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Exploratory Process Development of Pexidartinib through the Tandem Tsuji–Trost Reaction and Heck Coupling

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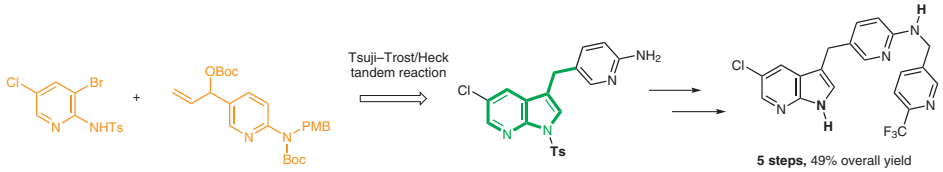

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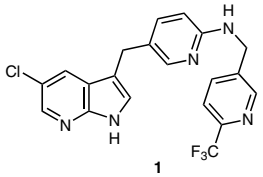
Abstract A novel synthetic route to CSF1R inhibitor pexidartinib was designed and demonstrated. Crucial to the successful synthesis is a tandem Tsuji–Trost reaction and Heck coupling in combination with palladium and silver catalysis. The final product was obtained via five steps in 49% yield with purity as high as 99.2%. The cheap and available materials and reagents and easy operations for workup and purification make this route more practical.

Key words pexidartinib, palladium-silver-catalyzed, tandem, Tsuji–Trost reaction, Heck coupling

Tenosynovial giant cell tumor (TGCT) is usually a benign tumor that appears in joints or soft tissues.[1] Because of the special location of TGCT, the high risk of surgical therapy makes the damage to the patients greater than the benefit. Therefore, drug therapy has become a preferred choice. Pexidartinib (**1**, Figure 1) is a CSF1R inhibitor developed by Daiichi Sankyo Company,[2] which effectively inhibits the binding of CSF1 (colony stimulating factor-1) to CSF1R (colony stimulating factor-1 receptor), a primary growth driver of abnormal cells in the synovium that cause TGCT. Therefore, pexidartinib can control the occurrence of CGCT from the root. At present, the drug has achieved multiple endpoints in the phase III clinical trial of TGCT treatment.



1

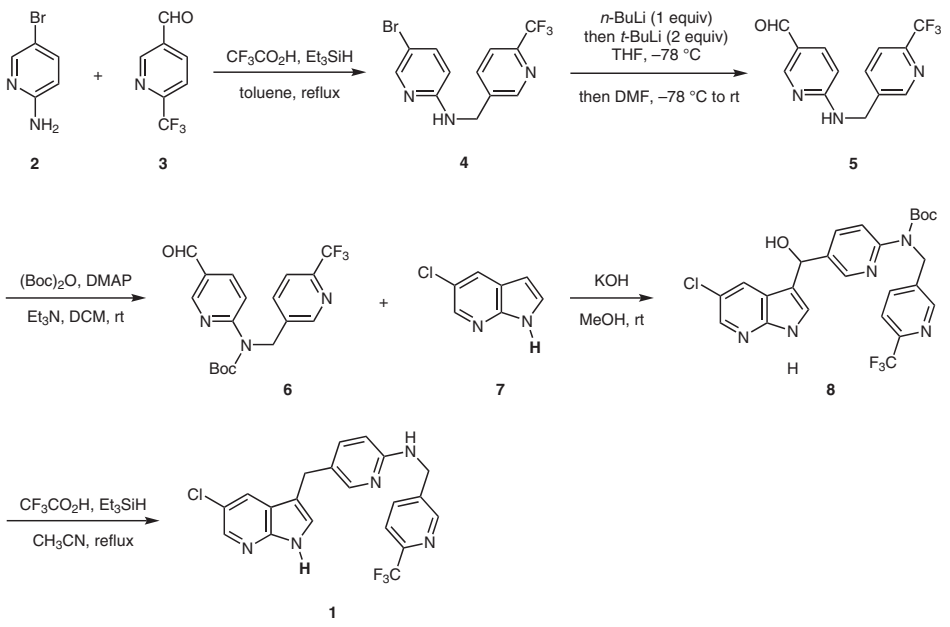
Figure 1 Chemical structure of pexidartinib (**1**)

Prior to this work, there were only two reported synthetic routes, which were both developed by Daiichi Sankyo Company for the preparation of pexidartinib (**1**).[3] In the lead optimization phase, a few hundred milligrams had been prepared using the first-generation synthesis depicted in Scheme 1.[3a] Specific problems with this synthetic route include the following: (1) The very expensive material **3** was used in the first step, which significantly increased costs; (2) The introduction of the aldehyde group required ultra-low temperature and used the quite dangerous reagent *tert*-butyllithium; (3) The yield of the reaction of fragment **6** and relatively expensive material **7** was quite low; and (4) Compounds **6**, **8**, and **1** were purified by column chromatography. For these reasons, it is not suitable for a large-scale preparation of **1**.

The second-generation route (Scheme 2) provided a much more concise method for the preparation of **1** with a high overall yield on a scale of a few hundred grams.[3b] However, the materials **7**, **9**, and **3** are expensive. Especially, compound **9** is not easy to prepare and difficult to obtain commercially. Additionally, corrosive trifluoroacetic acid was used in large quantities in the last two steps, which increased the requirement for equipment and made the process of workup and purification quite complicated.

Therefore, a more practical and low-cost synthetic method is needed to enable the large-scale preparation of peridartinib. Herein we report our efforts to develop a novel peridartinib synthesis using a palladium- and silver-catalyzed cross-coupling via Tsuji–Trost/Heck tandem reaction.

In our work, we first performed a retrosynthetic analysis on the target product **1** (Scheme 3). Retrosynthetically, **1** can be accessed from **11** and **3** by reductive amination. The fragment **11**, which has the basic skeleton similar to indole-3-acetic acid could be synthesized theoretically from moieties **12** and **13** through Tsuji–Trost/Heck tandem reaction

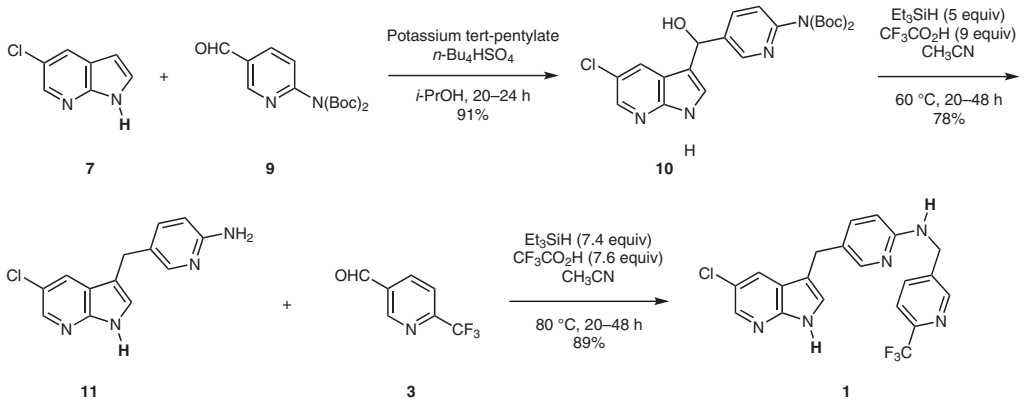


Scheme 1 First-generation synthesis of **1**

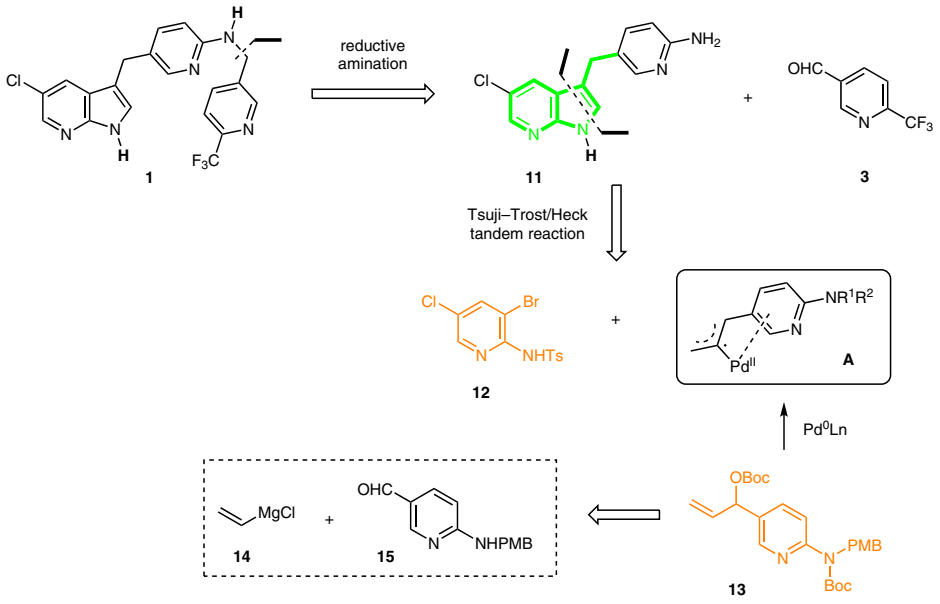
developed previously by our group.[4] Furthermore, the intermediate **13** could be obtained easily from materials **14** and **15**. The advantage of this retrosynthetic approach is that the core fragment **11** could be prepared from quite simple starting materials. So, the key to our new route is whether the construction of 9-azaindole ring of **11** could be completed in one-pot process via Tsuji–Trost/Heck tandem reaction.[5,6]

Our next work was to prepare the intermediate **13**. However, the material **15** is a new compound and was difficult to access commercially, so we had to synthesize it. Initially, we tried to lithiate the material **16** with *n*-butyllithium,[3a] but this could not be performed smoothly at low temperature because of its poor solubility in THF (Table 1, entry 1). The transformation of **16** to Grignard reagent was also failed when using isopropylmagnesium bromide (entry 2).[7] Ultimately, some modifications to the reaction conditions were successfully made as follows:[8] one equivalent of isopropyl Grignard reagent was first added to the suspension of **16** to form a soluble magnesium salt, then two equivalents of *n*-butyllithium was added at 0 ° for metalization of **16**, and finally DMF was added to introduce the aldehyde group (entry 3). Those modifications avoided the ultra-low temperature required for the use of *n*-butyllithium alone.

Subsequently, the intermediate **13** was obtained smoothly in a one-pot process under mild conditions. However, the purification of **13** was somewhat difficult due to its small polarity and low melting point (Scheme 4).



Scheme 2 Second-generation synthesis of **1**

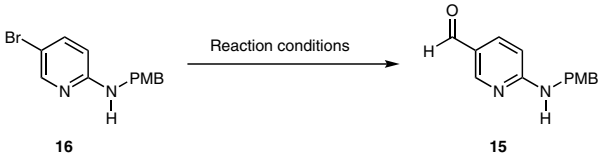


Scheme 3 Novel retrosyntheses for the preparation of **1**

With intermediates **12** and **13** in hand, we put our focus on the key step for the construction of 9-azaindole ring of intermediate **11** through a novel tandem transition-metal-catalyzed coupling (Table 2). At first, the reaction was performed under the conditions developed previously by our group as follows: $Pd(OAc)_2$ (5 mol%), P(*o*-tol)$_3$ (10 mol%), and DIPEA (2.0 equiv) in DMA at 100 ° for 12 hours. Excitingly, the reaction could smoothly generate a large amount of Tsuji–Trost product **17** and a small amount of target product **18**, which was the Ts-protected compound **11**. Although **17** was not the desired product, it could be further converted to **18** via Heck coupling. Next, we tried to increase the conversion rate for **18** by prolonging the reaction time and increasing the reaction temperature, but the results were not satisfactory (Table 2, entries 1, 2).

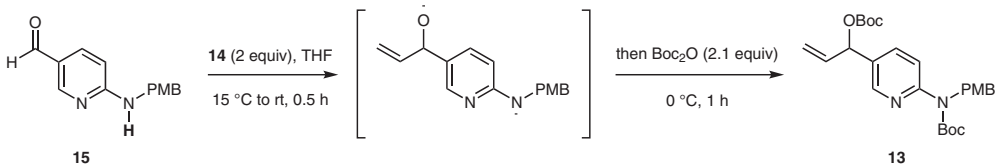
Observing the structure of **17** and analyzing the bond formation process of Heck coupling (Scheme 5), we envisioned that the formation of **17c** is the key to the conversion of **17** to **18**. In terms of mechanism,[9] the formation of **17c** needs to undergo the stages of oxidative addition, alkene coordination, and migratory insertion. Therefore, in order to perform the Heck coupling smoothly, it is necessary to increase the activity of palladium(0) in the oxidative addition stage or the activity of palladium(II) in the alkene coordination and migratory insertion stages. In theory, the activities of palladium(0) and palladium(II) are affected by

Table 1 Optimization for the Preparation of Compound **15**



16 15

Entry	Reaction conditions	Results
1	*n*-BuLi (1 equiv), THF, 0 °C; *n*-BuLi (1 equiv), –78 °C; DMF (2.8 equiv), –78 °C → rt	No reaction
2	*i*-PrMgBr (2.2 equiv), THF, rt → 50 °C; DMF (2.8 equiv), 0 °C → rt	No reaction
3	*i*-PrMgCl (1 equiv), THF, 0 °C → rt, 0.5 h; *n*-BuLi (2 equiv), 0 °C, 0.5 h; DMF (2.8 equiv), 0 °C → rt, 1 h	Yield: 73% HPLC: 99.8%



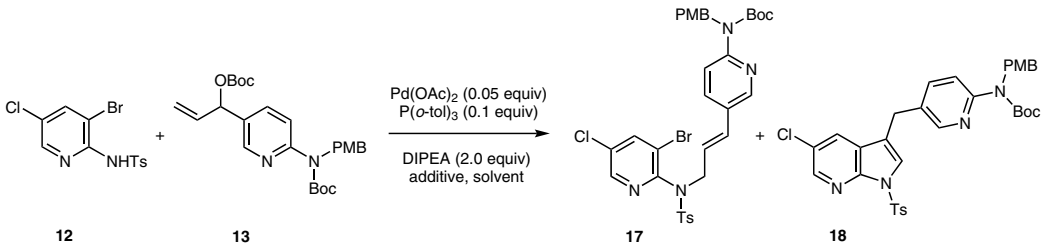
15 13

Scheme 4 One-pot synthesis of intermediate **13**

factors such as catalysts, ligands, solvents, and additives. To make minimum changes to the reaction conditions, we envisaged optimizing the reaction conditions by screening solvents and additives while maintaining the $Pd(OAc)_2$/P(*o*-tol)$_3$/DIPEA catalytic system.

When the solvent DMA was replaced by NMP, the reaction did not improve at all (Table 2, entry 3). After replacing DMA and NMP with DMSO as solvent,[10] the reaction was obviously accelerated, but the yield of **18** was still low (entry 4).

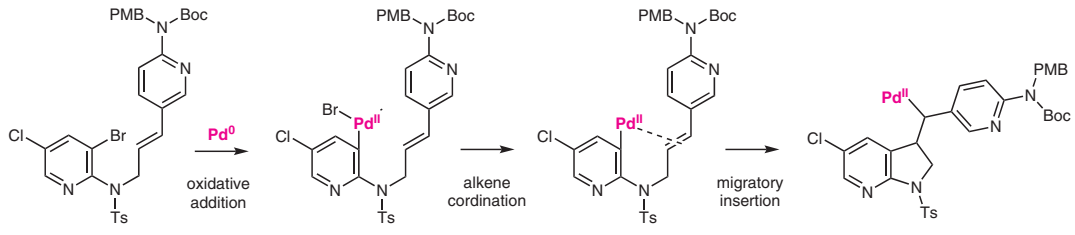
Table 2 Summary of Tsuji–Trost/Heck Tandem Reaction Conditions[a]



12 13 17 18

Entry	Additive	Solvent	Temp (°C)	Time (h)	Yield (%)[b] **17**	Yield (%)[b] **18**
1	–	DMA	100	24	65	13
2	–	DMA	120	24	60	17
3	–	NMP	120	24	59	15
4	–	DMSO	120	24	63	14
5	–	DMSO	70–120	24	64	16
6	*n*-Bu_4NBr (1.0 equiv)	DMSO	70–120	24	57	21
7	Ag_2CO_3 (1.0 equiv)[c]	DMSO	70–100	12	–	70
8	AgOAc (2.0 equiv)[c]	DMSO	70–100	12	49	26
9	Ag_3PO_4 (0.67 equiv)[c]	DMSO	70–100	12	–	58
10	Ag_2CO_3 (0.8 equiv)[c]	DMSO	70–100	12	–	67
11	Ag_2CO_3 (0.6 equiv)[c]	DMSO	70–100	12	–	64
12	Ag_2CO_3 (0.8 equiv)	DMSO	70–100	12	–	68
13[d]	Ag_2CO_3 (1.0 equiv)	DMSO	70–100	24	–	69
14[e]	Ag_2CO_3 (1.0 equiv)	DMSO	70–100	24	–	56
15[f]	Ag_2CO_3 (0.8 equiv)	DMSO	70–100	36	–	57

[a] Reaction conditions: **12** (1.0 mmol), **13** (1.2 mmol), *c* = 0.2 M, N_2 atmosphere.
[b] Isolated yields.
[c] Silver salts were added after the completion of Tsuji–Trost reaction.
[d] Reaction scale: **12** (25 g, 99.1% HPLC, 68 mmol), **13** (40 g, 96.3% HPLC, 82 mmol).
[e] Reaction scale: **12** (22 g, 99.1% HPLC, 60 mmol), **13** (40 g, 86.9% HPLC, 74 mmol).
[f] Reaction scale: **12** (112 g, 99.1% HPLC, 307 mmol), **13** (218 g, 86.9% HPLC, 403 mmol).



17 17a 17b 17c

Scheme 5 The bond formation process of Heck coupling

During the experiment we found that a lower temperature was favorable for the Tsuji–Trost reaction. So the transformation was carried out at 70 °C for 12 hours and then 120 °C for another 12 hours (Table 2, entry 5). As a result, there was hardly any improvement in the overall yield of **17** and **18**, as well as for the transformation to **18**. Based on entry 5, we attempted to increase the stability of palladium(0) by adding phase transfer catalyst such as *n*-Bu_4NBr to increase its catalytic activity,[11] but the effect was not significant (entry 6).

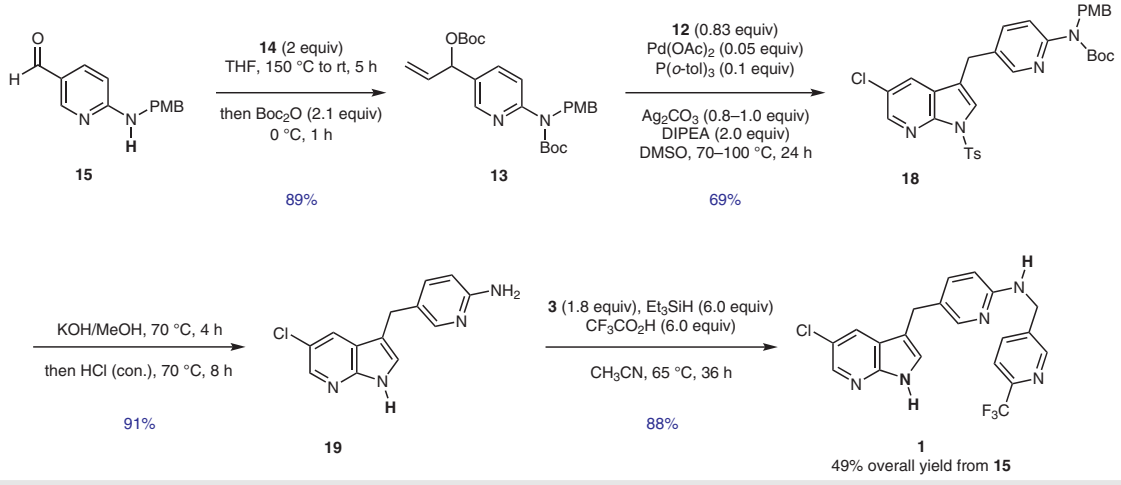
According to the literature,[12] the use of silver salt could convert the neutral palladium(II) generated in the stage of oxidative addition into the more active cationic palladium(II), which is beneficial to the alkene coordination and migratory insertion of nucleophilic olefin bonds, by precipitating halogen ions. Excitingly, the yield of the desired product **18** was significantly improved as expected when silver salts such as AgOAc, Ag_2CO_3, and Ag_3PO_4 were added to the reaction system after the completion of the Tsuji–Trost reaction at 70 °C (Table 2, entries 7, 8, and 9). In particular, the presence of Ag_2CO_3 made the transformation of **17** more complete and the yield of **18** was up to 70%. Furthermore, the investigation of the amount of Ag_2CO_3 used showed that 0.8–1.0 equivalent was preferable (entries 10, 11). And the same result as entry 10 could be achieved by adding Ag_2CO_3 before the Tsuji–Trost reaction (entry 12). Finally, the optimal reaction conditions were determined as follows: **12** (1.0 equiv), **13** (1.2 equiv), $Pd(OAc)_2$ (5 mol%), P(*o*-tol)$_3$ (10 mol%), Ag_2CO_3 (0.8–1.0 equiv), and DIPEA (2.0 equiv) in DMSO.

Based on the optimized reaction conditions, the scale application of this tandem reaction was then examined. The reaction gave a 69% isolated yield under the scale of 40 g of **13** (Table 2, entry 13) with 96.3% purity, while it gave a 56% isolated yield under the scale of 40 g of **13** (entry 14) with 86.9% purity. The difference between those two reactions was the purity of intermediate **13**. The higher the purity of **13**, the better the yield of **18**. It seems that impurities inhibited the catalytic process. The reaction could give a similar result as entry 14 by increasing the scale of **13** (entry 15). It is worth mentioning that compound **18** has poor solubility, which makes **18** easy to precipitate from the reaction system, and it could be furnished with high purity after slurring sequentially with dimethyl sulfoxide and ethyl acetate.

Deprotection of **18** was completed with a one-pot operation (Scheme 6).[13] The protecting group Ts was first removed under the condition of KOH/MeOH at 70 °C for 4 hours, PMB and Boc were then removed with concentrated hydrochloric acid at the same temperature for another 8 hours after distillation of methanol.[14] Thus, after crystallization from toluene, compound **19** was smoothly obtained in 91% yield and 98.9% HPLC purity.

Ultimately, the target product **1** was achieved in 88% yield and 99.2% HPLC purity under the conditions reported by Daiichi Sankyo Company (Scheme 6).

In conclusion, we have successfully developed a novel efficient synthetic route for pexidartinib (**1**) via Tsuji–Trost/Heck tandem reaction in combination with palladium and silver catalysis. The new synthesis avoids the need for ultra-low temperature and greatly reduces the amount of corrosive trifluoroacetic acid. The cheap and easily available materials and reagents and easy operations for workup and purification make this route more practical. Currently, we are focusing on establishing a scalable manufacturing process. Further modifications are carried out to improve and stabilize the yield of the tandem reaction through improving the purity of intermediate **13** and reducing the amount of catalysts. These efforts will be discussed in a future paper.



Scheme 6 The novel synthetic route to pexidartinib (**1**)

All commercially available chemicals and solvents were used directly as received. ^{1}H NMR spectra were recorded on a Bruker Avance 400 and 600 MHz NMR spectrometer. ^{13}C NMR spectra were recorded on a Bruker Avance 100 and 150 MHz NMR spectrometer. Chemical shifts are reported in ppm (δ) ($CDCl_3$ δ = 7.26 for ^{1}H NMR and 77.1 for ^{13}C NMR; DMSO-d_6 δ = 2.50 for ^{1}H NMR and 39.5 for ^{13}C NMR). Standard abbreviations were used to denote proton coupling patterns. HRMS spectra were measured on a Waters Xevo G2-XS QTof. Reactions were monitored by TLC or reversed-phase HPLC (Dionex U3000) under the following conditions: Column: Ultimate XB-C18 column (5 µm, 250 × 4.6 mm). Eluent: (A) 1% H_3PO_4/99% H_2O; (B) 100% CH_3CN. The flow rate was 1.0 mL/min with a column temperature of 35 °C. The detection wavelength was 220 nm. The HPLC gradient method is shown in Table 3.

Table 3 HPLC Gradient Method

Time (min)	Eluent A (%)	Eluent B (%)
0	90	10
10	50	50
20–30	5	95
35–40	90	10

6-[(4-Methoxybenzyl)amino]nicotinaldehyde (15)

To a four-necked flask charged with compound **16**[15] (500 g, 1.71 mol) and anhyd THF (2 L) was added slowly isopropylmagnesium chloride (2.0 M, 0.94 L, 1.88 mol) under N_2 atmosphere below 20 °C, after which the mixture was stirred for 0.5 h, and then *n*-BuLi (2.5 M solution in hexanes, 1.37 L, 2.42 mol) was subsequently added below 20 °C. After the disappearance of compound **16**, the mixture was cooled to 0 °C, and anhyd DMF (350 g, 4.8 mol) was added slowly below 20 °C, after which the reaction mixture was stirred for 2 h below 20 °C and monitored by TLC until the reaction was complete. The mixture was poured into sat. aq NH_4Cl (4 L) at 0 °C. After stirring for 20 min, the mixture was added to EtOAc (4 L) and filtered through a pad of kieselgur. The layers were separated and the organic layer was concentrated in vacuo to a volume of about 4 L. The concentrate was added to DMF (0.1 L) and H_2O (2 L) and stirred at 50 °C until complete dissolution, after which $NaHSO_3$ (355 g, 3.42 mol) was added. The reaction mixture was stirred for another 5 h at 50 °C, cooled to rt, and filtered. The filter cake was washed subsequently with EtOAc (1 L) and H_2O (1 L), and transferred to a mixture of EtOAc (4 L) and H_2O (2 L). To this suspension was added NH_4OAc (660 g, 8.5 mol), heated to 70 °C and stirred for 12 h, then cooed to rt. The layers were separated and the organic layer was washed with brine (2 × 2 L), concentrated in vacuo, and then dried to give a light yellow solid with 99.7% HPLC purity; yield: 302 g (73%); mp 133.6–134.5 °C; HPLC: t_R = 10.2 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.67 (s, 1 H), 8.51 (d, *J* = 2.0 Hz, 1 H), 8.15 (t, *J* = 5.8 Hz, 1 H), 7.75 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.60 (d, *J* = 9.2 Hz, 1 H), 4.52 (d, *J* = 4.0 Hz, 2 H), 3.73 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 189.6, 161.9, 158.8, 155.7, 135.0, 131.6, 129.2, 122.6, 114.0, 110.0, 55.5, 44.0.

HRMS (ESITOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1128; found: 243.1126.

***tert*-Butyl (5-{1-[(*tert*-Butoxycarbonyl)oxy]allyl}pyridin-2-yl)(4-methoxybenzyl)carbamate (13)**

To a four-necked flask charged with compound **15** (29 g, 0.12 mol) and anhyd THF (0.12 L) was added slowly vinylmagnesium chloride (**14**; 1.0 M, 0.24 L, 0.24 mol) under N_2 atmosphere at 10–20 °C. After completion of the addition of compound **15**, the mixture was cooled to 0 °C, and a solution of Boc_2O (55 g, 0.252 mol) in anhyd THF (0.05 L) was added slowly below 10 °C, after which the reaction mixture was stirred for 2 h below 10 °C and monitored by TLC until the reaction was complete. The mixture was poured into sat. aq NH_4Cl (0.6 L) at 0 °C. After stirring for 20 min, the mixture was added to EtOAc (0.2 L), and filtered through a pad of kieselgur. The layers were separated and the organic layer was washed with brine (2 × 0.1 L), concentrated in vacuo, and purified by silica gel column chromatography (200–300 mesh, EtOAc/hexane 1:20) to give a colorless oil with 96.3% HPLC purity, which turned to a hard white solid on keeping for 24 h; yield: 50 g (89%); mp 88.8–89.2 °C; HPLC: t_R = 19.7 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.37 (d, *J* = 2.0 Hz, 1 H), 7.75 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.63 (d, *J* = 8.8 Hz, 1 H), 7.14–7.16 (m, 2 H), 6.83–8.85 (m, 2 H), 6.03–6.12 (m, 2 H), 5.26–5.34 (m, 2 H), 5.03 (s, 2 H), 3.70 (s, 3 H), 1.40 (s, 9 H), 1.39 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.6, 154.3, 153.8, 152.3, 146.6, 136.5, 136.2, 131.3 (2 C), 130.4, 128.7, 119.6, 117.9 (2 C), 114.0, 82.5, 81.4, 76.6, 55.4, 49.1, 28.2 (3 C), 27.8 (3 C).

HRMS (ESITOF): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{35}N_2O_6$: 471.2490; found: 471.2503.

Larger scale: To a four-necked flask charged with compound **15** (290 g, 1.2 mol) and anhyd THF (1.2 L) was added slowly vinylmagnesium chloride (1.0 M, 2.4 L, 2.4 mol) under N_2 atmosphere at 10–20 °C. After completion of the addition of compound **15**, the mixture was cooled to 0 °C, and a solution of Boc_2O (550 g, 2.52 mol) in anhyd THF (0.5 L) was added slowly below 10 °C, after which the reaction mixture was stirred for 2 h below 10 °C and monitored by TLC until the reaction was complete. The mixture was poured into sat. aq NH_4Cl (6 L) at 0 °C. After stirring for 20 min, the mixture was added to EtOAc (2 L) and filtered through a pad of kieselgur. The layers were separated and the organic layer was concentrated in vacuo to a volume of about 1.2 L. To the concentrate was added silica gel (200–300 mesh, 350 g) and stirred for 10 min at rt, filtered through a pad of kieselgur, which was washed with a mixed solution of EtOAc and PE (1 L/1 L). The filtrate was concentrated in vacuo to a volume of about 1.2 L. To the concentrate was added again silica gel (200–300 mesh, 350 g) and stirred for 10 min at rt, filtered through a pad of kieselgur, which was washed with a mixed solution of EtOAc and PE (1 L/1 L). The filtered solution was concentrated in vacuo until no solvent was left. Cyclohexane (2 L) was then added to the residue over 10 min while stirring at rt, at which time a grayish yellow solid was precipitated. After stirring for another 20 min, the solution was filtered through a pad of kieselgur and washed with brine (2 × 1 L), dried ($MgSO_4$), filtered, and concentrated in vacuo until dryness to provide a yellow oil with 86.9% HPLC purity, which was used directly in the next step without further purification; yield: 477 g (85%).

***tert*-Butyl {5-[(5-Chloro-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methyl]pyridin-2-yl}(4-methoxybenzyl)carbamate (18) (Table 2, entry 13)**

To a three-necked flask charged with DMSO (170 mL) was added compound **12**[16] (25 g, 99.1% HPLC purity, 68 mmol), compound **13** (40 g, 96.3% HPLC purity, 82 mmol), $Pd(OAc)_2$ (0.76 g, 3.4 mmol), P(*o*-tol)$_3$ (2.1 g, 6.8 mmol), Ag_2CO_3 (18.8 g, 68 mmol), and DIPEA (17.6 g, 136 mmol). The mixture was stirred under N_2 atmosphere at 70 °C for

about 10 h until compound **12** had disappeared, and then heated to 100 °C. After stirring for another 14 h, silica gel (200–300 mesh, 25 g) was added. The reaction mixture was stirred for 20 min and filtered immediately through a pad of kieselgur, which was washed with hot DMSO (100 °C, 30 mL). The filtered solution was cooled at ambient conditions to about 20–24 °C while stirring, at which time a yellow solid precipitated. The precipitate was filtered and DCM (200 mL) was added to the filtrate. The DCM layer was washed with H_2O (3 × 100 mL), and concentrated in vacuo to give a gray solid, which was combined with the above precipitate and treated with DMSO (50 mL). The slurry was heated to 80 °C and stirred for about 1 h. The mixture was cooled at ambient conditions to about 20–24 °C while stirring. The precipitate was filtered, washed with a mixture of DMSO and EtOAc (25 mL/25 mL) at 0 °C. The filter cake was slurried in EtOAc (50 mL) at 80 °C for about 1 h. Then the mixture was cooled to about 0–5 °C while stirring. The precipitate was filtered, washed with EtOAc (50 mL) at 0 °C, and dried to provide a bright yellow powder with 99.1% HPLC purity; yield: 29.7 g (69%); mp 204.3–205.8 °C; HPLC: t_R = 12.9 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.44 (d, J = 1.6 Hz, 1 H), 8.18 (dd, J = 16.0, 2.4 Hz, 2 H), 7.98 (d, J = 8.0 Hz, 2 H), 7.80–7.73 (m, 2 H), 7.38 (d, J = 8.0 Hz, 2 H), 7.26 (t, J = 3.0 Hz, 1 H), 7.19 (d, J = 8.4 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 5.21 (d, J = 2.8 Hz, 2 H), 5.09 (s, 2 H), 3.71 (s, 3 H), 2.36 (s, 3 H), 1.42 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.6, 154.7, 154.1, 153.6, 147.7, 146.9, 144.7, 135.9, 135.1, 131.2, 129.7, 128.6, 127.9, 127.8, 126.7, 126.2, 125.4, 118.9, 118.7, 113.6, 81.9, 55.2, 53.9, 49.1, 28.2, 21.6.

HRMS (ESITOF): m/z [M + H]$^+$ calcd for $C_{33}H_{34}ClN_4O_5S$: 633.1933; found: 633.1938.

tert-Butyl {5-[(5-Chloro-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methyl]pyridin-2-yl}(4-methoxybenzyl)carbamate (18) (Table 2, entry 15)

To a three-necked flask charged with DMSO (0.8 L) was added compound **12** (112 g, 99.1% HPLC purity, 0.31 mol), compound **13** (218 g, 86.9% HPLC purity, 0.4 mol), $Pd(OAc)_2$ (2.8 g, 12.4 mmol), P(*o*-tol)$_3$ (7.5 g, 24.8 mmol), Ag_2CO_3 (68 g, 0.25 mol), and DIPEA (80 g, 0.62 mol). The mixture was stirred under N_2 atmosphere at 70 °C for about 12 h until compound **12** had disappeared, and then heated to 100 °C. After stirring for another 24 h, silica gel (200–300 mesh, 110 g) was added. The reaction mixture was stirred for 20 min and filtered immediately through a pad of kieselgur, which was washed with hot DMSO (100 °C, 0.3 L). The filtered solution was cooled under ambient conditions to about 20–24 °C while stirring, at which time a yellow solid was precipitated. The precipitate was filtered and the filtrate was added to DCM (1 L). The DCM layer was washed with H_2O (3 × 0.6 L), concentrated in vacuo to give a gray solid, which was combined with the above precipitate and was added to DMSO (0.3 L). The slurry was heated to 80 °C and stirred for about 1 h. The mixture was cooled under ambient conditions to about 20–24 °C while stirring. The precipitate was filtered, washed with a mixed solution of DMSO and EtOAc (0.15 L/0.15 L) at 0 °C. The filter cake was slurried in EtOAc (0.3 L) at 80 °C for about 1 h. Then the mixture was cooled to about 0–5 °C while stirring. The precipitate was filtered, washed with EtOAc (0.3 L) at 0 °C, and dried to provide a grayish yellow powder with 96.7% HPLC purity; yield: 112 g (57%).

5-[(5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methyl]pyridin-2-amine (19)

A two-necked flask fitted with a condenser was charged with compound **18** (95 g, 0.15 mol) and MeOH (0.24 L). To this mixture was added KOH (27 g, 0.48 mol) and the flask was heated in an oil bath at 70 °C and the reaction mixture was stirred for 4 h until compound **18** had disappeared. The solvent was evaporated and to the residue was added aq 12 M HCl (0.24 L). The mixture was stirred for 8 h at 70 °C until the reaction was completed, cooled to about 20–24 °C, and added to H_2O (0.24 L). The mixture was extracted with EtOAc (2 × 0.24 L) and the aqueous layer was adjusted pH to 8–9 by adding K_2CO_3 under cooling in an ice bath. The precipitate formed was filtered, washed with H_2O (0.12 L), and then transferred to a mixture of MeOH and toluene (0.05 L/0.1 L). The suspension was heated to 70 °C until complete dissolution and then MeOH was evaporated off to leave about 45–48 mL. The residual solution was cooled under ambient conditions to 20–24 °C while stirring, at which time a light yellow solid was precipitated. The precipitate was filtered, washed with toluene and hexane in sequence, and dried to provide a light yellow powder with 98.9% HPLC purity; yield: 35 g (91%); mp 212.4–213.5 °C; HPLC: t_R = 8.317 min.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.64 (s, 1 H), 8.16 (d, J = 1.8 Hz, 1 H), 7.91 (dd, J = 18.6, 1.8 Hz, 2 H), 7.36 (s, 1 H), 7.26 (dd, J = 8.4, 1.8 Hz, 1 H), 6.37 (d, J = 8.4 Hz, 1 H), 5.69 (s, 2 H), 3.82 (s, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 158.6, 147.5, 147.4, 147.8, 130.8, 126.3, 126.0, 124.3, 122.2, 120.5, 113.8, 108.3, 27.6.

HRMS (ESITOF): m/z [M + H]$^+$ calcd for $C_{13}H_{12}ClN_4$: 259.0745; found: 259.0743.

5-[(5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methyl]-*N*-{[6-(trifluoromethyl)pyridin-3-yl]methyl}pyridin-2-amine (Pexidartinib, 1)

The process of preparation for **1** starting from **19** (26 g) was the same as given in the literature.[3b] The reaction provided a light yellow powder with 99.2% HPLC purity; yield: 37 g (88%); mp 197.1–198.8 °C; HPLC: t_R = 11.3 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.65 (s, 1 H), 8.70 (s, 1 H), 8.15 (d, J = 2.0 Hz, 1 H), 7.95–7.94 (m, 3 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.36 (d, J = 1.6 Hz, 1 H), 7.31 (dd, J = 8.4, 2.4 Hz, 1 H), 7.10 (t, J = 6.0 Hz, 1 H), 6.48 (d, J = 8.8 Hz, 1 H), 4.56 (d, J = 6.0 Hz, 2 H), 3.82 (s, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 157.2, 149.8, 147.4, 147.1, 145.2, 141.2, 140.9, 137.8, 137.1, 126.3, 126.0, 124.9, 123.2, 122.3, 120.8, 120.4, 113.7, 108.8, 42.1, 27.5.

HRMS (ESITOF): m/z [M + H]$^+$ calcd for $C_{20}H_{16}ClF_3N_5$: 418.1041; found: 418.1053.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612421.

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(15) The preparation of compound **16** is described in the Supporting Information.

(16) The preparation of compound **12** is described in the Supporting Information.