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Supporting Information

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Organocatalytic Diastereo- and Enantioselective Annulation Reactions – Construction of Optically Active 1,2-Dihydro-isoquinoline and -Phthalazine Derivatives

Kim Frisch, Aitor Landa, Steen Saaby and Karl Anker Jørgensen*

[*] The Danish National Research Foundation: Center for Catalysis
Department of Chemistry, Aarhus University
DK-8000 Aarhus C, Denmark
Fax (45) 8919 6199, e-mail: kaj@chem.au.dk

Supporting Information

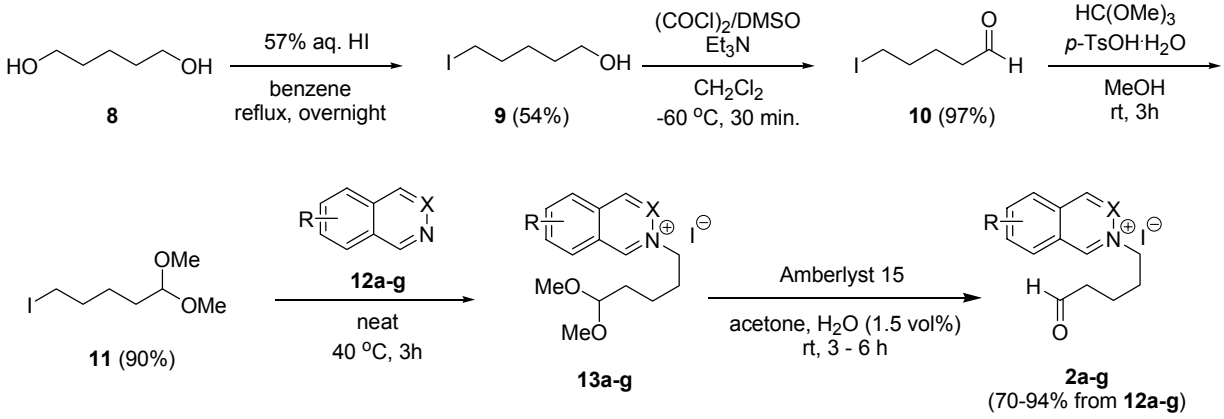
General. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively. The chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 7.26) or the central acetone-d_6 resonance (δ = 2.05) for ^{1}H NMR and relative to the central resonances of $CDCl_3$ (δ = 77.0) or acetone-d_6 (δ = 30.83) for ^{13}C NMR. The ^{19}F NMR spectra were recorded in $CDCl_3$ at 376 MHz. The chemical shifts are reported in ppm relative to hexafluorobenzene (δ = -162.9).[1] Chromatography was carried out by flash chromatography using Merck silica gel 60 (230-400 mesh) or by preparative TLC using Merck silica gel 60 F_{254} (20 x 20 cm, 2 mm) with mixtures of Et_2O and CH_2Cl_2 as eluents.

Materials. All solvents were of p.a. quality and were dried by standard procedures prior to use if necessary. Isoquinoline, 5-bromoisoquinoline, 5-nitroisoquinoline, phenanthridine and phthalazine were all commercially available. 5,7-Dimethoxy-isoquinoline, 6,7-dimethoxyisoquinoline[2] and 4-phenylisoquino-line[3] were prepared as described in the literature. Catalysts **1a-d** were commercially available. Catalyst **1e**[4] and **1f**[5] were prepared

as described in the literature. For catalysts **1g**, **1h** and **1i** see below.

Experimental procedures and characterizations.

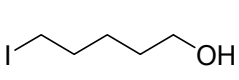
General description of the preparation of compounds 2a-g. The following procedure for the preparation of compounds **2a-g** has been devised (Scheme 2):



Scheme 2.

Iodo-alcohol **9** was prepared from readily available 1,5-pentanediol (**8**) by treatment with aq. HI in benzene. The alcohol was subsequently oxidized under Swern-conditions to give **10**, which was immediately protected as its dimethyl acetal (**11**). Treatment of isoquinoline derivatives **12a-g** with neat **11** gave **13a-g**, respectively, which by deprotection with Amberlyst 15 yielded the desired substrates (**2a-g**) in good overall yield. The detailed experimental procedures are given below. It should be noted, that **2a-g** could not be synthesized by a mere addition of 5-iodo-pentanal (**10**) to the respective isoquinoline derivatives due to the instability of the iodo-aldehyde.

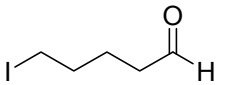
Preparation of 5-iodo-pentan-1-ol (9)



9

1,5-pentanediol (**8**) (6.0 mL, 57 mmol) in benzene (180 mL) was added 57% aqueous HI (12.0 mL, 91 mmol) and the mixture was refluxed overnight in the dark. The mixture was then concentrated somewhat *in vacuo* and washed with saturated $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were washed first with saturated NH_4Cl (2 x 100 mL), then with saturated $Na_2S_2O_3$ (100 mL). After drying ($MgSO_4$) the solvents were evaporated to give 5-iodo-1-pentanol (**9**) (6.6 g, 54%). ^1H NMR ($CDCl_3$) δ 3.58 (t, J = 6.4 Hz, 2H), 3.16 (t, J = 7.0 Hz, 2H), 2.38 (s, 1H), 1.81 (quintet, J = 7.1 Hz, 2H), 1.49-1.57 (m, 2H), 1.37-1.48 (m, 2H) ppm. ^{13}C NMR δ 62.2, 33.0, 31.4, 26.6, 7.0.

Preparation of 5-iodo-pentanal (10)

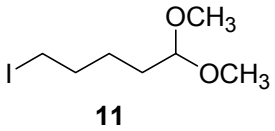


10

CH_2Cl_2 (100 mL) and $(COCl)_2$ (3.9 mL, 46 mmol, 1.5 eq.) were successively place in an oven dried three-necked flask and the solution was cooled to -60 °C under dry Ar. DMSO (4.8 mL, 68 mmol) in CH_2Cl_2 (15 mL) was added at a rate where a temperature below -60 °C was maintained. The mixture was then stirred for ca. 5 min followed by addition of 5-iodo-1-pentanol (**9**) (6.6 g, 31 mmol) in CH_2Cl_2 (25 mL) over a periode of ca. 5 min. The mixture was stirred for an additional 25 min, then rapidly quenched with Et_3N (22 mL, 0.16 mol). The obtained white slurry was stirred for ca. 5 min and then allowed to warm to room temperature. The reaction mixture was washed with water (300 mL) and the aqueous layer was extracted with Et_2O (300 mL). The combined organic layers were washed with 1 N HCl until the wash was acidic. The organic layers were then washed successively with saturated $NaHCO_3$ (2 x 200 mL) and brine (2 x 200 mL). After drying ($MgSO_4$) the solvents were evaporated to give 5-iodo-pentanal (**10**) (6.4 g, 97%). ^1H NMR ($CDCl_3$) δ 9.77 (s, 1H), 3.19 (t, J = 6.7 Hz,

2H), 2.48 (t, *J* = 7.2 Hz, 2H), 1.92-180 (m, 2H), 1.79-1.69 (m, 2H). ^{13}C NMR δ 201.4, 42.3, 32.3, 22.6, 6.0.

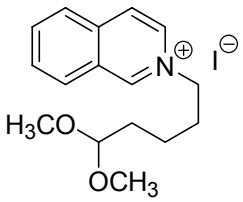
Preparation of 5-iodo-1,1-dimethoxy-pentane (11)



11

$CH(OCH_3)_3$ (6.7 mL, 61 mmol) and *p*TsOH·H_2O (0.29 g, 1.5 mmol) were added to 5-iodo-pentanal (**10**) (6.4 g, 30 mmol) in MeOH (65 mL). The mixture was stirred for 3 h at room temperature. After dilution with CH_2Cl_2 (65 mL) the mixture was washed with 1% aqueous Na_2CO_3 (130 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 65 mL). The combined organic layers were dried ($MgSO_4$) and the solvents removed by evaporation to give 5-iodo-1,1-dimethoxy-pentane (**11**) (7.0 g, 90%). The compound was stored under dry Ar in the dark at ca. 4 °C. ^{1}H NMR ($CDCl_3$) δ 4.32 (t, *J* = 5.6 Hz, 1H), 3.28 (s, 6H), 3.15 (t, *J* = 7.0 Hz, 2H), 1.76-1.86 (m, 2H), 1.55-1.60 (m, 2H), 1.36-1.46 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 104.0, 52.6, 33.1, 31.3, 25.5, 6.6. HRMS: $C_7H_{15}IO_2$ $[M+Na]^+$ calcd.: 281.0009, found: 281.0003.

Preparation of 2-(5,5-dimethoxy-pentyl)-isoquinolinium iodide (13a)

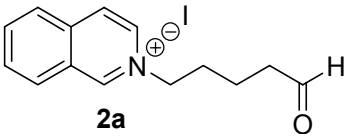


13a

A mixture of isoquinoline (**12a**) (0.36 mL, 0.40 g, 3.1 mmol) and 5-iodo-1,1-dimethoxy-pentane (**11**) (0.95 g, 3.7 mmol) was stirred for 3 h at 40 °C. The mixture was allowed to cool to room temperature and the obtained tar was washed with Et_2O (5 x 5 mL) to give a yellow paste. After evaporation of the remaining solvent at low heat (ca. 30 °C) followed by cooling (ca. 4 °C) overnight 2-(5,5-dimethoxy-pentyl)-isoquinolinium iodide (**13a**) (1.1 g, 92%) was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 10.75 (s, 1H), 8.81 (d, *J* = 6.9 Hz, 1H), 8.62 (d, *J* = 8.3 Hz, 1H), 8.40 (d, *J* = 6.8 Hz, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.06 (t, *J* = 7.1 Hz, 1H), 7.88 (t, *J* = 7.4 Hz, 1H), 4.97 (t, *J* = 7.4 Hz, 2H), 4.24

(t, J = 5.4 Hz, 1H), 3.18 (s, 6H), 2.08-2.15 (m, 2H), 1.54-1.61 (m, 2H), 1.36-1.47 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 149.1, 137.1, 136.9, 134.3, 131.1, 130.5, 127.4, 127.0, 126.3, 103.9, 60.9, 53.0, 31.2, 20.7. HRMS: $C_{16}H_{22}INO_2$ $[M-I^-]^+$ calcd: 260.1645, found: 260.1649.

Preparation of 2-(5-oxo-pentyl)-isoquinolinium iodide (2a)



2a

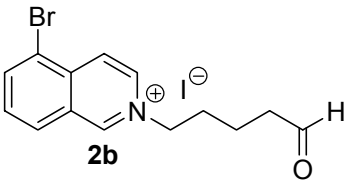
2-(5,5-Dimethoxy-pentyl)-isoquinolinium iodide (**13a**) (1.1 g, 28 mmol) was dissolved in acetone (12 mL) and H_2O (0.18 mL, 1.5 vol %). Amberlyst 15 (128 mg) was then added and the heterogeneous mixture was stirred for 5 h. Dry molecular sieves (3Å) were then added and the mixture was stirred for ca. 30 min. The solids were filtered off and washed with acetone. After evaporation at low heat (ca. 30 °C) a brown oil was obtained which solidified on standing at ca. 4 °C to give 2-(5-oxo-pentyl)-isoquinolinium iodide (**2a**) as a yellow solid in a quantitative yield. ^{1}H NMR ($CDCl_3$) δ 10.82 (s, 1H), 9.74 (s, 1H), 8.87 (d, J = 6.8 Hz, 1H,), 8.66 (d, J = 8.3, 1H), 8.39 (d, J = 6.8 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 8.11 (t, J = 8.2 Hz, 1H), 7.96 (t, J = 8.2 Hz, 1H), 5.09 (t, J = 7.6 Hz, 2H), 2.63 (t, J = 7.1 Hz, 2H), 2.20 (quintet, J = 7.6 Hz, 2H), 1.76 (quintet, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 201.9, 149.3, 137.4, 137.2, 134.5, 131.4, 130.7, 127.6, 127.1, 126.3, 60.7, 42.8, 30.8, 18.2. HRMS: $C_{14}H_{16}INO$ $[M-I^-]^+$ calcd: 214.1221, found: 214.1224.

Preparation of 2-(5-oxo-pentyl)-isoquinolinium and -phthazinium iodides 2b-g.

2-(5-Oxo-pentyl)-isoquinolinium and -phthazinium iodides **2b**-**2g** were prepared from the corresponding isoquinolines and phthazine by the procedure described for compound **13a**/**2a**. Occasionally, for the deprotection of the aldehyde $CHCl_3$ was added in order to overcome solubility problems of the starting dimethylacetals in the acetone/H_2O mixture. Also, evaporation was for the more

sensitive compounds carried out using a flow of N_2 instead of a rotary evaporator.

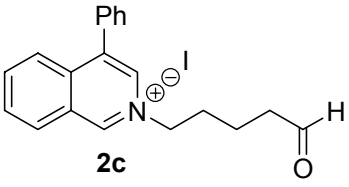
5-Bromo-2-(5-oxo-pentyl)-isoquinolinium iodide (2b)



2b

Brown oil. Yield: 71% from 5-bromoisoquinoline. ^{1}H NMR ($CDCl_3$) δ 11.27 (s, 1H), 9.80 (s, 1H), 8.78 (m, 2H), 8.60 (d, *J* = 6.8 Hz, 1H), 8.39 (d, *J* = 6.8 Hz, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 5.17 (t, *J* = 8.0 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.26 (m, 2H), 1.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 201.8, 149.9, 140.4, 136.5, 135.9, 132.1, 130.7, 128.7, 125.5, 60.8, 42.7, 30.7, 18.2. HRMS: $C_{14}H_{15}BrINO$ $[M-I^-]^+$ calcd: 292.0332, found: 292.0327.

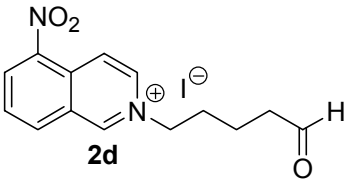
2-(5-Oxo-pentyl)-4-phenyl-isoquinolinium iodide (2c)



2c

Brown oil. Yield: 81% from 4-phenyliso-quinoline. ^{1}H NMR ($CDCl_3$) δ 11.25 (s, 1H), 9.80 (s, 1H), 8.86 (d, *J* = 8.0 Hz, 1H), 8.29 (s, 1H), 8.10 (d, *J* = 4.0 Hz, 2H), 8.01 (m, 1H), 7.61 (m, 5H), 5.16 (t, *J* = 7.6 Hz, 2H), 2.71 (t, *J* = 6.8 Hz, 2H), 2.28 (m, 2H), 1.83 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 201.7, 147.7, 139.1, 136.8, 135.8, 132.5, 131.9, 130.9, 130.8, 129.6, 129.5, 128.8, 127.6, 125.0, 60.4, 42.4, 30.4, 17.9 ppm. HRMS: $C_{20}H_{20}INO$ $[M-I^-]^+$ calcd: 290.1539, found: 290.1530.

5-Nitro-2-(5-oxo-pentyl)-isoquinolinium iodide (2d)

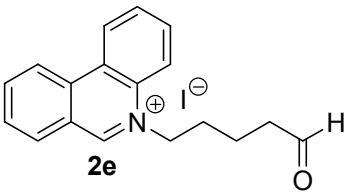


2d

Brown oil. Yield: 55% from 5-nitroisoquinoline. ^{1}H NMR ($CDCl_3$) δ 11.57 (s, 1H), 9.77 (s, 1H), 9.26 (d, *J* = 8.0 Hz, 1H), 9.23 (d, *J* = 7.6 Hz, 1H), 9.00 (d, *J* = 6.4 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.19 (t, *J* = 8.0 Hz, 1H), 5.11 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 6.8 Hz, 2H), 2.15-1.70 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 201.6,

151.0, 138.6, 136.5, 134.7, 130.8, 128.8, 122.6, 53.7, 42.7, 29.6, 18.1. HRMS: $C_{14}H_{15}IN_2O_3$ $[M-I^-]^+$ calcd: 259.1077, found: 259.0948.

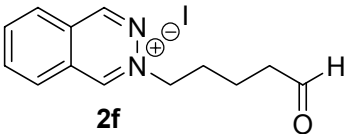
5-(5-Oxo-pentyl)-phenanthridinium iodide (2e)



2e

Brown oil: Yield: 70% from phenanthridine. ^{1}H NMR ($CDCl_3$) δ 11.60 (s, 1H), 9.78 (s, 1H), 8.92 (d, *J* = 8.2 Hz, 1H), 8.87 (d, *J* = 8.2 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.41 (d, *J* = 8.6 Hz, 1H), 8.28 (t, *J* = 7.2 Hz, 1H), 8.10 (t, *J* = 7.2 Hz, 1H), 7.94-8.07 (m, 2H), 5.43 (t, *J* = 7.8 Hz, 2H), 2.72 (t, *J* = 6.9 Hz, 2H), 2.20-2.33 (m, 2H), 1.89-2.00 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 201.9, 154.4, 138.3, 134.8, 133.8, 133.0, 132.4, 130.53, 130.47, 126.3, 124.8, 123.7, 122.3, 119.2, 57.2, 42.8, 29.2, 18.6. HRMS: $C_{18}H_{18}INO$ $[M-I^-]^+$ calcd: 264.1383, found: 264.1386.

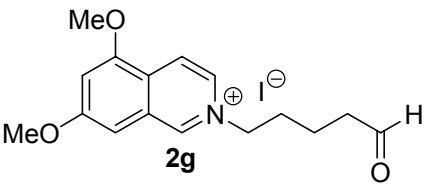
2-(5-Oxo-pentyl)-phthalazin-2-ium iodide (2f)



2f

Orange oil. Yield: 77% from phtalazine. ^{1}H NMR ($CDCl_3$) δ 11.64 (s, 1H), 9.96 (s, 1H), 9.67 (s, 1H), 8.77 (d, *J* = 8.1 Hz, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 8.37 (t, *J* = 7.4 Hz, 1H), 8.26 (t, *J* = 7.7 Hz, 1H), 4.96 (t, *J* = 7.2 Hz, 2H), 2.55, (t, *J* = 7.0 Hz, 2H), 2.18 (quintet, *J* = 7.3 Hz, 2H), 1.66 (quintet, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 201.6, 154.2, 150.2, 139.3, 136.2, 130.5, 128.1, 127.6, 127.5, 63.4, 42.5, 28.7, 18.1. HRMS: $C_{13}H_{15}IN_2O$ $[M-I^-]^+$ calcd: 215.1179, found: 215.1185.

5,7-Dimethoxy-2-(5-oxo-pentyl)-isoquinolinium iodide (2g)

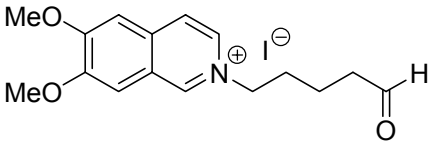


2g

Yellow solid. Yield: 92% from 5,7-dimethoxyisoquinoline. ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 9.70 (s, 1H), 8.66 (d, *J* = 6.7 Hz, 1H), 8.37 (d, *J* = 6.8 Hz, 1H), 7.49 (s, 1H), 6.89 (s, 1H), 4.97 (t, *J* = 7.5 Hz, 2H), 3.97 (s, 3H),

3.94 (s, 3H), 2.60 (t, J = 7.1 Hz, 2H), 2.15 (quintet, J = 7.5 Hz, 2H), 1.71 (quintet, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 201.7, 162.3, 155.1, 146.1, 131.8, 130.1, 126.2, 120.9, 107.4, 98.9, 60.5, 56.5, 56.4, 42.7, 30.7, 18.1. HRMS: $C_{16}H_{20}INO_3$ $[M-I^-]^+$ calcd: 274.1438, found: 274.1443.

6,7-Dimethoxy-2-(5-oxo-pentyl)-isoquinolinium iodide

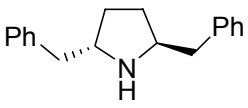


Yellow solid. Yield: 94% from 6,7-dimethoxyisoquinoline. ^{1}H NMR ($CDCl_3$) δ 10.22 (s, 1H), 9.70 (s, 1H), 8.54 (d, J = 6.8 Hz, 1H), 8.18 (d, J = 6.7 Hz, 1H), 7.86 (s, 1H), 7.51 (s, 1H), 4.87 (t, J = 7.4 Hz, 2H), 4.09 (s, 3H), 4.01 (s, 3H), 2.58 (t, J = 7.0 Hz, 2H), 2.10 (quintet, J = 7.6 Hz, 2H), 1.68 (quintet, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 201.7, 158.0, 152.9, 144.3, 135.6, 132.7, 124.3, 123.6, 107.1, 105.3, 59.9, 57.4, 57.0, 42.7, 30.6, 18.1. HRMS: $C_{16}H_{20}INO_3$ $[M-I^-]^+$ calcd: 274.1438, found: 274.1443.

Note: The NMR spectra of the isoquinolinium iodides synthesized are concentration dependent. For the reported spectra the sample concentrations were 50-200 mg/mL.

Preparation of catalysts 1g, 1h and 1i.

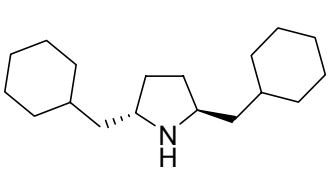
(2*S*,5*S*)-2,5-Dibenxyl-pyrrolidine (1g)



1g

Catalyst **1g** was prepared as described in the literature[6] with the exception that the final deprotective hydrogenation was carried out at room temperature in MeOH/CH_3CO_2H (5/2) under 45 bar H_2 with 20% $Pd(OH)_2/C$ as the catalyst. The obtained data for characterization was similar to the data reported in the literature.[6c]

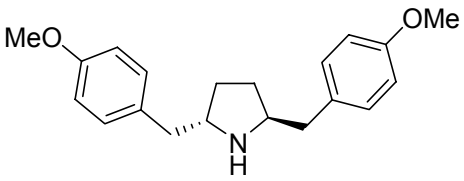
(2*S*,5*S*)-2,5-Bis-cyclohexylmethyl-pyrrolidine (1h)



1h

Catalyst **1h** was prepared by the procedure reported for **1g** with the exception that the final hydrogenation was performed under 50 bar H_2 at room temperature with PtO_2 as catalyst. ^{1}H NMR ($CDCl_3$) δ 3.28-3.10 (m, 2H), 1.95-1.78 (m, 2H), 1.77-1.48 (m, 10H), 1.36-1.26 (m, 2H), 1.31-0.97 (m, 12H), 0.91-0.68 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 54.9, 45.1, 35.5, 33.6, 33.5, 32.9, 26.5, 26.2. HRMS: $C_{18}H_{33}N$ $[M+H]^+$ calcd.: 264.2686, found: 264.2690. $[\alpha]^{22}_D$ = -6.5 (c = 10 mg/mL, $CDCl_3$).

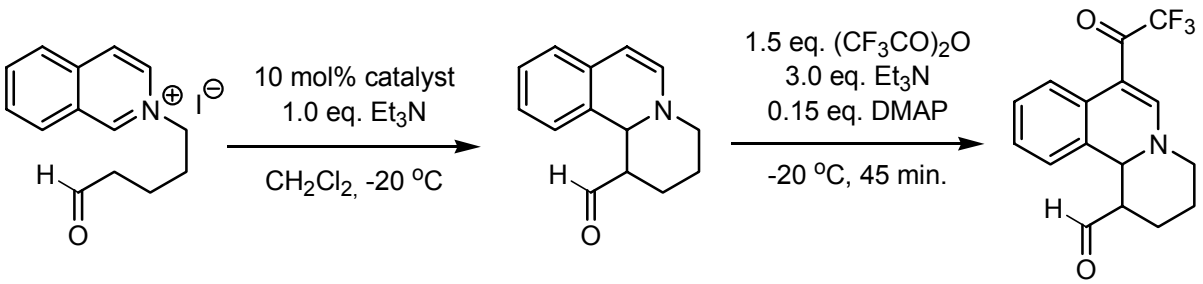
(2*S*,5*S*)-2,5-Bis-(4-methoxy-benzyl)-pyrrolidine (1i)



1i

Catalyst **1i** was prepared by the procedure reported for catalyst **1g**. ^{1}H NMR ($CDCl_3$) δ 7.08 (d, *J* = 8.7 Hz, 4H), 6.82 (d, *J* = 8.6 Hz, 4H), 3.78 (s, 6H), 3.43 (quintet, *J* = 6.4 Hz, 2H), 2.65-2.70 (dd, *J* = 7.1, 13.4 Hz, 2H), 2.56-2.61 (dd, *J* = 6.9, 13.4 Hz, 2H), 1.78-1.99 (m, 3H), 1.39-1.51 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 157.8, 132.0, 129.7, 113.7, 58.9, 55.1, 42.0, 31.1. HRMS: $C_{20}H_{25}NO_2$ $[M+H]^+$ calcd.: 312.1964, found: 312.1965. $[\alpha]^{22}_D$ = +29.0 (c = 10 mg/mL, $CDCl_3$).

Organocatalytic asymmetric annulation reaction of 2-(5-oxo-pentyl)-isoquinolinium iodide (2a) to produce 7-(2,2,2-trifluoro-acetyl)-1,3,4,11b-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinoline-1-carbaldehyde (6a)

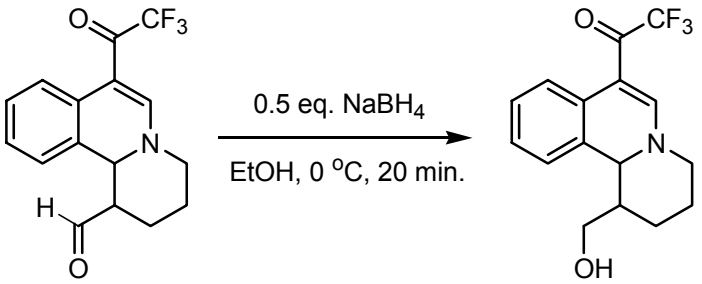


2a **5a** **6a**

2-(5-Oxo-pentyl)-isoquinolinium iodide (**2a**) (137 mg, 0.40 mmol) was placed in a flame dried Schlenk tube fitted with a rubber septum. Freshly distilled CH_2Cl_2 (2.0 mL) was added and the mixture was cooled to -40 °C under Ar or N_2. (2*S*,5*S*)-2,5-Dibenzyl-pyrrolidine (10.2 μL, 0.04 mmol) was added, followed by dry Et_3N (56 μL, 0.40 mmol). The mixture was stirred at -40 °C under Ar or N_2 overnight (formation of the product 1,3,4,11b-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinoline-1-carbaldehyde (**5a**) was observed by ^{1}H NMR ($CDCl_3$) δ 9.48 (s, 1H), 7.32-6.77 (m, 4H), 6.07 (d, *J* = 7.3 Hz, 1H), 5.45 (d, *J* = 7.4, 1H), 4.53 (d, *J* = 9.9 Hz, 1H), 3.44-3.25 (m, 2H), 3.13-3.00 (m, 1H), 1.99-1.53 (m, 4H). Dry Et_3N (167 μL 1.20 mmol) was then added directly to the mixture followed by DMAP (7.3 mg, 0.06 mmol). $(CF_3CO)_2O$ (85 μL, 0.60 mmol) was now added dropwise and the mixture was stirred for 45 min. under dry Ar or N_2 at -20 °C. The reaction was quenched with saturated $NaHCO_3$ (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic phases were washed first with 0.5 M aqueous HCl (30 mL), then with brine (50 mL). The organic layer was dried ($MgSO_4$) and filtered. Finally, the solvent was evaporated to obtain 7-(2,2,2-trifluoro-acetyl)-

1,3,4,11b-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinoline-1-carbaldehyde (**6a**).

Reduction of 7-(2,2,2-trifluoro-acetyl)-1,3,4,11b-tetrahydro-2*H*-pyrido[2,1-*a*]-isoquinoline-1-carbaldehyde (6a) to produce 2,2,2-trifluoro-1-(1-hydroxymethyl-1,3,4,11b-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolin-7-yl)-ethanone (7a)



6a **7a**

The crude 7-(2,2,2-trifluoro-acetyl)-1,3,4,11b-tetra-hydro-2*H*-pyrido[2,1-*a*]-iso-quinoline-1-carbaldehyde (**6a**) was added EtOH (2 mL) and the solution was cooled on an ice-bath. $NaBH_4$ (7.6 mg, 0.20 mmol, 0.5 eq.) was added and the mixture was stirred at 0 °C for 20 min (TLC: 15% Et_2O in CH_2Cl_2). The reaction mixture was then quenched with saturated NH_4Cl (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was finally evaporated and the crude compound was purified by chromatography (eluent: 10% Et_2O in CH_2Cl_2) to obtain 2,2,2-trifluoro-1-(1-hydroxymethyl-1,3,4,11b-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolin-7-yl)-ethanone (**7a**) as a yellow solid (51 mg, 41% based on 2-(5-oxo-pentyl)-isoquinolinium iodide (**2a**)). ^{1}H NMR ($CDCl_3$) δ 8.59 (d, J = 8.0 Hz , 1H), 7.61 (s, 1H), 7.31 (dt, J = 1.8, 7.6 Hz, 1H), 7.17 (m, 2H), 4.61 (d, J = 9.2 Hz , 1H), 3.68 (d, J = 12.8 Hz , 1H), 3.54 (m, 1H), 3.43 (m, 2H), 2.03-1.81 (m, 5H), 1.33 (t, J = 3.6 Hz , 1H). ^{13}C NMR ($CDCl_3$) δ 173.3 (q, J = 31.1 Hz, **C**OCF_3), 152.5, 128.4, 128.2, 127.1, 126.3,

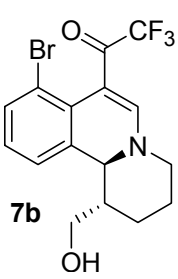
125.9, 124.5, 118.1 (q, *J* = 291.4 Hz, **C**F_3), 102.0, 62.8, 62.3, 56.3, 43.3, 27.4, 27.3. ^{19}F NMR ($CDCl_3$) δ -67.76. HRMS: $C_{16}H_{16}F_3NO_2$ $[M+Na]^+$ calcd.: 334.1025, found: 334.1026. HPLC: Daicel Chiralpak AD, hexane/2-propanol (85/15), flow rate = 1.0 mL/min (τ_1 = 7 and 11 min. (major diastereomer); τ_2 = 9 and 14 min. (minor diastereomer)).

Organocatalytic asymmetric annulation reaction of 2-(5-oxo-pentyl)-isoquinolinium and phthazinium iodides 2b-g followed by reduction to produce the corresponding cyclized compounds 7b-g.

Compounds **7b-g** were prepared from **2b-g**, respectively, by the procedure described for **6a**/**7a**. However, the procedure differed for the compounds based on **2c,e,f** in that the *in situ* protection with $(CF_3CO)_2O$ was unnecessary. In these cases workup consisted of a simple filtration through silica (or alumina for **2f**) followed by washing with CH_2Cl_2. After evaporation of the solvent the compounds **7b-g** were subjected to the reduction conditions described for **7a**. For yields of the respective final compounds consult Table 4 in the main paper.

It should be noted that the purity of the produced compounds **7a-g** were often suitable for HPLC analysis without purification by chromatography.

(1*S*,11b*S*)-1-(8-Bromo-1-hydroxymethyl-1,3,4,11b-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolin-7-yl)-2,2,2-trifluoro-ethanone (7b)

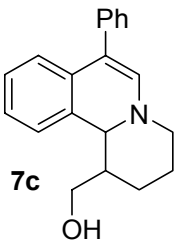


7b

White solid. ^{1}H NMR ($CDCl_3$) δ 7.66 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 4.49 (d, *J* = 10.4 Hz, 1H), 3.68-3.59 (m, 2H), 3.45 (d, *J* = 10.5 Hz, 1H), 3.34 (dt, *J* = 3.2, 13.0 Hz, 1H), 2.05-1.77 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 172.4 (q, *J* = 32.4 Hz, **C**OCF_3), 153.0 134.3, 131.8, 128.7, 127.4, 126.5, 120.5, 118.5 (q, *J* = 290.6 Hz, **C**F_3), 106.9, 64.4, 62.3, 55.3, 40.5, 27.3,

27.0. ^{19}F NMR ($CDCl_3$) δ -69.56. HRMS: $C_{16}H_{15}BrF_3NO_2$ $[M+Na]^+$ calcd.: 412.0130, found: 412.0135. HPLC: Daicel Chiralpak AD+AS, hexane/2-propanol (90/10), flow rate = 0.5 mL/min (τ_1 = 48 and 69 min. (major diastereomer); τ_2 = 59 and 77 min. (minor diastereomer)).

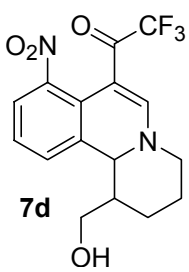
(7-Phenyl-1,3,4,11b-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolin-1-yl)-methanol (7c)



7c

Yellow oil. ^1H NMR ($CDCl_3$) δ 7.39-7.08 (m, 9H), 6.26 (s, 1H,), 4.27 (d, *J* = 9.6 Hz, 1H), 3.48-3.37 (m, 3H), 3.14 (dt, *J* = 4.2, 11.4 Hz, 1H), 2.30 (m, 1H,), 1.97 (m, 1H), 1.78-1.56 (m, 3H), 1.10 (t, *J* = 4.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 138.8, 137.1, 132.6, 128.4, 128.4, 127.6, 127.1, 125.7, 125.2, 121.8, 113.3, 63.9, 62.6, 53.5, 37.1, 27.8, 25.6. HRMS: $C_{20}H_{21}NO$ $[M+Na]^+$ calcd.: 314.1515, found: 314.1525. HPLC: Daicel Chiralpak AD, hexane/2-propanol (95/5), flow rate = 1.0 mL/min (τ_1 = 12 and 19 min. (major diastereomer); τ_2 = 16 and 31 min. (minor diastereomer)).

2,2,2-Trifluoro-1-(1-hydroxymethyl-8-nitro-1,3,4,11b-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolin-7-yl)-ethanone (7d)

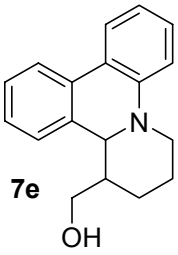


7d

Orange solid. ^1H NMR (acetone-d_6) δ 8.09 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), (t, *J* = 7.8 Hz, 1H), 4.84 (d, *J* = 9.6 Hz, 1H) , 4.11 (dd, *J* = 4.8, 13.2 Hz, 1H), 4.02 (t, *J* = 4.8 Hz, 1H), 3.53 (m, 2H), 3.40 (m, 1H), 2.87 (m, 2H), 2.01 (m, 2H), 1.86 (m, 1H). ^{13}C-NMR (acetone-d_6) δ 155.9, 148.5, 133.9, 133.3, 127.9, 125.8, 123.2, 119.6 (q, *J* = 289.8 Hz, **C**F_3), 102.2, 64.9, 62.4 (d, *J* = 12.9 Hz), 56.7, 43.8, 29.1, 28.8 (carbonyl not observed due to solubility problems). ^{19}F NMR ($CDCl_3$) δ -69.37. HRMS: $C_{16}H_{15}F_3N_2O_4$ $[M+Na]^+$ calcd.: 379.0876, found: 379.0871. HPLC: Daicel Chiralcel OD, hexane/2-propanol (85/15), flow rate = 1.0 mL/min (τ_1 = 25 and

34 min. (major diastereomer); τ_2 = 47 and 51 min. (minor diastereomer)).

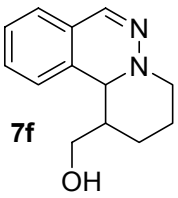
(7,8,9,9a-Tetrahydro-6*H*-pyrido[1,2-*f*]phenanthridin-9-yl)-methanol (7e)



7e

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz , 2H), 7.34 (t, *J* = 8.0 Hz, 1H,), 7.52-7.21 (m, 3H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.82 (t, *J* = 7.6 Hz, 1H), 4.31 (d, *J* = 10.0 Hz , 1H), 4.08 (d, *J* = 14.8 Hz , 1H), 3.39 (s, 2H), 3.18 (t, *J* = 13.6 Hz, 1H,), 2.18-1.59 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 144.6, 133.1, 129.5, 128.2, 127.4, 127.0, 124.0, 122.9, 118.0, 114.0, 64.3, 64.2, 47.8, 38.8, 28.9, 20.7. HRMS: $C_{18}H_{19}NO$ $[M+H]^+$ calcd.: 266.1539, found: 266.1538. HPLC: Daicel Chiralpak AD+AS, hexane/2-propanol (90/10), flow rate = 0.5 mL/min (τ_1 = 40 and 43 min. (major diastereomer); τ_2 = 54 and 62 min. (minor diastereomer)).

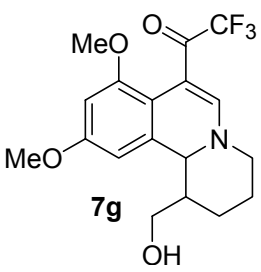
(1,3,4,11b-Tetrahydro-2*H*-pyrido[2,1-*a*]phthalazin-1-yl)-methanol (7f)



7f

Pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.43 (s, 1H), 7.30-7.22 (m, 2H), 7.11-7.09 (m, 2H), 4.20 (d, *J* = 10.8 Hz, 1H), 3.69 (d, *J* = 13.0 Hz, 1H), 3.28 (m, 2H), 3.14 (t, *J* = 13.4 Hz, 1H), 2.01-1.85 (m, 3H), 1.67-1.53 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 138.2, 131.1, 129.7, 128.0, 126.7, 124.9, 124.1, 63.3, 59.2, 55.0, 35.1, 27.3, 23.8. HRMS: $C_{13}H_{16}N_2O$ $[M+H]^+$ calcd.: 217.1335, found: 217.1348. HPLC: Daicel Chiralpak AS, hexane/2-propanol (90/10), flow rate = 1.0 mL/min (τ_1 = 7 and 9 min. (major diastereomer); τ_2 = 15 min. (minor diastereomer)).

2,2,2-Trifluoro-1-(1-hydroxymethyl-8,10-dimethoxy-1,3,4,11b-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolin-7-yl)-ethanone (7g)



7g

Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 1H), 6.39 (d, *J* = 2.40 Hz, 1H), 6.35 (d, *J* = 2.40 Hz, 1H), 4.37 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.47-3.65 (m, 4H), 3.24 (m, 1H), 2.05-1.75 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 178.9 (q, *J* = 33.4 Hz, **C**OCF_3), 159.4, 154.9, 148.5, 129.4, 125.5, 117.6 (q, *J* = 289.8 Hz, **C**F_3), 111.6, 104.1, 97.8, 63.9, 63.2, 55.2 (d, *J* = 34.0 Hz), 54.6, 39.8, 29.7, 27.3, 26.9. ^{19}F NMR ($CDCl_3$) δ -74.40. HRMS: $C_{18}H_{20}F_3NO_4$ $[M+Na]^+$ calcd.: 394.1237, found: 394.1249. HPLC: Daicel Chiralpak AD, hexane/2-propanol (85/15), flow rate = 1.0 mL/min (τ_1 = 12 and 14 min. (major diastereomer); τ_2 = 26 and 27 min. (minor diastereomer)).

Racemic annulation reactions of 2-(5-oxo-pentyl)-isoquinolinium Iodides 2a-g followed by reduction to produce the corresponding cyclized compounds 7a-g.

Racemic **6a-g**/**7a-g** were prepared be the procedure described for the asymmetric cases with the exception that the chiral catalyst and Et_3N were replaced by DBU (1.0 eq.) and the annulation reactions were run at room temperature instead of -40 °C.

Crystal Data for compound 7b.[7]

References

[1] M. Fujita, H. Egawa, T. Miyamoto, J. Nakano, J. Matsumoto, *Eur. J. Med. Chem*. **1996**, *31*, 981.

[2] D. L. Boger, C. E. Brotherton, M. D. Kelley, *Tetrahedron* **1981**, *37*, 3977.

[3] R. B. Miller, J. J. Svoboda, *Synth. Commun*. **1994**, *24*, 1187.

[4] N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem*. **2002**, 67, 8331.

[5] J. M. Chong, I. S. Clarke, I. Koch, P. C. Olbach, N. J. Taylor, *Tetrahedron: Asymmetry* **1995**, *6*, 409.

[6] (a) Y. Yamamoto, J.Hoshino, Y.Fujimoto, J.Ohmoto, S. Sawada, *Synthesis* **1993**, 298; b) M. Nakajima, K. Tomioka, K. Koga, *Tetrahedron* **1993**, *49*, 9735; c) K. T. Sprott, E. J. Corey, *Org. Lett.* **2003**, *5*, 2465.

[7] CCDC xxxx contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).