Organic Process Research & Development

Full Paper

Asymmetric Fluorination Approach to the Scalable Synthesis of a SYK Inhibitor

Neil R Curtis, Suzanne Davies, Matthew Gray, Stuart Grahame Leach, Ross A. McKie, Lois E. Vernon, and Andrew Walkington

Org. Process Res. Dev., **Just Accepted Manuscript** • Publication Date (Web): 15 Jun 2015

Just Accepted

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Asymmetric Fluorination Approach to the Scalable Synthesis of a SYK Inhibitor

Neil R. Curtis, Suzanne H. Davies, Matthew Gray,* Stuart G. Leach,* Ross A. McKie, Lois E. Vernon †

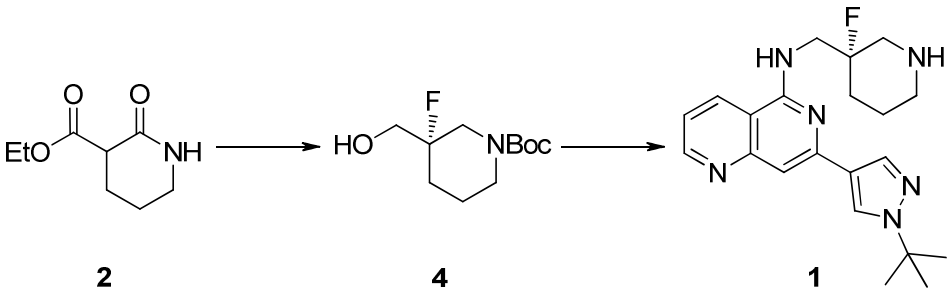
and Andrew J. Walkington

Product Development, GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK

* Matthew.2.Gray@gsk.com; Stuart.G.Leach@gsk.com

† Deceased

TABLE OF CONTENTS GRAPHIC



2 **4** **1**

ABSTRACT

A large scale process for the synthesis of SYK inhibitor **1** has been developed and used to deliver multi-kilos of API. Integral to the scalable process is a combined chiral auxiliary and chiral catalyst mediated diastereoselective fluorination to provide **14**. Safe processes for BH_3·DMS mediated reduction of ester and amide functions and azide introduction, and a robust Suzuki-Miyaura coupling of pyrazyl boronate **10** with chloronapthyridine **9** are described.

KEYWORDS

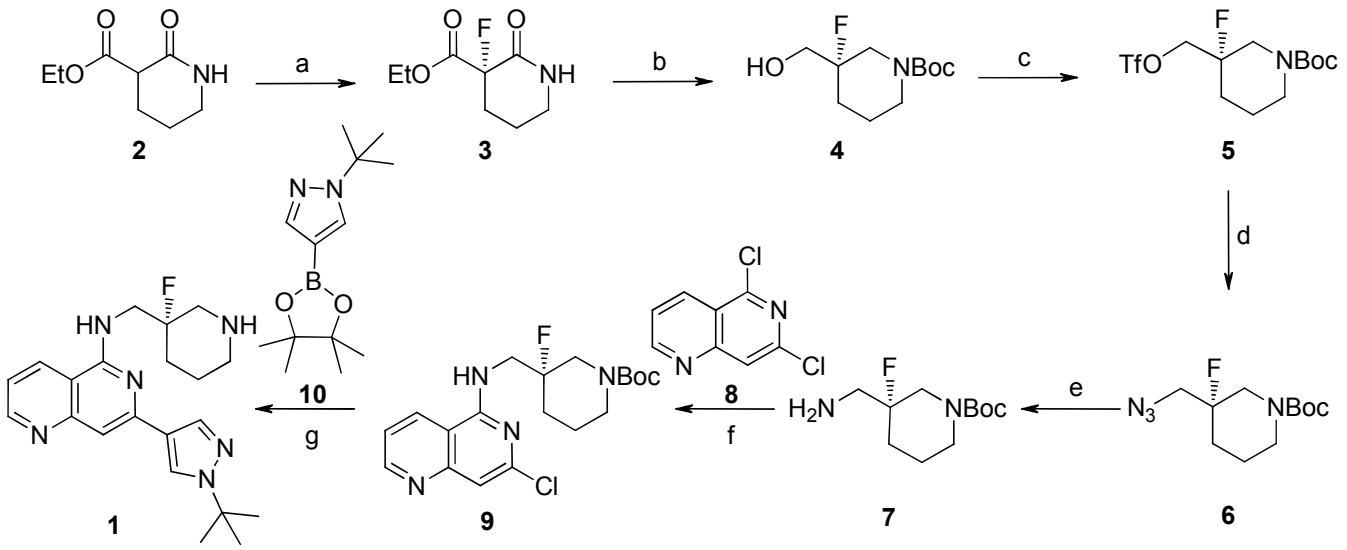
Fluorination, Asymmetric, Borane, Safety, Scalable, Suzuki

INTRODUCTION

7-[1-(1,1-Dimethylethyl)-1*H*-pyrazol-4-yl]-*N*-{[(3*S*)-3-fluoro-3-piperidinyl]methyl}-1,6-naphthyridin-5-amine **1**[1] is a potent and selective inhibitor of spleen tyrosine kinase (SYK),[2] a non-receptor kinase implicated in the mediation of diverse cellular responses, including proliferation, differentiation and phagocytosis. As such, SYK inhibitors may have application in a number of therapeutic areas, including rheumatoid arthritis,[3] B-cell lymphoma[4] and asthma/rhinitis.[5] To support pre-clinical and clinical evaluation, the project required rapid preparation of multi-hundred gram quantities of **1**, shortly followed by supply of multi-kilo quantities. Herein we describe the development of a synthetic route to allow operation on multi-kilo scale, along with a discussion of salient issues relating to the safe operation thereof.

The medicinal chemistry route was used to prepare multi-gram quantities of **1** (Scheme 1). However, a number of issues were identified which would need to be addressed prior to further scale-up. The use of a poorly enantioselective fluorination reaction with *N*-fluorobenzenesulfonimide (NFSI)[6] necessitated chiral HPLC purification, and inherently unsafe procedures using borane, sodium azide and TFA respectively would all need to be circumvented.

Scheme 1.[a] Medicinal Chemistry Route to **1**.



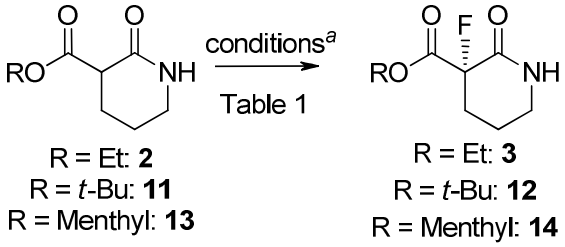
[a]Reagent and conditions: (a) (i) (*S*)-BINAP-Pd(OTf)$_2$(H$_2$O)$_2$, 2,6-lutidine, NFSI, EtOH, 0 °C, 18 h; (ii) chiral HPLC, 50%, >99% ee; (b) (i) BH_3·THF (1 M in THF), THF, reflux, 24 h; (ii) Boc_2O, NEt_3, CH_2Cl_2, 20 °C, 3 h, 86%; (c) Tf_2O, NEt_3, DCM, −10 °C, quant.; (d) NaN_3, DMF, 80 °C, 1 h, quant.; (e) H_2 (atmospheric), Pd/C, EtOH, 20 °C, 18 h, quant.; (f) DIPEA, NMP, 130 °C, 16 h, 86%; (g) (i) Pd(PPh_3)$_4$, Cs_2CO_3, 5:1 dioxane/water, μW, 130 °C, 2 h; (ii) TFA, CH_2Cl_2, 20 °C, 20 min, 57%.

RESULTS AND DISCUSSION

Development of the Asymmetric Fluorination. The medicinal chemistry preparation of **3** (Scheme 1) gave a modest 44% ee in favour of the required enantiomer, and required flash column chromatography followed by lengthy chiral HPLC to upgrade the ee to >99%, giving enantiomerically pure **3** in 50% yield. While this method could theoretically be used for the initial scale-up campaign, the time, cost and solvent waste associated with this approach made it attractive to explore alternatives, especially as this would be impracticable for further scale-up. A survey of recent literature[7] indicated that the current conditions represented state-of-the-art for 1,3-dicarbonyls, although there might be scope for improved enantioselectivity using bulkier palladium ligands (such as xylyl-BINAP, DM-SEGPHOS or DTBM-SEGPHOS).[8] Reactions using these bulkier ligands gave improved enantioselectivities (Scheme 2,

Table 1), although reducing the catalyst loading from 5 mol% to 1 mol% caused a significant drop in ee (entries 5 and 6), presumably due to competing background racemic reaction. Unsubstituted BINAP catalyst was more tolerant to reduction in loading (entries 1 and 7). Considering the high cost of these ligands in combination with the need for extensive optimisation to achieve useful ee's (>98%), alternative solutions were sought. One possibility was replacement of the ethyl ester with a bulkier ester. This was investigated using the *t*-butyl ester, giving some improvement in ee (entry 8). However, even in combination with xylyl-BINAP, 87% ee was some way off an acceptable level (entry 9). It was rationalised that a bulky chiral ester might confer favourable chiral influence, in combination with the matched chiral catalyst to allow higher selectivity through the formation of diastereoisomers. Menthol was an ideal candidate, since it is a low cost chiral secondary alcohol, with significant steric bulk. The (–)-menthyl ester was initially used with both enantiomers of the catalyst, with (*S*)-BINAP indicating a mismatched case due to poor diastereoselectivity (entries 10 and 12). Gratifyingly, the matched example using (*R*)-BINAP gave 99% de with 5 mol% loading at 20 ºC (entry 11), while reaction at -10 ºC gave only 91% de (entry 13). It was also possible to drop the catalyst loading to 1% while still achieving 94% de (entry 15). This was a synthetically useful compromise due to purging of the minor diastereoisomer by crystallisation (100% de).[9] It should be noted that crystallisation did not enhance the ee of the ethyl or *t*-butyl esters.

Scheme 2.[a] Screen of Asymmetric Fluorination Reaction Conditions.



[a]Reagent and conditions: (a) (i) Ln*-Pd(OTf)$_2$(MeCN)$_2$, 2,6-lutidine, NFSI, EtOH, 18 h.

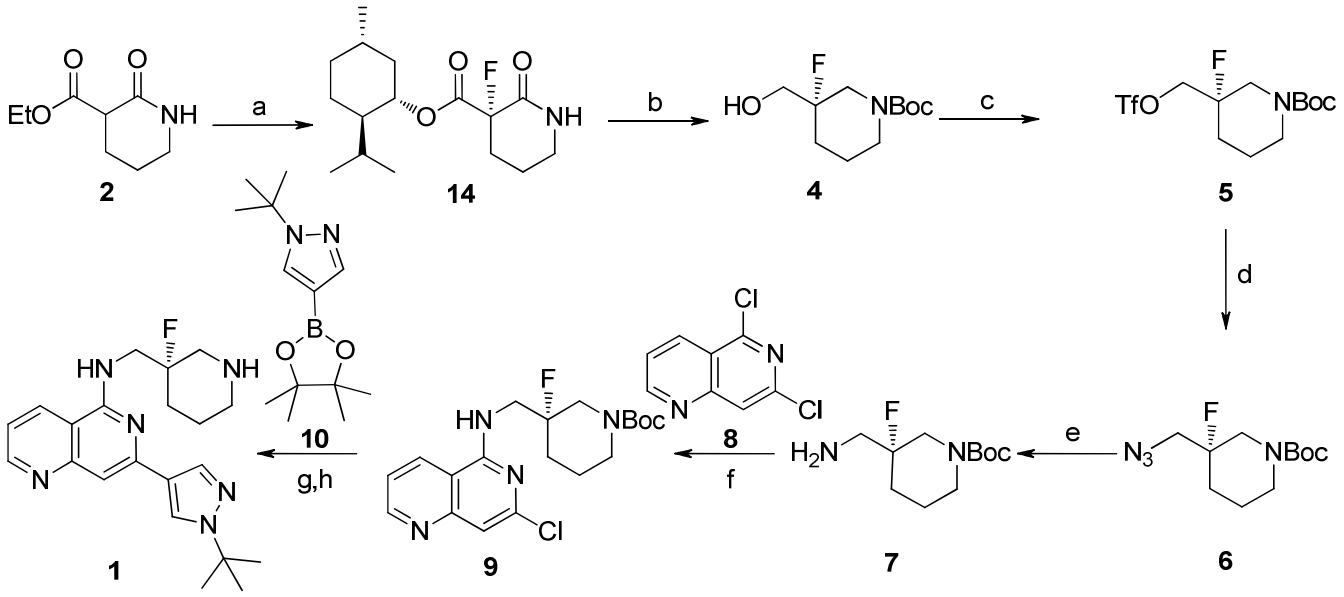
Table 1. Asymmetric Fluorination Reactions.

Entry	Substrate	Ln*	Catalyst Loading (mol%)	Temp (^{o}C)	Yield (%th)[a]	ee/de (%)
1	**2**	BINAP	5	20	103	53
2	**2**	BINAP	5	-10	97	56
3	**2**	DM-SEGPHOS	5	-10	75	76
4	**2**	DTBM-SEGPHOS	5	-10	97	72
5	**2**	Xylyl-BINAP	5	20	100	63
6	**2**	Xylyl-BINAP	1	20	82	31
7	**2**	BINAP	1	20	99	47
8	**11**	BINAP	5	20	100	64
9	**11**	Xylyl-BINAP	5	20	100	87
10	(–)-**13**	(*S*)-BINAP	5	20	81	-25
11	(–)-**13**	(*R*)-BINAP	5	20	88	99
12	(–)-**13**	(*S*)-BINAP	5	-10	95	5
13	(–)-**13**	(*R*)-BINAP	5	-10	83	91
14	(+)-**13**	(*S*)-BINAP	0.5	20	n/d	90
15	(+)-**13**	(*S*)-BINAP	1	20	n/d	94

[a] Isolated yield after chromatography, uncorrected.

20 L Scale Synthesis (Scheme 3). The preparation of **14** from commercially available ethyl ester **2** required preparation of menthyl ester **13**. Preparation or isolation of the corresponding acid proved difficult, due to the tendency of this compound to undergo decarboxylation. Therefore, direct transesterification methods were explored, leading to development of a DMAP catalysed process in toluene with distillative removal of ethanol to drive the equilibrium.[10] After a basic wash, the menthyl ester was isolated by concentration to dryness.

Scheme 3.[a] 20 L Scale Route to **1**



[a] Reagent and conditions: (a) (i) (+)-menthol, 4-DMAP, toluene, reflux, 7 d; (ii) (*S*)-BINAP-$Pd(OTf)_2(MeCN)_2$, 2,6-lutidine, NFSI, EtOH, 20 °C, 24 h, 70%, 100% de; (b) (i) BH_3·DMS, THF, reflux, 2 d; (ii) Boc_2O, NaOH (aqueous), CH_2Cl_2, 20 °C, 15 h, 77%; (c) Tf_2O, pyridine, -10 °C, 4 h, 92%; (d) NaN_3, DMF, 20-30 °C, 6 h, 93%; (e) H_2 (atmospheric), Pt/C (Johnson Matthey type 128), THF, NH_3 (aqueous), 20 °C, 39 h, quant.; (f) DIPEA, NMP, 110 °C, 17 h, 92%; (g) (i) Pd(di-*t*-bpf)Cl_2 (Johnson Matthey Pd-118), $NaHCO_3$, 4:1 dioxane/water, reflux, 3 h; (ii) Silicycle® Si-thiol, toluene, 60-65 °C, 2 h; (iii) HCl/dioxane, toluene, 60 °C; (h) (i) NaOH (aqueous); (ii) *n*-BuOAc/TBME, 57% from **9**.

In order for the fluorination chemistry to be carried out on multikilo scale, an improved, scalable synthesis of the catalyst (*S*)-BINAP-$Pd(OTf)_2(MeCN)_2$ was required. Literature methods require either the use of stoichiometric silver triflate,[11] or handling of the palladium triflate intermediate,[12] which is very air sensitive. A telescoped process in acetonitrile followed by antisolvent crystallisation was developed whereby multiple kilos of the bench stable catalyst could be readily prepared without requirement for rigorous inertion or drying (see experimental section).

Following fluorination chemistry as described above (Table 1, entry 15), optimisation of the reaction conditions allowed direct crystallisation of a mixture of product and the reduced NFSI by-product [*N*-(phenylsulfonyl)benzenesulfonamide], avoiding the need for flash chromatography. This was achieved using a sub-stoichiometric amount (0.95 equivalents) of NFSI, avoiding the troublesome removal of excess NFSI. Subsequent basic work-up removed the reduced NFSI by-product and crystallisation removed other impurities as well as unreacted starting material. 2.5 kg of **14** was prepared using this method, in 70% yield, 100% a/a HPLC purity and 100% de. The next steps were reduction and Boc protection to give **4**, an intermediate common to the medicinal chemistry route. The reduction conditions described for ethyl ester **3** (Scheme 1) were successfully applied to the analogous menthyl ester **14** on small scale. However, these conditions were unsuitable for scale-up due to inherent safety concerns.[13] Diborane gas, which can be easily evolved from BH_3·THF, has a low auto-ignition temperature of about 38-52 °C and a wide explosive range in air (0.8-90% vol).[14] A number of alternatives were evaluated for this conversion, including BH_3·THF at 40 ºC, DEANB, $LiAlH_4$ and Red-Al®, all of which gave incomplete and/or messy reactions. Boc protection prior to reduction was also explored, although competing reduction of the carbamate was problematic. BH_3·DMS in THF at reflux provided a safer alternative,[13] giving clean reduction after 2 days provided >5 equivalents were used. Methanol quench, followed by acidification with 2 M HCl allowed the menthol by-product to be removed by extraction into toluene. Subsequent free-basing, Boc protection and crystallisation gave **4** in 77% yield on 1 kg scale.

The triflation of **4** to **5** using triflic anhydride and triethylamine in dichloromethane was not in itself an issue for early scale-up. However, dichloromethane is incompatible with sodium azide[15] used in the subsequent step, so its avoidance was preferred. Use of other solvents with triethylamine as base gave messy reactions, but switching to pyridine as both solvent and base provided a good alternative, with improved product purity. The azide reaction to provide **6** could be carried out under ambient conditions, and the requirement for chromatography was negated by the improved input quality. However, the downstream hydrogenation was adversely affected. When the medicinal chemistry conditions of

triethylamine/DCM were employed in the triflation, azide **6** derived from this sequence gave a failed hydrogenation, although the reaction went cleanly after filtering off the catalyst and starting again. Conversely, when pyridine was used in the triflation, the hydrogenation worked first time, but also resulted in significant formation of a dimeric impurity **15**.[16] Addition of acetic acid did not significantly suppress dimer formation and solvent screening provided limited success, with a best ratio of 4:1 using ethyl acetate. Catalyst screening was therefore revisited, and, in combination with ammonia as an additive,[17] using platinum on carbon catalyst with THF solvent achieved quantitative hydrogenation to amine **7** with only 0.3% dimer **15**.

The coupling of amine **7** with 5,7-dichloro-1,6-naphthyridine **8** was carried out in NMP with DIPEA as base; conditions which gave a good reaction profile, with the exception of competing Boc deprotection. The yield was improved by reducing the temperature from 130 ºC to 110 ºC, and addition of water as anti-solvent crystallised naphthyridine **9** in high purity directly from the reaction mixture.

The medicinal chemistry method for Suzuki–Miyaura coupling of **9** with pyrazole boronate **10**[1] used a high loading of tetrakis(triphenylphosphine)palladium(0) under microwave conditions and required chromatography for purification. Focussed screening found that 0.5 mol% of bis(di-*tert*-butylphosphino)ferrocenepalladium dichloride in aqueous 1,4-dioxane with sodium hydrogen carbonate as base was a highly effective alternative. Palladium removal was effected by treatment with thiol functionalised silica (Silacycle® Si-thiol) in toluene. It was found convenient to isolate the coupled product by precipitation of **1** as the dihydrochloride, following Boc deprotection, hence avoiding column chromatography. Free basing and operation of a fit-for-purpose crystallisation from *n*-butyl acetate/TBME afforded **1** in reasonable overall yield (57% from **9**) with excellent purity (99.8% a/a, 100% ee) and very low palladium content (2 ppm). A second crop of **1** (16%) was isolated by reworking the liquors.

Multi-kilo Scale Synthesis (Scheme 4). The 20 L scale synthesis employed a number of concentrations to dryness which would be impractical for pilot plant operation. To avoid a concentration to dryness, in

the first stage of the synthesis, the menthyl ester solution in toluene was solvent swapped into ethanol using an efficient 'put and take' distillation and this solution used directly in the fluorination chemistry giving **14** in 68% yield, 100% de, over the two steps from **2**.

Operation of the borane-dimethyl sulfide reduction of **14** on pilot plant scale was challenging due to the high inventory required for complete reaction (6 equivalents). A very slow addition of the reaction mixture into methanol to quench the excess reagent was required to limit the rate of hydrogen evolution. The addition of hydrochloric acid and subsequent heat up to liberate the piperidine borane complex also required very careful control. A large volume of basic bleach in the scrubbers prevented release of dimethylsulfide to the atmosphere. DCM was replaced with TBME for the free basing of the intermediate hydroxymethylpiperidine hydrochloride and Boc protection. Alcohol **4** was produced in a single batch in 72% yield (23.3 kg), comparable to the first scale-up campaign.

On further scale-up to pilot plant, the triflation, azide formation, hydrogenation and coupling with naphthiridine were telescoped together such that no intermediates were isolated between compounds **4** and **9**. The triflation was run as before, in pyridine, with extraction into TBME using citric acid to wash out the pyridine. The concentrated TBME solution was diluted with DMF and reacted with sodium azide. This was slower than the reaction in neat DMF but allowed avoidance of evaporation to dryness on large scale. To ensure safe operation, vessel choice and fill volume were optimized for good stirring to keep the azide suspended. The vessel was also pretreated with dilute hydrochloric acid, prior to neutralisation and cleaning to remove acid residues, to ensure that no metal particulates were present. A solvent screen for the hydrogenation, revealed that TBME/ammonia could be used in place of THF, facilitating telescoping of this step.

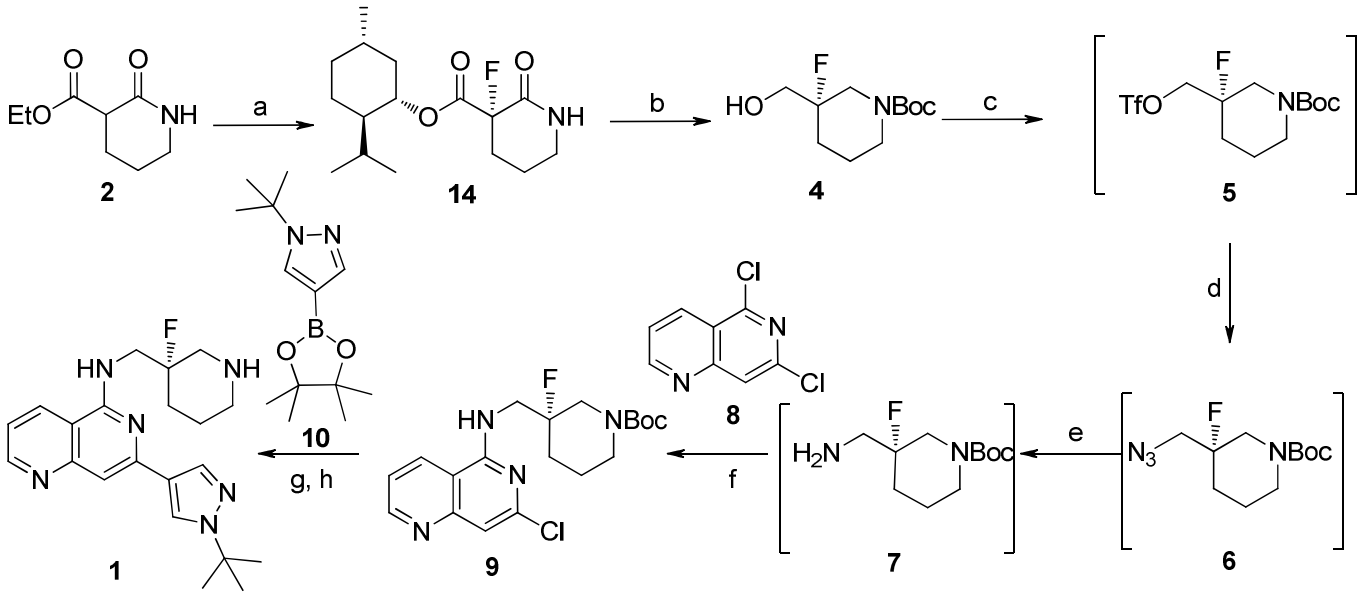
The coupling of amine **7** with the napthyridine **8** was accomplished in DMF with 1 volume of TBME present, thus allowing a concentrated solution of **7** in TBME to be used directly. Careful water addition allowed **9** to be crystallised from the reaction mixture in 38% overall yield from **4**, with excellent purity (HPLC 99.2% a/a).

Only minor modifications of the Suzuki–Miyaura/Boc deprotection protocol were envisaged to facilitate pilot plant preparation of **1**. However, use of functionalised silica for palladium removal was unattractive. In addition, the combination of refluxing dioxane and liberation of carbon dioxide as a consequence of using sodium hydrogen carbonate as base was regarded as undesirable because of the risk of loss of a class A VOC to the atmosphere. However, investigation of reactions at sub-reflux temperature and with alternative bases uncovered an underlying issue with the Suzuki–Miyaura chemistry. It was found that rigorous exclusion of oxygen was required to avoid stalling, despite the fact that the initial campaign had been successfully performed without special degassing precautions. Aqueous dioxane at reflux proved to be preferred over alternative solvent combinations, particularly to minimise protodeboronation of **10**. Sodium hydrogen carbonate was replaced by sodium carbonate as base. Environmental loss of dioxane was kept well below acceptable limits. A larger excess of boronate **10** (1.4 instead of 1.2 equivalents) was used compared to the first campaign to ensure robust consumption of chloride **9**. Palladium removal was performed by treating the aqueous dioxane reaction mixture with *L*-cysteine at 60 °C and a CUNO charcoal filtration after extractive workup and dilution with toluene. Boc deprotection was carried out with HCl/dioxane in toluene at 60 °C as before. The dihydrochloride salt of **1** (HPLC 96.4% a/a) was isolated with comparable purity to the first delivery campaign. However, an unidentified minor impurity caused problems with the subsequent free base crystallisation. A rework of **1** dihydrochloride was instigated to obviate this issue. Hence, **1** dihydrochloride was slurried in industrial methylated spirit (IMS) at 25 °C then filtered. **1** Dihydrochloride of high purity (HPLC 100% a/a) and low palladium content (6 ppm) was isolated in 84% overall yield from **9** for the telescoped Suzuki–Miyaura/Boc deprotection and IMS slurry.

The hydrochloride salt of **1** was free-based with aqueous sodium carbonate and extracted into ethyl acetate. The organic layer was azeotropically dried under reduced pressure and **1** was crystallized from ethyl acetate/diisopropyl ether. The slurry was size reduced, by rotor-stator wet-milling, before **1** was isolated as a yellow solid in 73% yield from the hydrochloride salt as a quarter hydrate, labelled as Form 1, of excellent purity (100% a/a, 100% ee, Pd 2 ppm). A further 8% yield of **1** was subsequently isolated

as a second crop. A polymorph screen found two polymorphs of similar stability (Form 1 and Form 2) and identified a number of solvates. From the data generated, Form 2 seems to be more stable than Form 1 at ambient temperatures (lower solubility in several systems, turnover in competitive experiments). However, throughout the development of the particle forming step, Form 2 has been challenging to prepare which may be due to the very close energy relationship between the two forms. Ostwalds rule[18] of stages suggests that the least stable polymorph of a given system will crystallize first and then turnover to the more stable polymorph over time. In this case, if the driving force to go from Form 1 to Form 2 is very small in terms of an absolute energy difference, then the kinetics will be very slow. This has been demonstrated in a turnover experiment which took more than a week to give significant amounts of Form 2. Both Forms 1 and Form 2 were found to have very similar dissolution properties in physiological media, so producing either Form 1 or Form 2 was deemed acceptable for initial safety and clinical studies.

Scheme 4.[a] Multi-kilo Scale Route to **1**.



[a] Reagents and conditions: (a) (i) (+)-menthol, 4-DMAP, toluene; (ii) (*S*)-BINAP-Pd(OTf)$_2$(MeCN)$_2$, 2,6-lutidine, NFSI, EtOH, 68%, 100% de; (b) (i) BH_3·DMS, THF; (ii) Boc_2O, NaOH (aqueous), TBME, 72%; (c) Tf_2O, pyridine; (d) NaN_3, TBME/DMF; (e) H_2 (2 barg), Pt/C, TBME, NH_3 (aqueous); (f)

DIPEA, TBME/NMP, 38% (from **4**); (g) (i) Pd(di-*t*-bpf)Cl_2, Na_2CO_3, dioxane/water; (ii) HCl/dioxane, toluene; (iii) IMS, 84%; (h) (i) Na_2CO_3 (aqueous), EtOAc; (ii) EtOAc, diisopropyl ether, 73% (+ 8% second crop).

In conclusion, a combined chiral auxiliary and chiral catalyst mediated diastereoselective fluorination was developed and successfully operated on large scale. 8 kg of SYK inhibitor **1** was synthesised using this methodology *via* a single-batch strategy. This involved development of safe pilot plant scale processes for reduction to prepare alcohol **4**, subsequent azide introduction, and a robust late-stage Suzuki-Miyaura coupling.

EXPERIMENTAL SECTION

General procedures. All reagents and solvents used were obtained commercially unless stated, and were employed without further purification. The experimental conditions below refer to the procedures used for the multikilogram pilot-plant campaign. NMR data were obtained on Bruker AV 400, AV 500 or AV 700 spectrometers. High resolution mass spectrometry data were obtained a Thermo-Finnigan Orbitrap Fourier-transform mass spectrometer running in positive electrospray ionisation mode.

[(*S*)-BINAP]bis(acetonitrile)palladium(II) ditriflate

Palladium acetate (300 g) was dissolved in acetonitrile (1.2 L) and stirred at 20±3 °C for 1 h. The reaction mixture was cooled to 0±3 °C. Trifluoromethanesulfonic acid (225 mL) was added over 30 min, maintaining the temperature below 3 °C, then rinsed in with acetonitrile (90 mL). After stirring for 18 min at 0±3 °C the reaction mixture was heated to 20±3 °C and stirred for 31 min. (*S*)-BINAP (831 g) was added followed by a wash of acetonitrile (90 mL) and the mixture was stirred at 20±3 °C for 2 h. Diisopropyl ether (3 L) was added over 30 min to give a slurry which was aged for 30 min. The solid was filtered off under suction and washed with acetonitrile:diisopropyl ether (1:3, 2.4 L) followed

by diisopropyl ether (2.4 L). The product was dried under vacuum at 20±3 °C to afford a yellow solid 1304g (88%).

(3*S*)-(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl 3-fluoro-2-oxopiperidine-3-carboxylate **14**.

Ethyl 2-oxopiperidine-3-carboxylate **2** (37.0 kg), 4-dimethylaminopyridine (DMAP) (12.95 kg), (1*S*,2*R*,5*S*)-menthol (35.2 kg) were charged. Toluene (370 L) was added and the reaction mixture heated to reflux, and stirred under constant volume distillation by adding toluene at the same rate as toluene is removed for 5 days. The reaction mixture was cooled to 22±3 °C and washed with 2 N aqueous hydrochloric acid (2 x 148 L) and then water (148 L). The reaction mixture was distilled under atmospheric pressure to *ca*. 111 L, ethanol (666 L) was added, the mixture distilled under atmospheric pressure to *ca*. 111 L then cooled to 22±3 °C. *N*-Fluorobenzenesulfonimide (68.1 kg) was added, followed by Pd(*S*)-BINAP(OTf)$_2$ (2.26 kg), washing in the residual *N*-fluorobenzenesulfonimide and catalyst with further ethanol (55 L). The reaction mixture was cooled to <5 °C and 2,6-lutidine (13.0 L) was charged dropwise keeping the temperature <10 °C. The reaction mixture was stirred at 22±3 ºC for 42 h. The reaction mixture was then cooled to 0 ºC and stirred for an additional 2 h. The precipitated solids were isolated by filtration, washed with chilled ethanol (111 L) and dried under vacuum overnight at 40 ºC. The solids were re-charged to a vessel at 22±3 ºC, followed by dichloromethane (303 L) and stirred until a solution was obtained. The solution was washed sequentially with 2 M aqueous sodium hydroxide (185 L), water (185 L), 2 N aqueous hydrochloric acid (185 L) and finally water (185 L). IMS (277 L) was added and the mixture was distilled under atmospheric pressure to ca. 111 L, then diluted with IMS (74 L). Water (185 L) was added over 2 h whilst maintaining the temperature at 22±3 ºC then the mixture was cooled to 0±3 °C and stirred for a further 2 h. The solid was collected by filtration, washed with chilled water/IMS (3:1, 74 L) and dried under vacuum at 40 °C to give **14** (43.7 kg, 68%) as an orange crystalline solid (mp 167-169°C).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (3H, d, *J* = 5 Hz), 0.89 (3H, d, *J* = 10 Hz), 0.92 (3H, d, *J* = 5 Hz), 1.03-1.11 (2H, m), 1.43-1.55 (2H, m), 1.67-1.74 (2H, m), 1.85-2.06 (4H, m), 2.22-2.37 (2H, m), 3.37-

3.46 (2H, m), 4.84 (1H, dt, J = 10, 5 Hz), 7.35 (1H, brs). MS Found for $C_{16}H_{27}FNO_3$ [M+H] = 300.1965, Calc for $C_{16}H_{27}FNO_3$ [M+H] = 300.1970.

1,1-Dimethylethyl (3*S*)-3-fluoro-3-(hydroxymethyl)-1-piperidinecarboxylate **4**.

(3*S*)-(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl 3-fluoro-2-oxopiperidine-3-carboxylate **14** (41.85 kg) was suspended in THF (240 L) and treated with borane dimethyl sulfide complex (64.0 kg). The resulting solution was stirred at 67±3 °C for 43 h. The reaction mixture was cooled to 0±5 °C and slowly added to cold (0±5 °C) methanol (126 L) over at least 90 min, maintaining the internal temperature below 20 °C. 2 M Hydrochloric acid (166 L) was added over at least 60 min, maintaining the internal temperature below 20 °C. The mixture was stirred at 20±3 °C for at least 30 min then stirred at 60±5 °C for at least 60 min then cooled to 20-25 °C. Toluene (168 L) was added, the mixture stirred for 15 min then filtered. The filter cake was washed with toluene (84 L). The filtrate was separated and the lower acidic aqueous phase was run off. The filter cake was washed with 2 M hydrochloric acid (83 L) and the wash used for a second extraction of the toluene phase. The acidic aqueous phases were combined. 32% Sodium hydroxide solution (105 kg) was added over at least 60 min, maintaining the temperature below 25 °C. The mixture was diluted with TBME (84 L). A 70% w/w solution of di-*tert*-butyl-dicarbonate in TBME (48.3 kg) was added and rinsed in with more TBME (63 L). The two-phase mixture was stirred vigorously at 20±5 °C for 2 h. The phases were separated and the upper organic phase washed with 5% w/w sodium chloride in water (168 L). The aqueous phase was extracted with a further portion of TBME (168 L) and the extract was washed with the previously used brine. The combined organics were diluted with heptane (168 L) and concentrated by vacuum distillation to *ca.* 168 L at 40±3 °C. Heptane (168 L) was added and the mixture concentrated by vacuum distillation to *ca.* 252 L at 40-45 °C. The solution was seeded at 40-45 °C with **4** (84 g). The mixture was concentrated by vacuum distillation at 40-45 °C to *ca.* 168 L then the concentrate was cooled and stirred at 20±5 °C for 90 min. The solid was filtered off, washed with heptane (2 x 42 L) and dried under vacuum at 25±5 °C to give **4** (23.3 kg, 72%) as a colourless solid (mp 97-98°C).

^{1}H NMR (500 MHz, DMSO-d_6) δ 1.39 (9H, s), 1.44-1.76 (4H, m), 2.82-3.08 (2H, m), 3.35-3.48 (2H, m), 3.80 (1H, d, J = 10 Hz), 3.93 (1H, brs), 4.99 (1H, t, J = 5 Hz). MS Found for $C_{11}H_{21}FNO_3$ [M+H] = 234.1499, Calc for $C_{11}H_{21}FNO_3$ [M+H] = 234.1500.

1,1-Dimethylethyl-(3*R*)-3-{[(7-chloro-1,6-naphthyridin-5-yl)amino]methyl}-3-fluoro-1-piperidinecarboxylate **9**.

1,1-Dimethylethyl (3*S*)-3-fluoro-3-(hydroxymethyl)-1-piperidinecarboxylate **4** (21.0 kg) dissolved in pyridine (64 L) was cooled to -10 °C. Triflic anhydride (16.8 L) was added over 1 h, keeping the contents below 5 °C. The reaction was stirred at -10±3 °C for 90 min. The reaction was warmed to 0 °C. TBME (105 L) was added, followed by 50 wt% citric acid (105 L) over 30 min. The mixture was stirred at 20 °C for at least 5 min, allowed to settle and the layers separated. The organic phase was further washed with 50 wt% citric acid solution (105 L), water (63 L), 7 wt% sodium bicarbonate solution (63 L) and water (63 L) The resulting organic solution was partially dried by distilling down to *ca.* 61 L, adding a further aliquot of TBME (53 L) and distilling to *ca.* 53 L. This solution was assayed and added to a stirred mixture of sodium azide (5.2 kg) in DMF (47 L) and TBME (26 L) at room temperature. The resulting suspension was stirred at 22±3 °C for 47 h. Water (73.5 L) was added to the reaction mixture and the mixture was stirred for at least 5 min before allowing to settle and separating. The aqueous phase was back extracted with TBME (63 L). The TBME phases were combined and washed with water (2 x 42 L). The TBME solution was diluted with further TBME to give a total volume of *ca.* 273 L and charged to a pressure reactor. 10% Pt/C (type 128, 50% wet paste, 168 g) and 33% aqueous ammonia (42 L) were added. The reaction mixture was hydrogenated at 2 barg and 22±3 °C for 22 h. The reaction mixture was filtered through a bed of celite and washed with TBME (63 L). The lower aqueous phase was removed and the organic washed with 2 N aqueous hydrochloric acid (2 x 42 L). The aqueous layer was basified with 32 wt% aqueous sodium hydroxide and extracted with TBME (2 x 105 L). The TBME phases were combined, washed with water (42 L) and evaporated under atmospheric distillation to give a concentrated TBME solution (*ca.* 21 L). NMP (126 L) was added, followed by 5,7-dichloro-1,6-

naphthyridine (6.34 kg) and diisopropylethylamine (36.8 L). The mixture was stirred at 105±5 °C for 8 h. The solution was cooled to 60-65 °C and water (84 L) was added over at least 15 min. The mixture was further cooled to 40-45 °C and seeded with authentic 1,1-dimethylethyl-(3*R*)-3-{[(7-chloro-1,6-naphthyridin-5-yl)amino]methyl}-3-fluoro-1-piperidinecarboxylate **9** (6.3 g). The mixture was aged for at least 1 h to give a slurry. Water (13 L) was added over at least 15 min, the mixture was aged for at least 30 min and then cooled to 20-25 °C over at least 30 min. The mixture was aged for at least 2 h. The solid was collected under suction. The filter cake was washed with 1:2 v/v NMP/water (13 L) then water (2 x 26 L) and dried under vacuum at 40±5 °C to give **9** (13.5 kg, 38%, 99.2% a/a HPLC purity) as a colourless solid (mp 158-159°C).

^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33 (9H, brd, J = 20 Hz), 1.57-1.88 (4H, m), 2.86-3.11 (2H, m), 3.73-3.92 (4H, m), 7.03 (1H, s), 7.52 (1H, dd, J = 10, 5 Hz), 8.23 (1H, t, J = 5 Hz), 8.79 (1H, d, J = 10 Hz), 8.93 (1H, d, J = 5 Hz). MS Found for $C_{19}H_{25}ClFN_4O_2$ [M+H] = 395.1645, Calc for $C_{19}H_{25}ClFN_4O_2$ [M+H] = 395.1645.

7-[1-(1,1-Dimethylethyl)-1*H*-pyrazol-4-yl]-*N*-{[(3*S*)-3-fluoro-3-piperidinyl]methyl}-1,6-naphthyridin-5-amine dihydrochloride **1**.2HCl

A degassed mixture of 1,1-dimethylethyl-(3*R*)-3-{[(7-chloro-1,6-naphthyridin-5-yl)amino]methyl}-3-fluoro-1-piperidinecarboxylate **9** (13.45 kg), 1-(1,1-dimethylethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole **10** (11.9 kg) sodium carbonate (10.8 kg) and 1,1-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (111 g) in 1,4-dioxane (108 L) and water (54 L) was stirred at reflux (88±2 °C) for 4 h. The reaction mixture was diluted with water (54 L) and *L*-cysteine (1.4 kg) was added. The mixture was stirred at 60±3 °C for 34 h. Toluene (54 L) was charged and the phases separated at 50±3 °C. The hot organic phase was passed through a CUNO cartridge containing charcoal (type R55S), washing through with hot (50 °C) toluene (54 L). The organic solution was concentrated to *ca.* 160 L by vacuum distillation. The solution was diluted with 1,4-dioxane (54 L) and toluene (54 L), heated to 60±3 °C and treated with 4 M hydrogen chloride in 1,4-dioxane (40 L). The

mixture was stirred at 60±3 °C for 25 h. The thick slurry was cooled to 20±3 °C and aged for 8 h. The solid was filtered and washed with 1:2 v/v 1,4-dioxane/toluene (40 L), toluene (40 L) then TBME (2 x 40 L). The product was dried in vacuo at 40±5 °C to give crude 7-[1-(1,1-dimethylethyl)-1*H*-pyrazol-4-yl]-*N*-{[(3*S*)-3-fluoro-3-piperidinyl]methyl}-1,6-naphthyridin-5-amine dihydrochloride **1**.2HCl. The crude product was slurried in IMS (230 L) and stirred at 25±3 °C for 8 h. The mixture was warmed to 50±3 °C and stirred for 1 h, cooled to 20±3 °C over 1 h and stirred at this temperature for 1 h. The solid was collected by filtration and washed with IMS (30 L) then TBME (2 x 45 L). The solid was dried under vacuum at 40 °C to give 7-[1-(1,1-dimethylethyl)-1*H*-pyrazol-4-yl]-*N*-{[(3*S*)-3-fluoro-3-piperidinyl]methyl}-1,6-naphthyridin-5-amine dihydrochloride **1**.2HCl (13.1 kg, 84%, 100% a/a HPLC purity) as an orange solid (mp 243-244°C).

^{1}H NMR (500 MHz, DMSO-d_6) δ 1.61 (9H, s), 1.80-1.99 (4H, m), 2.85-2.92 (1H, m), 3.14-3.46 (4H, m), 3.97-4.09 (2H, m), 7.38 (1H, s), 7.71 (1H, dd, J = 10, 5 Hz), 8.20 (1H, s), 8.51 (1H, s), 8.63-8.70 (2H, m), 9.03 (1H, d, J = 5 Hz), 9.31 (1H, d, J = 10 Hz), 9.64-9.71 (1H, m).

7-[1-(1,1-Dimethylethyl)-1*H*-pyrazol-4-yl]-*N*-{[(3*S*)-3-fluoro-3-piperidinyl]methyl}-1,6-naphthyridin-5-amine **1**

7-[1-(1,1-Dimethylethyl)-1*H*-pyrazol-4-yl]-*N*-{[(3*S*)-3-fluoro-3-piperidinyl]methyl}-1,6-naphthyridin-5-amine dihydrochloride **1**.2HCl (13.1 kg) was dissolved in water (92 L) and the solution basified to pH 10-11 with a solution of sodium carbonate (7.34 kg) in water (39 L). The resulting mixture was extracted with ethyl acetate (1 x 130 L and 1 x 26 L). The extracts were combined and washed with water (2 x 26 L), filtered through a line filter, washing through with ethyl acetate (65 L), and distilled under reduced pressure to *ca*. 52 L, keeping the contents temperature ≤40 °C. Ethyl acetate (65 L) was added and the solution distilled under reduced pressure to *ca*. 52 L, keeping the contents temperature ≤40 °C. Ethyl acetate (65 L) was added and the solution distilled under reduced pressure to *ca*. 39 L, keeping the contents temperature ≤40 °C. The mixture was cooled to 20 °C and a further charge of ethyl acetate (20 L) was added (to bring the ethyl acetate volume to 5 vol with respect to **1**). The solution was

heated to 60±3 °C and diisopropyl ether (53 L) was added slowly keeping the temperature above 50 °C. The mixture was seeded at 50 °C with authentic 7-[1-(1,1-dimethylethyl)-1*H*-pyrazol-4-yl]-*N*-{[(3*S*)-3-fluoro-3-piperidinyl]methyl}-1,6-naphthyridin-5-amine **1** (10.56 g) and diisopropyl ether (53 L) was added keeping the temperature above 45 °C. The mixture was cooled to 45 °C, stirred at this temperature for 1 h then cooled to 3 °C over 3 h. The slurry was stirred at 3 °C for 1 h then wet-milled. The slurry was re-cooled to 3 °C and stirred for 4 h. The solid was collected by filtration, washed with diisopropyl ether (53 L) and dried at 40 °C under vacuum to give 7-[1-(1,1-dimethylethyl)-1*H*-pyrazol-4-yl]-*N*-{[(3*S*)-3-fluoro-3-piperidinyl]methyl}-1,6-naphthyridin-5-amine **1** (8.01 kg, 73%, 100% a/a HPLC purity) as a yellow solid, form 1 by XRPD (mp 150-151°C).

^{1}H NMR (700 MHz, $CDCl_3$) δ 1.63 (1H, m), 1.66 (9H, s), 1.74-1.82 (2H, m), 2.01 (1H, m), 2.72 (1H, m), 2.85-2.94 (2H, m), 3.03 (1H, m), 3.87 (1H, m), 4.15 (1H, m), 5.76 (1H, t, J = 5.8 Hz), 7.25 (1H, dd, J = 8.2, 4.3 Hz), 7.36 (1H, s), 8.04 (1H, s), 8.08 (2H, m), 8.88 (1H, d, J = 4.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.6 (d, $J_{C,F}$ = 2.7 Hz), 29.8, 32.1 (d, $J_{C,F}$ = 21.5 Hz), 45.8, 46.8 (d, $J_{C,F}$ = 21.1 Hz), 51.9 (d, $J_{C,F}$ = 23.8 Hz), 58.7, 94.1 (d, $J_{C,F}$ = 172 Hz), 106.4, 111.8, 119.5, 123.1, 124.5, 130.1, 137.4, 148.1, 153.5, 153.8, 155.2. MS Found for $C_{21}H_{28}FN_6$ [M+H] = 383.2355, Calc for $C_{21}H_{28}FN_6$ [M+H] = 383.2354.

ACKNOWLEDGMENT

This paper is dedicated in memory of Lois Vernon, a skilled chemist and highly valued member of Product Development. We thank our medicinal chemistry colleagues for work on the original synthetic route and useful discussions, and our partners in analytical sciences, process safety, pilot plant operations, technical sourcing and particles sciences.

REFERENCES

1 Atkinson, F. L.; Barker, M. D.; Douault, C.; Garton, N. S.; Liddle, J.; Patel, V. K.; Preston, A. G. S.; Wilson, D. M. Preparation of 7-(1H-pyrazol-4-yl)-1,6-naphthyridine compounds as therapeutic SYK inhibitors. WO 2011/134971 A1, 3 Nov 2011 (CAN 155:615311).

2 (a) Mócsai, A.; Ruland, J.; Tybulewicz, V. L. J. *Nat. Rev. Immunol*. **2010**, *10*, 387; (b) Tan, S.-L.; Liao, C.; Lucas, M. C.; Stevenson, C.; DeMartino, J. A. *Pharmacol. Ther.* **2013**, *138*, 294.

3 Weinblatt, M. E.; Kavanaugh, A.; Genovese, M. C.; Musser, T. K.; Grossbard, E. B.; Magilavy, D. B. *N. Engl. J. Med*. **2010**, *363*, 1303.

4 (a) Gururajan, M.; Dasu, T.; Shahidain, S.; Jennings, C. D.; Robertson, D. A.; Rangnekar, V. M.; Bondada, S. *J. Immunol.* **2007**, *178*, 111; (b) Friedberg, J. W.; Sharman, J.; Sweetenham, J.; Johnston P. B.; Vose, J. M.; LaCasce, A.; Schaefer-Cutillo, J.; De Vos, S.; Sinha, R.; Leonard, J. P.; Cripe, L. D.; Gregory, S. A.; Sterba, M. P.; Lowe, A. M.; Levy, R.; Shipp, M. A. *Blood* **2010**, *115*, 2578.

5 Matsubara, S.; Li, G.; Takeda, K.; Loader, J. E.; Pine, P.; Masuda, E. S.; Miyahara, N.; Miyahara, S.; Lucas. J. J.; Dakhama, A.; Gelfand, E. W. *Am. J. Respir. Crit. Care Med.* **2006**, *173*, 56.

6 Differding, E.; Ofner, H. *Synlett* **1991**, 187.

7 For selected examples see (a) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc*. **2002**, *124*, 14530; (b) Hamashima, Y.; Sodeoka, M. *Synlett* **2006**, 1467; (c) Suzuki T.; Goto T.; Hamashima Y.; Sodeoka M. *J. Org. Chem.* **2007**, *72*, 246; (d) Sodeoka M.; Hamashima Y. *Pure Appl. Chem.* **2008**, *80*, 763. For reviews of asymmetric fluorination methods see (e) Kirk, K. L. *Org. Process. Res. Dev*. **2008**, *12*, 305. (f) Brunet, V. A.; O'Hagan, D. *Angew. Chem.* **2008**, *47*, 1179

8 Hamashima, Y.; Sodeoka, M. *J. Synth. Org. Chem. Jpn*. **2007**, *65*, 1099.

9 (+)-Menthol in combination with (*S*)-BINAP is the matched combination which ultimately gave the desired enantiomeric series.

10 Decicco, C. P.; Buckle, R. N. *J. Org. Chem.* **1992**, *57*, 1005.

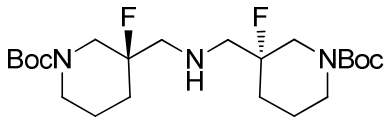
11 Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Organomet. Chem.* **2003**, *665*, 250.

12 Jensen, R. S.; Umeda, K.; Okazaki, M.; Ozawa, F.; Yoshifuji, M. *J. Organomet. Chem.* **2007**, *692*, 286.

13 Atkins, W. J., Jr.; Burkhardt, E. R.; Matos, K. *Org. Process Res. Dev*. **2006**, *10*, 1292.

14 Guercio, G.; Manzo, A. M.; Goodyear, M.; Bacchi, S.; Curti, S.; Provera, S. *Org. Process Res. Dev*. **2009**, *13*, 489.

15 Urben, P. G., Ed. *Brethericks Handbook of Reactive Chemical Hazards, 7th ed*.; Academic Press: Oxford, 2007; Vol. 1, pp 1886-1888.

16 

15

17 Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal*. **2002**, *344*, 1037.

18 (a) Ostwald, W. *Z. Phys. Chem*. **1897**, *22*, 289. (b) Threlfall, T. *Org. Process Res. Dev*. **2003**, *7*, 1017.