Organic Process Research & Development

Article

pubs.acs.org/OPRD

Exploiting the Differential Reactivities of Halogen Atoms: Development of a Scalable Route to IKK2 Inhibitor AZD3264

Andiappan Murugan,* Sreekanth Bachu, Sulur G. Manjunatha, Ravi Ramakrishnan, Vasantha Krishna Kadambar, Chandrasekhara Reddy, Venkata Rao Torlikonda, Sajan George, Sridharan Ramasubramanian, and Sudhir Nambiar

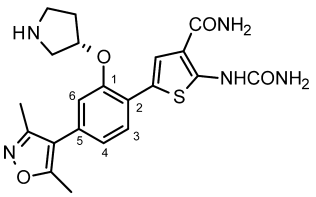
Pharmaceutical Development, AstraZeneca India Pvt. Ltd, Hebbal, Off Bellary Road, Bangalore 560024, India

Supporting Information

ABSTRACT: An efficient and scalable synthesis of AZD3264 is described in which the differential reactivities of various halogen atoms have been employed. The process involves five linear chemical steps with three isolated stages starting from commercially available fragments.

INTRODUCTION

Inhibition of IkB-kinase IKK2 has been identified as one of the novel pathways to treat inflammatory conditions such as asthma, chronic pulmonary obstructive disorder (COPD) and rheumatoid arthritis.[1] AZD3264 (**1** in Figure 1) is a small molecule inhibitor of IKK2 currently in preclinical development for the potential treatment of COPD and asthma.



AZD3264 (**1**)

Figure 1.

The medicinal chemistry synthesis of **1** is presented in Scheme 1. The synthesis began with the aromatic nucleophilic substitution reaction of 2-fluorobromobenzene (**2**) with (*S*)-*N*-Boc-3-pyrrolidinol **3** to give the bromo intermediate **4**, which was borylated via halogen metal exchange using *n*-hexLi in THF followed by treatment with triisopropyl borate and acidic work-up to give the boronic acid intermediate **5**. Suzuki coupling of the boronic acid **5** with bromothiophene **6**[2] afforded the intermediate **7**. Intermediate **7** was subjected to regioselective bromination using bromine in acetic acid. This reaction was nonregioselective and yielded 17% of the required isomer **8**. The bromo compound **8** was coupled with isoxazole boronate ester **9** by another Suzuki reaction to get the title compound. The overall yield of the synthesis was <6%. Moreover, the last step involved Pd-catalyzed Suzuki reaction; the product, having a free secondary amine function, posed significant challenge in scavenging residual palladium from the API (active pharmaceutical ingredient). Though this route was suitable to deliver gram quantities of API for early development, it was undesirable for large multikilogram scale manufacture to support the clinical development.

Evaluating New Synthetic Approaches. The API **1** could be disconnected into four simpler molecular fragments that could be assembled in a suitable sequence to access the title compound as shown in Figure 2.

The disconnection provided the three commercially available fragments **3**, **6**, and **9** (which were also used in the MedChem synthesis), which are to be regioselectively reacted with a suitably substituted central aromatic ring. To select such a suitably substituted aromatic ring, we envisaged to exploit the differential reactivities of the different halogen atoms and accordingly had three different commercially available halo-aromatic substrates as starting materials as shown in Figure 3.

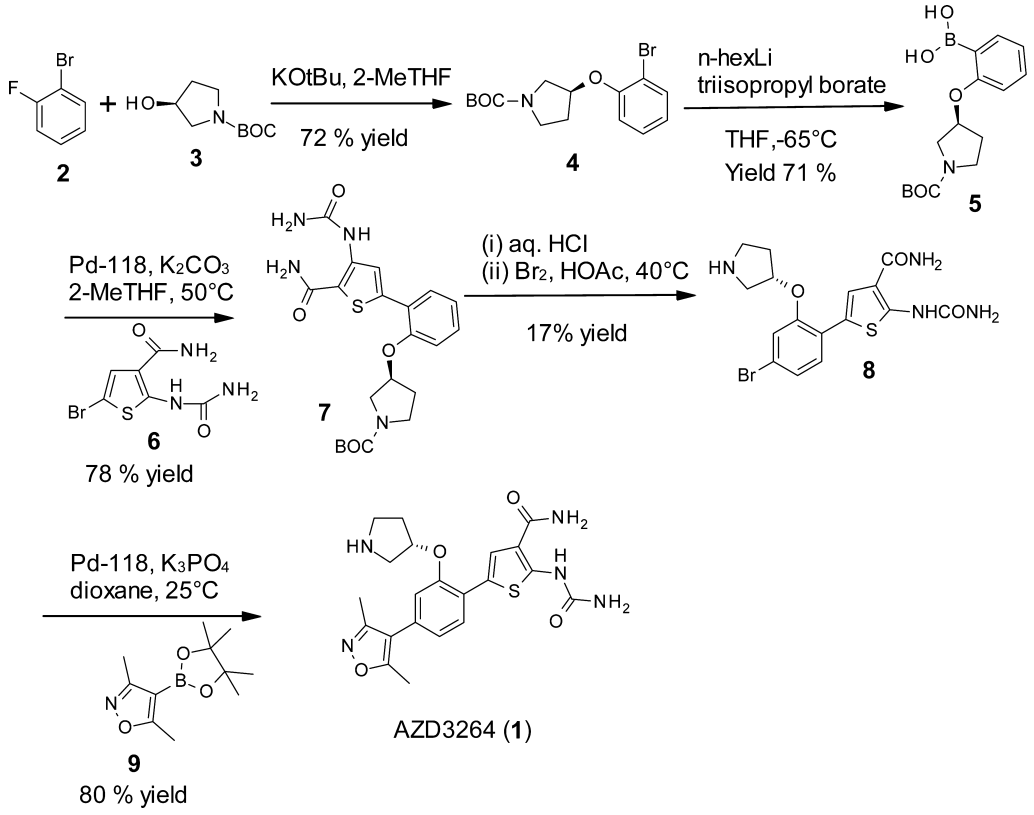
The plan was to introduce the pyrrolidinol fragment using the relatively noncomplicated base-promoted nucleophilic substitution of fluorine with *N*-boc-pyrrolidinol at C1. It was important to sequence the introduction of bromothiophene system at C2 and isoxazole system at C5, for which we made use of the reactivity differences between chlorine, bromine and iodine substituents on the aromatic system.

Evaluation of New Route 1. The new route to **1** (Scheme 2) was designed to start from 1-bromo-4-chloro-2-fluorobenzene (**10**). The aromatic nucleophilic substitution reaction with *N*-Boc-3-pyrrolidinol (**3**) in 2-MeTHF using potassium *tert*-butoxide gave the bromo intermediate **13** in near quantitative yield. The borylation of **13** via halogen metal exchange with *n*-hexLi followed by quenching with triisopropyl borate and acidic work-up yielded boronic acid **14**. The Suzuki reaction of **14** with bromothiophene **6** proceeded smoothly using Pd-118 catalyst and potassium carbonate as base in DMF as solvent. The chloro intermediate **15** was precipitated by the addition of water. The next challenge was to carry out the Suzuki reaction of **15** with isoxazole boronate **9**. Although there are several efficient Pd catalytic systems reported in the literature to activate the chloro substituent towards Suzuki reactions,[3] this substrate **15** failed to give the Suzuki product **16** in acceptable yields. After a thorough catalytic screen, we have identified a catalytic system (Neolyst CX21 iPr catalyst, NaOH as base in

Received: March 27, 2014
Published: April 29, 2014

dx.doi.org/10.1021/op500105n | *Org. Process Res. Dev.* 2014, 18, 646−651

Scheme 1. MedChem route to AZD3264



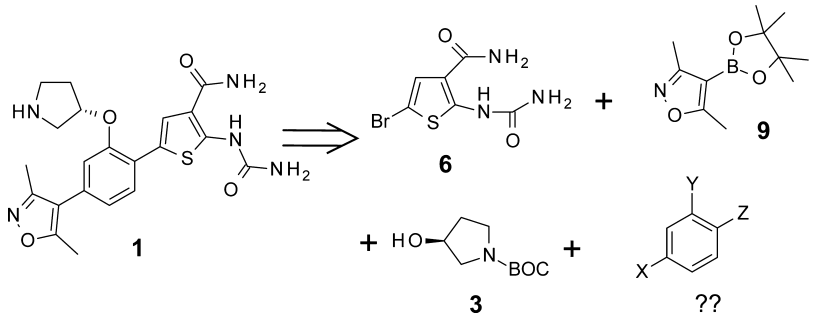


Figure 2.

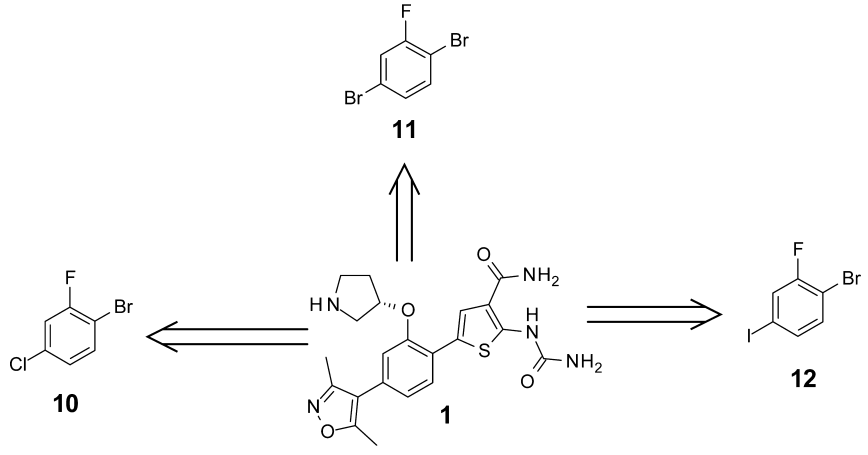
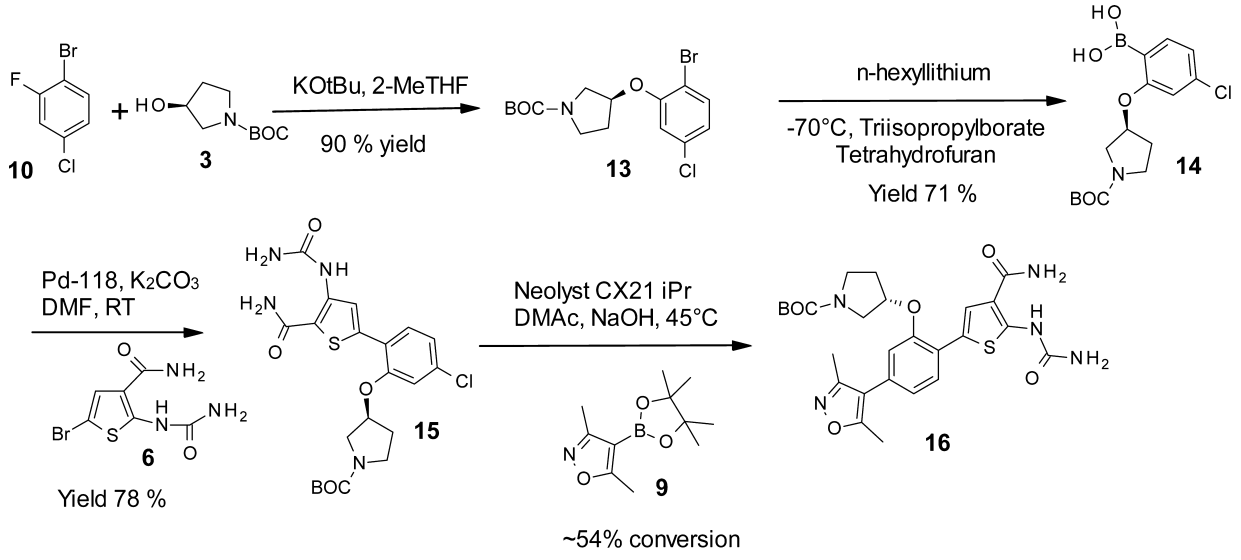


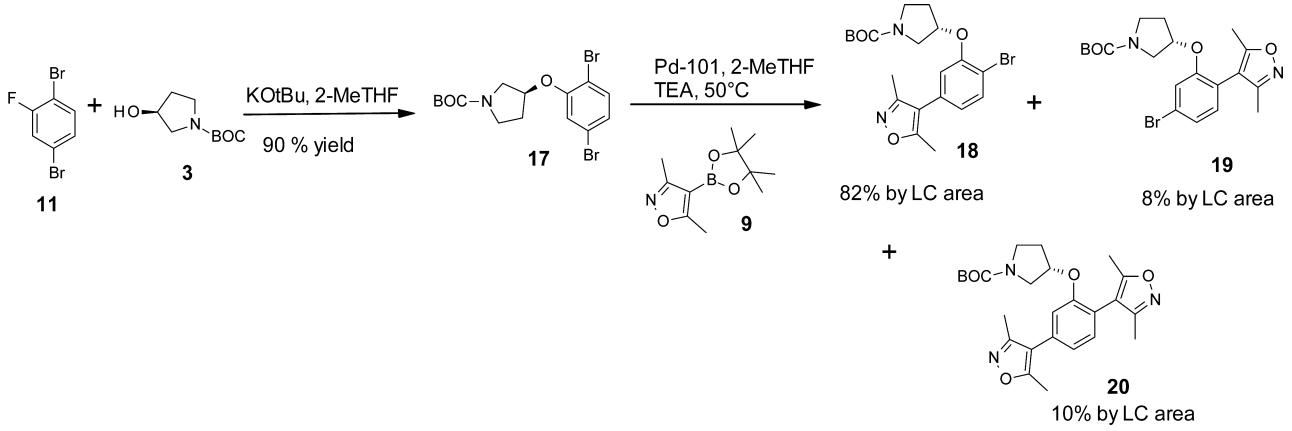
Figure 3.

dx.doi.org/10.1021/op500105n | Org. Process Res. Dev. 2014, 18, 646−651

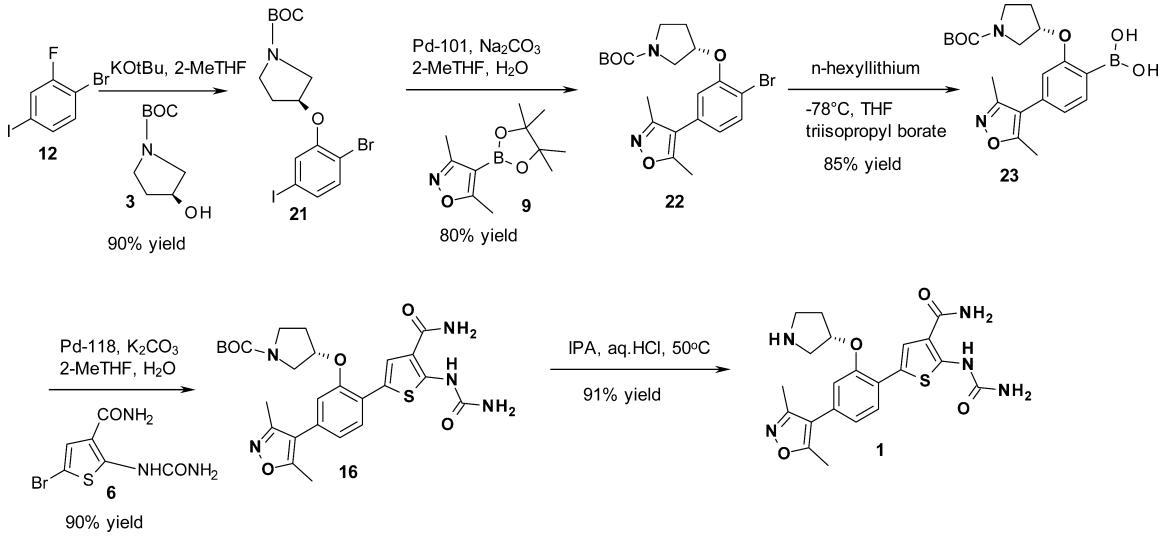
Scheme 2



Scheme 3



Scheme 4

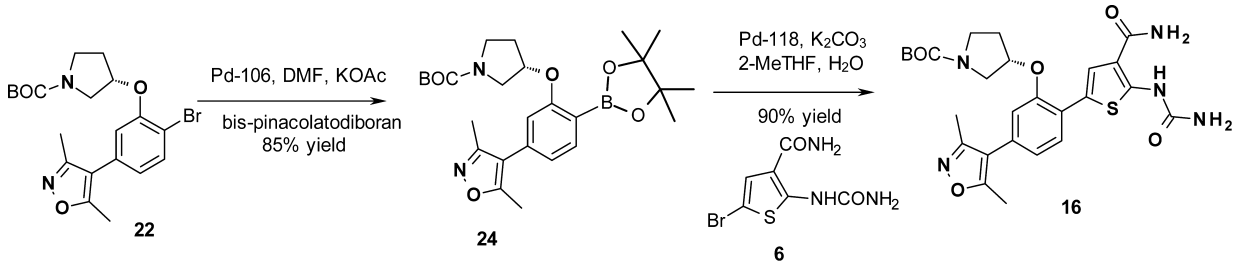


DMAc solvent) that gave a maximum conversion of 54%. This conversion was unsatisfactory for a practical synthesis, and hence this route was dropped.

Evaluation of Route 2: From 1,4-Dibromo-2-fluorobenzene. This route (Scheme 3) was designed to obtain the desired regioselectivity by utilizing the stereoelectronic differ-

dx.doi.org/10.1021/op500105n | Org. Process Res. Dev. 2014, 18, 646−651

Scheme 5



ences between the two bromo substituents. The fluoro displacement of **11** with **3** worked well using KOtBu in 2-MeTHF. The next challenge was to introduce the isoxazole function at C5 by regioselective Suzuki reaction. We predicted that the steric hindrance offered by the pyrrolinol ether function at C1 should differentiate the bromine functions at C2 and C5 (carbons are numbered with reference to Figure 1) towards Suzuki reaction, and also the electron-donating nature of the ether function would further enhance the regioselectivity. Accordingly the Suzuki reaction of **17** with boronate ester **9** was performed using the relatively weaker catalyst Pd-101 in the presence of triethylamine and water in 2-MeTHF. Although the perceived concept of the regioselection was proved to be correct, the maximum selectivity towards the required product **18** was 82% (by HPLC area %) along with 8% of regioisomer **19** and 10% of bis-coupled product **20**. The other catalytic systems did not offer any better selectivity. The separation of these impurities was found to be challenging, and hence this route was also dropped.

Evaluation of Route 3: From 1-Iodo-4-bromo-2-fluorobenzene. To enhance the regioselectivity of the Suzuki reaction on **17**, we replaced the 5-bromo function with an iodo function (Scheme 4). Accordingly, we began the synthesis with the iodo compound **12**. The fluoro displacement worked well using the standard protocol to give the iodo-bromo intermediate **21**. The Suzuki reaction of **21** with isoxazole boronate ester **9** using Pd-101 in 2-MeTHF gave more than 98% selectivity and 100% conversion. The product **22** was isolated as a solid by the addition of *n*-heptane as anti-solvent.

The bromo intermediate **22** could be borylated in two ways: (i) halogen metal exchange with *n*-hexLi followed by quenching with triisopropyl borate and acidic work-up yielded boronic acid **23**. The boronic acid **23** reacted smoothly with bromothiophene **6** in the presence of Pd-118 catalyst in 2-MeTHF to give *N*-Boc-protected API **16**. (ii) Miyaura borylation of **22** with bis-pincolatodiboran using Pd-106 in DMF yielded boronate ester **24** (Scheme 5); **24** reacted with **6** under similar reaction conditions as those of **23**.

However, the Miyaura borylation was found to be inconsistent and sensitive to the catalyst quality. Moreover, our efforts to develop one-pot borylation[4] and Suzuki reaction also failed to yield the desired results.

Route Decision and Process Development. Route 3 (Scheme 4) appeared to be superior to all other routes. Hence it was decided to develop this route for the large scale synthesis. The first step reaction of fluoro compound **12** with **3** in the presence of potassium *tert*-butoxide in 2-MeTHF was fairly straightforward and provided a clean reaction. However, the intermediate **21** is a gummy mass that is difficult to isolate. Since the reaction profile was clean, this was telescoped to the next stage. The 2-MeTHF solution of **21** was reacted with the isoxazole **9** using Pd-101 catalyst and aqueous sodium carbonate as base. The reaction worked well with >98% regioselectivity. After the usual aqueous work-up, the intermediate **22** was precipitated by the addition of *n*-heptane to the organic phase. The isolated yield stood at 80% over 2 steps.

The halogen metal exchange on **22** with *n*-hexLi required cryogenic conditions. The optimized reaction condition required a controlled addition of *n*-hexLi to a mixture of **22** and tris-isopropylborate in THF at −78 °C. The isolation of the boronic acid **23** seemed to be challenging due to its instability, and hence telescoping was seen as a better option. After quenching of the above reaction mixture with dilute HCl, the boronic acid intermediate was extracted in 2-MeTHF and subjected to Suzuki coupling with bromothiophene **6** using Pd-118 as catalyst and aqueous potassium carbonate as base. The *N*-Boc-protected API **16** precipitated out during the course of the reaction and was isolated by simple filtration in 78% yield over two steps.

The other important challenge was the removal of residual palladium. We felt that the intermediate **16** in its nitrogen-protected state would offer better solubility and would also have less affinity towards Pd. After abbreviated solvent and scavenger screens, 2-butanone was selected as solvent and Quadrasil MP (from Johnson Matthey) was selected as solid scavenger, which reduced the residual palladium to <50 ppm as desired. Finally the *N*-Boc deprotection was performed using HCl in a 2-propanol/water system, and the API **1** was isolated by basification with aqueous ammonia.

CONCLUSIONS

A highly efficient and scalable synthesis of AZD3264 from readily available building blocks has been developed. We made use of the difference in the reactivities of halogen atoms to devise a regioselective synthesis of the title compound.

EXPERIMENTAL DETAILS

General. All reactions were performed under a nitrogen atmosphere unless otherwise specified. Water is distilled water. All reagents and solvents were obtained from commercial suppliers and were used without any further purification.

^{1}H NMR and ^{13}C NMR spectra were acquired on a 400 MHz instrument. NMR spectra were recorded on Bruker spectrometers operating at the specified proton frequencies in DMSO-d_6 solution with tetramethylsilane (TMS) as internal reference. LC−MS spectra were obtained using an Agilent 1200 series LC instrument and LC/MSD SL detector with +ve atmospheric pressure electrospray ionization (APESI).

***tert*-Butyl (3*S*)-3-[2-Bromo-5-(3,5-dimethylisoxazol-4-yl)phenoxy]pyrrolidine-1-carboxylate (22).** To a stirred suspension of potassium *tert*-butoxide (1.71 kg, 15.10 mol) and

dx.doi.org/10.1021/op500105n | Org. Process Res. Dev. 2014, 18, 646−651

tert-butyl (3*S*)-3-hydroxypyrrolidine-1-carboxylate (**3**) (2.52 kg, 12.78 mol) in 2-MeTHF (52.44 L) was added 1-bromo-2-fluoro-4-iodobenzene (**20**) (3.56 kg, 11.62 mol) at ambient temperature. The resultant mixture was heated to 70−75 °C and maintained at that temperature under stirring until complete conversion was confirmed by HPLC. The reaction mixture was cooled to 25 °C and quenched with water (17.48 L). The aqueous layer was discarded. To the organic layer was charged sodium carbonate (5.57 kg, 52.28 mol) and water (31.45 L). After degassing with nitrogen, to the resultant reaction mass were added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (**9**) (2.93 kg, 12.78 mol) and tetrakis(triphenylphosphine)palladium (Pd-101) (0.67 kg, 0.58 mol), and the mixture was heated to 50 °C for 15 h and then 70 °C for 5 h. The reaction completion was confirmed by HPLC. The reaction mixture was cooled to 25 °C and concentrated under reduced pressure, and the product was crystallized by addition of *n*-heptane (34.96 L) and isolated by filtration. This product was formed as a mixture of rotamers. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.38−1.41 (br, 9H), 2.08−2.15 (m, 2H), 2.24 (s, 3H), 2.42 (s, 3H), 3.35−3.57 (m, 4H), 5.18 (s, 1H), 6.93 (d, 1H, J = 8 Hz), 7.15 (s, 1H), 7.66 (d, 1H, J = 8 Hz). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 10.35, 11.30, 28.10, 30.09, 30.90 (rotamer), 43.68, 43.94 (rotamer), 50.93, 51.17 (rotamer), 76.88, 77.76 (rotamer), 78.47, 111.45, 115.22, 115.86, 123.01, 130.76, 133.46, 153.52, 158.06, 165.43. DEPT NMR (DMSO-d_6, 100.6 MHz): δ 10.36, 11.30, 28.08, 30.09, 30.90 (rotamer), 43.68, 43.94 (rotamer), 50.93, 51.17 (rotamer), 76.86, 77.75 (rotamer), 115.84, 123.00, 133.46. HRMS calcd for $C_{20}H_{26}BrN_2O_4$ $(M + H)^+$: 437.1070, found 437.1026. $[\alpha]^{25}_D$ −4.60 (*c* 0.5, DMSO).

***tert*-Butyl (3*S*)-3-[2-(4-Carbamoyl-5-ureido-2-thienyl)-5-(3,5-dimethylisoxazol-4-yl)phenoxy]pyrrolidine-1-carboxylate (16).** A stirred solution of *tert*-butyl (3*S*)-3-[2-bromo-5-(3,5-dimethylisoxazol-4-yl)phenoxy]pyrrolidine-1-carboxylate (**22**) (2.04 kg, 4.11 mol) and tri-isopropyl borate (2.37 kg, 12.33 mol) in tetrahydrofuran (14.40 L) was cooled to −75 °C. To the above mixture was slowly added *n*-hexyllithium (33.00%w/w solution in THF, 2.15 kg, 6.99 mol) while the temperature of the reaction mass was maintained below −65 °C. The reaction completion was confirmed by HPLC. The reaction mass was diluted with 2-MeTHF (18.00 L) and quenched with aqueous dilule HCl (1 M, 24.66 L, 24.66 mol). The organic layer containing [2-[(3*S*)-1-*tert*-butoxycarbonyl-pyrrolidin-3-yl]oxy-4-(3,5-dimethylisoxazol-4-yl)phenyl]-boronic acid (**23**) was concentrated to 11.45 L, and 5-bromo-2-ureido-thiophene-3-carboxamide (**6**) (0.88 kg, 3.29 mmol), potassium carbonate (0.86 kg, 6.16 mol), and water (1.98 L) were added. After degassing of the resultant mixture with nitrogen, Pd-118 catalyst (0.05 kg, 0.08 mol) was added, and the mixture was heated to 35 °C. The reaction was monitored by HPLC. The product was crystallized by adding excess of water at 50 °C. After the reaction mass cooled to the room temperature, the product was isolated by filtration.

Palladium Scavenging of 16. A solution of *tert*-butyl (3*S*)-3-[2-(4-carbamoyl-5-ureido-2-thienyl)-5-(3,5-dimethylisoxazol-4-yl)phenoxy]pyrrolidine-1-carboxylate (**16**) (2.89 kg, 4.90 mol) and Quadrasil MP (1.45 kg, 16.04 mol) in 2-butanone (43.40 L) was heated to 70 °C for 5 h. The resultant reaction mixture was cooled to 30 °C and filtered through Celite bed to remove quadrasil and undissolved matter. The filtrate was concentrated to 14.45 L, crystallized by addition of *n*-heptane (28.93 L), and filtered to isolate the product in 94% yield. This product was formed as a mixture of rotamers. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.34 (s, 9H), 2.23−2.28 (m, 5H), 2.45 (s, 3H), 3.38−3.62 (m, 4H), 5.22 (s, 1H), 6.89−6.94 (m, 1H), 7.04−7.08 (m, 2H), 7.3 (br, 1H), 7.70−7.75 (m, 2H), 7.83 (s, 1H), 10.95 (s, 1H). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 10.49, 11.40, 28.02, 30.39, 31.21 (rotamers), 43.84, 44.13 (rotamers), 50.61, 50.99 (rotamers), 76.34, 77.20 (rotamers), 78.38, 111.77, 114.10, 114.34, 115.61, 122.00, 125.12, 127.19, 128.94, 150.33, 152.03, 153.72, 154.37, 158.19, 165.22, 167.02. DEPT NMR (DMSO-d_6, 100.6 MHz): δ 10.51, 11.41, 28.01, 30.39, 31.21 (rotamers), 43.85, 44.14 (rotamers), 50.60, 50.98 (rotamers), 76.33, 77.18 (rotamers), 114.06, 114.32 (rotamers), 120.88, 121.70, 121.80 (rotamers), 127.14. HRMS calcd for $C_{26}H_{31}N_5NaO_6S$ $(M + Na)^+$: 564.1893, found 564.1844. $[\alpha]^{25}_D$ +44.20 (*c* 0.5, DMSO).

AZD3264 (1). A stirred solution of *tert*-butyl (3*S*)-3-[2-(4-carbamoyl-5-methyl-2-thienyl)-5-(3,5-dimethylisoxazol-4-yl)-phenoxy]pyrrolidine-1-carboxylate (**16**) (2.65 kg, 4.63 mol) in tetrahydrofuran (25 L) was subjected to clear filtration to remove the heterogeneous particles at 25 °C. The filtrate was swapped with 2-propanol to prepare a solution of the reactant in 13.3 L of 2-propanol. To this mixture was added water (12.54 L) followed by aqueous HCl solution (11 M in water, 0.84 L, 9.26 mol) at 25 ± 5 °C, and the mixture was heated to 65 ± 5 °C until complete conversion was confirmed by HPLC. The reaction mass was basified with the ammonia solution (25% w/w in water, 3.34 L, 46.29 mol) and diluted with water (7.5 L), and the precipitated mass was stirred and filtered to obtain the title compound in 91% yield.

Purification. To a stirred suspension of crude AZD3264 (**1**) (1.75 kg, 3.98 mol) in methanol (23.75 L) and water (2.64 L) was added formic acid (0.24 kg, 5.18 mol), and the mixture was heated to 40 °C for 1.5 h, cooled to 25 °C, and basified with aqueous ammonia (12.29 M in water, 1.62 L, 19.92 mol). The product was isolated by filtration. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.92−2.10 (m, 2H), 2.28 (s, 3H), 2.46 (s, 3H), 2.75−2.82 (m, 1H), 3.00−3.12 (m, 3H), 5.11−5.12 (m, 1H), 6.90 (br, 2H), 7.00−7.03 (m, 2H), 7.30 (br, 1H), 7.70−7.72 (m, 2H), 7.83 (s, 1H), 10.93 (s, 1H). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 10.54, 11.42, 32.94, 45.51, 53.00, 79.37, 111.76, 114.17, 115.66, 120.70, 121.20, 122.77, 125.39, 126.92, 128.84, 150.12, 152.54, 154.50, 158.13, 165.14, 167.06. DEPT NMR (DMSO-d_6, 100.6 MHz): δ 10.54, 11.43, 32.94, 45.51, 53.01, 79.35, 114.17, 120.70, 121.20, 126.92. HRMS calcd for $C_{21}H_{24}N_5O_4S$ $(M + H)^+$: 442.1543, found 442.1554. $[\alpha]^{25}_D$ −13.80 (*c* 0.5, DMSO)

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

HPLC and UHPLC methods for AZD3264 and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: andiappan.murugan@astrazeneca.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the management team of AstraZeneca for timely support.

ABBREVIATIONS

Pd-118: dichloro[1,1′-bis(di-*tert*-butylphosphino)ferrocene] palladium(II); CAS no. 95408-45-0
Pd-101: tetrakis(triphenylphosphine)palladium(0); CAS no. 14221-01-3
Pd-106: dichloro[1,1′-bis(diphenylphosphino)ferrocene] palladium(II)-dichloromethane adduct; CAS no. 95464-05-4
Neolyst CX21 iPr: allylchloro-[1,3-bis(diisopropylphenyl)-imidazole-2-ylidene]palladium(II); CAS no. 478980-03-9
2-MeTHF: 2-methyltetrahydrofuran
THF: tetrahydrofuran
DMF: *N*,*N*-dimethylformamide

REFERENCES

(1) (a) Li, J.; Peet, G. W.; Pullen, S. S. *J. Biol. Chem.* **1998**, *273*, 30736. (b) Hu, Y.; Baud, V.; Delhase, M. *Science* **1999**, *284*, 316. (c) Bamborough, P.; Callahan, J. F.; Christopher, J. A.; Kerns, J. K.; Liddle, J.; Miller, D. D.; Morse, M. A.; Rumsey, W. L.; Williamson, R. *Top. Med. Chem.* **2009**, *9*, 623.
(2) Baxter, A.; Brough, S.; Faull, A.; Johnstone, C.; Mcinally, T. WO2001058890A1, 2001.
(3) (a) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787−1789. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876. (d) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173−3180. (e) Harkal, S.; Ratabul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 1742−1748. (f) Zapf, A.; Jackstell, R.; Rataboul, F.; Reirmeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38−39. (g) Colacot, T. J.; Shea, H. A. *Org. Lett.* **2004**, *6*, 3731−3734. (h) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194−16195. (i) Bedford, R. B.; Cazin, C. S. J.; Hzelwood, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4120−4122. (j) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553−5566. (k) Gstottmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363−1365. (l) Yin, J.; Rainka, M. P.; Zhang, X.-X; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162−1163. (m) Kirshhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945. (n) Liu, S.-Y.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408. (o) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677−8678. (p) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540−1541. (q) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153−4155. (r) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797−6803. (s) Bei, X.; Crevier, T.; Guram, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855−3858.
(4) (a) Billingsley, K.; Barder, T.; Buchwald, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359−5363. (b) Baudoin, O.; Cesario, M.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2002**, *67*, 1199−1207. (c) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268−9271. (d) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447−3450.