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Development of a Modified Process for the Kilogram-Scale Synthesis of c-Met/ALK inhibitor HS-10168

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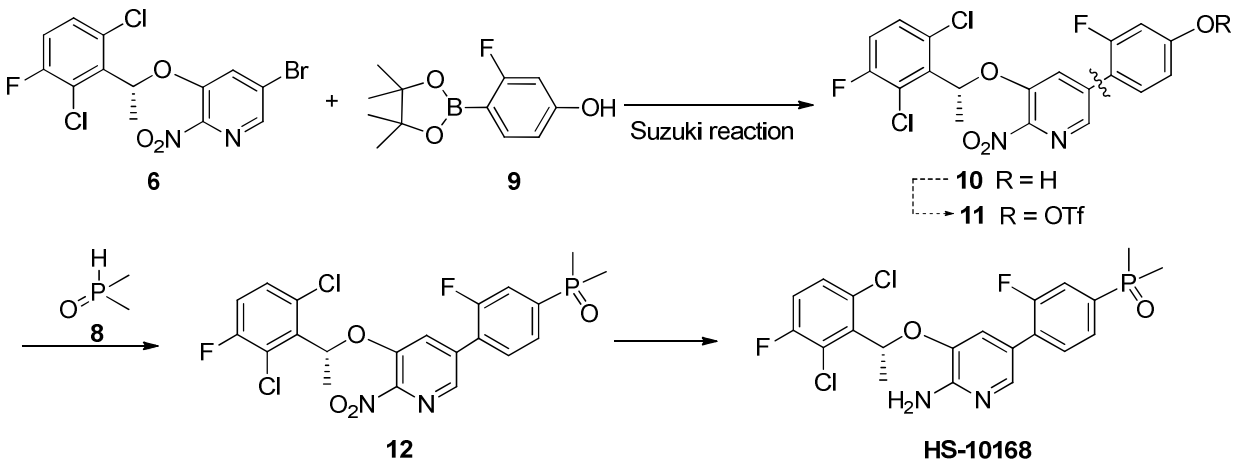
TOC graphic: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HS-10168

Abstract: A modified synthetic route to c-Met/ALK inhibitor HS-10168 has been developed on a kilogram scale. The key steps of the new process include a Suzuki coupling reaction of nitro containing bromopyridine **6** and *para*-phenol boronate **9** to give the intermediate **10** which was then converted into its triflate **11**. The phosphorus group was introduced by coupling of **11** and dimethylphoshine oxide **8** to give compound **12**, which was reduced to produce HS-10168.

Key words: c-Met/ALK inhibitor, HS-10168, catalyst, Suzuki reaction

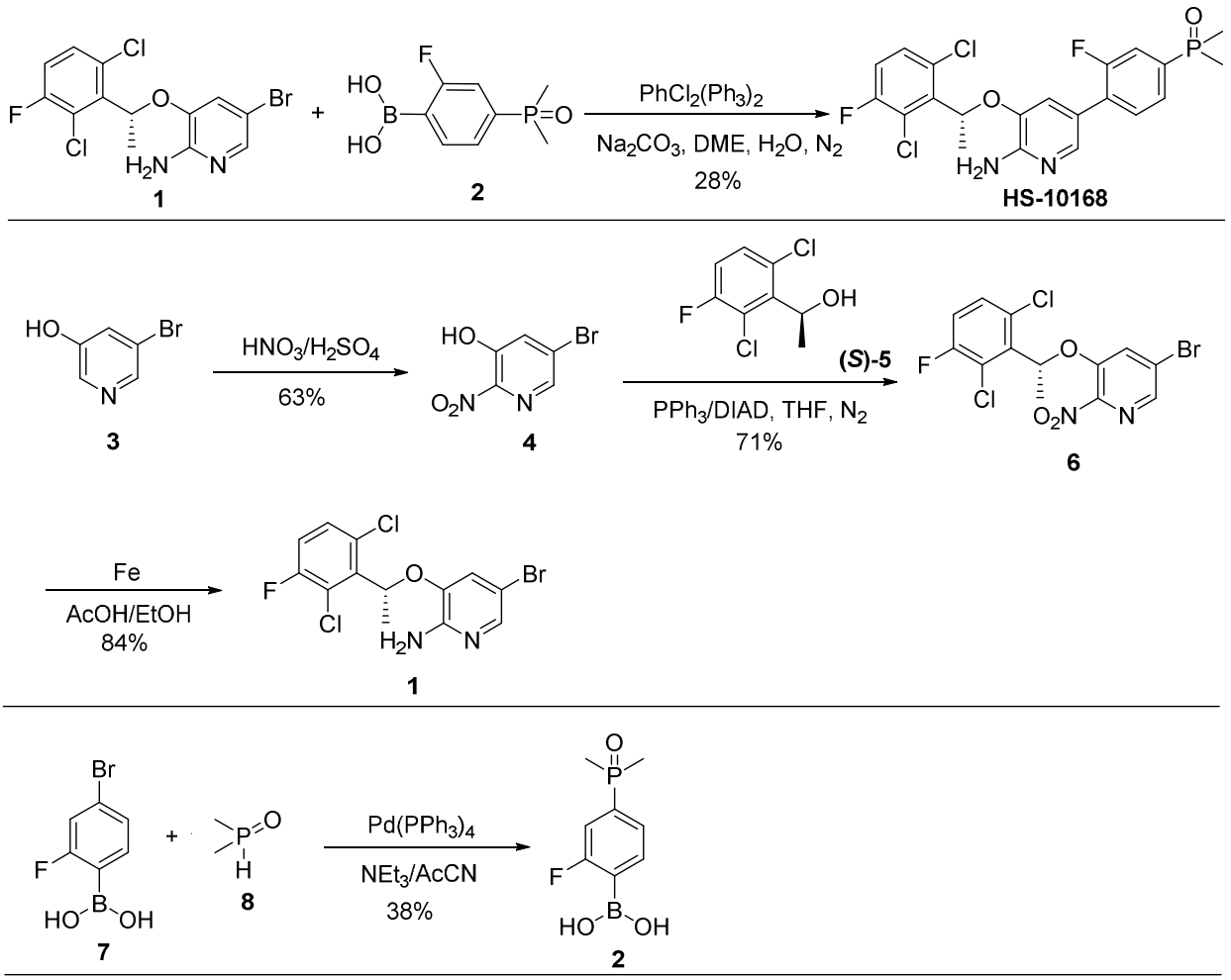
INTRODUCTION

HS-10168 is a potent and selective Mesenchymal epithelial transition factor/Anaplastic lymphoma kinase(c-Met/ALK) inhibitor which has advanced into Phase I clinical trials.[1,2] The original *gram*-scale synthetic route to HS-10168 developed by the medicinal chemistry group was used for preparation of the compound for early biological screening. As a result of the robust antitumor activity of HS-10168 observed in tumor xenograft mouse models, the preclinical development was rapidly accelerated which resulted in a great increase in drug substance demand. This paper describes the development of a scalable synthetic process that enabled kilogram-scale production of HS-10168.

RESULTS AND DISSCUSSION

The original medicinal chemistry route towards HS-10168 is shown in scheme 1[2] and involved a Suzuki coupling of two key structural elements, bromopyridine **1** and the phosphorus containing phenylboronic acid **2** under N_2 atmosphere. The bromopyridine **1** was synthesized in a 3 step sequence, starting with nitration of 5-bromo-3-hydroxylpyridine **3** to give compound **4**. The Mitsunobu reaction of **4** and the chiral alcohol (*S*)-**5** provided the compound **6**. Chemoselective reduction of the nitro group of **6** with iron and acetic acid afforded the desired intermediate **1**. The phosphorus containing phenylboronic acid **2** was obtained by the palladium catalyzed coupling reaction of the 2-fluoro-4-bromo-phenylboronic **7** and dimethylphoshine oxide **8**.

Scheme 1. Original medicinal chemistry route to HS-10168.

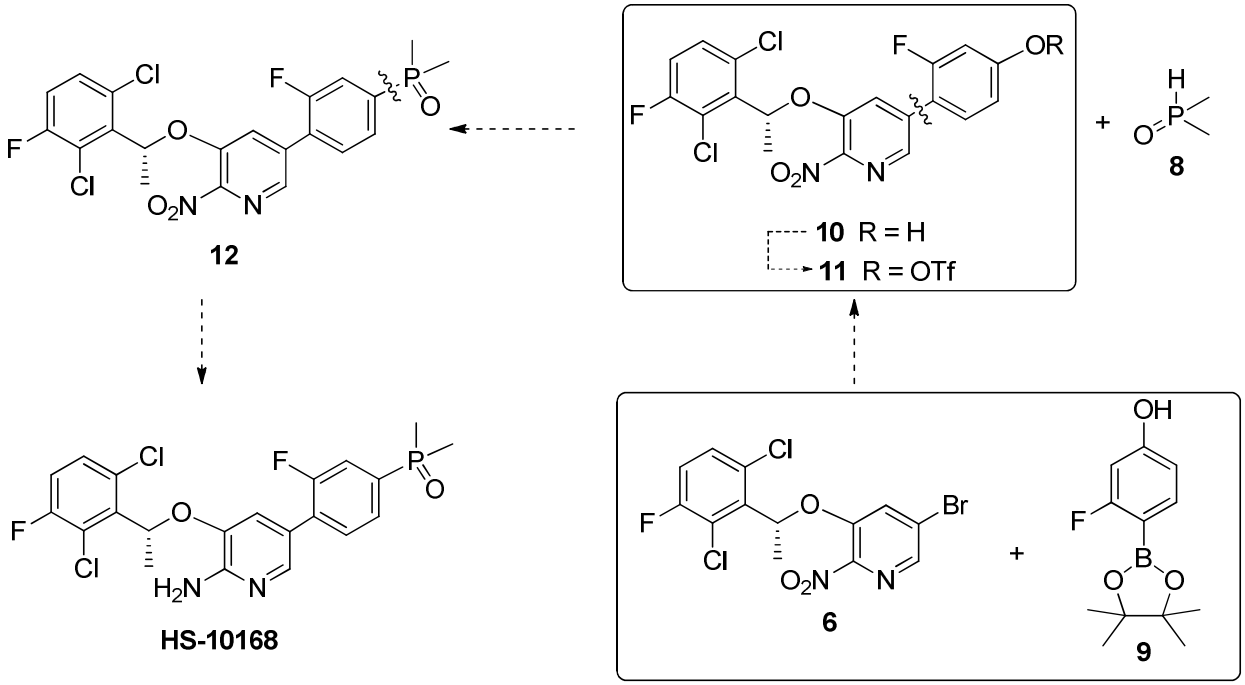


Although this route was successfully used to prepare *gram*-scale of HS-10168 for use in early preclinical studies, the scale-up of this route still suffered from some challenges. Firstly, the Suzuki coupling between 1 and 2 failed to go to completion and gave a complex mixture of products. The yield of the final product obtained by semi-preparative HPLC was very low (28%). The coupling of 2-fluoro-4-bromo-phenylboronic **7** and dimethylphoshine oxide **8** also gave a complex mixture of products because of the self-coupling reaction of 7 under the palladium catalyzed reaction conditions. This led to the formation of 2 in a low yield of 38%.

Central to the development work was to drive the Suzuki coupling to completion in order to give a clean reaction profile and eliminate the semi-preparative HPLC preparation of the final product.

The coupling partners of Suzuki coupling reaction are a halide and an organoboron compound.[3] In the original medicinal chemistry route, the bromopyridine **1** with an electron-donating amine group was used as the halide. It is noted that the presence of an electron-withdrawing group such as nitro group in the arylhalide benefits the progression of the coupling reaction due to the accelerating effect in the oxidative addition step.[3] Thus, the nitro containing bromopyridine **6** would be a better choice for the halide substrate. On the other hand, the scale-up preparation of the phosphorus containing phenylboronic acid **2** was challenging because of the easy self-coupling of the starting material **7** under the palladium catalyzed conditions. Our strategy was to use *para*-phenol boronate **9** instead of **2** to couple with **6** to give compound **10**, and avoided the formation of the homo-coupling side product. Compound **10** could be easily converted into its triflate **11**. The phosphorus group could be introduced by coupling of **11** and **8** to give compound **12**, which was reduced to produce the final product (Scheme 2).

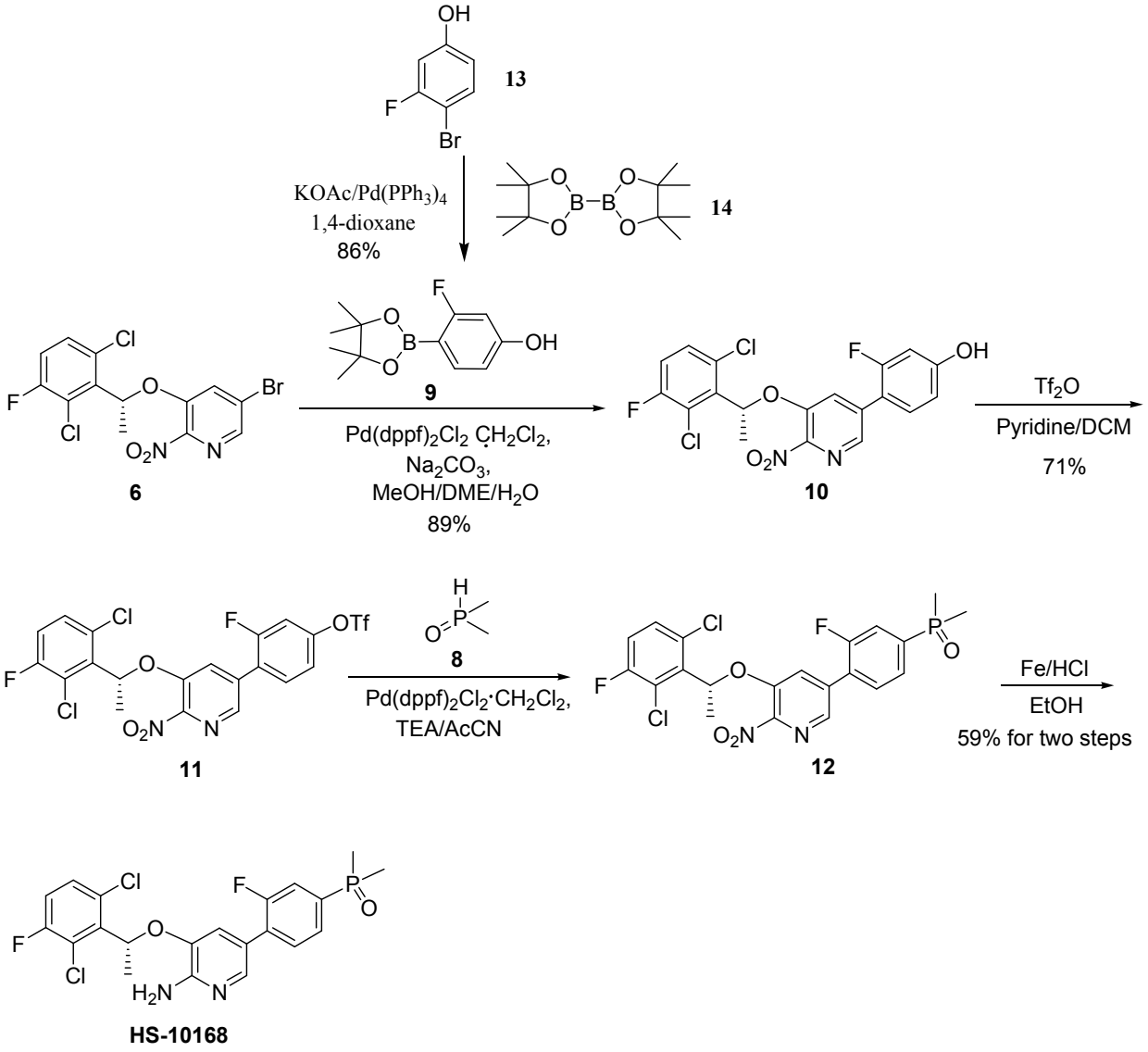
Scheme 2. The synthetic strategy to HS-10168.



On the basis of the above considerations, the modified synthetic route to HS-10168 was designed as shown in Scheme 3. The boronation of 4-bromo-3-fluorophenol **13** with bis(pinacolato)diboron **14** was smoothly realized by using $Pd(PPh_3)_4$(5 mol%) as the catalyst and potassium acetate as the base in 1,4-dioxane at reflux.[4] The desired intermediate **9** was obtained in 86% yield within 3 h. The Suzuki coupling of nitro containing bromopyridine **6** and *para*-phenol boronate **9** was conducted also using $Pd(PPh_3)_4$ (4 mol%) as the catalyst and sodium carbonate (Na_2CO_3) as the base in the solvent mixture of dimethoxyethane (DME) and water at 80 ℃. Unfortunately, the reaction failed to reach completion and gave a complex mixture of products after 19 h. It is noted that $Pd(PPh_3)_4$ often is a capricious catalyst[5] because of its air-sensitivity, which might led to the failure of Suzuki coupling. In order to improve the efficiency of the reaction, a more robust and active catalyst [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex ($PdCl_2(dppf)_2{\cdot}CH_2Cl_2$) (5 mol%), was tried instead of $Pd(PPh_3)_4$ using Na_2CO_3 as the base in the solvent mixture of methanol, DME and water at reflux. It was found that this catalytic system not only successfully gave complete reaction but also provided a more clean reaction profile within 1 h. Further investigation indicated that 1 mol% of $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$ was enough for the completion of the reaction although a longer reaction time 5 h was required. Upon reaction completion, EtOAc and water were added. The separated aqueous phase was re-extracted with EtOAc. The combined organic phase was washed with aqueous HCL and brine. After concentration of organic solvent, the residue was dissolved in EtOAc, followed by the slow addition of hexane to guarantee the deposition of black viscous byproduct. The upper clear solution was decanted, the black viscous residue was re-dissolved in EtOAc and hexane was added slowly. After deposition of black viscous byproduct again, the upper clear solution was

decanted. The combined organic phase was then concentrated and the resulting product was dried under vacuum to afford **10** in 89% yield.The intermediate **10** was easily converted into its triflate using Tf_2O in dichloromethane at room temperature, and the intermediate **11** was obtained in 71% isolated yield.[6] The coupling reaction of **11** and dimethylphoshine oxide **8**[7] was carried out still using $PdCl_2(dppf)_2 \cdot CH_2Cl_2$ (5 mol %) as the catalyst and triethylamine as the base in acetonitrile at reflux temperature.[8,9] The reaction successfully provided the desired intermediate **12** but with low conversion of **11** being about 60% even after 24 h. Increasing the loading of catalyst to 10 mol% led to a complete reaction within 1.5 h. Other palladium catalyst including $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$ and $Pd(dba)_2$ were also tested, but none of them showed superior results over $PdCl_2(dppf)_2 \cdot CH_2Cl_2$. Reduction of intermediate **12** with iron-HCl/ethanol system produced the HS-10168 within 59% yield for two steps.

Scheme 3. Modified synthetic route to HS-10168



CONCLUSION

We have developed a modified synthetic process that enabled a kilogram-scale production of HS-10168. The process features a robust Suzuki coupling reaction of nitro containing bromopyridine **6** with *para*-phenol boronate **9**, followed by a phosphorus group introduction by coupling of the triflate **11** with dimethylphoshine oxide **8**. The process was repeated in several campaigns on 1kg scale to support the preclinical and early clinical trials.

EXPERIMENTAL SECTION

General information. All reagents were purchased from the suppliers without further purification. Proton NMR data were collected on a Bruker AVANCE 400 at 400 MHz for proton or on a Bruker AVANCE 500 at 500 MHz for proton and 125 MHz for carbon. IR spectra were recorded on a Nicolet FT-IR spectrometer in KBr pellets. Mass spectral analyses were performed on Agilent 6224 Q-TOF mass spectrometer equipped with an electron-spray ionization source.

5-bromo-2-nitropyridin-3-ol (4)

5-bromopyridin-3-ol (1690g，8.67 mol) was added to concentrated sulfuric acid (95-98%，4.23 L，77.67 mol) in portions within 45 min at 0~10 ℃. Then HNO_3 (65%，845 mL，12.21 mol) was added dropwise over 1 h while maintaining temperature at 0~10 ℃. The resulting mixture was warmed to room temperature and stirred for 20 h. The reaction mixture was slowly poured into (within 10 min) ice water (13 L) and stirred for 45 min. The precipitated solid was filtered and washed with ice water (2.5 L × 3). The filter cake was dried at ordinary pressure (50 ℃, 18 h) to give compound **4** (1.35 kg, 63% yield) as a yellow solid. ^{1}H NMR（400 MHz, DMSO-d_6）δ (ppm) 7.85 (d, J = 2.0 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 12.07 (brs, 1H).

(R)-5-bromo-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-2-nitropyridine (6)

Diisopropyl azodicarboxylate (1.27 kg，6.27 mol) was added dropwise to a solution of compound **4** (1.11 kg，5.07 mol), compound **5** (1.01 kg，4.83 mol) and triphenylphosphine (1.65 kg，6.27 mol) in THF (4 L) over 3 h while maintaining temperature at 0~15 ℃. Then the mixture was warmed to room temperature and stirred for 20 h. Hexane (8 L) was added to the

mixture and stirred for 1h. The resulting precipitate was filtered and washed with a mixture (1.5 L × 2) of ethyl acetate/hexane (v/v = 1:2.5). The combined filtrate was concentrated, and then *i*-propanol (4.5 L) was added. The resulting slurry was granulated for 15 h. The slurry was filtered, the filter cake was washed with *i*-propanol (650 mL × 2) and dried at ordinary pressure (50 ℃, 18 h) to give the compound **6** (1.47 kg, 71% yield) as a yellow solid. The HPLC purity was 99.36% and the ee value was over 99.8%. ^{1}H NMR（400 MHz, DMSO-d_6）δ (ppm) 1.81(d, J = 6.4 Hz, 3H), 6.40(q, J = 6.4 Hz, 1H), 7.50-7.54(m, 1H), 7.60-7.64(m, 1H), 7.88 (d, J = 1.6 Hz, 1H), 8.30 (d, J = 1.6 Hz, 1H).

3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (9)

A mixture of 4-bromo-3-fluorophenol **13** (1.21 kg，6.31 mol), bis(pinacolato)diboron **14** (2.06 kg，8.12 mol), potassium acetate (1.54 kg，15.71 mol), and Tetrakis(triphenylphosphine)palladium (0.36 kg，0.32 mol) in dioxane (14 L) was refluxed for 3 h. Then cooling to room temperature, the mixture was filtered through celite and washed with ethyl acetate (1.5 L × 2). The filtrate was poured into water (25 L) and extracted with ethyl acetate (10 L × 3). The combined organic phase was washed with brine (20 L × 2) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to about 1-2 L at 40-45 ℃. The residue was suspended in petrol ether (8.0 L) and stirred for 20 h. The resulting precipitated solid was filtered, and the filter cake was washed with petrol ether (1.5 L × 2) and dried under vacuum (40 ℃, 5 h) to give compound **9** (1.29 kg, 86% yield) as a brown solid. The HPLC purity was 93.9%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.18-1.27 (m, 12H), 6.49 (dd, J = 11.2, 2.0 Hz, 1H), 6.63 (dd, J = 8.4, 2.0 Hz, 1H), 7.46-7.50 (m, 1H), 10.29 (s, 1H).

(R)-4-(5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-6-nitropyridin-3-yl)-3-fluorophenol (10)

[1,1-Bis(diphenylphosphino)ferrocene]dichloropalladium(Ⅱ) dichloromethane complex (74.90 g, 97.54 mmol) and sodium carbonate (2.59 kg, 24.38 mol) was added to a solution of Compound **6** (4.00 kg, 9.75 mol), **9** (3.25 kg , 13.66 mol) in DME (17 L), MeOH (8.5 L) and purified water (8.5 L) at room temperature. The reaction was refluxed for 5 h. After cooling to room temperature, ethyl acetate (40 L) and water (40 L) were added to the mixture and then the phases were separated. The lower aqueous phase was re-extracted with ethyl acetate (40 L). The combined organic phase was washed with aqueous 2N HCl (30 L), brine (30 L x 2) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to a constant weight at 40-45 ℃. The residue was dissolved in ethyl acetate (17 L) and hexane (35 L) was added slowly to the mixture. After stirring for 17 h, the upper clear solution was decanted. The residue was re-dissolved in ethyl acetate (4 L). Hexane (4 L) was added slowly to the mixture and the mixture was stirred for 2~3 h. The upper clear solution was decanted. After concentration of the combined organic phase under vacuum at 40-45 ℃, the resulting product was dried under vacuum (40 ℃, 16~18 h), affording **10** (3.81 kg, 89% yield) as a yellow solid. ^{1}H NMR（400 MHz, DMSO-d_6）δ (ppm) 1.81 (d, J = 6.4 Hz, 3H), 6.53 (q, J = 6.4 Hz, 1H), 6.71-6.75 (m, 1H), 6.78-6.81 (m, 1H), 7.40-7.52 (m, 2H), 7.58-7.61 (m, 2H), 8.23 (s, 1H), 10.45 (s, 1H).

(R)-4-(5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-6-nitropyridin-3-yl)-3-fluorophenyl trifluoromethanesulfonate (11)

Trifluoromethanesulfonic anhydride (4.07 L, 24.20 mol) was added to a solution of **10** (3.81 kg, 8.64 mol) and pyridine (2.78 L, 34.55 mol) in dichloromethane over 5-6 h, while maintaining the

internal temperature at 25~30 ℃. The reaction mixture was agitated for another 17-19 h until the reaction was deemed complete by TLC. Then the mixture was washed with water (35 L x 2). The combined aqueous phase was re-extracted with dichloromethane (35 L). The combined organic phase was washed by brine (40 L) and dried over anhydrous Na_2SO_4. After concentration of the organic phase under vacuum to a constant weight, the residue was purified on silica gel column to give the crude product. Then the product was suspended in hexane and stirred for 2-3 h. The slurry was filtered, the filter cake was dried under vacuum (40 ℃, 16~18 h), affording **11** (3.52 kg, 71% yield) as a light yellow solid. ^{1}H NMR（400 MHz, DMSO-d_6）δ (ppm) 1.81 (d, J = 6.8 Hz, 3H), 6.42 (q, J = 6.4 Hz, 1H), 7.48-7.53 (m, 1H), 7.57-7.63 (m, 2H), 7.81 (s, 1H), 7.84-7.89 (m, 2H), 8.36 (s, 1H).

(R)-(4-(5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-6-nitropyridin-3-yl)-3-fluorophenyl)dimethylphosphine oxide (12)

[1,1`-Bis(diphenylphosphino)ferrocene]dichloropalladium(Ⅱ) dichloromethane complex (0.10 kg，0.12 mol) was added to a solution of compound **11** (3.52 kg, 6.13 mol), compound **8** (1.10 kg, 14.11 mol) and triethylamine (3.42 L, 24.54 mol) in acetonitrile (6 L) and the reaction was refluxed for 1-1.5 h until the reaction was deemed complete by TLC. After cooling to room temperature, water (20 L) was added with stirring followed by ethyl acetate (25 L), and then the phases were separated. The water phase was re-extracted with ethyl acetate (10 L). The combined organic phase was washed with brine (15 L) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to a constant weight at 40-45 ℃to give compound **12** (3.71 kg) as a brown oil. The intermediate **12** was used for the next step without further purification. ^{1}H NMR（400 MHz, DMSO-d_6）δ (ppm) 1.72 (s, 3H), 1.76 (s, 3H), 1.81 (d,

J = 6.8 Hz, 3H), 6.42 (q, *J* = 6.4 Hz, 1H), 7.49-7.53 (m, 1H), 7.58-7.62 (m, 1H), 7.74-7.82 (m, 2H), 8.36 (s, 1H).

(R)-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-3-fluorophenyl)dimethylphosphine oxide **(HS-10168)**

Concentrated hydrochloric acid (1.71 L，17.07 mol) was added to a solution of compound **12** (3.71 kg，7.76 mol) in ethanol (32.5 L) followed by iron powder (2.61 kg，46.55 mol) and the mixture was refluxed for 2-2.5 h until the reaction was deemed complete by TLC. The mixture was then cooled to 50^{o}C and the solvent was removed under vacuum. The residue was diluted with ethyl acetate (50 L) and aqueous 2.5 N NaOH (50 L). After standing, the mixture was filtered through celite and the filter cake was washed with ethyl acetate/methanol (4:1, 5 L × 4). Then the phases were separated and the water phase was re-extracted with ethyl acetate (22.0 L). The combined organic phase was diluted with purified water (75 L), and concentrated hydrochloric acid (6 L) was added with agitation. Then the organic phase was separated and washed with aqueous 2 N hydrochloric acid (14 L). The combined aqueous washes were extracted with ethyl acetate, followed by neutralization with aqueous 7.5 N sodium hydroxide (14 L) and then extracted with ethyl acetate (22 L × 3). The combined organic phase was washed with aqueous 2 N sodium hydroxide (50 L), purified water (50 L × 2), brine (50 L × 2) separately and dried over anhydrous Na_2SO_4. After filtration and concentration organic phase under vacuum to a constant weight at 40-45^{o}C, the residue was purified on silica gel column to give the crude product. The product was suspended in acetone (1.7 L) and stirred for 17-18 h. The resulting slurry was filtered and washed with acetone (0.5 L). The filter cake was dried at atmospheric pressure (45 ℃, 17-18 h) to afford the crude product of **HS-10168** (1.70 kg, 59%

yield for two steps) as a yellow solid. The HPLC purity was 99.44% and the ee value was over 99.8%. The palladium level is 3.2 ppm. ^{1}H NMR（500 MHz, $CDCl_3$）δ (ppm) 1.75 (s, 3H), 1.77 (s, 3H), 1.86 (d, J = 6.7 Hz, 3H), 5.12 (brs, 2H), 6.08 (q, J = 6.6 Hz, 1H), 6.99 (s, 1H), 7.04-7.07 (m, 1H), 7.28-7.31 (m, 1H), 7.40-7.43 (m, 1H), 7.44-7.53 (m, 2H), 7.85 (s, 1H). ^{13}C NMR (125 MHz): δ(ppm) 17.7, 18.2, 18.8, 72.5, 116.4-116.6, 117.3, 117.4-117.7, 120.3, 121.9-122.0, 125.5-125.6, 128.9, 129.5-129.6, 129.9, 130.0-130.1, 134.9-136.7, 135.6-135.7, 136.7, 139.1, 150.4, 156.4-158.4, 158.3-160.5; IR (KBr): 3478, 3268, 3081, 2982, 1627, 1514, 1483, 1551, 1455, 1427, 1397, 1189, 1274, 1096, 860, 819, 775 cm^{-1}; MS(*m/z*):471.06 $[M + H]^+$.

ASSOCIATED CONTENT

Supporting Information.

NMR, IR and mass spectra are provided in the Supporting Information. This material is available free of charge via Internet at http://pubs.acs.org.

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