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Asymmetric Organocatalytic Michael Addition–Cyclisation Cascade of Cyclopentane-1,2-dione with Alkylidene Malononitriles

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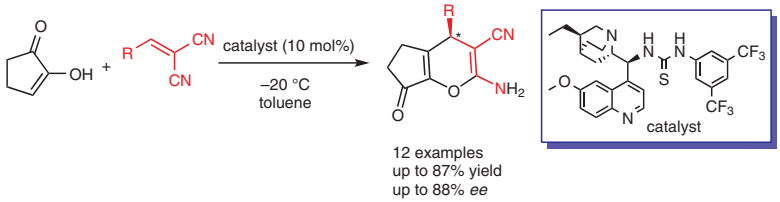

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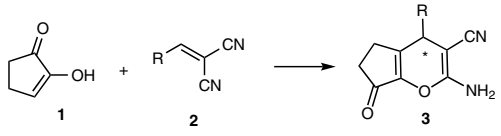
Abstract An asymmetric organocatalytic cascade reaction between cyclopentane-1,2-diones and alkylidene malononitriles affords highly substituted 4*H*-pyrans in moderate to high enantiomeric excess. The selective reduction of a bridged double bond leads to the formation of *cis*-substituted cyclopentanone with three contiguous stereogenic centres.

Key words organocatalysis, asymmetric catalysis, diketone, pyran, cascade reaction

Cascade reactions have been an interesting topic for many researchers over the years.[2] Such transformations are atom- and step-economical and proceed in a one-pot manner; thus, there is no need for additional protection/deprotection steps or purification of intermediates. These synthetic and operational advantages make this approach more sustainable and environmentally friendly than classical syntheses. Forming several bonds in one step is very appealing for the development of new strategies for the construction of complex molecules, even more so if high stereoselectivity is achieved in the presence of a chiral catalyst or auxiliary. In the last two decades organocatalysis[3] has proven to be competitive with metal[2c,4] and enzymatic catalysis,[5] so asymmetric organocatalytic cascade reactions are now a valuable approach for synthetic chemists.[3b,3c] Starting with the pioneering work by Barbas[6] of a consecutive Michael addition and aldol condensation (i.e., Robinson annulation), synthetic chemists have proceeded to quadruple asymmetric cascades, where several chemical bonds and stereogenic centres are formed in complex structures in controlled ways.[7]

Among the different starting materials suitable for cascade reactions, cyclic diketones are widely used. Various cyclic 1,3-diketones have been investigated in one-pot reactions with unsaturated aldehydes,[8–10] acetates of nitroalkenes,[11] cyanoacrylates and alkylidene malononitrile derivatives.[12] Cyclic 1,2-dicarbonyl compounds have been investigated less in cascade reactions. It has been previously shown that cyclohexane-1,2-diones undergo a cascade with nitroolefins,[13] benzylidenemalononitriles[14] and α,β-unsaturated aldehydes.[15] However, cyclopentane-1,2-diones are less reactive and do not afford the cascade reactions with Michael acceptors characteristic of cascades involving cyclohexane-1,2-diones. Only single-bond-forming organocatalytic enantioselective reactions with nitroolefins[16] and cascade reactions with α,β-unsaturated aldehydes[17] were described by our group recently. Highly reactive (*E*)-2-oxobut-3-enoates[18] were needed to run the cascade reaction.[19] Considering the previous research that our group has conducted on cyclopentane-1,2-dione and the reported cascade reactions using diketones, we assumed that the cyclopentane-1,2-dione **1** would undergo a Michael reaction with alkylidene malononitriles **2**, followed by the intramolecular cyclisation of the adduct to afford multifunctionalised bicycles **3** with one stereocentre (Scheme 1).



Scheme 1 General scheme for the cascade reaction

Derived compounds are highly substituted 4*H*-pyrans with a comprehensive list of biological and pharmacological properties, such as kinase inhibition,[20] IK_{CA} channel blocker behaviour[21] and antitumor properties.[22]

Chiral thioureas[23] and squaramides[24] are widely used as catalysts in asymmetric Michael additions. We assumed that H-bonds could activate alkylidene malononitrile suffi-

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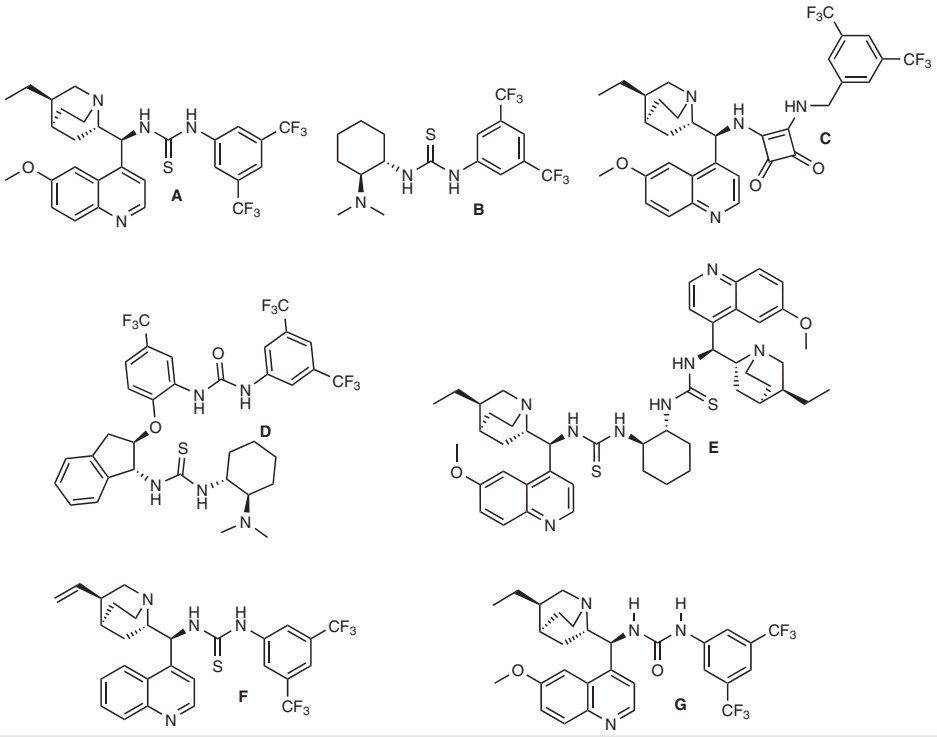


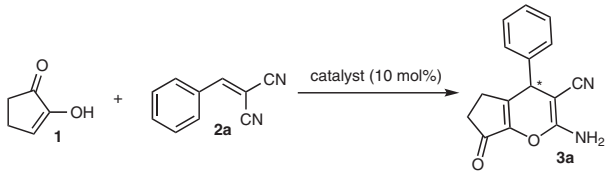
Figure 1 Catalysts screened in the model reaction

ciently to trigger the cascade. Therefore, various H-bond catalysts (Figure 1) were screened in the model reaction between cyclopentane-1,2-dione and benzylidene malonitrile (Table 1).

First, different catalysts were screened at room temperature. The model reaction in the presence of 10 mol% thiourea **A** afforded the product within two hours in 74% yield (Table 1, entry 1). Soos's bifunctional catalysts **F** (entry 6) gave the same stereoselectivity (54% *ee*), eliminating the influence of the double bond and the methoxy substituent. With Takemoto's catalyst **B** and squaramide **C** (entries 2 and 3) the product was obtained with low enantioselectivity. The enantioselectivity found with double-activated Pihko's catalyst[25] **D** (entry 4) was similar to that obtained with thiourea **A**. Double thiourea **E** afforded the product in low enantiomeric purity (13% *ee*). Since the synthetic pathway for catalyst **A** is less time- and resource-consuming than for catalyst **D**, the former was seen as the most reasonable catalyst. Next, we looked into solvent effects on the reaction. The stereoselectivity was very dependent on the solvent used (entries 1 and 7–9). Compared to toluene, the enantiomeric excess was slightly lower in THF. Its greener alternative, 2-MeTHF, gave a racemic product and in CH_2Cl_2 the product obtained was almost racemic. In addition, the reaction was run at various temperatures (entries 1 and 10). The results indicated that catalyst aggregation[26] might take place. Finally, to minimise that effect, the reaction mixture was diluted 10 times and an increase in enantioselectivity was achieved (entry 11), even more so at lower temperature (entry 14). The overall best result was attained using alkaloid-derived thiourea **A** and toluene at –20 °C (entry 14).

Using these optimal conditions, the scope of the reaction was investigated. Both electron-withdrawing (**3d–j**; Scheme 2) and electron-donating groups (**3b**, **3c**; Scheme 2) were tolerated. The electronic properties of the aromatic ring and also the position of the substituent did not seem to have a significant influence on the yield; however, the enantioselectivity was more influenced when nitro-substituted benzylidene malononitriles were used. It is supposed that the nitro group competes with the H-bonding acceptor to influence the enantioselectivity. In addition, heteroaromatic malononitrile derivative **2k** afforded the product in slightly lower yield but with good *ee*. Furthermore, alkylidene malononitrile could also be used in this cascade, although it affords the product in much lower yield and lower enantioselectivity. Pyrrole derived malononitrile **2m** is probably too electron-rich and therefore did not react with cyclopentane-1,2-dione **1**. It is assumed that the product **3n** did not form because the substrate **2n** was too sterically hindered for the first addition to take place.

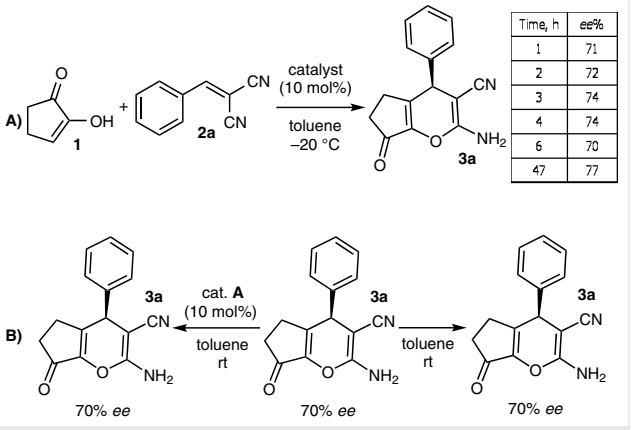
Table 1 Screening Conditions for the Reaction



Entry[a]	Catalyst	Solvent	Time (h)	Temp (°C)	*ee* (%)[b]	Yield (%)[c]
1	**A**	toluene	2	r.t.	54	74
2	**B**	toluene	1	r.t.	31	nd
3	**C**	toluene	1	r.t.	27	nd
4	**D**	toluene	3	r.t.	56	nd
5	**E**	toluene	1	r.t.	13	nd
6	**F**	toluene	3	r.t.	54	74
7	**A**	CH_2Cl_2	3	r.t.	5	nd
8	**A**	THF	2.5	r.t.	47	77
9	**A**	2-MeTHF	2.5	r.t.	*rac*	nd
10	**A**	toluene	4.5	–20	53	nd
11	**A**	toluene[d]	2	r.t.	70	82
12	**A**	mesitylene[d]	15	r.t.	70	79
13	**G**	toluene[d]	20	–20	65	78
14	**A**	toluene[d]	3	–20	75	78
15	**A**	toluene[d]	2	60	31	74
16	**A**	toluene[d]	13 days	–78	53	nd

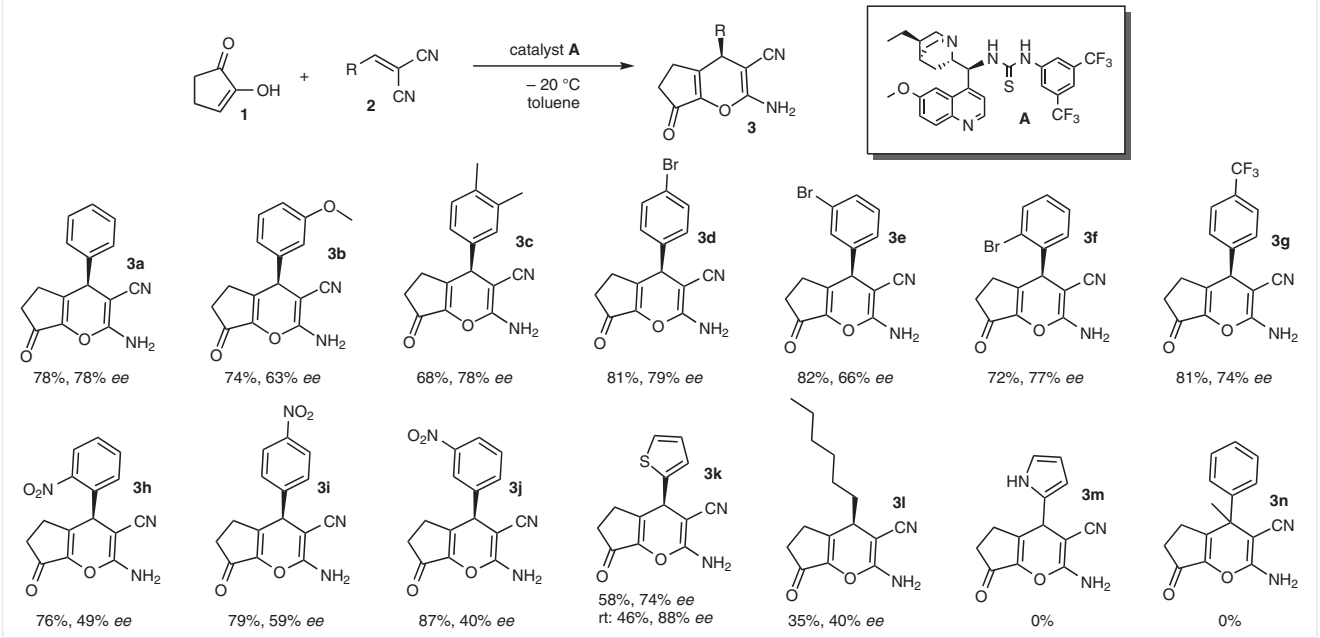
[a] Reaction conditions: 0.2 M solution of **1** (1 equiv), **2a** (1.1 equiv), catalyst (0.1 equiv).
[b] *ee* determined by chiral HPLC analysis either from isolated product or preparative TLC.
[c] Isolated yield after column chromatography; nd = not determined.
[d] 0.02 M solution of **1**.

To eliminate racemisation from consideration, the enantiomeric purity of the product was checked throughout the reaction for a period of 47 hours (Scheme 3). The *ee* was constant and varied only within the detection error. Two additional experiments with the product were also carried out. The product **3a** was stirred for 24 hours in toluene either with 10 mol% of catalyst **A** or without it (Scheme 3). The results showed that no racemisation was observed under either of these conditions.



Scheme 3 Racemisation studies: (A) throughout the reaction, (B) with the product **3a**

The *R*-absolute configuration of compound **3a** was determined by single-crystal X-ray diffraction (Figure 2) and the absolute configurations of the products **3** were assigned by analogy.



Scheme 2 Scope of the reaction. *Reagents and conditions*: 0.02 M solution **1** (1 equiv), **2** (1.1 equiv), catalyst **A** (0.1 equiv), toluene, –20 °C; isolated yields after column chromatography; *ee* determined by chiral HPLC.

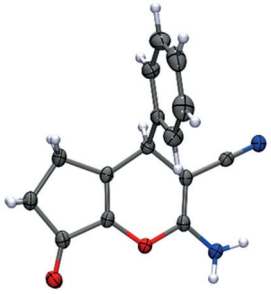
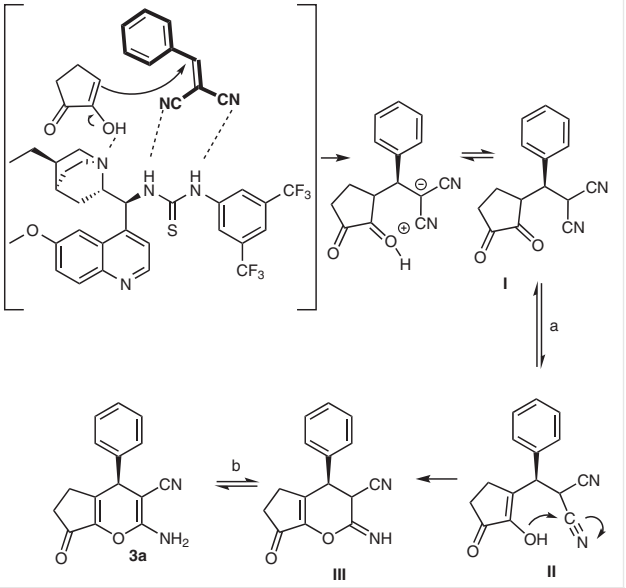


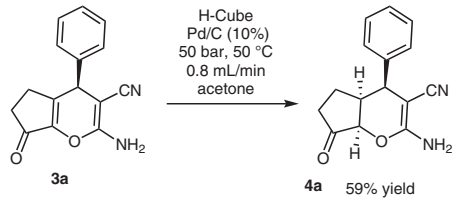
Figure 2 X-ray crystal structure of compound **3a**

A plausible reaction pathway is shown in Scheme 4. It is believed that both reactants are activated by the catalyst: alkylidene malononitrile via hydrogen bonds with thiourea moiety and diketone via hydrogen bond with a tertiary amino group of quinuclidine moiety. The stereodetermining step is the first Michael addition step. According to the geometry of **3a**, the attack of the cyclopentane-1,2-dione on alkylidene malononitrile occurs from the *Si*-face, affording intermediate **I** with *R*-configuration of the stereogenic centre. An O-nucleophile attack of the enol form **II** on the cyano group leads to the cyclisation. The target compound **3a** is isolated as an enamine tautomer of imine **III**.



Scheme 4 Proposed transition state and reaction pathway: a) keto–enol tautomerisation; b) imine–enamine tautomerisation

To show the synthetic utility of the obtained substituted pyrans, compound **3a** was reduced using an H-Cube Pro continuous-flow reactor in the presence of a Pd catalyst (Scheme 5). The reduction was *cis*-selective, affording only *cis*-substituted cyclopentanone. The configuration of the main diastereomer **4a** was confirmed by NOE experiments (see Supporting Information for details).



Scheme 5 The reduction of **3a**

In summary, we have developed a new, efficient organocatalytic cascade for the synthesis of substituted 4*H*-pyrans. The cascade is efficiently catalysed by chiral bifunctional thiourea **A** to provide bicyclic 4*H*-pyrans **3a–l** in moderate to high yields and enantioselectivities. The selective reduction of the bridged double bond leads to cyclopentanone derivatives with three contiguous stereogenic centres.

Full assignment of ^{1}H and ^{13}C chemical shifts were based on the 1D and 2D FT NMR spectra measured with a Bruker Avance III 400 MHz instrument. Residual solvent signals were used ($CDCl_3$: δ = 7.26 ^{1}H NMR, δ = 77.2 ^{13}C NMR; $(CD_3)_2CO$: δ = 2.05 ^{1}H NMR, δ = 29.84/206.26 ^{13}C NMR) as internal standards. High-resolution mass spectra were recorded with an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionisation. Optical rotations were obtained with an Anton Paar GWB Polarimeter MCP 500. Chiral HPLC was performed by using Chiralpak AD-H, Chiralcel OJ-H, Chiralcel OD-H columns. Precoated silica gel 60 F254 plates were used for TLC. Commercial reagents and solvents were generally used as received. Toluene was distilled over sodium and CH_2Cl_2 was distilled over phosphorus pentoxide.

Racemic compounds were prepared by following the general procedure using DABCO as catalyst. Cyclopentane-1,2-dione (**1**) was prepared according to a reported procedure[27] from commercially available cyclopentanone. Alkylidene malononitriles were prepared via Knoevenagel condensation from commercially available malononitrile and commercially available aldehydes. Catalysts **A**, **E**, **F**,[28] **C**,[29] **B**,[30] **D**[25] and **G**[31] were prepared according to reported procedures.

Synthesis of 3; General Procedure

To a solution of cyclopentane-1,2-dione (0.07 mmol) and catalyst (0.007 mmol) in toluene (3.5 mL) was added substituted malononitrile (0.08 mmol). The mixture was stirred until the reaction was complete (TLC and/or NMR monitoring). The mixture was purified by column chromatography (CH_2Cl_2/EtOAc, 19:1) to afford the product.

(*R*)-2-Amino-7-oxo-4-phenyl-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3a)

By following the general procedure (1.5 mmol scale), compound **3a** (78% yield, 301 mg) was obtained as an off-white solid; mp 215 °C (decomp); 78% *ee* [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 7:3; 35 °C; 0.9 mL/min; 254 nm): t_r = 21.2 (minor), 30.8 (major) min]; $[\alpha]_D^{20}$ –117.5 (*c* 0.14, acetone).

IR: 3339, 2191, 1713, 1679, 1621, 1593, 1491, 1404, 1111, 752, 698 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.43–7.35 (m, 2 H), 7.35–7.28 (m, 3 H), 6.28 (s, 2 H), 4.5 (s, 1 H), 2.55–2.28 (m, 3 H), 2.20–2.09 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.4, 148.5, 146.1, 142.3, 129.7, 129.0, 128.5, 119.8, 58.3, 43.1, 33.4, 23.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{13}N_2O_2]^+$: 253.0972; found: 253.0960.

(*R*)-2-Amino-4-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3b)

By following the general procedure, compound **3b** (74% yield, 14.9 mg) was obtained as a yellow solid; mp 143 °C (decomp); 63% *ee* [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 7:3; 35 °C; 0.9 mL/min; 254 nm): t_r = 24.2 (minor), 40.0 (major) min]; $[\alpha]_D^{20}$ –78.8 (*c* 0.07, acetone).

IR: 3323, 2194, 1714, 1678, 1639, 1593, 1492, 1412, 1284, 1113, 1048, 750 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.35–7.27 (m, 1 H), 6.91–6.86 (m, 3 H), 6.28 (s, 2 H), 4.47 (s, 1 H), 3.8 (s, 3 H), 2.52–2.30 (m, 3 H), 2.23–2.14 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.4, 161.2, 148.4, 146.1, 143.9, 130.8, 121.1, 119.8, 114.8, 113.7, 58.2, 55.5, 45.1, 33.4, 23.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{15}N_2O_3]^+$: 283.1077; found: 283.1074.

(*R*)-2-Amino-4-(3,4-dimethylphenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3c)

By following the general procedure, compound **3c** (68% yield, 13.6 mg) was obtained as a yellow-brown solid; mp 144 °C (decomp); 78% *ee* [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 7:3; 35 °C; 0.9 mL/min; 254 nm): t_r = 12.0 (minor), 13.9 (major) min]; $[\alpha]_D^{20}$ –51.3 (*c* 0.03, acetone).

IR: 3345, 2923, 2198, 1718, 1680, 1644, 1608, 1503, 1412, 1383, 1357, 1109, 773 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.14 (d, *J* = 7.7 Hz, 1 H), 7.07 (s, 1 H), 7.02 (dd, *J* = 7.7, 1.6 Hz, 1 H), 6.23 (s, 1 H), 4.40 (s, 1 H), 2.50–2.41 (m, 1 H), 2.40–2.33 (m, 2 H), 2.24 (d, *J* = 5.3 Hz, 6 H), 2.18–2.11 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.2, 148.9, 139.8, 137.8, 136.7, 130.8, 130.0, 126.4, 119.9, 58.5, 42.7, 23.6, 19.8, 19.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{17}H_{17}N_2O_2]^+$: 281.1285; found: 281.1283.

(*R*)-2-Amino-4-(4-bromophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3d)

By following the general procedure, compound **3d** (81% yield, 19.1 mg) was obtained as a brownish solid; mp 184 °C (decomp); 79% *ee* [HPLC (Chiralcel OD-H; hexane/*i*-PrOH, 9:1; 25 °C; 1 mL/min; 254 nm): t_r = 26.5 (minor), 34.2 (major) min]; $[\alpha]_D^{20}$ –13.6 (*c* 0.05, acetone).

IR: 3325, 2191, 1716, 1681, 1633, 1590, 1486, 1402, 1111, 1010, 754 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.61–7.55 (m, 2 H), 7.34–7.27 (m, 2 H), 6.34 (s, 2 H), 4.54 (s, 1 H), 2.53–2.30 (m, 3 H), 2.24–2.12 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.4, 147.6, 146.3, 147.7, 122.0, 119.7, 57.8, 42.5, 33.4, 23.5.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $[C_{15}H_8BrN_2O_2]^-$: 326.9775; found: 326.9757.

(*R*)-2-Amino-4-(3-bromophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3e)

By following the general procedure, compound **3e** (82% yield, 19.1 mg) was obtained as a yellowish solid; mp 162 °C (decomp); 65% *ee* [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 7:3; 35 °C; 0.9 mL/min; 254 nm): t_r = 18.4 (minor), 21.3 (major) min]; $[\alpha]_D^{20}$ –67.4 (*c* 0.07, acetone).

IR: 3317, 2191, 1720, 1678, 1638, 1607, 1471, 1415, 1110, 1071, 749 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.56–7.47 (m, 2 H), 7.39–7.33 (m, 2 H), 6.37 (s, 2 H), 4.56 (s, 1 H), 2.56–2.28 (m, 3 H), 2.25–2.11 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.5, 147.4, 146.4, 145.0, 131.9, 131.8, 131.7, 128.1, 123.4, 119.6, 57.7, 42.7, 33.4, 23.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $[C_{15}H_{11}BrN_2O_2Na]^+$: 352.9896; found: 352.9887.

(*R*)-2-Amino-4-(2-bromophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3f)

By following the general procedure, compound **3f** (72% yield, 17 mg) was obtained as a dark-yellow solid; mp 144 °C (decomp); 77% *ee* [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 7:3; 35 °C; 0.9 mL/min; 254 nm): t_r = 20.9 (minor), 24.0 (major) min]; $[\alpha]_D^{20}$ –77.5 (*c* 0.08, acetone).

IR: 3381, 2197, 1718, 1677, 1645, 1594, 1463, 1417, 1109, 1051, 767, 749 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.65 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.49–7.37 (m, 2 H), 7.27 (ddd, *J* = 8.0, 7.2, 1.9 Hz, 1 H), 6.38 (br s, 2 H), 5.10 (s, 1 H), 2.63–2.51 (m, 1 H), 2.39 (qdd, *J* = 18.8, 6.5, 1.5 Hz, 2 H), 2.22–2.11 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 196.9, 161.8, 147.3, 134.0, 131.8, 130.5, 129.5, 124.2, 119.4, 100.9, 57.2, 33.4, 23.6.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $[C_{15}H_8BrN_2O_2]^-$: 326.9775; found: 326.9757.

(*R*)-2-Amino-7-oxo-4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3g)

By following the general procedure, compound **3g** (81% yield, 18.4 mg) was obtained as a yellow solid; mp 167 °C (decomp); 74% ee [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 8:2; 1 mL/min; 254 nm): t_r = 24.9 (major), 30.0 (minor) min]; $[\alpha]_D^{20}$ –72.6 (*c* 0.09, acetone).

IR: 3328, 2190, 1720, 1682, 1638, 1589, 1420, 1331, 1123, 764 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.76 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 6.41 (s, 2 H), 4.67 (s, 1 H), 2.57–2.30 (m, 3 H), 2.23–2.11 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.5, 147.2, 146.8, 146.5, 129.9, 126.7, 126.6, 119.6, 57.4, 42.8, 33.4, 23.5.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $[C_{16}H_{10}F_3N_2O_2]^-$: 319.0700; found: 319.0691.

(*R*)-2-Amino-4-(2-nitrophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3h)

By following the general procedure, compound **3h** (76% yield, 16.1 mg) was obtained as an orange solid; mp 157 °C (decomp); 49% *ee* [HPLC (Chiralcel OD-H; hexane/*i*-PrOH, 8:2; 25 °C; 1 mL/min; 254 nm): t_r = 21.6 (major), 26.8 (minor) min]; $[\alpha]_D^{20}$ –21.5 (*c* 0.05, acetone).

IR: 3321, 2197, 1721, 1679, 1643, 1590, 1526, 1420, 1402, 1113, 765 cm^{-1}.

^1H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.99–7.95 (m, 1 H), 7.84–7.75 (m, 1 H), 7.67–7.56 (m, 2 H), 6.54 (s, 2 H), 5.19 (s, 1 H), 2.65–2.31 (m, 3 H), 2.24–2.14 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.0, 161.8, 150.6, 146.8, 146.6, 136.3, 134.6, 132.5, 129.9, 125.1, 119.3, 57.3, 38.0, 33.4, 23.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $[C_{15}H_{10}N_3O_4]^-$: 296.0677; found: 296.0657.

(*R*)-2-Amino-4-(4-nitrophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3i)

By following the general procedure, compound **3i** (79% yield, 16.7 mg) was obtained as an orange solid; mp 214 °C (decomp); 59% *ee* [HPLC (Chiralpak AD-H; hexane/*i*-PrOH, 8:2; 25 °C; 1 mL/min; 254 nm): t_r = 21.6 (major), 30.0 (minor) min]; $[\alpha]_D^{20}$ –65.8 (*c* 0.14, acetone).

IR: 3330, 2193, 1716, 1679, 1610, 1519, 1491, 1458, 1425, 1107, 746 cm^{-1}.

^1H NMR (400 MHz, $(CD_3)_2CO$): δ = 8.33–8.22 (m, 2 H), 7.71–7.62 (m, 2 H), 6.46 (br s, 2 H), 4.75 (s, 1 H), 2.53 (ddt, *J* = 17.2, 6.4, 1.8 Hz, 1 H), 2.45–2.30 (m, 2 H), 2.20 (ddt, *J* = 17.2, 6.2, 1.3 Hz, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.0, 161.2, 149.5, 148.5, 146.6, 130.3, 124.8, 119.5, 57.1, 42.7, 33.4, 23.5.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $[C_{15}H_{10}N_3O_4]^-$: 296.0677; found: 296.0520.

(*R*)-2-Amino-4-(3-nitrophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3j)

By following the general procedure, compound **3j** (87% yield, 18.8 mg) was obtained as a pale-yellow solid; mp 208 °C (decomp); 40% *ee* [HPLC (Chiralpak AD-H; hexane/*i*-PrOH, 8:2; 25 °C; 1 mL/min; 254 nm): t_r = 20.0 (major), 27.5 (minor) min]; $[\alpha]_D^{20}$ –48.8 (*c* 0.11, acetone).

IR: 3318, 2192, 1722, 1683, 1648, 1590, 1526, 1413, 1112, 758 cm^{-1}.

^1H NMR (400 MHz, $(CD_3)_2CO$): δ = 8.24–8.19 (m, 2 H), 7.85 (dt, *J* = 7.6, 1.3 Hz, 1 H), 7.77–7.70 (m, 1 H), 6.47 (br s, 1 H), 4.80 (s, 1 H), 2.54 (ddt, *J* = 17.5, 6.4, 1.9 Hz, 1 H), 2.49–2.31 (m, 2 H), 2.20 (ddt, *J* = 17.5, 6.4, 1.8 Hz, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.7, 149.7, 146.8, 146.6, 144.6, 135.5, 131.2, 123.7, 123.6, 119.5, 57.3, 42.7, 33.5, 23.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{12}N_3O_4]^+$: 298.0822; found: 298.0804.

(*R*)-2-Amino-7-oxo-4-(thiophen-2-yl)-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3k)

By following the general procedure, compound **3k** (58% yield, 10.7 mg) was obtained as a brown solid; mp 207 °C (decomp); 74% *ee* [HPLC (Chiralpak AD-H; hexane/EtOH/IPA, 90:5:5; 25 °C; 1 mL/min; 254 nm): t_r = 44.0 (major), 63.3 (minor) min]; $[\alpha]_D^{20}$ –94.4 (*c* 0.06, acetone).

IR: 3323, 3108, 2921, 2195, 1715, 1678, 1637, 1590, 1402, 1111, 779, 728 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 1 H), 7.02–6.7 (m, 2 H), 4.80 (br s, 1 H), 4.74 (s, 1 H), 2.57–2.39 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.0, 159.5, 147.2, 145.0, 143.9, 127.3, 126.1, 126.13, 126.07, 118.8, 59.9, 37.1, 32.9, 23.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{13}H_{11}N_2O_2S]^+$: 259.0536; found: 259.0517.

(*R*)-2-Amino-4-hexyl-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3l)

By following the general procedure, compound **3l** (62% yield, 24.5 mg) was obtained as an off-white solid; mp 106–111 °C; 40% *ee* [HPLC (Chiralpak AD-H; hexane/*i*-PrOH, 9:1; 25 °C; 1 mL/min; 254 nm): t_r = 10.9 (major), 18.9 (major) min]; $[\alpha]_D^{20}$ –60.4 (*c* 0.08, acetone).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.68 (br s), 3.44 (t, *J* = 4.6 Hz, 1 H), 2.63–2.38 (m, 4 H), 1.85–1.61 (m, 2 H), 1.43–1.23 (m, 7 H), 1.18–1.04 (m, 1 H), 0.91–0.83 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.0, 160.6, 149.8, 146.9, 119.5, 58.0, 35.5, 33.0, 32.8, 31.8, 29.4, 25.1, 23.3, 22.7, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{21}N_2O_2]^+$: 261.1598; found: 261.1575.

(4*S*,4a*S*,7a*R*)-2-Amino-7-oxo-4-phenyl-4,4a,5,6,7,7a-hexahydrocyclopenta[*b*]pyran-3-carbonitrile (4a)

Compound **3a** (35 mg, 0.14 mmol) was dissolved in acetone (14 mL, 0.01 M). The reaction parameters were set on the H-Cube Pro: full H_2, 50 bar, 50 °C and 0.8 mL/min flow rate. The instrument was fitted with 10% Pd/C CatCart and the process was started. After evaporation the mixture was purified by column chromatography (CH_2Cl_2/EtOAc, 12:1→5:1) to afford the product **4a** (58% yield, 20.5 mg) as a light-orange solid; mp 148–150 °C.

IR: 3340, 2948, 2183, 1752, 1596, 1492, 1453, 1411, 1129, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) = 7.36–7.31 (m, 2 H), 7.31–7.27 (m, 1 H), 7.24–7.18 (m, 2 H), 4.61 (br s, 2 H), 4.35 (d, *J* = 5.1 Hz, 1 H), 4.05 (d, *J* = 6.7 Hz, 1 H), 2.65 (dtd, *J* = 9.4, 6.7, 5.3 Hz, 1 H), 2.00 (dd, *J* = 8.7, 4.7 Hz, 2 H), 1.86 (dq, *J* = 13.3, 9.1 Hz, 1 H), 1.55 (ddt, *J* = 13.0, 7.7, 4.4 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (major diastereomer) = 209.7, 162.9, 138.7, 128.8, 128.5, 127.8, 120.4, 79.5, 57.5, 39.0, 38.0, 34.5, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{15}N_2O_2]^+$: 255.1128; found: 255.1134.

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Supporting Information

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