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Exploring the Scope of the Isothiourea-mediated Synthesis of Dihydropyridinones

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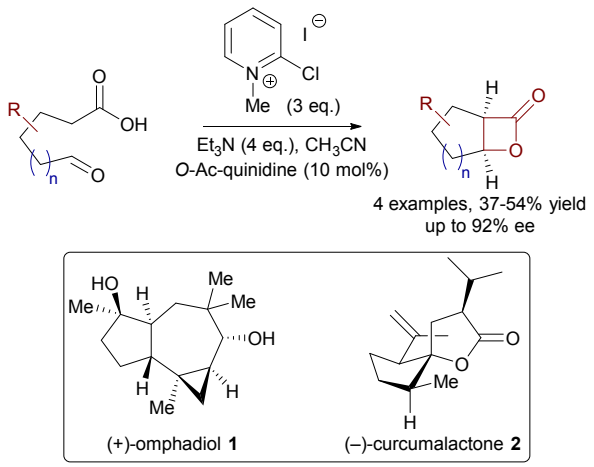
The exploration and expansion of the scope of the isothiourea-mediated synthesis of dihydropyridinones is presented. The use of ketimines derived from α,β-unsaturated γ-ketoesters as the Michael acceptor in a Michael addition / lactamisation cascade gives access to a range of dihydropyridinones with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

Introduction

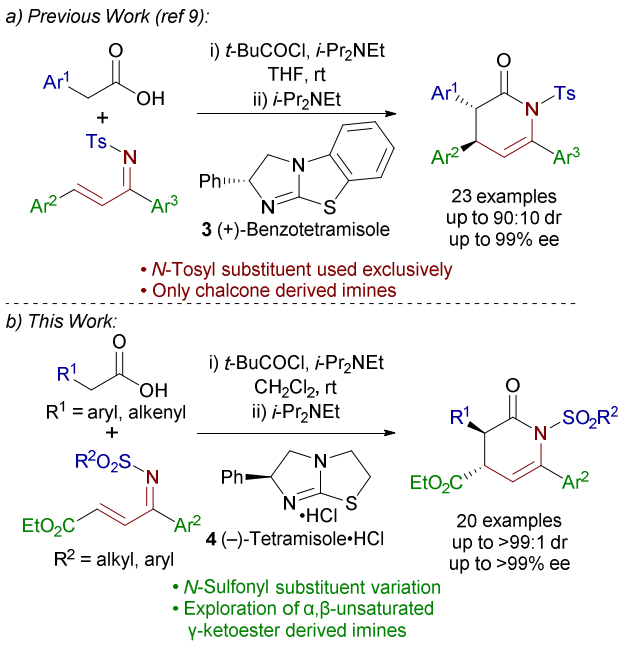
The direct organocatalytic asymmetric functionalisation of readily available, bench-stable carboxylic acids[1] towards value-added products has received much attention since the seminal report by Romo and co-workers in 2001 on the intramolecular nucleophile-catalysed aldol / lactonisation (NCAL) reaction (Scheme 1).[2] 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,[3] including the application to the total synthesis of (+)-omphadiol[3j] **1** and (−)-curcumalactone **2** (Scheme 1), amongst others.[3l]



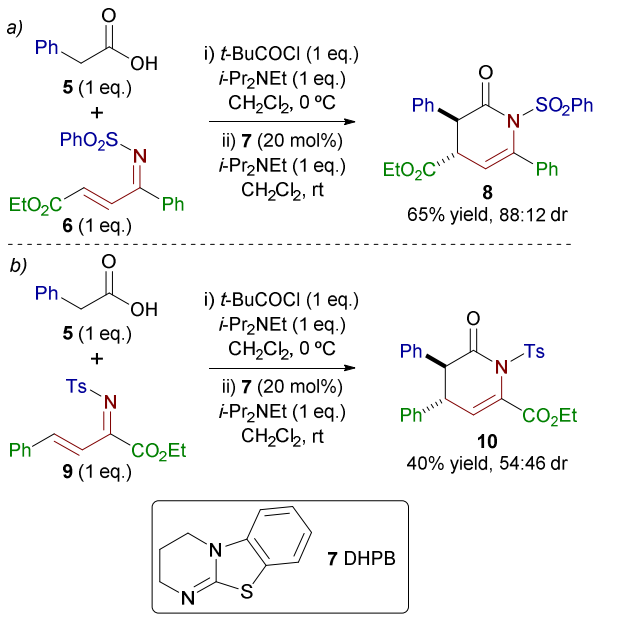
Scheme 1 Romo and co-wokers' intramolecular NCAL reaction[2] and select examples of natural products accessed using this reaction.[3j,3l]

We have previously explored the scope of the intramolecular reactions of ammonium and isothiouronium enolates,[4] allowing access to dihydrobenzofurans,[5] 2*H*-indenes,[5a] THFs,[5b] as well as pyrrolidines.[6] 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,[5a,7] β-lactams,[8] dihydropyridinones,[9] pyridines,[10] 2-pyrones[11] and a variety of acyclic products from further derivatisation of the heterocyclic cores.[12]

Our previous synthesis of dihydropyridinones reacted isothiouronium enolates generated from carboxylic acids with *N*-tosyl chalcone-derived ketimines in a Michael addition / lactamisation cascade (Scheme 2a).[9] This afforded a range of dihydropyridinones in high yields and excellent stereoselectivity. In this methodology the *N*-tosyl substituent was employed exclusively in the ketimine Michael acceptor. Furthermore, the use of chalcones as the backbone of the ketimine, alongside the requirement for aryl or heteroaryl acetic acids, resulted in dihydropyridinones furnished with three (hetero)aryl substituents thereby constraining the scope of the hetercyclic products. To extend these studies, alternative ketimine backbones incorporating more versatile functional handles, whilst maintaining the reactivity of the Michael acceptor were explored. Herein we report the successful incorporation of ketimines derived from α,β-unsaturated γ-ketoesters within this



Scheme 2 Organocatalytic synthesis of dihydropyridinones



Scheme 3 Initial investigations

methodology,[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.

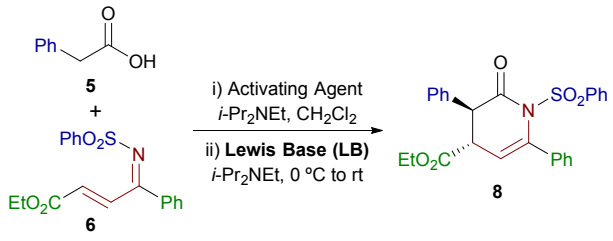
Results and Discussion

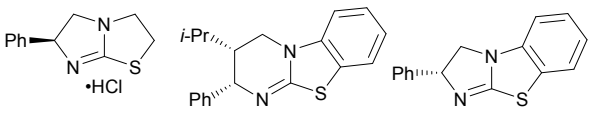
Optimisation

Initial studies showed that α,β-unsaturated γ-ketimine ester **6** was a competent electrophile for intermolecular Michael addition / lactamisation with the isothiouronium 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).[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 over a range of benzoyl chloride derivatives (entries 6-8). Tetramisole free base (entry 9) and excess *i*-Pr_2NEt (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 bench 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[a]



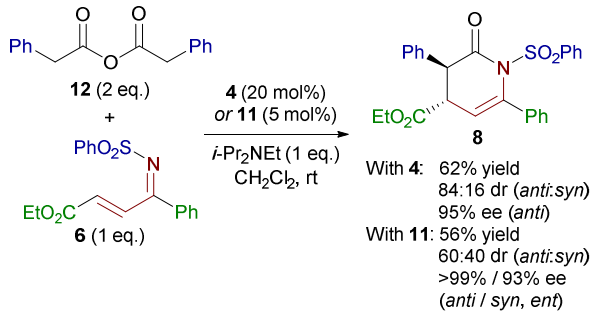


4 (–)-Tetramisole•HCl **11** HyperBTM **3** (+)-Benzotetramisole

Entry	**LB** (mol%)	Activating Agent (eq.)	time (h)	yield (%)[b]	dr (*anti:syn*)[c] / ee (*anti*, %)[d]
1	**4** (20)	*t*-BuCOCl (1)	3	46	97:3 / 98
2	**11** (20)	*t*-BuCOCl (1)	16	33	75:25 / 95 (*ent*)
3	**3** (20)	*t*-BuCOCl (1)	16	28	>95:5 / 98 (*ent*)
4	**4** (40)	*t*-BuCOCl (1)	3	75	93:7 / 98
5	**4** (10)	*t*-BuCOCl (1)	24	38	97:3 / 98
6	**4** (20)	PhCOCl (1)	3	32	91:9 / 90
7	**4** (20)	PMPCOCl[e] (1)	24	17	90:10 / 98
8	**4** (20)	PNPCOCl[f] (1)	3	29	83:17 / 94
9[g]	**4** (20)	*t*-BuCOCl (1)	3	62	93:7 / 98
10[h]	**4** (20)	*t*-BuCOCl (1)	3	31	98:2 / 98
11[i]	**4** (20)	*t*-BuCOCl (2)	1	62	93:7 / 98
12[ij]	**4 (20)**	***t*-BuCOCl (2)**	**1**	**65**	**92:8 / 98**
13[i]	**4** (10)	*t*-BuCOCl (2)	3	45	97:3 / 95
14[k]	**4** (20)	*t*-BuCOCl (2)	1	64	92:8 / 98

[a] Reaction Conditions: **5** (1 eq.), Activating agent (1 eq.), *i*-Pr_2NEt (1 eq.), CH_2Cl_2; then **6** (1 eq.), **LB**, *i*-Pr_2NEt (1 eq.); [b] Isolated yield; [c] Measured by ^1H NMR; [d] Measured by chiral HPLC; [e] PMP = 4-methoxyphenyl; [f] PNP = 4-nitrophenyl; [g] Tetramisole free base was used; [h] *i*-Pr_2NEt (1.2 eq.) was used. [i] **5** (2 eq.), activating agent (2 eq.) and *i*-Pr_2NEt (2 eq.) were used. [j] Bench-grade solvents used; [k] 5.0 mmol of **6**.

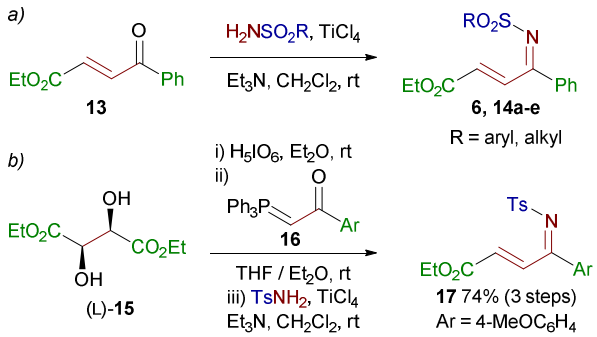
In an attempt to simplify the experimental procedure the possibility of using preformed homoanhydrides was explored (Scheme 4), with 2-phenylacetic anhydride **12** used in place of the combination of 2-phenylacetic acid and pivaloyl chloride. The purification of **8** was greatly simplified under this protocol, however lower diastereo- and enantioselectivity was observed with (−)-tetramisole·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 dihydropyridinone 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

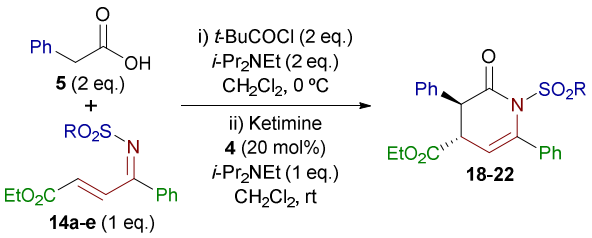
Having optimised the model system, exploration of the scope and limitations of this process required a general synthetic route to a range of ketimines. Their synthesis was achieved either directly from commercially available ethyl 3-benzoylacrylate **13** through $TiCl_4$-mediated imine formation (Scheme 5a),[13,15] or efficiently in three steps from (+)-diethyl L-tartrate **15** *via* oxidative cleavage, Wittig reaction of the resulting aldehyde,[16] and imine formation using $TiCl_4$ (Scheme 5b). In most cases the crude ketimines were purified through trituration and recrystallisation, thereby avoiding silica gel chromatography that leads to significant hydrolysis of these somewhat sensitive imines.[17]

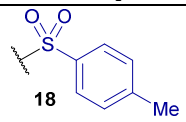
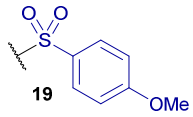
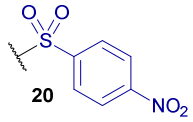
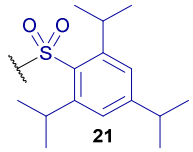


Scheme 5 Synthesis of *N*-sulfonyl ketimines

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 SO_2PMP **19**, and electron-withdrawing 4-nosyl **20** without significant variation in yield of dihydropyridinone. The sterically bulky 2,4,6-triisopropylbenzene 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



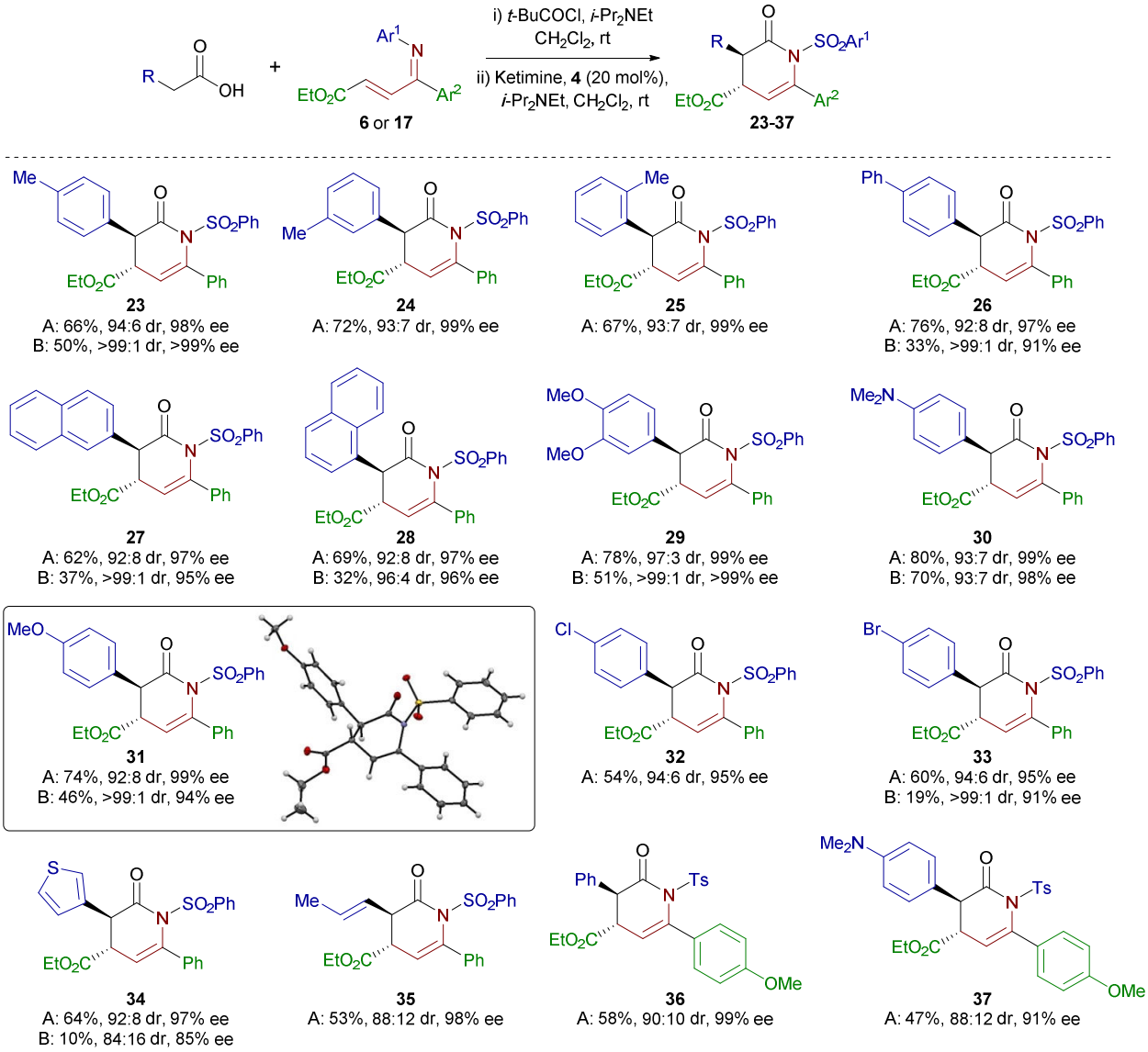
Entry	-SO_2R	yield (%)[a]	dr (*anti*:*syn*)[b]	ee (*anti*, %)[c]
1	 **18**	62	93:7	>99
2	 **19**	59	90:10	99
3	 **20**	66	>95:5	98
4	 **21**	13	>95:5	93
5	 **22**	59	92:8	99

[a] Isolated yield; [b] Measured by ^{1}H 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 benzenesulfonyl 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 dihydropyridinones[9] amongst other examples.[7,12a,12c] *para*-Phenyl as well as 1- and 2-naphthyl substitution gave the desired dihydropyridinones (**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 (*cf.* **8**). The relative and absolute configuration of **31** was determined by X-ray diffraction, with all other products assigned by analogy.[18]

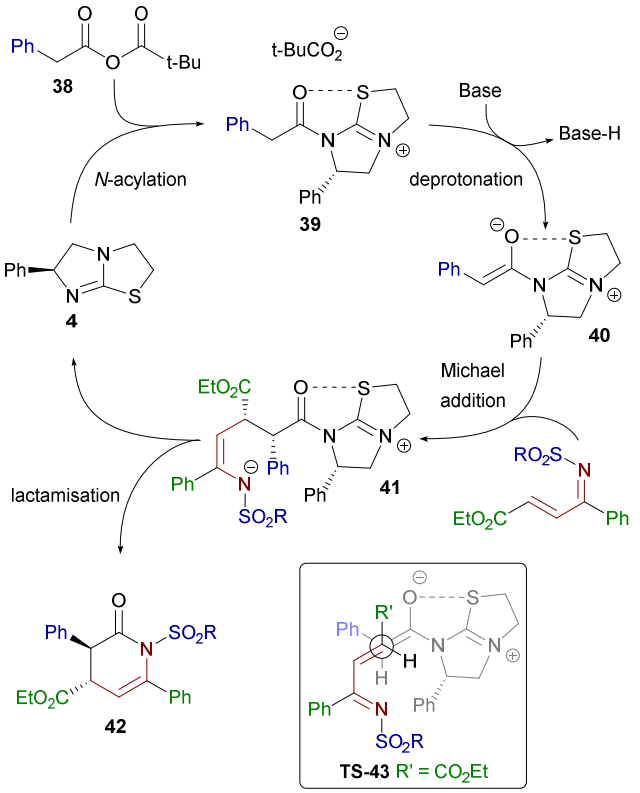
Other substituents included the heteroaromatic 3-thiophenyl dihydropyridinone **34**, which was formed without consequence as long as two equivalents of activated acetic acid were employed, and the 3-pentenoic acid derivative **35**,[12d] further expanding the scope of accessible motifs with functional 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.



Scheme 6 Variation of acetic acid and ketimine and molecular representation of X-ray structure **31**. Reaction conditons, A: Acetic acid (2 eq.), *t*-BuCOCl (2 eq.), *i*-Pr_2NEt (2 eq.), CH_2Cl_2; *then* ketimine (1 eq.), **4** (20 mol%), *i*-Pr_2NEt (1 eq.), CH_2Cl_2. B: Acetic acid (1 eq.), *t*-BuCOCl (1 eq.), *i*-Pr_2NEt (1 eq.), CH_2Cl_2; *then* ketimine (1 eq.), **4** (20 mol%), *i*-Pr_2NEt (1 eq.), CH_2Cl_2. Isolated yields; dr measured by ^1H NMR; ee measured by chiral HPLC.

Mechanistic Rationale

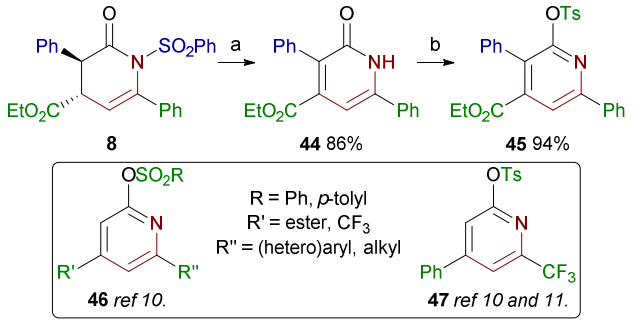
The proposed mechanism of the reaction is outlined in Scheme 7. Firstly, *N*-acylation of (−)-tetramisole **4** with mixed anhydride **38**, formed *in situ* from phenylacetic acid and pivaloyl chloride, generates acyl isothiouronium **39**. Deprotonation forms the (*Z*)-isothiouronium enolate, which 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,[17] thereby preventing *Re*-face attack through the stereodirecting phenyl group on tetramisole.



Scheme 7 Mechanistic rationale

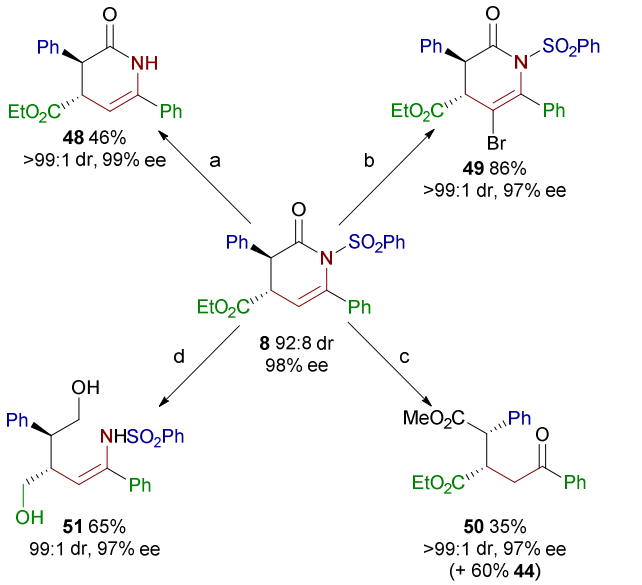
Derivatisation of the Dihydropyridinone Core

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 pyridone **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**)[10-11] 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.[10]



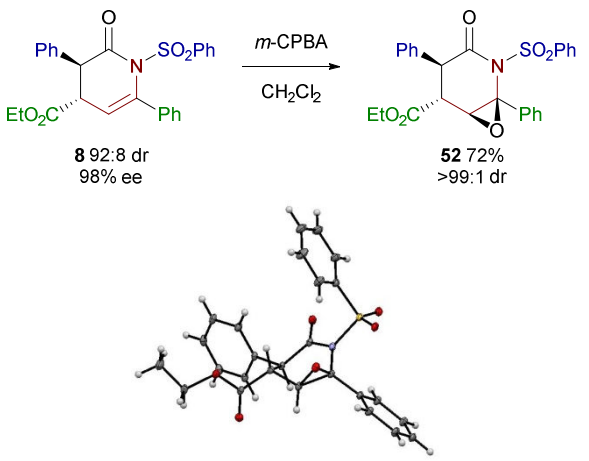
Scheme 8 Formation of tetrasubstituted pyridine **45**. Reaction conditions: a) Pd/C, HCO_2Na, DMF, 60 °C; b) NaH, TsCl, DMF.

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_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-diester **50** in high enantioselectivity, alongside 60% of pyridone **44** from competing dehydrogenation / desufonylation under these more forcing conditions (Scheme 9c). Reduction of **8** with $LiAlH_4$ followed by an acidic workup afforded a good yield of acyclic enamine-diol **51** as a single diastereoisomer without loss of enantiopurity (Scheme 9d). It is perhaps surprising that the *N*-sulfonyl enamine is isolable under these conditions, but the good isolated yield indicates significant stability of this functionality.[20]



Scheme 9 Derivatisations of the dihydropyridinone core. Reaction conditions: a) Na / naphthalene (4 eq.), −78 °C; b) Br_2, *i*-Pr_2NEt; c) Mg / MeOH; d) i) 2 M $LiAlH_4$, THF; ii) 0.1 M HCl.

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*-CPBA.[21] 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.[22]



Scheme 10 Epoxidation of **8** and molecular representation of X-ray structure **52**

Conclusions

In conclusion, the scope of the isothiourea catalysed Michael addition / lactamisation of aryl and alkenyl acetic acids with α,β-unsaturated ketimines has been expanded, thereby allowing the synthesis of a variety of dihydropyridinone products. Derivatisation of the dihydropyridinone 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

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Experimental

General Information

Anhydrous CH_2Cl_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 Chiralcel 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 (ν_{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 {δ_H (300 MHz), δ_C (75 MHz), δ_F (282 MHz)}, a Bruker Avance II 400 {δ_H (400 MHz), δ_C (101 MHz), δ_F (376 MHz)} or a Bruker Ultrashield 500 {δ_H (500 MHz), δ_C (126 MHz), δ_F (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_2Cl_2 (*ca.* 0.2 M). The resulting solution was stirred and cooled to 0 °C before Et_3N (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_2O 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_2O (*ca.* 5 mL / g) with stirring. The resultant solid was collected by filtration and washed with further portions of cold Et_2O. The solid was dried *in vacuo* to leave the pure ketimines.

General Procedure B: Synthesis of Dihydropyridinones

A flask containing a stirrer bar was charged with CH_2Cl_2 (to give 0.4 M acid] , aryl acetic acid (2 eq.), *i*-Pr_2NEt (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*-Pr_2NEt (1 eq.) in CH_2Cl_2 (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 CH_2Cl_2 (2 × eq. vol.). The combined organics were dried over $MgSO_4$, 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)imino)but-2-enoate 6[13a]

Following general procedure A, the reaction of ethyl 3-benzoylacrylate **13** (1.84 mL, 10 mmol), benzenesulfonamide (1.57 g, 10.0 mmol), NEt_3 (2.8 mL, 20 mmol) and $TiCl_4$ (1.1 mL, 10 mmol) in CH_2Cl_2 (60 mL) gave the title compound after trituration as white crystals (2.04 g, 6.0 mmol, 60%); mp 51-52 °C {Lit.[13a] 51-53 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.35 (3H, t, *J* 7.0, OCH_2CH_3), 4.30 (2H, q, *J* 6.3, OCH_2CH_3), 6.24 (1H, d, *J* 16.2, C(2)*H*), 7.44 (2H, t, *J* 7.7, Ph*H*), 7.51-7.56 (3H, m, Ph*H*), 7.62 (1H, t, *J* 7.4, Ph*H*), 8.03 (2H, s, Ph*H*), 8.24 (1H, d, *J* 16.1, C(3)*H*). Data consistent with literature.[13a]

(2*E*,3*E*)-Ethyl 4-phenyl-2-(tosylimino)but-3-enoate 9[23]

The starting ketone, (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate, was prepared according the procedure outlined by Smith *et al*.[5a]

Following general procedure A, the reaction of the above ketone (2.0 g, 9.8 mmol), *p*-toluenesulfonamide (1.68 g, 9.8 mmol), NEt_3 (2.8 mL, 19.6 mmol) and $TiCl_4$ (1.1 mL, 9.8 mmol) in CH_2Cl_2 (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%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.48 (3H, t, *J* 7.1, OCH_2CH_3), 2.43 (3H, s, NTsC*H*$_3$), 4.55 (2H, q, *J* 7.1, OCH_2CH_3), 6.82 (1H, d, *J* 16.5, C(2)*H*), 7.29-7.56 (8H, m, Ar*H* and C(3)*H*), 7.90 (2H, d, *J* 8.3, Ar*H*). Data consistent with literature.[23]

(2*E*,4*E*)-Ethyl 4-phenyl-4-(tosylimino)but-2-enoate 14a

Following general procedure A, the reaction of ethyl 3-benzoylacrylate (1.84 mL, 10 mmol), *p*-toluenesulfonamide (1.68 g, 10.0 mmol), NEt_3 (2.8 mL, 20 mmol) and $TiCl_4$ (1.1 mL, 10 mmol) in CH_2Cl_2 (60 mL) gave the title compound after trituration (1.22 g, 3.4 mmol, 34%) as white crystals; mp 53-54 °C; ν_{max} (ATR): 2938, 1714, 1545, 1304, 1157, 1094; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.35 (3H, t, *J* 6.8, OCH_2CH_3), 2.44 (3H, s, NTsC*H*$_3$), 4.30 (2H, q, *J* 6.6, OCH_2CH_3), 6.22 (1H, d, *J* 16.2, C(2)*H*), 7.34 (2H, d, *J* 7.9, Ar*H*), 7.43 (2H, t, *J* 7.6, Ar*H*), 7.56 (1H, t, *J* 7.4, Ar*H*), 7.72 (2H, s, Ar*H*), 7.84-7.96 (2H, br s, Ar*H*), 8.24 (1H, d, *J* 16.1, C(3)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 14.1, 21.5, 61.5, 127.4, 128.5, 129.5, 130.1, 132.8, 133.3, 135.7, 136.7, 137.6, 144.0, 164.5, 174.5; HRMS (ESI+): $C_{19}H_{20}NO_4S$ $[M+H]^+$ found 358.1107, requires 358.1108 (−0.2 ppm).

(2*E*,4*E*)-Ethyl 4-(((4-methoxyphenyl)sulfonyl)imino)-4-phenylbut-2-enoate 14b

Following general procedure A, the reaction of ethyl 3-benzoylacrylate (0.92 mL, 5.0 mmol), 4-methoxybenzenesulfonamide (0.94 g, 5.0 mmol), NEt_3 (1.39 mL, 10.0 mmol) and $TiCl_4$ (0.55 mL, 5.0 mmol) in CH_2Cl_2 (30 mL), gave the title compound after trituration (0.95 g, 2.5 mmol, 50%) as an orange solid; mp 76-78 °C; ν_{max} (ATR): 2985, 1716, 1552, 1494, 1311, 1255, 1184, 1143, 1089, 1002, 975; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.35 (1H, t, *J* 6.4, OCH_2CH_3), 3.38 (3H, s, ArOC*H*$_3$), 4.18-4.40 (2H, m, OCH_2CH_3), 6.21 (1H, d, *J* 16.2, C(2)*H*), 7.00 (2H, d, *J* 8.3, Ph*H*), 7.43 (2H, t, *J* 7.5, Ph*H*), 7.56 (1H, t, *J* 7.2, Ph*H*), 7.63-7.80 (2H, m, $NSO_2ArC(3)H$), 7.97 (2H, d, *J* 3.7, $NSO_2ArC(2)H$), 8.25 (1H, d, *J* 16.2, *C*(3)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 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+): $C_{19}H_{20}NO_5S$ $[M+H]^+$ found 374.1054, requires 374.1057 (−0.7 ppm).

(2*E*,4*E*)-Ethyl 4-(((4-nitrophenyl)sulfonyl)imino)-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), NEt_3 (1.39 mL, 10.0 mmol) and $TiCl_4$ (0.55 mL, 5.0 mmol) in CH_2Cl_2 (30 mL), gave the title compound after trituration as a yellow solid (1.32 g, 3.4 mmol, 68%); mp 84-86 °C; ν_{max} (ATR): 3115, 2978, 1724, 1519, 1294, 1271, 1184, 1161, 1147, 1091, 1029, 983; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.35 (1H, t, *J* 7.1, OCH_2CH_3), 4.18 (2H, q, *J* 7.1, OCH_2CH_3), 6.32 (1H, d, *J* 16.1, C(2)*H*), 7.47 (2H, d, *J* 7.8, Ph*H*), 7.61 (1H, t, *J* 7.5, Ph*H*), 7.65-7.80 (2H, m, Ph*H*), 8.20-8.27 (3H, m, $NSO_2ArC(2)H$ and C(3)*H*), 8.39 (2H, d, *J* 8.8, $NSO_2ArC(3)H$); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 14.3, 61.9, 124.4, 128.8, 129.0, 130.4, 134.0, 134.1, 135.3, 146.4, 150.4, 164.5, 176.6; HRMS (ESI+): $C_{18}H_{17}N_2O_6S$ $[M+H]^+$ found 389.0802, requires 389.0802 (±0.0 ppm).

(2*E*,4*E*)-Ethyl 4-phenyl-4-(((2,4,6-triisopropylphenyl)sulfonyl)imino)but-2-enoate 14d

Following general procedure A, the reaction of ethyl 3-benzoylacrylate (7.3 mL, 40.0 mmol), 2,4,6-triisopropylbenzenesulfonamide (11.34 g, 40.0 mmol), NEt_3 (11.2 mL, 80.0 mmol) and $TiCl_4$ (4.4 mL, 5.0 mmol) in CH_2Cl_2 (120 mL), gave the title compound after trituration as a white solid (14.50 g, 30.8 mmol, 77%); mp 104-106 °C; ν_{max} (ATR): 2964, 1720, 1622, 1150, 939; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.25 (18H, app t, *J* 6.9, $Ar(CH(CH_3)_2)_3$), 1.31 (3H, t, *J* 7.1, OCH_2CH_3), 2.90 (1H, septet, *J* 6.8, ArC(4)C*H*$(CH_3)_2$), 4.20-4.29 (4H, m, OCH_2CH_3 and ArC(2)C*H*$(CH_3)_2$), 6.09 (1H, d, *J* 16.3, C(2)*H*), 7.16 (2H, s, $NSO_2ArC(3)H$), 7.42 (2H, t, *J* 7.1, Ph*H*), 7.49-7.61 (1H, m, Ph*H*), 7.76 (2H, d, *J* 6.1, Ph*H*), 8.05 (1H, d, *J* 16.3, C(3)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.3, 23.8, 24.8, 30.2, 34.4, 61.6, 123.7, 128.8, 130.3, 132.4, 133.3, 134.2, 136.2, 136.7, 150.0, 153.3, 164.6, 173.8; HRMS (ESI+): $C_{35}H_{41}N_1O_5Na_1S_1$ ($[M+Na]^+$), found 610.2603 requires 610.2592 (−1.2 ppm).

(2*E*,4*E*)-Ethyl 4-((methylsulfonyl)imino)-4-phenylbut-2-enoate 14e

Following general procedure A, the reaction of ethyl 3-benzoylacrylate (0.92 mL, 5.0 mmol), methanesulfonamide (0.48 g, 5.0 mmol), NEt_3 (1.39 mL, 10.0 mmol) and $TiCl_4$ (0.55 mL, 5.0 mmol) in CH_2Cl_2 (30 mL), gave the title compound after trituration as an orange solid (0.87 g, 3.1 mmol, 62%); mp 76-78 °C; ν_{max} (ATR): 2991, 1718, 1639, 1579, 1554, 1442, 1365, 1309, 1292, 1269, 1184, 1134, 1026, 970; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.32 (3H, t, *J* 7.1, OCH_2CH_3), 3.26 (3H, s, SO_2CH_3), 4.28 (2H, q, *J* 7.1,

OCH_2CH$_3$), 6.25 (1H, d, *J* 16.2, C(2)*H*), 7.47 (2H, t, *J* 7.8, Ph*H*), 7.60 (1H, t, *J* 7.1, Ph*H*), 7.76 (2H, d, *J* 7.2, Ph*H*), 8.13 (1H, d, *J* 16.2, C(3)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1, 43.0, 61.6, 128.8, 130.1, 133.3, 133.5, 135.7, 136.2, 164.5, 175.3; HRMS (ESI+): $C_{13}H_{16}NO_4S$ $[M+H]^+$, found 282.0792, requires 282.0795 (−0.9 ppm).

(2*E*,4*E*)-Ethyl 4-(4-methoxyphenyl)-4-(tosylimino)but-2-enoate 17[13a]

A flame-dried flask containing a stirrer bar was charged with (+)-diethyl (L)-tartrate **15** (0.66 mL, 3.0 mmol, 1 eq.) and anhydrous Et_2O (6 mL). Periodic acid (0.68 g, 3.0 mmol, 1 eq.) was added and the reaction stirred for 3 h at rt. The suspension was filtered through cotton wool into a second flask, washing with anhydrous THF (7.5 mL). The filtrate was treated with $MgSO_4$ (1.0 g) and the resulting suspension cooled to 0 °C. 1-(4-Methoxyphenyl)-2-(triphenylphosphoranylidene)ethanone **16** (1.85 g, 4.5 mmol, 1.5 eq.) was then added in one portion. The reaction was allowed to warm slowly to rt and stirred overnight. The solution was filtered and the solvent was removed *in vacuo* before purification of the crude material by flash chromatography on silica gel (Et_2O / hexane 0:100 to 30:70) to give (*E*)-ethyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate **17** (0.92 g, 3.9 mmol, 87%) as a yellow solid.

Following general procedure A with a modified work up, the reaction of (*E*)-ethyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate (0.77 g, 3.3 mmol), *p*-toluenesulfonamide (0.57 g, 3.3 mmol), NEt_3 (0.92 mL, 6.6 mmol) and $TiCl_4$ (0.36 mL, 3.3 mmol) in CH_2Cl_2 (17 mL) was followed by aqueous work up. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (×3), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mLmin^{-1}, hexane:EtOAc (75:25 2CV, 57:43 7CV)] to give the title compound **17** (1.08 g, 2.8 mmol, 85%) as a thick yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 6.7, OCH_2CH_3), 2.43 (3H, s, NTsCH_3), 3.85 (3H, s, ArOCH_3), 4.29 (2H, q, *J* 6.9, OCH_2CH$_3$), 6.18 (1H, d, *J* 16.2, C(2)*H*), 6.90 (2H, d, *J* 8.2, NSO_2Ar*H*), 7.32 (2H, d, *J* 7.5, C(4)Ar*H*), 7.75 (2H, d, *J* 7.0, NSO_2Ar*H*), 7.89 (2H, d, *J* 7.4, C(4)Ar*H*), 8.01-8.21 (1H, m, C(3)*H*). Data consistent with literature.[13a]

Preparation of Dihydropyridinones

(3*S*,4*S*)-Ethyl 2-oxo-3,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 8

Following general procedure B, the reaction of phenylacetic acid (1.36 g, 10.0 mmol), *i*-Pr_2NEt (1.73 mL, 10.0 mmol) and pivaloyl chloride (1.23 mL, 10.0 mmol) in CH_2Cl_2 (25 mL), followed by (−)-tetramisole·HCl **4** (0.24 g, 1.0 mmol, 20 mol%), ketimine **6** (1.72 g, 5.0 mmol), *i*-Pr_2NEt (0.87 mL, 5.0 mmol) and CH_2Cl_2 (50 mL), for 1 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **8** (1.48 g, 3.2 mmol, 64%, 92:8 dr) as a white solid; mp 128-129 °C; ν_{max} (ATR): 2970, 1722, 1448, 1155, 989; $[\alpha]_D^{20}$ +32.9 (*c* 0.55, $CHCl_3$); HPLC (Chiralpak IA, 20% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 13.2 min, t_R (3*R*, 4*R*): 33.1 min, 98% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.04 (3H, t, *J* 7.1, OCH_2CH_3), 3.75 (1H, dd, *J* 9.6, 4.8, C(4)*H*), 4.02 (2H, qd, *J* 7.5, 3.4, OCH_2CH$_3$), 4.10 (1H, d, *J* 9.6, C(3)*H*), 5.87 (1H, d, *J* 4.8, C(5)*H*), 7.01 (2H, dd, *J* 6.4, 2.4, C(3)Ph*H*), 7.26-7.27 (3H, m, C(3)Ph*H*), 7.38-7.40 (5H, m, C(6)Ph*H*), 7.50 (2H, t, *J* 7.9, NSO_2Ph*H*), 7.65 (1H, t, *J* 7.4, NSO_2Ph*H*), 7.95 (2H, d, *J* 8.0, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 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$^+$): $C_{26}H_{24}NO_5S$ $[M+H]^+$ found 462.1373, requires 462.1370 (+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*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by DHPB **7** (7.6 mg, 0.04 mmol, 20 mol%), ketimine **9** (71.6 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 59:41 dr. Purification by flash chromatography (Et_2O / petrol, 1:4) gave **10** (37.9 mg, 0.08 mmol, 40%, 54:46 dr) as a white solid; mp 118-120 °C; ν_{max} (ATR): 2987, 1724, 1597, 1363, 1170, 1085, 1028; ^{1}H NMR (300 MHz, $CDCl_3$, *both diastereoisomers*) δ_H: 1.37-1.43 (3H, m, OCH_2CH_3), 2.44 (3H, s, NTsCH_3), 3.85 (1H, d, *J* 10.2, C*H*), 4.03 (1H, d, *J* 5.8, C*H*), 4.08 (2H, q, *J* 5.3, 4.5, OCH_2CH$_3$), 4.28-4.52 (3H, m, OCH_2CH$_3$ and C*H*), 6.54-6.63 (1H, m, Ar*H*), 6.65 (1H, d, *J* 4.2, Ar*H*), 6.69 (1H, d, *J* 6.0, Ar*H*), 6.85 (1H, dd *J* 7.9, 1.5, Ar*H*), 6.87-6.94 (1H, m, Ar*H*), 7.00 (1H, dd, *J* 7.4, 5.8, Ar*H*), 7.04-7.13 (2H, m, Ar*H*), 7.12-7.25 (7H, m, Ar*H*), 7.32 (2H, t, *J* 8.2, Ar*H*), 8.11 (2H, d, *J* 8.4, Ar*H*), 8.14-8.23 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2) δ_C: 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, 127.9, 128.5, 128.5, 128.8, 128.8, 128.9, 129.3, 129.3, 129.4, 129.5 129.6, 129.9, 131.9, 132.8, 133.2, 135.4, 135.7, 138.8, 145.8, 170.2, 170.9; HRMS (ESI$^+$): $C_{27}H_{26}NO_5S$ $[M+H]^+$ found 476.1527, requires 476.1526 (+0.2 ppm).

(3*S*,4*S*)-Ethyl 2-oxo-3,6-diphenyl-1-tosyl-1,2,3,4-tetrahydropyridine-4-carboxylate 18

Following general procedure B, the reaction of phenylacetic acid (1.36 g, 10.0 mmol), *i*-Pr_2NEt (1.73 mL, 10.0 mmol) and pivaloyl chloride (1.23 mL, 10.0 mmol) in CH_2Cl_2 (25 mL), followed by (−)-tetramisole·HCl **4** (0.24 g, 1.0 mmol, 20 mol%), ketimine **14a** (1.79 g, 5.0 mmol), *i*-Pr_2NEt (0.87 mL, 5.0 mmol) and CH_2Cl_2 (50 mL), for 1 h gave a crude residue of 92:8 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **18** (1.47 g, 3.1 mmol, 62%, 93:7 dr) as a white solid. Further recrystallisation (Et_2O) gave **18** as a single diastereoisomer (0.80 g, 1.68 mmol, 33%) as a white solid; mp 129-130 °C; ν_{max} (ATR): 2978, 1726, 1363, 1166, 927; $[\alpha]_D^{20}$ +50.2 (*c* 0.49, $CHCl_3$); HPLC (Chiralpak IA, 30% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 20.0 min, t_R (3*R*, 4*R*): 40.6 min, >99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.08 (3H, t, *J* 7.1, OCH_2CH_3), 2.49 (3H, s, TsCH_3), 3.79 (1H, dd, *J* 9.6, 4.8, C(4)*H*), 4.05 (2H, qd, *J* 7.0, 3.7, OCH_2CH$_3$), 4.13 (1H, d, *J* 9.6, C(3)*H*), 5.89 (1H, d, *J* 4.8, C(5)*H*), 7.06 (2H, dd, *J* 6.9, 2.2, C(3)Ph*H*), 7.30-7.33 (8H, m, Ph*H*), 7.40-7.45 (2H, d, *J* 9.0, NTs*H*), 7.87 (2H, d, *J* 9.0, NTs*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 14.0, 21.9, 45.3, 54.1, 61.7, 115.8, 126.2, 128.1, 128.6, 128.7, 128.8, 128.9, 129.3, 129.6, 135.5, 136.4, 136.8, 141.4, 145.3, 170.9, 172.0; HRMS (ESI+): $C_{29}H_{26}NO_5S$ $[M+H]^+$ found 476.1526, requires 476.1526 (±0.0 ppm).

(3*S*,4*S*)-Ethyl 1-((4-methoxyphenyl)sulfonyl)-2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate 19

Following general procedure B, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **14b** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0

mL), for 1 h gave a crude residue of 95:5 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **19** (58.2 mg, 0.12 mmol, 59%, 90:10 dr) as a white solid; mp 114-115 °C; ν_{max} (ATR): 2976, 1720, 1593, 1531, 1496, 1446, 1365, 1303, 1261, 1161, 1087, 1024, 979; $[\alpha]_D^{20}$ +18.1 (*c* 0.52, $CHCl_3$); HPLC (Chiralpak AD-H, 30% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 17.5 min, t_R (3*R*, 4*R*): 55.6 min, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.04 (3H, t, *J* 7.1, OCH_2CH_3), 3.74 (1H, dd, *J* 9.7, 4.8, C(4)*H*), 3.89 (3H, s, $ArOCH_3$), 4.01 (2H, qd, *J* 7.1, 1.7, OCH_2CH_3), 4.08 (1H, d, *J* 9.7, C(3)*H*), 5.83 (1H, d, *J* 4.8, C(5)*H*), 6.93 (2H, d, *J* 9.1, NSO_2ArH), 7.01-7.07 (2H, m, C(3)Ph*H*), 7.26-7.30 (3H, m, C(3)Ph*H*), 7.34-7.42 (5H, m, C(6)Ph*H*), 7.87 (2H, d, *J* 9.1, NSO_2ArH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.0, 45.2, 54.1, 55.9, 61.7, 113.7, 115.7, 126.1, 128.1, 128.5, 128.7, 128.9, 129.8, 130.5, 131.9, 135.5, 136.8, 141.3, 164.1, 170.9, 172.0; HRMS (ESI+): $C_{27}H_{26}NO_6S$ $[M+H]^+$ found 492.1470, requires 492.1475 (−1.1 ppm).

(3*S*,4*S*)-Ethyl 1-((4-nitrophenyl)sulfonyl)-2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate 20

Following general procedure B, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **14c** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 95:5 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **20** (67 mg, 0.13 mmol, 66%, >95:5 dr) as a white solid; mp 178-180 °C; ν_{max} (ATR): 3066, 1728, 1521, 1373, 1348, 1261, 1172, 1147, 1107, 1083, 1026, 931; $[\alpha]_D^{20}$ +4.5 (*c* 0.65, $CHCl_3$); HPLC (Chiralpak IA, 30% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 14.8 min, t_R (3*R*, 4*R*): 25.4 min, 98% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.12 (3H, t, *J* 7.1, OCH_2CH_3), 3.79 (1H, dd, *J* 7.8, 5.6, C(4)*H*), 4.07 (2H, qd, *J* 7.8, 2.8, OCH_2CH_3), 4.15 (1H, d, *J* 5.6, C(3)*H*), 5.84 (1H, d, *J* 5.6, C(5)*H*), 7.13 (1H, dd, *J* 7.5, 1.8, C(3)Ph*H*), 7.28-7.44 (8H, m, Ph*H*), 8.10 (2H, d, *J* 9.0, NSO_2ArH), 8.30 (2H, d, *J* 9.0, NSO_2ArH); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 14.1, 44.9, 53.7, 62.0, 116.2, 123.7, 126.3, 128.4, 128.4, 128.7, 129.1, 129.3, 131.0, 135.0, 136.2, 141.1, 144.4, 150.8, 170.7, 172.0; HRMS (ESI+): $C_{26}H_{23}N_2O_7S$ $[M+H]^+$ found 507.1213, requires 507.1220 (−1.5 ppm).

(3*S*,4*S*)-Ethyl 2-oxo-3,6-diphenyl-1-((2,4,6-triisopropylphenyl)sulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 21

Following general procedure B, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **14d** (93.9 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of >95:5 dr. Recrystallisation (pet. ether) gave **21** (15.4 mg, 0.03 mmol, 13%, >95:5 dr) as a white solid; mp 215-216 °C; ν_{max} (ATR): 2960, 1734, 1715, 1599, 1172, 938; $[\alpha]_D^{20}$ +110 (*c* 0.15, CH_2Cl_2); HPLC (Chiralpak AD-H, 5% IPA / hexane, 1.5 mL/min, 254 nm, 40 °C): t_R (3*S*, 4*S*): 3.44 min, t_R (3*R*, 4*R*): 3.66 min, 93% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.96 (3H, t, *J* 7.1, OCH_2CH_3), 1.27 (6H, d, *J* 6.5, $NSO_2ArCH(CH_3)_2$), 1.29-1.37 (12H, m, $NSO_2ArCH(CH_3)_2$), 2.96 (1H, septet, *J* 6.9, $NSO_2ArCH(CH_3)_2$), 3.72 (1H, dd, *J* 12.9, 3.4, C(4)*H*), 3.95 (2H, q, *J* 7.1, OCH_2CH_3), 4.04 (1H, d, *J* 12.9, C(3)*H*), 4.18 (2H, d, *J* 6.6, $NSO_2ArCH(CH_3)_2$), 5.80 (1H, d, *J* 3.4, C(5)*H*), 6.71-6.84 (2H, m, Ph*H*), 7.17-7.23 (5H, m, Ph*H* and NSO_2ArH), 7.39-7.47 (3H, m, Ph*H*), 7.61-7.63 (2H, m, Ph*H*); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 13.9, 23.7, 23.8, 25.0, 25.4, 29.9, 34.4, 45.9, 53.3, 61.5, 114.8, 123.8, 126.2, 127.8, 128.4, 128.6, 129.0, 129.2, 133.7, 135.5, 137.1, 142.1, 152.4, 154.2, 171.0, 171.2; HRMS (ESI+): $C_{35}H_{41}NO_5SNa$ $[M+Na]^+$ found 610.2592, requires 610.2603 (−1.2 ppm).

(3*S*,4*S*)-Ethyl 1-(methylsulfonyl)-2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate 22

Following general procedure B, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **14e** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 91:9 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **22** (47.1 mg, 0.12 mmol, 59%, 92:8 dr) as a white solid; mp 131-132 °C; ν_{max} (ATR): 2916, 1708, 1653, 1496, 1446, 1344, 1165, 1151, 1118, 960; $[\alpha]_D^{20}$ −6.3 (*c* 0.51, $CHCl_3$); HPLC (Chiralpak IA, 30% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 41.5 min, t_R (3*R*, 4*R*): 45.0 min, 99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.18 (1H, t, *J* 7.1, OCH_2CH_3), 3.46 (3H, s, $MsCH_3$), 3.78 (1H, t, *J* 6.3, C(4)*H*), 4.14 (2H, q, *J* 7.1, OCH_2CH_3), 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, Ph*H*); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 14.1, 43.9, 44.9, 53.2, 62.0, 114.3, 125.5, 128.2, 128.3, 128.8, 129.9, 129.1, 135.0, 137.0, 141.2, 171.2, 173.0; HRMS (ESI+): $C_{21}H_{22}NO_5S$ $[M+H]^+$ found 400.1216, requires 400.1213 (+0.7 ppm).

(3*S*,4*S*)-Ethyl 2-oxo-6-phenyl-1-(phenylsulfonyl)-3-(*p*-tolyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 23

Following general procedure B, the reaction of *p*-tolylacetic acid (60.1 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 92:8 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **23** (63.2 mg, 0.13 mmol, 66%, 94:6 dr) as a white solid; mp 100-102 °C; ν_{max} (ATR): 2933, 1730, 1516, 1355, 1159, 929; $[\alpha]_D^{20}$ +31.1 (*c* 0.54, CH_2Cl_2); HPLC (Chiralpak IA, 20% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 30.4 min, t_R (3*R*, 4*R*): 55.2 min, 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.06 (3H, t, *J* 7.1, OCH_2CH_3), 2.29 (3H, s, *p*-tolylArCH_3), 3.72 (1H, dd, *J* 9.7, 4.8, C(4)*H*), 3.97-4.07 (3H, m, C(3)*H* and OCH_2CH_3), 5.84 (1H, d, *J* 4.8, C(5)*H*), 6.88 (2H, d, *J* 8.1, C(3)Ar*H*), 7.07 (2H, d, *J* 7.9, C(3)Ar*H*), 7.31-7.42 (5H, m, C(6)Ph*H*), 7.49 (2H, t, *J* 7.4, NSO_2PhH), 7.64 (1H, t, *J* 7.4, NSO_2PhH), 7.94 (2H, d, *J* 1.5, NSO_2PhH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.2, 21.2, 45.2, 53.7, 61.7, 116.0, 126.2, 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+): $C_{27}H_{26}NO_5S$ $[M+H]^+$ found 476.1524, requires 476.1526 (−0.5 ppm).

(3*S*,4*S*)-Ethyl 2-oxo-6-phenyl-1-(phenylsulfonyl)-3-(*m*-tolyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 24

Following general procedure B, the reaction of *m*-tolylacetic acid (60.1 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 92:8 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **24** (69.6 mg, 0.15 mmol, 72%, 93:7 dr) as a white solid; mp 134-136 °C; ν_{max} (ATR):

2922, 1726, 1516, 1359, 1155, 887; $[\alpha]_D^{20}$ +27.9 (*c* 0.64, CH_2Cl_2); HPLC (Chiralpak IA, 10% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 22.7 min, t_R (3*R*, 4*R*): 62.7 min, 99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.05 (3H, t, *J* 7.1, OCH_2CH_3), 2.26 (3H, s, *m*-tolylArCH_3), 3.72 (1H, dd, *J* 9.5, 4.9, C(4)*H*), 3.98-4.07 (3H, m, C(3)*H* and OCH_2CH_3), 5.84 (1H, d, *J* 4.9, C(5)*H*), 6.77-6.81 (2H, m, C(3)Ar*H*), 7.05 (1H, d, *J* 7.6, C(3)Ar*H*), 7.14 (1H, t, *J* 7.6, C(3)Ar*H*), 7.33-7.42 (5H, m, C(6)Ph*H*), 7.50 (2H, t, *J* 7.9, NSO_2Ph*H*), 7.65 (1H, t, *J* 7.4, NSO_2Ph*H*), 7.96 (2H, d, *J* 1, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.0, 21.5, 45.2, 53.9, 61.7, 115.8, 125.6, 126.1, 128.6 (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+): $C_{27}H_{26}NO_5S$ $[M+H]^+$ found 476.1522, requires 476.1526 (−0.9 ppm).

(3*S*,4*S*)-Ethyl 2-oxo-6-phenyl-1-(phenylsulfonyl)-3-(*o*-tolyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 25

Following general procedure B, the reaction of *o*-tolylacetic acid (60.1 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 92:8 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **25** (63.9 mg, 0.13 mmol, 67%, 93:7 dr) as a white solid; mp 78-80 °C; ν_{max} (ATR): 2922, 1726, 1516, 1359, 1155, 887; $[\alpha]_D^{20}$ +45.8 (*c* 0.55, CH_2Cl_2); HPLC (Chiralpak IA, 10% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 16.3 min, t_R (3*R*, 4*R*): 56.5 min, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.00 (1H, t, *J* 7.1, OCH_2CH_3), 2.25 (3H, s, *o*-tolylArCH_3), 3.85 (1H, dd, *J* 10.9, 4.3, C(4)*H*), 4.00 (2H, q, *J* 7.1, OCH_2CH_3), 4.31 (1H, d, *J* 10.9, C(3)*H*), 5.90 (1H, d, *J* 4.3, C(5)*H*), 6.80 (1H, d, *J* 7.8, C(3)Ar*H*), 7.09 (1H, td, *J* 7.8, C(3)Ar*H*), 7.12-7.20 (2H, m, C(3)Ar*H* and C(3)Ar*H*), 7.37-7.48 (5H, m, C(6)Ph*H*), 7.51 (2H, td, *J* 7.6, 1.7, NSO_2Ph*H*), 7.65-7.67 (1H, m, NSO_2Ph*H*), 7.97 (2H, d, *J* 8.6, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 13.9, 19.8, 44.4, 51.3, 61.7, 116.5, 126.2, 126.6, 128.2, 128.5, 128.6, 128.7, 129.0, 129.5, 130.9, 133.0, 134.2, 136.6, 137.0, 139.2, 141.3, 170.1, 172.2; HRMS (ESI+): $C_{27}H_{26}NO_5S$ $[M+H]^+$ found 476.1520, requires 476.1526 (−1.3 ppm).

(3*S*,4*S*)-Ethyl 3-([1,1'-biphenyl]-4-yl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 26

Following general procedure B, the reaction of 4-biphenylacetic acid (84.8 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 92:8 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **26** (82.2 mg, 0.15 mmol, 76%, 92:8 dr) as a white solid; mp 72-74 °C; ν_{max} (ATR): 2978, 1730, 1489, 1448, 1369, 1170, 1112, 1087, 916; $[\alpha]_D^{20}$ +16.2 (*c* 0.73, CH_2Cl_2); HPLC (Chiralpak IA, 10% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 59.4 min, t_R (3*R*, 4*R*): 77.6 min, 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.06 (3H, t, *J* 7.1, OCH_2CH_3), 3.79 (1H, dd, *J* 9.9, 4.7, C(4)*H*), 4.03 (2H, q, *J* 7.1, OCH_2CH_3), 4.13 (1H, d, *J* 9.9, C(3)*H*), 5.89 (1H, d, *J* 4.7, C(5)*H*), 7.08 (2H, d, *J* 8.2, C(3)Ar*H*), 7.27-7.57 (14H, m, Ar*H* and NSO_2Ph*H*), 7.54-7.66 (1H, m, C(3)*p*-Ph*H*), 7.96 (2H, dd, *J* 8.5, 1.0, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 14.0, 45.3, 53.9, 61.8, 116.1, 126.2, 127.2, 127.6 (2 × *C*), 128.6, 128.7, 128.9, 129.0, 129.1, 129.5, 134.2, 134.4, 136.6, 139.2, 140.6, 141.1, 141.4, 170.9, 172.1; HRMS (ESI+): $C_{32}H_{28}NO_5S$ $[M+H]^+$ found 538.1677, requires 538.1683 (−1.1 ppm).

(3*S*,4*S*)-Ethyl 3-(naphthalen-2-yl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 27

Following general procedure B, the reaction of 2-naphthaleneacetic acid (74.5 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 91:9 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **27** (63.7 mg, 0.12 mmol, 62%, 92:8 dr) as a white solid; mp 178-180 °C; ν_{max} (ATR): 2978, 1774, 1446, 1359, 1166, 1124, 1097, 1012; $[\alpha]_D^{20}$ +17.3 (*c* 0.55, CH_2Cl_2); HPLC (Chiralpak AD-H, 30% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 18.6 min, t_R (3*R*, 4*R*): 30.8 min, 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.95 (1H, t, *J* 7.1, OCH_2CH_3), 3.86 (1H, dd, *J* 9.9, 4.7, C(4)*H*), 3.96 (2H, qd, *J* 10.8, 7.1, OCH_2CH_3), 4.26 (1H, dd, *J* 9.9, C(3)*H*), 5.84 (1H, d, *J* 5.2, C(5)*H*), 7.05 (1H, dd, *J* 8.5, 1.9, C(3)Ar*H*), 7.34-7.57 (10H, m, Ar*H*), 7.62-7.83 (4H, m, Ar*H*), 7.97 (2H, dd, *J* 6.8, 1.2, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 14.0, 45.2, 54.3, 61.7, 116.0, 126.0, 126.2, 126.4, 127.8, 128.2, 128.6, 128.7, 128.7, 128.8, 129.0, 129.6, 132.8, 133.0, 133.3, 134.2 (2 × *C*), 136.7, 139.2, 141.4, 170.8, 172.0; HRMS (ESI+): $C_{30}H_{26}NO_5S$ $[M+H]^+$ found 512.1522, requires 512.1526 (−0.8 ppm).

(3*S*,4*S*)-Ethyl 3-(naphthalen-1-yl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 28

Following general procedure B, the reaction of 1-naphthaleneacetic acid (74.5 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 91:9 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave lactam **28** (70.8 mg, 0.14 mmol, 69%, 92:8 dr) as a white solid; mp 176-178 °C; ν_{max} (ATR): 2978, 1721, 1446, 1166, 931; $[\alpha]_D^{20}$ −14.7 (*c* 0.58, CH_2Cl_2); HPLC (Chiralpak IA, 10% IPA / hexane, 1.0 mL/min, 211 nm, 30 °C): t_R (3*S*, 4*S*): 30.7 min, t_R (3*R*, 4*R*): 98.1 min, 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.95 (1H, t, *J* 7.1, OCH_2CH_3), 3.89-4.06 (3H, m, C(4)*H* and OCH_2CH_3), 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)Ar*H*), 7.33-7.36 (1H, m, C(3)Ar*H*), 7.39-7.50 (5H, m, C(6)Ph*H*), 7.50-7.56 (2H, t, *J* 7.4, NSO_2Ph*H*), 7.66-7.72 (1H, m, NSO_2Ph*H*), 7.72-7.76 (1H, m, C(3)Ar*H*),7.80 (1H, d, *J* 8.3, C(3)Ar*H*), 7.87 (1H, dd, *J* 6.8, 2.7, C(3)Ar*H*), 7.99 (2H, dd, *J* 6.8, 1.2, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 13.8, 44.6, 51.3, 61.7, 115.8, 123.2, 125.2, 125.9, 126.2, 126.7, 126.8, 128.6, 128.6, 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+): $C_{30}H_{26}NO_5S$ $[M+H]^+$ found 512.1523, requires 512.1526 (−0.6 ppm).

(3*S*,4*S*)-Ethyl 3-(3,4-dimethoxyphenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 29

Following general procedure B, the reaction of 3,4-dimethoxyphenylacetic acid (78.4 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 93:7 dr. Purification by flash chromatography (Et_2O / pet. ether, 2:3) gave **29**

(81.0 mg, 0.16 mmol, 78%, 97:3 dr) as a white solid; mp 126-128 °C; ν_{max} (ATR): 2937, 1782, 1593, 1516, 1448, 1367, 1298, 1224, 1143, 1087, 1026, 979; $[\alpha]_D^{20}$ +32.6 (*c* 0.53, CH_2Cl_2); HPLC (Chiralpak IA, 30% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 38.0 min, t_R (3*R*, 4*R*): 53.5 min, 98% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.08 (3H, t, *J* 7.1, OCH_2CH_3), 3.72 (1H, dd, *J* 9.8, 4.8, C(4)*H*), 3.75 (3H, s, C(3)ArOCH_3), 3.83 (3H, s, C(3)ArOCH_3), 3.94-4.11 (3H, m, C(3)*H* and OCH_2CH_3), 5.86 (1H, d, *J* 4.7, C(5)*H*), 6.50 (1H, d, *J* 1.9, C(3)Ar*H*), 6.58 (1H, dd, *J* 8.2, 2.0, C(3)Ar*H*), 6.75 (1H, d, *J* 8.3, C(3)Ar*H*), 7.35-7.40 (5H, m, C(6)Ph*H*), 7.40 (2H, t, *J* 7.9, NSO_2Ph*H*), 7.64 (1H, t, *J* 7.5, NSO_2Ph*H*), 7.95 (2H, d, *J* 7.4, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1, 45.3, 53.7, 56.0 (2 × *C*), 61.7, 111.2, 111.6, 116.0, 121.1, 126.1, 127.7, 128.6, 128.7, 129.0, 129.5, 134.1, 136.7, 139.3, 141.3, 148.9, 149.0, 170.9, 172.2; HRMS (ESI+): $C_{28}H_{31}N_2O_7S$ $[M+NH_4]^+$ found 539.1842, requires 539.1846 (−0.8 ppm).

(3*S*,4*S*)-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)phenylacetic acid (71.7 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 92:8 dr. Purification by flash chromatography (Et_2O : pet. ether, 2:3) gave **30** (80.3 mg, 0.16 mmol, 80%, 93:7 dr) as a white solid; mp 178-180 °C; ν_{max} (ATR): 2933, 1730, 1516, 1355, 1159, 929; $[\alpha]_D^{20}$ +30.6 (*c* 0.51, CH_2Cl_2); HPLC (Chiralpak IA, 10% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 30.4 min, t_R (3*R*, 4*R*): 55.2 min, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.09 (3H, t, *J* 7.1, OCH_2CH_3), 2.90 (6H, s, $N(CH_3)_2$), 3.68 (1H, dd, *J* 9.4, 5.0, C(4)*H*), 3.95-4.08 (3H, m, C(3)*H* and OCH_2CH_3), 5.85 (1H, d, *J* 5.0, C(5)*H*), 6.59 (2H, d, *J* 8.8, C(3)Ar*H*), 6.85 (2H, d, *J* 8.7, C(3)Ar*H*), 7.36-7.40 (5H, m, C(6)Ph*H*), 7.45-7.53 (2H, m, NSO_2Ph*H*), 7.64 (1H, tt, *J* 7.1, 1.2, NSO_2Ph*H*), 7.94 (2H, dd, *J* 8.5, 1.2, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1, 40.6, 45.4, 53.3, 61.6, 112.7, 116.2, 122.7, 126.2, 128.6, 128.6, 128.8, 129.3, 129.5, 134.0, 136.9, 139.4, 141.2, 150.3, 171.1, 172.5; HRMS (ESI+): $C_{28}H_{29}N_2O_5S$ $[M+H]^+$ found 505.1786, requires 505.1792 (−1.1 ppm).

(3*S*,4*S*)-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-methoxyphenylacetic acid (66.4 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 92:8 dr. Purification by flash chromatography (Et_2O / pet. ether, 2:3) gave **31** (75.5 mg, 0.15 mmol, 74%, 92:8 dr) as a white solid; mp 152-154 °C; ν_{max} (ATR): 2960, 1732, 1716, 1514, 1165, 920; $[\alpha]_D^{20}$ +28.9 (*c* 0.54, CH_2Cl_2); HPLC (Chiralpak AD-H, 20% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 25.5 min, t_R (3*R*, 4*R*): 42.8 min, 98% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.06 (3H, t, *J* 7.1, OCH_2CH_3), 3.71 (1H, dd, *J* 10.0, 4.6, C(4)*H*), 3.76 (3H, s, C(3)ArOCH_3), 3.97-4.06 (3H, m, C(3)*H* and OCH_2CH_3), 5.86 (1H, d, *J* 4.6, C(5)*H*), 6.76-6.84 (2H, m, C(3)Ar*H*), 6.88-6.96 (2H, m, C(3)Ar*H*), 7.31-7.43 (5H, m, C(6)Ph*H*), 7.46-7.54 (2H, m, NSO_2Ph*H*), 7.65 (1H, m, NSO_2Ph*H*), 7.90-7.97(2H, m, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1, 45.4, 53.6, 53.5, 61.7, 114.2, 116.2, 126.2, 127.3, 128.6, 128.6, 128.9, 129.5, 129.8, 134.1, 136.7, 139.2, 141.2, 159.4, 171.0, 172.3; HRMS (ESI+): $C_{27}H_{26}NO_6S$ $[M+H]^+$ found 492.1473, requires 492.1475 (−0.5 ppm).

(3*S*,4*S*)-Ethyl 3-(4-chlorophenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 32

Following general procedure B, the reaction of 4-chlorophenylacetic acid (68.2 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 2 h gave a crude residue of 92:8 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **32** (53.5 mg, 0.11 mmol, 54%, 94:6 dr) as a white solid; mp 136-138 °C; ν_{max} (ATR): 2978, 1724, 1683, 1448, 1367, 1168, 1087, 921; $[\alpha]_D^{20}$ +33.3 (*c* 0.55, CH_2Cl_2); HPLC (Chiralpak IA, 30% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 26.6 min, t_R (3*R*, 4*R*): 42.0 min, 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.06 (1H, t, *J* 7.1, OCH_2CH_3), 3.72 (1H, dd, *J* 10.5, 4.2, C(4)*H*), 3.94-4.09 (3H, m, C(3)*H* and OCH_2CH_3), 5.86 (1H, d, *J* 4.5, C(5)*H*), 6.93 (2H, d, *J* 8.4, C(3)Ar*H*), 7.25 (2H, d, *J* 8.5, C(3)Ar*H*), 7.35-7.39 (5H, m, C(6)Ph*H*), 7.46-7.54 (2H, m, NSO_2Ph*H*), 7.66 (1H, tt, *J* 7.1, 1.2, NSO_2Ph*H*), 7.93 (2H, dd, *J* 8.5, 1.2, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.0, 45.1, 53.6, 61.9, 116.0, 126.2, 128.7, 128.7, 129.1, 129.1, 129.5, 130.2, 133.9, 134.2, 134.3, 136.4, 139.1, 141.4, 170.7, 171.8; HRMS (ESI+): $C_{26}H_{23}N^{35}ClO_5S$ $[M+H]^+$ found 496.0981, requires 496.0980 (+0.2 ppm).

(3*S*,4*S*)-Ethyl 3-(4-bromophenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate 33

Following general procedure B, the reaction of 4-bromophenylacetic acid (86.0 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 2 h gave a crude residue of 92:8 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **33** (64.6 mg, 0.13 mmol, 60%, 94:6 dr) as a white solid; mp 140-142 °C; ν_{max} (ATR): 2976, 1726, 1710, 1448, 1168, 925; $[\alpha]_D^{20}$ +31.1 (*c* 0.54, CH_2Cl_2); HPLC (Chiralpak IA, 30% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 30.4 min, t_R (3*R*, 4*R*): 45.8 min, 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.07 (1H, t, *J* 7.1, OCH_2CH_3), 3.72 (1H, dd, *J* 10.5, 4.2, C(4)*H*), 3.94-4.09 (3H, m, C(3)*H* and OCH_2CH_3), 5.85 (1H, d, *J* 4.5, C(5)*H*), 6.87 (2H, d, *J* 8.4, C(3)Ar*H*), 7.32-7.44 (7H, m, C(3)Ar*H* and C(6)Ph*H*), 7.46-7.55 (2H, m, NSO_2Ph*H*), 7.66 (1H, tt, *J* 7.1, 1.2, NSO_2Ph*H*), 7.93 (2H, d, *J* 8.5, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 14.0, 45.1, 53.6, 61.9, 115.9, 122.3, 126.2, 128.7, 128.7, 129.1, 129.5, 130.5, 132.0, 134.3, 134.4, 136.4, 139.1, 141.4, 170.6, 171.7; HRMS (ESI+): $C_{26}H_{23}N^{79}BrO_5S$ $[M+H]^+$ found 540.0473, requires 540.0475 (−0.3 ppm).

(3*S*,4*S*)-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-thiophenylacetic acid (56.9 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **6** (68.7 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 85:15 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **34** (59.7 mg, 0.13 mmol, 64%, 92:8 dr) as a white solid; mp 112-114 °C; ν_{max} (ATR):

2924, 1728, 1448, 1357, 1303, 1219, 1165, 1120, 1083, 1056, 1029, 1001, 842; $[\alpha]_D^{20}$ +29.3 (*c* 0.59, CH_2Cl_2); HPLC (Chiralpak IA, 20% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 40.3 min, t_R (3*R*, 4*R*): 72.1 min, 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.14 (3H, t, *J* 7.1, OCH_2CH_3), 3.68 (1H, dd, *J* 8.1, 5.5, C(4)*H*), 4.08 (2H, qd, *J* 7.4, 3.6, OCH_2CH_3), 4.24 (1H, dd, *J* 8.1, C(3)*H*), 5.85 (1H, d, *J* 5.5, C(5)*H*), 6.77 (1H, dd, *J* 5.0, 1.3, C(3)Ar*H*), 7.03 (1H, ddd, *J* 2.9, 1.3, 0.6, C(3)Ar*H*), 7.23-7.26 (1H, m, C(3)Ar*H*), 7.34-7.37 (5H, m, C(6)Ph*H*), 7.43-7.54 (2H, m, NSO_2Ph*H*), 7.64 (1H, tt, *J* 7.4, 1.2, NSO_2Ph*H*), 7.92 (2H, dd, *J* 8.5, 1.2, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1, 44.6, 49.2, 61.8, 115.3, 123.6, 126.1, 126.5, 126.9, 128.6, 128.6, 128.9, 129.4, 134.1, 134.9, 136.6, 139.1, 141.4, 170.7, 171.0; HRMS (ESI+): $C_{24}H_{22}NO_5S_2$ $[M+H]^+$ found 468.0933, requires 468.0934 (−0.2 ppm).

(3*R*,4*S*)-Ethyl 2-oxo-6-phenyl-1-(phenylsulfonyl)-3-((*E*)-prop-1-en-1-yl)-1,2,3,4-tetrahydropyridine-4-carboxylate 35

Following general procedure B, the reaction of (*E*)-pent-3-enoic acid (82 µL, 0.8 mmol), *i*-Pr_2NEt (140 µL, 0.8 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (2.0 mL), followed by (−)-tetramisole·HCl **4** (19.2 mg, 0.08 mmol, 20 mol%), ketimine **6** (137.2 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and CH_2Cl_2 (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; ν_{max} (ATR): 2976, 1732, 1448, 1367, 1170, 1085, 1026, 926; $[\alpha]_D^{20}$ +67.0 (*c* 0.53, CH_2Cl_2); HPLC (Chiralpak OD-H, 5% IPA / hexane, 1.0 mL/min, 2211 nm, 40 °C): t_R (3*S*, 4*R*): 15.8 min, t_R (3*R*, 4*S*): 19.5 min, 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.25 (3H, t, *J* 7.1, OCH_2CH_3), 1.66 (3H, dd, *J* 6.3, 1.4, C(3)CHCHCH_3), 3.37 (1H, dd, *J* 8.4, 5.4, C(4)*H*), 3.47 (1H, t, *J* 8.2, C(3)*H*), 4.15 (2H, qd, *J* 7.1, 1.4, OCH_2CH_3), 5.30 (1H, ddq, *J* 15.1, 8.1, 1.5, C(3)C*H*CHCH$_3$), 5.64 (1H, m, C(3)CHC*H*CH$_3$), 5.80 (1H, d, *J* 5.4, C(5)*H*), 7.30-7.38 (5H, m, C(6)Ph*H*), 7.44-7.51 (2H, m, NSO_2Ph*H*), 7.62 (1H, tt, *J* 7.0, 1.2, NSO_2Ph*H*), 7.90 (2H, dt, *J* 8.6, 1.5, NSO_2Ph*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 14.3, 18.2, 43.7, 51.5, 61.7, 115.7, 123.8, 126.1, 128.5, 128.6, 128.8, 129.4, 132.1, 134.1, 136.9, 139.2, 141.2, 170.9, 171.8; HRMS (ESI+): $C_{23}H_{24}NO_5S$ $[M+H]^+$ found 426.1368, requires 426.1370 (−0.4 ppm).

(3*S*,4*S*)-Ethyl 6-(4-methoxyphenyl)-2-oxo-3-phenyl-1-tosyl-1,2,3,4-tetrahydropyridine-4-carboxylate 36

Following general procedure B, the reaction of phenylacetic acid (55 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (49 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **17** (77 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 24 h gave a crude residue of 90:10 dr. Purification by flash chromatography (Et_2O / pet. ether, 40:60) gave **36** (59 mg, 0.12 mmol, 58%, 90:10 dr) as a white solid; mp 132-134 °C; ν_{max} (ATR): 2929, 1718, 1606, 1501, 1361, 1161, 926; $[\alpha]_D^{20}$ +32.5 (*c* 0.52, CH_2Cl_2); HPLC (Chiralpak IA, 30% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 14.1 min, t_R (3*R*, 4*R*): 22.4 min, 99% ee; ^{1}H NMR (500 MHz, CD_2Cl_2) δ_H: 1.04 (3H, t, *J* 7.0, OCH_2CH_3), 2.47 (3H, s, NSO_2ArCH_3), 3.67 (1H, dd, *J* 9.7, 4.9, C(4)*H*), 3.84 (3H, s, C(6)ArOCH_3), 3.99 (2H, qd, *J* 7.2, 2.8, OCH_2CH_3), 4.05 (1H, d, *J* 9.7, C(3)*H*), 5.78 (1H, d, *J* 4.8, C(5)*H*), 6.89-6.95 (4H, m, C(3)Ph*H* and C(6)Ar*H*), 7.22-7.28 (3H, m, C(3)Ph*H*), 7.32-7.40 (4H, m, NSO_2Ar*H* and C(6)Ar*H*), 7.77-7.82 (2H, m, NSO_2Ar*H*); ^{13}C{^{1}H} NMR (125 MHz, CD_2Cl_2) δ_C: 14.2, 22.0, 45.4, 54.3, 55.9, 62.0, 114.3, 114.7, 127.7 (×2), 128.4, 129.1, 129.7, 129.9, 130.1, 136.2, 136.8, 141.4, 146.1, 160.6, 171.2, 172.4; HRMS (ESI+): $C_{28}H_{28}NO_6S$ $[M+H]^+$ found 506.1625, requires 506.1632 (−1.4 ppm).

(3*S*,4*S*)-Ethyl 3-(4-(dimethylamino)phenyl)-6-(4-methoxyphenyl)-2-oxo-1-tosyl-1,2,3,4-tetrahydropyridine-4-carboxylate 37

Following general procedure B, the reaction of 4-(dimethylamino)phenylacetic acid (71.7 mg, 0.4 mmol), *i*-Pr_2NEt (70 µL, 0.4 mmol) and pivaloyl chloride (50 µL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl **4** (9.6 mg, 0.04 mmol, 20 mol%), ketimine **17** (77.5 mg, 0.2 mmol), *i*-Pr_2NEt (35 µL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 95:5 dr. Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **37** (52.0 mg, 0.095 mmol, 47%, 88:12 dr) as a white solid; mp 144-146 °C; ν_{max} (ATR): 2926, 1728, 1610, 1512, 1361, 1247, 1165, 1087, 1027, 812; $[\alpha]_D^{20}$ +23.8 (*c* 0.55, CH_2Cl_2); HPLC (Chiralpak IA, 30% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 16.7 min, t_R (3*R*, 4*R*): 19.9 min, 91% ee; ^{1}H NMR (500 MHz, CD_2Cl_2) δ_H: 1.09 (3H, t, *J* 7.1, OCH_2CH_3), 2.48 (3H, s, NSO_2ArCH_3), 2.90 (6H, s, C(3)ArN(CH_3)$_2$), 3.61 (1H, dd, *J* 9.5, 5.0, C(4)*H*), 3.85 (3H, s, C(6)ArOCH_3), 3.93 (1H, d, *J* 9.5, C(3)*H*), 4.02 (2H, qd, *J* 7.1, 3.9, OCH_2CH_3), 5.77 (1H, d, *J* 5.0, C(5)*H*), 6.58 (2H, d, *J* 8.8, C(3)Ar*H*), 6.76 (2H, d, *J* 8.7, C(3)Ar*H*), 6.83-6.99 (2H, m, C(6)Ar*H*), 7.26-7.44 (4H, m, NSO_2Ar*H* and C(6)Ar*H*), 7.80 (2H, d, *J* 8.4, NSO_2Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2) δ_C: 14.1, 21.8, 40.6, 45.4, 53.3, 55.7, 61.7, 112.6, 114.1, 114.8, 123.1, 127.5, 129.5, 129.4, 129.5, 129.6, 130.0, 136.8, 141.0, 145.8, 150.5, 160.4, 171.3, 172.8; HRMS (ESI+): $C_{30}H_{33}N_2O_6S$ $[M+H]^+$ found 549.2047, requires 549.2054 (−1.2 ppm).

Derivatisations

Ethyl 2-oxo-3,6-diphenyl-1,2-dihydropyridine-4-carboxylate 44[24]

A solution of dihydropyridinone **8** (46.2 mg, 0.1 mmol, 1 eq.) and HCOONa (34.0 mg, 0.5 mmol, 5 eq.) in DMF (0.5 mL) was treated with 10% 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 Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2 / 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)}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.95 (3H, t, *J* 7.1, OCH_2CH_3), 4.07 (2H, q, *J* 7.1, OCH_2CH_3), 6.77 (1H, s, C(5)*H*), 7.37-7.41 (7H, m, Ph*H*), 7.46 (2H, d, *J* 6.9, C(6)Ph*H*), 7.78 (2H, d, *J* 7.7 C(6)Ph*H*), 12.17 (1H, br s, N*H*); ^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2) δ_C: 13.7, 62.0, 104.7, 126.7, 128.1, 128.2, 129.4, 129.6, 130.7, 132.4, 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 pyridone **44** (31.9 mg, 0.1 mmol, 1 eq.) in anhydrous THF (1 mL) at −78 °C under an argon atmosphere was treated with NaH (60% wt., 6.0 mg, 0.15 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 K_2CO_3, and extracted with $CHCl_3$ (3 × 10 mL). The combined organics were

dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was purified by flash chromatography (Et_2O / pet. ether, 3:7) to give pyridine **45** (44.6 mg, 0.094 mmol, 94%) as a white solid; mp 122-134 °C; ν_{max} (ATR): 2924, 1732, 1597, 1539, 1375, 1327, 1247, 1192, 1178, 1168, 1155, 1024, 968; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.94 (3H, t, *J* 7.1, OCH_2CH_3), 2.47 (3H, s, OTsCH_3), 4.07 (2H, q, *J* 7.1, OCH_2CH_3), 7.29 (2H, d, *J* 8.1, OTs*H*), 7.31-7.35 (2H, m, Ph*H*), 7.37-7.49 (6H, m, Ph*H*), 7.75-7.85 (4H, m, Ts*H* and Ph*H*), 7.99 (1H, s, C(5)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 13.6, 21.9, 62.0, 118.1, 126.3, 127.1, 128.3, 128.4, 128.7, 128.7, 128.9, 129.6, 129.6, 130.1, 133.3, 135.1, 136.6, 144.4, 144.9, 155.0, 155.3, 166.5; HRMS (ESI+): $C_{27}H_{24}NO_5S$ $[M+H]^+$ found 474.1364, requires 474.1370 (−1.2 ppm).

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

A solution of dihydropyridinone **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 organics were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to obtain the crude product (>99:1 dr). Purification by flash chromatography (Et_2O / 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; ν_{max} (ATR): 3246, 2964, 1728, 1670, 1651, 1456, 1265, 1155; $[\alpha]_D^{20}$ +136.5 (*c* 0.26, CH_2Cl_2); HPLC (Chiralpak OD-H, 30% IPA / hexane, 0.5 mL/min, 270 nm, 30 °C): t_R (3*S*, 4*S*): 36.4 min, t_R (3*R*, 4*R*): 29.2 min, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.18 (3H, *J* 7.1, OCH_2CH_3), 3.76 (1H, dd, *J* 7.5, 4.8, C(4)*H*), 4.13 (2H, q, *J* 7.1, OCH_2CH_3), 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 (5H, m, C(3)Ph*H*), 7.40-7.43 (2H, m, C(6)Ph*H*), 7.45-7.47 (2H, m, C(6)Ph*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 14.2, 46.7, 48.5, 61.5, 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+): $C_{20}H_{20}NO_3$ $[M+H]^+$ found 322.1443, requires 322.1438 (+1.6 ppm).

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

A stirred solution of dihydropyridinone **8** (46.2 mg, 0.1 mmol, 1 eq.) in anhydrous CH_2Cl_2 (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*-Pr_2NEt (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 $Na_2S_2O_3$ (10 mL), the layers separated and the aqueous extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (Et_2O / 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; ν_{max} (ATR): 2924, 1750, 1732, 1446, 1371, 1181, 1066, 885; $[\alpha]_D^{20}$ −26.7 (*c* 0.61, CH_2Cl_2); HPLC (Chiralpak IA, 30% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 10.9 min, t_R (3*R*, 4*R*): 15.3 min, 97% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.36 (3H, t, *J* 7.1, OCH_2CH_3), 4.00 (1H, d, *J* 3.4, C(4)*H*), 4.33 (2H, ddq, *J* 47.0, 10.8, 7.1, OCH_2CH_3), 4.54 (1H, d, *J* 3.4, C(3)*H*), 7.19 (2H, d, *J* 7.5, C(3)Ph*H*), 7.23-7.39 (10H, m, Ph*H*), 7.55 (1H, t, *J* 7.4, NSO_2PhH), 7.59 (2H, t, *J* 7.4, NSO_2PhH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.2, 53.8, 54.4, 62.8, 110.2, 127.6, 127.9, 128.4, 128.6, 129.0, 129.1, 129.3, 129.8, 133.9, 134.2, 134.9, 137.1, 139.0, 168.9, 170.4; HRMS (ESI+): $C_{26}H_{23}N^{79}BrO_5S$ $[M+H]^+$ found 540.0469, requires 540.0475 (−1.1 ppm).

(2*S*,3*S*)-1-Ethyl 4-methyl 2-(2-oxo-2-phenylethyl)-3-phenylsuccinate 50

A solution of dihydropyridinone **8** (46.2 mg, 0.1 mmol, 1 eq.) and magnesium turnings (24.3 mg, 1 mmol, 10 eq.) in MeOH (15 mL) was stirred at rt overnight. The reaction was quenched with 1 M HCl (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (Et_2O / pet. ether, 1:9) to give **50** (12.4 mg, 0.035 mmol, 35%, >99:1 dr) as a white solid; mp 80-82 °C; ν_{max} (ATR): 2916, 1718, 1681, 1448, 1398, 1336, 1271, 1251, 1153, 1002; $[\alpha]_D^{20}$ +79.7 (*c* 0.47, CH_2Cl_2); HPLC (Chiralpak IA, 30% IPA / hexane, 0.5 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 13.6 min, t_R (3*R*, 4*R*): 16.7 min, 97% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.88 (3H, t, *J* 7.1, OCH_2CH_3), 3.17 (1H, dd, *J* 17.3, 3.3, C(4)H^AH^B), 3.58 (1H, dd, *J* 17.3, 10.3, C(4) H^AH^B), 3.67-3.77 (4H, m, C(3)*H* and OCH_2CH_3), 3.85 (2H, m, OCH_2CH_3), 3.92 (1H, d, *J* 9.5, C(2)*H*), 7.26-7.34 (5H, m, Ph*H*), 7.45 (2H, dd, *J* 8.3, 7.2, Ph*H*), 7.52-7.59 (1H, m, Ph*H*), 7.90-7.97 (2H, m, Ph*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 13.8, 38.4, 44.8, 52.5, 53.5, 60.8, 128.0, 128.2, 128.7, 128.8 (2 × *C*), 133.4, 135.8, 136.5, 172.6, 173.2, 197.7; HRMS (ESI+): $C_{21}H_{23}O_5$ $[M+H]^+$ found 355.1542, requires 355.1540 (+0.6 ppm). Pyridone **44** (19.2 mg, 0.06 mmol, 60%) was also isolated from this reaction.

***N*-((3*S*,4*S*)-5-hydroxy-3-(hydroxymethyl)-1,4-diphenylpent-1-en-1-yl)benzenesulfonamide 51**

A solution of dihydropyridinone **8** (46.2 mg, 0.1 mmol, 1 eq.) in anhydrous THF (1 mL) at 0 °C under an argon atmosphere was treated dropwise with 2.0 M $LiAlH_4$ in THF (0.1 mL, 0.2 mmol, 2 eq.). The reaction was stirred at 0 °C for 1 h and quenched with 0.1 M HCl (5 mL). The reaction mixture was extracted with Et_2O (3 × 5 mL), the combined organic layers dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (Et_2O / pet. ether, 1:19) to give **51** (27.6 mg, 0.065 mmol, 65%, >99:1 dr) as a white solid; mp 74-76 °C; ν_{max} (ATR): 2953, 1887, 1490, 1448, 1330, 1170, 1112, 1039, 1010, 950; $[\alpha]_D^{20}$ −1.1 (*c* 0.45, CH_2Cl_2); HPLC (Chiralpak AD-H, 30% IPA / hexane, 1.0 mL/min, 254 nm, 30 °C): t_R (3*S*, 4*S*): 9.2 min, t_R (3*R*, 4*R*): 11.1 min, 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.65 (1H, ddd, *J* 11.7, 4.9, 3.1, C(4)*H*), 2.67-1.81 (1H, m, C(3)*H*), 3.18 (2H, d, *J* 5.2, C(3)CH_2OH), 3.60 (1H, dd, *J* 11.5, 4.7, C(5)H^AH^B), 3.65-3.73 (1H, m, C(5)H^AH^B), 5.59 (1H, dd, *J* 9.6, C(2)*H*), 7.09-7.19 (2H, m, C(4)Ph*H*), 7.20-7.42 (6H, m, Ph*H*), 7.41-7.50 (4H, m, Ph*H* and NSO_2PhH), 7.50-7.59 (1H, m, NSO_2PhH), 7.75 (2H, dd, *J* 8.4, 1.3, NSO_2PhH), 8.11 (1H, br s, N*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 41.5, 48.6, 65.0, 65.8, 125.5, 127.4, 127.5, 127.5, 128.2, 128.3, 128.6, 128.9, 129.0, 132.8, 137.5, 138.2, 140.3, 140.7; HRMS (ESI+): $C_{24}H_{25}NO_4SNa$ $[M+Na]^+$ found 446.1389, requires 446.1397 (−1.7 ppm).

(1*S*,4*S*,5*R*,6*S*)-Ethyl 3-oxo-1,4-diphenyl-2-(phenylsulfonyl)-7-oxa-2-azabicyclo[4.1.0]heptane-5-carboxylate 52

A solution of dihydropyridinone **8** (46.2 mg, 0.1 mmol, 1 eq.) in CH_2Cl_2 (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. $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer extracted with

CH_2Cl_2 (3 × 5 mL). The combined organics were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to obtain the crude product (>99:1 dr). Purification by flash chromatography (Et_2O / pet. ether, 1:4) gave **52** (34.2 mg, 0.072 mmol, 72%, >99:1 dr) as a white solid; mp 116-118 °C; ν_{max} (ATR): 2976, 2360, 2322, 1726, 1448, 1361, 1273, 1174; $[\alpha]_D^{20}$ −29.8 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ_H: 0.84 (3H, *J* 7.1, OCH_2CH_3), 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, OCH_2CH_3), 4.02 (1H, d, *J* 13.1, C(3)*H*), 6.87 (2H, dd, *J* 7.3, 2.0, C(3)Ph*H*), 7.24-7.28 (3H, m, C(3)Ph*H* and C(6)Ph*H*), 7.42-7.55 (7H, m, Ph*H*), 7.63-7.55 (1H, m, NSO_2PhH), 7.85-7.90 (2H, m, NSO_2PhH); ^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2) δ_C: 13.9, 49.9, 51.1, 62.2, 64.6, 70.0, 125.9, 128.8, 129.0, 129.2, 129.4, 129.6, 129.9 (2 × *C*), 134.2, 134.8, 136.5, 138.7, 169.9, 170.8; HRMS (ESI+): $C_{24}H_{25}NO_4SNa$ $[M+Na]^+$ found 446.1389, requires 446.1397 (−1.7 ppm).

Notes and references

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† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C {^{1}H} NMR spectra of all novel compounds and HPLC data. See DOI: 10.1039/b000000x/

1 For a review on the organocatalytic activation of carboxylic acids see: L. C. Morrill and A. D. Smith, *Chem. Soc. Rev.*, 2014, **43**, 6214.

2 G. S. Cortez, R. L. Tennyson and D. Romo, *J. Am. Chem. Soc.*, 2001, **123**, 7945.

3 (a) G. S. Cortez, S. H. Oh and D. Romo, *Synthesis*, 2001, 1731; (b) S. H. Oh, G. S. Cortez and D. Romo, *J. Org. Chem.*, 2005, **70**, 2835; (c) H. Henry-Riyad, C. Lee, V. C. Purohit and D. Romo, *Org. Lett.*, 2006, **8**, 4363; (d) G. Ma, H. Nguyen and D. Romo, *Org. Lett.*, 2007, **9**, 2143; (e) V. C. Purohit, A. S. Matla and D. Romo, *J. Am. Chem. Soc.*, 2008, **130**, 10478; (f) H. Nguyen, G. Ma and D. Romo, *Chem. Commun.*, 2010, **46**, 4803; (g) K. A. Morris, K. M. Arendt, S. H. Oh and D. Romo, *Org. Lett.*, 2010, **12**, 3764; (h) C. A. Leverett, V. C. Purohit and D. Romo, *Angew. Chem. Int. Ed.*, 2010, **49**, 9479; (i) H. Nguyen, G. Ma, T. Gladysheva, T. Fremgen and D. Romo, *J. Org. Chem.*, 2010, **76**, 2; (j) G. Liu and D. Romo, *Angew. Chem. Int. Ed.*, 2011, **50**, 7537; (k) G. Liu, M. E. Shirley and D. Romo, *J. Org. Chem.*, 2012, **77**, 2496; (l) C. A. Leverett, V. C. Purohit, A. G. Johnson, R. L. Davis, D. J. Tantillo and D. Romo, *J. Am. Chem. Soc.*, 2012, **134**, 13348.

4 For a review on isothiourea catalysis see: J. E. Taylor, S. D. Bull, J. M. J. Williams, *Chem. Soc. Rev.* 2012, **41**, 2109.

5 (a) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.*, 2011, **133**, 2714; (b) D. Belmessieri, A. de la Houpliere, E. D. D. Calder, J. E. Taylor and A. D. Smith, *Chem. Eur. J.*, 2014, **20**, 9762.

6 D. Belmessieri, D. B. Cordes, A. M. Z. Slawin and A. D. Smith, *Org. Lett.*, 2013, **15**, 3472.

7 L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox and A. D. Smith, *Chem. Sci.*, 2013, **4**, 4146.

8 S. R. Smith, J. Douglas, H. Prevet, P. Shapland, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2014, **79**, 1626.

9 C. Simal, T. Lebl, A. M. Z. Slawin and A. D. Smith, *Angew. Chem. Int. Ed.*, 2012, **51**, 3653.

10 D. G. Stark, L. C. Morrill, P.-P. Yeh, A. M. Z. Slawin, T. J. C. O'Riordan and A. D. Smith, *Angew. Chem. Int. Ed.*, 2013, **52**, 11642.

11 P.-P. Yeh, D. S. B. Daniels, D. B. Cordes, A. M. Z. Slawin and A. D. Smith, *Org. Lett.*, 2014, **16**, 964.

12 (a) L. C. Morrill, T. Lebl, A. M. Z. Slawin and A. D. Smith, *Chem. Sci.*, 2012, **3**, 2088; (b) E. R. T. Robinson, C. Fallan, C. Simal, A. M. Z. Slawin and A. D. Smith, *Chem. Sci.*, 2013, **4**, 2193; (c) L. C. Morrill, L. A. Ledingham, J.-P. Couturier, J. Bickel, A. D. Harper, C. Fallan and A. D. Smith, *Org. Biomol. Chem.*, 2014, **12**, 624; (d) L. C. Morrill, S. M. Smith, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2014, **79**, 1640; (e) S. R. Smith, S. M. Leckie, R. Holmes, J. Douglas, C. Fallan, P. Shapland, D. Pryde, A. M. Z. Slawin and A. D. Smith, *Org. Lett.*, 2014, **16**, 2506; (f) L. C. Morrill, D. G. Stark, J. E. Taylor, S. R. Smith, J. A. Squires, A. C. A. D'Hollander, C. Simal, P. Shapland, T. J. C. O'Riordan and A. D. Smith, *Org. Biomol. Chem.*, 2014, **12**, 9016.

13 (a) T.-Y. Jian, P.-L. Shao and S. Ye, *Chem. Commun.*, 2011, **47**, 2381; (b) T.-Y. Jian, L.-H. Sun and S. Ye, *Chem. Commun.*, 2012, **48**, 10907.

14 Reaction of Michael acceptor **9** with enantiopure isothiourea (−)-**4** did not improve the diastereoselectivity. For this reason it was not investigated further.

15 D. L. Boger and A. M. Kasper, *J. Am. Chem. Soc.*, 1989, **111**, 1517.

16 H.-H. Lu, X.-F. Wang, C.-J. Yao, J.-M. Zhang, H. Wu and W.-J. Xiao, *Chem. Commun.*, 2009, 4251.

17 Ketimines **6** and **17** were purified on a Biotage® Isolera™ 4, using Biotage® Snap Ultra cartridges and exhibited increased stability.

18 CCDC 1034010 contains the supplementary crystallographic data for dihydropyridinone **31**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

19 (a) Y. Nagao, T. Hirata, S. Goto, S. Sano, A. Kakehi, K. Iizuka and M. Shiro, *J. Am. Chem. Soc.*, 1998, **120**, 3104; (b) V. I. Minkin and R. M. Minyaev, *Chem. Rev.*, 2001, **101**, 1247; (c) K. A. Brameld, B. Kuhn, D. C. Reuter and M. Stahl, *J. Chem. Inf. Model.*, 2008, **48**, 1; (d) P. Liu, X. Yang, V. B. Birman and K. N. Houk, *Org. Lett.*, 2012, **14**, 3288.

20 J. Cheng, Z. Huang and Y. R. Chi, *Angew. Chem. Int. Ed.*, 2013, **52**, 8592.

21 *m*-CPBA oxidation of related dihydropyrones lead to γ-lactones, see: S. Chen, L. Hao, Y. Zhang, B. Tiwari and Y. R. Chi, *Org. Lett.*, 2013, **15**, 5822.

22 CCDC 1034010 contains the supplementary crystallographic data for epoxide **52**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

23 D. L. Boger and W. L. Corbett, *J. Org. Chem.*, 1992, **57**, 4777.

24 S. Perrin, K. Monnier, B. Laude, M. M. Kubicki and O. Blacque, *Tetrahedron Lett.*, 1998, **39**, 1753.