1H), 4.83 (dd, *J* = 10.2, 6.8 Hz, 1H), 4.69 (dd, *J* = 14.6, 6.5 Hz, 1H), 3.08–3.02 (m, 1H), 3.00–2.88 (m, 1H), 2.83–2.73 (m, 1H), 2.13–2.09 (m, 1H), 1.95–1.85 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, *d8*-tetrahydrofuran) major diastereomer: δ 173.4 (C), 171.4 (C), 148.3 (C), 142.6 (C), 140.0 (C), 130.9 (2CH), 128.2 (CH), 127.4 (CH), 126.3 (CH), 124.4 (2CH), 79.1 (CH_2), 45.8 (CH), 41.9 (CH), 33.0 (CH_2), 22.2 (CH_2); minor diastereomer: δ 173.0 (C), 171.4 (C), 148.3 (C), 142.8 (C), 139.8 (C), 130.9 (2CH), 127.4 (CH), 127.3 (CH), 126.0 (CH), 124.4 (2CH), 78.1 (CH_2), 46.0 (CH), 39.3 (CH), 32.3 (CH_2), 20.1 (CH_2). **HPLC**: Chiralpak IC eluted with 3:2 heptane/ethanol at 1 mL/min at 25 °C, UV detection 254 nm, retention time: major diastereomer 9.82 min (major enantiomer) and 7.46 min (minor enantiomer), minor diastereomer 8.88 min (major enantiomer) and 12.51 min (minor enantiomer).

Compound 4n: Following the general procedure, **3n** (70 mg, 0.19 mmol, dr = 15:1, er = 48:1) reacted with **DPHB** (7 mg, 0.037 mmol) for 15 h to provide **4n** (57 mg, 81%, dr = 2:1, er = 28:1 and 46:1) as a white solid. R_f = 0.28 (petrol ether/ethyl acetate, 3:1). **HRMS** (ESI+) *m/z* calcd for $C_{17}H_{19}N_4O_7^+$ $[M+NH_4]^+$ = 391.1248, found = 391.1248. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.31 (d, *J* = 8.8 Hz, 2H), 7.43 (br s, 1H), 7.37 (br s, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.30 (br s, 1H), 5.12 (dd, *J* = 13.3, 7.5 Hz, 1H), 4.91 (dd, *J* = 13.3, 7.6 Hz, 1H), 3.89 (ddd, *J* = 7.5, 7.5, 3.0 Hz, 1H), 3.11 (ddd, *J* = 12.2, 5.6, 3.1 Hz, 1H), 3.00–2.90 (m, 1H), 2.85–2.71 (m, 1H), 2.14–1.98

(m, 2H); minor diastereomer: δ 8.30 (d, J = 8.8 Hz, 2H), 7.45 (br s, 1H), 7.35 (br s, 1H), 7.21 (d, J = 8.8 Hz, 2H), 6.28 (br s, 1H), 4.89 (dd, J = 12.9, 8.4 Hz, 1H), 4.71 (dd, J = 12.9, 7.1 Hz, 1H), 4.35 (dd, J = 13.5, 7.5 Hz, 1H), 2.99 (dd, J = 10.4, 4.8 Hz, 1H), 2.97–2.87 (m, 1H), 2.85–2.71 (m, 1H), 2.14–1.98 (m, 1H), 1.92–1.81 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, *d8*-tetrahydrofuran) major diastereomer: δ 173.7 (C), 171.4 (C), 148.2 (C), 144.3 (CH), 142.7 (CH), 142.2 (CH), 130.9 (2CH), 124.4 (2CH), 122.0 (CH), 111.1 (CH), 78.3 (CH_2), 45.7 (CH), 37.6 (CH), 33.0 (CH_2), 22.2 (CH_2); minor diastereomer: δ 173.3 (C), 171.4 (C), 148.2 (C), 144.2 (CH), 142.7 (CH), 141.9 (CH), 130.9 (2CH), 124.4 (2CH), 121.6 (CH), 110.7 (CH), 77.4 (CH_2), 45.1 (CH), 35.2 (CH), 32.3 (CH_2), 19.8 (CH_2). **HPLC**: Chiralpak IC eluted with 4:1 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 254 nm, retention times: major diastereomer 24.80 min (major enantiomer) and 17.08 min (minor enantiomer), minor diastereomer 18.98 min (major enantiomer) and 43.32 min (minor enantiomer).

Compound 4o: Following the general procedure, **3o** (89 mg, 0.22 mmol, dr = 28:1, er = 24:1) reacted with **DPHB** (8 mg, 0.042 mmol) for 24 h to provide **4o** (59 mg, 66%, dr = 1.9:1, er = 19:1 and 15:1) as a white solid. R_f = 0.43 (petrol ether/ethyl acetate, 3:1). **HRMS** (ESI+) *m/z* calcd for $C_{21}H_{25}N_4O_6^+$ $[M+NH_4]^+$ = 429.1769, found = 429.1770. **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 8.30 (d, J = 9.0 Hz, 2H), 7.35–7.14 (m, 7H), 4.76 (dd, J = 12.6, 6.8 Hz, 1H), 4.57–4.48 (m, 1H), 3.03–2.61 (m, 6H), 2.17–1.64 (m, 4H); minor diastereomer: δ 8.31 (d, J = 9.0 Hz, 2H), 7.35–7.14 (m, 7H), 4.62–4.48 (m, 2H), 3.15–3.05 (m, 1H), 3.03–2.61 (m, 5H), 2.17–1.64 (m, 4H). **^{13}C{^{1}H} NMR** (100 MHz, *d8*-tetrahydrofuran) major diastereomer: δ 173.6 (C), 171.6 (C), 148.2 (C), 142.8 (C), 142.2 (C), 130.9 (2CH), 129.0 (2CH), 129.0 (2CH), 126.7 (CH), 124.3 (2CH), 77.9 (CH_2), 44.3 (CH), 38.9 (CH), 34.2 (CH_2), 33.3 (CH_2), 31.7 (CH_2), 20.6 (CH_2); minor diastereomer: δ 173.5 (C), 171.6 (C), 148.2 (C), 142.9 (C), 142.2 (C), 130.9 (2CH), 128.9 (2CH), 128.8 (2CH), 126.6 (CH), 124.3 (2CH), 77.0 (CH_2), 44.7 (CH), 38.2 (CH), 34.2 (CH_2), 33.1 (CH_2), 32.2 (CH_2), 19.2 (CH_2). **HPLC**: Chiralpak IE eluted with 1:1 heptane/ethanol at 1 mL/min at 25 °C, UV detection at 260 nm, retention times: major diastereomer 9.27 min (major enantiomer) and 13.88 min (minor enantiomer), minor diastereomer 11.56 min (major enantiomer) and 19.83 min (minor enantiomer).

Computational Work

See the Supporting Information.

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