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The Synthesis of a Novel Inhibitor of B-Raf Kinase

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Abstract:

A scaleable synthetic route to [4,7′]bis-isoquinolinyl-1-yl-(2-*tert*-butyl-pyrimidine-5-yl)amine (1), an inhibitor of B-Raf kinase is described. The key step in the synthesis is the Pd-catalyzed Negishi coupling of 4-bromo-1-chloroisoquinoline with trifluoromethanesulfonic acid isoquinoline-7-yl ester to yield 1-chloro-[4,7′]bis-isoquinolinyl. This intermediate is transformed to the desired drug substance in one additional step, by reaction with 2-*tert*-butyl-5-aminopyrimidine in the presence of NaH. A special focus was put on the finally successful removal of traces of Zn and Pd in the drug substance, which came from the Negishi coupling.

Introduction

An encouraging approach to the treatment of cancer involves the disruption of kinase activity and signal transduction pathways.[1] These signaling pathways transmit a number of signals from the cell surface to the nucleus, which can lead to the survival and proliferation of cancer cells. In fact, the deregulation of signaling pathways has been demonstrated to cause cancers, most dramatically in the case of the fusion kinase bcr-abl, which is now treated with the kinase inhibitor Gleevec.[2]

The signal transduction pathway in which Raf kinase operates has long been implicated in oncogenesis and is critical for proliferation, survival, and angiogenesis in various cancer models.[3] In addition, recent data indicate that several cancers, most notably melanoma, have activating mutations in the B-Raf gene, providing further evidence of the importance of this pathway in human cancer.[4]

Based on the encouraging epidemiology, a program to identify inhibitors of B-Raf kinase was initiated. Towards that end aryl-isoquinoline structures **A**, e.g. [4,7′]bis-isoquinolinyl-1-yl-(2-*tert*-butyl-pyrimidine-5-yl)amine (**1**) and [4,7′]bis-isoquinolinyl-1-yl-(4-*tert*-butyl-phenyl)amine (**2**) (Figure 1), were identified as effective inhibitors of B-Raf kinase, and compound **1** was ultimately promoted for development as a drug candidate for the treatment of melanoma.

Synthesis Evaluation

Two general synthetic approaches to the biaryl scaffold of **A** (Figure 1) were initially evaluated as part of the medicinal chemistry effort. The first route utilized a Suzuki disconnection while the second utilized the complementary Negishi cross-coupling reaction.[5] These two synthetic schemes provided a considerable degree of flexibility for generating analogues, the former allowing facile modification of the "southern" portion of the molecule while the later allowed modification of the "northern" aniline portion of the molecule. Both synthetic routes were used in the course of analogue synthesis and evaluation, as exemplified in Scheme 1 by the synthesis of **2**.

The Suzuki synthetic scheme (Scheme 1) began with 2-chloroisoquinoline (**3**), which was readily coupled to 4-*tert*-butyl aniline (**4**) in 79% yield under acidic conditions. Bromination of **5** was effected most efficiently by treatment with phenyltrimethylammonium tribromide, yielding the desired bromide **6** in 82% yield. Lithium−halogen exchange, trapping with tri-isopropyl borate, and subsequent hydrolysis yielded boronic acid **7** in 73% yield. The boronic acid was then coupled with triflate **8** under Suzuki conditions to obtain the desired coupled product **2** in 61% yield.

The second synthetic approach, utilizing a key Negishi coupling, is outlined in Scheme 2. The central aryl building block 4-bromo-1-chloroisoquinoline (**9**) was regioselectively metalated with *n*-BuLi, transmetalated with $ZnBr_2$, and coupled with **8** in the presence of catalytic amounts of Pd-$[PPh_3]_4$ to yield biaryl compound **10** in 52% yield. The synthesis was completed by coupling the chloride **10** to 4-*tert*-butyl aniline (**4**) in an acid-promoted reaction to afford **2** in 65% yield. The synthetic methodology developed for the synthesis of **2** was then evaluated for the technical synthesis of **1** in development.

Synthesis of 1 on Technical Scale. The Negishi disconnection was chosen for the first technical synthesis of **1**, since we have previously found the Negishi cross-coupling to be rapid and straightforward, and thus particularly suitable for

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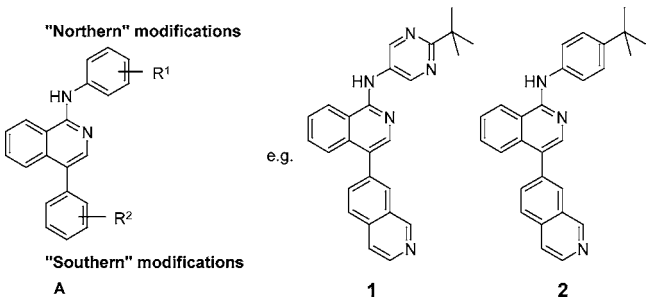

Figure 1.

time-critical preparations. Additionally, the "northern" aminopyrimidine building block needed for the synthesis of **1** was not readily available, and therefore late introduction of this fragment was preferable. Precedence from the medicinal chemistry group, as well as the literature, provided further support for the viability of this disconnection.[6]

Building Blocks 8, 9, and 14. Three aryl building blocks, trifluoromethanesulfonic acid isoquinolin-7-yl ester **8**, 4-bromo-1-chloroisoquinoline (**9**)**,** and 2-*tert*-butyl-5-aminopyrimidine (**14**) were required for the assembly of **1**. These compounds were prepared in-house since no commercial sources for immediate supply of these building blocks could be identified.

The first scale-up of the "southern" building block, triflate **8,** proved challenging (Scheme 3). Initial reaction conditions for this transformation treated the commercially available 7-hydroxyisoquinoline (**11**) with trifluoromethansulfonic acid anhydride in EtOAc/pyridine at 0 °C. The amount of base and stringent control of temperature during reagent addition were found to be crucial to subdue the arylsulfonating side reactions and obtain an acceptable conversion to **8**. After aqueous workup, the crude product was purified by high vacuum distillation on a thin film evaporator. The first run on technical scale yielded the triflate **8** in a disappointing 48% yield, although in good purity (>98%).

The loss of material was found to be the incompatibility of **8** with the ethylene glycol ether lubricant used in the thin film distillation to fluidize solid pyridinium salt residues. Changing the reaction solvent from EtOAc to *tert*-butyl methyl ether allowed for more efficient removal of the pyridinium salts during the hydrolytic workup with the benefit that the amount of lubricant as well as the distillation temperature now could be significantly lowered. These simple modifications raised the yield to an acceptable 75−85%.

The bifunctional isoquinoline **9** was readily prepared from the commercially available 4-bromoisoquinoline (**12**) in two steps (Scheme 4). The isoquinoline **12** was oxidized to the corresponding *N*-oxide **13** with 30% aqueous H_2O_2 in the presence of Na_2WO_4 as a catalyst.[7] However, the conversion of **12** to **13** was incomplete at ca. 60% and could not be pushed further to completion by addition of further reagent or catalyst. This yield was acceptable since **13** could be isolated conveniently in a simple crystallization. The *N*-oxide **13** was then subjected to Meisenheimer conditions by treatment with $POCl_3$ in DMF/toluene[8] to give the 1-chloro-isomer **9** regioselectively in good purity and an acceptable yield.

The "northern" building block **14**, was obtained in three steps from commercially available glycine hydrochloride (**15**), via the vinamidinium hexafluorophosphate salt **16** (Scheme 5a). Compound **16** exhibited no undesirable thermal and shock-sensitive properties, in contrast to the corresponding perchlorate salt.[9] In practice, reaction of glycine hydrochloride with the formylating agent prepared from DMF and $POCl_3$, followed by precipitation with HPF_6, afforded a salt mixture of dihexafluorophosphate and monohexafluorophosphate salts. Treatment of the mixture of salts with Et_3N in ethanol furnished the pure vinamidinium hexafluorophosphate salt **16** in high yield.[10] Pyrimidine **19** was obtained from **16** upon base-catalyzed condensation with *tert*-butylcarbamidine hydrochloride (**18**) in moderate yield.[11] Finally, hydrolysis of **19** afforded the desired 2- *tert*-butyl-5-aminopyrimidine (**14**) in good yield.

Due to the limited availability of the starting material **18** and the use of highly corrosive HPF_6 another synthetic approach to compound **14** was investigated, employing the commercially available 2-bromo-5-*tert*-butylpyrimidine **(20)**. Bromopyrimidine **20** was transformed in a Buchwald amination with benzophenone imine[12,13] into intermediate **21**, which was readily hydrolyzed to the desired intermediate **14** (Scheme 5b).

The Buchwald amination reaction was carried out in xylene instead of the typical toluene, since the reaction at 130 °C was significantly faster without compromising thermal safety. Best results were obtained with *tert*-BuONa as base, in the presence of BINAP (racemic) as ligand. Additionally, it was demonstrated that the expensive $Pd_2(dba)_3$ can be replaced with $Pd(OAc)_2$; however, this finding came too late to be implemented into the technical scale-up campaign. The imine adduct **21** was not isolated but was directly hydrolyzed with a substoichiometric amount of aqueous HCl in THF. For workup with additional HCl the water-soluble hydrochloride of **14** was produced. This allowed the direct extractive removal of the benzophenone byproduct that otherwise disturbed the crystallization of **14**. On large scale**,** however**,** an additional purification operation became necessary since **14** proved to be not very stable under the acidic conditions. Significant amounts of the hydrolysis product **22** were formed and had to be removed by an additional washing operation with 2 M NaOH**.** The desired

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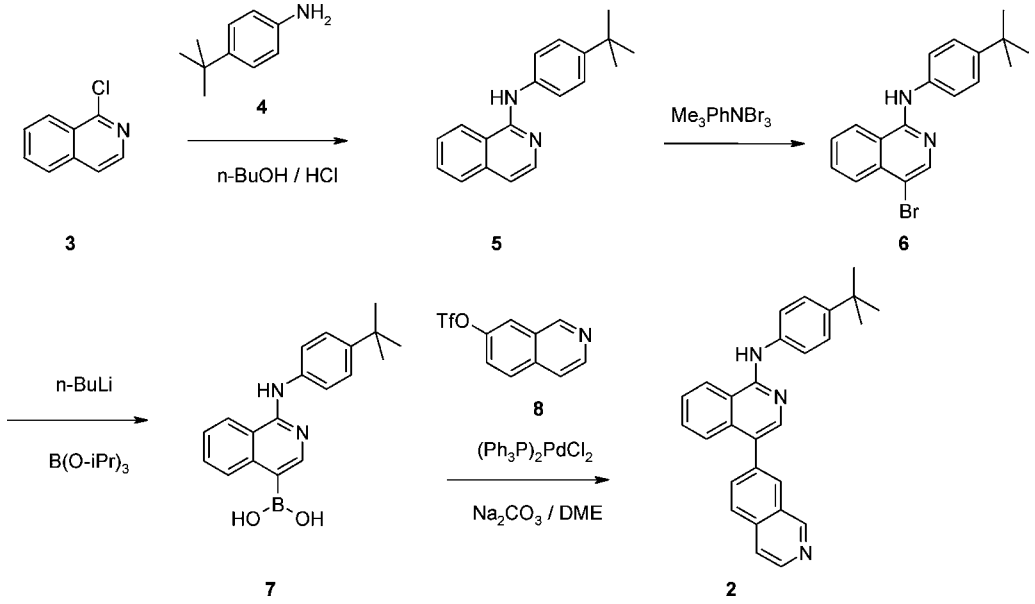
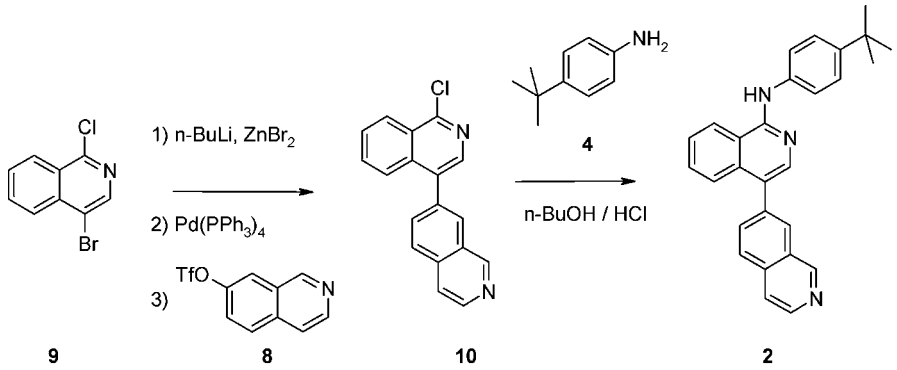
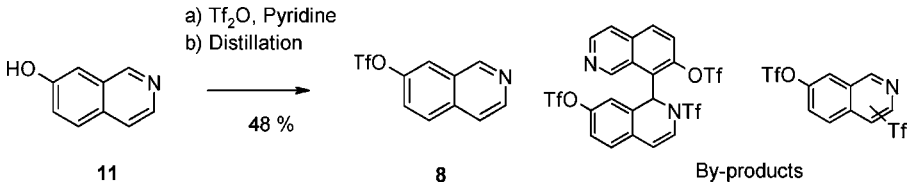
Scheme 1. **Synthesis of 2 via the Suzuki approach**



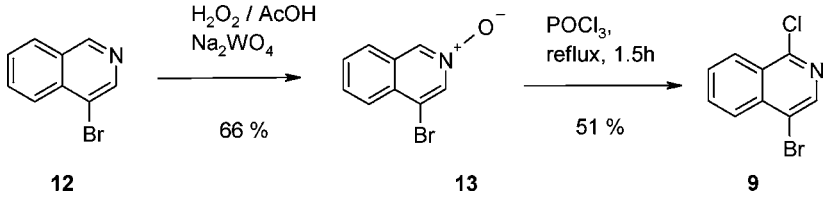
Scheme 2. **Synthesis of 2 via Negishi cross-coupling**



Scheme 3. **Synthesis of "southern" building block 8 and structures of observed byproducts**



Scheme 4. **Synthesis of "central" isochinoline 9**

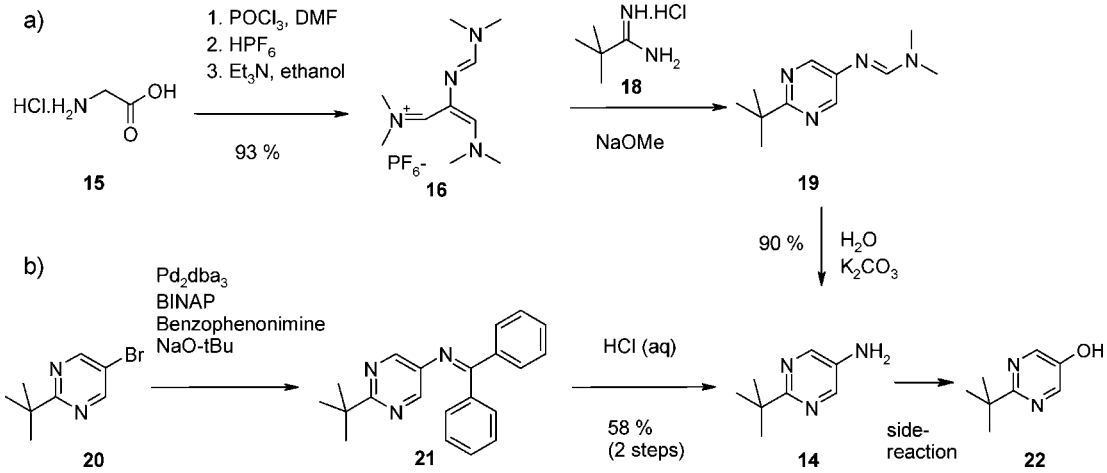


product **14** was finally obtained after a crystallization from *tert*-butyl methyl ether/heptane in 58% overall yield. In further experiments with protocols using a lower concentration of 2 M HCl in THF (5% instead of 10%) the hydrolysis of **21** could be completed in 2−3 h without hydrolysis to **22**, and the crystallized yield of **14** thus could be improved up to 87%.

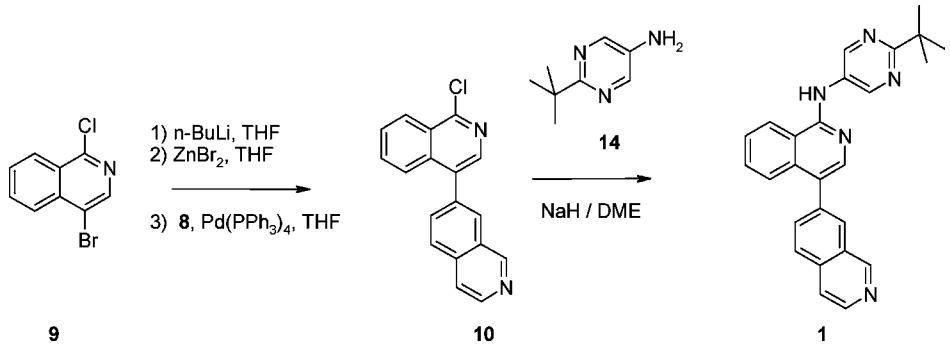
Negishi Coupling to 10. The key Negishi cross-coupling reaction of **8** and **9** (Scheme 6) proceeded uneventfully in the presence of 1 mol equiv $ZnBr_2$ and <1 mol % of Pd-$(PPh_3)_4$ catalyst in THF to provide crude **10**.

The crude product **10** (79% yield), however, contained substantial amounts of complex-bound Zn (7−14 wt % Zn), and was insoluble in most solvents, except DMF, DMA, or pyridine. The Zn in **10** affected the final coupling to intermediate **14**, so the material could not be taken on crude. After several recrystallization attempts (from DMA/water or DMF/water mixtures) that did not significantly reduce the

Scheme 5. **Synthesis of the "northern" aminopyrimidine 14 (a) via vinamidinium chemistry and (b) Buchwald amination**



Scheme 6. **Negishi route to 1**



zinc content, the complex-bound zinc finally could be removed simply by suspending **10** in a solution of ethylenediamine in H_2O/THF. That purification profited from the excellent water solubility of the zinc ethylenediamine complex while THF moderated the solubility of **10** and eased its recrystallisation. The zinc content of the first technical batch was thus decreased to 0.45% with a chemical yield of 52% (based on **9**). In later experiments the Zn level was further lowered to <0.05% at this stage by optimizing the water/THF ratio (4:1), the temperature (40 °C), and the volume of water used for washing the filter cake. The wash had the further benefit of removing the excess ethylenediamine, avoiding side reactions in the final coupling step. After removal of the zinc impurities, **10** was readily soluble in THF.

Given the key nature of the cross coupling reaction in the process sequence, the reaction was further evaluated in parallel to the scale-up to understand the process robustness. We first focused on the metal−halogen exchange of **9**. In THF with 1 equivalent n-BuLi at ca. −70 °C, the bromo-lithium exchange of **9** occurred rapidly, however even in the presence of 1.5 equivalent n-BuLi the exchange reaction was not complete and typically 2−5% remained unreacted after quenching a sample with H_2O. This was tentatively attributed to the slow octane formation by the consumption of *n*-BuLi with the *n*-butyl bromide from the metal halogen exchange reaction.[14] As expected, there was no observable chloro/lithium exchange at C-1. The C-4 lithiated species of **9** was stable in THF solution over at least 3 h at −75 °C; however, it began to decompose above ca. −50 °C. It therefore became clear that efficient temperature control was crucial for the lithium/zinc transmetalation reaction. Additionally, since $ZnBr_2$ exothermally forms a 1:1 complex with THF, addition of $ZnBr_2$ as a preformed THF solution was favored over addition as a solid. In the absence of electrophiles the C-4 zincate intermediate of **9** was quite stable, but began to decompose above 30 °C. On the basis of our previous experience with the Negishi coupling on scale, **8** was first premixed with $Pd[PPh_3]_4$ in THF to initiate the oxidative addition process and then added to the aryl zincate intermediate.[14] The cross-coupling reaction thus proceeded rapidly at 0−5 °C, and all aryl zinc precursors in the reaction were consumed in ca. 1−3 h.

The quality and amount of the $Pd[PPh_3]_4$ catalyst had the strongest effect on the cross-coupling rate. The pronounced sensitivity of commercial amorphous $Pd[PPh_3]_4$ catalyst to air, humidity, and light was identified as a major factor for incomplete reaction conversion at catalyst loading below 1 mol %. In particularly, older lots of catalyst (as indicated by a red-brownish or yellowish-grey color) were less active, and up to 15 mol % catalyst were required to achieve reasonable conversion.[15] The increasing catalyst load, however, resulted in high residual palladium in the product; thus only new catalyst, stored under Argon in airtight containers, was used. Finally, yields up to 65% of **10** were obtained

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after ethylenediamine treatment (ca. 200−1000 ppm Zn; ca. 20−50 ppm Pd).

The aminopyrimidine **14** was deprotonated with excess NaH in DME, and reacted with **10** to obtain drug substance **1** (Scheme 6). The acid-catalyzed protocol that had been useful for the preparation of **2** (Scheme 2) required longer reaction times on scale and led to unacceptable levels of impurities. The solvent for the NaH-promoted coupling was switched from THF in the medicinal chemistry protocol to DME, eliminating the need for an autoclave reaction.

Due to the strong hydrogen evolution occurring during the final coupling step, two modes of reagent addition were evaluated. In the first set of conditions, solid **10** was charged to a reactor containing aminopyrimidine **14** and NaH in DME, and the temperature was gradually raised to reflux. Alternatively, a cold slurry of NaH in DME was charged in portions directly to a 70−90 °C solution of **14** and **10**. In both cases conversion to **1** was rapid, but with the former conditions there was a considerable accumulation of sodium hydride that occasionally led to erratic liberation of hydrogen when heating the reaction mixture to reflux. The later addition mode required more equipment, but was deemed more suitable for larger-scale batches since it was almost addition controlled, and hydrogen evolution occurred more regularly at approximately the rate the base was added.

The purification of crude drug substance **1** was initially complicated due to the presence of unreacted reaction partners, side products, and the mineral oil from the NaH. The drug substance was purified by column chromatography; a dimesylate salt was generated and then further purified by crystallization. Finally, the free base was liberated to yield the drug substance in an overall yield of 34%. It was later observed that crude **1** can be crystallized directly from toluene, and thus the workup was considerably simplified. The reaction mixture was diluted with toluene and washed with an aqueous solution of *N*-acetylcysteine, and then the lower-boiling solvent DME was removed from the toluene solution by distillation to induce crystallization of the product. The crude product occasionally contained Pd (<10−30 ppm) and Zn traces (<10 ppm). These impurities could be removed by recrystallization from ethanol/H_2O in the presence of *N*-acetylcysteine,[16] or ethylenediamine tetraacetic acid disodiumsalt when required. The purified product **1** was isolated in 85% yield, exhibited an excellent purity of 99.4 area % in HPLC and contained <1 ppm Pd and Zn.

In conclusion we have demonstrated the feasibility of the chosen synthesis concept to **1** by exploiting the Negishi cross-coupling reaction that on technical scale rarely is used. The presented work from the time-critical early development phase may be seen as an example that also with a known chemical methodology the scale-up and particularly the workup may lead into special challenges but that these first scale-up experiences are very useful for guiding the further process optimizations. Particularly the answer to the encountered severe problem with the used metals carried over into the products may be of more general interest. For us the findings around the Zn removal with ethylenediamine and the implementation of the previously known acetyl cysteine-based removal of Pd impurities proved to be most crucial for meeting the quality requirements of the drug substance and finally the project's tight timelines.

Experimental Section

The starting materials, solvents, and reagents were of technical grade, available in bulk. Butyllithium hexane solution was obtained from Chemetall. All reactions were carried out under an atmosphere of nitrogen. The procedures described are not fully optimized and reflect the early development stage of the project. Typically, the protocol for the largest scale is provided. The NMR spectra were measured on a Bruker Avance 400 spectrometer. The chemical shifts are given in δ (ppm). HPLC purity is given as area normalization.

(4-*tert*-Butyl-phenyl)isoquinolin-1-yl-amine (5). A suspension of 2-chloroisoquinoline **(3)** (15.01 g; 91.74 mmol) and 4-*tert*-butyl aniline **(4)** (14.94 g, 100.1 mmol) in *n*-butanol (100 mL) and concentrated HCl (9.5 mL; 110.2 mmol) was heated at 70 °C for 3 h. The *n*-butanol was evaporated in vacuo, and the resulting syrupy mixture was mixed with pentane, forming a white solid which was filtered and dried. The solid was redissolved in EtOAc and dichloromethane and made slightly basic with sodium bicarbonate. The organic layer was filtered, dried, and concentrated to afford **5** as a white solid (20 g; 78.9%).

^{1}H NMR (DMSO): δ 1.32 (s, 9H), 7.37 (d, 2H), 7.57 (m, 4H), 7.72 (d, 1H), 7.90 (d, 3H), 8.08 (d, 1H). MS: 277.2 M + 1 (100%).

(4-Bromoisoquinolin-1-yl)-(4-*tert*-butyl-phenyl)amine (6). To a 0 °C solution of (4- *tert*-Butyl-phenyl)isoquinolin-1-yl-amine **(5)** (18.7 g, 67.7 mmol) in THF (100 mL) was added phenyltrimethylammonium tribromide (25.12 g, 66.47 mmol) as a solution in THF (200 mL) over 2 h. The reaction was allowed to rise to room temperature overnight, and then was poured into hexane (2 L) with stirring, forming a yellow solid. The solid was filtered, dried, and redissolved in dichloromethane. The solution was washed with saturated sodium bicarbonate solution (2 × 250 mL), followed by water (250 mL), dried, concentrated to a slurry that was mixed with hexane, filtered, and dried, affording **6** (19.8 g; 82.3%) as an off-yellow solid.

^{1}H NMR (DMSO): δ 1.33 (s, 9H), 7.07 (bs, 1H), 7.38 (d, 2H), 7.56 (m, 3H), 7.73 (t, 1H), 8.08 (d, 1H), 8.23 (s, 1H). MS: 355 M^+ (100%).

(4-Boronoic Acid Isoquinolin-1-yl)-(4-*tert*-butylphenyl)-amine (7). To a −74 °C solution of **6** (10.3 g, 29.0 mmol) in anhydrous THF (130 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 30.0 mL, 75.0 mmol) over 1 h. Triisopropyl borate (8.0 mL, 34.7 mmol) was added dropwise, and the mixture was stirred at −74 °C for 4.5 h, then warmed to room temperature, and quenched with water (20 mL). The THF was removed under vacuum, and the solution was

(15) Surprisingly, highest catalyst activities were found for an old, crystalline "Pd[PPh_3]$_4$" lot whose brilliant orange color indicated some air-oxidation and that according to elemental analysis contained one equivalent of triphenylphosphine oxide. This crystalline form, however, is no longer commercially available. Other more stable Pd- or Ni catalysts and ligands known to be useful for the Negishi coupling were not tested at this stage of development.

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acidified with 1 N HCl (aqueous) to produce a white solid **7**, which was collected by filtration and dried (6.74 g, 73%).

^{1}H NMR (DMSO-d_6): δ 1.36 (s, 9H), 7.50 (d, 2H), 7.62 (d, 2H), 7.76 (s, 1H), 7.82 (t, 1H), 8.01 (t, 1H), 8.61 (broad s), 8.72 (d, 1H), 8.95 (d, 1H), 11.59 (s, 1H). MS 321.3 *m*/*z* (M + H).

[4,7′]Bis-isoquinolinyl-1-yl-(4-*tert*-butyl-phenyl)-amine (2). a) To a solution of (4- *tert*-butyl-aniline)-isoquinolin-1-yl boronic acid **(7)** (8.9 g, 27.8 mmol), isoquinolin-7-yl triflate **(8)** (7.0 g, 25.3 mmol), and dichlorobis(triphenylphosphine) palladium(II) (1.75 g, 2.5 mmol) in DMF (500 mL) was slowly added a solution of 1 M K_2CO_3 (65 mL, 65 mmol) at room temperature with vigorous stirring [some yellowish solid precipitated from the solution]. After stirring at 100 °C for 2 h, the black solution was concentrated to remove off most of DMF. The residue was diluted with CH_2Cl_2 (50 mL) and filtered through a short silica gel plug, then further purified by flash chromatography with CH_2Cl_2 95% and EtOAc 5% to give a light yellow solid (6.52 g). The product was further purified by reverse phase HPLC to yield pure product **2** (6.2 g, 60.9% yield) as free base.

(b) A suspension of 1-chloro-[4,7′]bis-isoquinolinyl **(10)** (5.0 g, 17.2 mmol), 4-*tert*-butylaniline **(4)** (4.0 mL, 1.5 equiv), and 4.0 M HCl/dioxane (6.45 mL/1.5 equiv) in EtOH (100 mL) was stirred for 20 h in a sealed tube at 80 °C. The reaction mixture was cooled and concentrated to a yellow oil. The oil was dissolved in EtOAc (100 mL) and neutralized with 3 N NaOH. The organic phase was separated, dried ($MgSO_4$), concentrated, and purified on silica gel chromatography (9:1 hexane/EtOAc and then 4:1 hexane/EtOAc). The product **2** was isolated as a yellow solid (4.5 g; 65%); mp 217−219 °C.

^{1}H NMR (DMSO-d_6) δ 1.31 (s, 9H), 7.37 (d, 2H), 7.73 (m, 2H), 7.80 (m, 2H), 7.92 (m, 2H), 8.04 (s, 1H), 8.09 (d, 1H), 8.24 (s, 1H), 8.57 (d, 1H), 8.67 (d, 1H), 9.31 (s, 1H), 9.40 (s, 1H). MS 404.21 *m*/*z* (M + H).

Trifluoromethanesulfonic Acid Isoquinolin-7-yl ester (8). To a suspension of 7-hydroxyisoquinoline **(11)** (11.7 kg, 80.6 mol) in EtOAc (157 L) and pyridine (31.9 kg, 403 mol) at 0 °C was added trifluormethansulfonic acid anhydride (25 kg, 88.6 mol) within 95 min, at such a rate that the temperature was maintained between 0 and 5 °C. The temperature was raised to 22 °C within 40 min and the batch stirred for 19 h. To the reaction mixture was added $NaHCO_3$ (8% (aq), 100 L), and the phases were separated. The organic phase was washed with $NaHCO_3$ (8% (aq), 100 L), and H_2O (100 L). The aqueous layers were re-extracted with EtOAc (100 L). The combined organic layers were dried over $MgSO_4$ (11 kg), filtered, and evaporated to dryness to yield crude product (27.3 kg). This crude product was distilled as a solution in 25 kg of Triton X over a thin film evaporator at <1mbar (120 °C), to yield **8** as an almost colorless oil (10.8 kg; 48.2% yield; HPLC > 98 area %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (dd, J = 2.5; 8.9; 1H), 7.70 (d, J = 5.9; 1H), 7.88 (d, J = 2.4; 1H), 7.92 (d, 9.0; 1H), 8.60 (d, J = 5.9; 1H), 9.29 (s, 1H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ (114.9; 117.4; 120.0; 122.5); 119.1; 120.1; 124.3; 128.4; 129.6; 134.7; 144.4; 147.4; 152.4. MS: 278 (M^+), 277, 144. Anal. Calcd for $C_{10}H_6F_3NO_3S$: C, 43.33; H, 2.18; N, 5.05. Found: C, 43.40; H, 2.42; N, 4.88.

4-Bromoisoquinoline-*N*-oxide (13). 4-Bromoisoquinoline **(12)** (7.2 kg, 34.6 mol) and Na_2WO_4·2 H_2O (360 g, 1.1 mol) were charged into a reactor. AcOH (72 L) and 30% H_2O_2 (8.64 L, 76 mol) were added. The reaction mixture was heated to 80 °C (external temperature) and stirred for 3 h at this temperature. The reaction was checked by HPLC (product/starting material, 60:24). Further H_2O_2 (720 mL, 6.4 mol) was added. The mixture was stirred for another 2 h (62:22 = product/starting material). Another portion H_2O_2 (720 mL, 6.4 mol) was added, and the reaction mixture was stirred at 80 °C (external temperature) for 15 h (63:19 = product: starting material). Further Na_2WO_4 (120 g, 0.364 mol)· 2 H_2O was added, followed by H_2O_2 (720 mL, 6.4 mol). After another 3 h the reaction was checked by HPLC again (64:19 = product/starting material) and another portion H_2O_2 (720 mL, 6.4 mol) was added. After 3 h further heating at 80 °C, the reaction was again checked by HPLC (67:20). A part of HOAc (55.5 L) was distilled off. Then at 60 °C H_2O (47 L) was added, followed by 30% NaOH (aq) (35 L). The mixture was seeded and stirred at 10 °C for 20 h. The suspension was filtered and washed with H_2O (24 L). The crude product was crystallized from toluene (60 L) to yield purified product **13** (4.45 kg; HPLC purity 98.5%). From the mother liquor a further 652 g of product (98.5% HPLC purity) could be isolated (total yield: 65.8%).

^{1}H NMR (d_6-DMSO, 400 MHz): δ 7.75−7.85 (m, 2H), 7.95−8.07 (m, 2H), 8.68 (s, 1H), 9.08 (s,1H). MS: 226 (M^+), 224 (M^+), 209, 207.

4-Bromo-1-chloroisoquinoline (9). The suspension of **13** (5.1 kg, 22.8 mol) in toluene (38 L) and DMF (13 L) was cooled to 5 °C. Phosphorus oxychloride (5.095 kg, 33.2 mol) was added within 1 h. After the addition was complete, the temperature was raised to 20 °C. After 1 h the reaction mixture was added to H_2O (55 L) at 45 °C. Then NaOH (30%, 13 L) was added, and the reaction mixture (pH = 7) was filtered and the filter residue washed with toluene (10 L). The layers were separated, and the H_2O phase was extracted with toluene (30 L). The combined organic layers were washed with brine (2 × 30 L), and the aqueous phase was reextracted with toluene (30 L). The toluene layer was dried over $MgSO_4$, filtered, and evaporated to dryness. Methanol (18 L) was added to the residue and then evaporated again to dryness. Then methanol (26 L) was added and the mixture heated to reflux. The mixture was cooled to 0 °C within 4−6 h, stirred over the weekend at 0 °C, filtered, and washed with methanol (2 L). This product was dried at 45 °C to yield **9** (2.846 kg; 51.5%; 98.5% HPLC purity).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72−7.75 (m, 1H), 7.84−7.88 (m, 1H), 8.16−8.18 (m, 1H), 8.32−8.34 (m, 1H), 8.46 (s, 1H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 118.6; 126.2; 126.5; 127.4; 129.0; 132.0; 135.8; 142.4; 150.6. MS: 246 (M^+), 244 (M^+), 242 (M^+). Anal. Calcd for C_9H_5NClBr: C, 44.58; H, 2.08; N, 5.78. Found: C, 44.74; H, 2.41; N, 5.71.

1-Chloro-[4,7′]bis-isoquinolinyl (10). A solution of **9** (7.05 kg, 29 mol) in THF (80.8 L) was cooled to − 70 °C.

Within 30 min *n*-BuLi (1.6 M in hexane; 13.37 kg, 30.6 mol) was added at such a rate that the temperature was maintained below − 70 °C. After the addition was complete, transfer lines were rinsed with THF (2.3 L). The reaction mixture was stirred for an additional 10 min, and then a solution of $ZnBr_2$ (6.5 kg, 28.9 mol) in THF (17.3 L) was added at such a rate to maintain temperature <−70 °C. The reaction mixture was stirred for another 10 min at −70 °C, and then the temperature was raised to 0 °C within 35 min. At ca. 0 °C a solution of **8** (7.62 kg, 27.5 mol) and $Pd(PPh_3)_4$ (0.46 kg, 0.4 mol) in THF (17.3 L) was added within 10 min. After rinsing with THF (3.4 L), the temperature was raised to 25 °C within 30 min, and the mixture stirred for 1 h at 25 °C. For hydrolysis NH_4Cl (10% in H_2O, 25 L) was slowly added, the layers were separated, and the organic phase was washed with NaCl (10% in H_2O, 2 × 25 L). The combined aqueous layers were extracted with EtOAc (40 L). From the first organic layer some THF (82 L) was distilled off, then the EtOAc layer was added, and further solvent (65 L) was distilled off. The resulting product suspension was cooled to 10 °C and kept at that temperature for 2 h. The solids were isolated by centrifugation, washed with EtOAc (7 L), and dried under reduced pressure to yield crude **10** (6.29 kg; 78.7%; 93.6% HPLC area %; 11.5% Zn).

To the suspension of crude **10** (6.0 kg) in H_2O (65.5 L) and THF (16.4 L) was added ethylenediamine (6.0 kg). This mixture was heated to 45 °C for 2 h. The fine solids were isolated by filtration, washed with H_2O (50 L), and dried at 50 °C under reduced pressure to yield purified **10** (3.99 kg; 52.3% overall yield; HPLC 96.0% area %; 4500 ppm Zn; 200 ppm Pd).

^{1}H NMR (d_6-DMSO, 400 MHz): δ 7.94−8.00 (m, 3H), 8.11 (dd, J = 1.6; 8.4; 1H), 8.17 (d, J = 6.1; 1H), 8.31 (d, J = 8.4; 1H), 8.45−8.52 (m, 3H), 8.71 (d, J = 5.9; 1H), 9.61 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 120.31, 125.24, 126.64, 126.91, 127.01, 128.63, 128.66, 128.78, 131.64, 132.33, 132.76, 135.22, 135.31, 136.17, 141.42, 143.81, 151.60, 152.76. Anal. Calcd. for $C_{18}H_{11}N_2Cl$: C, 74.36; H, 3.81; N, 9.63; Cl, 12.19. Found: C, 74.42; H, 3.85; N, 9.48; Cl, 12.07.

[(*E*)-3-Dimethylamino-2-(dimethylamino-methyleneamino)allylidene]dimethylammonium hexafluorophosphate (16). Phosphorus oxychloride (6.18 kg, 40.3 mol) was added to DMF (8.1 L) at such a rate that 0−5 °C was maintained. At this temperature glycine hydrochloride **15** (1.5 kg, 13.5 mol) was added in three portions within 10 min. The temperature was raised to 125 °C within 6 h and kept for 2.5 h. After cooling to 30 °C the mixture was stirred at 30 °C overnight. For hydrolysis H_2O (deionized, 6.75 L) was slowly added (*Exotherm!* Temperature rose to 70 °C). This mixture was added to deionized H_2O (8.5 L). After rinsing with DMF (2 L) the hydrolyzed reaction mixture was cooled to 0−5 °C, and hexafluorophosphoric acid (10.25 kg, 64% in H_2O) was added within 1 h. The suspension was stirred for 1.75 h at 0 °C, and finally the product was filtered and washed with ethanol (1 × 7 L; 5 × 2 L). This crude product was dried under reduced pressure overnight at 40 °C to yield a mixture of mono- and dihexafluorophosphates (8.48 kg). To the suspension of this hexafluorophosphate mixture (6 kg) in ethanol (31.8 L) was added triethylamine (2.12 L). This mixture was heated to 80 °C within 45 min and kept at 80 °C for 4 h. Then, further ethanol (5 L) was added, and the temperature was decreased to 20 °C within 2.5 h. The suspension of **16** was stirred overnight at 0 °C. The suspension was filtered and washed with ethanol (2 × 2 L). The crude product was dried under reduced pressure overnight at 45 °C to yield crude **16** (4.49 kg). Crude **16** (4.40 kg) was dissolved in ethanol (66.2 L) at reflux and clarified by filtration. After washing with warm ethanol (13 L) the crystallization was induced by cooling to 0 °C within 1.5 h. The product suspension was stirred at 0 °C overnight. The crystalline product was isolated by filtration, washed with ethanol (4 L), and finally dried under reduced pressure at 40 °C overnight to yield product **16** (2.99 kg; 93% yield based on **15**).

^{1}H NMR (d_6-DMSO, 400 MHz): δ 3.19 (s, 18 H), 7.16 (s, 2H), 7.36 (s, 1H). MS: 198, 197 (M^+), 101.

***N′*-(2-*tert*-Butylpyrimidine-5-yl)-*N*,*N*-dimethylformamidine (19).** To a suspension of **16** (2.26 kg, 6.6 mol) in methanol (25 L) at room temperature was added *tert*-butylcarbamidine hydrochloride **(18)** (690 g, 5.05 mol) within 30 min, followed by a solution of NaOMe (2.28 kg 30% (w/w), 12.7 mol). The addition funnel was rinsed with methanol (0.2 L). The turbid reaction mixture was heated to reflux for 3 h. After cooling to 45 °C deionized H_2O (185 mL) was added, and methanol was distilled off under reduced pressure at this temperature. To the evaporation residue NaCl solution (15%; 15 kg) was added and extracted with *tert*-butyl methyl ether (3 × 10 kg). The combined organic layers were washed with NaCl solution (15%, 5 kg). This washing solution was extracted again with *tert*-butyl methyl ether (5 kg). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated to dryness at 45 °C under reduced pressure to yield product **19** (584 g; 56% of theory; 95.7% HPLC area %), which was used in the next step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (s, 9H), 3.00 (s, 6H), 7.47 (s, 1H), 8.27 (s, 2H). MS: 208, 207 (MH^+).

2-*tert*-Butyl-5-aminopyrimidine (14). (a) From Vinamidinium Route. A mixture of **19** (573 g, 2.78 mol) and an aqueous solution of K_2CO_3 (5%, 5.8 kg) was heated to 91 °C for 24 h until conversion was complete as indicated by HPLC. The reaction mixture was cooled to room temperature and extracted with isopropyl acetate (1 × 10 L; 2 × 5 L). The combined organic layers were washed with brine (5 L), dried over $MgSO_4$, and evaporated to dryness to yield product **14** (377 g; 89.7% yield; HPLC 99.4% area %), which was used in the next step without further purification.

(b) From Buchwald Amination Route. A solution of 5-bromo-2-*tert*-butyl pyrimidine **(20)** (8 kg, 37.2 mol), benzophenonimine (7.74 kg, 42.71 mol), racemic BINAP (176 g, 0.283 mol), tris(dibenzylidenacetone) palladium (0) ($Pd_2(dba)_3$) (52 g, 0.0568 mol), and *tert*-BuONa (5.04 kg, 52.4 mol) in xylene (84 L) was heated to reflux (125−130 °C; *Exotherm*!) for 2 h until conversion was complete as indicated by HPLC. The reaction mixture was cooled to room

temperature, stirred overnight, and H_2O (40 L) and isopropyl acetate (40 L) were added. The organic layer was separated and washed with H_2O (20 L). The combined aqueous layers were extracted with isopropyl acetate (20 L). The organic phase was clarified by filtration and evaporated to dryness to yield intermediate **21** (13.3 kg).

The evaporation residue (13.3 kg) was dissolved in THF (64 L) and at room temperature a solution of concentrated HCl (1.2 L) in H_2O (4.8 L) was added. The reaction mixture was stirred at room temperature overnight until conversion was complete as indicated by HPLC. Concentrated HCl (2 L) in H_2O (38 L) and heptane (72 L) were added. The biphasic mixture was stirred vigorously for 15 min, and the layers were separated. The organic phase was washed with a solution of concentrated HCl (2.4 L) in H_2O (21.6 L). To the combined H_2O phases was added isopropyl acetate (40 L). The aqueous phase was cooled to 8 °C, and the pH was adjusted to >11 by adding NaOH (30%, 5.4 L). The layers were separated, and the aqueous phase was extracted with isopropyl acetate (2 × 25 L). The combined organic phases were evaporated to dryness to yield a brown crude product (4.34 kg).

This crude product (4.3 kg) was dissolved in *tert*-butyl methyl ether (45 L) and washed with 2 M NaOH (2 × 11.5 L). The combined aqueous layers were extracted with *tert*-butyl methyl ether (2 × 10 L). The combined organic layers were washed with a 16% aqueous NaCl solution (18 kg). The organic phases were dried over $MgSO_4$ (2 kg), filtered, and evaporated to a volume of 12 L. To this solution heptane (32 L) was added at an internal temperature of 55 °C. The mixture was cooled to 0 °C within 40 min and stirred at 0 °C overnight. The solids were isolated by filtration, washed with heptane (10 L), and dried at 50 °C under reduced pressure to yield **14** (3.23 kg; 57.5% yield over two steps from **20**).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35 (s, 9H), 4.09 (br s, 2H), 8.19 (s, 2H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 29.3; 37.9; 137.0; 142.5; 167.4. MS: 153, 152 (MH^+), 109. Anal. Calcd for $C_8H_{13}N_3$: C, 63.55; H, 8.67; N, 27.79. Found: C, 63.68; H, 8.73; N, 27.55.

[4,7′]Bis-isoquinolinyl-1-yl-(2-*tert*-butyl-pyrimidine-5-yl)amine (1). To a solution of **14** (1.615 kg, 10.7 mol) in DME (40 L) at room temperature was added NaH (1.074 kg, 26.9 mol; 60% dispersion in mineral oil) within 10 min. The temperature raised to 24 °C. Then within 20 min **10** (3.42 kg; 11.76 mol) was added. Gradually a red solution appeared that indicated the start of the reaction. The temperature was gradually raised to reflux. (*Caution! ca. 22.5 mol hydrogen evolution!*) The temperature was kept for another 1 h at reflux until complete conversion was indicated by HPLC (<0.1% **10**). The reaction mixture was cooled to 20 °C, diluted with toluene (40 L), and hydrolyzed by slow addition of a solution of *N*-acetyl cysteine (0.2 kg) in deionized H_2O (30 L). The phases were separated, and the aqueous layer was extracted with toluene (20 L). The combined organic layers were washed with deionized H_2O (20 L) and concentrated to a volume of 20 L. To this residue was added toluene (2 × 30 L) and was concentrated to a volume of 19 L. The resulting suspension was cooled to 0 °C and stirred overnight at that temperature. Finally solids were isolated by filtration, washed with toluene (3 × 5 L) and dried under reduced pressure at 55 °C to yield crude **1** (4.78 kg; 27 ppm Pd; 17 ppm Zn). The crude product (4.73 kg) was added to a suspension of activated charcoal (240 g) in ethanol (86 L) and deionized H_2O (4.5 L). The mixture was heated to reflux for 1 h and clarified by filtration; the filter washed with hot ethanol (5 L). A solution of *N*-acetylcysteine (240 g) and ethylenediamine tetraacetic acid disodium salt (430 g) in H_2O deionized (9.5 L) was added at 70 °C. Finally, further deionized H_2O (94 L) was added at 70 °C. After the complete addition the temperature was decreased to 0 °C within 5 h, and the suspension was stirred overnight at 0 °C. The suspension was filtered, washed with deionized H_2O (95 L), and dried under reduced pressure at 60 °C, to yield **1** (3.7 kg; 85% of theory; HPLC: 99.4%; Pd/Zn: < 1 ppm).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 9H), 7.60−7.70 (m, 2H), 7.80−7.90 (m, 4H), 7.97−7.99 (m, 1H), 8.07−8.09 (m, 1H), 8.25−8.28 (m, 1H), 8.58 (m, 1H), 9.25 (s, 2H), 9.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 29.8; 38.9; 118.0; 120.4; 121.8; 125.5; 126.2; 126.7; 127.0; 128.4; 128.8; 130.6; 132.5; 133.0; 135.0; 135.8; 136.7; 140.7; 143.2; 148.3; 151.4; 152.6; 171.2. MS: 406, 405 (M^+), 404. Anal. Calcd for $C_{26}H_{23}N_5$: C, 77.01; H, 5.72; N, 17.27. Found: C, 77.28; H, 5.84; N, 17.05.

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