Template-Induced Enantioselectivity in the Reductive Radical Cyclization of 3-(3-Iodopropoxy)propenoic Acid Derivatives Depending on the Binding Motif

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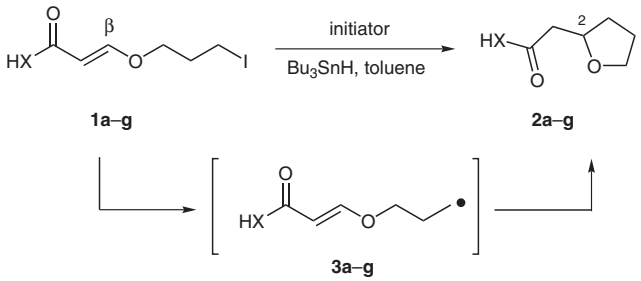
Abstract: Different binding motifs HXC=O have been screened in the enantioselective radical cyclization of various linear derivatives of 3-(3-iodopropoxy)propenoic acid. The reactions were performed in the presence of an enantiomerically pure, chiral 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one derivative, which acts as a hydrogen-binding template. The cyclized products were obtained in good to excellent yields (66–88%). Enantioselectivities up to 59% ee were achieved.

Key words: cyclizations, enantioselectivity, lactams, radical reactions, supramolecular chemistry

Enantioselective radical reactions have received considerable attention in recent years.[1,2] Among these reactions, conjugate addition reactions are particularly useful as they often allow for the concomitant formation of a carbon–carbon bond and a new stereogenic center.[3] Enantioselective radical-cyclization reactions[4] of acrylates are rare.[5,6] In the single example (up to 48% ee) reported to date,[5] a chiral Lewis acid was employed to control the conformation of the acrylate and to provide an efficient enantioface differentiation. A 5-*exo-trig* cyclization of chiral β-alkoxyvinyl sulfoxides has been reported for the construction of tetrahydrofurans with good diastereoselectivity.[7]

In this study, we conducted 5-*exo-trig* radical cyclization reactions with various derivatives **1** of the title compound, 3-(3-iodopropoxy)propenoic acid. These compounds react in the presence of tributyltin hydride and an appropriate initiator to give the corresponding tetrahydrofurans **2** (Scheme 1). The former β-carbon atom of the acrylic acid derivative is converted into a stereogenic center at C-2 of the tetrahydrofuran, with the radical addition step (intermediates **3**) being stereoselectivity determining. In earlier work,[8] we have shown that a radical cyclization reaction in the presence of a chiral template can proceed enantioselectively if binding of the substrate to the template is feasible by hydrogen bonding.[9] Quinolones have been shown to exhibit a very effective binding motif for this coordination, often allowing high enantioselectivities.[10,11] Other binding motifs have not yet been extensively studied. Since a modification 'HX' of the acrylic acid at the terminal carboxy group was considered to be facile, we speculated that we could use this specific cyclization to identify viable binding motifs for association. In an ideal scenario,



Scheme 1 Radical cyclization of various derivatives **1** of 3-(3-iodopropoxy)propenoic acid via radical intermediates **3** to the corresponding tetrahydrofurans **2**

the fragment HXC=O (depicted as ❍ in Figure 1) binds by two hydrogen bonds to the template.

The starting materials **1** for the radical cyclization were prepared from methyl propiolate (**4**) and 3-chloropropanol via intermediate ester **5** (Scheme 2). Saponification led to 3-(3-chloropropoxy)propenoic acid (**6**), which was used as starting material for amide **1a** and benzimidazolone **1d** (Table 1). They were generated via the respective chloro derivative by a Finkelstein reaction (Method A). While amide formation (product **1a**) was facile with gaseous ammonia, benzimidazolone was deprotonated (NaH, DMF) prior to acylation (product **1d**). The Finkelstein reaction could also be used to convert 3-(3-chloropropoxy)propenoic acid (**6**) into the title compound **1b**, from which the derivatives **1c**, **1e–g** were synthesized via the corresponding 3-(3-iodopropoxy)propenoyl chloride (Method B). Detailed reactions conditions are provided in the experimental section.

Racemic products **2** were smoothly obtained in all cases by treating the corresponding precursors **1** with tributyltin hydride and an initiator, yields ranging between 74 and 94% (Table 1). Except for the reaction of **1c** to **2c**, which required AIBN as the initiator in refluxing benzene, all reactions were conducted in toluene at ambient temperature using triethylborane as the initiator. Separation of enantiomers by chiral HPLC (Daicel Chiralpak AD-H) was possible in all cases. This fact facilitated the assessment of the enantiomeric excess (ee) for reactions which were conducted in the presence of template **7** (Figure 1). In the latter set of reactions, the radical cyclization was performed at –78 °C in toluene employing 2.5 equivalents of the complexing reagent **7**.

The yields remained very good in most cases, entry 7 being the exception, and the products **2** were obtained in

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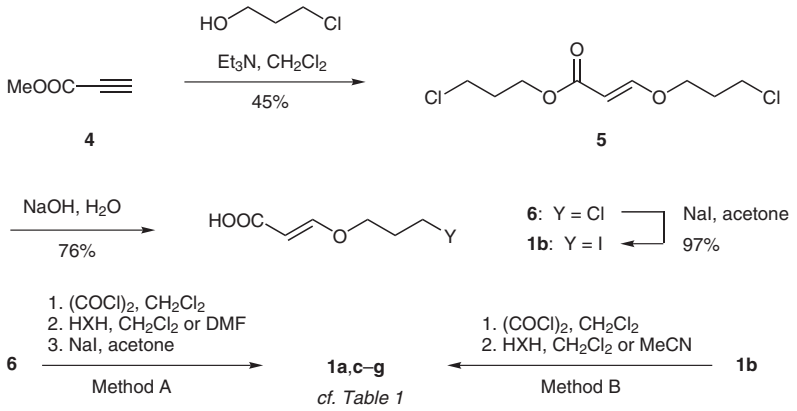
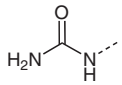
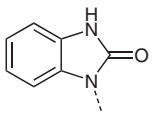
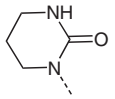
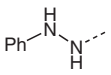
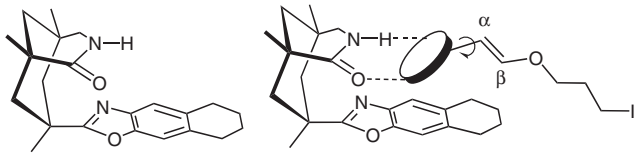


Scheme 2 Preparation of substrates **1** from 3-(3-chloropropoxy)propenoic acid (**6**) via intermediate product **5**

Table 1 Reaction Conditions, Yields and Enantioselectivities in the Radical Cyclization Reaction of Substrates **1a–g**

Entry	HX	Method[a] Yield[b] (%)	Substrate	Initiator[c] (equiv)	Template **7** (equiv)	Temp (°C)	Product	Yield[d] (%)	ee (%)
1	H_2N---	A 71	**1a**	Et_3B (0.25) Et_3B (0.25)	– 2.5	25 –78	**2a**	83 87	– 20
2	HO---	– –	**1b**	Et_3B (0.25) Et_3B (0.25)	– 2.5	25 –78	**2b**	94 70	– 31
3		B 63	**1c**	AIBN (0.20) Et_3B (0.25)	– 2.5	80 –78	**2c**	90 83	– <5
4		A 41	**1d**	Et_3B (0.25) Et_3B (0.25)	– 2.5	25 –78	**2d**	85 86	– 37
5		B 36	**1e**	Et_3B (0.25) Et_3B (0.25) UV (300 nm)	– 2.5 2.5	25 –78 –75	**2e**	74 73 80	– 59 55
6		B 78	**1f**	Et_3B (0.25) Et_3B (0.25)	– 2.5	25 –78	**2f**	84 88	– 5
7		B 79	**1g**	Et_3B (0.25) Et_3B (0.25)	– 2.5	25 –78	**2g**	74 66	– 24

[a] Preparation according to Method A or B, as specified in Scheme 2.
[b] Yield of isolated product **1a**,**c**–**g**.
[c] Radical reactions were conducted at a substrate concentration of 15 mM in toluene as the solvent (see experimental section).
[d] Yield of isolated product **2a**–**g**.



7 **7•1**

Figure 1 Complexation of template **7** with substrates **1a–g**

enantiomerically enriched form. Remarkably, the simple binding motifs carboxylic amide (H_2NCO) and carboxylic acid (HOCO) accounted for significant ee values, indicating that a binding of substrates **1a** and **1b** (entries 1, 2) to template **7** occurs and that the binding persists in the radical cyclization process via intermediates **3**.

In addition, the enantioselective reaction course also indicates that there is a conformational preference with regard to rotation around the CO–C_α bond (Figure 1). Linear amides are constrained by the geometrical properties of the amide bond, in particular by the almost perfect planarity around the C–N bond, which shows partial double bond character. One would consequently expect an *s-trans* conformation to be preferred for the CO–C_α bond due to 1,3-allylic strain. The expectation is substantiated by recent calculations conducted on acrylamide.[12] As a consequence of the preferred *s-trans* conformation, the

major enantiomer of the radical cyclization should be formed by *Si*-face attack at carbon atom C_β (Figure 1). We considered hydrazides as carboxylic acid derivatives which could possibly exhibit an increased preference for the *s-trans* conformation, but the results recorded with the hydrazine derivates, e.g. with **1f** and **1g**, were disappointing (Table 1, entries 6, 7). The linear urea **1c** (entry 3) was equally unsuited for achieving high enantiomeric excesses. It was also the only substrate in which the cyclization could not be induced by triethylborane in the absence of template **7**; AIBN was required for initiation at elevated temperature. Interestingly, the triethylborane-initiated cyclization did work in the presence of template **7** at –78 °C but, as already mentioned, the enantiomeric excess of product **2c** was very low. In contrast, the cyclic ureas **1d** and **1e** (entries 4 and 5) delivered relatively high enantioselectivities given the distance between the binding motif and the reaction center at C_β. Indeed, binding to the template presumably occurs via two hydrogen bonds at the lactam part of the urea, which is four bonds away from the prostereogenic carbon atom C_β. Due to this distance, the tetrahydronaphthalene backbone is apparently no longer capable of completely shielding one of the two enantiotopic faces around C_β. The possibility that the polar initiator triethylborane is responsible for a decreased enantioselectivity was ruled out by initiating the cyclization of **1e** to **2e** with UV light. The enantiomeric excess recorded with this protocol (55% ee) was, in fact, slightly lower than the ee obtained in the triethylborane case (59% ee, entry 5).

In summary, the results indicate that the association to template **7** increases for acrylic acid derivatives in the order hydrazide < amide < acid < cyclic urea. The as yet incomplete enantioselectivity in the case of ureas **1d** and **1e** is most likely due to the insufficient face differentiation exerted by the tetrahydronaphthalene shield of template **7**. To prove this assumption and to employ the urea binding motif in a general fashion, further experiments will be directed at the synthesis of templates with even more extended shields. Studies along these lines are underway in our laboratories and will be reported in due course.

All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under argon. Anhydrous Et_3N and CH_2Cl_2 were distilled from CaH_2 prior to use. Common solvents (Et_2O, pentane, EtOAc, CH_2Cl_2, MeOH) were distilled prior to use. All other solvents and reagents were used as received. TLC was performed on glass plates (0.25 mm silica gel 60, F_{254}); detection was by coloration with ceric ammonium molybdate or phosphomolybdic acid. Column chromatography was performed on silica gel 60 (230–400 mesh; ca. 50 g for 1 g of material to be separated) with the eluent mixture indicated. ^1H and ^{13}C NMR spectra were recorded on Bruker AV-250 and AV-360 instruments at 303 K. Chemical shifts are reported relative to tetramethylsilane as internal standard. Apparent multiplets which occur as a result of accidental equality of coupling constants of magnetically nonequivalent protons are marked as virtual (virt.). The multiplicities of the ^{13}C NMR signals were determined by DEPT experiments and standard two-dimensional NMR experiments. IR spectra were recorded with a Perkin-Elmer 1600 instrument and mass spectra were recorded with an Agilent 5973 or a Finnigan MAT 8200 mass spectrometer. The unstable iodo compounds **1**, for some of which MS (EI) and/or HRMS data could not be obtained, were not stored but used immediately after preparation.

3-Chloropropyl 3-(3-Chloropropoxy)propenoate (5)

Et_3N (3 mL) was added to a stirred soln of methyl propiolate (**4**; 5.0 g, 59.5 mmol) and 3-chloropropanol (15 mL) in CH_2Cl_2 (60 mL) at 0 °C. After an exothermic reaction, the solution was stirred at rt for 2 h, then washed with 1 N HCl (20 mL) and H_2O (20 mL), and dried (Na_2SO_4). Kugelrohr distillation (135 °C/0.2 mbar) gave **5**.

Yield: 6.1 g (45%); R_f = 0.25 (Et_2O–pentane, 1:3).

IR (neat): 2962 (w), 2880 (w), 1707 (s), 1620 (s), 1440 (s), 1329 (m), 1285 (m), 1207 (m), 1116 (vs), 1038 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.13 (virt. quin, $J \cong 6.5$ Hz, 2 H, 2″-H), 2.18 (virt. quin, $J \cong 6.5$ Hz, 2 H, 2′-H), 3.62–3.69 (2 × t, J = 6.5 Hz, 4 H, 3′-H, 3″-H), 4.03 (t, J = 5.8 Hz, 2 H, 1″-H), 4.28 (t, J = 5.8 Hz, 2 H, 1′-H), 5.24 (d, J = 12.6 Hz, 1 H, 2-H), 7.61 (d, J = 12.6 Hz, 1 H, 3-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 32.1 (t), 32.2 (t), 41.2 (t), 41.7 (t), 61.0 (t), 67.6 (t), 97.0 (d), 162.7 (d), 167.9 (s).

MS (EI, 70 eV): *m/z* (%) = 240/242 (3/1) [M^+], 205/207 (14/5), 177/179 (15/5), 147/149 (100/33), 101 (21), 71 (89).

HRMS (EI): *m/z* calcd for $C_9H_{14}Cl_2O_3$: 240.0320/242.0291; found: 240.0310/242.0292.

3-(3-Chloropropoxy)propenoic Acid (6)

A mixture of ester **5** (6.0 g, 25.0 mmol) in 0.5 N aq NaOH (115 mL) was stirred at 40 °C for 24 h. The aqueous layer was washed with Et_2O (2 × 25 mL), then acidified with 6 N HCl and extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and the solvent was removed to afford **6** as white crystals.

Yield: 3.1 g (76%); mp 93 °C; R_f = 0.62 (CH_2Cl_2–MeOH, 10:1).

IR (KBr): 3421 (br), 3100 (m), 3087 (m), 2962 (m), 2927 (m), 2897 (m), 1700 (vs), 1610 (vs), 1466 (m), 1306 (s), 1208 (vs), 731 (s) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.17 (virt. quin, $J \cong 6.1$ Hz, 2 H, 2′-H), 3.66 (t, J = 6.1 Hz, 2 H, 3′-H), 4.04 (t, J = 5.8 Hz, 2 H, 1′-H), 5.22 (d, J = 12.6 Hz, 1 H, 2-H), 7.67 (d, J = 12.6 Hz, 1 H, 3-H), 11.05 (br s, 1 H, OH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 31.6 (t), 40.7 (t), 67.5 (t), 96.3 (d), 164.0 (d), 173.4 (s).

MS (EI, 70 eV): *m/z* (%) = 164/166 (20/7) [M^+], 146/148 (3/1), 101 (25), 88 (50), 76 (30), 70 (56), 55 (6), 49 (13), 41 (100).

HRMS (EI): *m/z* calcd for $C_6H_9ClO_3$: 164.0240; found: 164.0240.

3-(3-Iodopropoxy)propenamide (1a)

Oxalyl chloride (170 μL, 3.2 equiv) was added to a soln of acid **6** (100 mg, 0.61 mmol) in CH_2Cl_2 (2 mL), and the mixture was heated for 1 h under reflux. The mixture was concentrated under reduced pressure to afford crude 3-(3-chloropropoxy)propenoyl chloride. Ammonia was introduced over 5 min to a soln of this acid chloride in CH_2Cl_2 (5 mL) at –15 °C. The solvent was removed and the crude product was purified by column chromatography (CH_2Cl_2–MeOH, 200:1 → 50:1). The resulting amide (72 mg, 0.44 mmol) and NaI (166 mg, 2.5 equiv) were heated in acetone (15 mL) under reflux for 48 h. The acetone was removed, the residue was suspended in H_2O (10 mL) and the product was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed to give **1a** as white crystals.

Yield: 111 mg (71%); mp 138–140 °C; R_f = 0.56 (CH_2Cl_2–MeOH, 10:1).

IR (KBr): 3345 (br), 3080 (w), 2947 (m), 2924 (m), 2874 (m), 1676 (s), 1593 (vs), 1419 (m), 1330 (m), 1203 (s), 1128 (s), 1025 (m), 825 (m) cm^{-1}.

^1H NMR (360 MHz, DMSO-d_6): δ = 2.09 (virt. quin, $J \cong 6.6$ Hz, 2 H, 2′-H), 3.20 (t, $J = 6.7$ Hz, 2 H, 3′-H), 3.82 (t, $J = 5.9$ Hz, 2 H, 1′-H), 5.28 (d, $J = 12.4$ Hz, 1 H, 2-H), 5.74 (br s, 1 H, NH), 6.50 (br s, 1 H, NH), 7.39 (d, $J = 12.4$ Hz, 1 H, 3-H).

^{13}C NMR (90 MHz, DMSO-d_6): δ = 3.4 (t), 32.0 (t), 69.8 (t), 99.7 (d), 158.1 (d), 167.3 (s).

MS (EI, 70 eV): *m/z* (%) = 255 (1) [M^+], 239 (2), 184 (12), 169 (18), 128 (15), 98 (28), 41 (100).

HRMS (EI) : *m/z* [$M^+ - NH_2$] calcd for $C_6H_8IO_2$: 238.9569; found: 238.9569.

3-(3-Iodopropoxy)propenoic Acid (1b)

Acid **6** (500 mg, 3.04 mmol) and NaI (900 mg, 2 equiv) were heated in acetone (15 mL) under reflux for 48 h. The solvent was removed, the residue was suspended in H_2O (10 mL) and the product was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed to give **1b** as yellowish crystals.

Yield: 750 mg (97%); mp 118–119 °C; $R_f = 0.62$ (CH_2Cl_2–MeOH, 10:1).

IR (KBr): 3442 (br), 3080 (w), 2924 (m), 2852 (m), 1677 (s), 1618 (vs), 1416 (m), 1332 (m), 1219 (s), 1181 (s), 1158 (s) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.20 (virt. quin, $J \cong 6.0$ Hz, 2 H, 2′-H), 3.27 (t, $J = 6.7$ Hz, 2 H, 3′-H), 3.97 (t, $J = 6.0$ Hz, 2 H, 1′-H), 5.23 (d, $J = 12.7$ Hz, 1 H, 2-H), 7.66 (d, $J = 12.7$ Hz, 1 H, 3-H), 11.0 (br s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 1.1 (t), 32.3 (t), 70.5 (t), 96.3 (d), 164.0 (d), 173.3 (s).

MS (EI, 70 eV): *m/z* (%) = 256 (1) [M^+], 239 (1), 169 (21), 141 (5), 129 (12), 111 (7), 99 (13), 83 (31), 71 (10), 55 (6), 41 (100).

HRMS (EI): *m/z* calcd for $C_6H_9IO_3$: 255.9596; found: 255.9599.

N-[3-(3-Iodopropoxy)propenoyl]urea (1c)

Oxalyl chloride (0.22 mL, 3.3 equiv) was added to a soln of acid **1b** (200 mg, 0.78 mmol) in CH_2Cl_2 (4 mL) and the mixture was heated under reflux for 1 h. Then, the mixture was concentrated under reduced pressure. The resulting acid chloride was dissolved in MeCN (2 mL) and added dropwise to a suspension of pulverized urea (55 mg, 1.2 equiv) in MeCN (8 mL) under reflux. After 30 min under reflux, the solution was cooled to 0 °C, and the precipitated product was collected by filtration and washed with Et_2O (2 × 10 mL) to afford **1c** as white crystals.

Yield: 145 mg (63%); mp 175–178 °C; $R_f = 0.55$ (CH_2Cl_2–MeOH, 10:1).

IR (neat): 3370 (m), 3311 (m), 3210 (m), 2962 (w), 1697 (s), 1668 (s), 1591 (s), 1396 (m), 1247 (m), 1154 (s), 1101 (s), 956 (m), 800 (s) cm^{-1}.

^1H NMR (360 MHz, DMSO-d_6): δ = 2.12 (virt. quin, $J \cong 6.8$ Hz, 2 H, 2′-H), 3.28 (t, $J = 6.8$ Hz, 2 H, 3′-H), 3.94 (t, $J = 6.1$ Hz, 2 H, 1′-H), 5.55 (d, $J = 12.6$ Hz, 1 H, 2″-H), 7.12 (br s, 1 H, NH_2), 7.59 (d, $J = 12.6$ Hz, 1 H, 3″-H), 7.86 (br s, 1 H, NH_2), 9.88 (br s, 1 H, NH).

^{13}C NMR (90 MHz, DMSO-d_6): δ = 3.1 (t), 32.0 (t), 71.0 (t), 98.8 (d), 154.2 (s), 161.6 (d), 167.2 (s).

MS (EI, 70 eV): *m/z* (%) = 299 (1) [M + H^+], 173 (2), 146 (6), 103 (44), 87 (45), 75 (31), 60 (21), 44 (100).

1-[3-(3-Iodopropoxy)propenoyl]-1,3-dihydro-2*H*-benzimidazol-2-one (1d)

NaH (60% in oil, 35 mg) was washed with pentane (2 × 2 mL) and suspended in DMF (2 mL). Benzimidazolone (122 mg, 0.91 mmol) was added at r.t. and the mixture was stirred for 30 min. 3-(3-Chloropropoxy)propenoyl chloride (0.91 mmol), prepared as described above (see **1a**), in DMF (2 mL) was added dropwise and the solution was stirred for 24 h at r.t. After workup, the product was separated by column chromatography (EtOAc–pentane, 1:4 → 1:2) to give white crystals (104 mg, 41%) of 1-[3-(3-chloropropoxy)propenoyl]-1,3-dihydro-2*H*-benzimidazol-2-one. This compound (104 mg, 0.37 mmol) and NaI (277 mg, 5 equiv) were stirred in acetone (5 mL) for 48 h under reflux. The solvent was removed, the residue was suspended in H_2O (10 mL) and the product was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed to give **1d** as white crystals.

Yield: 140 mg (41%); mp 158–160 °C; $R_f = 0.78$ (EtOAc–pentane, 1:1).

IR (neat): 3088 (w), 3069 (w), 2971 (m), 2938 (m), 2875 (m), 1678 (s), 1610 (s), 1421 (m), 1334 (m), 1300 (m), 1212 (s), 1164 (s), 941 (m), 824 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.28 (virt. quin, $J \cong 6.1$ Hz, 2 H, 2″-H), 3.25 (t, $J = 6.5$ Hz, 2 H, 3″-H), 4.12 (t, $J = 6.1$ Hz, 2 H, 1″-H), 7.04–7.12 (m, 4 H, 2′-H, 3 × H_{Ar}), 7.96 (d, $J = 12.2$ Hz, 1 H, 3′-H), 8.22 (d, $J = 7.2$ Hz, 1 H, H_{Ar}), 8.86 (br s, 1 H, NH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 1.2 (t), 32.4 (t), 70.9 (t), 98.6 (d), 109.0 (d), 116.3 (d), 122.8 (d), 124.4 (s), 127.6 (d), 128.0 (s), 153.4 (s), 164.6 (d), 166.0 (s).

MS (EI, 70 eV): *m/z* (%) = 372 (37) [M^+], 239 (100), 169 (81), 134 (30), 106 (12), 71 (25), 41 (68).

HRMS (EI): *m/z* calcd for $C_{13}H_{13}IN_2O_3$: 371.9971; found: 371.9965.

1-[3-(3-Iodopropoxy)propenoyl]tetrahydropyrimidin-2(1*H*)-one (1e)

Oxalyl chloride (0.11 mL, 3.3 equiv) was added to a soln of acid **1b** (100 mg, 0.39 mmol) in CH_2Cl_2 (4 mL) and the mixture was heated under reflux for 1 h. Then, the mixture was concentrated under reduced pressure. The resulting acid chloride was dissolved in MeCN (2 mL) and added dropwise to a suspension of pulverized trimethyleneurea (78 mg, 2 equiv) in MeCN (8 mL) under reflux. After 30 min under reflux, the MeCN was removed and the product was purified by column chromatography (CH_2Cl_2–MeOH, 200:1 → 100:1) to give **1e** as a viscous oil.

Yield: 47 mg (36%); $R_f = 0.70$ (CH_2Cl_2–MeOH, 10:1).

IR (neat): 3263 (m), 2952 (w), 2875 (w), 1687 (s), 1644 (s), 1586 (m), 1479 (m), 1343 (s), 1300 (s), 1187 (m), 1145 (s), 1038 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 1.95–2.00 (m, 2 H, 5-H), 2.21 (virt. quin, $J \cong 6.1$ Hz, 2 H, 2″-H), 3.28 (t, $J = 6.8$ Hz, 2 H, 3″-H), 3.36 (dt, $J = 2.6$, 6.1 Hz, 2 H, 4-H), 3.81–3.85 (m, 2 H, 6-H), 3.97 (t, $J = 6.1$ Hz, 2 H, 1″-H), 5.38 (br s, 1 H, NH), 6.75 (d, $J = 12.2$ Hz, 1 H, 2′-H), 7.70 (d, $J = 12.2$ Hz, 1 H, 3′-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 1.5 (t), 21.8 (t), 32.5 (t), 40.8 (t), 41.4 (t), 70.0 (t), 101.2 (d), 161.9 (d), 168.6 (s); one signal missing.

MS (EI, 70 eV): *m/z* (%) = 284 (15), 256 (20), 211 (9) [$M^+ - I$], 172 (61), 155 (25), 127 (43), 100 (100), 84 (60), 56 (91).

1-[3-(3-Iodopropoxy)propenoyl]pyrazolidine (1f)

Et_3N (166 μL, 3 equiv) was added to a mixture of pyrazolidine dihydrochloride (84 mg, 1.5 equiv) in CH_2Cl_2 (5 mL). To this solution, 3-(3-iodopropoxy)propenoyl chloride (0.39 mmol), prepared as described above (see **1e**), dissolved in CH_2Cl_2 (2 mL) was added

and the mixture was stirred for 30 min at r.t. The mixture was concentrated and the product was purified by column chromatography (CH_2Cl_2–MeOH, 200:1 → 100:1) to give **1f** as an unstable yellowish oil.

Yield: 94 mg (78%); R_f = 0.70 (CH_2Cl_2–MeOH, 10:1).

IR (neat): 3214 (w), 2938 (w), 2880 (w), 1639 (s), 1580 (s), 1450 (m), 1421 (m), 1319 (m), 1188 (s), 1125 (m), 1033 (m), 965 (m), 819 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.06 (virt. quin, $J \cong 7.3$ Hz, 2 H, 4-H), 2.18 (virt. quin, $J \cong 5.9$ Hz, 2 H, 2″-H), 3.01 (t, J = 5.7 Hz, 2 H, 3-H), 3.25 (t, J = 6.7 Hz, 2 H, 3″-H), 3.56 (t, J = 7.6 Hz, 2 H, 5-H), 3.90 (t, J = 5.8 Hz, 2 H, 1″-H), 4.08 (br s, 1 H, NH), 6.07 (br s, 1 H, 2′-H), 7.52 (d, J = 12.5 Hz, 1 H, 3′-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 1.7 (t), 27.4 (t), 32.5 (t), 44.1 (t), 47.8 (t), 69.9 (t), 97.2 (d), 159.8 (d), 167.0 (s).

3-(3-Iodopropoxy)propenoic Acid *N*′-Phenylhydrazide (1g)

3-(3-Iodopropoxy)propenoyl chloride (0.39 mmol), prepared as described above (see **1e**), was dissolved in CH_2Cl_2 (2 mL) and added dropwise to a soln of phenylhydrazine (108 mg, 2 equiv) in CH_2Cl_2 (10 mL). The mixture was stirred for 30 min at r.t., then concentrated, and the product was purified by column chromatography (EtOAc–pentane, 1:2) to give **1g** as an unstable yellowish oil.

Yield: 106 mg (79%); R_f = 0.85 (CH_2Cl_2–MeOH, 10:1).

IR (neat): 3224 (w), 3045 (w), 3016 (w), 2938 (m), 2880 (m), 1648 (s), 1596 (s), 1494 (s), 1391 (m), 1314 (m), 1193 (s), 1111 (m), 965 (m), 815 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.09 (virt. quin, $J \cong 6.6$ Hz, 2 H, 2′-H), 3.20 (t, J = 6.6 Hz, 2 H, 3′-H), 3.80 (t, J = 5.8 Hz, 2 H, 1′-H), 4.74 (br s, 1 H, NH), 5.40 (br d, J = 12.2 Hz, 1 H, 2-H), 6.84 (br s, 1 H, NH), 7.21–7.43 (m, 5 H, H_{Ar}), 7.56 (d, J = 12.2 Hz, 1 H, 3-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 1.4 (t), 32.4 (t), 70.6 (t), 97.0 (d), 126.5 (d), 127.4 (d), 129.1 (d), 129.2 (s), 160.4 (d), 167.3 (s).

Enantioselective Radical Cyclization; General Procedure

A soln of the iodide **1a**–**g** (1.0 equiv) and template **7** (2.5 equiv) in toluene (15 mM) was cooled to –78 °C under argon. Bu_3SnH (2.0 equiv), Et_3B (0.25 equiv) and air (1 mL) were then added by syringe. The solution was stirred for 1 h (TLC control) at –78 °C and subsequently concentrated. Product and template **7** were separated by column chromatography with the indicated solvents (R_f). Enantiomeric excesses were obtained by chiral HPLC (Daicel Chiralpak AD-H) and are listed in Table 1. Specific rotations refer to enantiomerically enriched products with the given ee.

(Tetrahydrofuran-2-yl)acetamide (2a)

Yield: 87%; R_f = 0.52 (CH_2Cl_2–MeOH, 10:1).

IR (KBr): 3382 (br), 3198 (br), 2970 (m), 2873 (m), 1666 (s), 1414 (m), 1262 (w), 1206 (w), 1183 (w), 1063 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 1.48–1.58 (m, 1 H, 4′-H_A), 1.84–1.95 (m, 2 H, 3′-H_A, 4′-H_B), 2.02–2.10 (m, 1 H, 3′-H_B), 2.40 (dd, J = 15.3, 7.6 Hz, 1 H, 2-H_A), 2.46 (dd, J = 15.3, 4.5 Hz, 1 H, 2-H_B), 3.73–3.79 (m, 1 H, 5′-H_A), 3.86–3.93 (m, 1 H, 5′-H_B), 4.09–4.16 (m, 1 H, 2′-H), 5.74 (br s, 1 H, NH_2), 6.49 (br s, 1 H, NH_2).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 25.4 (t), 31.3 (t), 41.8 (t), 68.0 (t), 75.5 (d), 173.7 (s).

MS (EI, 70 eV): *m/z* (%) = 129 (3) [M^+], 114 (3), 101 (65), 86 (100), 71 (92), 59 (81), 56 (15), 43 (88).

HRMS (EI): *m/z* calcd for $C_6H_{11}NO_2$: 129.0790; found: 129.0789.

(Tetrahydrofuran-2-yl)acetic Acid (2b)[13]

Yield: 70%.

^1H NMR (360 MHz, $CDCl_3$): δ = 1.53–1.62 (m, 1 H, 4′-H_A), 1.90–1.98 (m, 2 H, 3′-H_A, 4′-H_B), 2.08–2.18 (m, 1 H, 3′-H_B), 2.54 (dd, J = 15.6, 5.7 Hz, 1 H, 2-H_A), 2.63 (dd, J = 15.6, 7.2 Hz, 1 H, 2-H_B), 3.77–3.82 (m, 1 H, 5′-H_A), 3.89–3.95 (m, 1 H, 5′-H_B), 4.24–4.32 (m, 1 H, 2′-H), 8.90 (br s, 1 H, OH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 25.5 (t), 31.2 (t), 40.3 (t), 68.0 (t), 75.0 (d), 176.3 (s).

N-(Tetrahydrofuran-2-ylacetyl)urea (2c)

Yield: 83%; mp 151–155 °C; R_f = 0.45 (CH_2Cl_2–MeOH, 10:1).

IR (neat): 3380 (m), 3224 (w), 3152 (w), 2972 (w), 2871 (w), 1702 (vs), 1586 (s), 1503 (m), 1391 (s), 1198 (s), 1106 (m), 1067 (s), 829 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 1.41–1.51 (m, 1 H, 4′-H_A), 1.76–1.86 (m, 2 H, 3′-H_A, 4′-H_B), 1.92–2.01 (m, 1 H, 3′-H_B), 2.42 (dd, J = 14.5, 5.5 Hz, 1 H, 2-H_A), 3.25 (dd, J = 14.5, 7.7 Hz, 1 H, 2-H_B), 3.56–3.61 (m, 1 H, 5′-H_A), 3.70–3.76 (m, 1 H, 5′-H_B), 4.07–4.14 (m, 1 H, 2′-H), 7.19 (br s, 1 H, NH_2), 7.74 (br s, 1 H, NH_2), 10.09 (br s, 1 H, NH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 24.9 (t), 30.6 (t), 42.0 (t), 66.8 (t), 74.9 (d), 153.7 (s), 172.6 (s).

MS (EI, 70 eV): *m/z* (%) = 171 (1) [$M^+ - H$], 144 (18), 129 (68), 102 (18), 84 (21), 71 (62), 60 (75), 44 (100).

HRMS (EI): *m/z* calcd for $C_7H_{12}N_2O_3$: 172.0848; found: 172.0848.

1-(Tetrahydrofuran-2-ylacetyl)-1,3-dihydro-2*H*-benzimidazol-2-one (2d)

Yield: 86%; mp 118–120 °C; $[\alpha]_D^{25}$ –7.4 (*c* 0.31, MeOH); 37% ee; R_f = 0.65 (EtOAc–pentane, 1:1).

IR (KBr): 3205 (w), 3064 (w), 2957 (m), 2928 (m), 2856 (m), 1730 (s), 1701 (s), 1479 (m), 1319 (m), 1276 (m), 1149 (m), 1096 (m), 1047 (m), 960 (m), 756 (s) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 1.65–1.73 (m, 1 H, 4″-H_A), 1.90–2.02 (m, 2 H, 3″-H_A, 4″-H_B), 2.20–2.25 (m, 1 H, 3″-H_B), 3.34 (dd, J = 16.8, 5.0 Hz, 1 H, 2′-H_A), 3.49 (dd, J = 16.8, 7.7 Hz, 1 H, 2′-H_B), 3.78–3.84 (m, 1 H, 5″-H_A), 3.90–3.96 (m, 1 H, 5″-H_B), 4.48–4.55 (m, 1 H, 2″-H), 7.02 (ddd, J = 7.4, 1.5, 0.6 Hz, 1 H, 4-H), 7.13 (dt, J = 7.7, 1.5 Hz, 1 H, 5-H), 7.18 (dt, J = 7.6, 1.5 Hz, 1 H, 6-H), 8.20 (ddd, J = 7.8, 1.5, 0.6 Hz, 1 H, 7-H), 8.48 (br s, 1 H, NH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 25.6 (t), 31.6 (t), 43.4 (t), 68.1 (t), 74.7 (d), 109.0 (d), 116.2 (d), 122.8 (d), 124.7 (d), 127.4 (s), 127.7 (s), 153.1 (s), 171.3 (s).

MS (EI, 70 eV): *m/z* (%) = 246 (7) [M^+], 134 (100), 106 (10), 71 (15).

HRMS (EI): *m/z* calcd for $C_{13}H_{14}N_2O_3$: 246.1005; found: 246.1004.

1-(Tetrahydrofuran-2-ylacetyl)tetrahydropyrimidin-2(1*H*)-one (2e)

Yield: 73%; mp 76–77 °C; $[\alpha]_D^{25}$ –5.0 (*c* 0.32, MeOH); 59% ee; R_f = 0.55 (CH_2Cl_2–MeOH, 10:1).

IR (KBr): 3229 (w), 3108 (w), 2967 (w), 2938 (w), 2890 (w), 2846 (w), 1697 (s), 1673 (s), 1484 (m), 1421 (m), 1305 (m), 1227 (m), 1159 (m), 1057 (m), 1023 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 1.50–1.60 (m, 1 H, 4″-H_A), 1.83–1.97 (m, 4 H, 3″-H_A, 4″-H_B, 5-H), 2.04–2.13 (m, 1 H, 3″-H_B), 3.17 (dd, J = 16.8, 5.2 Hz, 1 H, 2′-H_A), 3.25 (dd, J = 16.8, 7.5 Hz, 1 H, 2′-H_B), 3.32 (dt, J = 6.0, 2.6 Hz, 2 H, 4-H), 3.67–3.78 (m, 2 H, 6-H), 3.82–3.90 (m, 2 H, 5″-H), 4.33–4.41 (m, 1 H, 2″-H), 5.38 (br s, 1 H, NH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 21.7 (t), 25.6 (t), 31.4 (t), 40.7 (t), 41.5 (t), 44.8 (t), 67.9 (t), 75.4 (d), 154.3 (s), 173.7 (s).

MS (EI, 70 eV): *m/z* (%) = 212 (6) [M$^+$], 195 (2), 184 (58), 169 (45), 153 (15), 142 (39), 127 (5), 111 (12), 101 (100), 85 (35), 71 (61), 56 (25), 43 (41).

HRMS (EI): *m/z* calcd for $C_{10}H_{16}N_2O_3$: 212.1161; found: 212.1159.

1-(Tetrahydrofuran-2-ylacetyl)pyrazolidine (2f)
Yield: 88%; R_f = 0.60 (CH_2Cl_2–MeOH, 10:1).

IR (neat): 3462 (w), 2957 (w), 2875 (w), 1639 (s), 1596 (m), 1450 (s), 1431 (s), 1280 (w), 1062 (s), 1018 (m), 927 (m), 839 (m) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.54–1.64 (m, 1 H, 4″-H_A), 1.80–2.10 (m, 5 H, 3″-H, 4-H, 4″-H_B), 2.66 (dd, *J* = 14.1, 5.3 Hz, 1 H, 2′-H_A), 2.91–3.06 (m, 3 H, 2′-H_B, 3-H), 3.48–3.56 (m, 2 H, 5-H), 3.69–3.75 (m, 1 H, 5″-H_A), 3.82–3.89 (m, 1 H, 5″-H_B), 4.23–4.30 (m, 1 H, 2″-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 25.5 (t), 27.5 (t), 31.4 (t), 40.1 (t), 43.9 (t), 48.0 (t), 67.8 (t), 76.5 (d), 171.1 (s).

MS (EI, 70 eV): *m/z* (%) = 182 (13) [M$^+$ – 2 H], 154 (20), 139 (25), 112 (29), 70 (100), 43 (36).

HRMS (EI): *m/z* calcd for $C_9H_{14}N_2O_2$: 182.1055; found: 182.1055.

(Tetrahydrofuran-2-yl)acetic Acid *N*′-Phenylhydrazide (2g)
Yield: 66%; mp 112–115 °C; $[\alpha]_D^{25}$ +4.6 (*c* 0.24, MeOH); 24% ee; R_f = 0.78 (CH_2Cl_2–MeOH, 10:1).

IR (neat): 3321 (m), 3257 (m), 3045 (w), 3030 (w), 2951 (m), 2923 (m), 2868 (m), 1643 (vs), 1599 (s), 1550 (m), 1491 (s), 1437 (m), 1259 (m), 1058 (m), 974 (m), 752 (s) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.52–1.62 (m, 1 H, 4′-H_A), 1.85–2.98 (m, 2 H, 3′-H_A, 4′-H_B), 2.04–2.13 (m, 1 H, 3′-H_B), 2.49 (dd, *J* = 15.1, 8.2 Hz, 1 H, 2-H_A), 2.55 (dd, *J* = 15.1, 3.8 Hz, 1 H, 2-H_B), 3.78–3.84 (m, 1 H, 5′-H_A), 3.92–3.98 (m, 1 H, 5′-H_B), 4.15–4.22 (m, 1 H, 2′-H), 5.28 (br s, 1 H, NH), 6.82–6.90 (m, 3 H, H_{Ar}), 7.19–7.23 (m, 2 H, H_{Ar}), 8.31 (br s, 1 H, NH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 25.5 (t), 31.4 (t), 40.8 (t), 68.2 (t), 75.4 (d), 113.5 (d), 120.9 (d), 129.1 (d), 148.0 (s), 171.0 (s).

MS (EI, 70 eV): *m/z* (%) = 220 (33) [M$^+$], 161 (10), 108 (100), 77 (14), 71 (64), 43 (31).

HRMS (EI): *m/z* calcd for $C_{12}H_{16}N_2O_2$: 220.1212; found: 220.1211.

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