

Scale-Up of Flow-Assisted Synthesis of C_2 -Symmetric Chiral PyBox Ligands

Claudio Battilocchio,^{a,c} Marcus Baumann,^a Ian R. Baxendale,^a Mariangela Biava,^c Matthew O. Kitching,^a Steven V. Ley,^a Rainer E. Martin,^{*b} Stephan A. Ohnmacht,^b Nicholas D. C. Tappin^a

^a Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK
E-mail: theitc@ch.cam.ac.uk

^b F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, Chemistry Technology and Innovation, 4070 Basel, Switzerland

^c Department of Pharmaceutical Chemistry and Technology, Sapienza University of Rome, Rome, Italy

Received 19 November 2011; revised 13 December 2011

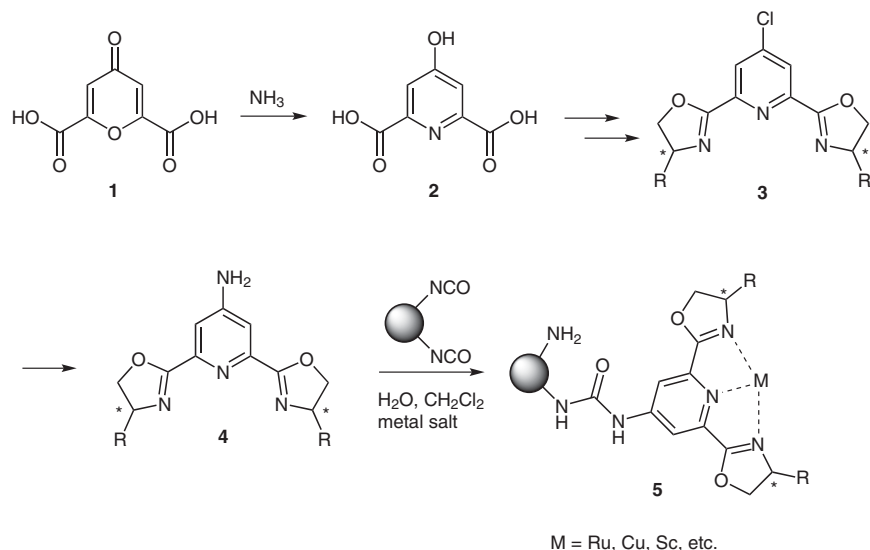
Abstract: A series of PyBox ligands were prepared from commercially available chelidonic acid by a multistep flow sequence using mesoreactor technology. A chloro group introduced onto the ligand scaffold was subsequently exploited to give amine derivatives ready for immobilization through microencapsulation technologies.

Key words: ligands, macrocycles, flow chemistry, solid-supported reagent, asymmetric synthesis, scale up

Improvements in the understanding and design of asymmetric syntheses have led to the discovery of a versatile class of chiral C_2 -symmetric chelators that are commonly referred to as PyBox ligands.¹ In combination with metals such as scandium, copper, or ruthenium, these chiral ligands have been used in various transformations, including asymmetric cycloadditions, aldol reactions, hydrocyanation, cyclopropanation, and ene-type reactions.² As the application of such species is always associated with loss or incomplete recovery of the precious ligand, chemists have been attracted to immobilization strategies to mitigate this inefficiency.³ For instance, Cornejo demonstrated the immobilization of PyBox ligands onto Merrifield

resin, as well as the preparation of monolithic constructs, both used in flow cyclopropanations.⁴ In addition, Tilliet has reported asymmetric silacyanations, epoxide ring openings, and imine alkynylations using PyBox ligands immobilized via a Huisgen cycloaddition reaction to establish the tether.⁵ Recently, PyBox systems have also been immobilized on triiron tetraoxide (Fe_3O_4) nanoparticles to create magnetically recoverable catalysts for use in the addition of terminal alkynes to imines.⁶ As a general class, PyBox ligands show excellent utility and continue to generate significant interest; however, their scalable synthesis and immobilization is not always straightforward due to the highly reactive intermediates that are involved in their preparation.

As part of our ongoing interest in developing and applying new encapsulated catalyst systems,⁷ we decided to study the immobilization of PyBox ligands within a polyurea matrix with the ultimate aim of evaluating the capability of the resulting catalysts in continuous asymmetric flow synthesis. For this purpose, we wished to achieve the rapid preparation of multi-gram quantities of various 4-amino-PyBox ligands **4**, ready for encapsulation. The strategy



Scheme 1 Strategy for the synthesis and immobilization of Py-Box ligands

SYNTHESIS 2012, 44, 635–647

Advanced online publication: 25.01.2012

DOI: 10.1055/s-0031-1289676; Art ID: N108111SS

© Georg Thieme Verlag Stuttgart · New York

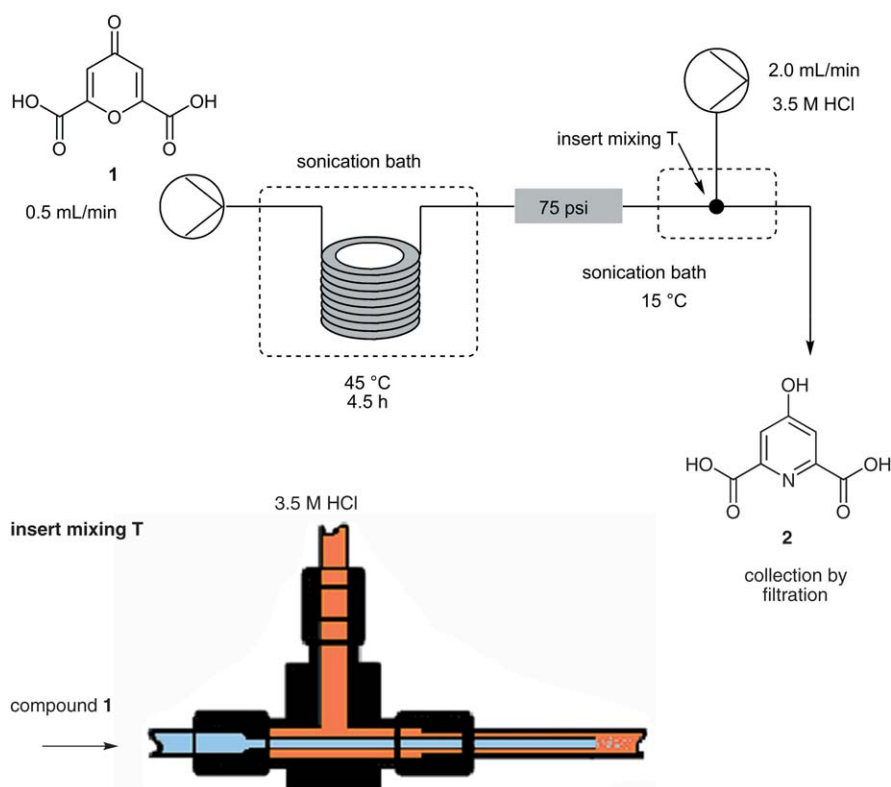
for this preparation is outlined in Scheme 1 and involves the elaboration of commercial chelidonic acid (**1**; 4-oxo-4*H*-pyran-2,6-dicarboxylic acid) into the desired 4-chloro-PyBox system **3** in several steps; the presence of the chloro group permits the subsequent introduction of an amine functionality through incorporation and reduction of an azide group. The resulting 4-amino-PyBox ligands could subsequently be encapsulated by intercepting the wall-forming sequence during an intrafacial polymerization⁸ of a polyfunctional isocyanate residue.

Our route to the PyBox ligands is similar to previously reported procedures,⁹ but we decided to establish a flow sequence, as it was noted that upon scale-up the reported yields varied dramatically and the potential hazards associated with scaling increased significantly. Furthermore, in addition to gaining benefits through higher reproducibility due to constant heat and mass transfer provided by the micro-mixing in flow, we also expected to obtain increased processing efficiencies through automation and to achieve improved safety profiles in the handling of toxic or hazardous reagents, as reported in several recent publications.^{10,11}

Our starting point was commercially available chelidonic acid (**1**), which we transformed into the analogous chelidamic acid (**2**; 4-oxo-1,4-dihydropyridine-2,6-dicarboxylic acid) by treatment with 25% aqueous ammonia under sonication conditions. A 1 M solution of the chelidonic acid in aqueous ammonia was pumped at 0.5 mL/min through a 135-mL coil of fluorinated ethylene propylene copolymer (FEP), with an internal diameter of 3 mm, to

give a residence time of 4.5 hours. The reactor was submerged in an ultrasonically agitated water bath held at 45 °C, and the system was maintained under a positive pressure by a 75-psi back-pressure regulator at the outlet to the first reactor coil. The yellow–orange solution that left the first reactor coil was combined with a second flow stream consisting of 3.5 M aqueous hydrochloric acid. A tube-displaced T-piece connector (see Scheme 2)¹² was used to add the acid solution (2 mL/min) to the flow stream of the ammonia solution, resulting in neutralization and immediate formation of a fine white precipitate. The use of a standard T-union led to blockages as a result of solid buildup at the joints as a resulting of back-mixing; this was completely avoided by the use of the modified displacement T-connector. To maintain a free-flowing slurry, a second sonicator (isothermal water temperature 15 °C) was used to break up any aggregate that formed,¹³ simply by submerging the connecting T-unit and a short length of the downstream tubing (3.5 m × 3 mm id.) in the water well of the sonicator.¹⁴ A further length of the tube reactor (1.5 m) was used to direct the output onto a sintered filter that was maintained under vacuum suction to permit isolation of the product. The resulting white solid was dried under vacuum at 40 °C to give chelidamic acid (**2**) as its pure monohydrate in 81% isolated yield. The identity of the product was confirmed by ¹H NMR spectroscopy and by elemental analysis, and the compound was used in the next step without any further purification.

In the next step of the sequence, the acid **2** was polychlorinated to give the diacyl dichloride core building block **6** (Scheme 3). The reported batch conditions¹⁵ for this pro-

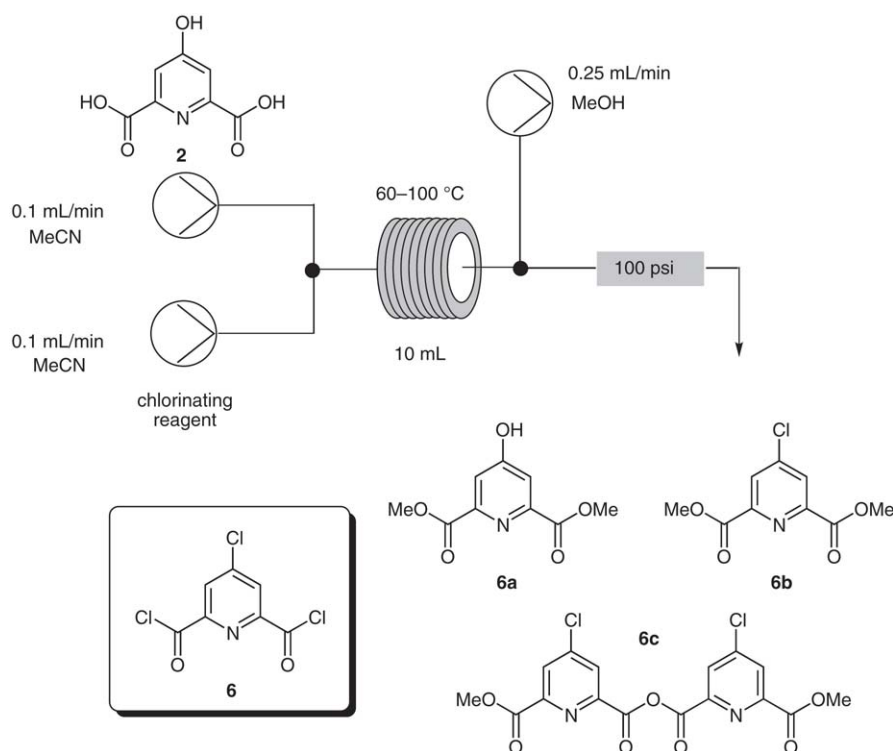


Scheme 2 Flow synthesis of chelidamic acid (**2**) by using sonication

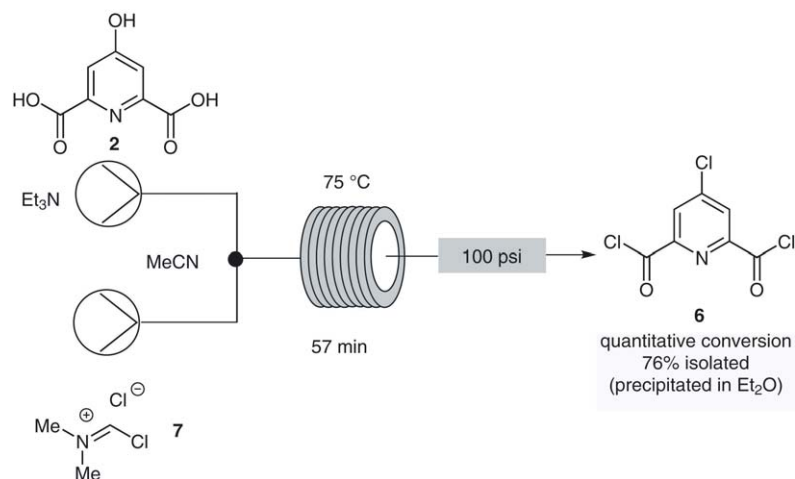
cedure involve refluxing the substrate in excess thionyl chloride for several hours. This is an efficient reaction when conducted on a small scale, but on scaling up results in problems of reaction containment and workup (**CAUTION:** extremely exothermic/delayed runaway, with the liberation of large quantities of hydrogen chloride and sulfur dioxide). Consequently, we performed this crucial chlorination step as a flow process, preferably by using stoichiometric amounts of various chlorinating reagents to minimize workup. Our initial attempts using oxalyl chloride in acetonitrile resulted in incomplete formation of the chlorinated product **6**. Quenching the output stream with excess methanol to aid characterization led to the isolation of a mixture of the 4-hydroxy and the 4-chloro dimethyl esters **6a** and **6b**, respectively, as the corresponding monohydrochloride salts, together with the symmetrical 4-chloro anhydride **6c** (Scheme 3). Changing the residence time and temperature of the process failed to alter the ratio of products significantly, whereas increasing the stoichiometry of the oxalyl chloride led to more of the desired product **6b**, but also raised new problems with regard to quenching and isolation. We therefore evaluated the use of thionyl chloride, but the results of this process mirrored those achieved with oxalyl chloride, requiring the use of an excess of the reagent to achieve good conversions into **6b**. It is well documented in the literature¹⁶ that the addition of catalytic quantities of *N,N*-dimethylformamide can improve yields from chlorination reactions involving oxalyl chloride or thionyl chloride. Although this indeed proved to be the case, it also led us to consider the use of the Vilsmeier's intermediate (**7**) as an alternative reagent for the reaction.

We found that commercially available Vilsmeier reagent¹⁷ (**7**) dissolved in acetonitrile was capable of converting the hydroxy diacid **2** into the trichloride **6** in excellent yields in a Vapourtec R2+/R4 flow system.¹⁸ A 0.2 M solution of substrate **2** (1 equiv) and triethylamine (2 equiv) in acetonitrile and a 0.45 M solution of Vilsmeier reagent (5.625 equiv) in a 9:1 mixture of acetonitrile and *N,N*-dimethylformamide were separately loaded into individual sample loops mounted on the R2+ unit. The solutions were combined at a T-piece connector and the resulting mixture was passed through a convection flow coil (CFC) heated at 75 °C. We found that a residence time of 57 minutes was suitable for full chlorination of chelidamic acid (**2**) and we isolated product **6b** in quantitative conversion after quenching the reaction with methanol. In practice, the corresponding acid chloride **6** could be isolated by collecting the output from the reactor in a stirred solution of anhydrous diethyl ether to precipitate the triethylammonium salts, which could then be filtered off. This procedure allowed the isolation of the pure trichlorinated product **6** with acceptable recovery simply by evaporation of the solvent (Scheme 4).

Alternatively, the output stream could be combined directly with a quench stream of methanol with incubation in a second 10-mL flow coil (20 minutes residence time), followed by evaporation of the solvents (**NOTE:** The use of a hydrochloric acid trap when evaporating the solvent is recommended), thereby permitting the isolation of **6b** as its hydrochloride salt in quantitative yield. The free base from **6b** could also be isolated by directing the combined methanolic stream through a cartridge of a dimethylamino-functionalized resin (Quadrapure-DMA; 4



Scheme 3 Chlorination of chelidamic acid (**2**) in flow



Scheme 4 Preparation of diacyl dichloride building block **6** using Vilsmeier's agent

equivalents) before evaporation of the solvent, although this process resulted in a slightly lower recovery (91%).¹⁹

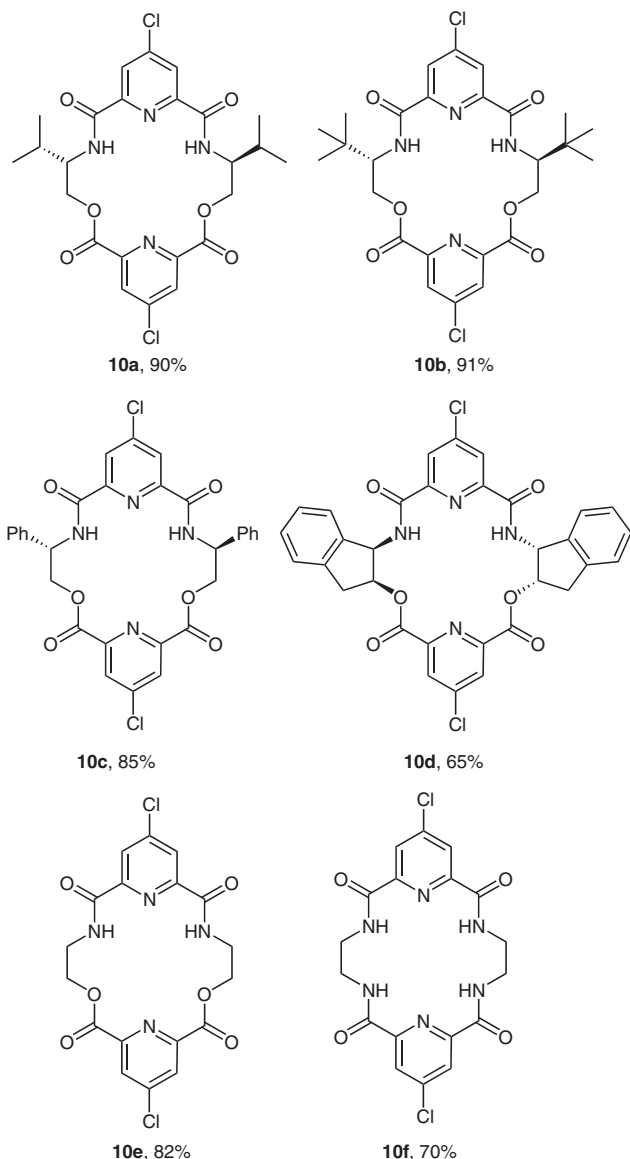
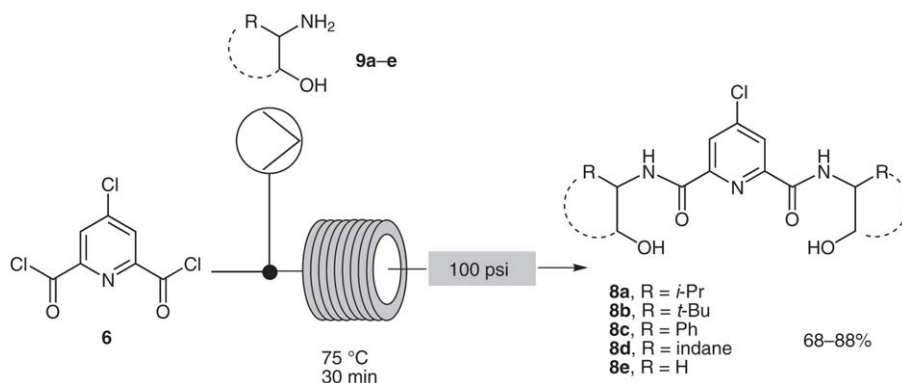


Figure 1 Structures of macrocycles **10a–f** prepared in flow

Our previous experience showed that batch procedures²⁰ for the preparation of amido alcohols **8a–e** (Scheme 5) – the next step in the sequence (the amide-forming step) – are troublesome because of the formation of a number of impurities as a result of the presence of local excesses of reagents during the coupling process. These impurities were identified by liquid chromatography/mass spectroscopy as dimerized or partially dimerized material that were difficult to separate by column chromatography because their R_f values were similar to those of the desired products.

However, because macrocycles of the type **10a–f** (Figure 1) represent an interesting new class of structures with considerable potential for selective chelation of small molecules or ions,²¹ we set ourselves the challenge of deliberately preparing these structures. We felt that this would not be easily accomplished in a selective and efficient manner by batch-processing techniques for the reasons discussed above. However, because flow microreactors permit better control over mixing of substrate streams, we were confident that such reactors could be used to perform the transformation efficiently. Indeed, when we adjusted the pump delivery speeds to produce a 1:1 stoichiometry of reagent streams (each 0.1 M in acetonitrile) with a 60-minute residence time in a CFC reactor maintained at 80 °C, we obtained the macrocyclic structures shown in Figure 1 in high yields and high purities.

By performing the amide formation from the diacyl dichloride **6** in a flow process and by using a 1:2 stoichiometric ratio of **6** and amino alcohol **9**, we succeeded in the clean formation of the desired bisamides **8a–e** through precise mixing of the starting materials in an exact and constant ratio (Scheme 5). We also found that the same amide products could be produced by mixing the corresponding amino alcohols **9a–e** with diester **6b** (free base form, previously prepared in flow) in a 2:1 ratio, and melting the components together for 3.5 h at 120 °C. Trituration of the resulting light-brown gum with a 10:1 mixture of diethyl ether and methanol gave the desired amides as



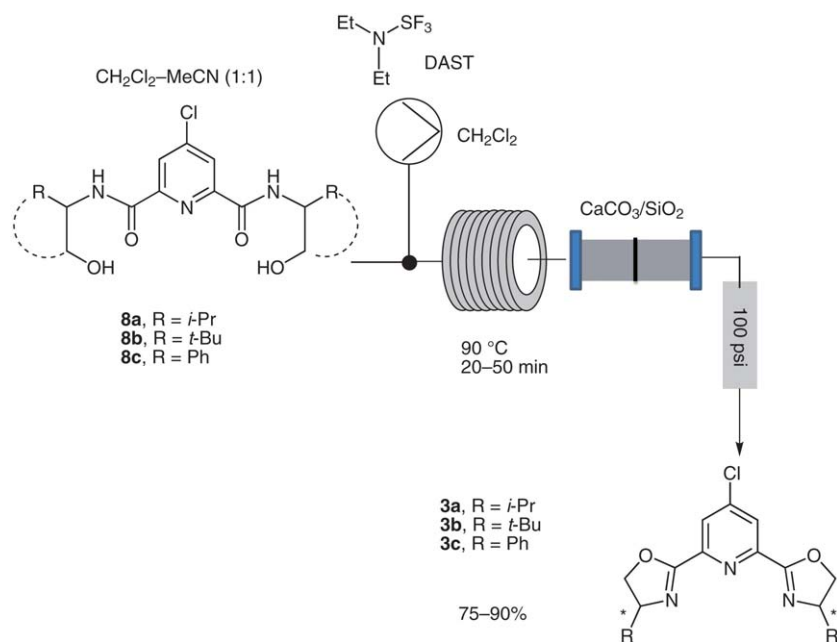
Scheme 5 Preparation of chlorobisamides **8a–d**

a white solid in >85% isolated yield. The resulting material was of sufficient purity (>90%) for use in the subsequent stages of the synthesis.

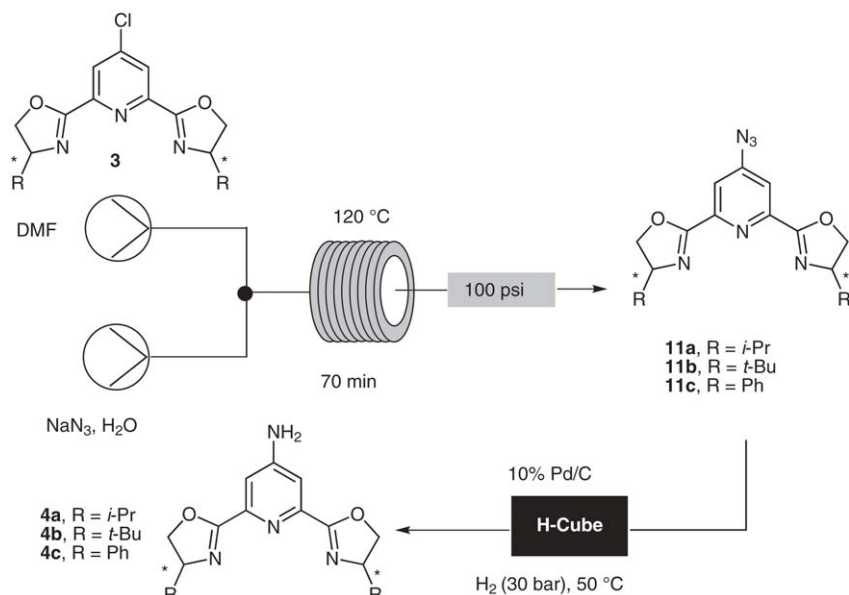
Next, we turned our attention to the cyclodehydration of the chiral bis-amides **8a–d** (*R* and *S* enantiomeric series) by using a previously described diethylaminosulfur trifluoride (DAST)-promoted flow procedure (Scheme 6).²² The use of this reagent in flow provided rapid and clean access to the bisoxazolines **3a–c** without the need for manual handling of large quantities of the hazardous DAST reagent, as would be required in a batch process. Additionally, we were able to benefit from the use of an in-line calcium carbonate quench to remove the liberated hydrogen fluoride and to trap any inorganic fluoride contaminants,²³ thereby allowing the isolation of clean 4-chloro-PyBox ligands merely by removing the solvent. This procedure proved high successful in providing the oxazolines **3a–c** in high yields and in permitting ready scale-up to gram quantities with excellent reproducibility (approximately 1–3 g per aliquot injection). Unfortunately, the synthesis of the indane derivative **8d** proved prob-

lematic as a result of insufficient solubility, which prevented us from progressing through the sequence. The desired bisoxazoline product tended to precipitate from solution upon meeting the calcium carbonate quenching column, making recovery difficult. After considering the safety aspects of excluding the in-line fluoride scavenge, we decided not to progress further with this particular substrate.

In the final stage of the sequence, a 0.1 M solution of the oxazoline starting material **3** in *N,N*-dimethylformamide was combined in a standard T-mixing piece with a 5.0 M aqueous solution of sodium azide. The resulting mixture was then directed through a CFC reactor at 120 °C (residence time 70 min) to effect an S_NAr reaction on the 4-chloro substituent (Scheme 7). The desired azide derivatives **11a–c** were generated in excellent yields²⁴ and were subsequently reduced to the corresponding amines by using an H-Cube flow hydrogenator.²⁵ Although this reduction can be performed under standard batch conditions, we found that the use of the H-Cube in combination with catalyst cartridges filled with 10% palladium/carbon was



Scheme 6 Synthesis of 4-chloro-PyBox ligands in flow



Scheme 7 Synthesis of 4-amino-PyBox ligands **4a–c** in flow

advantageous, as the controlled mode (30 bar, 50 °C, 0.01 M in MeOH) allowed a complete and clean conversion into the desired amines within minutes as opposed to the hours required by the batch method. The desired 4-amino PyBox ligands **4a–c** were isolated in analytical purity by crystallization from diethyl ether. The structure and chirality of (*S*)-**4b** was confirmed by high-resolution single-crystal X-ray analysis (Figure 2). The structures of the other compounds were inferred by analogy.

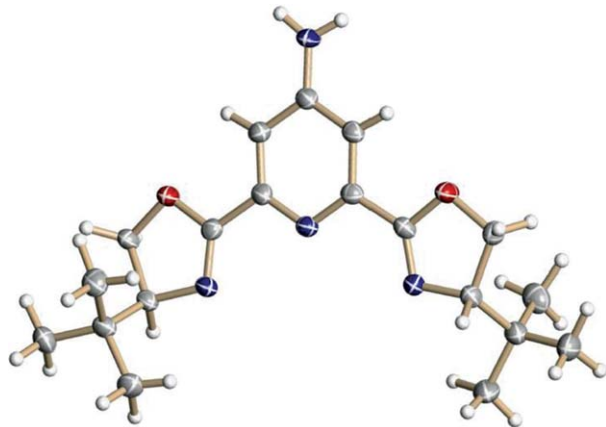


Figure 2 Single-crystal X-ray diffraction analysis of 4-amino-*tert*-butyl-PyBox ligand (*S*)-**4b**. The ORTEP drawing shows thermal ellipsoids at a 30% probability level.

This three-step sequence consisting of DAST-mediated cyclodehydration, high-temperature azide substitution, and hydrogenation shows the advantages of flow techniques over batch processing in a number of powerful yet cumbersome reaction steps (Schemes 5 and 6). Furthermore, all the above steps proved to be readily scalable, successfully generating sufficient quantities (10-gram amounts) of the final materials, which we are currently en-

capsulating for application in asymmetric flow transformations.

In summary, we have devised a scalable flow route to a number of functionalized PyBox ligands. Improvements to previous syntheses have been achieved through the use of flow techniques that resulted in better reproducibility, greater automation, and improved safety standards; moreover, the flow techniques permit in-line purification, making the demonstrated route both rapid and highly efficient.

Unless stated otherwise, reagents were obtained from commercial sources and used without purification. Laboratory reagent grade EtOAc, PE 40–60, and CH₂Cl₂ were obtained from Fischer Scientific and distilled before use. Laboratory reagent-grade toluene was obtained from Fischer Scientific, azeotropically distilled to remove H₂O, and then distilled from CaH₂ before use. Solvent were removed under reduced pressure by using a standard rotary evaporator (Genevac EZ-2 Plus personal evaporator or Vapourtec V-10 evaporator). All column chromatography was carried out by using silica gel (0.040–0.063 mm), purchased from Breckland Scientific Supplies. TLC analyses were performed on Merck 60 F254 silica gel plates, visualized by short- and long-wave UV radiation in combination with standard laboratory stains (acidic potassium permanganate or acidic ammonium molybdate). Preparative TLC was conducted on PLC 20 × 20 × 1 cm plates impregnated with silica gel 60 F254, purchased from Merck. Melting points were measured on a Stanford Research Systems MPA100 (OptiMelt) automated melting point system.

IR spectra were recorded neat on a PerkinElmer Spectrum One FT-IR spectrometer with Universal ATR sampling accessories. Letters in parentheses refer to the relative absorbance of the peak: w = weak (≤40% of the most intense peak); m = medium (41–69% of the most intense peak); s = strong (70% of the most intense peak).

¹H NMR spectra were recorded on Bruker Avance DPX-400, Bruker Avance DRX-600, Avance 400 QNP Cryo, or Avance 500 Cryo spectrometers with the residual solvent peak as the internal reference (CDCl₃ = 7.26 ppm, DMSO-*d*₆ = 2.50 ppm, CD₃OD = 3.31). ¹H resonances are reported to the nearest 0.01 ppm. ¹³C NMR Spectra were recorded on the same spectrometers with the central reso-

nance of the solvent peak as the internal reference ($\text{CDCl}_3 = 77.16$ ppm, $\text{DMSO}-d_6 = 39.52$ ppm, $\text{CD}_3\text{OD} = 49.00$). All ^{13}C resonances are reported to the nearest 0.1 ppm. DEPT 135, COSY, HMQC, and HMBC experiments were used to aid structural determination and spectral assignment. Where specified, NOESY and gradient NOE spectra were used to aid the assignment of ^1H spectra. Coupling constants (J) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the values of the coupling constants.

High-resolution mass spectra were recorded on a Waters Micro-mass LCT Premier spectrometer operating in the time-of-flight mode with a positive ESI; some were recorded by Mr. Paul Skelton on a Bruker BioApex 47e FTICR spectrometer operating in the positive ESI or EI mode at 70 eV to within a tolerance of 5 ppm of the theoretically calculated value.

LC-MS analyses were performed on an Agilent HP 1100 series chromatography [Mercury Luna 3u C18 (2) column] attached to a Waters ZQ2000 mass spectrometer 102 with an ESCi ionization source operating in the ESI mode. Elution was carried out at a flow rate of 0.6 mL/min using a reverse-phase gradient of MeCN and H_2O containing 0.1% formic acid. The gradient used is shown in Table 1. The retention time (t_R) is given in minutes to the nearest 0.1 minutes, and the m/z value is reported to the nearest mass unit (m.u.).

Table 1 Solvent Gradient for HPLC Purification

Time	MeCN (%)
0.0	5
1.0	5
4.0	95
5.0	95
7.0	5
8.0	5

Optical rotations were measured by using a PerkinElmer Model 343 polarimeter equipped with a sodium lamp ($\lambda = 589$ nm, D-line); $[\alpha]_D^{25}$ values are reported in 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$.

CIF numbers are reported as part of compound characterization. Elemental analyses within a tolerance of $\pm 0.5\%$ of the theoretical values were performed by Mr. Alan Dickerson and Mrs. Patricia Irele in the microanalytical laboratories at the Department of Chemistry, of the University of Cambridge.

4-Hydroxypyridine-2,6-dicarboxylic Acid (**2**)²⁶

[CAS Reg. No. 499–51–4]

A 1 M soln of chelidonic acid (**1**) in 25% aq NH_3 was pumped at 0.5 mL/min through a 135-mL FEP coil (3 mm i.d.; 4.5 h residence time). The entire tubular reactor was submerged in an ultrasonic water bath (isothermal regulation 45 °C) and the system was maintained under positive pressure by using a 75-psi back-pressure regulator at the outlet of the reactor coil. The yellow/orange soln that exited the initial reactor coil was combined with a second flow stream consisting of 3.5 M aq HCl. A tube-displaced T-piece connector (see Scheme 2) was used to mix the acid soln (2 mL/min) with the flow stream (3.5 m $\times$ 3 mm i.d.) of the ammonia soln, resulting in neutralization and immediate formation of a fine white precipitate. The mixture was maintained as a free-flowing slurry by using a second sonicator (isothermal water regulation 15 °C). An additional 1.5-m length of the tube reactor directed the output onto

a sintered filter that was maintained under vacuum suction to permit isolation of the product. The resulting white solid was dried under vacuum at 40 °C to give chelidamic acid (**2**) monohydrate as a white solid; yield: 41.02 g (81%); molecular formula $\text{C}_7\text{H}_5\text{NO}_5$.

IR (neat): 3604 (m), 3443 (m), 3122 (w), 2993 (w), 2857 (w), 2455 (br m) 1720 (m), 1608 (s), 1470 (s), 1422 (s), 1393 (s), 1337 (s), 1259 (s), 1132 (s), 1022 (s), 986 (s), 935 (s), 916 (s), 895 (s), 782 (s), 761 (s), 704 (s), 697 (s) cm^{-1} .

^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 7.53$ (s, 2 H, Py-CH).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta = 167.0$ (C), 165.7 (C), 149.6 (C), 115.2 (CH).

LC-MS: $t_R = 0.34$ min; $m/z = 182.09$ [M – H].

HRMS (ESI): m/z calcd for $[\text{C}_7\text{H}_6\text{NO}_5]^+$: 184.0259; found: 184.0257.

PyBox Cyclization; General Procedure

A 0.24 M soln of Et_2NSF_3 (DAST) in CH_2Cl_2 was loaded into a 10-mL sample loop, and a 0.1 M soln of the appropriate bisamide **8** in 1:1 MeCN– CH_2Cl_2 was separately loaded into a second 10-mL sample loop. The solns were injected into the system and combined at a standard T-piece mixer before flowing through a 10-mL CFC (0.5 mL/min, 1:1 ratio, residence time: 20 min, system solvent: CH_2Cl_2) maintained at 90 °C. The outflow was directed through a glass column loaded sequentially with a layer of CaCO_3 and a layer of silica gel (2 g each). The soln was collected for 2 h and then the solvent was removed in vacuo to yield the corresponding cyclized material **3**.

4-Chloro-2,6-bis[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine [(*S*)-**3a**]²⁷

Yield: 298 mg (89%); colorless oil; $[\alpha]_D^{25} +96.9$ (c 1.1, CHCl_3).

IR (neat): 3441 (w), 2960 (m), 2916 (m), 2874 (m), 1642 (s), 1562 (s), 1468 (m), 1426 (w), 1382 (s), 1366 (m), 1324 (w), 1270 (m), 1237 (s), 1151 (m), 1020 (w), 975 (s), 937 (m), 887 (m), 788 (s), 731 (s) cm^{-1} .

^1H NMR (600 MHz, CDCl_3): $\delta = 8.18$ (s, 2 H), 4.53 (app. t, $J = 8.9$ Hz, 2 H), 4.22 (app. t, $J = 8.4$ Hz, 2 H), 4.12–4.17 (m, 2 H), 1.85 (sext, $J = 6.6$ Hz, 2 H), 1.03 (d, $J = 6.6$ Hz, 6 H), 0.93 (d, $J = 6.6$ Hz, 6 H).

^1H NMR (400 MHz, CDCl_3): $\delta = 8.12$ (s, 2 H), 4.48 (dd, $J = 8.4$, 8.4 Hz, 2 H), 4.18 (dd, $J = 8.4$, 8.4 Hz, 2 H), 4.13–4.07 (m, 2 H), 1.82 (sext, $J = 6.6$ Hz, 2 H), 1.00 (d, $J = 6.6$ Hz, 6 H), 0.89 (d, $J = 6.6$ Hz, 6 H).

^{13}C NMR (150 MHz, CDCl_3): $\delta = 161.4$ (C), 148.0 (C), 145.5 (C), 125.8 (CH), 72.8 (CH), 71.3 (CH_2), 32.8 (CH), 18.9 (CH_3), 18.3 (CH_3).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 161.4$ (C), 148.0 (C), 145.4 (C), 125.8 (CH), 73.0 (CH), 71.3 (CH_2), 32.8 (CH), 19.0 (CH_3), 18.4 (CH_3).

LC-MS: $t_R = 4.57$ min, $m/z = 335.9$ [M + H]⁺.

HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{23}\text{ClN}_3\text{O}_2$: 336.1479; found: 336.1494.

4-Chloro-2,6-bis[(4*R*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine [(*R*)-**3a**]

Yield: 281 mg (84%); colorless oil; $[\alpha]_D^{25} -47.6$ (c 0.5, CHCl_3).

IR (neat): 2959 (m), 2932 (w), 1666 (m), 1642 (s), 1561 (s), 1529 (m), 1381 (s), 1366 (m), 1147 (m), 1123 (m), 976 (s), 937 (s), 886 (s), 790 (s), 730 (s) cm^{-1} .

^1H NMR (400 MHz, CDCl_3): $\delta = 8.18$ (s, 2 H), 4.49 (dd, $J = 8.8$ and 8.8 Hz, 2 H), 4.19 (app. t, $J = 8.4$ Hz, 2 H), 4.13–4.07 (m, 2 H), 1.83 (m, 2 H), 1.01 (d, $J = 6.6$ Hz, 6 H), 0.88 (d, $J = 6.6$ Hz, 6 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 161.45 (C), 148.12 (C), 145.39 (C), 125.87 (CH), 72.98 (CH), 71.29 (CH_2), 32.86 (CH), 19.01 (CH_3), 18.36 (CH_3).

LC-MS: t_{R} = 4.58 min, m/z = 336.1 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{23}\text{ClN}_3\text{O}_2$: 336.1479; found: 336.1487.

2,6-Bis[(4S)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]-4-chloropyridine [(S)-3b]²⁰

Yield: 327 mg (90%); off-white solid; mp 177–179 °C; $[\alpha]_{\text{D}}^{25}$ –25.8 (c 1.0, CHCl_3).

IR (neat): 3334 (br w), 2932 (br w), 2170 (w), 2158 (w), 1673 (s), 1644 (s), 1550 (s), 1520 (s), 1467 (m), 1397 (m), 1231 (w), 1218 (w), 1205 (w), 1155 (m), 1112 (w), 1044 (m), 1006 (w), 766 (m), 712 (s) cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.30 (s, 2 H), 4.52 (dd, J = 10.2 and 9.0 Hz, 2 H), 4.37 (m, 2 H), 4.15 (dd, J = 10.2 and 9.0 Hz, 2 H), 1.01 (br s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.2 (C), 148.3 (C), 145.6 (C), 126.5 (CH), 75.7 (CH_2), 70.2 (CH), 34.6 (C), 26.4 (CH_3).

LC-MS: t_{R} = 4.87 min, m/z = 364.2 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{26}\text{ClN}_3\text{O}_2\text{Na}$: 386.1611; found: 386.1628.

4-Chloro-2,6-bis[(4S)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine [(S)-3c]

Yield: 353 mg (88%); off-white solid; mp 160–163 °C; $[\alpha]_{\text{D}}^{25}$ –15.6 (c 1.0, CHCl_3).

IR (neat): 3313 (br w), 2930 (br w), 2161 (w), 1671 (s), 1639 (s), 1561 (m), 1518 (s), 1454 (m), 1406 (w), 1380 (m), 1314 (w), 1235 (w), 1189 (w), 1148 (m), 1063 (m), 1029 (m), 914 (w), 755 (m), 700 (s) cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.35 (s, 2 H), 7.39–7.31 (m, 10 H), 5.46 (dd, J = 8.8 and 10 Hz, 2 H), 4.93 (dd, J = 8.4 and 10.0 Hz, 2 H), 4.44 (dd, J = 8.4 and 8.8 Hz, 2 H).

^1H NMR (600 MHz, CDCl_3): δ = 8.34 (s, 2 H), 7.36 (t, J = 7.8 Hz, 4 H), 7.28–7.35 (m, 6 H), 5.46 (app. t, J = 9.6 Hz, 2 H), 4.93 (app. t, J = 9.0 Hz, 2 H), 4.93 (app. t, J = 10.2 Hz, 2 H).

^{13}C NMR (150 MHz, CDCl_3): δ = 162.8 (C), 148.0 (C), 145.6 (C), 141.3 (C), 128.9 (CH), 127.9 (CH), 126.8 (CH), 126.4 (CH), 75.7 (CH_2), 70.3 (CH).

LC-MS: t_{R} = 4.74 min, m/z = 404.2 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{19}\text{ClN}_3\text{O}_2$: 404.1166; found: 404.1169.

4-Chloro-2,6-bis[(4R)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine [(R)-3c]

Yield: 301 mg (75%); white solid; mp 159–161 °C; $[\alpha]_{\text{D}}^{25}$ +12.4 (c 0.9, CHCl_3).

IR (neat): 2959 (s), 2932 (w), 1666 (s), 1642 (s), 1561 (m), 1529 (s), 1468 (m), 1424 (w), 1381 (s), 1366 (s), 1235 (m), 1147 (m), 1123 (m), 976 (s), 886 (s), 790 (s) cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.36 (s, 2 H), 7.39–7.31 (m, 10 H), 5.45 (dd, J = 9.1 and 11.0 Hz, 2 H), 4.98 (dd, J = 8.4 and 11.0 Hz, 2 H), 4.36 (dd, J = 8.4 and 9.1 Hz, 2 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 163.1 (C), 148.3 (C), 145.8 (C), 141.1 (C), 129.1 (CH), 128.2 (CH), 126.9 (CH), 126.6 (CH), 75.7 (CH_2), 70.4 (CH).

LC-MS: t_{R} = 4.72 min, m/z = 404.1 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{18}\text{ClN}_3\text{O}_2$: 404.1088; found: 404.1092.

Anal. Calcd for $\text{C}_{23}\text{H}_{18}\text{ClN}_3\text{O}_2$: C, 67.4; H, 4.49; N, 10.4. Found: C, 66.95; H, 4.49; N, 10.28.

2,6-Bis[(4S)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-4-amine [(S)-4a]:²⁷ Typical Procedure

A 0.1 M soln of chloropyridine (S)-3a in DMF flowing at 0.5 mL/min was mixed with a stream consisting of a 5.0 M aq soln of NaN_3 flowing at 0.1 mL/min. The combined stream was passed through four 10-mL CFCs heated at 120 °C, giving a residence time of ~67 min. The output stream was diluted 9:1 with MeOH, and the soln was passed at a flow rate of 2 mL/min through an H-cube hydrogenator containing a 10% Pd/C cartridge at 50 °C at 30 bar H_2 pressure. The soln was then passed through a short plug of silica gel and the solvent was evaporated.

Yield: 10.8 g (84%); mp >230 °C (dec.); $[\alpha]_{\text{D}}^{25}$ –76.1 [c 0.7, MeOH– CHCl_3 (1:1)].

IR (neat): 3290 (br w), 3162 (br s), 2960 (m), 1663 (s), 1588 (s), 1536 (s), 1466 (m), 1349 (m) cm^{-1} .

^1H NMR (400 MHz, DMSO- d_6): δ = 7.27 (s, 2 H), 6.44 (br s, 2 H, NH_2), 4.40 (t, J = 8.8 Hz, 2 H), 4.02–4.11 (m, 4 H), 1.74 (sext, J = 6.4 Hz, 2 H), 0.95 (d, J = 6.4 Hz, 6 H), 0.88 (d, J = 6.4 Hz, 6 H).

^{13}C NMR (150 MHz, DMSO- d_6): δ = 162.7 (C), 155.5 (C), 147.1 (C), 110.5 (CH), 72.3 (CH), 70.3 (CH_2), 32.7 (CH), 19.0 (CH_3), 18.7 (CH_3).

LC-MS: t_{R} = 3.61 min, m/z = 317.2 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{25}\text{N}_4\text{O}_2$: 317.1978; found: 317.1973.

Anal. Calcd for $\text{C}_{17}\text{H}_{25}\text{N}_4\text{O}_2$: C, 64.5; H, 7.65; N, 17.71. Found: C, 64.1; H, 7.57; N, 17.2.

The structure was unambiguously confirmed by X-ray crystallography. Molecular formula: $\text{C}_{17}\text{H}_{24}\text{N}_4\text{O}_2$; space group: orthorhombic $\text{P}2(1)2(1)2(1)$, a = 6.1451(1), b = 13.9669(3), c = 20.2757(5), β = 90.896°.

4-Azido-2,6-bis[(4S)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine (11a)²⁷

To isolate the intermediate 11a, a small sample (3 mL) of the output from the reaction of (S)-3a with NaN_3 was collected and mixed with acetone (20 mL) to give an off-white precipitate; yield: 7.4 mg (72%).

^1H NMR (400 MHz, CDCl_3): δ = 7.82 (s, 2 H), 4.53 (t, J = 8.6 Hz, 2 H), 4.22 (t, J = 8.6 Hz, 2 H), 4.10–4.16 (m, 2 H), 1.86 (sext, J = 6.8 Hz, 2 H), 1.05 (d, J = 6.8 Hz, 6 H), 0.89 (d, J = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.5 (C), 150.3 (C), 148.6 (C), 115.8 (CH), 73.0 (CH), 71.2 (CH_2), 32.8 (CH), 19.0 (CH_3), 18.3 (CH_3).

LC-MS: t_{R} = 4.24 min, m/z = 343.2 $[\text{M} + \text{H}]^+$.

2,6-Bis[(4R)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-4-amine [(R)-4a]²⁶

Yield: 6.89 g (81%); white solid; mp >235 °C (dec.); $[\alpha]_{\text{D}}^{25}$ +62.8 [c 0.45, MeOH– CHCl_3 (1:1)].

IR (neat): 3260 (br w), 3165 (br s), 2957 (m), 1666 (s), 1585 (s), 1535 (s), 1470 (m), 1343 (m) cm^{-1} .

^1H NMR (400 MHz, DMSO- d_6): δ = 7.21 (s, 2 H), 6.36 (br s, 2 H, NH_2), 4.37 (t, J = 8.8 Hz, 2 H), 4.11 (t, J = 8.8 Hz, 2 H), 4.01 (m, 2 H), 1.71 (sext, J = 6.0 Hz, 2 H), 0.91 (d, J = 6.0 Hz, 6 H), 0.85 (d, J = 6.0 Hz, 6 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.79 (C), 153.68 (C), 147.51 (C), 111.06 (CH), 72.75 (CH), 70.90 (CH_2), 32.89 (CH), 19.11 (CH_3), 18.37 (CH_3).

LC-MS: t_{R} = 3.63 min, m/z = 317.2 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $[\text{C}_{17}\text{H}_{25}\text{N}_4\text{O}_2]^+$: 317.1978; found: 317.1973.

Anal. calcd for $[\text{C}_{17}\text{H}_{24}\text{N}_4\text{O}_2]$: C, 64.5; H, 7.65; N, 17.71. Found: C, 64.3; H, 7.55; N, 17.5.

2,6-Bis[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]pyridin-4-amine [(*S*)-4b]

Yield: 9.87 g (82%); white solid; mp: 254.4–257.2 °C; $[\alpha]_{\text{D}}^{25}$ –10.0 [c 0.25, CHCl_3 –MeOH (1:1)].

IR (neat): 3370 (w), 3285 (w), 3193 (m), 2985 (m), 1629 (m), 1588 (s), 1357 (m), 1304 (m), 1235 (s), 1224 (s), 1164 (s), 983 (s), 967 (m), 881 (m), 868 (m), 695 (m) cm^{-1} .

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 7.27 (s, 2 H), 6.51 (s, 2 H, NH_2), 4.36 (app. t, J = 9.6 Hz, 2 H), 4.22 (app. t, J = 8.8 Hz, 2 H), 3.99 (dd, J = 8.8 and 9.6 Hz, 2 H), 0.88 (s, 18 H).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ = 162.3 (C), 155.3 (C), 146.6 (C-1), 110.0 (CH), 75.4 (CH), 68.4 (CH_2), 33.5 (C), 25.7 ($3 \times \text{CH}_3$).

LC-MS: t_{R} = 2.07 min, m/z = 345.3 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{28}\text{N}_4\text{O}_2$: 344.2212; found: 344.2205.

The structure was unambiguously confirmed by X-ray crystallography. Molecular formula $\text{C}_{19}\text{H}_{28}\text{N}_4\text{O}_4$; space group: orthorhombic $\text{P}2(1)2(1)2(1)$, a = 6.0689(3), b = 14.2417(6), c = 22.2350(10).

2,6-Bis[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridin-4-amine [(*S*)-4c]

Yield: 5.22 g (88%); white solid; mp >250 °C (dec.); $[\alpha]_{\text{D}}^{25}$ –8.0 (c 0.1, MeOH).

IR (neat): 3290 (w), 3144 (m), 2892 (w), 1665 (m), 1581 (s), 1411 (m), 1233 (s), 1167 (s), 983 (s), 968 (m), 756 (m), 697 (s) cm^{-1} .

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 7.40–7.20 (m, 12 H), 6.64 (br s, 2 H, NH_2), 5.40 (t, J = 8.9 Hz, 2 H), 4.75 (t, J = 8.9 Hz, 2 H), 4.25 (t, J = 8.9 Hz, 2 H).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ = 163.4 (C), 162.5 (C), 157.6 (C), 142.6 (C), 128.7 (CH), 127.5 (CH), 126.6 (CH), 117.4 (CH), 75.3 (CH_2), 69.2 (CH).

LC-MS: t_{R} = 4.60 min, m/z = 385.1 $[\text{M} + \text{H}]^+$, 407.1 $[\text{M} + \text{Na}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{21}\text{N}_4\text{O}_2$: 385.1665; found: 385.1672.

2,6-Bis[(4*R*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridin-4-amine [(*R*)-4c]

Yield: 7.81 g (80%); white solid; mp >250 °C (dec.); $[\alpha]_{\text{D}}^{25}$ +13.0 (c 0.1, MeOH).

IR (neat): 3333 (w), 3205 (m), 2890 (w), 1641 (m), 1583 (s), 1352 (m), 1238 (s), 1044 (m), 984 (m), 926 (m), 756 (m), 698 (s) cm^{-1} .

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 7.38–7.20 (m, 12 H), 6.60 (br s, 2 H, NH_2), 5.39 (t, J = 8.9 Hz, 2 H), 4.80 (t, J = 8.9 Hz, 2 H), 4.20 (t, J = 8.9 Hz, 2 H).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ = 163.1 (C), 162.5 (C), 153.6 (C), 141.3 (C), 128.7 (CH), 127.5 (CH), 126.6 (CH), 116.4 (CH), 75.7 (CH_2), 70.4 (CH).

LC-MS: t_{R} = 4.59 min, m/z = 385.1 $[\text{M} + \text{H}]^+$, 407.1 $[\text{M} + \text{Na}]^+$.

HRMS (ESI): m/z calcd for $[\text{C}_{23}\text{H}_{21}\text{N}_4\text{O}_2]^+$: 385.1665; found: 385.1670.

4-Chloropyridine-2,6-dicarbonyl Dichloride (6)²⁶: Batch Synthesis

[CAS Reg. No. 71022–75–8]

DMF (1.75 mL) was added dropwise to a soln of chelidamic acid (**2**; 10.0 g) in SOCl_2 (125 mL). The yellow reaction mixture was stirred under reflux for 8 h and then excess SOCl_2 was removed in vacuo. The resulting yellow solid was suspended in toluene (15 mL) and the solvent was removed in vacuo to give an off-white solid; yield: 13.0 g (quant).

4-Chloropyridine-2,6-dicarbonyl Dichloride (6)²⁶: Flow Synthesis

A first stock soln was prepared containing Vilsmeier's reagent ($\text{ClCH}=\text{N}^+\text{Me}_2 \text{Cl}^-$; 4.5 mmol) in a mixture of MeCN (9 mL) and DMF (1 mL), and a second stock soln was prepared containing chelidamic acid (**2**; 2 mmol) and Et_3N (4 mmol) in MeCN (25 mL). These solns were pumped at flow rates of 100 $\mu\text{L}/\text{min}$ and 250 $\mu\text{L}/\text{min}$, respectively, to meet at a T-piece. The combined flow stream was then directed through two 10-mL CFCs linked in series and heated at 75 °C (residence time ~57 min), followed by a cartridge containing Quadrapure Dimethylamine resin (QP-DMA; 6 g). The output stream was collected for 2.5 h and the solvent was evaporated; yield: 431 mg (91%); white solid; molecular formula: $\text{C}_7\text{H}_2\text{Cl}_3\text{NO}_2$.

Alternatively, the QP-DMA column was omitted and the output stream was collected in a stirred Et_2O (100 mL) to precipitate the triethylammonium salts. After evaporation of the solvent, the product was isolated in 76% yield.

IR (neat): 3082 (w), 1759 (s), 1614 (w), 1584 (m), 1556 (m), 1431 (w), 1416 (w), 1371 (w), 1259 (s), 1190 (m), 1144 (m), 1123 (m), 1101 (m), 1044.5 (w), 1022 (w), 990 (m), 947 (s), 907 (s), 806 (m), 726 (s) cm^{-1} .

^1H NMR (600 MHz, CDCl_3): δ = 8.32 (s, 2 H).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 8.25 (s, 2 H).

^{13}C NMR (150 MHz, CDCl_3): δ = 168.6 (C), 150.1 (C), 147.9 (CH), 128.9 (C).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ = 164.5 (C), 149.9 (C), 145.3 (CH), 127.3 (C).

HRMS (ESI): m/z calcd for $\text{C}_7\text{H}_2\text{Cl}_3\text{NNaO}_2$: 259.9049; found: 259.9087.

Anal. Calcd for $\text{C}_7\text{H}_2\text{Cl}_3\text{NO}_2$: C, 35.26; H, 0.85; Cl, 44.60; N, 5.87. Found: C, 35.12; H, 0.98; Cl, 43.40; N, 6.00.

Dimethyl 4-Hydroxypyridine-2,6-dicarboxylate (6a)^{21b,26,28}

[CAS Reg. No. 20443–03–2]

White solid.

IR (neat): 3346 (w), 3213 (m), 2917 (w), 1723 (s), 1611 (m), 1459 (w), 1419 (m), 1355 (s), 1266 (m), 1207 (s), 1182 (s), 1155 (m), 973 (m), 948 (s), 922 (m), 878 (s), 853 (s), 777 (s) cm^{-1} .

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 11.62 (s, 1 H), 7.59 (s, 2 H), 3.89 (s, 6 H).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ = 167.2 (C), 165.5 (C), 150.3 (CH), 116.8 (C), 54.7 (CH_3).

LC-MS: t_{R} = 3.85 min, m/z = 230.11 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_9\text{H}_{10}\text{NO}_5$: 212.0559; found: 212.0574.

Dimethyl 4-Chloropyridine-2,6-dicarboxylate (6b)^{27–29}

[CAS Reg. No. 5371–70–0]

A soln of Vilsmeier reagent ($\text{ClCH}=\text{N}^+\text{Me}_2 \text{Cl}^-$) (4.5 mmol) in a mixture of MeCN (8 mL) and DMF (2 mL) flowing at 150 $\mu\text{L}/\text{min}$ was combined at a T-piece with a soln of chelidamic acid (**2**; 2

mmol) and Et₃N (4 mmol) in MeCN (20 mL) flowing at 300 µL/min. The combined stream was then pumped through two 10-mL CFCs at 75 °C linked in series. The exiting soln was quenched by the addition of an auxiliary stream containing distilled MeOH (flow rate 1 mL/min). The volatile solvent was removed in vacuo to give an orange soln that was diluted with EtOAc (30 mL). The DMF was then removed by washing with sat. aq LiCl (3 × 15 mL), and the organic phase was dried (Na₂SO₄) and concentrated in vacuo to give a white solid; yield: 380 mg (83%); mp 140–141 °C (Lit.²⁵ 139–140).

Alternatively, the MeOH-quenched soln was passed through a column of QP-DMA (4 equiv) and the solvent was evaporated; yield 417 mg (91%).

IR (neat): 3085 (m), 2954 (m), 1720 (s), 1574 (m), 1467 (w), 1448 (m), 1438 (s), 1328 (s), 1263 (m), 1249 (s), 1199 (s), 1145 (s), 1105 (m), 986 (m), 971 (s), 911 (m), 889 (s), 842 (s), 783 (s), 762 (s), 739 (s), 692 (s) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.29 (s, 2 H), 4.03 (s, 6 H).

¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.28 (s, 2 H), 3.92 (s, 6 H).

¹³C NMR (150 MHz, CDCl₃): δ = C 164.3 (C), 149.6 (CH), 147.0 (C), 128.4 (C), 53.6 (CH₃).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 164.0 (C), 149.5 (CH), 145.8 (C), 128.2 (C), 53.3 (CH₃).

LC-MS: *t*_R = 3.85 min, *m/z* = 230.11 [M + H]⁺.

HRMS (ESI): *m/z* calcd for C₉H₉NO₄Cl: 230.0220; found: 230.0225.

The structure was unambiguously confirmed by single X-ray crystallography. Molecular formula C₉H₈NO₄Cl; space group: orthorhombic P2(1)2(1)2(1), *a* = 3.8361(1), *b* = 13.7763(3), *c* = 18.2100(4), β = 91.542°.

4-Chloro-6-(methoxycarbonyl)pyridine-2-carboxylic Acid

The anhydride **6c**, obtained as a byproduct in the synthesis of **6b**, was isolated and characterized as the corresponding title carboxylic acid.

White solid.

IR (neat): 3371 (w), 3100 (br w), 3080 (w), 1724 (s), 1695 (s), 1650 (s), 1577 (m), 1558 (m), 1434 (s), 1375 (s), 1283 (s), 1201 (w), 1174 (w), 1146 (m), 1101 (w), 976 (m), 893 (m), 839 (s), 782 (s), 748 (s) cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.25 (s, 1 H), 7.96 (br s, 1 H), 3.94 (s, 3 H).

¹H NMR (400 MHz, CDCl₃): δ = 8.41 (s, 1 H), 8.23 (s, 1 H), 4.05 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 164.5 (C), 164.0 (C), 152.6 (C), 148.6 (C), 146.1 (C), 127.3 (CH), 125.4 (CH), 53.3 (CH₃).

¹³C NMR (100 MHz, CDCl₃): δ = 165.0 (C), 164.3 (C), 151.5 (C), 148.4 (C), 147.5 (C), 128.2 (CH), 126.5 (CH), 53.6 (CH₃).

LC-MS: *t*_R = 3.50 min, *m/z* = 214.99 [M + H]⁺.

HRMS (ESI): *m/z* calcd for C₈H₇ClNO₄: 214.9985; found: 214.9991.

The structure was unambiguously confirmed by single X-ray crystallography. Molecular formula C₈H₆ClNO₄; space group: triclinic P-1, *a* = 7.3283(2), *b* = 10.2281(2), *c* = 12.2785(3), α = 91.641°, β = 96.796°, γ = 95.470°.

Bisamides 8: General Procedure

A soln of the appropriate amino alcohol (7.5 mmol) and Et₃N (7.5 mmol, 1 equiv) in anhyd MeCN (50 mL) and a soln of dicarbonyl dichloride **5** (3.75 mmol, 0.5 equiv) in anhyd MeCN (50 mL) were

delivered separately, each at a flow rate of 250 µL/min, to a standard T-piece connector. The combined soln was then passed into a 10-mL CFC heated at 75 °C (20 min residence time). The exiting soln was subjected to scavenging by elution through a glass column packed with polystyrene-bound guanidine base (PS-TBD; 15 mmol), and collected for 2.5 h. The solvent was finally removed in vacuo to give the required product.

4-Chloro-*N,N'*-bis[(1*R*)-1-(hydroxymethyl)-2-methylpropyl]pyridine-2,6-dicarboxamide [(*R*)-**8a**]

Yield: 1035 mg (74%); cream solid; mp 127–130 °C; [α]_D +41.9 (*c* 1.00, CHCl₃).

IR (neat): 3500–3200 (br w), 2966 (w), 1684 (m), 1650 (s), 1583 (w), 1536 (s), 1517 (s), 1478 (m), 1390 (m), 1370 (w), 1337 (m), 1294 (w), 1240 (w), 1142 (w), 1092 (w), 1065 (s), 1015 (s), 970 (m), 891 (m), 779 (w), 698 (s), 727 (s) cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 8.30 (s, 2 H), 7.97 (d, *J* = 8.4 Hz, 2 H), 3.96–3.91 (m, 2 H), 3.85 (dd, *J* = 11.2 and 5.4 Hz, 2 H), 3.81 (dd, *J* = 11.1 and 3.6 Hz, 2 H), 2.64 (br s, 2 H), 1.05 (d, *J* = 6.6 Hz, 6 H), 1.01 (d, *J* = 6.6 Hz, 6 H).

¹³C NMR (150 MHz, CDCl₃): δ = 162.9 (C), 150.1 (C), 148.0 (C), 125.4 (CH), 63.6 (CH₂), 57.2 (CH), 29.3 (CH), 19.6 (CH₃), 18.6 (CH₃).

LC-MS: *t*_R = 4.26 min, *m/z* = 396.1 [M + Na]⁺, 372.1 [M + H]⁺, 370.3 [M – H]⁺.

HRMS (ESI): *m/z* calcd for C₁₇H₂₇ClN₃O₄: 372.1690; found: 372.1993.

4-Chloro-*N,N'*-bis[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]pyridine-2,6-dicarboxamide [(*S*)-**8a**]²⁰

[CAS Reg. No. 477779–36–5]

Yield: 1141 mg (82%); white solid; mp 130–134 °C; [α]_D²⁵ –47.4 (*c* 1.23, MeOH); [α]_D –38.3 (*c* 0.97, CHCl₃).

IR (neat): 3500–3150 (br m); 2964 (m), 1683 (m), 1649 (s), 1582 (w), 1536.5 (s), 1478 (m), 1391 (m), 1337 (m), 1240 (m), 1132 (w), 1065 (s), 1016 (s), 971 (m), 892 (m), 850 (w), 814 (w), 779 (w), 748 (s), 727 (m) cm⁻¹.

¹H NMR (400 MHz, CD₃OD): δ = 8.28 (s, 2 H, Py-H), 3.88–3.93 (m, 2 H), 3.76 (m, 4 H), 2.04 (sext, *J* = 6.8 Hz, 2 H), 1.04 (d, *J* = 6.8 Hz, 6 H), 0.98 (d, *J* = 6.8 Hz, 6 H).

¹H NMR (600 MHz, CDCl₃): δ = 8.32 (d, *J* = 8.4 Hz, 2 H, 2 × NH), 8.19 (2 s, H, Py-H), 4.66 (br s, 2 H, 2 × OH), 3.75–3.87 (m, 4 H), 3.74 (dd, *J* = 11.0 and 2.9 Hz, 2 H), 2.02 (sext, *J* = 6.7 Hz, 2 H), 0.96 (d, *J* = 6.7 Hz, 6 H, 2 × Me), 0.93 (d, *J* = 6.7 Hz, 6 H, 2 × Me).

¹³C NMR (100 MHz, CD₃OD): δ = 163.9 (C), 151.3 (C), 147.5 (C), 125.1 (CH), 62.1 (CH₂), 58.1 (CH), 29.3 (CH), 19.2 (CH₃), 18.5 (CH₃).

¹³C NMR (150 MHz, CDCl₃): δ = 163.1 (C), 150.4 (C), 147.6 (C), 125.2 (CH), 62.9 (CH₂), 57.5 (CH), 29.1 (CH), 19.6 (CH₃), 18.9 (CH₃).

LC-MS: *t*_R = 4.27 min, *m/z* = 372.1 [M + H]⁺, 394.1 [M + Na]⁺, 370.1 [M – H]⁺.

HRMS (ESI): *m/z* calcd for C₁₇H₂₇ClN₃O₄: 372.1690; found: 372.1707.

Anal. Calcd for C₁₇H₂₆ClN₃O₄: C, 54.91; H, 7.05; Cl, 9.73; N, 11.30. Found: C, 54.29; H, 6.98; Cl, 9.80; N, 10.95.

4-Chloro-*N,N'*-bis[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]pyridine-2,6-dicarboxamide [(*S*)-**8b**]²⁰

Yield: 1392 mg (93%); white solid; mp 121.5–123.0 °C; [α]_D –32.5 (*c* 0.85, CHCl₃).

IR (neat): 3378 (w), 3289 (w), 3088 (m), 2966 (m), 1670 (m), 1530 (s), 1483 (m), 1478 (m), 1360 (m), 1284 (s), 1229 (s), 1123 (s), 954 (m), 883 (m), 788 (m), 690 (m) cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.31 (s, 2 H), 8.04 (d, J = 10.0 Hz, 2 H), 4.00 (m, 4 H), 3.78 (dd, J = 10.0 and 8.2 Hz, 2 H), 1.06 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 163.2 (C), 150.3 (C), 148.5 (C), 125.7 (CH), 63.2 (CH), 60.2 (CH_2), 34.2 (C), 27.2 (CH_3).

LC-MS: t_{R} = 4.45 min, m/z = 400.3 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{31}\text{N}_3\text{O}_4\text{Cl}$: 400.2003; found: 400.2016.

4-Chloro-*N,N'*-bis[(1*S*)-2-hydroxy-1-phenylethyl]pyridine-2,6-dicarboxamide [(*S*)-8c]

Yield: 1613 mg (98%); white solid; mp >248 °C (dec.); $[\alpha]_{\text{D}}^{25}$ +69.5 (*c* 1.00, CHCl_3).

IR (neat): 3291 (w), 3065 (w), 2936 (w), 1655 (s), 1523 (s), 1454 (m), 1407 (m), 1308 (m), 1238 (w), 1070 (m), 1030 (s), 898 (m), 847 (w), 729 (s), 698 (s) cm^{-1} .

^1H NMR (600 MHz, CDCl_3): δ = 8.56 (d, J = 7.2 Hz, 2 H), 8.29 (s, 2 H), 7.38–7.31 (m, 10 H), 5.25–5.21 (m, 2 H), 4.00 (app. d, J = 4.5 Hz, 4 H), 2.20 (br s, 2 H).

^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ = 8.74 (d, J = 7.8 Hz, 2 H, 2 $\times$ NH), 8.18 (s, 2 H, Py), 7.30 (m, 10 H, Ph), 5.21 (app. quin, J = 5.6 Hz, 2 H), 3.95 (d, J = 6.6 Hz, 4 H).

^{13}C NMR (150 MHz, CDCl_3): δ = 162.4 (C), 150.0 (C), 148.0 (C), 138.5 (C), 129.0 (CH), 128.1 (CH), 126.6 (CH), 125.5 (CH), 66.3 (CH_2), 55.8 (CH).

^{13}C NMR (150 MHz, $\text{DMSO}-d_6$): δ = 162.7 (C), 150.1 (C), 147.8 (C), 138.6 (C), 128.9 (CH), 127.9 (CH), 126.7 (CH), 125.4 (CH), 65.8 (CH_2), 55.8 (CH).

LC-MS: t_{R} = 4.46, m/z = 440.03 $[\text{M} + \text{H}]^+$, 437.99 $[\text{M} - \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{22}\text{ClN}_3\text{NaO}_4$: 462.1197; found: 462.1201.

4-Chloro-*N,N'*-bis[(1*R*)-2-hydroxy-1-phenylethyl]pyridine-2,6-dicarboxamide [(*R*)-8c]

Yield: 1580 mg (96%); off-white solid; mp >250 °C (dec.); $[\alpha]_{\text{D}}^{25}$ –63.1 (*c* 0.97, CHCl_3).

IR (neat): 3600–3150 (br w), 1655 (s), 1524 (s), 1453 (m), 1407 (w), 1306 (m), 1239 (w), 1070 (m), 1029 (m), 996 (w), 896 (m), 846 (w), 743 (s), 699 (s) cm^{-1} .

^1H NMR (600 MHz, CDCl_3): δ = 8.56 (d, J = 7.2 Hz, 2 H), 8.27 (s, 2 H), 7.38–7.31 (m, 10 H), 5.25–5.21 (m, 2 H), 4.00 (app. d, J = 4.5 Hz, 4 H), 2.20 (br s, 2 H).

^{13}C NMR (150 MHz, CDCl_3): δ = 162.4 (C), 150.0 (C), 148.0 (C), 138.5 (C), 129.0 (CH), 128.1 (CH), 126.6 (CH), 125.5 (CH), 66.3 (CH), 55.8 (C).

LC-MS: t_{R} = 4.48, m/z = 440.01 $[\text{M} + \text{H}]^+$, 438.01 $[\text{M} - \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{22}\text{ClN}_3\text{NaO}_4$: 462.1197; found: 462.1186.

4-Chloro-*N,N'*-bis[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]pyridine-2,6-dicarboxamide [(1*S*,2*R*)-8d]

Yield: 1178 mg (68%); white solid; mp 245.3–252.1 °C; $[\alpha]_{\text{D}}^{25}$ –21.0 (*c* 0.25, CHCl_3).

IR (neat): 3430 (m), 3382 (m), 2941 (w), 1661 (s), 1581 (m), 1518 (s), 1495 (s), 1478 (m), 1328 (w), 1300 (w), 1264 (w), 1173 (w), 1081 (w), 1053 (m), 957 (m), 895 (w), 825 (w), 750 (s), 721 (s) cm^{-1} .

^1H NMR (600 MHz, CDCl_3): rotamers of the amide cause degeneracy of the signals for the amide, pyridine, and chiral protons; *Rotamer A*: δ = 8.66 (d, J = 13.2 Hz, 2 H), 8.34 (s, 2 H), 7.30–7.12 (m, 8 H), 5.57 (dd, J = 13.2 and 10.5 Hz, 2 H), 4.63–4.61 (m, 2 H), 3.15–3.05 (m, 2 H). *Rotamer B*: δ = 8.56 (d, J = 12.6 Hz, 2 H), 8.28 (s, 2 H), 7.30–7.12 (m, 8 H), 5.45 (dd, J = 12.6 and 18.1 Hz, 2 H), 4.63–4.61 (m, 2 H), 3.15–3.05 (m, 2 H).

^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ = 8.90 (d, J = 8.4 Hz, 2 H, NH), 8.32 (s, 2 H, Py), 7.19 (m, 8 H, Ar), 5.42 (t, J = 1.8 Hz, 2 H), 5.24 (d, J = 3.6 Hz, 2 H, OH), 4.52 (d, J = 3.6 Hz, 2 H), 3.11 (dd, J = 16.2 and 3.6 Hz, 2 H), 2.82 (d, J = 16.2 Hz, 2 H).

^{13}C NMR (150 MHz, $\text{DMSO}-d_6$): δ = 162.7 (C), 151.3 (C), 146.7 (C), 142.0 (C), 141.3 (C), 128.0 (CH), 126.9 (CH), 125.4 (CH), 125.1 (CH), 124.7 (CH), 72.3 (CH), 57.7 (CH), 40.4 (CH_2).

LC-MS: t_{R} = 4.56 min, m/z = 486.2 $[\text{M} + \text{Na}]^+$, 461.99 $[\text{M} - \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{25}\text{H}_{23}\text{ClN}_3\text{O}_4$: 464.1377; found: 464.1398.

4-Chloro-*N,N'*-bis(2-hydroxyethyl)pyridine-2,6-dicarboxamide (8e)

Yield: 969 mg (90%); white solid; mp >178 °C (dec.).

IR (neat): 3296 (br m), 3065 (m), 2908 (w), 1649 (s), 1614 (s), 1538 (s), 1495 (m), 1447 (m), 1330 (m), 1223 (w), 1040 (m), 996 (m), 861 (m), 710 (s) cm^{-1} .

^1H NMR (600 MHz, CDCl_3): δ = 8.15 (2 H, s), 7.15 (app. t, 2 H), 4.78 (br s, 2 H), 3.53 (m, 4 H), 3.36 (m, 4 H).

^{13}C NMR (150 MHz, CDCl_3): δ = 162.6 (C), 156.5 (C), 151.1 (C), 126.6 (CH), 60.3 (CH_2), 59.7 (CH_2).

LC-MS: t_{R} = 3.55 min, m/z = 286.19 $[\text{M} - \text{H}]^+$.

HRMS (ESI): m/z calcd for $\text{C}_{11}\text{H}_{15}\text{ClN}_3\text{O}_4$: 288.0751; found: 288.0761, calcd for $\text{C}_{11}\text{H}_{14}\text{ClN}_3\text{NaO}_4$: 310.0571; found: 288.0581.

Macrocycles 10a–d: General Procedure

A soln of the appropriate amino alcohol (5 mmol) and Et_3N (10 mmol, 2 equiv) in anhyd MeCN (50 mL) and a soln of dicarbonyl dichloride **6** (2.5 mmol) in anhyd MeCN (50 mL) were separately delivered, each at a flow rate of 250 $\mu\text{L}/\text{min}$, to a standard T-piece connector. The combined fluidic flow was then passed into three 10-mL interlinked CFCs heated to 80 °C (60 min residence time). A 75-psi back-pressure regulator at the exit of the reactor maintained the system pressure. The exiting soln was concentrated and suspended in EtOAc (50 mL), which was extracted with sat. aq NaHCO_3 (2 $\times$ 30 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo to yield the desired product.

(5*S*,15*S*)-10,21-Dichloro-5,15-diisopropyl-3,17-dioxo-6,14,23,24-tetraazatricyclo[17.3.1.1^{8,12}]tetracos-1(23),8(24),9,11,19,21-hexaene-2,7,13,18-tetrone (10a)

Yield: 1206 mg (90%); white solid; mp >254 °C (dec.); $[\alpha]_{\text{D}}^{25}$ –303.2 (*c* 1.2, CHCl_3).

IR (neat): 3664 (w), 3450 (br w), 2969 (s), 1732 (m), 1676 (s), 1528 (s), 1465 (w), 1383 (m), 1321 (s), 1235 (m), 1163 (w), 1066 (s), 1056 (s), 898 (w), 763 (w) cm^{-1} .

^1H NMR (600 MHz, CDCl_3): δ = 8.43 (s, 2 H), 8.38 (s, 2 H), 8.26 (d, J = 10.2 Hz, 2 H), 5.36 (dd, J = 1.2 and 11.4 Hz, 2 H), 4.30 (app. t, 2 H), 4.16 (dd, J = 1.8 and 11.4 Hz, 2 H), 1.94–1.89 (m, 2 H), 1.05 (d, J = 6.6 Hz, 6 H), 0.96 (d, J = 6.6 Hz, 6 H).

^{13}C NMR (150 MHz, CDCl_3): δ = 163.7 (C), 162.2 (C), 150.4 (C), 149.1 (C), 147.8 (C), 146.8 (C), 128.8 (CH), 126.1 (CH), 66.1 (CH_2), 54.4 (CH), 29.7 (CH), 19.8 (CH_3), 19.7 (CH_3).

LC-MS: t_{R} = 5.29, m/z = 536.98 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $C_{24}H_{27}Cl_2N_4O_6$: 537.1308; found: 537.1332.

The structure was unambiguously confirmed by X-ray crystallography; space group: orthorhombic $P2(1)2(1)2(1)$, $a = 12.2197(2)$, $b = 9.4134(2)$, $c = 12.3527(3)$, $\beta = 108.897^\circ$.

(5S,15S)-5,15-Di-*tert*-butyl-10,21-dichloro-3,17-dioxo-6,14,23,24-tetraazatricyclo[17.3.1.1^{8,12}]tetracos-1(23),8(24),9,11,19,21-hexaene-2,7,13,18-tetrone (10b)

Yield: 1283 mg (91%); pale-yellow solid; mp $>230^\circ\text{C}$ (dec.); $[\alpha]_D^{25} -10.0$ (c 0.25, CHCl_3).

IR (neat): 3373 (br w), 2964 (w), 1729 (m), 1679 (s), 1520 (s), 1368 (m), 1234 (s), 1155 (m), 895 (m), 780 (m) cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.43 (s, 2 H), 8.37 (s, 2 H), 8.32 (d, J = 10.4 Hz, 2 H), 5.54 (d, 2 H, J = 10.4 Hz), 4.43 (dd, J = 1.8 and 10.4 Hz, 2 H), 4.14 (dd, J = 1.8 and 10.4 Hz, 2 H), 0.95 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 163.8 (C), 162.5 (C), 150.6 (C), 149.3 (C), 147.8 (C), 146.7 (C), 128.6 (CH), 126.3 (CH), 66.0 (CH_2), 55.5 (CH), 35.2 (C), 28.0 (CH_3).

LC-MS: t_R = 5.57, m/z = 565.19 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $C_{26}H_{31}Cl_2N_4O_6$: 565.1621; found: 565.1625.

(5S,15S)-10,21-Dichloro-5,15-diphenyl-3,17-dioxo-6,14,23,24-tetraazatricyclo[17.3.1.1^{8,12}]tetracos-1(23),8(24),9,11,19,21-hexaene-2,7,13,18-tetrone (10c)

Yield: 1284 mg (85%); white solid; mp $270\text{--}273^\circ\text{C}$; $[\alpha]_D^{25} -16$ (c 0.25, CHCl_3).

IR (neat): 3400 (w), 3084 (br w), 1728 (s), 1682 (s), 1582 (w), 1560 (w), 1510 (s), 1454 (w), 1415 (m), 1375 (w), 1356 (w), 1300 (m), 1258 (w), 1224 (m), 1149 (s), 1050 (w), 1028 (w), 995 (w), 902 (m), 779 (m), 752 (w), 721 (w), 698 (s) cm^{-1} .

^1H NMR (600 MHz, CDCl_3): δ = 9.02 (d, J = 10.0 Hz, 2 H, NH), 8.41 (s, 2 H), 8.27 (s, 2 H), 7.51 (d, J = 7.0 Hz, 4 H, Ph), 7.25 (m, 6 H), 5.77 (d, J = 9.9 Hz, 2 H), 5.37 (d, J = 11.4 Hz, 2 H), 4.58 (dd, J = 11.4 and 3.0 Hz, 2 H).

^{13}C NMR (150 MHz, CDCl_3): δ = 163.4 (C), 161.5 (C), 150.9 (C), 147.6 (C), 146.5 (C), 138.2 (C), 129.0 (CH), 128.1 (CH), 128.05 (CH), 126.7 (CH), 126.3 (CH), 69.3 (CH_2), 50.9 (CH).

LC-MS: t_R = 5.26, m/z = 605.1 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $C_{30}H_{23}Cl_2N_4O_6$: 605.0995; found: 605.1003.

(4R,12S,22S,30R)-17,35-Dichloro-13,21-dioxo-3,31,37,38-tetraazaheptacyclo[31.3.1.1^{15,19}.0^{4,12}.0^{5,10}.0^{22,30}.0^{24,29}]octatriaconta-1(37),5,7,9,15(38),16,18,24,26,28,33,35-dodecaene-2,14,20,32-tetrone (10d)

Yield: 1021 mg (65%); white solid; mp $>260^\circ\text{C}$ (dec.); $[\alpha]_D^{25} -5.0$ (c 0.25, CHCl_3).

IR (neat): 2357 (w), 2128 (br w), 1727 (m), 1674 (m), 1512 (s), 1356 (w), 1317 (m), 1241 (m), 1158 (s), 1036 (w), 879 (w), 783 (w), 750 (s), 723 (m) cm^{-1} .

^1H NMR (600 MHz, CDCl_3): δ = 8.76 (d, J = 7.1 Hz, 2 H, NH), 8.44 (s, 2 H), 8.07 (s, 2 H), 7.23 (m, 8 H, Ar), 5.96 (m, 2 H), 5.76 (m, 2 H), 3.44 (m, 2 H), 3.31 (m, 2 H).

^{13}C NMR (150 MHz, CDCl_3): δ = 164.6 (C), 163.4 (C), 150.0 (C), 147.6 (C), 146.5 (C), 139.6 (C), 139.0 (C), 128.4 (CH), 127.8 (CH), 127.3 (CH), 126.3 (CH), 125.1 (CH), 123.7 (CH), 79.4 (CH), 56.3 (CH), 37.7 (CH_2).

LC-MS: t_R = 5.38, m/z = 629.1 $[\text{M} + \text{H}]^+$.

HRMS (ESI): m/z calcd for $C_{32}H_{22}Cl_2N_4NaO_6$: 651.0820; found: 651.0814; calcd for $C_{32}H_{23}Cl_2N_4O_6$: 629.0995; found: 629.1000.

10,21-Dichloro-3,17-dioxo-6,14,23,24-tetraazatricyclo[17.3.1.1^{8,12}]tetracos-1(23),8(24),9,11,19,21-hexaene-2,7,13,18-tetrone (10e)

Yield: 927 mg (82%); white solid; mp $>190^\circ\text{C}$ (dec.).

IR (neat): 3380 (br w), 2964 (w), 1715 (m), 1669 (s), 1520 (s), 1234 (s), 1155 (m), 890 (w), 780 (m) cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.82 (app. t, 2 H), 8.38 (s, 2 H), 8.29 (s, 2 H), 4.65 (t, J = 8.9 Hz, 4 H), 3.96 (m, 4 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 164.2 (C), 162.8 (C), 150.3 (C), 149.1 (C), 147.8 (C), 146.7 (C), 129.6 (CH), 126.3 (CH), 67.2 (CH_2), 48.5 (CH_2).

LC-MS: t_R = 4.61, m/z = 453.03 $[\text{M} + \text{H}]^+$, 450.99 $[\text{M} - \text{H}]^+$.

HRMS (ESI): m/z calcd for $C_{18}H_{15}Cl_2N_4O_6$: 453.0369; found: 453.0381; calcd for $C_{18}H_{14}Cl_2N_4NaO_6$: 475.0183; found: 453.0165.

10,21-Dichloro-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1^{8,12}]tetracos-1(23),8(24),9,11,19,21-hexaene-2,7,13,18-tetrone (10f)

Yield: 788 mg (70%); off-white solid; mp $>285^\circ\text{C}$ (dec.).

IR (neat): 3330 (br w), 1655 (s), 1530 (s), 1446 (w), 1306 (w), 896 (w), 787 (m), 737 (m) cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.37 (s, 4 H), 8.24 (br s, 2 H), 3.77 (s, 8 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 164.1 (C), 148.3 (C), 145.0 (C), 126.1 (CH), 49.2 (CH_2).

LC-MS: t_R = 4.42, m/z = 451.1 $[\text{M} + \text{H}]^+$, 448.98 $[\text{M} - \text{H}]^+$.

HRMS (ESI): m/z calcd for $[\text{C}_{18}\text{H}_{17}\text{N}_6\text{O}_4\text{Cl}_2]^+$: 451.0688; found: 451.0687.

Crystallographic data for compounds (*S*)-**4a**, (*S*)-**4b**, **6b**, 4-chloro-6-(methoxycarbonyl)pyridine-2-carboxylic acid, and **10a** have been deposited with the accession numbers CCDC 850877, 849198, 850875, 850878, and 850876, respectively, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

Acknowledgment

The authors would like to thank the following for their financial support: the Ralph Raphael studentship award and the Cambridge European Trust (M.B.); the Royal Society (I.R.B.); the EPSRC (M.O.K.); F. Hoffmann-La Roche, Basel (R.E.M. and S.A.O.); and the BP Endowment (S.V.L.). X-ray crystal structures were determined by Dr John Davies at the Department of Chemistry, of the University of Cambridge and by Dr André Alker, of Parma Research Basel.

References

- (1) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119.
- (2) (a) Evans, D. A.; Sweeny, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095. (b) Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829. (c) Keith, J. M.; Jacobsen, E. N. *Org. Lett.* **2004**, *6*, 153. (d) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001.

- (3) (a) Bhattacharyya, S. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 752. (b) Ley, S. V.; Baxendale, I. R. *Chem. Rec.* **2002**, *2*, 377. (c) Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discovery* **2002**, *1*, 573. (d) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 650. (e) Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324.
- (4) (a) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Luis, S. V.; Martínez-Merino, V.; Mayoral, J. A. *J. Org. Chem.* **2005**, *70*, 5536. (b) Cornejo, A.; Fraile, J. M.; García, J. I.; García-Verdugo, E.; Gil, M. J.; Legarreta, G.; Luis, S. V.; Martínez-Merino, V.; Mayoral, J. A. *Org. Lett.* **2002**, *4*, 3927.
- (5) Tilliet, M.; Lundgren, S.; Moberg, C.; Levacher, V. *Adv. Synth. Catal.* **2007**, *349*, 2079.
- (6) Zeng, T.; Yang, L.; Hudson, R.; Song, G.; Moores, A. R.; Li, C.-J. *Org. Lett.* **2011**, *13*, 442.
- (7) (a) Bremeyer, N.; Ley, S. V.; Ramarao, C.; Shirley, I. M.; Smith, S. C. *Synlett* **2002**, 1843. (b) Yu, J.-Q.; Wu, H. C.; Ramarao, C.; Spencer, J. B.; Ley, S. V. *Chem. Commun.* **2003**, 678. (c) Mitchell, C.; Pears, D.; Ley, S. V.; Yu, J.-Q.; Zhou, W. *Org. Lett.* **2003**, *5*, 4665. (d) Siu, J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 160. (e) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Chem. Eur. J.* **2006**, *12*, 4407. (f) Sedelmeier, J.; Ley, S. V.; Lange, H.; Baxendale, I. R. *Eur. J. Org. Chem.* **2009**, 4412.
- (8) (a) Kobayashi, S. *Chem. Rev.* **2009**, *109*, 594. (b) Pears, D. A.; Smith, S. C. *Aldrichimica Acta* **2005**, *38*, 23.
- (9) (a) Nishijama, H.; Sakaguchi, H.; Nakamura, T.; Horikata, M.; Kondo, M.; Kenji, I. *Organometallics* **1989**, *8*, 846. (b) Desimoni, G.; Faïta, G.; Guala, M.; Pratelli, C. *Tetrahedron: Asymmetry* **2002**, *13*, 1651. (c) Lundgren, S.; Lutsenko, S.; Jönsson, C.; Moberg, C. *Org. Lett.* **2003**, *5*, 3663.
- (10) (a) Martin, L. J.; Marzinzik, A. L.; Ley, S. V.; Baxendale, I. R. *Org. Lett.* **2011**, *13*, 320. (b) Baumann, M.; Baxendale, I. R.; Kirschning, A.; Ley, S. V.; Wegner, J. *Heterocycles* **2011**, *82*, 1297. (c) Polyzos, A.; Baxendale, I. R.; Petersen, T.; Ley, S. V. *Angew. Chem. Int. Ed.* **2011**, *50*, 1190. (d) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596. (e) Hopkin, M. D.; Baxendale, I. R.; Ley, S. V. *Chem. Commun.* **2010**, 46, 2450. (f) Qian, Z.; Baxendale, I. R.; Ley, S. V. *Synlett* **2010**, 505. (g) Carter, C. F.; Lange, H.; Ley, I. R.; Baxendale, I. R.; Wittkamp, B.; Goode, J. G.; Gaunt, N. L. *Org. Process Res. Dev.* **2010**, *14*, 393. (h) Malet-Sanz, L.; Madrzak, J.; Ley, S. V.; Baxendale, I. R. *Org. Biomol. Chem.* **2010**, *8*, 5324.
- (11) (a) Riva, E.; Rencurosi, A.; Gagliardi, S.; Passarella, D.; Martinelli, M. *Chem. Eur. J.* **2011**, *17*, 6221. (b) Lange, P. P.; Gooßen, L. J.; Podmore, P.; Underwood, T.; Sciammetta, N. *Chem. Commun.* **2011**, 47, 3628. (c) Batoul, A.-O.; Sanderson, A. J. *Org. Biomol. Chem.* **2011**, *9*, 3854. (d) Rasheed, M.; Elmore, S. C.; Wirth, T. In *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques, and Applications*; Gruttadauria, M.; Giacalone, F., Eds.; Wiley: Hoboken, **2011**, 345. (e) Ahmed-Omer, B.; Barrow, D. A.; Wirth, T. *ARKIVOC* **2011**, (iv), 26. (f) Rasheed, M.; Wirth, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 357. (g) Brandt, J. C.; Elmore, S. C.; Robinson, R. I.; Wirth, T. *Synlett* **2010**, 3099. (h) Brasholz, M.; Macdonald, J. M.; Saubern, S.; Ryan, J. H.; Holmes, A. B. *Chem. Eur. J.* **2010**, *16*, 11471. (i) Wegner, J.; Ceylan, S.; Friese, C.; Kirschning, A. *Eur. J. Org. Chem.* **2010**, 4372. (j) Grafton, M.; Mansfield, A. C.; Fray, M. J. *Tetrahedron Lett.* **2010**, *51*, 1026. (k) Tamborini, L.; Conti, P.; Pinto, A.; Micheli, C. D. *Tetrahedron: Asymmetry* **2010**, *21*, 222. (l) Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; Broadwater, S. J.; McQuade, D. T. *Angew. Chem. Int. Ed.* **2009**, *48*, 8547. (m) Seeberger, P. H. *Nat. Chem.* **2009**, *1*, 258. (n) Bogdan, A.; McQuade, D. T. *Beilstein J. Org. Chem.* (o) Rolland, J.; Cambeiro, X. C.; Rodríguez-Esrich, C.; Pericàs, M. A. *Beilstein J. Org. Chem.* **2009**, *5*, 56. (p) Hessel, V. *Chem. Eng. Technol.* **2009**, *32*, 1655.
- (12) The use of a standard T or Y union gave rise to problems of back-mixing and build-up of blockages in the flow channel.
- (13) Browne, D. L.; Deadman, B. J.; Ashe, R.; Baxendale, I. R.; Ley, S. V. *Org. Process Res. Dev.* **2011**, *15*, 693.
- (14) Sedelmeier, J.; Ley, S. V.; Baxendale, I. R.; Baumann, M. *Org. Lett.* **2010**, *12*, 3618.
- (15) (a) Tse, M. K.; Bhor, S.; Klawonn, M.; Anikumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem. Eur. J.* **2006**, *12*, 1855. (b) Bhattacharya, S.; Snehaltha, K.; Kumar, V. P. *J. Org. Chem.* **2003**, *68*, 2741.
- (16) Clayden, J. *Organic chemistry*; Oxford University Press: Oxford, **2001**, 276–296.
- (17) Commercially available from TCI Europe: Vilsmeier reagent *N*-(chloromethylene)-*N*-methylmethanaminium chloride [CAS Reg. No. 3724-43-4].
- (18) The Vapourtec R2+/R4 flow system used in this study is commercially available from Vapourtec; Web site: <http://www.vapourtec.co.uk>.
- (19) Quadrapure-DMA. Available from Johnson Matthey, see: <http://www.scavengingtechnologies.com/site.asp?id=1297&pageid=1299>.
- (20) (a) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122. (b) Wang, H.; Wang, H.; Liu, P.; Yang, H.; Xiao, J.; Can Li, C. *J. Mol. Catal. A: Chem.* **2008**, *285*, 128.
- (21) For the chelation properties of dimeric macrocycles, see: (a) Mammoliti, O.; Allasia, S.; Dixon, S.; Kilburn, J. D. *Tetrahedron* **2009**, *65*, 2184. (b) Bradshaw, J. S.; Colter, M. L.; Nakatsuji, Y.; Spencer, N. O.; Brown, M. F.; Izatt, R. M.; Arena, G.; Tse, P.-K.; Wilson, B. E.; Lamb, J. D.; Dalley, N. K. *J. Org. Chem.* **1985**, *50*, 4865.
- (22) Baumann, M.; Baxendale, I. R.; Ley, S. V. *Synlett* **2008**, 2111.
- (23) Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. *Tetrahedron* **2009**, *65*, 6611.
- (24) For other examples of azide chemistry in flow from our group, see: (a) Smith, C. J.; Smith, C. D.; Nikbin, N.; Ley, S. V.; Baxendale, I. R. *Org. Biomol. Chem.* **2011**, *9*, 1927. (b) Smith, C. J.; Nikbin, N.; Ley, S. V.; Lange, H.; Baxendale, I. R. *Org. Biomol. Chem.* **2011**, *9*, 1938. (c) Smith, C. D.; Baxendale, I. R.; Lanners, S.; Hayward, J. J.; Smith, S. C.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 1559. (d) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D. *Org. Biomol. Chem.* **2008**, *6*, 1587. (e) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D.; Tierney, J. P. *Org. Biomol. Chem.* **2008**, *6*, 1577. (f) Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, 2566.
- (25) The H-Cube flow hydrogenator is commercially available from ThalesNano, see: <http://www.thalesnano.com>. See also: Bryan, M. C.; Wernick, D.; Hein, C. D.; Petersen, J. V.; Eschelbach, J. W.; Doherty, E. M. *Beilstein J. Org. Chem.* **2011**, *7*, 1141.
- (26) Horvath, G.; Rusa, C.; Montos, Z.; Gerencser, J.; Huszthy, P. *Synth. Commun.* **1999**, *29*, 3719.
- (27) Preston, A. J.; Gallucci, J. C.; Parquette, J. R. *Chem. Commun.* **2005**, 3280.
- (28) Bradshaw, J. S.; Huszthy, P.; Wang, T.-M.; Zhu, C.-Y.; Nazarenko, A. Z.; Izatt, R. M. *Supramol. Chem.* **1993**, *1*, 267.
- (29) Chessa, G.; Canovese, L.; Visentin, F.; Santo, C.; Seraglia, R. *Tetrahedron* **2005**, *61*, 1755.