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Convergent Asymmetric Synthesis of Two Complex TRPV1 Antagonists

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Supporting Information

ABSTRACT: The convergent scale-up synthesis of two complex TRPV1 antagonists to support exploratory toxicology studies is described. Both compounds contain three chiral centers introduced by asymmetric synthesis with chiral control being critical for the success of the project. Preparation of the key cyclopropyl intermediate utilised an asymmetric cyclopropanation using thermally unstable ethyl diazoacetate. Ellman's auxiliary was used to synthesize the chiral α-methyl benzylamine fragments. This paper highlights some of the key synthetic challenges, processing issues, and safety aspects from the scale-up of this chemistry.

INTRODUCTION

The transient vanilloid receptor TRPV1 has been identified as a potential target for the treatment of chronic pain.[1] TRPV1 antagonists inhibit the transmission of inflammatory pain signals from the periphery to the CNS and so provide the possibility of developing novel analgesic and anti-inflammatory agents.[2] Capsazepine was published as the first competitive TRPV1 antagonist by Novartis in 1994,[3] and subsequently this has led to further development in this area.

Previous work has shown that for a series of α-substituted *N*-(4-*tert*-butylbenzyl)-*N*-[4-(methylsulfonylamino)benzyl]-thiourea analogues the incorporation of a benzylic α-methyl group with specific (*R*)-configuration enhanced the specific binding to the TRPV1 receptor when compared with capsaicin, a TRPV1 antagonist.[4]

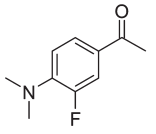
Two potential TRPV1 antagonists (**1** and **2**) have been discovered which incorporate both a benzylic α-methyl group with an (*R*)-configuration along with a chiral cyclopropyl group.[5] The synthesis of these two highly complex compounds was rapidly enabled within our process development group in order to support early-phase toxicology studies. Retrosynthetic analysis of both targets highlighted a suitable amide disconnection strategy which provided a convergent synthesis allowing rapid parallel enabling which we describe here (Scheme 1).

RESULTS AND DISCUSSION

Preparation of α-Methyl Benzylamine Fragments (3 and 4). The routes chosen for the synthesis of the α-methyl benzylamine fragments (**3** and **4**) were based on literature precedent (Scheme 2).[4,5] Several issues were identified which needed addressing prior to scale-up; these included improving the synthesis of the acetophenone fragments, **10** and **11**, due to poor regioselectivity of the Heck chemistry and improving the diastereoselectivity along with overcoming the safety concerns of the sodium borohydride ($NaBH_4$) quench for the Ellman's sulfinamide chemistry.

Two routes were investigated for the preparation of the acetophenone intermediates (**10** and **11**) needed for the Ellman's sulfinamide chemistry (Scheme 2).

Preparation of **10** and **11** was initially trialled using literature precedent,[4,5] involving the installation of the ketone via a Heck coupling with butyl vinyl ether. This approach, however, was found to be low yielding without the addition of toxic thallium salts.[6] The S_NAr approach, implemented by medicinal chemistry, proved more efficient. Formation of byproduct **16**, formed from the degradation of DMF,[7] could be eliminated by switching solvent from DMF to DMSO which gave the products in high yield (75−82%) with only a 2% impurity, believed to be **17** by mass spectrometry.



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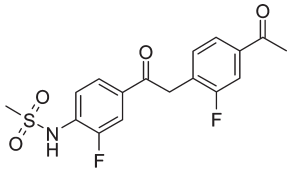

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The resulting potassium salts of **10** and **11** were taken into the aqueous layer, and the pH was adjusted with aqueous acid; however, we were concerned about the potential generation of hydrogen fluoride (HF) during this acidic work up. We reasoned that a pH window between pH 5−8 would protonate the product, allowing extraction without the risk of HF generation. Acetic acid was therefore selected as the acid of choice, as an accidental overcharge would not exceed the designated pH range.

The aqueous soluble potassium salts of **10** and **11** enabled us to remove DMSO and any impurities by extraction with ethyl

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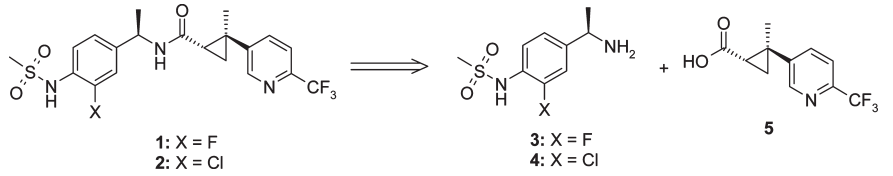
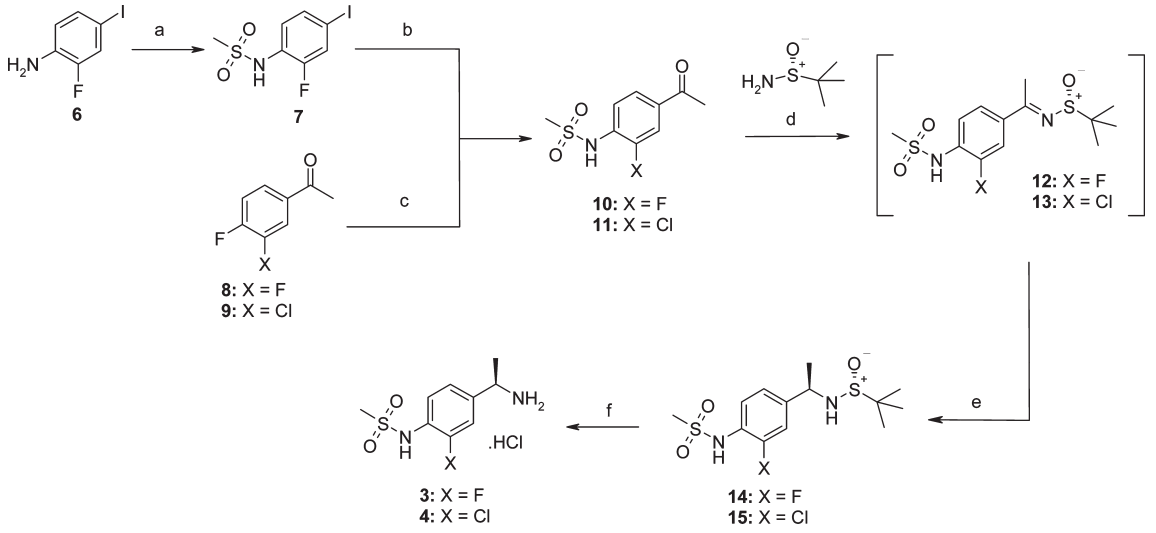
Scheme 1. Retrosynthetic approach to desired compounds 1 and 2



Scheme 2. Synthesis of α-methyl benzylamine fragments 3 and 4[a]



[a] Reagents and conditions: (a) CH_3SO_2Cl, pyridine, 0 °C, 95%; (b) butyl vinyl ether, $Pd(OAc)_2$, DPPP, TlOAc, DMF, 95 °C, 78%; (c) $CH_3SO_2NH_2$, K_2CO_3, DMSO, 130 °C, 75−82%; (d) $Ti(OEt)_4$, THF, 66 °C; (e) $NaBH_4$, −20 °C, 42−53%; (f) 1.25 M HCl/MeOH, rt, 86%.

acetate (EtOAc) prior to pH adjustment with acetic acid and isolation. This resulted in the products being isolated in high purity.[8]

Installation of the chiral α-methyl benzylamine was achieved using Ellman's protocol.[9,4] Sulfinyl ketimines **12** and **13** were formed using (*R*)-butanesulfinamide and then were diastereoselectively reduced in situ with $NaBH_4$ to give the chiral *tert*-butanesulfinyl-protected amines (**14** and **15**). The final α-methyl benzylamines (**3** and **4**) were produced by cleaving the sulfinyl group with 1.25 M hydrochloric acid in methanol (Scheme 2).

The diastereoselectivity of the reduction of **12** and **13** was found to be solvent dependent, with THF providing the best selectivity.[10] The use of titanium ethoxide ($Ti(OEt)_4$) in the reaction is also important as it serves not only as a Lewis acid and water scavenger for the imine condensation but also to enhance the rates and distereoselectivity of the reduction.[11] Initially $NaBH_4$ was charged at room temperature, resulting in a low 60% de with column purification being required; however, this ratio was significantly improved to 96% de[12] by lowering the internal temperature to −20 °C. Further upgrade to >98% de[12] was achieved by slurrying the isolated product in methyl *tert*-butyl ether (MTBE).

A major hindrance to the scalability of this chemistry was the quench of the $NaBH_4$ and $Ti(OEt)_4$. The initial quench of $NaBH_4$[13] following reduction of the ketimine posed safety concerns due to vigorous evolution of hydrogen gas. To eliminate the formation of hydrogen the reaction was first quenched with acetone, resulting in a scalable quench and also controlling any exotherm. The equivalents of $NaBH_4$ relative to ketone were also reduced from 3 equiv to 2 equiv without any detrimental effect to the reaction.

The quench of the $Ti(OEt)_4$ with water resulted in significant deposits of titanium oxide on the vessel walls and a slow filtration of the titanium residues. These issues were overcome, enabling the reaction to be carried out on scale, by reducing the water quench to only 3 L/kg ketone (**10** or **11**) and adding Arbocel filter aid to the vessel prior to filtration to bind the titanium salts.

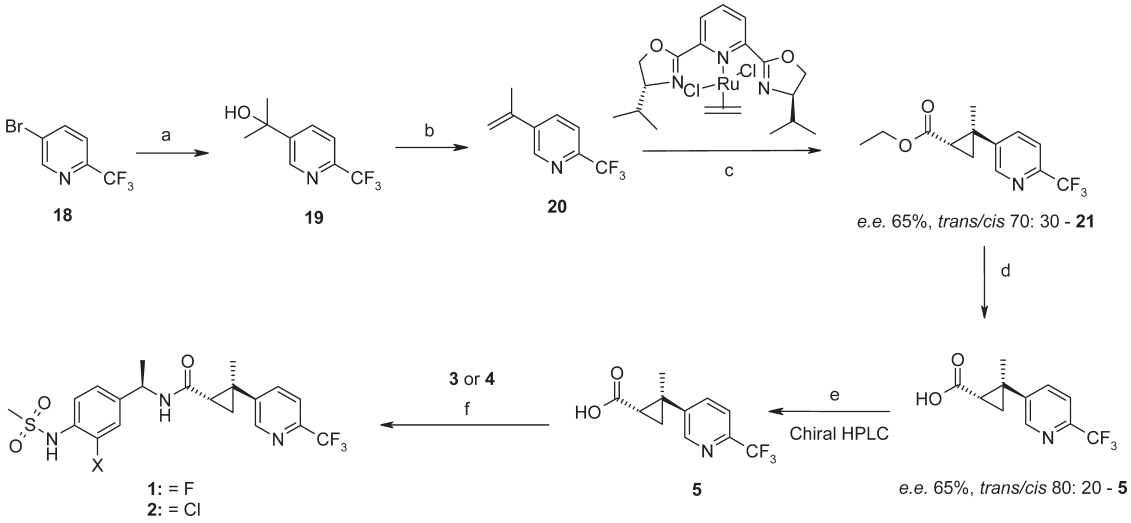
Following asymmetric reduction, the *N*-*tert*-butanesulfinyl group was hydrolysed using hydrochloric acid in methanol to give the α-methyl benzylamine (**3** and **4**). The hydrochloride salt was isolated in high yield (86−87%) following a solvent swap into ethyl acetate.

Preparation of the Cyclopropyl Acid Core (5). The initial synthesis of cyclopropyl acid core **5** was developed by medicinal chemistry (Scheme 3). Several issues were highlighted with this chemistry which included a nonrobust synthesis of styrene **20**, a complex chiral cyclopropanation, and the need for chiral preparative purification.

20 required for the cyclopropanation was synthesised in two steps from a commercial starting material **18**, involving Grignard initiation using Knochel's[14] protocol followed by an acetone quench and an acidic dehydration.

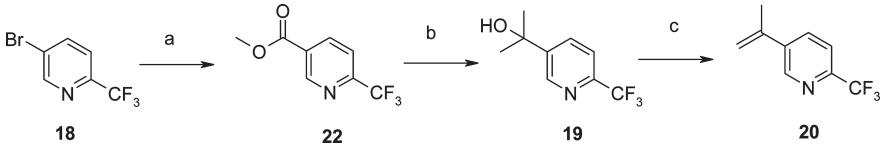
The initial Grignard reaction was capricious and produced yields varying from 40 to 80%. Additionally, process groups in Merck[15] and Pfizer[16] highlighted the use of Grignard reagents in the presence of fluoro-alkyl groups as potentially hazardous;

Scheme 3. Initial discovery route to targets 1 and 2[a]



[a] Reagents and conditions: (a) ^{i}PrMgCl·LiCl, THF, acetone, −5 °C, 47%; (b) TsOH·H_2O, toluene, reflux, 94%; (c) ethyldiazoacetate (EDA), toluene, 80 °C, 80%; (d) EtOH, LiOH, H_2O, rt, 81% ; (e) chiral HPLC purification; (f) T3P in EtOAc, MeCN, DIPEA, 50 °C, 63−77%.

Scheme 4. Synthesis of 5-isopropenyl-2-trifluoromethyl-pyridine 20[a]



[a] Reagents and conditions: (a) Pd(dppf)Cl_2, $CO_{(g)}$, MeOH, 100 °C, 50Psi, 70%; (b) 1 M MeMgBr in THF, −10 °C, 100%; c) TsOH·H_2O, toluene, Dean−Stark, 94%.

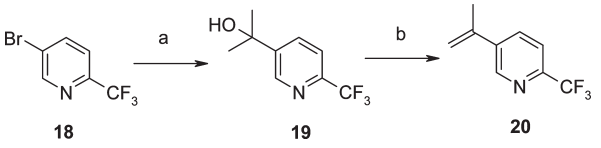
consequently, all chemistry was assessed to ensure these safety concerns were alleviated. Safety implications over the use of ethyldiazoacetate (EDA), a thermally unstable reagent,[17] in the cyclopropanation of **20** at elevated temperature required closer investigation. Finally, alternative purification of the **5** was needed as the chiral chromatography previously used would not be amenable for scale-up.

Initial investigations centered on an alternative synthesis of **20** from the same commercially available starting material **18** (Scheme 4).

Knochel's chemistry to form tertiary alcohol **19** from **18** using ^{i}PrMgCl·LiCl in THF followed by acetone quench produced variable yields and purity with aldol byproduct being the main concern. Methyl Grignard addition to **22**, however, proved more robust and scalable. Careful consideration of the Grignard reagent used was required as significant differences in reaction profile was seen with 1 M MeMgBr in THF being preferable to 3 M MeMgCl in THF. Formation of **20** from **19** was then achieved by dehydration using toluene sulfonic acid monohydrate (TsOH·H_2O) in toluene under Dean−Stark conditions, with variable yields obtained on the basis of its volatility. A salt screen was performed by our technology group as an alternative method of isolation of **20** but was unsuccessful. **20** could be purified by column chromatography; however, purification was also achieved by vacuum distillation with an excellent yield obtained.

Preparation of **20** was outsourced to an external vendor who demonstrated that the original organometallic addition of **18** to acetone could be reliably carried out with ^{n}BuLi in place of

Scheme 5. Outsourced synthesis of 20[a]



[a] Reagents and conditions: (a) ^{n}BuLi, toluene, −60 °C, acetone, 99%; (b) TsOH·H_2O, toluene, Dean−Stark, 75%.

Knochel's reagent (Scheme 5). Ultimately, these alternative ^{n}BuLi conditions were scaled up as accessing **22** involved carbonylation of **18** which adds an extra processing step to the route.

Cyclopropanation of **20** proved the most challenging step due to poor enantioselectivity (ee ∼60−65%) and *trans/cis* selectivity (70/30) (Scheme 6). Nishiyama and co-workers[18] highlight the use of chiral Ru-pybox ligand systems which afford good enantioselectivity for a range of substrates. However, most literature precedent for cyclopropanations of this nature are performed on substrates without a pyridine functionality present and no other substitution on the styrene. Attempts to prepare trisubstituted cyclopropanes generally result in either poor ee or poor *trans/cis* ratio,[19] and there is only one report of an alkenylpyridine substrate in a noncatalysed racemic system.[20] We wondered if the inferior *trans/cis* selectivity and enantioselectivity of **21** could be explained by competitive co-ordination

or ligation of the pyridine to the chiral ruthenium catalyst and sought an improved catalyst and ligand system. A high-throughput reaction screen[21] including copper-, cobalt-, and palladium-based catalysts with several oxazoline-substituted ligands failed to identify any improvement from the original conditions (Table 1).

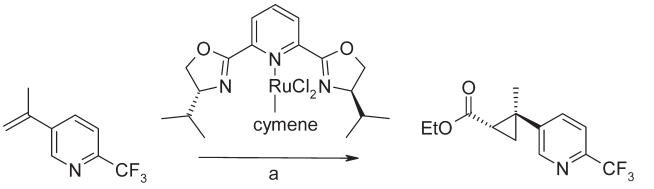
On the basis of literature precedent of thermal instability of ethyl diazoacetate (EDA),[17] investigations of the cyclopropanation reaction were considered necessary as it was performed at 80 °C. Slow addition of EDA to the reaction was key in providing a controlled evolution of nitrogen gas, suitable reaction conversion, and the minimising of byproduct associated with EDA dimerization. *tert*-Butyl diazoacetate was attempted as an alternative diazo source but offered no advantage in either enantioselectivity or *trans/cis* selectivity. Achiral cobalt conditions[22] were trialled with the aim of improving the *trans/cis* selectivity, but these proved unsuccessful. The original catalyst was prepared by mixing dichloro(*p*-cymene)ruthenium(II) dimer with 2,6-bis[-(4*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine ligand in dichloromethane and then bubbling ethylene through the solution before isolation. It was found that the intermediate cymene catalyst was just as effective in the reaction and could be telescoped directly into the cyclopropanation, negating any stability issues seen with catalyst isolation[23] with similar chiral results being obtained (Scheme 6).

Purification of Crude Cyclopropyl Intermediate (5). Following the cyclopropanation it was considered necessary to upgrade the *trans/cis* ratio of **21** from 70/30. This was achieved via silica plug purification to give a *trans/cis* ratio of 80/20. Hydrolysis of **21** to give **5** was achieved using lithium hydroxide (LiOH) in ethanol (EtOH). Careful examination of the reaction indicated a subtle rate difference which upgraded the *trans/cis* selectivity further to 85:15.

The complete removal of chiral chromatography was desirable for the purification of **5**, consequently, a series of chiral bases were screened[21] to upgrade the *trans/cis* selectivity and enantioselectivity. Unfortunately, no salt provided the desired upgrade in a single step, quinine was identified as a method to upgrade the *trans/cis* selectivity to >95:5 with no upgrade of the enantioselectivity. Following a salt-break process using 2 M $HCl_{(aq)}$/MTBE, chiral upgrade was achieved using (*S*)-1,2,3,4-tetrahydro-1-naphthylamine to provide >93% ee[24] on a first crystallization. This could be further recrystallised to upgrade the ee or taken into the amide coupling directly with the unwanted diastereoisomer being purged via traditional crystallisation methods (Scheme 7).

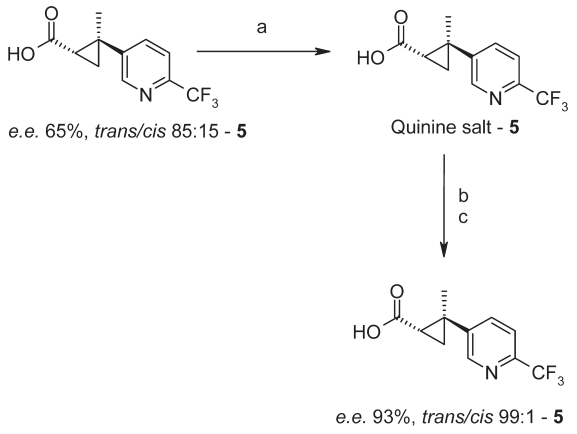
A biocatalytic alternative for purifying the crude cyclopropyl acid **5**, avoiding the use of chiral chromatography, was investigated.

Scheme 6. Modified cyclopropanation of 20[a]



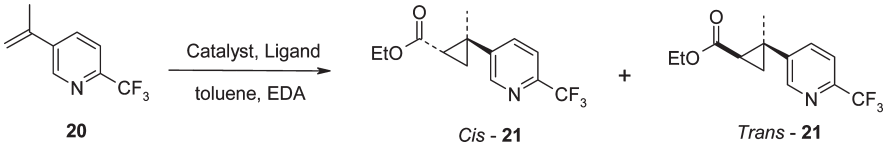
[a] Reagents and conditions: (a) toluene, EDA, 80 °C, 80%.

Scheme 7. Chiral purification of cyclopropyl acid 5[a]



[a] Reagents and conditions: (a) quinine, MTBE, 55 °C, 75%; (b) 2 M $HCl_{(aq)}$, MTBE 25 °C, 100%; (c) (*S*)-1,2,3,4-tetrahydro-1-naphthylamine, 2-propanol, 50 °C, 77%).

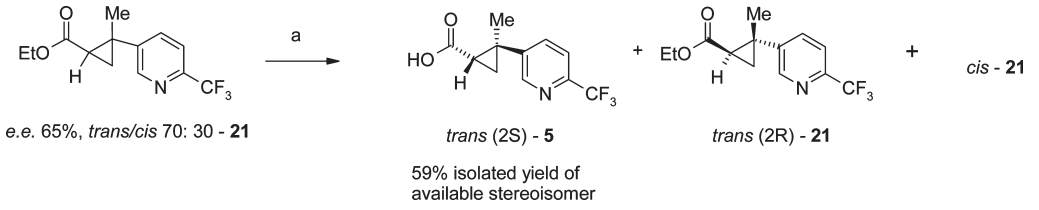
Table 1. Selected results from cyclopropanation screen[a,21]



		HPLC analysis (area %)		
metal/precatalyst	ligand	**20**	*cis*-**21**	*trans*-**21**
Cl_2(*p*-cymene)$_2$ruthenium(II) dimer	2,6-bis[(4*S*)-(−)-isopropyl-2-oxazolin-2yl]pyridine	6	10	30
ruthenium(II) catalyst [b]	N/A	11	1	20
carbonylhydridotris(triphenylphosphine)rhodium(I)	(+)-*N*-methylephedrine	5	9	16
$Cu(OTf)_2$	(*R*,*S*)-*tert*-Butyl−Josiphos	8	7	13
$CoCl_2$	(*R*,*S*)-*tert*-butyl-Josiphos	1	1	10
$Pd_2(dba)_3$	BINAP	6	1	1

[a] **NOTE:** All the reactions were carried out in 2.5 mL of HPLC crimp-cap vials on 10-mg scale. The reaction mixtures were analysed by HPLC using an SB-C18 column, a gradient of 95:5 to 5:95%, 0.1% TFA in water/MeCN, over 3.75 min with a flow rate of 3 mL/min and using 0.04 μL injections. [b] Chloro[(1*S*)-(−)-5,5′-dichloro-6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl](*p*-cymene)ruthenium(II)chloride DCM adduct.

Scheme 8. Biocatalytic hydrolysis of crude cyclopropane mixture[a]



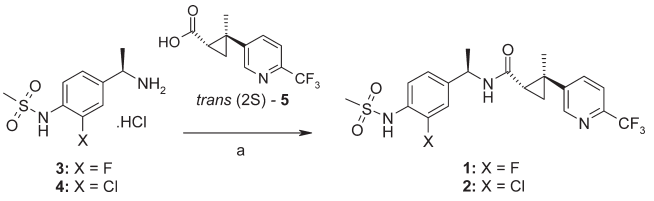
[a] Reagents and conditions: (a) alcalase (*Bacillus licheniformis* protease), pH 9.0 carbonate buffer, 30 °C, 14 days.

Table 2. Screen of commercial enzymes for hydrolysis of 21[a]

enzyme description	vendor	conversion to **5** (chiral HPLC)/%	chiral purity of **5** (% ee.)
control (no enzyme)	n/a	0	n/a
Bacillus lentus protease Esperase 8.0 L	Novozymes	1.1	>99 (2S)
acid protease II	Amano	2.1	>99 (2S)
Bacillus licheniformis protease Alcalase 2.5 L	Novozymes	4.3	>99 (2S)
PROTIN SD-AY 10	Amano	4.2	unknown
Protex 6 L (A01424)	Geneco	5.8	>99 (2S)
Protease P "Amano" 6	Amano	6.5	>99 (2S)
Rhizomucor miehei lipase	Novozymes	5.1	54 (2R)

[a] **NOTE**: All reactions were carried out on 10-mg scale.

Scheme 9. Convergent coupling to synthesize final product 1 and 2[a]



[a] Reagents and conditions: (a) 50% T3P in EtOAc, DIPEA, 50 °C, 63−77%.

This investigation centred around the use of enzymes to selectively give the required diastereoisomer via enzymatic hydrolysis of **21** (65% ee *trans/cis* 70:30) (Scheme 8).

A set of commercially available enzymes were screened for the selective hydrolysis of the desired *trans*-2*S*-stereoisomer using the protocol described by Tao and co-workers[25] and Novozymes' protease 'Alcalase' from *Bacillus licheniformis* was selected for further development based on cost and previous experience (Table 2).

This enzyme displayed >99% selectivity for the desired *trans*-(2*S*) isomer. Unfortunately, despite efforts to optimize the reaction conditions, the biocatalyst displayed very low activity, and therefore long reaction times of multiple days and multiple 1000 wt % charges of the crude liquid enzyme preparation were required to reach high conversion (Scheme 8). A yield comparable to the chemical hydrolysis and stereoselective crystallisation route could be obtained via this method (59% of the available stereoisomer), although for scale-up we decided to scale up the previous conditions due to the confidence we had in the chemistry.

Convergent Coupling to Give Final Products (1 and 2). Following parallel synthesis of the α-methyl benzylamine fragments (**3** and **4**) and cyclopropyl acid core (**5**) the two fragments were coupled to complete the convergent synthesis (Scheme 9). It was found that high chiral purity of the two fragments prior to coupling was critical, as all attempts to purge high levels of the diastereoisomers in the product were unsuccessful.[26,27]

Alternative conditions to the initial discovery conditions involving 1-propylphosphonic acid cyclic anhydride (T3P) were evaluated; these included traditional 1,1′-carbonyldiimidazole (CDI) activation, thionyl chloride activation via acid chloride formation, and boronic acid coupling methodologies.[28] None of these conditions provided a superior reaction profile, and in some cases there were indications of epimerization; thus, T3P in THF was used. Following coupling both products (**1** and **2**) required a reslurry in MTBE, and **2** was recrystallised from acetonitrile to reduce the level of diastereoisomers to 1%, resulting in an HPLC achiral purity >95%.

SUMMARY

In summary, we have developed a safe and scalable process to convergently produce two complex chiral compounds (**1** and **2**) in high purity in support of toxicology studies. This has involved delivering two chirally pure α-methyl benzylamine fragments (**3** and **4**) by utilizing Ellman's sulfinamide chemistry which was successfully scaled. The safe scale-up of a complex cyclopropanation step involving thermally unstable ethyl diazoacetate was also achieved. This was then followed by a stereoselective purification of **5** via traditional crystallisation techniques (without the need for chiral preparative chromatography) and coupling of the convergent fragments.

EXPERIMENTAL SECTION

General. All starting materials are available commercially or described in the literature. Chromatography was carried out

using Merck silica gel 60 (9385) using standard glassware. Thin layer chromatography (TLC) was carried out on Biotage kp-Sil flash TLC plates. ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer or Jeol ECS 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a Jeol ECS spectrometer at 100.5 MHz. HPLC analyses were performed using a reverse-phase technique. LC/MS analysis was performed using the following system: Hewlett-Packard 1100 with SB C18 3.0 mm × 50 mm, 1.8 μm particles; mobile phase consisting of solvent A, 0.05% TFA in water, solvent B, 0.05% TFA in acetonitrile; 0 min = 5% solvent B; 3.5 min = 100% solvent B; 4.5 min = 100% solvent B; 4.6 min = 5% solvent B; run time 5 min; column temperature 50 °C; λ = 225 nm; with Waters Micromass ZQ 2000/4000 mass detector. Combustion analyses were performed by Warwick Analytical Service, University of Warwick Science Park, The Venture Centre, Sir William Lyons Road, Coventry CV4 7EZ, U.K.

*N-(4-Acetyl-2-fluorophenyl)methanesulfonamide (**10**).* To a solution of 1-(3,4-difluorophenyl)ethanone (125.0 g, 0.80 mol) in DMSO (625 mL, 5 mL/g) was added potassium carbonate (221.3 g, 1.60 mol), followed by methane sulfonamide (152.3 g, 1.60 mol). The reaction mixture was heated to 120 °C with overhead stirring for 16 h and then cooled to room temperature. The cooled mixture was poured into water (1.6 L) and washed with ethyl acetate (4 × 625 mL). The pH of the aqueous layer was adjusted to pH 6 by controlled addition of 1:1 acetic acid/water and the resulting solid collected by filtration and dried to give the title compound **10** as a brown solid (139.7 g, 0.60 mol, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.51 (s, 3H), 3.10 (s, 3H), 7.50−7.55 (dd, 1H), 7.72−7.77 (m, 2H), 10.06 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.5, 155.2, 152.7, 134.4, 134.4, 131.0, 130.9, 125.7, 125.7, 123.4, 116.2, 115.9, 41.22, 27.11; Anal. Calcd for $C_9H_{10}FNO_3S$: C, 46.75; H, 4.36; N, 6.06; F, 8.22; S, 13.87. Found: C, 46.60; H, 4.31; N, 5.94; F, 8.29; S, 14.02.

*N-(4-Acetyl-2-chlorophenyl)methanesulfonamide (**11**).* To a solution of 1-(3-chloro-4-fluorophenyl)ethanone (93.2 g, 0.54 mol) in DMSO (466 mL, 5 mL/g) was added potassium carbonate (149.2 g, 1.1 mol), followed by methane sulfonamide (102.7 g, 1.1 mol). The reaction mixture was heated to 120 °C with overhead stirring for 16 h and then cooled to room temperature. Water (1.2 L) and ethyl acetate (475 mL) were added to the vessel, and the aqueous layer was retained and washed with ethyl acetate (3 × 400 mL). To the aqueous layer was added 2MeTHF (750 mL) followed by controlled addition of 1:1 acetic acid/2MeTHF (200 mL). The organic layer was retained and the aqueous layer extracted with 2MeTHF (800 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated *in vacuo* to give the title compound **11** as a light-brown solid (110.0 g, 0.44 mol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.53 (s, 3H), 3.12 (s, 3H), 7.57−7.59 (d, 1H), 7.85−7.88 (dd, 1H), 7.98−7.99 (d, 1H), 9.66 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.5, 139.2, 134.9, 130.3, 128.4, 127.1, 124.7, 41.7, 27.2; Anal. Calcd for $C_9H_{10}ClNO_3S$: C, 43.64; H, 4.07; N, 5.65; Cl, 14.31; S, 12.94. Found: C, 44.44; H, 3.96; N, 5.31; Cl, 14.56; S, 12.25.

*N-(4-{(1R)-1-[(tert-Butylsulfinyl)amino]ethyl}-2-fluorophenyl)methanesulfonamide (**14**).* To a solution of **10** (40.0 g, 173 mmol) in THF (320 mL, 8 mL/g), was added $Ti(OEt)_4$ (59.7 mL, 285 mmol) followed by (*R*)-*tert*-butylsulfinamide (22.2 g, 182 mmol) and the reaction mixture heated to reflux with stirring. After heating at reflux for 16 h the reaction was cooled to −30 °C, and $NaBH_4$ (12.4 g, 346 mmol) was slowly charged to the vessel. The reaction mixture was stirred at −20 °C (internal temperature) for approximately 16 h and then warmed to −10 °C. Acetone (76.3 mL, 1.04 mol) was added slowly followed by methanol (26.8 mL, 662 mmol) and the reaction allowed to warm to room temperature and stirred for 2 h. To the reaction mixture was added water (100 mL) followed by Arbocel filter aid (32 g, 0.80 g/g) and stirred for 1 h before filtering the titanium salts. The cake was washed with 2MeTHF (3 × 100 mL) and the filtrate concentrated to remove THF and methanol. 2MeTHF (300 mL) was added followed by water (300 mL) and aqueous hydrochloric acid (1 M, 60 mL), and the organic layer was retained. The aqueous was extracted with 2MeTHF (300 mL), and then the organic layers were combined. The organic layer was washed with water (300 mL) and brine (300 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by slurrying in MTBE (120 mL) at room temperature for 2 h to give the title compound **14** as an off-white solid (30.9 g, 91.8 mmol, 53%, 98.2% de[12]). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.19 (s, 9H), 1.45−1.48 (d, 3H), 2.97 (s, 3H), 4.29−4.37 (m, 1H), 5.62−5.66 (d, 1H), 7.14−7.18 (dd, 1H), 7.25−7.31 (m, 2H), 9.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 1.57.4, 155.0, 154.9, 154.8, 127.3, 123.8, 123.7, 123.3, 123.3, 114.9, 114.7, 55.8, 54.6, 40.9, 24.5, 23.1; LC/MS *m*/*z* (ES$^+$) 337 [MH]$^+$.

*N-(4-{(1R)-1-[(tert-Butylsulfinyl)amino]ethyl}-2-chlorophenyl)methanesulfonamide (**15**).* To a solution of **11** (105 g, 424 mmol) in THF (840 mL, 8 mL/g), was added $Ti(OEt)_4$ (146 mL, 699 mmol) followed by (*R*)-*tert*-butylsulfinamide (54.4 g, 445 mmol) and the reaction mixture heated to reflux with stirring. After heating at reflux for 16 h the reaction was cooled to −30 °C, and $NaBH_4$ (45.6 g, 1.27 mol) was slowly charged to the vessel. The reaction mixture was stirred at −20 °C (internal temperature) for approximately 5 h and then warmed to −10 °C for 12 h. Acetone (280 mL, 3.82 mol) was added slowly followed by methanol (105 mL, 2.59 mol) and the reaction allowed to warm to room temperature and stirred for 2 h. To the reaction mixture was slowly added aqueous hydrochloric acid (1 M, 840 mL) followed by Celite filter aid (150 g, 1.0 g/g) and stirred for 1 h before filtering the titanium salts. The cake was washed with THF and the filtrate concentrated to remove THF and methanol. 2MeTHF (500 mL) was added, and the organic layer was retained. The aqueous layer was extracted with 2MeTHF (500 mL), and then the organic layers were combined. The organic layer was washed with water (300 mL) and brine (300 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by slurrying in MTBE (480 mL) at room temperature for 3 h to give the title compound **15** as an off-white solid. (62.8 g, 178 mmol, 42%, 99.6% de[12]). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (s, 9H), 1.32−1.36 (d, 3H), 2.99 (s, 3H), 4.29−4.37 (m, 1H), 5.66−5.70 (d, 1H), 7.29−7.36 (m, 2H), 7.52−7.53 (m, 1H) 9.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.7, 133.1, 129.3, 128.5, 128.1, 126.6, 55.8, 54.6, 41.5, 24.5, 23.1; LC/MS *m*/*z* (ES$^+$) 353 [MH]$^+$

*N-{4-[(1R)-1-Aminoethyl]-2-fluorophenyl}methanesulfonamide Hydrochloride (**3**).* To a vessel containing **14** (100 g, 297 mmol) was added hydrochloric acid (1.25 M)/ methanol (713 mL, 7 mL, g) and the reaction mixture was stirred at room temperature for 16 h. The solution was evaporated *in vacuo* to give a yellow powder. The solid was purified by slurrying in EtOAc (400 mL) for 2 h at room temperature and the resulting solid collected by filtration and dried to give the title compound **3** as an off-white solid (68.7 g, 256 mmol, 86%). ^{1}H NMR

(400 MHz, MeOD) δ 1.60−1.62 (d, 3H), 3.00 (s, 3H), 4.43−4.49 (q, 1H), 7.25−7.28 (m, 1H), 7.31−7.36 (dd, 1H), 7.54−7.59 (t, 1H); ^{13}C NMR (100 MHz, MeOD) δ 158.3, 153.8, 136.8, 136.7, 126.3, 126.1, 125.4, 123.0, 122.9, 114.4, 114.2, 50.1, 39.0, 19.1;

*N-{4-[(1R)-1-Aminoethyl]-2-chlorophenyl}methanesulfonamide Hydrochloride (**4**).* To a vessel containing **15** (60 g, 170 mmol) was added hydrochloric acid (1.25 M)/ methanol (600 mL, 10 mL/g) and the reaction mixture was stirred at room temperature for 3 h. The solution was evaporated *in vacuo* to give an off-white powder. The solid was slurried in EtOAc (240 mL) for 0.5 h at room temperature and then cooled to 0−5 °C for 0.5 h before being collected by filtration. The compound was dried to give the title compound **4** as an off-white solid (42.2 g, 148 mmol, 86%). ^{1}H NMR (400 MHz, MeOD) δ 1.60−1.63 (d, 3H), 3.01 (s, 3H), 4.43−4.49 (q, 1H), 7.40−7.43 (m, 1H), 7.60−7.63 (m, 2H); ^{13}C NMR (100 MHz, MeOD) δ 137.0, 135.1, 128.3, 127.9, 126.2, 126.0, 50.0, 39.6, 19.1; Anal. Calcd for $C_9H_{13}ClN_2O_2S\cdot HCl$: C, 37.90; H, 4.95; N, 9.82; Cl, 24.86; S, 11.24. Found: C, 37.73; H, 4.92; N, 9.71; Cl, 24.86; S, 11.23.

*Methyl 6-(Trifluoromethyl)pyridine-3-carboxylate (**22**).* To a solution of 5-bromo-2-(trifluoromethyl) pyridine (0.5 g, 2.21 mmol) in methanol (15 mL, 30 mL/g) was added Pd(dppf)Cl_2 (81.2 mg, 0.11 mmol) followed by DIPEA (1.16 mL, 6.64 mmol). The resulting mixture was carbonylated under $CO_{(g)}$ atmosphere at 100 °C and 50 Psi and left for 12 h. Upon reaction completion the mixture was filtered through Celite filter aid, and the solvent was removed via distillation *in vacuo*. The solid was redissolved in EtOAc (20 mL). The organic layer was washed with aqueous sodium carbonate (1 M, 2 × 20 mL) followed by saturated aqueous brine (2 × 20 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was redissolved in minimal DCM and purified via silica plug using heptane/EtOAc (75:25). The product fractions were combined and evaporated *in vacuo* to give the title compound **22** as a solid (320 mg, 1.55 mmol, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) 4.00 (s, 3H), 7.78−7.81 (dd, 1H), 8.47−8.50 (dd, 1H), 9.31 (s, 1H); LC/MS *m/z* (ES^+) 206 $[MH]^+$

*2-(6-Trifluoromethyl-pyridin-3-yl)-propan-2-ol (**19**): from Grignard Addition to **22**.* MeMgBr (1 M in THF, 731.2 mL, 731 mmol) was charged to a vessel and cooled to −10 °C. A preformed solution of **22** (50 g, 243 mmol) in anhydrous THF (500 mL, 10 mL/g) was added over 2 h while maintaining the internal temperature at −10 °C. Following addition, the reaction mixture was warmed to 10 °C and analysed by HPLC (>97% conversion to desired product). The mixture was recooled to 0 °C, and aqueous NH_4Cl (500 mL) was added. The product was extracted with 2MeTHF (500 mL), and the lower aqueous layer was re-extracted with 2MeTHF (250 mL). The organic layers were combined and washed with brine (250 mL), dried over $MgSO_4$, and evaporated *in vacuo* to yield the title compound **19** quantitatively as an oil (51 g, 248 mmol, >100%).

*2-(6-Trifluoromethyl-pyridin-3-yl)-propan-2-ol (**19**): Direct Addition of **18** to Acetone.* To a solution of toluene (1.75 L, 6 mL/g) at −75 °C was added ^{n}BuLi in hexane (1.6 M, 912 mL, 1.46 mol) over 5 min. A preformed solution of **18** (300 g, 1.33 mol) in anhydrous toluene (750 mL, 2.5 mL/g) was added over 15 min while maintaining the internal temperature below −60 °C. Following addition the reaction mixture was left for 30 min and then a solution of acetone (195 mL, 2.65 mol) in THF (600 mL) was added over 30 min while maintaining the internal temperature below −55 °C. The reaction was warmed to −25 °C over 45 min, and aqueous HCl (2 M, 863 mL) was then added. The organic layer was retained, and the aqueous layer was extracted with diethyl ether (1.9 L). The organic layers were combined and washed with brine (2× 1.9 L), dried over $MgSO_4$, and evaporated *in vacuo* to yield the title compound **19** quantitatively as an oil (51 g, 248 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) 1.60 (s, 6H), 7.60 (dd, 1H), 7.95−8.00 (dd, 1H) and 8.75−8.85 (s, 1H); ^{19}F NMR (400 MHz, $CDCl_3$) −68 (s, 3F); ^{13}C NMR (400 MHz, DMSO-d_6) δ 147.5, 146.5, 146.2, 133.6, 123.5, 119.9, 71.8, 32.0; LC/MS *m/z* (ES^+) 206 $[MH]^+$

*5-Isopropenyl-2-trifluoromethyl-pyridine (**20**).* To a solution of **19** (270 g, 1.31 mol) in toluene (2.3 L, 9 mL/g) was added $TsOH\cdot H_2O$ (95.0 g, 499 mmol), and the resulting mixture was heated to reflux under Dean−Stark conditions for 6 h. The reaction mixture was cooled to room temperature, and then sat. sodium carbonate (2.5 L) was charged to the vessel and the resulting mixture stirred for 20 min. The phases were separated, and the resulting organic layer was washed with brine (2 × 2.5 L), dried over $MgSO_4$, and evaporated *in vacuo* with temperature <45 °C (to minimise volatile product losses). Purification was by high vacuum distillation at 65 °C (bp 40 °C @ 0.17 mmHg) to yield the title compound **20** as an oil (131 g, 987 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) 2.18 (s, 3H), 5.29 (s, 1H), 5.50 (s, 1H), 7.62−7.70 (dd, 1H), 7.85−7.90 (dd, 1H) and 8.81 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 147.5, 139.9, 134.0, 129.0, 128.1, 125.2, 120.2, 116.1, 21.8; LC/MS *m/z* (ES^+) 188 $[MH]^+$

*2-Methyl-2-(6-trifluoromethyl-pyridin-3-yl)cyclopropanecarboxylic Acid Ethyl Ester (**21**).* Preforming the active catalyst: to a 100-mL round-bottomed flask was charged DCM (40 mL), followed by Ru(cymene)$_2Cl_2$ (4.91 g, 8.0 mmol) and 2,6-bis[-(4*R*)-(+)-isopropyl-2-oxazolin-2-yl] pyridine (4.83 g, 16 mmol), and the mixture was stirred at room temperature for 30 min, resulting in a deep-purple reaction mixture.

To a solution of **20** (100 g, 534 mmol) in toluene (1 L, 10 mL/g) was added the preformed catalyst solution, and the resulting mixture was heated to 80 °C over 30 min. A preformed solution of ethyldiazoacetate (EDA) (90.7 mL, 854 mmol) in toluene (400 mL) was added to the reaction mixture over a period of 5 h using a peristaltic pump to provide a constant feed of the EDA solution. After 5 h HPLC analysis indicated the reaction was complete with 77.5% *trans* product and 21.7% *cis* product. The reaction was cooled to room temperature and then evaporated *in vacuo* to give a purple residue. Purification by silica plug using heptane/EtOAc (80:20) gave the title compound **21** as an oil (132.25 g, 484 mmol, 81%, *trans/cis* ratio 80:20, 65% ee). ^{1}H NMR (400 MHz, $CDCl_3$) 1.25−1.30 (t, 3H), 1.41−1.46 (m, 1H), 1.52−1.56 (m, 4H), 1.95−2.0 (m, 1H), 4.15−4.25 (m, 2H), 7.55−7.61 (dd, 1H), 7.71−7.75 (dd, 1H), 8.65 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 171.0, 149.5, 146.0, 144.0, 136.0, 123.0, 120.0, 61.0, 28.0, 27.5, 20.5, 19.5 and 14.0; LC/MS *m/z* (ES^+) 274 $[MH]^+$

*2-Methyl-2-(6-trifluoromethyl-pyridin-3-yl)cyclopropanecarboxylic Acid (**5**).* To a solution of LiOH (17.24 g, 410 mmol) in water (1125 mL, 10 mL/g) was added a preformed solution of **21** (112.25 g, 410 mmol) in EtOH (560 mL, 5 mL/g). The addition was controlled to maintain the temperature <30 °C. HPLC analysis after 2 h showed full conversion of the desired *trans*-ester **21** to the corresponding acid **5**. To the reaction mixture was added aqueous K_2CO_3 (1 M, 140 mL) followed by addition of MTBE (800 mL), and the organic layer was retained. The lower aqueous layer was re-extracted with MTBE (600 mL). The organic layers were combined and washed with saturated brine

(300 mL), dried over $MgSO_4$, and evaporated *in vacuo* to yield the title compound **5** as an orange oil (81.40 g, 332 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) 1.54−1.59 (m, 2H), 1.60−1.65 (m, 3H), 1.99−2.05 (q, 1H), 7.60−7.65 (dd, 1H), 7.76−7.80 (dd, 1H), 8.70 (s, 1H), 11.35−11.80 (broad singlet, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 176.5, 149.5, 146.0, 144.2, 136.0, 123.5, 120.5, 29.0, 27.0, 21.0, 19.5; LC/MS *m*/*z* (ES^+) 246 $[MH]^+$ Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; F, 23.24; N, 5.71; O, 13.05. Found: C, 53.85; H, 4.07; N, 5.71

*2-Methyl-2-(6-trifluoromethyl-pyridin-3-yl)cyclopropanecarboxylic Acid Quinine Salt (**5**).* To a solution of **5** (102.47 g, 468 mmol) in MTBE (614 mL, 6 mL/g) was added quinine (135.58 g, 417 mmol). To the slurry was added further MTBE (500 mL, 5 mL/g), and the slurry was heated to 55 °C for a period of 2 h. The slurry was cooled to room temperature and filtered with the cake being washed with MTBE and pulled dry under vacuum. Isolated solid was dried in vacuum oven at 50 °C to yield title compound **5** as the quinine salt (202.38 g, 355 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) 1.15 (s, 3H), 1.15−1.30 (m, 2H), 1.45−1.49 (t, 1H), 1.59 (s, 3H), 1.65−1.72 (m, 1H), 1.92−2.00 (m, 3H), 2.54 (broad singlet, 1H) 2.91−3.03 (m, 1H), 3.19 (s, 1H), 3.22−3.30 (t, 1H), 3.35−3.43 (t, 1H), 3.73 (s, 3H), 4.15−4.26 (m, 1H), 4.93−5.0 (m, 2H), 5.48−5.58 (m, 1H), 6.20 (s, 1H), 6.92 (s, 1H), 7.13−7.16 (dd, 1H), 7.54−7.60 (m, 2H), 7.73−7.79 (m, 2H), 8.62 (s, 1H), 8.71 (s, 1H).

*2-Methyl-2-(6-trifluoromethyl-pyridin-3-yl)cyclopropanecarboxylic Acid (S)-1,2,3,4-tetrahydronaphthylamine salt (**5**).* To a solution of **5** (83.92 g, 342 mmol) in 2-propanol (840 mL, 10 mL/g) was added a preformed solution of (*S*)-1,2,3,4-tetrahydronaphthylamine (50.38 g, 342 mmol) in 2-propanol (200 mL, 4 mL/g). The reaction was heated to 50 °C for 3 h and was cooled to room temperature. The slurry was cooled using an ice bath, isolated by filtration, washed with 3 mL/g 2-propanol, and dried in a vacuum oven at 50 °C to yield title compound **5** as the (*S*)-1,2,3,4-tetrahydro-1-naphthylamine salt (104.54 g, 266 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) 1.19−1.26 (m, 1H), 1.28−1.32 (m, 1H), 1.48 (s, 3H), 1.71−1.80 (m, 2H), 1.81−1.98 (m, 2H), 2.04−2.13 (m, 1H), 2.66−2.80 (m, 2H), 4.16−4.21 (t, 1H), 7.00−7.15 (m, 6H), 7.40−7.45 (d, 1H), 7.54−7.57 (d, 1H), 7.62−7.67 (dd, 1H), 8.57 (s, 1H).

*(1S,2S)-N-[(1R)-1-{3-Fluoro-4-[(methylsulfonyl)amino]phenyl}-ethyl]-2-methyl-2-[6-(trifluoromethyl)pyridin-3-yl]cyclopropanecarboxamide (**1**).* To a solution of **5** (49.0 g, 200 mmol) in THF (250 mL, 5 mL/g) was added **3** (53.7 g, 200 mmol) followed by THF (125 mL, 2.5 mL/g). 1-propylphosphonic acid cyclic anhydride (T3P) (178 mL, 300 mmol) was added followed by diisopropylethylamine (209 mL, 1.20 mol) and THF (125 mL, 2.5 mL/g) and the reaction mixture heated to 55 °C for 2 h. The reaction was cooled to room temperature, and to the vessel was added water (500 mL) followed by ethyl acetate (500 mL). The organic layer was retained and washed with water (750 mL). sat. sodium carbonate (500 mL), sat. citric acid (500 mL), and water (500 mL), dried over $MgSO_4$, and evaporated *in vacuo* to give a foam. The residue was purified by slurrying in MTBE (450 mL) at 50 °C for 1 h, cooled to room temperature, and filtered to give the title compound **1** as an off-white solid. (71.1 g, 154 mmol, 77%, 98.9% de[27]). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38−1.43 (m, 1H), 1.47−1.50 (d, 3H), 1.58 (s, 3H), 1.59−1.62 (dd, 1H), 1.72−1.76 (dd, 1H), 3.00 (s, 3H), 5.07−5.16 (m, 1H), 6.20−6.25 (d, 1H), 6.60 (brs, 1H), 7.09−7.11 (m, 1H), 7.12−7.14 (m, 1H), 7.46−7.51 (m, 1H), 7.57−7.60 (d, 1H), 7.65−7.69 (dd, 1H), 8.60−8.62 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5, 157.6, 155.2, 149.3, 146.0, 145.3, 145.3, 145.1, 144.8, 144.5, 144.1, 136.6, 127.7, 126.4, 123.7, 123.7, 123.6, 122.8, 122.8, 121.0, 120.7, 118.3, 114.3, 114.1, 48.2, 30.3, 27.4, 25.8, 22.9, 19.6, 18.1; LC/MS *m*/*z* (ES^+) 460 $[MH]^+$; Anal. Calcd for $C_{20}H_{21}F_4N_3O_3S$: C, 52.28; H, 4.61; N, 9.15; F, 16.54; S, 6.98. Found: C, 52.28; H, 4.76; N, 8.86; F, 16.86; S, 6.95.

*(1S,2S)-N-[(1R)-1-{3-Chloro-4-[(methylsulfonyl)amino]phenyl}-ethyl]-2-methyl-2-[6-(trifluoromethyl)pyridin-3-yl]cyclopropanecarboxamide (**2**).* To a solution of **5** (63.1 g, 257 mmol) in THF (734 mL, 10 mL/g) was added **4** (73.4 g, 257 mmol) followed by 1-propylphosphonic acid cyclic anhydride (T3P) (232 mL, 386 mmol). Diisopropylethylamine (224 mL, 1.29 mol) was added and the reaction mixture heated to 60 °C for 2 h. The reaction was cooled to room temperature and to the vessel was added water (750 mL) followed by ethyl acetate (750 mL). The organic layer was retained and washed with water (750 mL), sat. sodium carbonate (750 mL), sat. citric acid (750 mL), and water (750 mL), dried over $MgSO_4$, and evaporated *in vacuo* to give a foam. The residue was purified by slurrying in MTBE (325 mL) at room temperature and recrystallised with acetonitrile (390 mL) to give the title compound **2** as an off-white solid. (65.0 g, 137 mmol, 63%, 98.5% de[27]). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40−1.45 (dd, 1H), 1.48−1.51 (d, 3H), 1.58 (s, 3H), 1.60−1.63 (dd, 1H), 1.70−1.75 (dd, 1H), 2.99 (s, 3H), 5.07−5.15 (m, 1H), 6.02−6.07 (d, 1H), 6.72 (brs, 1H), 7.24−7.27 (dd, 1H), 7.38−7.40 (d, 1H), 7.58−7.61 (dd, 1H), 7.66−7.70 (dd, 1H), 8.61−8.63 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5, 149.3, 146.0, 145.2, 144.8, 144.4, 144.1, 136.6, 133.0, 129.6, 128.5, 127.8, 126.4, 126.1, 123.7, 121.0, 120.7, 118.3, 48.2, 41.5, 30.3, 25.8, 22.9, 19.6, 18.1; LC/MS *m*/*z* (ES^+) 476 $[MH]^+$; Anal. Calcd for $C_{20}H_{21}F_4N_3O_3S$: C, 50.48; H, 4.45; N, 8.83; Cl, 7.45; S, 6.74. Found: C, 50.38; H, 4.42; N, 8.79; Cl, 7.52; S, 6.80.

■ ASSOCIATED CONTENT

Supporting Information. Further information summarizing the chiral base screen of cyclopropyl acid **5** and the cyclopropanation screen of **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) **5** with a chiral purity of 60% ee was trialled in the coupling, but a screen of column and crystallisation conditions failed to purge the diastereoisomer to acceptable levels. As a result, the salt resolution using (*S*)-1,2,3,4-tetrahydro-1-naphthylamine had to be implemented to increase the chiral purity of **5** to 93% ee.

(27) The diastereoisomers could be resolved by HPLC, providing confidence that the impurities could be accurately measured.

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