Exploring the Scope of the Isothiourea-mediated Synthesis of Dihydropyridinones

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The exploration and expansion of the scope of the isothiourea-mediated synthesis of dihydropyridinones is presented. The use of ketimines derived from α,β-unsaturated γ-ketoesters as the Michael acceptor in a Michael addition / lactamisation cascade gives access to a range of dihydropyridinones with high enantioselectivity. The nature of the N-sulfonyl group present on the ketamine is extensively investigated, with further studies into derivatisation of the dihydropyridinone core also reported.

Introduction

The direct organocatalytic asymmetric functionalisation of readily available, bench-stable carboxylic acids towards value-added products has received much attention since the seminal report by Romo and co-workers in 2001 on the intramolecular nucleophile-catalysed aldol / lactonisation (NCAL) reaction (Scheme 1). Further work from the Romo group has demonstrated the utility of ammonium and isothiouronium enolates generated from carboxylic acids in the stereoselective synthesis of β-lactones, including the application to the total synthesis of (+)-omphadiol 1 and (–)-curcumalactone 2 (Scheme 1), amongst others.

We have previously explored the scope of the intramolecular reactions of ammonium and isothiouronium enolates, allowing access to dihydrobenzofurans, 2H-indenes, THFs, as well as pyrrolidines. Intermolecular reactions have also been developed, with formal [2+2]- and [4+2]-cycloadditions between isothiouronium enolates and suitable electrophiles greatly expanding the range of valuable heterocyclic products that can be accessed directly from carboxylic acids. This has included dihydropyranones, dihydropyridinones, pyridines, and a variety of acyclic products from further derivatisation of the heterocyclic cores.

Our previous synthesis of dihydropyridinones reacted isothiouronium enolates generated from carboxylic acids with N-tosyl chalcone-derived ketamines in a Michael addition / lactamisation cascade (Scheme 2a). This afforded a range of dihydropyridinones in high yields and excellent stereoselectivity. In this methodology the N-tosyl substituent was employed exclusively in the ketamine Michael acceptor. Furthermore, the use of chalcones as the backbone of the ketamine, alongside the requirement for aryl or heteroaryl acetic acids, resulted in dihydropyridinones furnished with three (hetero)aryl substituents thereby constraining the scope of the heterocyclic products. To extend these studies, alternative ketamine backbones incorporating more versatile functional handles, whilst maintaining the reactivity of the Michael acceptor were explored. Herein we report the successful incorporation of ketamines derived from α,β-unsaturated γ-ketoesters within this
methodology,\textsuperscript{10,13} affording dihydropyridinone products containing ester substituents as functional handles (Scheme 2b). Extensive exploration of the sulfonyl substituent and the potential for derivatisation of the dihydropyridinone core is also described.

**Results and Discussion**

**Optimisation**

Initial studies showed that α,β-unsaturated γ-ketimine ester 6 was a competent electrophile for intermolecular Michael addition / lactamisation with the isothiourea enolate generated from phenylacetic acid 5 after in situ formation of a mixed anhydride using pivaloyl chloride and base, and reaction with achiral isothiourea DHPB 7. This allows formation of dihydropyridinone 8 in 65% isolated yield as an 88:12 mixture of diastereoisomers (Scheme 3a). In contrast, the related but isomeric Michael acceptor 9 resulted in a ca. 1:1 mixture of diastereoisomers in a poorer yield (Scheme 3b).\textsuperscript{14}

With reactivity and diastereoselectivity confirmed with Michael acceptor 6, a screen of common chiral isothiourea Lewis bases 3, 4 and 11 showed (--)tetramisole·HCl 4 to be optimum in terms of both isolated yield and stereoselectivity (Table 1, entries 1-3). Examining the catalyst loading revealed that although increasing to 40 mol\% 4 gave a higher isolated yield of 8, the diastereoselectivity suffered (entry 4). Conversely, lowering the loading to 10 mol\% resulted in incomplete conversion of 6 even after extended reaction times (entry 5). Next, the activating agent for generation of the in situ formed mixed anhydride was examined, showing that pivaloyl chloride was the best choice.

**Scheme 2** Organocatalytic synthesis of dihydropyridinones

**Scheme 3** Initial investigations

over a range of benzyol chloride derivatives (entries 6-8). Tetramisole free base (entry 9) and excess i-Pr\textsubscript{2}NEt (1.2 eq., entry 10) were examined, resulting in a slight reduction of diastereoselectivity and yield, respectively. Increasing the amount of carboxylic acid and pivaloyl chloride to two equivalents led to consistently higher isolated yields in a short reaction time, even under the more operationally simple non-anhydrous conditions of benzyl solvent and un-dried glassware (entries 11 and 12). Reducing the catalyst loading under these conditions was again found to be detrimental to the isolated yield of 8 (entry 13). The scalability of the reaction was examined with 5.0 mmol of 6 affording 1.48 g (3.2 mmol) of 8 (entry 14) in near identical yield and stereoselectivity to that on 0.2 mmol scale (cf. entry 12), demonstrated the ability of this methodology to deliver gram quantities of enantioenriched dihydropyridinones.
Table 1 Reaction Optimisation

| Entry | LB (mol%) | Activating Agent (eq.) | time (h) | yield (%) | dr (anti: syn) | ee (anti, %)
|-------|-----------|------------------------|----------|------------|---------------|---------------
| 1     | 4 (20)    | t-BuOCCl (1)           | 3        | 46         | 97.3 / 98     |               |
| 2     | 11 (20)   | t-BuOCCl (1)           | 16       | 33         | 75.25 / 95    | (ent)         |
| 3     | 3 (20)    | t-BuOCCl (1)           | 16       | 28         | >95.5 / 98    | (ent)         |
| 4     | 4 (40)    | t-BuOCCl (1)           | 3        | 75         | 95.67 / 98    |               |
| 5     | 10 (1)    | t-BuOCCl (1)           | 24       | 38         | 97.3 / 98     |               |
| 6     | 4 (20)    | PhOCOCI (1)            | 3        | 32         | 97.1 / 98     |               |
| 7     | 20 (20)   | PMPCCOCl †              | 24       | 17         | 92.0 / 98     |               |
| 8     | 20 (20)   | PNPCOCl †              | 3        | 29         | 83.17 / 94    |               |
| 9     | 20 (20)   | t-BuOCCl (1)           | 3        | 62         | 93.7 / 98     |               |
| 10    | 4 (20)    | t-BuOCCl (1)           | 3        | 31         | 98.2 / 98     |               |
| 11    | 4 (20)    | t-BuOCCl (2)           | 1        | 62         | 93.7 / 98     |               |
| 12    | 4 (20)    | t-BuOCCl (2)           | 1        | 65         | 92.8 / 98     |               |
| 13    | 4 (10)    | t-BuOCCl (2)           | 3        | 45         | 97.3 / 95     |               |
| 14    | 4 (20)    | t-BuOCCl (2)           | 1        | 64         | 92.8 / 98     |               |

* Reaction Conditions: 5 (1 eq.), Activating agent (1 eq.), t-PrNEt (1 eq.), CH₂Cl₂; then 6 (1 eq.), LB, t-PrNEt (1 eq.). *Isolated yield; † Measured by H NMR; ‡ Measured by chiral HPLC; § PMP = 4-methoxyphenyl; ¶ PNP = 4-nitrophenyl. † Tetramisole free base was used; ‡ t-PrNEt (1.2 eq.) was used. 1 5 (2 eq.), activating agent (2 eq.) and t-PrNEt (2 eq.) were used. 1 Bench-grade solvents used; 5 0.5 mmol of 6.

In an attempt to simplify the experimental procedure the possibility of using preformed homoanhydrides was explored (Scheme 4), with 2-phenylacetic anhydride 12 used in place of the combination of 2-phenylacetic acid and pivaloyl chloride. The purification of 8 was greatly simplified under this protocol, however lower diastereo- and enantioselectivity was observed with (−)-tetrалisole HCl 4. HyperBTM 11 performed better in terms of enantioselectivity at the lower loading of 5 mol %, although 60:40 dr was observed. This may be owing to in situ epimerisation of the dihydropyrimidine product, a conjecture that is supported by the high ee observed for the syn-diastereoisomer in this case. Therefore, the use of pre-activated homoanhydrides was not explored further.

Scheme 4 Investigation of homoanhydride 12

Exploration of the N-Sulfonyl Substituent

Having optimised the model system, exploration of the scope and limitations of this process required a general synthetic route to a range of ketimines. Their synthesis was achieved either directly from commercially available ethyl 3-benzyloxyacrylate 13 through TiCl₄-mediated imine formation (Scheme 5a), or efficiently in three steps from (+)-diethyl L-tartarate 15 via oxidative cleavage, Wittig reaction of the resulting aldehyde, and imine formation using TiCl₄ (Scheme 5b). In most cases the crude ketimines were purified through tritration and recrystallisation, thereby avoiding silica gel chromatography that leads to significant hydrolysis of these somewhat sensitive imines.

Scheme 5 Synthesis of N-sulfonyl ketimines

Initially, the scope of the sulfonyl group was examined to probe the effect of varying the steric and electronic properties of the N-substituent on the Michael addition / lactamisation (Table 2). A range of different aryl groups was incorporated, including electron-donating tosyl 18 and SO₂PMP 19, and electron-withdrawing 4-nosyl 20 without significant variation in yield of dihydropyrimidine. The sterically bulky 2,4,6-trisopropylbenzene sulfonyl substituent could also be installed, although the isolated yield of 21 was much reduced. Pleasingly, an alkyl substituted sulfonyl ketimine also proved reactive, generating methanesulfonyl derivative 22 in good yield without loss of stereoselectivity.
Table 2 Variation of the Sulfonyl Substituent

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<th>Entry</th>
<th>SO₂R</th>
<th>Yield (%)</th>
<th>dr (anti-syn)</th>
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<td><img src="image5.png" alt="Structure" /></td>
<td>59</td>
<td>92.8</td>
<td>99</td>
</tr>
</tbody>
</table>

*a* Isolated yield; *b* Measured by ¹H NMR; *c* Measured by chiral HPLC.

Exploration of the Acetic Acid Nucleophile Scope

The scope of the acetic acid component was initially examined using α,β-unsaturated benzenesulfonfyl ketimine 6 (Scheme 6). Generally, the isolated yield of dihydropyridinone was higher when two equivalents of acetic acid was used rather than one (Method A c.f. Method B). Interestingly, product diastereoselectivity was marginally reduced in most cases when two equivalents of acetic acid was used. While the reason for this is not immediately clear, enantioselectivity remained excellent. Arylacetic acids containing para-, meta- and ortho-tolyl substituents were all incorporated in high yields and excellent stereoselectivities (23-25), demonstrating that ortho-substitution has no detrimental effect on the course of the reaction, unlike in our previous synthesis of dihydropyridinones⁹ amongst other examples⁷,¹²a,¹²c para-Phenyl as well as 1- and 2-naphthyl substitution gave the desired dihydropyridinines (26-28) in moderate yields, although stereoselectivities remained excellent. Electron-rich and halogenated aromatics could also be easily incorporated with excellent stereocontrol (29-33), with an improvement in isolated yield for the most electron-rich substituents (c.f. 8). The relative and absolute configuration of 31 was determined by X-ray diffraction, with all other products assigned by analogy.¹⁸

Other substituents included the heteroaromatic 3-thiophenyl dihydropyridinone 34, which was formed without consequence as long as two equivalents of activated acetic acid were employed, and the 3-pentenoic acid derivative 35,¹²d further expanding the scope of accessible motifs with functional handles for further derivatisation. Finally, the ketimine backbone was modified to incorporate a para-methoxyphenyl group in place of the phenyl substituent, resulting in the formation of 36 and 37 in moderate yield and high stereoselectivity.
Mechanistic Rationale

The proposed mechanism of the reaction is outlined in Scheme 7. Firstly, N-acylation of (−)-tetramisole 4 with mixed anhydride 38, formed in situ from phenylacetic acid and pivaloyl chloride, generates acyl isothiouronium 39. Deprotonation forms the (Z)-isothiouronium enolate, which undergoes a Michael addition / lactamisation cascade to give dihydropyridinone 42 with concomitant regeneration of the catalyst. A plausible pre-transition state assembly (43) that explains the relative and absolute configuration is shown. A stabilising interaction between the enolate oxygen and the sulfur of the isothiouronium ion locks the conformation of this species, thereby preventing Re-face attack through the stereodirecting phenyl group on tetramisole.
Derivatisation of the Dihydropyridinone Core

The potential for derivatisation of the dihydropyridinones was next examined, first considering the possibility of converting the dihydropyridinone into a pyridine derivative. Dehydrogenation and desulfonylation of 8 using Pd/C in the presence of sodium formate gave pyridine 44 (Scheme 8). Subsequent treatment of 44 with tosyl chloride gave tetrasubstituted pyridine 45 in excellent yield. This route is complementary to our previous work regarding isothiourea mediated pyridine formation, which generates 2,4,6-trisubstituted pyridines (cf. 46 and 47)\textsuperscript{16-11} in contrast to the 2,3,4,6-tetrasubstituted pyridine formed here. Additionally, this methodology retains the 2-tosylate as a potential functional handle for further derivatisation.\textsuperscript{10}

In contrast to Pd/C, selective desulfonylation without dehydrogenation was achieved using sodium naphthalenide, which gave unprotected dihydropyridinone 48 in modest yield without loss of stereoselectivity (Scheme 9a). Alternatively, bromination at the 5-position proceeded smoothly upon treatment with Br\textsubscript{2} to give the fully substituted dihydropyridinone 49 in excellent yield (Scheme 9b). Ring-opening of 8 proved challenging, for example catalytic DMAP in methanol returned only starting material. However, ring-opening of 8 was possible using magnesium in methanol, which gave a moderate yield of keto-diestere 50 in high enantioselectivity, alongside 60\% of pyridone 44 from competing dehydrogenation / desulfonylation under these more forcing conditions (Scheme 9c). Reduction of 8 with LiAlH\textsubscript{4} followed by an acidic workup afforded a good yield of acrylic amine-diol 51 as a single diastereoisomer without loss of enantiopurity (Scheme 9d). It is perhaps surprising that the N-sulfonyl amine is isolable under these conditions, but the good isolated yield indicates significant stability of this functionality.\textsuperscript{20}

While all attempts at homo- or heterogeneous hydrogenation of the C-5,6 double bond in 8 to form the 2-piperidone returned only starting material, epoxidation was successful with m-

\textsuperscript{21}CPBA. This resulted in the formation of a single diastereoisomer of epoxide 52, containing four contiguous stereocentres (Scheme 10). The relative and absolute stereochemistry of 52 was confirmed through X-ray crystallography.\textsuperscript{22}

\textbf{Scheme 9} Derivatisations of the dihydropyridinone core. Reaction conditions: a) Na / naphthalene (4 eq.), −78 °C; b) Br\textsubscript{2}, i-P\textsubscript{2}N\textsubscript{Et}; c) Mg / MeOH; d) i) 2 M LiAlH\textsubscript{4}, THF; ii) 0.1 M HCl.

\textbf{Scheme 8} Formation of tetrasubstituted pyridine 45. Reaction conditions: a) Pd/C, H\textsubscript{2}, Na\textsubscript{2}CO\textsubscript{3}, DMF, 60 °C; b) NaH, TsCl, DMF.

\textbf{Scheme 10} Formation of tetrasubstituted pyridine 45. Reaction conditions: a) Pd/C, H\textsubscript{2}, Na\textsubscript{2}CO\textsubscript{3}, DMF, 60 °C; b) NaH, TsCl, DMF.
Conclusions

In conclusion, the scope of the isothiourea catalysed Michael addition / lactamisation of aryl and alkynyl acetic acids with α,β-unsaturated ketimines has been expanded, thereby allowing the synthesis of a variety of dihydropyrindinone products. Derivatisation of the dihydropyrindinone core has also been further demonstrated, affording a range of valuable skeletons from a single starting material. Further work in our laboratory is directed towards new Lewis base-catalysed reactions and exploring derivatisations of the functional building blocks they provide.

Acknowledgements

We thank the Royal Society for a University Research Fellowship (ADS), the EU (IEF for CS) and the European Research Council under the European Union’s Seventh Framework Programme (FP7/2007-2013) ERC Grant Agreement No. 279850 (JET and CF) and the EPSRC grant numbers EP/J018139/1 (DSBD) and EP/K00445X/1 (EG) for funding. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Experimental

General Information

Anhydrous CH$_2$Cl$_2$ was obtained from an Mbraun SPS-800 system. Pet. ether is defined as petroleum ether 40-60 °C. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and –78 °C were obtained using ice/water and CO$_2$(s)/acetone baths, respectively.

Analytical thin layer chromatography (TLC) was performed on pre-coated aluminium plates (Kieselgel 60 F$_{254}$ silica). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous KMnO$_4$ solution and heating. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

Melting points were recorded on an Electrothermal 9100 apparatus.

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

HPLC analyses were obtained on a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatograph, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven which allowed the temperature to be set from 25-40 °C. Separation was achieved using a Chiracel OD-H column or Chiralpak AD-H, and IA, columns. Authentic racemic samples of chiral products were synthesised using achiral DHPB 7 or racemic tetramisole-HCl 4.

Infrared spectra ($\nu_{\text{max}}$) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer as thin films using Pike MiRacle ATR accessory. Analysis was carried out using Shimadzu IRsolution v1.50 and only characteristic peaks are reported.

$^1$H and $^{13}$C[$^1$H] spectra were acquired on either a Bruker Avance 300 (300 MHz), δ$_C$ (75 MHz), δ$_T$ (282 MHz), a Bruker Avance II 400 (400 MHz), δ$_C$ (101 MHz), δ$_T$ (376 MHz) or a Bruker Ultrashield 300 (300 MHz), δ$_C$ (126 MHz), δ$_T$ (471 MHz) spectrometer at ambient temperature in the deuterated solvent stated. Chemical shifts, δ, are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants, J, are quoted in Hertz (Hz) to the nearest 0.1 Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad.

Mass spectrometry (m/z) data were acquired by electrospray ionisation (ESI), electron impact (EI), chemical ionisation (CI), atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionisation (APCI) or nanospray ionisation (NSI) at the EPSRC National Mass Spectrometry Service Centre, Swansea.

General Procedure A: Synthesis of α,β-unsaturated γ-N-sulfonyl ketimines from ethyl 3-benzoylacrylate

A flame-dried flask containing a stirrer bar was charged with the requisite sulfonamide (1 eq.), ethyl 3-benzoylacrylate (1 eq.) and CH$_2$Cl$_2$ (ca. 0.2 M). The resulting solution was stirred and cooled to 0 °C before Et$_3$N (2 eq.) was added followed by TiCl$_4$ (1 eq.) dropwise. The reaction mixture was allowed to warm to rt, a reflux condenser fitted to the flask, and the reaction heated at reflux overnight. The solvent was removed in vacuo, the titanium salts precipitated with Et$_3$O and the suspension filtered. The filtrate was concentrated in vacuo, the residue cooled in an ice bath, and triturated with a small amount of Et$_3$O (ca. 5 mL / g) with stirring. The resultant solid was collected by filtration and washed with further portions of cold Et$_3$O. The solid was dried in vacuo to leave the pure ketimines.

General Procedure B: Synthesis of Dihydropyrindinones
A flask containing a stirrer bar was charged with CH₂Cl₂ (to give 0.4 M acid), aryl acetic acid (2 eq.), i-Pr₂NEt (2 eq.) and cooled to 0 °C. Pivaloyl chloride (2 eq.) was added and the reaction stirred for 30 minutes. (−)-Tetramisole HCl 4 (20 mol%) was added followed by the ketimine (1 eq.) and additional i-Pr₂NEt (1 eq.) in CH₂Cl₂ (to give 0.4 M of ketimine). The reaction was allowed to warm to rt and stirred until complete by TLC. The reaction was quenched with 0.1 M HCl (−20 mL / mmol acid), the layers separated and the aqueous layer extracted with CH₂Cl₂ (2 × eq. vol.). The combined organics were dried over MgSO₄, the solvent removed in vacuo on a rotary evaporator (<30 °C bath temp.), and the residue purified by flash chromatography in the solvent system stated.

Preparation of Ketimines

(2E,4E)-Ethyl 4-phenyl-4-((phenylsulfonyl)limino)but-2-enoate 6a–b

The starting ketone, (E)-ethyl 2-oxo-4-phenylbut-3-enoate, was prepared according the procedure outlined by Smith et al. Following general procedure A, the reaction of the above ketone (2.0 g, 9.8 mmol), p-toluenesulfonamide (1.68 g, 9.8 mmol), NEt₃ (2.8 mL, 19.6 mmol) and TiCl₄ (1.1 mL, 9.8 mmol) in CH₂Cl₂ (60 mL) gave 9 after purification by flash chromatography (EtOAc / pet. ether, 1:5) as a brown oil (1.51 g, 4.2 mmol, 43%); 1H NMR (500 MHz, CDCl₃) δH: 1.48 (3H, t, J 7.1, OCH₂CH₃), 2.43 (3H, s, NTSCH₃), 4.55 (2H, q, J 7.1, OCH₂CH₃), 6.82 (1H, d, J 16.5, C(2)H), 7.29–7.56 (8H, m, ArH and C(3)H), 7.90 (2H, d, J 8.3, ArH). Data consistent with literature.²¹

(2E,4E)-Ethyl 4-phenyl-4-((phenylsulfonyl)limino)but-2-enoate 6a–b

Following general procedure A, the reaction of ethyl 3-benzoylacrylate (1.84 mL, 10 mmol), p-toluenesulfonamide (1.68 g, 10.0 mmol), NEt₃ (2.8 mL, 20 mmol) and TiCl₄ (1.1 mL, 10 mmol) in CH₂Cl₂ (60 mL) gave the title compound after trituration as white crystals (2.04 g, 6.0 mmol, 60%); mp 51–52 °C [Lit.¹⁸ 51–53 °C]; 1H NMR (500 MHz, CDCl₃) δH: 1.35 (3H, t, J 7.0, OCH₂CH₃), 4.30 (2H, q, J 6.3, OCH₂CH₃), 6.24 (1H, d, J 16.2, C(2)H), 7.44 (2H, t, J 7.7, PhH), 7.51–7.56 (3H, m, PhH), 7.62 (1H, t, J 7.4, PhH), 8.03 (2H, s, PhH), 8.24 (1H, d, J 16.1, C(3)H). Data consistent with literature.²¹

(2E,4E)-Ethyl 4-((4-nitrophenoxy)sulfonyl)limino)-4-phenylbut-2-enoate 14c

Following general procedure A, the reaction of ethyl 3-benzoylacrylate (0.92 mL, 5.0 mmol), 4-nitrobenzenesulfonamide (1.01 g, 5.0 mmol), NEt₃ (1.39 mL, 10.0 mmol) and TiCl₄ (0.55 mL, 5.0 mmol) in CH₂Cl₂ (30 mL), gave the title compound after trituration (0.95 g, 2.5 mmol, 50%) as an orange solid; mp 76–78 °C; νmax (ATR): 2985, 1716, 1552, 1494, 1311, 1255, 1184, 1143, 1089, 1002, 975; 1H NMR (500 MHz, CDCl₃) δH: 1.35 (1H, t, J 6.4, OCH₂CH₃), 3.38 (3H, s, ArOCH₃), 4.18–4.40 (2H, m, OCH₂CH₃), 6.21 (1H, d, J 16.2, C(2)H), 7.00 (2H, d, J 8.3, PhH), 7.43 (2H, t, J 7.5, PhH), 7.56 (1H, t, J 7.2, PhH), 7.63–7.80 (2H, m, NSO₂Ar(C(3)H), 7.97 (2H, d, J 3.7, NSO₂Ar(C(2)H), 8.25 (1H, d, J 16.2, C(3)H); [Cl⁺] NMR (126 MHz, CDCl₃) δC: 14.3, 55.8, 61.7, 114.2, 128.7, 129.7, 130.3, 132.3, 132.9, 133.4, 136.0, 136.9, 160.8, 163.4, 170.3; HRMS (ESI+): C₁₈H₁₆NO₆S [M+H⁺] found 374.1054, requires 374.1057 (−0.7 ppm).

(2E,4E)-Ethyl 4-((4-nitrophenoxy)sulfonyl)limino)-4-phenylbut-2-enoate 14d

Following general procedure A, the reaction of ethyl 3-benzoylacrylate (0.92 mL, 5.0 mmol), methanesulfonamide (0.48 g, 5.0 mmol), NEt₃ (1.39 mL, 10.0 mmol) and TiCl₄ (0.55 mL, 5.0 mmol) in CH₂Cl₂ (30 mL), gave the title compound after trituration as an orange solid (0.87 g, 3.1 mmol, 62%); mp 76–78 °C; νmax (ATR): 2991, 1718, 1639, 1579, 1554, 1442, 1365, 1309, 1292, 1269, 1184, 1134, 1026, 970; 1H NMR (500 MHz, CDCl₃) δH: 1.32 (3H, t, J 7.1, OCH₂CH₃), 3.26 (3H, s, SO₂CH₃), 4.28 (2H, q, J 7.1,  
OCH₂CH₃), 6.25 (1H, d, J = 16.2, C(2)H), 7.47 (2H, t, J = 7.8, PhH), 7.60 (1H, t, J = 7.1, PhH), 7.76 (2H, d, J = 7.2, PhH), 8.13 (1H, d, J = 16.2, C(3)H) [3]¹, [1H] NMR (126 MHz, CDCl₃) δ: 14.1, 43.0, 61.6, 128.8, 130.1, 133.3, 133.5, 135.7, 136.2, 164.5, 175.3; HRMS (ESI+): C₉H₆NO₂S [M+H⁺] found 246.1373, requires 246.1370 (+0.7 ppm).

Ethyl 6-oxo-4,5-diphenyl-1-tosyl-1,4,5,6-tetrahydropyridine-2-carboxylate 10
Following general procedure B, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), i-Pr₄N⁺(70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH₂Cl₂ (1.0 mL), followed by DHPB 7 (7.6 mg, 0.04 mmol, 20 mol%), ketimine 9 (71.6 mg, 0.2 mmol), i-Pr₄N⁺(35 μL, 0.2 mmol) and CH₂Cl₂ (2.0 mL), for 1 h gave a crude residue of 59:41 dr. Purification by flash chromatography (Et₂O / petrol, 1:4) gave 10 (37.9 mg, 0.08 mmol, 40%, 54:46 dr) as a white solid; mp 118-120 °C; v_RIR (ATR): 2978, 1274, 1597, 1363, 1170, 1085, 1028; [1H NMR (300 MHz, CDCl₃), both diastereoisomers] δ: 1.37-1.43 (3H, m, OCH₃CH₂), 2.44 (3H, s, NtsCH₃), 3.85 (1H, d, J = 10.2, CH₂), 4.03 (1H, d, J = 5.8, CH₂), 4.08 (2H, q, J = 5.3, 4.5, OCH₂CH₃), 4.28-4.52 (3H, m, OCH₂CH₂CH₂), and 6.54-6.63 (1H, m, ArH), 6.65 (1H, d, J = 4.2, ArH), 6.69 (1H, d, J = 6.0, ArH), 6.85 (1H, dd J = 7.9, 1.5, ArH), 6.87-6.94 (1H, m, ArH), 7.00 (1H, dd, J = 7.4, 5.8, ArH), 7.04-7.13 (2H, m, ArH), 7.12-7.25 (7H, m, ArH), 7.32 (2H, t, J = 8.2, ArH), 8.11 (2H, d, J = 8.4, ArH), 8.14-8.23 (2H, m, ArH); [1H] NMR (101 MHz, CDCl₃) δ: 13.9, 21.5, 44.1, 44.5, 55.9, 57.2, 62.2, 126.9, 127.5, 127.6, 127.7, 127.8, 127.9, 128.5, 128.8, 128.8, 128.9, 129.3, 129.3, 129.4, 129.5 129.6, 129.9, 131.9, 133.2, 133.5, 135.4, 137.8, 143.8, 145.8, 170.2, 170.9; HRMS (ESI+): C₁₂H₁₀NO₂ [M+H⁺] found 476.1527, requires 476.1526 (+0.2 ppm).

Preparation of Dihydropyridinones
(3S,4S)-Ethyl 2-oxo-3,6-diphenyl-1-(phenylsulfonfyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 8
Following general procedure B, the reaction of phenylacetic acid (1.36 g, 10.0 mmol), i-Pr₄N⁺(1.73 mL, 10.0 mmol) and pivaloyl chloride (1.23 mL, 10.0 mmol) in CH₂Cl₂ (25 mL), followed by (--)-tartemisole HCl 4 (0.24 g, 1.0 mmol, 20 mol%), ketimine 6 (1.72 g, 5.0 mmol), i-Pr₄N⁺(0.87 mL, 5.0 mmol) and CH₂Cl₂ (50 mL), for 1 h gave a crude residue of 92:8 dr. Purification by flash chromatography (Et₂O / petrol, ether, 1:4) gave 8 (1.48 g, 3.2 mmol, 64%, 92:8 dr) as a white solid; mp 128-129 °C; v_RIR (ATR): 2979, 1722, 1448, 1155, 989; [α]₂⁰° C = 32.9 (c 0.55, CHCl₃); HPLC (Chiralpak IA, 20% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (3S, 4S): 13.2 min, t_R (3S, 4R): 33.1 min, 98% ee; [1H NMR (500 MHz, CDCl₃) δ: 1.04 (3H, t, J = 7.1, OCH₃CH₂), 3.75 (1H, dd, J = 9.6, 4.8, C(4)H), 4.02 (2H, q, J = 7.5, 3.4, OCH₂CH₂), 4.10 (1H, d, J = 9.6, C(3)H), 5.87 (1H, d, J = 4.8, C(5)H), 8.01 (2H, dd, J = 6.4, 2.4, C(3)PH₂H), 7.26-7.27 (3H, m, C(3)PH₂H), 7.38-7.40 (5H, m, C(6)PH₂H), 7.50 (2H, t, J = 7.9, NSO₂PhH), 7.65 (1H, t, J = 7.4, NSO₂PhH), 7.95 (2H, d, J = 8.0, NSO₂PhH); [3]¹ [1H] NMR (126 MHz, CDCl₃) δ: 13.9, 45.1, 54.0, 61.6, 115.9, 126.1, 128.5, 128.6, 128.7, 128.9, 129.5, 129.6, 132.3, 134.1, 136.7, 137.9, 139.2, 141.3, 170.9, 172.2; HRMS (ESI+): C₁₂H₁₀NO₂S [M+H⁺] found 246.1373, requires 246.1370 (+0.7 ppm).

Ethyl 6-oxo-4,5-diphenyl-1-tosyl-1,4,5,6-tetrahydropyridine-2-carboxylate 10
Following general procedure B, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), i-Pr₄N⁺(70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH₂Cl₂ (1.0 mL), followed by (--)-tartemisole HCl 4 (9.6 mg, 0.04 mmol, 20 mol%), ketimine 14b (68.7 mg, 0.2 mmol), i-Pr₄N⁺(35 μL, 0.2 mmol) and CH₂Cl₂ (2.0 mL),
Following general procedure B, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), i-PrNEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH2Cl2 (1.0 mL), followed by (−)-tartamisole·HCl 4 (9.6 mg, 0.04 mmol, 20 mol%), ketimine 14e (68.7 mg, 0.2 mmol), i-PrNEt (35 µL, 0.2 mmol) and CH2Cl2 (2.0 mL), for 1 h gave a crude residue of 95:65 dr. Purification by flash chromatography (EtOAc / pet. ether, 1:4) gave 72 (47.1 mg, 0.12 mmol, 59%, 92:8 dr) as a white solid; mp 131-132 °C; v_max (ATR): 2916, 1708, 1653, 1496, 1446, 1344, 1165, 1151, 1118, 960; [α]_D^20 −6.3 (c 0.51, CHCl3); HPLC (Chiralpak IA, 30% IPA / hexane, 0.5 mL/min, 30 °C): t_R (35, 4S): 41.5 min, t_R (3R, 4R): 45.0 min, 99% ee; 1H NMR (500 MHz, CDCl3) δ_H: 1.18 (1H, t, J 7.7, OCH2CH3), 3.46 (3H, s, Mc3H), 3.78 (1H, t, J 6.3, C(3)H), 4.14 (2H, q, J 7.1, OCH2CH2), 4.26 (1H, d, J 6.3, C(3)H), 5.76 (1H, d, J 6.2, C(5)H), 7.20-7.48 (10H, m, PhH); 13C[1]H NMR (101 MHz, CDCl3) δ_C: 14.1, 43.9, 44.9, 53.2, 62.0, 114.3, 125.5, 128.2, 128.3, 128.8, 129.9, 130.1, 135.0, 137.0, 141.2, 171.2, 173.0; HRMS (ESI+): C17H16NO3S [M+H]^+ found 400.1216, required 400.1213 (−0.7 ppm).

2-oxo-6-phenyl-1-(phenylsulfonyl)-3-(p-tolyl)tetrahydropyridine-4-carboxylate 24
Following general procedure B, the reaction of 3-tolylacetic acid (60.1 mg, 0.4 mmol), i-PrNEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH2Cl2 (1.0 mL), followed by (−)-tartamisole·HCl 4 (9.6 mg, 0.04 mmol, 20 mol%), ketimine 6 (68.7 mg, 0.2 mmol), i-PrNEt (35 µL, 0.2 mmol) and CH2Cl2 (2.0 mL), for 1 h gave a crude residue of 92:8 dr. Purification by flash chromatography (EtOAc / pet. ether, 1:4) gave 24 (69.6 mg, 0.15 mmol, 72%, 93:7 dr) as a white solid; mp 134-136 °C; v_max (ATR): 3405-3244 cm⁻¹ (carbonyl stretch).
2922, 1726, 1516, 1359, 1155, 887; [α]_D^28 +27.9 (c 0.64, CH2Cl2); HPLC (Chiralpak IA, 10% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (35, 45): 22.7 min, t_R (3R, 4R): 62.7 min, 99% ee; [b]_D^20 (500 MHz, CDCl3) δ_H: 1.05 (3H, t, J = 7.1, OCH2CH3), 2.26 (3H, s, n-toly-arylCH3), 3.72 (1H, dd, J = 9.5, 4.9, C(4)Hδ), 3.98–4.07 (3H, m, C(3)H and OCH2CH3), 5.84 (1H, d, J = 4.9, C(5)H), 6.77–6.81 (2H, m, C(3)ArH), 7.05 (1H, d, J = 7.6, C(3)ArH), 7.14 (1H, t, J = 7.6, C(3)ArH), 7.33–7.52 (5H, m, C(6)PhH), 7.50 (2H, t, J = 7.9, NSO-PhH), 7.65 (1H, t, J = 7.4, NSO-PhH), 7.96 (2H, d, J = 1, NSO-PhH); [c]_D^15 (1H) NMR (126 MHz, CDCl3) δ_H: 14.0, 21.5, 45.2, 53.9, 61.7, 115.8, 125.6, 126.1, 126.8 (2 × C), 128.6, 128.7, 128.9, 129.3, 129.5, 134.1, 135.3, 136.7, 138.4, 139.2, 141.3, 170.8, 172.0; HRMS (ESI+): C23H19NO3S [M+H]⁺ found 476.1522, requires 476.1526 (+0.9 ppm).

(35,4S)-Ethyl 2-oxo-6-phenyl-1-(phenylsulfonfonyl)-3-(3-toly)-1,2,3,4-tetrahydroxypropidine-4-carboxylate 25

Following general procedure B, the reaction of o-tolyloacetic acid (60.1 mg, 0.4 mmol), i-PrNEt (70 µL, 0.4 mmol) and pivaloyl chloride (50.0 µL, 0.4 mmol) in CH2Cl2 (1.0 mL), followed by (+)-tartemisole HCl 4 (9.6 mg, 0.04 mmol, 20 mol%), ketimine 6 (68.7 mg, 0.2 mmol), i-PrNEt (35 µL, 0.2 mmol) and CH2Cl2 (2.0 mL), for 1 h gave a crude residue of 91:9 dr. Purification by flash chromatography (EtOAc / pet ether, 1:4) gave 27 (63.7 mg, 0.12 mmol, 62%, 92:8 dr as a white solid; mp 178–180 °C; νmax (ATR): 2978, 1774, 1446, 1359, 1166, 1124, 1097, 1012; [α]_D^20 +17.3 (c 0.55, CH3Cl); HPLC (Chiralpak AD-H, 30% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (35, 4S): 18.6 min, t_R (3R, 4R): 38.0 min, 97% ee; [b]_D^20 (400 MHz, CDCl3) δ_H: 0.95 (1H, t, J = 7.1, OCH2CH3), 3.86 (1H, dd, J = 9.9, 4.7, C(4)Hδ), 3.96 (2H, q, J = 10.8, 7.1, OCH2CH3), 4.26 (1H, dd, J = 9.9, C(3)H), 5.84 (1H, d, J = 5.2), 7.05 (1H, dd, J = 8.5, 1.9, C(3)ArH), 7.34–7.57 (10H, m, ArH), 7.62–7.83 (4H, m, ArH), 7.97 (2H, dd, J = 6.8, 1.2, NSO-PhH); [b]_D^15 (1H) NMR (101 MHz, CDCl3) δ_H: 14.0, 45.2, 54.3, 61.7, 116.0, 126.0, 126.2, 126.4, 127.8, 128.7, 128.8, 129.0, 129.6, 132.8, 133.0, 133.4, 134.2 (2 × C), 136.7, 139.2, 141.4, 170.8, 172.0; HRMS (ESI+): C32H28NO3S [M+H]⁺ found 512.1522, requires 512.1526 (+0.8 ppm).

(35,4S)-Ethyl 2-oxo-6-phenyl-1-(phenylsulfonfonyl)-1,2,3,4-tetrahydroxypropidine-4-carboxylate 28

Following general procedure B, the reaction of 1-naphthaleneacetic acid (74.5 mg, 0.4 mmol), i-PrNEt (70 µL, 0.4 mmol) and pivaloyl chloride (50.0 µL, 0.4 mmol) in CH2Cl2 (1.0 mL), followed by (+)-tartemisole HCl 4 (9.6 mg, 0.04 mmol, 20 mol%), ketimine 6 (68.7 mg, 0.2 mmol), i-PrNEt (35 µL, 0.2 mmol) and CH2Cl2 (2.0 mL), for 1 h gave a crude residue of 91:9 dr. Purification by flash chromatography (EtOAc / pet ether, 1:4) gave 28 (70.8 mg, 0.14 mmol, 69%, 92:8 dr) as a white solid; mp 176–178 °C; νmax (ATR): 2978, 1721, 1446, 1166, 931; [α]_D^20 +14.7 (c 0.58, CH3Cl); HPLC (Chiralpak IA, 10% IPA / hexane, 1.0 mL/min, 211 nm, 30 °C): t_R (35, 4S): 40.7 min, t_R (3R, 4R): 98.1 min, 97% ee; [b]_D^20 (400 MHz, CDCl3) δ_H: 0.95 (1H, t, J = 7.1, OCH2CH3), 3.89–4.06 (3H, m, C(4)H and OCH2CH3), 4.91 (1H, d, J = 8.6, C(3)H), 5.84 (1H, d, J = 5.2, C(5)H), 7.12–7.20 (1H, m, C(3)ArH), 7.33–3.7 (6H, m, C(3)ArH), 7.39–7.50 (5H, m, C(6)PhH), 7.50–7.56 (2H, t, J = 7.4, NSO-PhH), 7.66–7.72 (1H, s, NSO-PhH), 7.72–7.76 (1H, m, C(3)ArH), 7.87 (1H, dd, J = 6.8, 2.7, C(3)ArH), 7.99 (2H, dd, J = 6.8, 1.2, NSO-PhH); [b]_D^15 (1H) NMR (126 MHz, CDCl3) δ_H: 13.8, 44.6, 51.3, 61.7, 115.8, 123.2, 125.2, 125.9, 126.2, 126.7, 126.8, 128.6, 128.9, 129.1, 129.3, 129.6, 131.0, 131.7, 134.2 (2 × C), 136.7, 139.0, 141.4, 170.9, 171.9; HRMS (ESI+): C32H28NO3S [M+H]⁺ found 512.1523, requires 512.1526 (+0.8 ppm).

(35,4S)-Ethyl 3-(3,4-dimethylphenyl)-2-oxo-6-phenyl-1-(phenylsulfonfonyl)-1,2,3,4-tetrahydroxypropidine-4-carboxylate 29

Following general procedure B, the reaction of 3,4-dimethylphenylacetic acid (78.4 mg, 0.4 mmol), i-PrNEt (70 µL, 0.4 mmol) and pivaloyl chloride (50.0 µL, 0.4 mmol) in CH2Cl2 (1.0 mL), followed by (+)-tartemisole HCl 4 (9.6 mg, 0.04 mmol, 20 mol%), ketimine 6 (68.7 mg, 0.2 mmol), i-PrNEt (35 µL, 0.2 mmol) and CH2Cl2 (2.0 mL), for 1 h gave a crude residue of 93:7 dr. Purification by flash chromatography (EtOAc / pet ether, 2:3) gave 29...
(35,4S)-Ethyl 3-(4-(dimethylamino)phenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 30

Following general procedure B, the reaction of 4-(dimethylamino)phenylethyl acetate (71.7 mg, 0.4 mmol), i-PrNET (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH₂Cl₂ (1.0 mL), followed by (−)-tetratramisole HCI 4 (9.6 mg, 0.04 mmol, 20 mol%) and ketimine 6 (68.7 mg, 0.2 mmol), i-PrNET (35 µL, 0.2 mmol) and CH₂Cl₂ (2.0 mL), for 1 h gave a crude residue of 92:8 dr. Purification by flash chromatography (EtO₂ / pet ether, 1:4) gave 30 (64.6 mg, 0.13 mmol, 60%, 94:6 dr) as a white solid; mp 140-142 °C; v_max (ATR): 2976, 1727, 1710, 1448, 1146, 925; [α]_D +31.1 (c 0.54, CH₂Cl₂); HPLC (Chiralpak IA, 30% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (35,4S): 30.4 min, t_K (3R, 4R): 55.2 min, 99% ee; [H] NMR (400 MHz, CDCl₃) δ_H: 1.09 (3H, t, J = 7.1, OCH₂CH₃), 2.90 (6H, s, N(CH₃)₂), 3.68 (1H, dd, J = 9.4, 5.0, C(4)H), 3.95-4.08 (3H, m, C(3)H and OCH₂CH₃), 5.85 (1H, d, J = 5.0, C(5)H), 6.59 (2H, d, J = 8.8, C(3)ArH), 6.85 (2H, d, J = 8.7, C(3)ArH), 7.36-7.40 (5H, m, C(6)PhH), 7.45-7.53 (2H, m, NSO-PhH), 7.64 (1H, t, J = 7.1, 1, 1.2, OCH₃CH₂), 7.94 (2H, d, J = 8.5, 1, 1.2, NSO-PhH); ¹³C (H) NMR (126 MHz, CDCl₃) δ_C: 14.1, 41.6, 45.4, 53.3, 61.6, 112.7, 116.2, 122.7, 126.2, 128.6, 128.8, 129.5, 129.3, 134.0, 133.6, 139.4, 141.2, 150.3, 171.1, 172.5; HRMS (ESI⁺): C₂₃H₂₁N₂O₄S [M+H⁺] found 505.1786, requires 505.1792 (−1.1 ppm).

(35,4S)-Ethyl 3-(4-(methoxyphenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 31

Following general procedure B, the reaction of 4-methoxyphenylethyl acetate (66.4 mg, 0.4 mmol), i-PrNET (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH₂Cl₂ (1.0 mL), followed by (−)-tetratramisole HCI 4 (9.6 mg, 0.04 mmol, 20 mol%) and ketimine 6 (68.7 mg, 0.2 mmol), i-PrNET (35 µL, 0.2 mmol) and CH₂Cl₂ (2.0 mL), for 2 h gave a crude residue of 92:8 dr. Purification by flash chromatography (EtO₂ / pet ether, 1:4) gave 31 (64.6 mg, 0.13 mmol, 60%, 94:6 dr) as a white solid; mp 140-142 °C; v_max (ATR): 2976, 1727, 1710, 1448, 1146, 925; [α]_D +31.1 (c 0.54, CH₂Cl₂); HPLC (Chiralpak IA, 30% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (35,4S): 30.4 min, t_K (3R, 4R): 45.8 min, 95% ee; [H] NMR (400 MHz, CDCl₃) δ_H: 1.07 (1H, t, J = 7.1, OCH₂CH₃), 3.72 (1H, dd, J = 10.5, 4.2, C(4)H), 3.94-4.09 (3H, m, C(3)H and OCH₂CH₃), 5.85 (1H, d, J = 4.5, C(5)H), 6.87 (2H, d, J = 8.4, C(3)ArH), 7.23-7.44 (7H, m, C(3)ArH and C(6)PhH), 7.46-7.55 (2H, m, NSO-PhH), 7.66 (1H, tt, J = 7.1, 1.2, NSO-PhH); ¹³C (H) NMR (101 MHz, CDCl₃) δ_C: 14.0, 45.1, 53.6, 61.9, 115.9, 122.3, 126.2, 128.7, 128.9, 129.1, 130.5, 132.0, 134.3, 136.4, 139.1, 141.4, 170.6, 171.7; HRMS (ESI⁺): C₂₃H₁₉NO₄S [M+H⁺] found 540.0473, requires 540.0475 (−0.3 ppm).

(35,4S)-Ethyl 2-oxo-6-phenyl-1-(phenylsulfonyl)-3-(thiophen-3-yl)-1,2,3,4-tetrahydropyridine-4-carboxylate 34

Following general procedure B, the reaction of 3-thiophenylethyl acetate (56.9 mg, 0.4 mmol), i-PrNET (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH₂Cl₂ (1.0 mL), followed by (−)-tetratramisole HCI 4 (9.6 mg, 0.04 mmol, 20 mol%) and ketimine 6 (68.7 mg, 0.2 mmol), i-PrNET (35 µL, 0.2 mmol) and CH₂Cl₂ (2.0 mL), for 1 h gave a crude residue of 85:15 dr. Purification by flash chromatography (EtO₂ / pet ether, 1:4) gave 34 (59.7 mg, 0.13 mmol, 64%, 92:8 dr) as a white solid; mp 112-114 °C; v_max (ATR):
Following general procedure B, the reaction of (E)-pent-2-enoic acid (82 µL, 0.8 mmol), i-Pr2NEt (140 µL, 0.8 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH2Cl2 (2.0 mL), followed by (-)-tartaric acid HCl 4 (19.2 mg, 0.08 mmol, 20 mol%), ketimine 6 (137.2 mg, 0.4 mmol), i-Pr2NEt (70 µL, 0.4 mmol) and CH2Cl2 (4.0 mL), for 1 h gave a crude residue of 92.8 dr. Purification by flash chromatography (EtOAc / pet ether, 1:9) gave 35 (89.5 mg, 0.21 mmol, 53%, 88:12 dr) as a white solid; mp 56-58 °C; vmax (ATR): 2976, 1732, 1448, 1367, 1170, 1085, 1026, 926; [α]D20 +670 (c 0.53, CHCl3); HPLC (Chiralpak OD-H, 5% IPA / hexane, 1.0 mL/min, 2211 nm, 40 °C); tR (3S, 4R): 15.8 min, tR (3S, 4S): 19.5 min, 98% ee; [α]D20 NMR (400 MHz, CDCl3) δ1: 1.30 (3H, dd, J 6.3, 1.4, C3(CHHCH)2), 3.37 (1H, dd, J 8.8, 5.4, C4(4H)), 3.47 (1H, t, J 8.2, C3(3H)), 4.15 (2H, qd, J 7.1, 1.4, OCH2CH), 5.30 (1H, dqq, J 15.1, 8.1, 1.5, C3(CHHCH)), 5.64 (1H, m, C3(CHHCH)3), 5.80 (1H, d, J 5.4, C5(5H)), 7.30-7.38 (5H, m, C6(Ph)H), 7.44-7.51 (2H, m, NSO2Ph), 7.62 (1H, t, J 7.0, 1.2, NSO2Ph), 7.90 (2H, dt, J 8.6, 1.5, NSO2Ph); 13C NMR (101 MHz, CDCl3) δc: 143.1, 18.2, 43.7, 51.5, 61.7, 115.7, 123.8, 126.1, 128.5, 128.6, 128.9, 132.1, 131.4, 136.9, 141.2, 170.9, 171.8; HRMS (ESI+): C22H17NO2S [M+H]+ found 426.1368, requires 426.1370 (-0.4 ppm).

Derivatisations

Ethyl 2-oxo-3,6-diphenyl-1,2-dihydropyridine-4-carboxylate 44

A solution of dihydropyridinone 8 (46.2 mg, 0.11 mmol, 1 eq.) and HCOONa (34.0 mg, 0.5 mmol, 5 eq.) in MeOH (5 mL) was treated with Pd/C (12 mol%) and stirred at 60 °C for 24 h. The reaction was allowed to cool to rt, diluted with water (5 mL), filtered through Celite®, and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na2SO4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (CH2Cl2 / MeOH, 19:1) to give 44 (27.6 mg, 0.086 mmol, 86%) as a white solid; mp 182-184 °C [Lit.24 214 °C (EtOAc)]; [α]D20 H NMR (500 MHz, CDCl3) δc: 0.95 (3H, t, J 7.1, OCH2CH), 4.07 (2H, q, J 7.1, OCH2CH), 6.77 (1H, d, J 5.7, C5(5H)), 7.57-7.41 (7H, m, PhH), 7.46 (2H, d, J 6.9, C6(Ph)H), 7.78 (2H, d, J 7.7 C6(Ph)H), 12.17 (1H, br s, NH); 11C NMR (126 MHz, CDCl3) δc: 13.7, 62.0, 104.7, 126.7, 128.1, 128.2, 129.4, 129.6, 130.7, 132.3, 134.4, 143.5, 146.0, 163.9, 165.7, 167.5. Data consistent with literature.24

Ethyl 3,6-diphenyl-2-(tosyloxy)isonicotinate 45

A stirred solution of pyridine 44 (31.9 mg, 0.11 mmol, 1 eq.) in anhydrous THF (1 mL) at -78 °C under an argon atmosphere was treated with NaH (60% wt., 0.6 mg, 0.015 mmol, 1.5 eq.) followed by a solution of tosyl chloride (28.6 mg, 0.15 mmol, 1.5 eq.) in anhydrous THF (0.5 mL). After 1 h, the reaction mixture was allowed to warm to rt, then heated to 60 °C for 3 h. The reaction was poured into ice water (10 mL), neutralised with K2CO3, and extracted with CHCl3 (3 × 10 mL). The combined organic was
dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (EtO₂ / pet. ether, 1:3) to give pyridine 45 (44.6 mg, 0.094 mmol, 94%) as a white solid; mp 122-134 °C; **1H** NMR (500 MHz, CDCl₃) δ: 0.94 (3H, t, J 7.1, OCH₂CH₃), 2.47 (3H, s, Ots′CH₃), 4.07 (2H, q, J 7.1, OCH₂CH₃), 7.29 (2H, d, J 8.1, Ots′CH₃), 7.31-7.35 (2H, m, PhH), 7.37-7.49 (6H, m, PhH), 7.75-7.85 (4H, m, TsgH and PhH), 7.99 (1H, s, C(5)H), 1.06 (1H) NMR (126 MHz, CDCl₃) δ: 13.6, 21.9, 62.0, 118.1, 126.3, 127.1, 128.3, 128.4, 128.7, 128.9, 129.6, 130.1, 133.3, 135.1, 136.6, 144.4, 144.9, 155.0, 155.3, 166.5; HRMS (ESI+): C₁₅H₂₁NO₄S [M+H]⁺ found 447.1364, requires 447.1370 (+1.2 ppm).

(5S,4S)-Ethyl 2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate 48

An solution of diphydropyridine 8 (92.3 mg, 0.2 mmol, 1 eq.) in anhydrous THF (2 mL) at −78 °C under an argon atmosphere was treated dropwise with a pre-formed solution of sodium (18.4 mg, 0.8 mmol, 4 eq.) and naphthalene (102.5 mg, 0.8 mmol, 4 eq.) in anhydrous THF (2 mL) that had been stirred for 1.5 h at rt. The reaction was monitored by TLC and when complete (1 h), quenched with brine (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over MgSO₄, filtered, and the solvent removed in vacuo to obtain the crude product (+99:1 dr). Purification by flash chromatography (EtO₂ / pet. ether, 1:1) to give 48 (29.5 mg, 0.092 mmol, 46%, +99:1 dr) as a white solid; mp 100-102 °C; **1H** NMR (ATR): 3246, 2964, 1728, 1670, 1651, 1456, 1155; [α]D₂⁰ +136.5 (c 0.26, CH₂Cl₂); HPLC (Chiralpak ODH-H, 30% IPA / hexane, 0.5 mL/min, 270 nm, 30 °C): [α]D₂⁰ +29.2 min, 99% ee; **1H** NMR (400 MHz, CDCl₃) δ: 1.18 (3H, t, J 7.1, OCH₂CH₃), 3.76 (1H, dd, J 7.3, 4.8, C(4)H), 4.13 (2H, q, J 7.1, OCH₂CH₃), 4.19 (1H, d, J 7.5, C(3)H), 5.43 (1H, dd, J 4.8, 1.5, C(5)H), 7.29-7.35 (3H, m, C(3)PhH), 7.40-7.43 (2H, m, C(6)PhH), 7.45-7.47 (2H, m, C(6)PhH); ¹³C¹H NMR (101 MHz, CDCl₃) δ: 14.2, 46.7, 48.5, 61.5, 61.9, 99.3, 125.3, 127.8, 128.4, 128.9, 129.2, 129.6, 134.5, 137.3, 138.2, 170.8, 171.9; HRMS (ESI+): C₁₅H₂₁NO₂ [M+]⁺ found 232.1443, requires 232.1438 (+1.6 ppm).

(5S,4S)-Ethyl 5-bromo-2-oxo-3,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 49

A stirred solution of diphydropyridine 8 (46.2 mg, 0.1 mmol, 1 eq.) in anhydrous CH₂Cl₂ (10 mL) at −78 °C under an argon atmosphere was treated dropwise with bromine (12.8 µL, 0.25 mmol, 2.5 eq.) dropwise. i-Pr₂NEt (19.0 µL, 0.11 mmol, 1.1 eq.) was added and the reaction mixture allowed to warm to rt. The reaction was monitored by TLC and complete in 2 h. The reaction mixture was quenched with saturated aqueous Na₂SO₄ (10 mL), the layers separated and the aqueous layer extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (EtO₂ / pet. ether, 1:4) to give 49 (46.3 mg, 0.086 mmol, 86%, +99:1 dr) as a white solid; mp 130-132 °C; **1H** NMR (ATR): 2924, 1750, 1732, 1436, 1371, 1181, 1066, 885; [α]D₂⁰ +26.7 (c 0.61, CH₂Cl₂); HPLC (Chiralpak IA, 30% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): [α]D₂⁰ +9.9 min, 96 (3R, 4R): 9.9 min, 4R (3S, 4S): 15.3 min, 99% ee; **1H** NMR (500 MHz, CDCl₃) δ: 1.36 (3H, t, J 7.1, OCH₂CH₃), 4.00 (1H, d, J 3.4, C(4)H), 4.33 (2H, ddq, J 47.0, 10.8, 7.1, OCH₂CH₃), 4.54 (1H, d, J 3.4, C(3)H), 7.19 (2H, d, J 7.5, C(3)PhH), 7.23-7.39 (10H, m, PhH), 7.55 (1H, t, J 7.4, NSO₂PhH), 7.59 (2H, t, J 7.4, NSO₂PhH); ¹³C¹H NMR (126 MHz, CDCl₃) δ: 14.2, 53.8, 54.4, 62.8, 110.2, 127.6, 127.9, 128.4, 128.6, 129.0, 129.1, 129.3, 133.9, 134.2, 134.9, 137.1, 139.0, 168.9, 170.4; HRMS (ESI+): C₁₅H₁₃NO₂S [M+H]^+ found 446.0496, requires 446.0487 (+1.1 ppm).

(5S,4R,5S,6S)-Ethyl 3-oxo-1,4-diphenyl-2-(phenylsulfonyl)-7-oxa-2-azabicyclo[4.1.0]heptane-5-carboxylate 50

A solution of diphydropyridine 8 (46.2 mg, 0.1 mmol, 1 eq.) in CH₂Cl₂ (1 mL) at 0 °C was treated with m-CPBA (70 wt %, 37.0 mg, 0.15 mmol, 1.5 eq.). The reaction was allowed to warm to rt and stirred for 24 h, before being quenched with sat. NaHCO₃ (2 mL). The layers were separated and the aqueous layer extracted with D.C.
CH₂Cl₂ (3 x 5 mL). The combined organics were dried over MgSO₄,
and the solvent removed in vacuo to obtain the crude product (99:1 dr).
Purification by flash chromatography (Et₂O / pet.
ether, 1:4) gave 52 (3.42 mg, 0.072 mmol, 72%, >99:1 dr) as a white
solid; mp 116-118 °C; νmax (ATR): 2976, 2360, 2322, 1726, 1448,
1361, 1273, 1174; [α]D²⁰ -29.8 (ε 0.50, CH₂Cl₂); 1H NMR (500
MHz, CDCl₃) δ: 0.84 (3H, t, J7.1, OCH₂CH₃), 3.13 (1H, dd, J 13.1,
3.7, C(4)H), 3.79 (1H, d, J 3.79, C(5)H), 3.85 (2H, q, J 7.1, OCH₂CH₃),
4.02 (1H, d, J 13.1, C(3)H), 6.87 (2H, dd, J 7.3, 2.0, C(3)PhH),
7.24-7.28 (3H, m, C(3)PhH and C(6)PhH); 7.42-7.55
(7H, m, PhH), 7.63-7.55 (1H, m, NSO₂PhH), 7.85-7.90 (2H, m, NSO₂PhH);
13C [¹H] NMR (126 MHz, CDCl₃) δ: 13.9, 49.9, 51.1,
52.0, 62.4, 64.6, 70.0, 125.9, 128.8, 129.0, 129.2, 129.4, 129.6, 129.9 (2 x
C), 134.2, 134.8, 135.6, 138.7, 169.9, 170.8; HRMS (ESI+):
C₂₃H₂₄NO₃Na [M+N+] found 446.1389, requires 446.1397 (−1.7
ppm).

Notes and references
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[¹H] NMR spectra of all novel compounds and HPLC data. See
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