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Direct Synthesis of a PDE 4 inhibitor by using Pd-Cu-Catalyzed C-H/C-Br Coupling of Benzoxazole with A Heteroaryl Bromide

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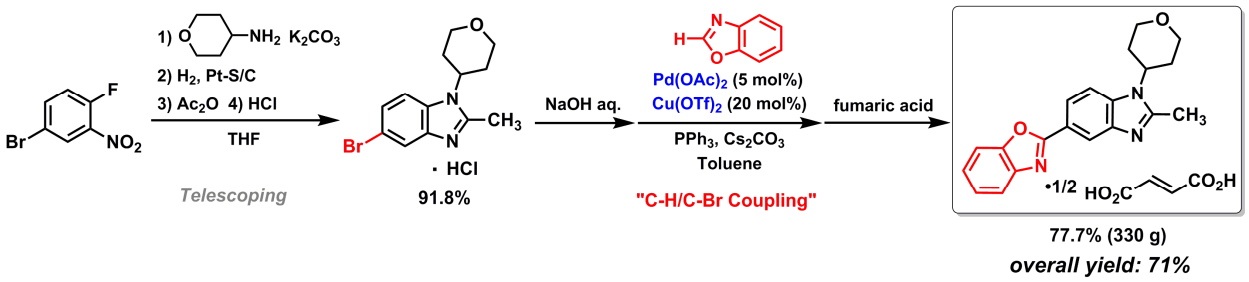
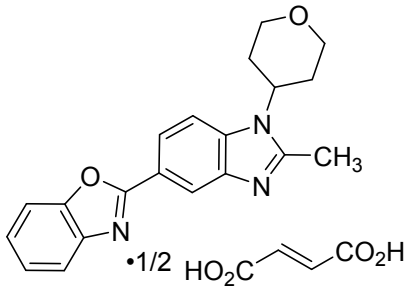


ABSTRACT : A short and practical synthetic route of a PDE4 inhibitor (**1**) was established by using Pd-Cu-catalyzed C-H/C-Br coupling of benzoxazole with a heteroaryl bromide. The combination of $Pd(OAc)_2$-$Cu(OTf)_2$-PPh_3 was found to be effective for this key step. Furthermore, telescoping methods were adopted to improve the yield and manufacturing time, and two-step synthesis of **1** was accomplished in 71% overall yield.

Keywords: C-H/C-Br Coupling, C-H activation, benzoxazole, telescoping

INTRODUCTION:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and dementia. Although Donepezil, Rivastigmine, Galanthamine, and Memantine are marketed as Alzheimer-type dementia, all of these compounds are used as symptomatic therapy and have not high satisfaction with treatment. Therefore, there are strong unmet medical needs in the development of AD therapy. **1** is PDE4 inhibitor and expected to improve memory impairment. In addition to the mechanism of action, **1** enhances BDNF signal transduction and induces NXF, a brain specific transcription factor, in the presence of low concentrations of BDNF. NXF induction is expected to lead to nerve regeneration and neuroprotective efficacy.



1

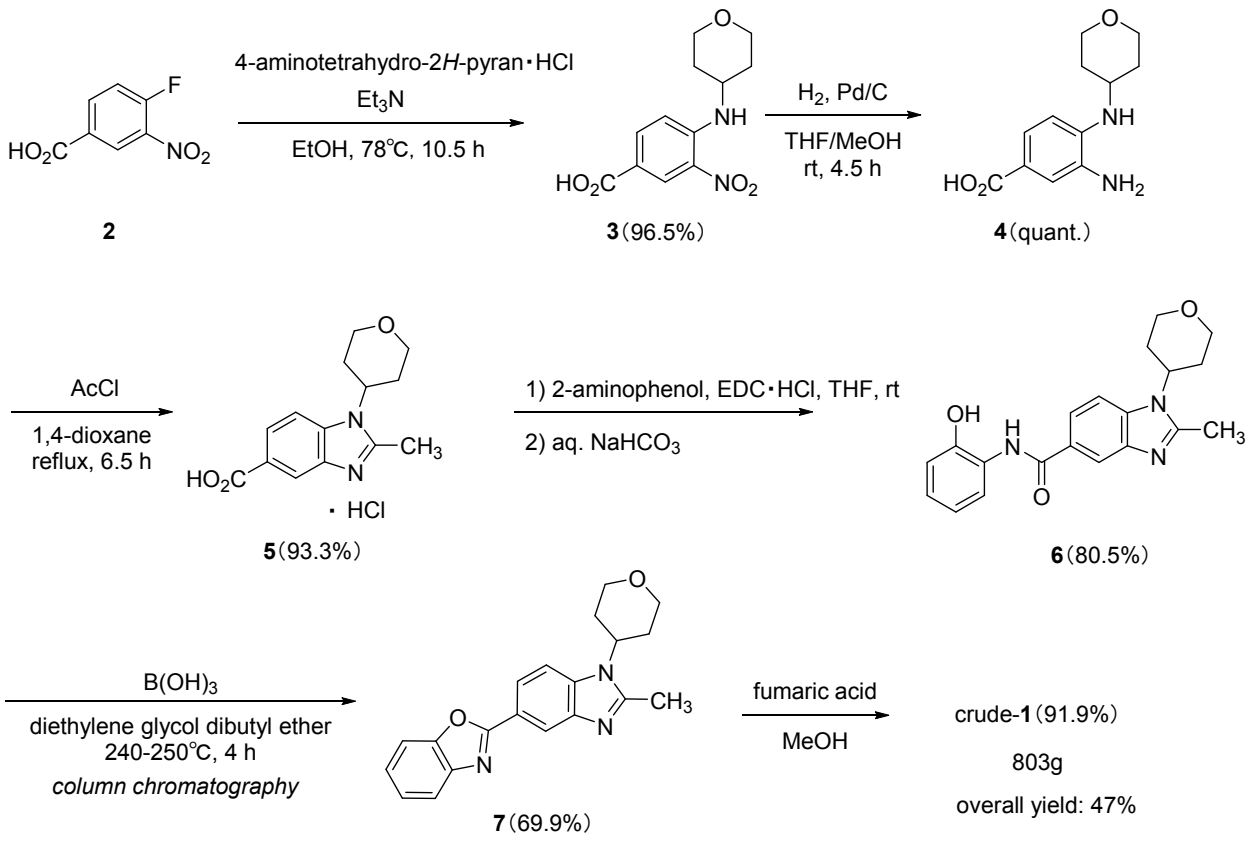
Figure 1. Chemical structure of **1**.

In this article, we would like to describe two synthetic methods of **1** developed for scale up. The First-generation synthesis was based on the medicinal chemistry route and successfully scaled up to produce 14 kg of active pharmaceutical ingredient (API) for early clinical trials. The Second-generation synthesis was devised that enables direct coupling of benzoxazole with a heteroaryl bromide, and confirmed by 300 g synthesis for scale up feasibility.

RESULTS AND DISCUSSION

First-generation synthesis: The initial medicinal chemistry route to **1** is shown in Scheme 1.[1] This route was capable for preparation of the small amounts of API needed for early toxicology studies, but it was not suitable for large-scale production due to the following issues: (i) the operational problem such as evaporation to dryness to obtain **4**, (ii) the use of possibly carcinogenic solvent 1,4-dioxane and a mutagenic 2-aminophenol, and (iii) the requirement for high temperature (240-250 ºC)[2] and chromatographic purification for the synthesis of **7**.

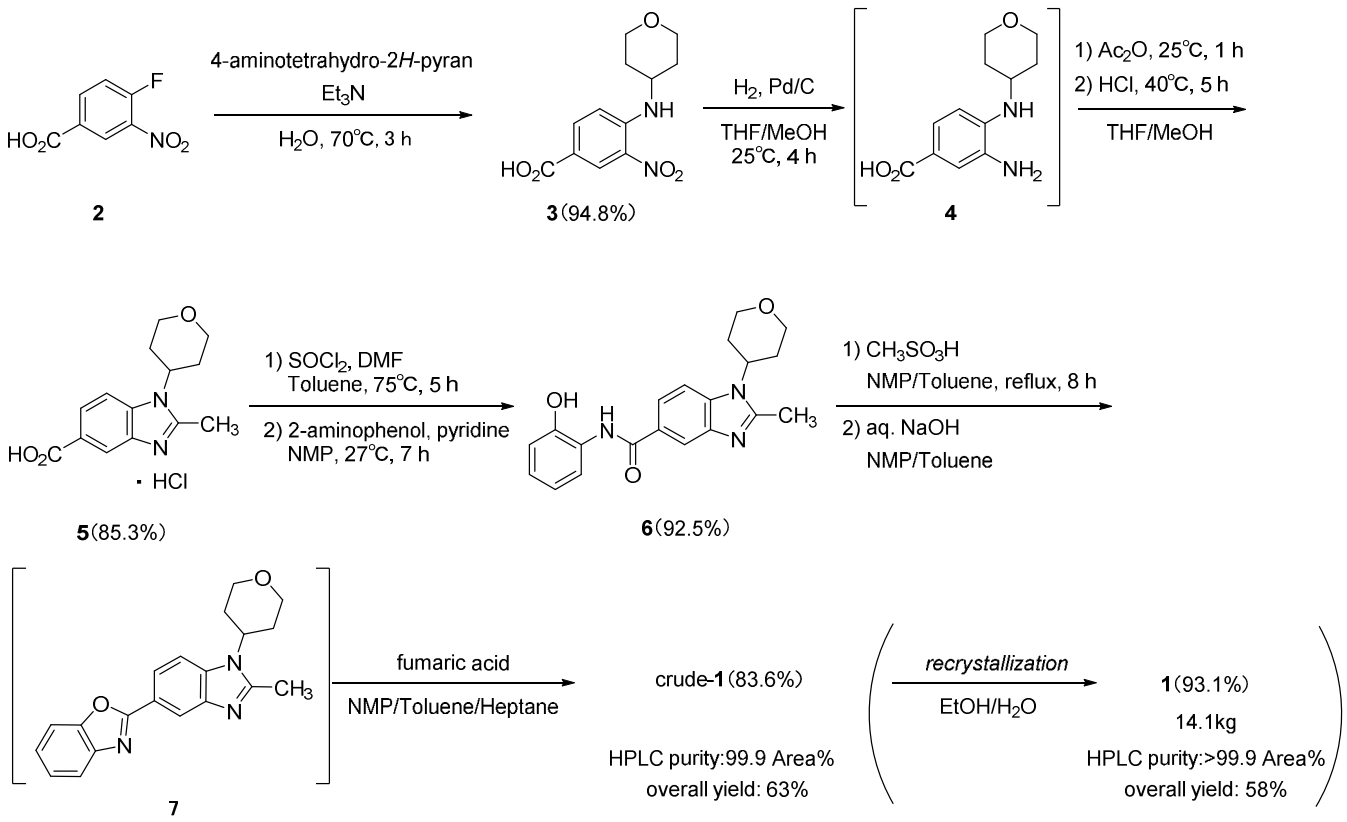
Scheme 1. Medicinal chemistry route



Since we need to provide API in a short period for early clinical trial, the first-generation synthesis was adopted by addressing the problems of medicinal chemistry route (Scheme 2). The improved results are shown as follows: (i) The solution of **4** was used in the next step without evaporation (Telescoping). (ii) 1, 4-Dioxane was switched to THF/MeOH which were used in the previous step. Acetyl chloride was also changed to acetic anhydride because the starting material **4** was not completely consumed in the use of acetyl chloride due to formation of hydrochloride of **4**. Furthermore, EDC・HCl was replaced with an inexpensive $SOCl_2$. (iii) Cyclization reaction of **6** was accomplished at 130 ºC under azeotropic dehydration by the use of methanesulfonic acid, and chromatographic purification of **7** was avoided by crystallizing **1** directly as fumarate of **7**. And the quality of **1** was controlled by recrystallization.

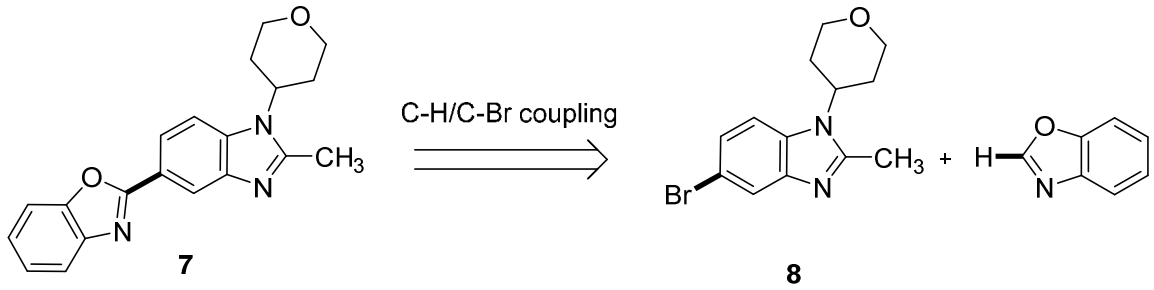
This first-generation synthesis was applied to 14 kg campaign for early clinical trial without a problem accompanying scale-up.

Scheme 2. First-Generation Synthesis.



Second-generation synthesis: After the manufacture by the first-generation route, we examined more efficient synthetic route of **1** for future material supply. In order to reduce the number of manufacturing steps, we planned to synthesize the API skelton **7,** by direct coupling of benzoxazole with an aryl bromide **8** (Scheme 3). The advantage of this method is not only to shorten a number of manufacturing steps, but also to avoid using 2-aminophenol, which is known to be mutagenic.

Scheme 3. New approach for the synthesis of 7 by C-H/C-Br coupling



7 **8**

Heterobiaryl compounds are very important motifs in biologically active natural products and pharmaceuticals.[3] These moieties has been synthesized by cross coupling of aryl-metal compounds with aryl halides (C-M/C-X coupling, M = metal).[4] On the other hand, recent advances in the metal mediated direct C-H arylations of aryl compounds with aryl halides (C-H/C-X coupling) provide an efficient and ideal access to the target molecules because it can avoid the need to prepare stoichiometric amounts of aryl-metal reagent.[5] Although the direct C-H arylations of arylazole with aryl halides have also been extensively studied to date, Miura and co-workers made a breakthrough in this area in 1998 by finding the catalyst system of $Pd(OAc)_2/PPh_3/Cs_2CO_3$ that is effective for the arylation of azole including (benzo)thiazoles

and (benz)oxazoles.[6,7] It was noted that the reaction was significantly accelerated by the addition of CuI (Scheme 4).

Scheme 4. Arylation of azole reported by Miura and co-workers

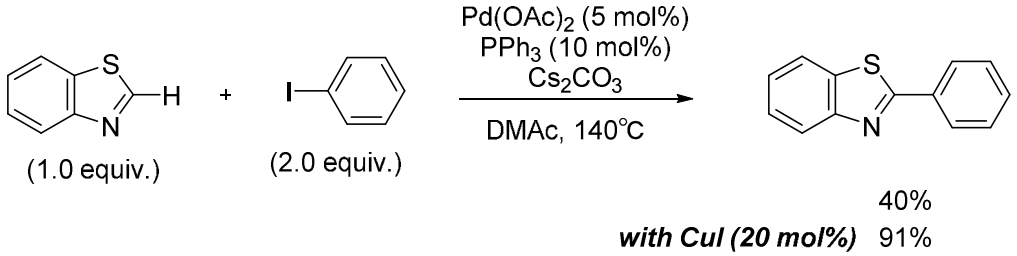
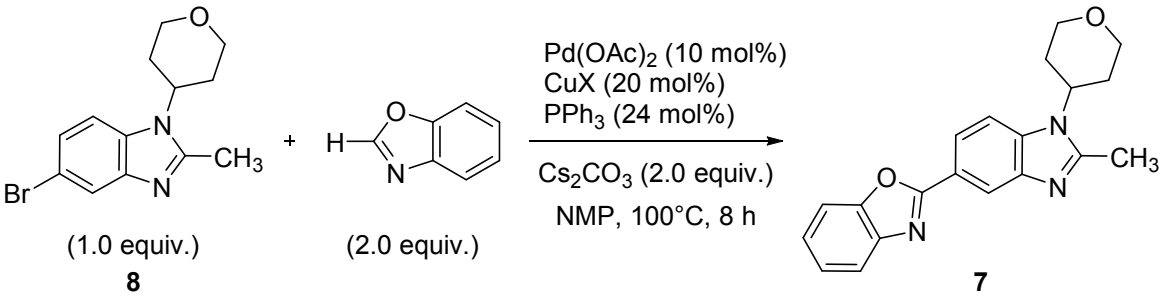


Table 1. Effects of the addition of copper salts



Entry	CuX(I)	Yield(%)[a]	Entry	CuX(II)	Yield(%)[a]
1	None	73	6	$Cu(OAc)_2$	77
2	CuI	29	7	CuO	84
3	CuBr	39	8	$CuBr_2$	86
4	CuCl	25	9	$Cu(OTf)_2$	87
5[b]	CuOTf	87	10	$Cu(OTf)_2$	N.D.[c]

[a]Reaction yields were quantified by HPLC.
[b]$(CuOTf)_2$•toluene complex was used.
[c]The reaction was carried out in the absence of $Pd(OAc)_2$.

Firstly, we applied the Miura's conditions to the coupling reaction of **8**[8] with benzoxazole in the absence of a copper salt, and obtained the desired product **7** in 73% yield (Table 1, Entry 1). The addition of CuI was not effective for this reaction and the yield was lowered to 29% (Entry 2). Next, the effects of the other copper salts were examined (Entries 3-9). When CuBr or CuCl was used, the yields of **7** were low while the reaction was significantly accelerated by the addition of CuOTf, and the yield of **7** increased up to 87% (Entries 3-5). The yield by addition of $Cu(OAc)_2$ was slightly improved compared to the no copper salt conditions (Entry 6). On the other hand, the reaction with copper (II) salts such as CuO, $CuBr_2$ and $Cu(OTf)_2$ afforded **7** in high yields as in the case in CuOTf (Entries 7-9). These results indicate that the higher Lewis acidities of copper salts increase the reactivity, probably due to the activation of benzoxazole.

When $Cu(OTf)_2$ was used without $Pd(OAc)_2$, **7** was not formed (Entry 10)[9,10]. In view of reactivity, cost and availability, $Cu(OTf)_2$ was selected as additive. To the best of our knowledge, this is the first example of the combination of $Pd(OAc)_2$ with $Cu(OTf)_2$ for C-H arylations of arylazole.[11]

In addition to above results, the solvent could be changed from NMP to toluene which was used for later crystallization. The amount of $Pd(OAc)_2$ could be reduced to 5 mol%.

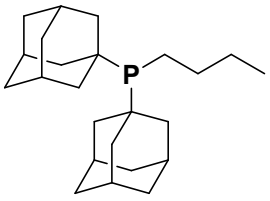
Although the effects of various ligands were examined next (Table 2), PPh_3 gave the best result (Entry 1). This reaction did not proceed without ligand (Entry 2), and the other ligands were not effective except for P^{t}Bu (Entries 3-8)[12]. As a result, readily available PPh_3 was chosen a ligand.

Since the conditions of copper salt and ligand were identified, the molar ratio of PPh_3/ Pd in coupling reaction was examined. It was found that the formation of unknown impurities was most suppressed in the case of the ratio of PPh_3/Pd 2.5 without depressing reactivity. Then, the reaction yield increased up to 94% under optimized conditions at 10 g scale.

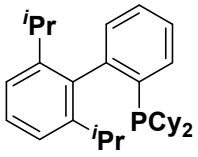
Table 2. Effects of the ligands[a]

Entry	Ligand	Time (h)	Residual ratio of **8** (LC area%)[b]
1	PPh_3	6	<1
2	none	4	97
3	P(*o*-Tol)$_3$	5	95
4	P^{t}Bu$_3$	8	<1
5	cataCXium® A	5	70
6	XPhos type	5	42
7	dppf	5	22
8[c]	PEPPI-IPr	6	67

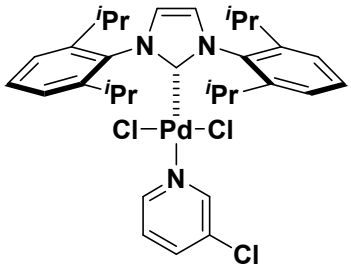
[a]The reaction was carried out by using $Pd(OAc)_2$ (5 mol%), $Cu(OTf)_2$ (20mol%), ligand (15 mol%), and Cs_2CO_3 (2.0 equiv.) in toluene at 100°C.
[b]Residual ratio of **8** is **8** / (**8** + **7**)
[c]The reaction was carried out in the absence of $Pd(OAc)_2$, $Cu(OTf)_2$ and PPh_3.



cataCXium® A



XPhos type

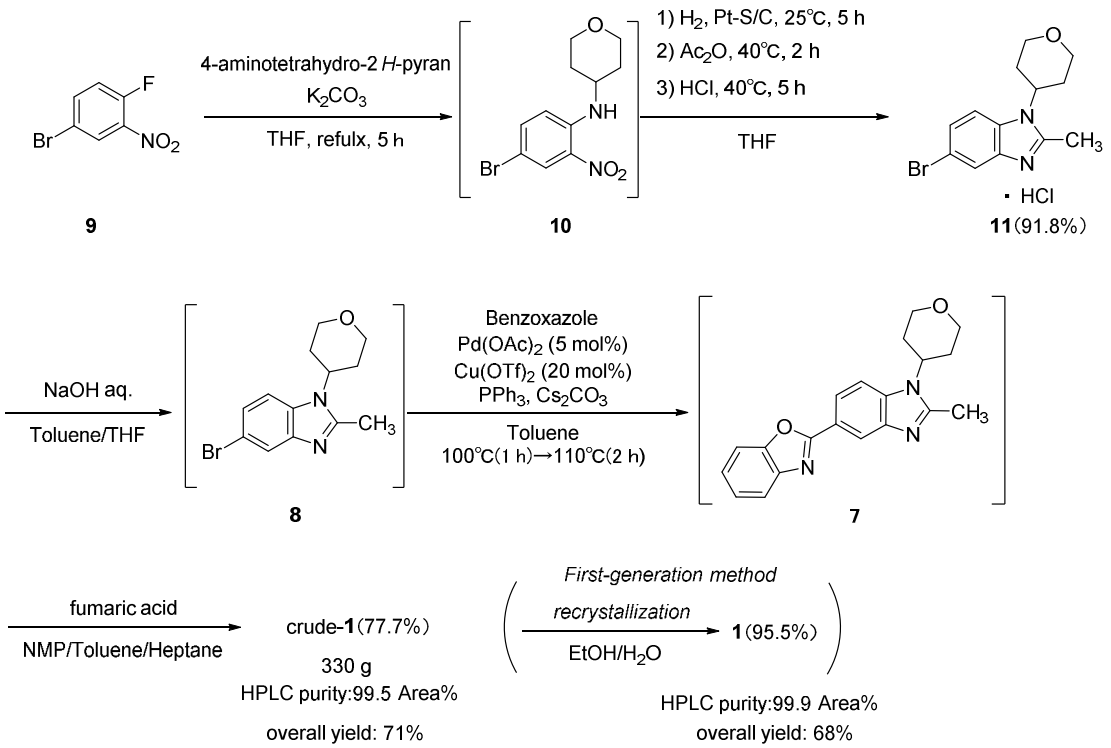


PEPPI - IPr

Lastly, the efficient telescoping synthesis of **11** was also studied (Scheme 5). The initial approach to **11** required the isolation of intermediate **10** to remove triethylamine hydrochloride. It could be omitted by switching the base from triethylamine to potassium carbonate which was easily removed by filtration, and then the solution of **10** was directly used in the next step. In the hydrogenation of the nitro group of **10**, the use of platinum, sulfide, on carbon instead of palladium on carbon controlled the produce of a debromo compound completely. Only THF was used as a solvent in the telescoping method of **11** from **9.**

In addition, the telescoping was also incorporated into the coupling reaction and salt formation. For this purpose, it was need to skip of isolation of **8** and **7**. When toluene/THF was used instead of methanol, **8** could be extracted into the organic layer. After evaporation of THF, the solution of **8** was used in the coupling reaction. After the work up of coupling reaction, **7** was treated with fumaric acid and **1** was directly crystallized in a manner similar to the first-generation method. Therefore, crude-**1** was synthesized in two-step from **9**. We demonstrated this second-generation route in multi-hundred grams scale manufacturing. In the demonstration, 330 g of **11** was synthesized from **9** in 71% over yield.

Scheme 5. Second-Generation Synthesis.



CONCLUSION

We have successfully developed two scalable synthetic methods of a PDE4 inhibitor **1**. Although first-generation synthesis based on the medicinal chemistry route was developed for early clinical trial use, the construction of a benzoxazole unit was not efficient and a mutagenic 2-aminophenol was used. In order to solve these problems, direct C-H arylation of benzoxazol was introduced to second-generation synthesis. It was found that the combination of $Pd(OAc)_2$-$Cu(OTf)_2$-PPh_3 is effective for C-H/C-Br coupling of benzoxazole with heteroaryl bromide. Furthermore, telescoping methods were adopted to improve the overall yield and operational efficiency, and two-step synthesis of **1** was accomplished in 71% over yield.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus spectrometer at 400 and 100.6 MHz, respectively. Chemical shifts (δ) are given in parts per million, and tetramethylsilane was used as the internal standard for spectra obtained in DMSO-*d*6 and D_2O. Mass spectra were recorded on JEOL JMS-T100GC "AccuTOF GC" mass spectrometer with EI resource. HPLC was performed on a Agilent 1100 system; XBridge C18 column (4.6 mm i.d. × 100 mm, 5 μ m); elutent: (a) 0.01 mol/L phosphate buffer (pH 6.8), (b) MeOH ; flow rate = 1.0 mL/min, Temperature: 40°C, UV detection at 220 nm, Gradient: (b/a) 10/90 (0 min) − 70/30 (0−30 min) −70/30 (30−35 min) −25/75 (35.1 min) −10/90 (35.1−40 min). The purity listed is determined by area %. Metal analysis was performed using ICP-MS analysis (PerkinElmer ELAN DRC II). All reactions were carried out under nitrogen or argon atmosphere unless otherwise mentioned. Reagents and solvents were used as obtained from commercial suppliers without further purification.

First-Generation Synthesis (Scheme 2).

3-nitro-4-((tetrahydro-2H-pyran-4-yl)amino)benzoic acid (3). To the solution of 4-fluoro-3-nitrobenzoic acid (15.97 kg, 86.27 mol) in water (95.8 kg) was added triethylamine (21.82 kg, 215.68 mol) and 4-aminotetrahydro-2H-pyran (9.60 kg, 94.90 mol) at 65−72°C. The reaction mixture was stirred at 70°C for 7 h and then allowed to cool to 47°C. Acetic acid (12.95 kg, 215.68 mol) was added to the mixture at 47−52°C and the resulting slurry was stirred at 50°C for 0.5 h. After cooling to 25°C over 2 h, the slurry was filtered. The wet cake was washed with water (24.0 kg) and isopropyl alcohol (24.0 kg), and dried at 50 °C under vacuum to a constant

weight to give **3** (21.82 kg, 94.9%) as a yellow solid. Spectral data are consistent with those of the literature.[1]

^{1}H NMR (400 MHz, DMSO-*d*6): δ 12.91 (br, 1H), 8.61 (d, *J* = 2.1 Hz, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 7.96 (d, *J* = 9.3, 2.1 Hz, 1H), 7.28 (d, *J* = 9.3 Hz, 1H), 3.46 (dt, *J* = 11.5, 2.1 Hz, 3H), 1.95 (dd, *J* = 2.4, 2.0 Hz, 2H), 1.67−1.58 (m, 2H).

^{13}C NMR (100 MHz, DMSO-*d*6): δ 165.81, 146.15, 136.04, 130.49, 128.53, 117.35, 114.96, 65.56, 48.29, 32.03.

2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-benzimidazole-5-carboxylic acid hydrochloride (5). To the solution of **3** (21.75 kg, 81.69 mol) in MeOH (108.8 kg) and THF (217.5 kg) was added 10% Pd/C (50% wet), and the mixture was stirred under hydrogen atmosphere (0.02 MPa) at 26 °C for 2 h. Acetic anhydride (9.17 kg, 89.86 mol) was added, and the mixture was stirred at 25−27 °C for 2 h. The mixture was filtered and washed with MeOH (10.88 kg). Aqueous HCl (35%, 8.51 kg, 81.69 mol) was added, and the mixture was stirred at 40°C for 4 h. The mixture was filtered and washed two times with MeOH (32.63 kg × 2), and dried at 50 °C under vacuum to a constant weight to give **5** (20.66 kg, 85.3%) as a yellow solid. Spectral data are consistent with those of the literature.[1]

^{1}H NMR (400 MHz, DMSO-*d*6): δ 8.27 (d, *J* = 1.3 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.05 (d, *J* = 8.8, 1.3 Hz, 1H), 4.86 (m, 1H), 4.06 (dd, *J* = 11.4, 4.2 Hz, 2H), 3.56 (t, *J* = 11.4, 2H), 2.94 (s, 3H), 2.42 (m, 2H), 1.99 (dd, *J* = 12.4, 2.6 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-*d*6): δ 166.49, 153.61, 133.32, 131.59, 127.56, 125.69, 115.83, 114.13, 66.13, 54.35, 30.00, 12.89.

N-(2-hydroxyphenyl)-2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-benzoimidazole-5-carboxamide (6). To the solution of **5** (18.07 kg, 60.89 mol) in toluene (306.0 kg) and DMF (8.87 kg) was added $SOCl_2$ (14.48 kg, 121.71 mol) at 75 °C. The reaction mixture was stirred at 75 °C for 7 h and then allowed to cool to 45°C. Toluene (108.0 kg × 2) was added to the mixture and concentrated below 50 °C until the amount of distillate was 108.0 kg. The mixture was cooling to 25 °C and the solution of 2-aminophenol (7.28 kg, 66.71 mol) in pyridine (10.57 kg, 133.62 mol) and NMP (90.1 kg) was added to the mixture, and was stirred at 27°C for 24 h. Aqueous NaOH (24%, 22.26kg, 133.56 mol) was added to the mixture at 27−31 °C over 1h and warmed up to 50°C. The water (180.0 kg) was added to the mixture at 51−53 °C over 1 h, and the slurry was stirred at 50 °C for 1 h and was cooling to 25 °C over 1.5 h. After stirring at 25 °C for 19 h, the slurry was filtered. The wet cake was washed with the mixture of NMP (9.00 kg) and water (18.0 kg), and acetone (27.0 kg × 2), and dried at 48 °C under vacuum to a constant weight to give **6** (19.78 kg, 92.5%) as a gray solid. Spectral data are consistent with those of the literature.[1]

^{1}H NMR (400 MHz, DMSO-*d*6): δ 9.76 (s, 1H), 9.54 (s, 1H), 8.20 (d, *J* = 1.4 Hz, 1H), 7.82 (dd, *J* = 8.6, 7.2 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.06−7.01 (m, 1H), 6.93 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.84 (td, *J* = 7.6, 1.4 Hz, 1H), 4.67−4.60 (m, 1H), 4.05 (dd, *J* = 7.6, 11.3, 4.3 Hz, 2H), 3.57 (dd, *J* = 11.3, 10 Hz, 2H), 2.65 (s, 3H), 2.45−2.35 (m, 2H), 1.88−1.84 (m, 2H).

^{13}C NMR (100 MHz, DMSO-*d*6): δ 165.73, 153.52, 149.07, 142.45, 135.97, 127.22, 126.28, 125.40, 123.76, 121.20, 119.08, 118.12, 116.16, 111.33, 66.51, 52.60, 30.68, 14.65.

2-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-benzimidazol-5-yl]-1,3-benzoxazole hemifumarate (1). To the solution of **6** (16.50 kg, 46.96 mol) in NMP (49.4 kg) and Toluene (25.1 kg) and DMF was added methanesulfonic acid (22.56 kg, 234.78 mol) at 23−56 °C. The mixture was heated to 125−129 °C and stirred for 8h under azeotropic dehydration. The mixture was cooled to 25°C, and toluene (256.0 kg) and aqueous NaOH (24%, 46.96 kg, 281.76 mol) was added. The aqueous layer was removed and the organic layer was washed two times with 20% aqueous NaCl (65.8 kg × 2). The organic layer was concentrated under reduced pressure bellow 50 °C to distill off 78.8 kg. Residue was adjusted to ca. 231.0 kg with additional toluene (1.2 kg) and heated to 69°C. Fumaric acid (0.16 kg, 1.41 mol) in NMP (1.7 kg) and seed crystal (17g) was added and stirred for 0.5 h. Additional fumaric acid (3.11 kg, 26.76 mol) in NMP (31.3 kg) was added dropwise over 0.5 h at 69°C and stirred for 0.5 h. Heptane (100.4 kg) was added dropwise over 0.5 h and stirred for 0.5h. The slurry was cooled to -1 °C over 11 h and filtered. The wet cake was washed two times with acetone (16.5 kg × 2), and dried at 48 °C under vacuum to a constant weight to give crude-**1** (15.36 kg, 83.6%, HPLC area 99.9%) as a pale brown solid.

The solution of crude-**16** (15.14 kg, 38.68 mol) in EtOH (230.6 kg) and water (57.6 kg) was filtered at 78 °C, and washed with the mixture of EtOH (12.13 kg) and water (3.03 kg). Filtrate was concentrated bellow 80 °C to distill off 91.3 kg and water (106.1 kg) was added. After stirring at 75−82°C for 1 h, the solution was cooled to 65°C and seed crystal (15g) was added and stirred at 60−62°C for 1 h. Water (197.2 kg) was added dropwise over 1 h at 58−50°C and stirred for 0.5 h. The slurry was cooled to 3 °C over 6.5 h and filtered. The wet cake was washed two times with acetone (15.2 kg × 2), and dried at 48 °C under vacuum to a constant weight to give **1** (14.1 kg, 93.1% , HPLC area >99.9%) as a pale brown solid. Spectral data are consistent

with those of the literature.[1]

^{1}H NMR (400 MHz, DMSO-*d*6): δ 13.1 (br, 1H), 8.33 (d, *J* = 1.5 HZ, 1H), 8.06 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.89 (d, *J* = 0.8 Hz, 1H), 7.82−7.76 (m, 2H), 7.43−7.38 (m, 2H), 6.64 (s, 1H), 4.71−4.62 (m, 1H), 4.06 (dd, *J* = 11.4, 4.3 Hz, 2H), 3.58 (dd, *J* = 11.7, 11.4 Hz, 2H), 2.67 (s, 3H), 2.47−2.36 (m, 2H) , 1.90−1.86 (m, 2H).

^{13}C NMR (100 MHz, DMSO-*d*6): δ 165.92, 163.26, 153.94, 150.20, 142.94, 141.75, 136.21, 133.93, 124.94, 124.67, 120.89, 119.40, 117.70, 112.44, 110.72, 66.50, 52.67, 30.70, 14.62.

Second-Generation Synthesis (Scheme 5).

5-bromo-2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-benzimidazole hydrochloride (11). The reaction of 4-bromo-1-fluoro-2-nitrobenzene (**9**) with 4-aminotetrahydro-*2H*-pyran and hydrogenation process of **10** was carried out in two batches at the same scale. To the solution of K_2CO_3 (109.3 g, 0.79 mol) and 4-aminotetrahydro-*2H*-pyran (73.3 g, 0.73 mol) in THF (507.5 kg) was added **9** (145.0 g, 0.66 mol) in THF (73.0 g) at 63−66 °C over 0.5 h. After stirring under reflux for 5h, the mixture cooled to room temperature, and THF (290.0 g) and 3% Pt-S/C (14.5 g) were added. The mixture was stirred under hydrogen atmosphere at 25 °C for 5 h and THF (290.0 g) was added. The mixture was filtered and washed two times with THF (290.0 g × 2). After filtrates (two batches) were combined into one batch, THF (870.0 g) was added at room temperature and heated to 40 °C. Acetic anhydride (67.29 g, 0.66 mol) was added dropwise over 0.5 h and seed crystal (1.5g) was added and stirred at 42°C for 20 min. Additional acetic anhydride (134.6 g, 1.32 mol) was added dropwise over 1 h and stirred for 3.5 h. Aqueous HCl (35%, 164.1 g, 1.58 mol) was added dropwise over 0.5 h at 40°C and the mixture was stirred for

5 h. After cooling to 0 °C, the mixture was filtered and washed two times with acetone (435.0 g × 2) , and dried at 40 °C under vacuum to a constant weight to give **11** (401.3 g, 91.8%) as a white solid.

^{1}H NMR (400 MHz, D_2O): δ 7.84 (d, *J* = 1.8 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.60 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.86−4.80 (m, 1H), 4.14 (dd, *J* = 11.8, 4.7 Hz, 2H), 3.65 (td, *J* = 12.1, 1.9 Hz, 2H), 2.55−2.45 (m, 2H), 2.01−1.96 (m, 2H).

^{13}C NMR (100 MHz, D_2O): δ 151.60, 131.49, 129.54, 128.59, 118.54, 117.00, 115.46, 66.71, 54.69, 29.68, 11.97.

HRMS (EI) exact mass calcd for $C_{13}H_{15}BrN_2O$ (M − HCl) 294.0368, found: 294.03711.

2-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-benzimidazol-5-yl]-1,3-benzoxazole hemifumarate (1). Spectral data are consistent with those of the first generation synthesis. To the solution of **11** (359.5 g, 1.08 mol) in Toluene (3200 g), THF (3200 g), and water (640.0 g) was added aqueous NaOH (27%, 176.7 g, 1.19 mol) and heated to 37 °C. The aqueous layer was removed and the organic layer was washed with water (960.0 g). After removing the aqueous layer, the organic layer was concentrated under reduced pressure bellow 50 °C to distill off 4302 g. Toluene (4554 g) was added and the organic layer was concentrated to distill off 4942 g. Additional toluene (4604 g) was added and the organic layer was concentrated to distill off 4877 g. After analyzing water and THF content in toluene solution (173 ppm and 0.01%, respectively), the solution was adjusted to 2528 g with additional toluene (388.0 g). To the solution of **8** was added PPh_3 (35.5 g, 0.136 mol), Cs_2CO_3 (706.4 g, 2.168 mol), $Cu(OTf)_2$ (706.4 g, 0.217 mol), $Pd(OAc)_2$ (12.2 g, 0.054 mol), benzoxazole (258.3 g, 2.168 mol) and toluene (32.0 g) under nitrogen flow. Additional nitrogen substitution was performed with vacuum deairing (three

times). After analyzing oxygen concentration (0.1%), the mixture was heated to 100 °C and stirred for 1 h. After additional heating to 110 °C, the mixture was stirred for 2 h. Toluene (4800 g) was added, and the mixture was filtered at 80 °C and washed two times with toluene (480.0 g × 2). Activated carbon (32.0 g) was added ant stirred for 1 h. ISOLUTE® Si-Thiol (32.0 g) was added as metal scavenger and stirred for 3 h. The mixture was filtered at 80 °C and washed two times with toluene (160.0 g × 2). The filtrate was concentrated to distill off 2129 g was adjusted to 6080 g with additional toluene (187.0 g). PPh_3 (14.2 g, 0.054 mol) was added at 80 °C ant stirred for 0.5 h. Fumaric acid (3.8 g, 0.033 mol) in NMP (32.0 g) and seed crystal (0.35 g) was added and stirred for 0.5 h. Additional fumaric acid (71.7 g, 0.618 mol) in NMP (608 g) was added dropwise over 1.5 h at 80 °C and stirred for 0.5 h. Heptane (1440 g) was added dropwise over 0.5 h and stirred for 0.5h. The slurry was cooled to 0 °C over 5 h and stirring was performed for another 14 h. The slurry was filtered and the wet cake was washed two times with acetone (640.0 g × 2), and dried at 50 °C under vacuum to a constant weight to give crude-**1** (329.8 g, 77.7%, HPLC area 99.5%) as a pale brown solid. The content of Pd and Cu was 18 and 0.8 ppm, respectively.

To the solution of crude-**16** (20.0 g, 51.00 mmol) in EtOH (304.0 g) and water (76.0 g) was added ISOLUTE® Si-Thiol (0.2 g) at 78 °C. After stirring 2 h, the mixture was filtered and washed with the mixture of Ethanol (16.0 g) and water (4.0 g). Filtrate was concentrated under reduced pressure to distill off 120.0 g and water (140.0 g) was added. After heating to 78 °C, the solution was cooled to 59°C and seed crystal (2.0 g) was added and stirred for 1.5 h. Water (260.0 g) was added dropwise over 1 h at 59 °C and cooled to 2 °C over 4 h. Stirring was performed for another 15 h and filtered. The wet cake was washed two times with acetone (20.0 g × 2), and dried at 40 °C under vacuum to a constant weight to give **1** (19.1 kg, 95.5% , HPLC

area 99.9%) as a white to pale yellow solid. The content of Pd and Cu was 0.3 and 0.1 ppm, respectively.

ASSOCIATED CONTENT

Supporting Information

NMR spectra for compounds (PDF)

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Notes

The authors declare no competing financial interest.

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