Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2022, **20**, 6384

Catalytic, asymmetric azidations at carbonyls: achiral and *meso*-anhydride desymmetrisation affords enantioenriched γ-lactams†

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Received 2nd June 2022,
Accepted 18th July 2022

DOI: 10.1039/d2ob01040b

rsc.li/obc

An unprecedented organocatalytic process involving the asymmetric addition of azide to *meso*-anhydrides has been developed, promoted by novel sulfamide-substituted *Cinchona* alkaloid-based catalysts. Readily available glutaric anhydrides can be smoothly converted to enantioenriched hemi-acyl azides and from there to either γ-amino acids or γ-lactams.

Since the first preparation of phenyl azide by Griess in 1864,[1] the reactivity of organic azides (R-N_3) as [1,3]-dipoles, electrophiles, nucleophiles and radical acceptors have been widely exploited.[2,3] In addition, the capacity of azide-containing compounds to liberate molecular nitrogen facilitates an array of reaction pathways with the capacity to yield complex products from relatively-simple precursors.

In nucleophilic substitution reactions, azide can either be a useful N1 synthon for the introduction of functional groups (primary amine, amide) or used to install a particular structural motif (1,2,3-triazoles, tetrazoles). Although the high reactivity of azide can be beneficial – with a Mayr nucleophilicity parameter[4] exceeding that of some α-effect nucleophiles – the utilisation of organic azides in a catalytic asymmetric context is challenging. Both organometallic and organocatalytic approaches to asymmetric azidations have been explored.[5] Jacobsen and co-workers[6] used the privileged 'salen' ligand in the Cr-catalysed silylazidation of *meso*-epoxides with trimethylsilyl azide ($TMSN_3$, Fig. 1A) – later expanded to the kinetic resolution of epoxides,[7] the desymmetrisation of *meso*-aziridines[8] and the first asymmetric β-azidation of α,β-unsaturated imides with excess hydrazoic acid (HN_3).[9] As the intrinsic properties of HN_3 (toxic, volatile and explosive) prevent its practical use,[10] the pursuit of organocatalytic, asymmetric strategies to obviate the direct use of HN_3 has been of interest.[11–16]

The first organocatalytic, asymmetric β-azidation, reported by Miller and co-workers in 2000,[11] relied on safer generation of HN_3 *in situ* through the use of $TMSN_3$ and an organic acid additive (Fig. 1B). Asymmetric β-azidations were further developed thereafter by other research groups,[16a] culminating recently in the first organic acid-free β-azidation of α,β-unsaturated ketones.[16b] Recently, we reported the first organocatalytic reactions between cyclic anhydrides and $TMSN_3$, which allowed controlled access to a variety of pharmaceutically-active γ-amino acid and γ-lactam derivatives from anhydrides.[17]

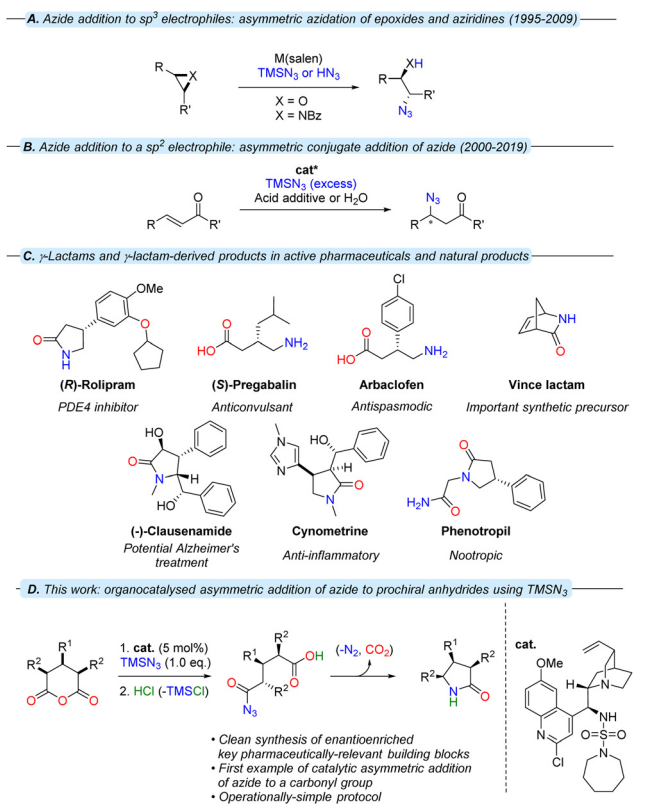

Fig. 1 Asymmetric nucleophilic azidations; the prevalence of chiral γ-lactams in the synthesis of biologically-active compounds and a summary of this work.

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2ob01040b

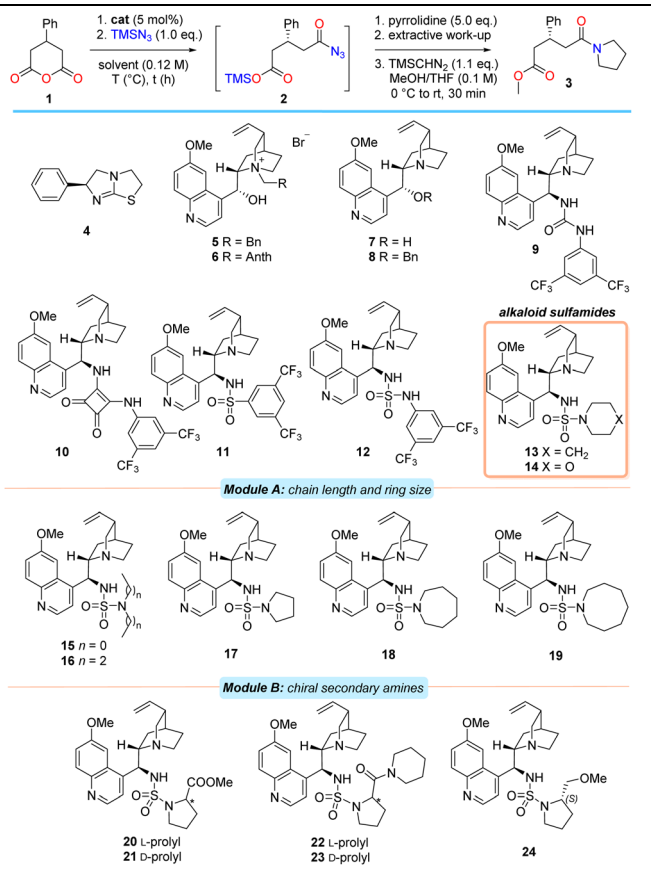
This bioactive class of compounds that contains the γ-aminobutyric acid (GABA) motif are potent central nervous system-active agents (Fig. 1C),[18–24] and are present in a wide variety of natural products and numerous APIs. The advantage of this reaction cascade lies in rapid access to valuable scaffolds from uncomplicated substrates in a robust manner. In a similar fashion, enantioselective desymmetrisations of achiral or *meso*-anhydrides *via* existing organocatalytic methodologies (alcoholysis, thiolysis, cycloaddition, *inter alia*) can offer a powerful strategy to access molecular complexity from inexpensive, accessible precursors.[25–28]

Though great advances have been made in the catalytic enantioselective azidations;[29,30] an analogous catalytic, asymmetric transformation involving the reaction of azide at a carbonyl centre has not yet been reported. In this report, we have expanded upon a study involving a racemic variant of this process[17] and demonstrate the first examples of the enantioselective desymmetrisation of prochiral cyclic anhydrides *via* azidolysis (Fig. 1D).

At the outset, **1** was chosen as the model substrate. After considerable experimentation (see ESI†), suitable reaction conditions were developed in order to facilitate an initial catalyst screen (Table 1). As in the racemic process,[17] tertiary amines were effective promoters of the silylazidation of **1** with equimolar $TMSN_3$ to produce the intermediate acyl azide **2** in $CHCl_3$ at −50 °C.[31] In order to separate any confounding factors that could alter the enantioselectivity in the desymmetrisation step, the intermediate acyl azide **2** was efficiently quenched with excess pyrrolidine to provide amido ester **3** after desilylation, extraction of the acid and methylation with $TMSCHN_2$.

Commercial (*S*)-benzotetramisole[32] (**4**), natural configuration *Cinchona* alkaloid-based phase-transfer agents **5–6** and bifunctional free-base alkaloid catalysts **7–8** were found to promote the reaction efficiently but with an almost complete absence of enantiocontrol (entries 1–6). Examination of the 9-*epi*-quinine-derived urea, -squaramide and -sulfonamide catalysts **9–11** with superior hydrogen bond donor (HBD) units provided amido acid **3** in only modest ee and curiously, with a preference for the formation of the opposite enantiomer in the case of squaramide **10** (entries 7–9).[16] Incorporation of the sulfamide motif as the HBD into the *Cinchona* alkaloid scaffold (*i.e.*, alkaloid **12**) proved advantageous and provided **3** in marginally improved ee (entry 10). Further modest improvement in enantioselectivity was observed after exchange of the aniline moiety for an aliphatic, secondary amine (*i.e.*, catalyst **13**, entry 11). This was somewhat surprising in view of both literature precedent[33] and the loss of the catalyst's ability to participate in efficient bifurcated hydrogen bond donation. However, substitution of the piperidine unit for morpholine did little to influence the enantioselectivity of the process, suggesting that the electronic characteristics at the secondary amine substituent of the sulfamide (*i.e.*, **14**) are unimportant (entry 12). After establishing the class of HBD most suitable, further modifications of both the tertiary sulfamide unit and alkaloid core were undertaken.

Table 1 Initial catalyst screen



Entry	Catalyst	*t* (h)	Conversion[a] (azide **2**, %)	ee[b] (%)
1	—	24	<5	—
2	**4**	16	67	−3
3	**5**	16	99	*rac*
4	**6**	16	99	16
5	**7**	16	90	8
6	**8**	16	90	*rac*
7	**9**	16	81	14
8	**10**	16	86	−28
9	**11**	16	72	24
10	**12**	16	72	34
11	**13**	16	90	55
12	**14**	16	90	54
13	**15**	24	90	47
14	**16**	18	89	40
15	**17**	18	90	48
16	**18**	18	99	58
17	**19**	18	99	40
18	**20**	24	80	56
19	**21**	18	90	33
20	**22**	24	99	29
21	**23**	24	90	23
22	**24**	18	99	57

[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Determined by CSP-UHPLC, see ESI.†

A modular catalyst design strategy was adopted (Table 1). Module A examined the effect of either incorporating acyclic amines or modifying amine ring size on enantioselectivity. Module B involved an additional peripheral chirality element.

Module C represents the later combination of the optimal structural features from modules A and B and the finalisation of catalyst development (Table 2).

Alteration of the secondary amine to either an acyclic amine or a reduction in ring size from 6 to 5 resulted in poorer enantioselectivities relative to **13** (*i.e.*, **15–17**, entries 13–15). While increasing the heterocycle ring size from 6 to 7 atoms was beneficial (*i.e.*, catalyst **18**, entry 16), further expansion to an azocane system resulted in substantially poorer ee (*i.e.*, **19**, entry 17).

Evaluation of **20** and **21**, prepared from proline methyl ester antipodes, revealed stark differences between the diastereomers with respect to reactivity and selectivity. In the case where the stereochemistry on the prolyl unit matched that at C9 of the alkaloid core (*i.e.*, 'matched' centres), the reaction required marginally extended reaction times, but provided the product in significantly higher ee compared to the 'mismatched' case (entries 18 and 19). The same (albeit less pronounced) effect was also observed in the case of the diastereomeric prolinamide-derived sulfamides **22** and **23** (entries 20 and 21). Separately, evaluation of the 'matched' case of methyl ether **24** provided the amido acid **3** in a slightly more selective process than obtained using **20** (entry 22).

Examination of model systems (see ESI†) based on fragments of catalyst **13** revealed that the quinoline endocyclic nitrogen atom (located far from the catalyst's stereochemical information) could independently participate in the activation of $TMSN_3$, thereby competing with catalysis at the quinuclidine moiety. This could be obviated in the model system through the installation of a chlorine atom at C2. In a similar vein, methoxy-quinolines were expected to be more active catalysts than quinoline itself.

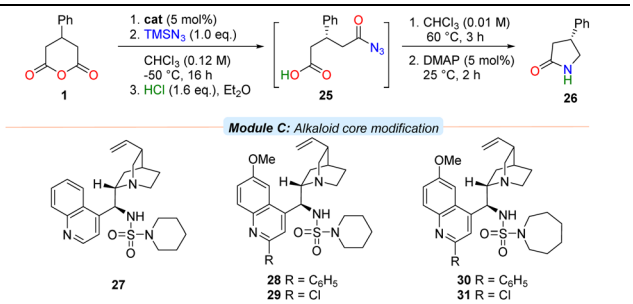
To test the hypothesis that the quinoline moiety negatively contributes to enantioselective reaction in bifunctional systems, the cinchonidine-derived piperidine sulfamide **27**, along with C2′-substituted analogues of **13** and **18** (*i.e.*, **28–29** and **30–31** respectively) were prepared and evaluated (Table 2). Anhydride **1** was subjected to the azidolysis conditions promoted by core-modified sulfamide catalysts **27–31**, and the intermediate silyl ester **2** then cleaved with anhydrous HCl to isolate the acyl azide **25**. Facile Curtius rearrangement and subsequent lactamisation provided the more potent enantiomer of (*R*)-phenibut lactam (**26**).

Gratifyingly, the cinchonidine-derived sulfamide **27** outperformed the analogous quinine-derived catalyst **13** (entry 1). A further increase in selectivity was observed on substitution of the C2′ position of the quinoline unit of the catalyst to incorporate either a phenyl group or a chlorine atom (entries 2 and 3). A consistent trend in enantioselectivity was observed upon examination of both the C2′-phenyl azepane sulfamide **30** (entry 4), and its C2′-chloro derivative **31**; the latter proved a marginally more selective promoter of the desymmetrisation process (entry 5, 70% ee).

With conditions in hand for the enantioselective azidolysis, a range of cyclic anhydrides **32** were subjected to the azidative desymmetrisation procedure to provide acyl azides **33**, promoted by sulfamide **31**. These intermediates could be telescoped into Curtius rearrangement and ring-contractive lactamisation steps (*vide supra*) to provide enantioenriched γ-lactams **34** in one-pot (Table 3).

Both electron-donating and electron-withdrawing substituents on the aromatic ring were well-tolerated; providing access to β-aryl-γ-lactams **26** and **35–40** in uniformly high yields and good ee, most notably arbaclofen lactam (**36**) and the PDE4 inhibitor rolipram (**37**). Regarding aliphatic substitution patterns: while methyl and isopropyl substituents were compatible when placed at the 3-position (*i.e.*, lactams **42** and **43**), the presence of larger silyl ether and isobutyl groups led to a small

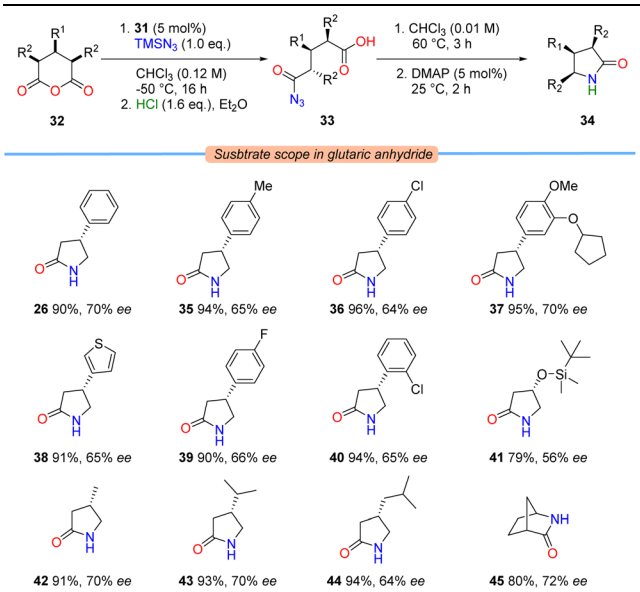
Table 2 Further catalyst development and optimisation



Entry	Catalyst	Conversion[a] (azide **25**, %)	Yield[b] (%)	ee[c] (%)
1	**27**	91	81	61
2	**28**	>99	90	64
3	**29**	>99	90	66
4	**30**	>99	90	65
5	**31**	>99	91	70

[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Isolated yield. [c] Determined by CSP-UHPLC, see ESI.†

Table 3 Substrate scope



loss in enantioselectivity, although reactivity in the subsequent lactamisation process was maintained (*i.e.*, lactam **41** and pregabalin lactam (**44**), respectively). Interestingly, comparable enantioselectivities were obtained when conformationally-locked norcamphoric anhydride was examined, providing access to the Vince lactam derivative **45**.

As is the case in the analogous sulfonamides,[34] *Cinchona* alkaloid-derived sulfamides are found to exist as a pair of two rotational isomers (rotamers) in a *ca.* 2 : 1 ratio at room temperature on the ^{1}H NMR spectroscopic timescale, which interconvert by rotation about the C9–C4′ bond axis (Fig. 2). Although it could be postulated that one rotamer could be contributing negatively to stereoselection; variable temperature-NMR spectroscopy of piperidine sulfamide **13** revealed temperature-dependent convergence of rotamer populations, with the major rotamer at room temperature (*i.e.*, rotamer A) present almost exclusively at low temperature when observed *in situ* during catalysis (see ESI†).

Although the isolated catalyst does not display this temperature-dependent behaviour as the free base form, the monoprotic acetate salt of **13** exhibited similar behaviour to that observed *in situ* (Fig. 3). Attempts to isolate the analogous hydrogen azide salt by several methods were unsuccessful. This can be adequately rationalised in the context of similar studies;[35] poor room temperature association has been observed in other amine complexes with HN_3, resulting in its dissociation on irreversible loss of $HN_{3(g)}$ by evaporation. However, as the pK_a (AcOH) ≅ pK_a (HN_3) at 25 °C, and given the similarities regarding the temperature-dependent behaviour (with respect to rotamer ratios and ^{1}H NMR spectroscopic chemical shifts) displayed by the catalyst species *in situ* and the isolated AcOH salt of **13** were found, the evidence suggests that the catalytically-active species in solution is the structurally-related HN_3 complex with **13**.

Furthermore, it can be proposed that the free base form of the model sulfamide catalyst **13** is first converted to the active hydrazoate complex **13a** by trapping of adventitious HN_3, which is present in small amounts in commercial samples of $TMSN_3$ (Fig. 4). This nucleophilic species then facilitates transfer of azide to the anhydride *via* a stereodetermining addition–elimination reaction at the prochiral carbonyl centre of **1**. The resulting carboxylate **13b** is then silylated by $TMSN_3$ to liberate the product **25** and regenerate the active catalyst **13a**.

A DFT conformational analysis exploring the low-energy chemical space associated with **13** was performed. Two predominant conformers differing by the rotation of the C9–C4′ bond were identified (Fig. 5). The Boltzmann population ratio (66 : 34) predicted by the calculation in $CHCl_3$ is in good agreement with those obtained from ^{1}H NMR spectroscopic analysis. In addition, a repeat of the calculations at 223 K yielded a very similar population ratio of 61 : 39.

A characterisation of the different intramolecular non-covalent interactions was also performed by means of the quantum theory of atoms in molecules (QTAIM) methodology (Fig. 5). An intramolecular hydrogen-bond between the quinuclidine N-atom and the sulfamide unit is a discernible rigidifying feature of both conformations. The other interactions identified appear to be weak in nature.

As is the case in the analogous sulfonamides,[34] the *Cinchona* alkaloid-derived sulfamide catalysts exist as a pair of rotamers in a *ca.* 2 : 1 ratio at 25 °C on the ^{1}H NMR spectro-

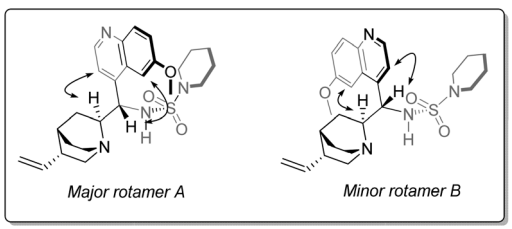


Fig. 2 The two rotamers associated with **13**, showing key NOE interactions involved in corroborating *in silico*-derived data.

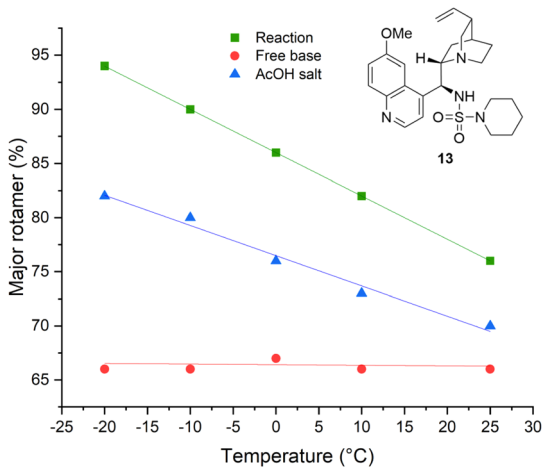


Fig. 3 Temperature-dependent populations of rotameric states of catalyst **13** as the free base, the acetic acid salt and the catalyst observed *in situ* by variable-temperature ^{1}H NMR spectroscopy.

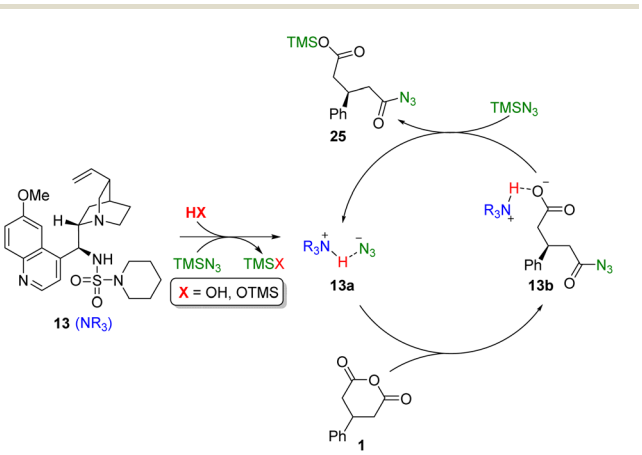


Fig. 4 Proposed catalytic cycle for the desymmetrisation of cyclic anhydrides with equimolar $TMSN_3$ promoted by *Cinchona* alkaloid sulfamide organocatalysts.

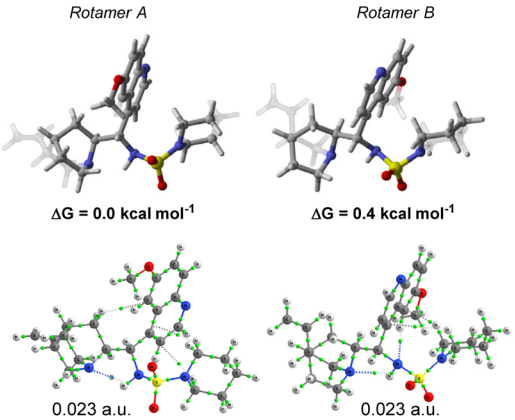
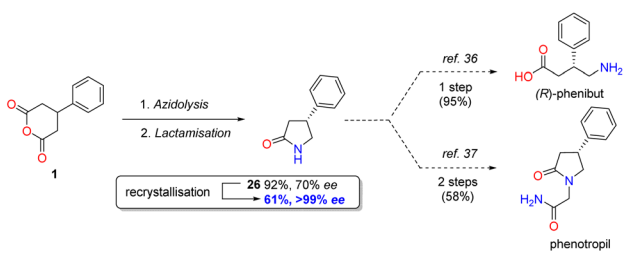


Fig. 5 DFT calculations: structures, relative stabilities and QTAIM analysis of the major rotamers of catalyst **13**.

scopic timescale, which interconvert by rotation about the C9–C4′ bond axis. Variable temperature-NMR spectroscopy revealed a convergence of rotamer populations, with the major rotamer at room temperature present almost exclusively at low temperature when observed *in situ* during catalysis (see ESI†). Although the isolated catalyst does not display this temperature-dependent behaviour as the free base form, the AcOH salt of **13** exhibited similar behaviour to that observed *in situ.* For spectroscopic evidence supporting a hydrazoic acid salt of **13** catalyst resting state, DFT calculations on the catalyst rotamers and a proposed reaction mechanism, see the ESI.†

In a demonstration of the potential synthetic utility of the desymmetrisation, lactam **26** could be prepared on a larger scale under the developed conditions and then converted to enantiopure form in 61% overall yield in a single recrystallisation, which can be transformed to either the anxiolytic phenibut[35] or the nootropic phenotropil[36] (Scheme 1).

In summary, the first catalytic asymmetric addition of azide to a carbonyl electrophile has been developed. In the presence of novel bifunctional *Cinchona* alkaloid-derived sulfamide catalysts, prochiral glutaric anhydride derivatives undergo desymmetrisation *via* addition of $TMSN_3$. The resulting enantioenriched acyl azide derivatives can be readily converted to either γ-amino acid derivatives or a wide range of γ-lactams of considerable medicinal/pharmaceutical interest. Further studies on the scope, utility and mechanism are underway.



Scheme 1 Recrystallisation of (*R*)-phenibut lactam **26**.

Experimental section

NMR spectral data were obtained from a Bruker DPX (400 MHz) or Bruker Avance II (600 MHz) using $CDCl_3$, DMSO-d_6 or D_2O with chemical shift data referenced relative to residual protic resonances of the deuterated solvent, (δ_H = 7.26, 2.50, and 4.79 ppm respectively). ^{13}C (100.9 or 150.9 MHz) spectra were recorded on the same instruments with total proton decoupling. Additional 2D spectral acquisitions (HSQC-ME, HMBC, TOCSY, NOESY/EXSY) were obtained in order to assist in the assignment of resonances where required. Conventional abbreviations for describing peak morphologies in NMR spectroscopic analysis are observed (*i.e.* s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets, *etc.*). All coupling constants (J) are reported in hertz (Hz). Infrared spectra were obtained as neat solids or liquids unless otherwise stated on a Perkin-Elmer Spectrum100 FT-IR instrument fitted with an attenuated-total reflectance (ATR) accessory. Abbreviations used for descriptions of transmission band intensities are as follows: w, weak; m, medium; s, strong; vs, very strong; br., broad.

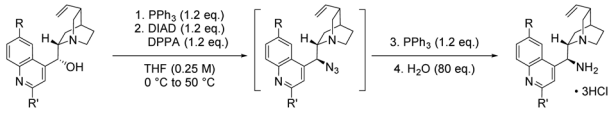
Thin-layer chromatography (TLC) analyses were performed using Merck-F_{254} silica gel plates and were visualised under ultraviolet (UV) irradiation, potassium permanganate, ninhydrin, ammonium molybdate or bromocresol green staining methods. Column and flash chromatography was performed using Sigma-Aldrich 60 Å, 230–400 mesh particle silica gel. Melting point data were recorded on a Griffin Melting Point Apparatus; readings were obtained in triplicate and are reported uncorrected. High-resolution mass spectrometry experiments were carried out in the Mass Spectrometry Unit, School of Chemistry, TCD.

Anhydrous $CHCl_3$ (amylene-stabilised) and HCl (as 2 M solution in Et_2O) were obtained from Sigma-Aldrich Ireland and transferred to reaction vessels using Schlenk techniques. Hünig's base on polystyrene (DIPEA@PS, product ID: 38343) was purchased from Sigma-Aldrich Ireland and all other chemicals were of regent-grade, obtained from commercial suppliers and used without further purification unless otherwise noted.

Safety considerations

While we have not experienced any issues surrounding the use of $TMSN_3$ in these studies, it is imperative that the appropriate safety precautions are taken, especially when working on reaction scales >1 mmol. In the following preparations, $TMSN_3$ has the potential to liberate toxic and explosive HN_3 on contact with H_2O or in acidic media. Any volatiles removed should be carried out in a well-ventilated fume hood and reactions performed with a blast shield in large-scale preparations. It is advised that all azide-containing waste should be quenched cautiously, and in an appropriate manner.[37]

General procedure A: preparation of 9-*epi*-9-amino *Cinchona* alkaloids from native configuration alkaloids

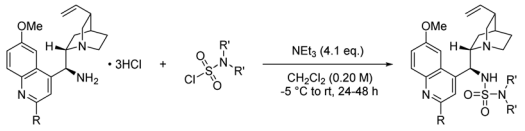


To an oven-dried 250 mL round bottomed flask containing a stirrer bar, *Cinchona* alkaloid derivative (18.50 mmol) and PPh_3 (5.82 g, 22.19 mmol) under Ar atmosphere, anhydrous THF (125 mL, 0.15 M) was added *via* syringe. The solution was cooled to 0 °C before DIAD (4.40 mL, 22.19 mmol) and DPPA (4.77 mL, 22.19 mmol), were added sequentially dropwise *via* syringe. The resulting yellow solution was warmed to room temperature and stirred at 20 °C for 24 h. The flask was fitted with a reflux condenser and the solution stirred at 50 °C for a further 2 h. PPh_3 (5.82 g, 22.19 mmol) was added portionwise with stirring and the solution heated at 50 °C for 2 h or until nitrogen evolution had ceased. H_2O (26.4 mL, 0.7 M) was added and the solution stirred at room temperature for 16 h. The resulting mixture was concentrated as far as possible *in vacuo* and the residue partitioned between 2 M HCl and CH_2Cl_2 (100 mL each). The aqueous phase was removed and the organic layer extracted with 2 M HCl (3 × 50 mL). The combined aqueous extracts were washed with CH_2Cl_2 (5 × 50 mL) and concentrated as far as possible. The viscous residue was stirred in EtOH and the resulting precipitate filtered and dried *in vacuo*. The precipitate can be purified by reprecipitation from boiling MeOH using EtOAc as antisolvent to give the alkaloid hydrochloride as a powder.

General procedure B: sulfamoyl chloride synthesis

SO_2Cl_2 (1.5 eq.) in anhydrous CH_2Cl_2 (1.00 M) was cooled to −20 °C under Ar atmosphere before a solution of NEt_3 (1.5 eq.) and the appropriate secondary amine (1.0 eq.) in anhydrous CH_2Cl_2 (2 M with respect to amine) was added dropwise *via* syringe (>30 min, exothermic). The resulting solution was stirred at −20 °C for 30 min before warming to room temperature over 1.5 h. The resulting yellow mixture was slowly poured into ice-H_2O using CH_2Cl_2 to effect the transfer. The biphasic mixture was partitioned and the organic layer washed with H_2O and brine before being dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in the minimum CH_2Cl_2 and passed through a short plug of silica, eluted with CH_2Cl_2 to provide the analytically-pure sulfamoyl chloride product after drying *in vacuo*.

General procedure C: *Cinchona* alkaloid sulfamide preparation from sulfamoyl chlorides



To a 25 mL round bottomed flask containing a magnetic stirrer bar and the appropriate alkaloid hydrochloride salt (1.00 mmol) was added anhydrous CH_2Cl_2 (5.00 mL, 0.20 M). To the resulting suspension, NEt_3 (4.20 mmol) was added dropwise at −5 °C and the resulting suspension stirred vigorously for 30 min before sulfamoyl chloride (1.20 mmol) was added dropwise *via* syringe. The resulting solution was stirred at room temperature for 24–48 h until consumption of the sulfamoyl chloride was observed by TLC analysis. The solution was diluted with CH_2Cl_2 (25 mL) and washed sequentially with half-saturated $NaHCO_{3(aq.)}$, H_2O and brine (2 × 10 mL each). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil which was purified by flash chromatography as appropriate.

Azepane-1-sulfonyl chloride

Prepared according to general procedure B using azepane (376 μL, 3.33 mmol) and purified by passing through a short plug of silica, eluting with CH_2Cl_2 to give the product as a colourless oil (394.4 mg, 60%). TLC (CH_2Cl_2, ninhydrin): R_f = 0.83. δ_H (400 MHz, $CDCl_3$): 3.46–3.53 (4H, m, H-1), 1.80–1.86 (4H, m, H-2) and 1.63–1.69 (4H, m, H-3) ppm. δ_C (101 MHz, $CDCl_3$): 50.1 (C-1), 27.5 (C-3) and 27.0 (C-2) ppm. ν_{max} (neat)/cm^{-1}: 2932 (m), 2860 (m), 1462 (w), 1386 (S═O, s), 1367 (s), 1172 (s), 1144 (m), 1042 (m), 888 (m) and 693 (s) cm^{-1}.

2′-Chloro-9-amino-(9-deoxy)-*epi*-quininium trihydrochloride (precursor to 31)

Prepared according to general procedure A using C2′-chloroquinine[38] (1.39 g, 3.88 mmol) and precipitated after co-evaporation of residual H_2O with EtOH to give the product as a bright yellow powder (1.09 g, 80%), m.p. 198–204 °C (decomp.); $[\alpha]_D^{24}$ = +2.5 (*c* = 0.20, H_2O). ^1H, ^{13}C NMR and EXSY spectroscopic analyses in DMSO-d_6 revealed rotameric species in the ratio 93 : 7 at 25 °C. ^{13}C resonances are clearly observable for the major rotamer only. Major rotamer: δ_H (400 MHz, DMSO-d_6): 11.12, 9.48 (3H, br s), 8.15 (1H, s), 7.97 (1H, d, *J* 9.2), 7.83 (1H, d, *J* 1.9), 7.58 (1H, dd, *J* 9.2, 1.9), 5.87–5.96 (1H, m), 5.82 (1H, d, *J* 10.4), 5.26 (1H, d, *J* 17.3), 5.16 (1H, d, *J* 10.5), 4.61–4.68 (1H, app. q), 4.09–4.18 (1H, m), 4.01 (3H, s), 3.70–3.76 (1H, m), 3.28–3.38 (2H, m), 2.76 (1H, br s), 1.80–1.92 (3H, m), 1.57–1.63 (1H, m) and 0.87 (1H, dd, *J* 13.3, 8.4) ppm. δ_C (151 MHz, DMSO-d_6): 158.7, 146.9, 143.6, 141.6, 138.3, 130.4, 126.7, 123.7, 122.0, 116.7, 103.0, 58.7, 56.4, 52.1, 47.7, 41.6, 35.9, 25.5, 23.6 and 23.4 ppm. Minor rotamer: δ_H (400 MHz, DMSO-d_6): 11.12, 9.48 (3H, br s), 8.11 (1H, s), 7.98 (1H, d, *J* 9.0), 7.54 (1H, dd, *J* 9.0, 2.0), 7.49 (1H, d, *J* 2.0), 5.77–5.86 (1H, m), 5.41 (1H, d, *J* 17.5), 5.22–5.25 (1H, m, *J* 10.4), 5.16 (1H, d, *J* 10.5), 4.96 (1H, app. q.), 4.06 (3H, s), 3.93–3.95 (1H, m), 3.70–3.76 (1H, m), 3.28–3.38 (2H, m), 2.76 (1H, br s), 1.99 (1H, br s), 1.80–1.92 (2H, m), 1.21–1.29 (1H, m) and 1.06–1.15 (1H, dd, *J* 13.3, 8.4) ppm. ν_{max} (neat)/cm^{-1}: 3478 (m, NH st.), 2560 (w), 1617 (s), 1510 (m), 1460 (m), 1395 (m), 1320 (w), 1279 (m), 1235 (s), 1140 (s), 1019 (m), 920 (s), 831 (s), 774 (s), 728 (w) and 681 (s) cm^{-1}. HRMS ($APCI^+$) *m*/*z*: Found: 358.1685 ($[M + H]^+$ $C_{20}H_{25}ClN_3O$; requires 358.1680).

C2′-Chloroquinine azepane sulfamide 31

Prepared according to general procedure C using 2′-chloro-9-amino-(9-deoxy)-*epi*-quininium trihydrochloride (573 mg, 1.33 mmol) and azepane-1-sulfonyl chloride (291.3 mg, 1.47 mmol), purified by flash chromatography (7 : 3 CH_2Cl_2/EtOAc) to give the title product as a white, crystalline powder (271 mg, 39%), m.p. 58–60 °C. TLC (98 : 2 CH_2Cl_2/MeOH): R_f = 0.44. $[\alpha]_D^{22}$ = +2.1 (*c* = 0.13, $CHCl_3$). ^1H, ^{13}C NMR and EXSY spectroscopic analyses in $CDCl_3$ revealed rotameric species in the ratio 70 : 30 at 25 °C. Major rotamer: δ_H (600 MHz, $CDCl_3$): 7.95 (1H, d, *J* 9.2), 7.56 (1H, s), 7.48 (1H, d, *J* 2.7), 7.42 (1H, dd, *J* 9.2, 2.7), 6.12 (1H, br. s), 5.68–5.74 (1H, m), 5.03 (1H), 4.94–4.99 (2H, m), 3.98 (3H, s), 3.19–3.26 (2H, m), 2.75–2.83 (2H, m), 2.55–2.72 (5H, m), 2.28–2.33 (1H, m), 1.57–1.68 (3H, m), 1.37–1.41 (1H, m), 1.27–1.38 (6H, m), 0.86–0.92 (1H, m) ppm. δ_C (151 MHz, $CDCl_3$): 158.4, 148.5, 148.0, 144.1, 141.0, 130.9, 127.5, 122.7, 121.2, 114.9, 101.5, 61.3, 55.8, 55.75, 53.0, 48.2, 40.4, 39.4, 28.6, 27.9, 27.4, 26.7, 25.2 ppm. Minor rotamer: δ_H (600 MHz, $CDCl_3$): 7.96 (1H, d, *J* 9.2), 7.87 (1H, d, *J* 2.8), 7.40 (1H, dd, *J* 9.2, 2.8), 7.30 (1H, s), 6.29 (1H, br. s), 5.60–5.66 (1H, m), 4.89–4.95 (2H, m), 4.34 (1H, d, *J* 10.9), 3.93 (3H, s), 3.35–3.40 (1H, m), 3.19–3.25 (1H, m), 3.05–3.12 (1H, m), 2.72–2.76 (1H, m), 2.55–2.72 (5H, m), 2.28–2.33 (1H, m), 1.73–1.76 (1H, m), 1.58–1.61 (2H, m), 1.27–1.38 (7H, m) and 0.94–0.99 (1H, m) ppm. δ_C (151 MHz, $CDCl_3$): 157.3, 147.5, 145.1, 144.7, 141.0, 131.0, 125.9, 124.0, 122.5, 114.8, 104.0, 62.6, 56.0, 55.7, 48.3, 40.0, 39.6, 28.6, 27.6, 27.4, 26.6, 26.5 ppm. ν_{max} (neat)/cm^{-1}: 3189 (w, br, N–H st.), 3073 (w, N–H st.), 2926 (m, C–H st.), 2862 (w), 1620 (s), 1581 (m), 1505 (s), 1455 (s), 1394 (m), 1234 (m), 1228 (m), 1143 (vs, br), 1101 (w), 1044 (w), 1030 (w), 987 (m), 941 (s), 880 (m), 828 (m), 768 (w), 692 (vs), 669 (m), 617 (w) and 576 (s) cm^{-1}. HRMS (APCI$^+$) *m*/*z*: Found: 519.2195 ($[M + H]^+$ $C_{26}H_{36}ClN_4O_3S$; requires 519.2192).

General procedure D: organocatalytic, enantioselective synthesis of chiral γ-lactams from prochiral anhydrides

To a 5 mL round bottomed flask containing a magnetic stirrer bar, sulfamide **31** (6.4 mg, 0.012 mmol) and achiral or *meso*-anhydride **32** (0.246 mmol) under Ar atmosphere, anhydrous $CHCl_3$ (2.00 mL, 0.12 M) was added *via* syringe before the solution was cooled to −50 °C for 30 min. $TMSN_3$ (32.4 μL, 0.246 mmol) was then added in one portion and the resulting solution stirred at −50 °C for 16 h. HCl in Et_2O (200 μL, 0.400 mmol) was added in one portion and the resulting solution stirred for 15 min at −50 °C. The solution was filtered, using anhydrous $CHCl_3$ (1 mL) to effect the transfer and volatiles removed expediently *in vacuo* to give the analytically-pure acyl azide **33**. The solid was placed under Ar atmosphere and anhydrous $CHCl_3$ (25.0 mL, 0.01 M) added *via* syringe. The resulting solution was heated gently (vigorous gas evolution observed at *ca.* 40 °C) to 60 °C for 3 h under Ar atmosphere. The solution of isocyanate was then cooled to 25 °C before DMAP (1.5 mg, 0.012 mmol) was added in one portion and the resulting solution stirred vigorously at 25 °C for 2 h. The solution was concentrated *in vacuo* and the residue purified by flash column chromatography to give the γ-lactam product.

(*R*)-Phenibut lactam (26). Prepared according to general procedure D using anhydride **1** (46.8 mg, 0.246 mmol) and purified by flash column chromatography (98 : 2 CH_2Cl_2/MeOH) to give the product as a white powder (35.7 mg, 90%, 69% ee), m.p. 75–76 °C (lit.,[39] m.p. 73–75 °C). TLC (CH_2Cl_2/MeOH, 98 : 2): R_f = 0.42. A larger scale preparation using anhydride **1** (190.2 mg, 1.00 mmol) afforded the title product by the same method (148.3 mg, 92%, 70% ee) which was recrystallised from hot Hex/EtOAc to provide large, colourless plate crystals (100.6 mg, 62%, >99% ee) with $[\alpha]_D^{22}$ = −39.6 (*c* = 0.91, $CHCl_3$), (lit.,[40] $[\alpha]_D^{25}$ = −39.4 (*c* = 0.90, $CHCl_3$) for 99% ee of the (*R*)-enantiomer). Spectroscopic data correlates well to that in the literature.[7] CSP-SFC analysis: step 3 was employed with UV detection at 254 nm; R_T: 3.45 min (minor enantiomer) and 3.56 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 7.33–7.36 (2H, m), 7.25–7.28 (3H, m), 6.09 (1H, br s), 3.79 (1H, dd, *J* 9.4, 8.3), 3.71 (1H, app. quin.), 3.43 (1H, dd, *J* 9.4, 7.3), 2.75 (1H, dd, *J* 17.0, 9.0) and 2.52 (1H, dd, *J* 17.0, 8.9) ppm. δ_C (100 MHz, $CDCl_3$): 177.7, 142.1, 129.1, 127.4, 126.9, 49.7, 40.5 and 38.1 ppm. HRMS (APCI$^+$) *m*/*z*: Found: 162.0912 ($[M + H]^+$; $C_{10}H_{12}NO$ requires: 162.0913).

(*R*)-Tolibut lactam (35). Prepared according to general procedure D using **S2** (50.2 mg, 0.246 mmol, see ESI†) and purified by flash column chromatography (98 : 2 CH_2Cl_2/MeOH) to give the product as a white powder (40.5 mg, 94%, 65% ee), m.p. 110–112 °C (lit.,[41] m.p. 108–110 °C). TLC (EtOAc): R_f = 0.40. $[\alpha]_D^{22}$ = −9.6 (*c* = 0.15, $CHCl_3$), (lit.,[40] $[\alpha]_D^{20}$ = −33.7 (*c* = 0.95, $CHCl_3$) for 99% ee). CSP-SFC analysis (see ESI†); R_T: 5.50 min (minor enantiomer) and 5.88 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 7.14 (4H, app. s), 6.71 (1H, br. s), 3.77 (1H, dd, *J* 9.4, 8.3), 3.61–3.70 (1H, m), 3.40 (1H, dd, *J* 9.4, 7.4), 2.77 (1H, dd, *J* 16.9, 8.8), 2.49 (1H, dd, *J* 16.9, 8.9) and 2.33 (3H, s) ppm. δ_C (100 MHz, $CDCl_3$): 177.9, 139.0, 136.8, 129.5, 126.7, 49.8, 40.0, 38.2 and 21.0 ppm.

(*R*)-Baclofen lactam (36). Prepared according to general procedure D using **S3** (55.3 mg, 0.246 mmol, see ESI†) and purified by flash chromatography (EtOAc) to give the product as a white powder (46.2 mg, 96%, 64% ee), m.p. 110–112 °C (lit.,[42] m.p. (from Hex/EtOAc) 108–110 °C). TLC (98 : 2 CH_2Cl_2/MeOH): R_f = 0.31. $[\alpha]_D^{22}$ = −16.5 (*c* = 0.15, $CHCl_3$), (lit.,[39] $[\alpha]_D^{20}$ = −39.0 (*c* = 1.00, $CHCl_3$) for 99% ee). CSP-SFC analysis (see ESI†): R_T: 3.47 min (major enantiomer) and 3.70 min (minor enantiomer). δ_H (600 MHz, $CDCl_3$): 7.30–7.32 (2H, m), 7.17–7.20 (2H, app. d.), 6.14 (1H, br. s, H-1), 3.78 (1H, dd, *J* 9.5, 8.3), 3.65–3.70 (1H, m), 3.38 (1H, dd, *J* 9.5, 7.1), 2.74 (1H, dd, *J* 16.9, 9.0) and 2.46 (1H, dd, *J* 16.9, 8.6) ppm. δ_C (151 MHz, $CDCl_3$): 177.2, 140.6, 133.0, 129.0, 128.1, 49.3, 39.7 and 37.7 ppm.

(*R*)-Rolipram (37). Prepared according to general procedure D using anhydride **S5** (74.9 mg, 0.246 mmol, see ESI†) and the crude residue purified by flash column chromatography (98 : 2 CH_2Cl_2/MeOH) to give the title product as an off-white crystalline powder (64.3 mg, 95%, 70% ee), m.p. 132–133 °C (lit.,[43] m.p. 131–133 °C). TLC (98 : 2 CH_2Cl_2/MeOH): R_f = 0.30. $[\alpha]_D^{22}$ =

−12.1 (c = 0.15, MeOH), (lit.,[39] $[\alpha]_D^{27}$ = −33.0 (c = 1.00, MeOH) for 99.3% ee). CSP-SFC analysis: R_T: 4.01 min (minor enantiomer) and 4.22 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 6.83–6.84 (1H, m), 6.76–6.79 (2H, m), 6.06 (1H, br s.), 4.74–4.79 (1H, m), 3.83 (3H, s), 3.75 (1H, dd, J 9.3, 8.2), 3.38 (1H, dd, J 9.3, 7.4), 2.71 (1H, dd, J 16.9, 8.8), 2.47 (1H, dd, J 16.9, 8.9)1.78–1.97 (6H, m) and 1.56–1.66 (2H, m) ppm. δ_C (100 MHz, $CDCl_3$): 177.6, 149.3, 148.0, 134.6, 118.9, 113.9, 112.3, 80.8, 56.2, 49.8, 40.1, 38.1, 32.9 and 24.1 ppm.

(*R*)-4-(Thiophen-3-yl)pyrrolidin-2-one (38). Prepared according to general procedure D using anhydride **S6** (48.3 mg, 0.246 mmol, see ESI†) and the crude residue purified by flash column chromatography (98 : 2 CH_2Cl_2/MeOH) to give the title product as a white crystalline powder (37.4 mg, 91%, 65% ee), m.p. 86–88 °C. TLC (98 : 2 CH_2Cl_2/MeOH): R_f = 0.28. $[\alpha]_D^{22}$ = −14.0 (c = 0.15, $CHCl_3$). CSP-SFC analysis (see ESI†): R_T: 3.35 min (major enantiomer) and 3.52 min (minor enantiomer). δ_H (400 MHz, $CDCl_3$): 7.32 (1H, dd, J 5.0, 2.9), 7.02 (1H, dd, J 2.9, 1.3), 6.99 (1H, dd, J 5.0, 1.3), 6.58 (1H, br. s), 3.73–3.82 (2H, m), 3.39–3.45 (1H, m), 2.70–2.77 (1H, m,) and 2.44–2.54 (1H, m, H-2b) ppm. δ_C (100 MHz, $CDCl_3$): 177.8, 142.7, 126.7, 126.2, 120.4, 49.2, 37.9 and 35.9 ppm.

(*R*)-Fluoribut lactam (39). Prepared according to general procedure D using **S4** (51.2 mg, 0.246 mmol, see ESI†) and purified by flash column chromatography (4 : 1 EtOAc/CH_2Cl_2) to give the product as a white, crystalline powder (39.5 mg, 90%, 66% ee), m.p. 97–99 °C (lit.,[44] m.p. 98–99 °C). TLC (1 : 1 EtOAc/CH_2Cl_2): R_f = 0.15. $[\alpha]_D^{22}$ = −7.8 (c = 0.15, MeOH), (lit.,[45] $[\alpha]_D^{25}$ = −26.2 (c = 1.00, MeOH) for 96% ee). CSP-SFC analysis (see ESI†): R_T: 3.01 min (major enantiomer) and 3.14 min (minor enantiomer). δ_H (400 MHz, $CDCl_3$): 7.18–7.23 (2H, m), 6.99–7.05 (2H, m), 6.70 (1H, br s), 3.77 (1H, dd, J 9.3, 8.3), 6.62–3.71 (1H, m), 3.37 (1H, dd, J 9.3, 7.2), 2.72 (1H, dd, J 16.9, 8.9) and 2.44 (1H, dd, J 16.9, 8.7) ppm. δ_F (376 MHz, $CDCl_3$): −115.53 (s) ppm. δ_C (100 MHz, $CDCl_3$): 177.8, 162.0 (d, $^1J_{C-F}$ 245.5), 138.0 (d, $^4J_{C-F}$ 3.1), 128.4 (d, $^2J_{C-F}$ 8.0), 115.8 (d, $^3J_{C-F}$ 21.2), 49.8, 39.8 and 38.2 ppm.

(*R*)-4-(2-Chlorophenyl)pyrrolidine-2-one (40). Prepared according to general procedure D using **S7** (55.3 mg, 0.246 mmol, see ESI†) and purified by flash column chromatography (98 : 2 CH_2Cl_2/MeOH) to give the product as a white, crystalline powder (45.2 mg, 94%, 65% ee), m.p. 112–114 °C (lit.,[41] m.p. 112–115 °C). TLC (EtOAc): R_f = 0.49. $[\alpha]_D^{22}$ = −9.4 (c = 0.10, $CHCl_3$). CSP-SFC analysis (see ESI†): R_T: 6.77 min (minor enantiomer) and 7.13 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 7.39 (1H, dd, J 7.8, 1.4), 7.33 (1H, dd, J 7.7, 1.6), 7.25–7.29 (1H, m), 7.18–7.23 (1H, m), 6.45 (1H, br. s), 4.12–4.20 (1H, m), 3.86 (1H, dd, J 9.7, 8.2), 3.42 (1H, dd, J 9.7, 6.0), 2.79 (1H, dd, J 17.0, 9.1) and 2.53 (1H, dd, J 17.0, 7.3) ppm. δ_C (101 MHz, $CDCl_3$): 177.5, 139.3, 133.8, 130.0, 128.4, 127.4, 127.2, 48.3, 36.68 and 36.66 (C-3) ppm.

(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)pyrrolidin-2-one (41). Prepared according to general procedure D using **S8** (60.0 mg, 0.246 mmol, see ESI†), to give a crude residue, which was purified by flash column chromatography (1 : 1 Hex/EtOAc) to give the title product as a white powder (42.4 mg, 80%, 56% ee), m.p. 78–80 °C (lit.,[46] m.p. (from PE/EtOAc) 84–86 °C). TLC (1 : 1 Hex/EtOAc, ninhydrin): R_f = 0.19. $[\alpha]_D^{22}$ = −2.4 (c = 0.15, $CHCl_3$), (lit.,[47] $[\alpha]_D^{22}$ = −7.4 (c = 1.30, $CHCl_3$)). CSP-SFC analysis (see ESI†): R_T: 2.61 min (minor enantiomer) and 2.73 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 5.98 (1H, br s), 4.53–4.58 (1H, m), 3.58 (1H, dd, J 10.0, 6.0), 3.24 (1H, dd, J 10.0, 3.4), 2.54 (1H, dd, J 17.0, 6.8) and 2.26 (1H, dd, J 17.0, 4.2) ppm. δ_C (100 MHz, $CDCl_3$): 176.2, 68.0, 51.6, 40.5, 25.8, 18.0, −4.7, and −4.8 ppm.

(*S*)-4-Methylpyrrolidin-2-one (42). Prepared according to general procedure D using **S9** (31.5 mg, 0.246 mmol, see ESI†) and the crude residue purified by flash column chromatography (98 : 2 CH_2Cl_2/MeOH) to give the product as a white powder (22.2 mg, 91%, 70% ee), m.p. 54–55 °C (lit.,[48] m.p. (from Hex) 53–55 °C). TLC (95 : 5 CH_2Cl_2/MeOH, $KMnO_4$): R_f = 0.50. $[\alpha]_D^{22}$ = −4.0 (c = 0.10, $CHCl_3$), (lit.,[49] $[\alpha]_D^{25}$ = −20.3 (c = 1.20, $CHCl_3$) for 99% ee). CSP-SFC analysis (see ESI†): R_T: 5.26 min (minor enantiomer) and 5.43 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 6.25 (1H, br s), 3.53 (1H, dd, J 9.4, 7.6), 2.99 (1H, dd, J 9.4), 2.51–2.64 (1H, m), 2.48 (1H, dd, J 16.5, 8.5), 1.97 (1H, dd, J 16.5, 7.1) and 1.16 (3H, d, J 6.7) ppm. δ_C (100 MHz, $CDCl_3$): 178.6, 49.6, 38.5, 29.6 and 19.7 ppm.

(*R*)-4-Isopropylpyrrolidin-2-one (43). Prepared according to general procedure D using **S10** (38.4 mg, 0.246 mmol, see ESI†) and the crude residue purified by flash column chromatography (98 : 2 CH_2Cl_2/MeOH) to give the product as a white powder (29.0 mg, 92%, 70% ee), m.p. 90–92 °C (lit.,[50] m.p. 96–97 °C). TLC (97 : 3 CH_2Cl_2/MeOH, ninhydrin): R_f = 0.25. $[\alpha]_D^{22}$ = +1.8 (c = 0.10, $CHCl_3$), (lit.,[50] $[\alpha]_D^{25}$ = +16.9 (c = 1.05, $CHCl_3$) for 99% ee). CSP-SFC analysis (see ESI†): R_T: 5.12 min (minor enantiomer) and 5.30 min (major enantiomer). δ_H (600 MHz, $CDCl_3$): 5.89 (1H br. s), 3.46 (1H, dd, J 9.3, 8.3), 3.09 (1H, dd, J 9.2, 8.3), 2.39 (1H, dd, J 16.7, 8.7), 2.17–2.26 (1H, m), 2.07 (1H, dd, J 16.7, 9.6), 1.56–1.64 (1H, m), 0.93 (3H, d, J 6.7) and 0.90 (3H, d, J 6.6) ppm. δ_C (151 MHz, $CDCl_3$): 178.3, 46.2, 42.3, 35.2, 32.5, 20.6 and 20.0 ppm.

(*S*)-Pregabalin lactam (44). Prepared according to general procedure D using **S11** (41.8 mg, 0.246 mmol, see ESI†) and purified by flash chromatography (Et_2O) to give the product as a colourless oil (32.6 mg, 94%, 64% ee). TLC (95 : 5 CH_2Cl_2/MeOH): R_f = 0.8. $[\alpha]_D^{22}$ = −0.81 (c = 0.16, $CHCl_3$), (lit.,[51] $[\alpha]_D^{20}$ = −2.42 (c = 1.00, $CHCl_3$) for 99% ee). CSP-SFC analysis (see ESI†): R_T: 1.88 min (minor enantiomer) and 2.00 min (major enantiomer). δ_H (600 MHz, $CDCl_3$): 6.28 (1H, br s), 3.47 (1H, dd, J 9.3, 7.9), 2.98 (1H, dd, J 9.3, 7.1), 2.53 (1H, app. sept.), 2.40 (1H, dd, J 16.7, 8.6), 1.97 (1H, dd, J 16.7, 8.5), 1.52–1.61 (1H, m), 1.30–1.37 (2H, m) and 0.89 (6H, app. t, J 6.5) ppm. δ_C (151 MHz, $CDCl_3$): 178.5, 48.3, 43.9, 37.1, 33.0, 26.2, 22.7 and 22.5 ppm. HRMS (ESI^+) m/z: Found: 164.1047 ($[M + Na]^+$; $C_8H_{15}NNaO$ requires: 164.1046).

(1*S*,4*R*)-2-Azabicyclo[2.2.1]heptan-3-one (45). Prepared according to general procedure D using **S12** (34.5 mg, 0.246 mmol, see ESI†) to give a crude residue which was purified by flash column chromatography (98 : 2 CH_2Cl_2/MeOH) to give title compound as a white powder (21.8 mg, 80%, 72% ee), m.p. 79–81 °C (lit.,[52] m.p. (from ^{i}PrOH) 78–81 °C. TLC

(98 : 2 CH_2Cl_2/MeOH, ninhydrin): R_f = 0.26. $[\alpha]_D^{22}$ = −48.6 (*c* = 0.15, $CHCl_3$), (lit.,[53] $[\alpha]_D^{22}$ = −160.0 (*c* = 1.00, $CHCl_3$)). CSP-SFC analysis (see ESI†): R_T: 2.67 min (major enantiomer) and 2.78 min (minor enantiomer). δ_H (400 MHz, $CDCl_3$): 6.02 (1H, br s), 3.86–3.89 (1H, m), 2.71–2.74 (1H, m), 1.77–1.93 (3H, m), 1.54–1.66 (2H, m) and 1.41 (1H, dt, *J* 9.3, 1.4) ppm. δ_C (100 MHz, $CDCl_3$): 181.2, 55.4, 45.1, 41.3, 30.2 and 23.7 ppm.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the Irish Research Council (IRC GOIPG/2017/972) is gratefully acknowledged.

Notes and references

1 J. P. Griess, *Proc. R. Soc. London*, 1864, **13**, 375.
2 E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, 1988, **88**, 297.
3 J. Aubé, C. Fehl, R. Liu, M. C. McLeod and H. F. Motiwala, *Compr. Org. Synth.*, 2014, **6**, 598.
4 T. B. Phan and H. Mayr, *J. Phys. Org. Chem.*, 2006, **19**, 706.
5 Selected reviews: (*a*) L. W. Xu and C. G. Xia, *Eur. J. Org. Chem.*, 2005, 633; (*b*) M. Goswami and B. de Bruin, *Eur. J. Org. Chem.*, 2017, 1152; (*c*) P.-G. Ding, X.-S. Hu, F. Zhou and J. Zhou, *Org. Chem. Front.*, 2018, **5**, 1542.
6 (*a*) L. E. Martínez, J. L. Leighton, D. H. Carsten and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1995, **117**, 5897; (*b*) K. B. Hansen, J. L. Leighton and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **118**, 10924.
7 (*a*) J. F. Larrow, S. E. Schaus, E. N. Jacobsen, V. Har, V. Uni and R. V. May, *J. Am. Chem. Soc.*, 1996, **14**, 7420; (*b*) E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421.
8 (*a*) B. Wu, J. R. Parquette and T. V. RajanBabu, *Science*, 2009, **326**, 1662; (*b*) B. Wu, J. C. Galluci, J. R. Parquette and T. V. RajanBabu, *Chem. Sci.*, 2014, **5**, 1102.
9 J. K. Myers and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1999, **121**, 8959.
10 F. González-Bobes, N. Kopp, L. Li, J. Deerberg, P. Sharma, S. Leung, M. Davies, J. Bush, J. Hamm and M. Hrytsak, *Org. Process Res. Dev.*, 2012, **16**, 2051.
11 T. E. Horstmann, D. J. Guerin and S. J. Miller, *Angew. Chem., Int. Ed.*, 2000, **39**, 3635.
12 D. J. Guerin and S. J. Miller, *J. Am. Chem. Soc.*, 2002, **124**, 2134.
13 M. Nielsen, W. Zhuang and K. A. Jørgensen, *Tetrahedron*, 2007, **63**, 5849.
14 E. B. Rowland, G. B. Rowland, E. Rivera-Otero and J. C. Antilla, *J. Am. Chem. Soc.*, 2007, **129**, 12084.
15 T. Bellavista, S. Meninno, A. Lattanzi and G. Della Sala, *Adv. Synth. Catal.*, 2015, **357**, 3365.
16 (*a*) M. S. Taylor, D. N. Zalatan, A. M. Lerchner and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2005, **127**, 1313; (*b*) J. Humbrías-Martín, M. C. Pérez-Aguilar, R. Mas-Ballesté, A. Dentoni Litta, A. Lattanzi, G. Della Sala, J. A. Fernández-Salas and J. Alemán, *Adv. Synth. Catal.*, 2019, **361**, 4790.
17 (*a*) S. N. Smith, R. Craig and S. J. Connon, *Chem. – Eur. J.*, 2020, **26**, 13378; (*b*) S. N. Smith and S. J. Connon, *Eur. J. Org. Chem.*, 2021, 5540.
18 (*a*) J. S. Bryans and D. J. Wustrow, *Med. Res. Rev.*, 1999, **19**, 149; (*b*) T. Ivšić and Z. Hameršak, *Tetrahedron: Asymmetry*, 2013, **24**, 21.
19 O. A. C. Petroff, *Neuroscientist*, 2002, **8**, 562.
20 A. V. Kalueff and D. J. Nutt, *Depression Anxiety*, 2007, **24**, 495.
21 W. Froestl, *Future Med. Chem.*, 2011, **3**, 163.
22 P. Nuss, *Neuropsychiatr. Dis. Treat.*, 2015, **1**, 165.
23 R. Vardanyan, V. Hruby, R. Vardanyan and V. Hruby, in *Synth. Best-Seller Drugs*, Academic Press, 2016, p. 155.
24 A. G. Malykh and M. R. Sadaie, *Drugs*, 2010, **70**, 287.
25 For selected reviews detailing anhydride desymmetrisation by alcoholysis see: (*a*) A. C. Spivey and B. I. Andrews, *Angew. Chem., Int. Ed.*, 2001, **40**, 3131; (*b*) Y. Chen, P. McDaid and L. Deng, *Chem. Rev.*, 2003, **103**, 2965; (*c*) I. Atodiresei, I. Schiffers and C. Bolm, *Chem. Rev.*, 2007, **107**, 5683; (*d*) Z. Rodriguez-Docampo and S. J. Connon, *ChemCatChem*, 2012, **4**, 151; (*e*) A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. W. Richardson and D. J. Dixon, *Chem. Soc. Rev.*, 2016, **45**, 5474.
26 Thiolysis: (*a*) T. Honjo, S. Saisno, M. Shiro and Y. Nagao, *Angew. Chem., Int. Ed.*, 2005, **44**, 5838; (*b*) A. Peschiulli, C. Quigley, S. Tallon, Y. K. Gun'ko and S. J. Connon, *J. Org. Chem.*, 2008, **73**, 6409; (*c*) A. Peschiulli, B. Procuranti, C. J. O'Connor and S. J. Connon, *Nat. Chem.*, 2010, **2**, 380.
27 Reductive and alkylative desymmetrisation: (*a*) H. Fernández-Pérez, P. Etayo, J. R. Lao, J. L. Núñez-Rico and A. Vidal-Ferran, *Chem. Commun.*, 2013, **49**, 10666; (*b*) E. A. Bercot and T. Rovis, *J. Am. Chem. Soc.*, 2005, **127**, 247; (*c*) E. E. Stache, T. Rovis and A. G. Doyle, *Angew. Chem., Int. Ed.*, 2017, **56**, 3679.
28 Anhydride desymmetrisation by fluoridation: R. Craig, M. Litvajova, S. A. Cronin and S. J. Connon, *Chem. Commun.*, 2018, **54**, 10108.
29 Catalytic (enantioselective) haloazidation is also possible: (*a*) P. K. Shyam and H.-Y. Jang, *Eur. J. Org. Chem.*, 2014, 1817; (*b*) P. Zhou, L. Lin, L. Chen, X. Zhong, X. Liu and X. Feng, *J. Am. Chem. Soc.*, 2017, **139**, 13414; (*c*) P. Zhou, X. Liu, W. Wu, C. Xu and X. Feng, *Org. Lett.*, 2019, **21**, 1170.
30 Recent radical-mediated carboazidation and diazidation reactions of α,β-unsaturated ketones: W. Liu, M. Pu, J. He, T. Zhang, S. Dong, X. Liu, Y.-D. Wu and X. Feng, *J. Am. Chem. Soc.*, 2021, **143**, 11856.
31 The superiority of chloroform as a solvent was surprising, as we have found ethereal solvents to be optimal – without exception – in multiple different reactions involving chiral bifunctional catalysts where the product is a carboxylic acid. We would suggest that this is due to the intermediacy

of a silylated carboxylic acid derivative. For examples see: (*a*) A. Peschiulli, Y. Gun'ko and S. J. Connon, *J. Org. Chem.*, 2008, **73**, 2454; (*b*) C. Cornaggia, F. Manoni, E. Torrente, S. Tallon and S. J. Connon, *Org. Lett.*, 2012, **14**, 1850; (*c*) F. Manoni, C. Cornaggia, J. Murray, S. Tallon and S. J. Connon, *Chem. Commun.*, 2012, **48**, 6502; (*d*) F. Manoni and S. J. Connon, *Angew. Chem., Int. Ed.*, 2014, **53**, 2628; (*e*) C. Cornaggia, S. Gundala, F. Manoni, N. Gopalasetty and S. J. Connon, *Org. Biomol. Chem.*, 2016, **14**, 3040; (*f*) S. A. Cronin, A. Gutiérrez Collar, S. Gundala, C. Cornaggia, E. Torrente, F. Manoni, A. Botte, B. Twamley and S. J. Connon, *Org. Biomol. Chem.*, 2016, **14**, 6955; (*g*) F. Manoni, U. Farid, C. Trujillo and S. J. Connon, *Org. Biomol. Chem.*, 2017, **15**, 1463; (*h*) R. Claveau, B. Twamley and S. J. Connon, *Chem. Commun.*, 2018, **54**, 3231; (*i*) M. L. Aiello, U. Farid, C. Trujillo, B. Twamley and S. J. Connon, *J. Org. Chem.*, 2018, **83**, 15499; (*j*) U. Farid, M. L. Aiello and S. J. Connon, *Chem. – Eur. J.*, 2019, **25**, 10074; (*k*) A. Gutiérrez Collar, C. Trujillo and S. J. Connon, *Chem. – Eur. J.*, 2019, **25**, 7270; (*l*) B. Lockett-Walters, C. Trujillo, B. Twamley and S. J. Connon, *Chem. Commun.*, 2019, **55**, 11283.

32 V. B. Birman and X. Li, *Org. Lett.*, 2006, **8**, 1351.

33 R. Claveau, B. Twamley and S. J. Connon, *Org. Biomol. Chem.*, 2018, **16**, 7574.

34 K. Blise, M. W. Cvitkovic, N. J. Gibbs, S. F. Roberts, R. M. Whitaker, G. E. Hofmeister and D. Kohen, *J. Org. Chem.*, 2017, **82**, 1347.

35 X. T. Guo, J. Shen, F. Sha and X. Y. Wu, *Synthesis*, 2015, **47**, 2063.

36 A. N. Reznikov, E. V. Golovin and Y. N. Klimochkin, *Russ. J. Org. Chem.*, 2013, **49**, 663.

37 F. González-Bobes, N. Kopp, L. Li, J. Deerberg, P. Sharma, S. Leung, M. Davies, J. Bush, J. Hamm and M. Hrytsak, *Org. Process Res. Dev.*, 2012, **16**, 2051.

38 M. Litvajova, E. Sorrentino, B. Twamley and S. J. Connon, *Beilstein J. Org. Chem.*, 2021, **17**, 2287.

39 C. Shao, H. J. Yu, N. Y. Wu, P. Tian, R. Wang, C. G. Feng and G. Q. Lin, *Org. Lett.*, 2011, **13**, 788.

40 J. P. Hilton-Proctor, O. Ilyichova, Z. Zheng, I. G. Jennings, R. W. Johnstone, J. Shortt, S. J. Mountford, M. J. Scanlon and P. E. Thompson, *Eur. J. Med. Chem.*, 2020, **191**, 112120.

41 I. J. Montoya-Balbás, B. Valentín-Guevara, E. López-Mendoza, I. Linzaga-Elizalde, M. Ordoñez and P. Román-Bravo, *Molecules*, 2015, **20**, 22028.

42 T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119.

43 P. L. Feldman, M. F. Brackeen, D. J. Cowan, B. E. Marron, F. J. Schoenen, J. A. Stafford, E. M. Suh, P. L. Domanico, D. Rose, M. A. Leesnitzer, E. S. Brawley, A. B. Strickland, M. W. Verghese, K. M. Connolly, R. Bateman-Fite, L. S. Noel, L. Sekut and S. A. Stimpson, *J. Med. Chem.*, 1995, **38**, 1505.

44 A. S. Paraskar and A. Sudalai, *Tetrahedron*, 2006, **62**, 4907.

45 Q. Lang, G. Gu, Y. Cheng, Q. Yin and X. Zhang, *ACS Catal.*, 2018, **8**, 4824.

46 M. Yar, M. G. Unthank, E. M. McGarrigle and V. K. Aggarwal, *Chem. – Asian J.*, 2011, **6**, 372.

47 A. G. H. Wee, G. J. Fan and H. M. Bayirinoba, *J. Org. Chem.*, 2009, **74**, 8261.

48 R. M. Wiedhopf, E. R. Trumbull and J. R. Cole, *J. Pharm. Sci.*, 1973, **62**, 1206.

49 V. Rodríguez, M. Sánchez, L. Quintero and F. Sartillo-Piscil, *Tetrahedron*, 2004, **60**, 10809.

50 D. Enders and O. Niemier, *Heterocycles*, 2005, **66**, 385.

51 J. Sietmann, M. Ong, C. Mück-Lichtenfeld, C. G. Daniliuc and J. M. Wiest, *Angew. Chem., Int. Ed.*, 2021, **60**, 9719.

52 Z. Galla, E. Forró and F. Fülöp, *Tetrahedron: Asymmetry*, 2016, **27**, 729.

53 M. L. Cardoso do Vale, J. E. Rodríguez-Borges, O. Caamaño, F. Fernández and X. García-Mera, *Tetrahedron*, 2006, **62**, 9475.