

Large-Scale Negishi Coupling as Applied to the Synthesis of PDE472, an Inhibitor of Phosphodiesterase Type 4D

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Abstract:

5-[2-Methoxy-5-(4-pyridinyl)phenyl]-2,1,3-benzoxadiazole (PDE472) is a selective inhibitor of the phosphodiesterase PDE4D isoenzyme, which is a recognised drug target for the treatment of asthma. Different synthetic routes to PDE472 were investigated, and the research synthesis was optimised to prepare a phase I batch on pilot-plant scale with the focus on the elimination or minimization of inherent process risks. An important refinement of the key Negishi aryl–aryl coupling involved preforming the arylpalladium complex, which was then added to the arylzinc intermediate. Residual palladium was removed from PDE472 via crystallization of the hemi-maleate salt, which afforded drug-substance containing <2 ppm Pd.

1. Introduction

Asthma is a chronic inflammatory disease of the airways, characterised by the infiltration of eosinophils, which are major protagonists in inflicting injury to the bronchial mucosa. This damage contributes to bronchial obstruction, to hyperreactivity, and to the symptoms (breathlessness and wheezing) of asthma. Inhibiting the infiltration of eosinophils and their ability to secrete proinflammatory mediators constitutes an attractive approach towards asthma therapy.¹ An increase in intracellular levels of adenosine 3',5'-cyclic monophosphate (cAMP) inhibits the activation of eosinophils, suppressing responses such as chemotaxis, oxidative burst, and cytotoxic protein release. Of the 11 groups of phosphodiesterase (PDE) isoenzymes,² the cAMP-specific PDE4 family is particularly important in regulating cAMP levels, and of the four subtypes within this family,^{3,4} PDE4A, PDE4B, and PDE4D are expressed within human eosinophils, as well as in T cells,⁵ where PDE4 inhibition reduces the release of cytokines, which are important regulators of

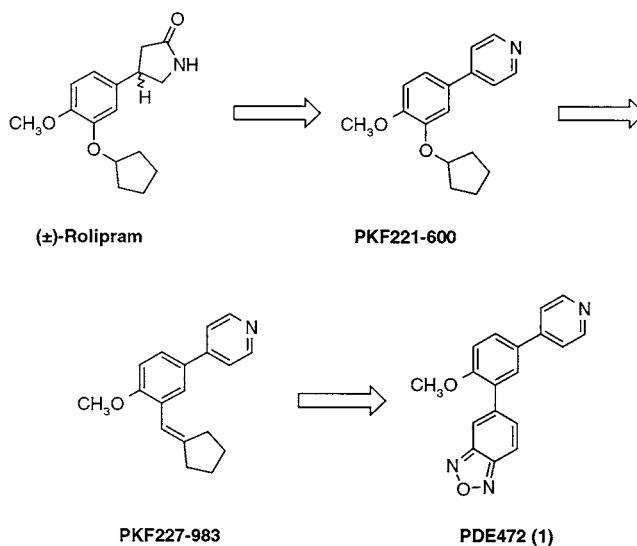


Figure 1. Genesis of PDE472.

eosinophil trafficking and activation. Airway smooth muscle cells also express PDE4 enzymes, and PDE4 inhibitors are able to reduce the contractile response to spasmogens,⁶ and suppress hyperreactivity,⁷ of airway smooth muscle. Consequently, selective inhibition of PDE4 enzymes is considered to be a promising approach towards asthma therapy and offers a conceptually attractive alternative to glucocorticosteroids for antiinflammatory therapy, with the added potential to exert symptomatic relief.

Utilizing the prototype PDE4 inhibitor rolipram as a lead structure,⁸ 5-[2-methoxy-5-(4-pyridinyl)phenyl]-2,1,3-benzoxadiazole (**1**, PDE472; Figure 1) was identified as a potent, selective, and orally active inhibitor of the phosphodiesterase, PDE4D.^{9,10} A key structural feature of **1** is the benzoxadiazole heterocycle, employed as a bioisostere for the potentially mutagenic nitrophenyl moiety, as utilised by Neumann in the design of the calcium antagonist, Lomir.¹¹ Introduction of the benzoxadiazole directly onto a phenyl ring was investigated using various strategies. As part of the development of **1**, multikilogram quantities of material were required

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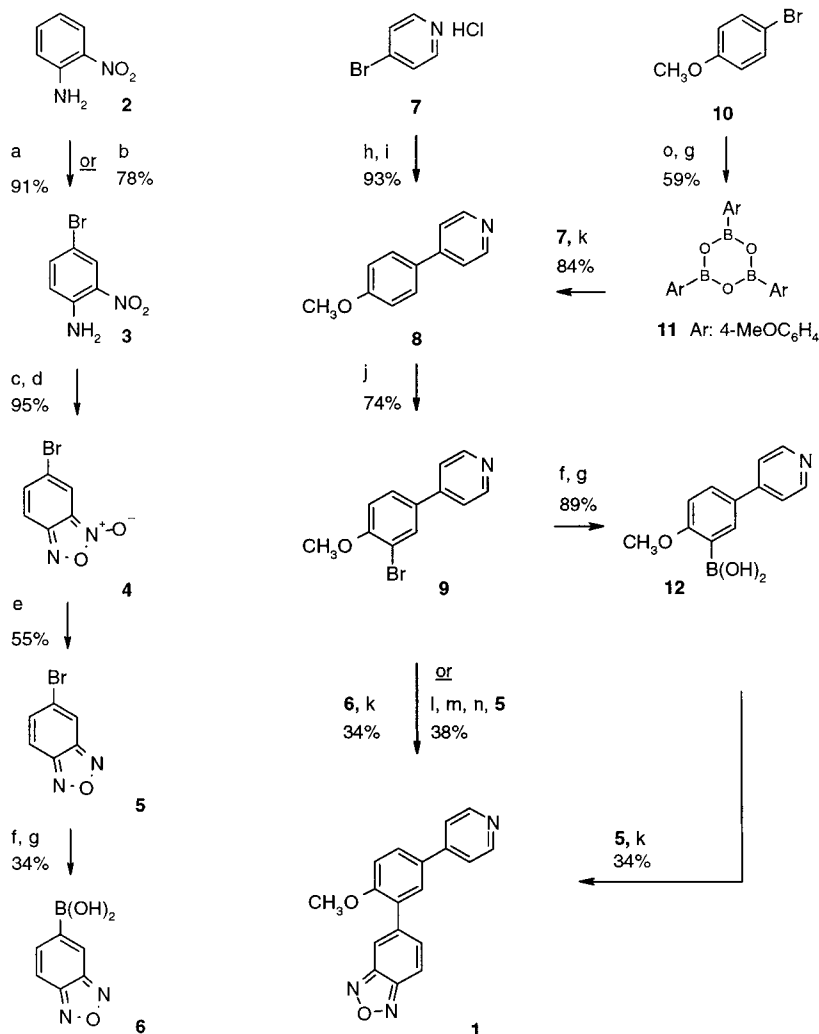
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Scheme 1. Research syntheses of 1 (PDE472) ^a

Synthesis of intermediates **5** and **6**

Synthesis of intermediate **9** & cross coupling routes to **1**



^a Reagents and conditions: a) NBS, HOAc; b) Br₂, NaOAc, HOAc; c) KOH, EtOH; d) 12% NaOCl; e) PPh₃, xylene, 130 °C; f) *n*-BuLi, THF, -80 °C; g) B(OEt)₃; h) 4-MeOC₆H₄MgBr (2 equiv), THF; i) NiCl₂(PPh₃)₂, THF; j) Br₂ (2 equiv), HOAc; k) Pd(OAc)₂, P(*n*-C₆H₅CH₂)₃, Na₂CO₃, DMF, water; l) *n*-BuLi, THF/pentane, -100 °C; m) ZnCl₂, -90-0 °C; n) Pd(PPh₃)₄, 0-20 °C; o) Mg, THF.

for drug development. This contribution describes the refinement of the research synthesis into a high-yield process, which was utilised in the pilot plant to produce highly-pure PDE472 in large quantities.

2. Results and Discussion

2.1. Research Syntheses of PDE472.

The convergent synthetic routes employed for the preparation of **1** are shown in Scheme 1. The benzoxadiazole moiety was coupled to arylpyridine **9**, via either Suzuki¹² or Negishi coupling.¹³⁻¹⁷

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Stille coupling was discounted due to concerns about tin impurities in the drug substance, leading to toxicity.¹⁸

The intermediate 5-bromobenzofurazan (**5**) was prepared in three steps from the commercially available 2-nitroaniline (**2**; Scheme 1). Regiospecific bromination of **2** with either *N*-bromosuccinimide (NBS) in acetic acid or bromine in acetate buffer afforded the bromide **3** in 91 and 78% yield, respectively. Oxidative ring-closure of **3** with alkaline hypochlorite according to the procedure of Green and Rowe,¹⁹ as modified by Britton and Noland,²⁰ then afforded the *N*-oxide **4** (98%). Employing triphenylphosphine to mediate deoxygenation, in place of hydrazine,²¹ then gave the benzofurazan, **5** in 55% yield. Use of tributylphosphine in place of triphenylphosphine facilitated the purification of

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5, but the method was less efficient (28% yield). Compound **5** was converted to the boronic acid derivative **6** by lithium–halogen exchange and subsequent addition of (EtO)₃B.

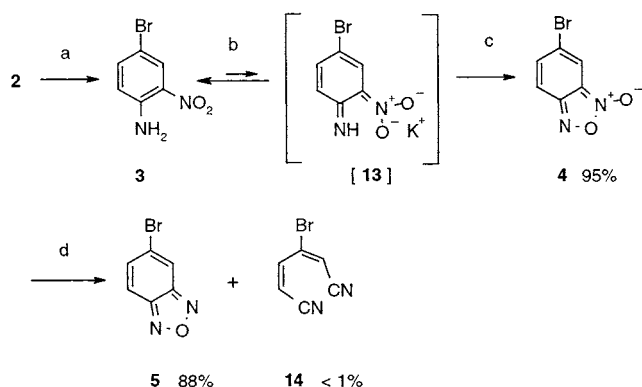
Katritzky first reported the regiospecific synthesis of 4-arylpiperidines, such as **8** (Scheme 1), utilizing the reaction of Grignard reagents with 2',6'-dimethyl-4'-oxo-1,1'(4'H)-bipyridinium salts.²² In our hands, although the Grignard reaction with 4-methoxyphenylmagnesium bromide and thermal cleavage of the dihydropyridine intermediate proceeded as reported, the preparation and isolation of the bipyridinium salt was rather capricious, and we therefore turned to other approaches. Bis(triphenylphosphine)nickel(II)chloride²³ catalysed Kumada cross-coupling of arylmagnesium bromides to 2- and 3-bromopyridine has been reported.^{24,25} With this as precedent we applied the reaction to 4-bromopyridine hydrochloride, **7**, obtaining the arylpyridine **8** in 93% yield, with 2,4-bis(4-methoxyphenyl)pyridine, arising from attack of two molecules of Grignard reagent, being the only other pyridine-containing product isolated (0.5%). However, due to the inconvenience of isolating the free 4-bromopyridine, which must be handled with care because it readily polymerises, we employed two equivalents of Grignard reagent for this reaction; in addition to being wasteful, the reaction was highly exothermic, necessitating extreme caution for control. Consequently, we adopted the Suzuki coupling using aqueous alkaline conditions as a safer alternative. Thus, the cyclic boronic acid anhydride **11**, readily prepared by reacting the Grignard reagent derived from 4-bromoanisole **10** with triethyl borate, was coupled under standard conditions to 4-bromopyridine hydrochloride **7** to afford the biaryl **8** in 84% yield (Scheme 1).

Subsequent bromination of **8**, using bromine in acetic acid at 60 °C for 72 h, proceeded regioselectively to give **9**, which was elaborated to the target PDE472, **1**, either by Suzuki coupling with the boronic acid **6**, derived from the benzofurazan **5** (34%), or advantageously (easier purification) by Negishi coupling of the arylzinc reagent derived from **9** with 4-bromobenzofurazan, **5** (38%).

An alternative Suzuki-coupling strategy was also evaluated using the boronic acid **12** (Scheme 1), which was prepared from the bromide **9** in high yield (89%). However the cross-coupling reaction with 4-bromobenzofurazan (**5**) afforded appreciable quantities of 4-(4-methoxyphenyl)pyridine **8**, from which it was difficult to separate the PDE472, **1**, and in view of the success of the Negishi coupling, this strategy was not further investigated.

2.2. Pilot-Plant Procedures for PDE472. On the basis of the experience from research syntheses, the route utilizing the Negishi coupling was selected for further development and scale-up. For this purpose, the yield of the Negishi coupling needed to be improved. In addition, critical issues regarding safety, ecology, handling, and purity of the drug

Scheme 2. Large scale synthesis of intermediate **5**^a



^a Reagents and conditions: a) NBS, HOAc; b) KOH, *tert*-butanol, water; c) 12% NaOCl; d) P(OEt)₃, ethanol, 75 °C.

substance had to be solved, including reduction of the Pd content of the drug substance from 800 to <2 ppm.

2.2.1. Large-Scale Synthesis of Intermediates **5** and **9**.

The high-yielding Green–Rowe oxidation procedure,^{26–28} as used in the research synthesis of **4** (Scheme 1), was judged critical for scale-up: DSC measurements showed that deprotonation of **3** with potassium hydroxide in ethanol solution at 60 °C occurred at the onset temperature of the exothermic decomposition of the *aci*-nitroanion intermediate **13**^{29,30} (Scheme 2, estimated TMR < 30 min at 60 °C). Furthermore, the combination of ethanol and excess sodium hypochlorite is a source for ethylhypochlorite, which is both volatile (bp 36 °C) and explosive.^{31,32} A third concern revealed by DSC measurements, was the marked destabilizing effect of trace (ppm) amounts of iron(III) chloride (hydrated and nonhydrated) on the thermal stability of **4**.

These inherent risks in the process could be reduced by taking advantage of the poor solubilities of compounds **3** and **4** in aqueous alkali mixtures at 25–35 °C (Scheme 2). By using only a slight excess of potassium hydroxide and replacing the ethanol with a water–*tert*-butyl alcohol mixture, only an equilibrium concentration of **13** was formed, from which **4** gradually crystallised upon adding sodium hypochlorite. In the absence of *tert*-butyl alcohol to mediate solubility, there was almost no reaction. Furthermore, the large excess of sodium hypochlorite could be reduced to an almost stoichiometric quantity, presumably because its concentration relative to the small concentration of **13** was sufficient throughout the reaction period. This was important, because not only did the safety and the time–space yield increase, but the waste situation also improved.³³

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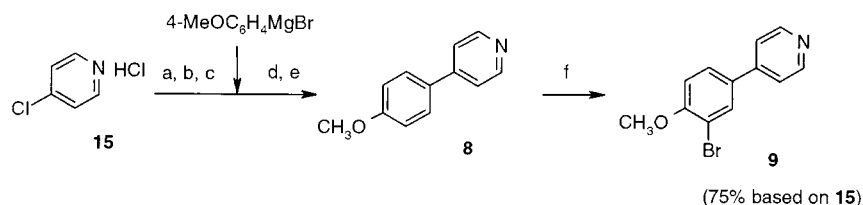
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Scheme 3. Kumada cross-coupling for large-scale synthesis of intermediate 9^a

^a Reagents and conditions: a) NaOH, toluene, water; b) azeotropic drying of base solution; c) NiCl₂(dppp) (0.1 mol %); d) HCl; e) NaOH; f) Br₂ (2 equiv); acetic acid; 24 h.

For the large-scale synthesis, the iron sensitivity of **4** and its marked tendency to sublime prompted the direct use of the water-washed filter cake as an ethanol solution in the deoxygenation to **5**. Triethyl phosphite in ethanol at 70 °C,³⁴ was favored over triphenylphosphine in xylene at 130 °C,²⁶ because **5** crystallised directly from the reaction mixture upon the addition of water, thus avoiding the purification by chromatography or steam distillation. Furthermore, with xylene as solvent, yields decreased with increasing scale and temperature, due to the lowered onset of the decomposition temperature of **4** when mixed with phosphines or phosphites. For reasons of reproducibility, it was therefore advantageous to add the reducing agent in the temperature range of 70–80 °C, which is probably optimal for electrocyclic ring-opening.^{34,35} The formation of **14**³⁶ (Scheme 2) as a minor side product may be taken as an indication that indeed deoxygenation from a ring-opened dinitroso species has taken place as proposed by Boyer.³⁴

Several industrial applications of efficient nickel-catalyzed Kumada cross-coupling reactions have been recently reviewed,³⁷ and the roles of reactants, catalysts and solvents on the catalytic cycle are well understood.^{38–40} The Kumada cross coupling was preferred over the Suzuki alternative for the preparation of **9** (Scheme 3) mainly for logistic and economic reasons. It allowed a higher cadence of batches and did not use reactor capacity for low-temperature reactions. Also, in place of the 4-bromopyridine hydrochloride, **7**, the less reactive but considerably cheaper 4-chloropyridine hydrochloride, **15** (Scheme 3), could be employed in this case. As a precondition for scale-up, however, the initially proposed procedure was changed to control the very strong exotherms and hazardous accumulation effects, which occurred when the hydrochloride **8** was reacted directly with two equivalents of Grignard reagent.⁴¹

Key to the successful scale-up of the Kumada coupling was the safe drying of the toluene solution of the volatile

chloropyridine base of **15** by azeotropic distillation under reflux using a water trap, which avoided autopolymerization and material loss. Another essential feature was the pre-reduction^{39,42} of the nickel catalyst with a small aliquot of the Grignard solution followed by the addition of the remainder of the Grignard solution at 40–50 °C which controlled the hazardous self-acceleration due to reagent accumulation. Furthermore, the more active 1,3-bis(diphenylphosphino)propane–nickel(II)chloride (NiCl₂(dppp))³⁸ was used in a quantity of only 0.1 mol %, because this resulted in substantially lower levels of residual nickel in crude **8** as compared to the reactions with the NiCl₂(PPh₃)₂ catalyst. During workup, the crude product **8** was purified by toluene extraction of its water-soluble hydrochloride and used directly for the bromination in acetic acid to give highly pure **9** after crystallization (75% yield based on **15**) without the need for chromatography.

2.2.2. The Negishi Coupling. The formation of aromatic carbon bonds using Negishi coupling is well described in the literature^{13–17} and has been applied for the coupling of aromatic heterocycles, including substituted pyridines.^{43–46} The Negishi coupling of an arylzinc with an aryl halide is a three-step reaction sequence (Scheme 4). This involves (i) formation of an aryllithium-intermediate from the aryl halide, (ii) zinc–lithium exchange to give the arylzinc intermediate, and (iii) Pd(0)-catalysed coupling of the arylzinc intermediate with an arylpalladium complex, which is formed in situ from the corresponding arylbromide and Pd(0). Thus, to improve the overall yield of the Negishi coupling each of these intermediate steps needed to be optimised.

For safety and environmental reasons, *n*-butyllithium was replaced by hexyllithium (HexLi)⁴⁷ to prepare the aryllithium intermediate **16**. The lithium–halogen exchange reaction between an aryl bromide and an alkyl lithium is a complex process. In the absence of side reactions, only one equivalent of HexLi would be needed for the formation of the aryllithium compound **16** and hexyl bromide. However, as

(33) Note: In industrial wastewater treatment facilities an untreated sodium hypochlorite waste stream is a known source for chloroform via haloform reactions.

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(36) Note: Structurally closely related dinitrile compounds have been previously found (a) in the thermal decomposition of 1,2-benzenediazides (Hall, H. J.; Patterson E. *J. Am. Chem. Soc.* **1967**, *89*, 5856) or (b) in the nickelperoxide oxidation of 1,2-benzenediamines (Nagakawa, K., Onoue, *Tetrahedron Lett.* **1965**, *6*, 1433).

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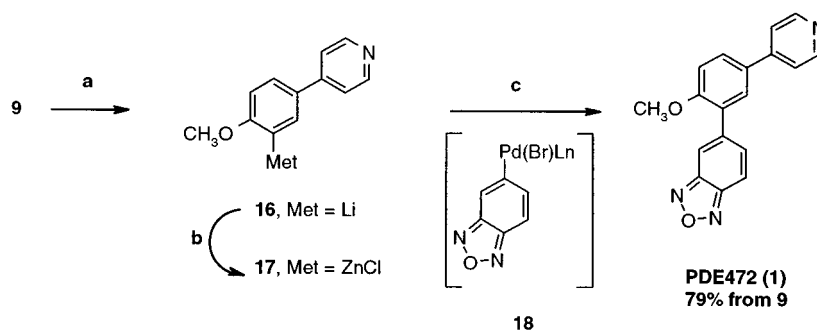
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(47) Note: With HexLi, the hexane produced by hydrolysis is maintained in the reaction mixture, whereas technical processes involving BuLi have to adequately address the safety and environmental aspects of potential butane emission. (See, e.g.: Baenziger, M.; Mak, C.-P.; Muehle, H.; Nobs, F.; Prikoszovich, W.; Reber, J.-L.; Sunay, U. *Org. Process Res. Dev.* **1997**, *1*, 395.)

Scheme 4. Intermediates of the Negishi coupling, as applied for the large-scale synthesis^a



^a Reagents and conditions: a) HexLi, THF/pentane; b) ZnCl₂, THF; c) **5**, Pd(PPh₃)₄, DMF.

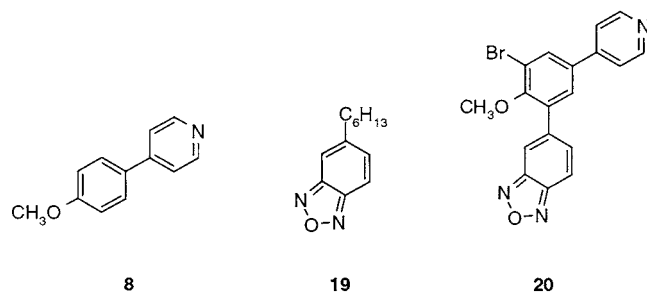


Figure 2. Isolated byproducts of the Negishi coupling.

the reaction progresses, the concentration of hexyl bromide increases, and this reacts with HexLi to form dodecane as byproduct. Consequently, more than one equivalent of HexLi is needed for complete lithiation. In many cases, this is not a problem since an excess of the aryllithium reagent can be used. However, in this particular case, excess HexLi had to be avoided because under the reaction conditions, it reacted with the bromide **5** to form byproduct **19** (Figure 2). The same side reaction was observed with BuLi. Consequently, the amount of HexLi was optimised empirically, to ensure complete lithium–bromine exchange and to minimise the formation of **19**. The best results and highest yields were obtained using 1.3 equiv of HexLi.

The temperature was another critical factor in the formation of the aryllithium intermediate **16** and for the subsequent trans-metalation step. At temperatures above $-95\text{ }^{\circ}\text{C}$, compound **16** was slowly protonated, presumably by tetrahydrofuran, to give **8** as byproduct (Figure 2). For solubility reasons, this protonation could not be detected directly with FT-IR. However, FT-IR experiments using 2-bromoanisole as a model compound⁴⁸ confirmed the slow protonation of 2-lithio anisole to form anisole in THF–pentane at temperatures above $-95\text{ }^{\circ}\text{C}$. On the other hand, conversion of **16** into the arylzinc compound **17** was very slow at $-95\text{ }^{\circ}\text{C}$ and needed higher temperatures. These difficulties were partly overcome by generating the aryllithium compound **16** at $-95\text{ }^{\circ}\text{C}$, then adding the ZnCl₂ solution at $-95\text{ }^{\circ}\text{C}$, and allowing the reaction mixture to warm to $0\text{ }^{\circ}\text{C}$. Once formed, the arylzinc intermediate **17** was quite stable, even at $0\text{ }^{\circ}\text{C}$.

For technical reasons, and for low-temperature reactions in particular, the time required to add reagents to a pilot-

Table 1. Effect of varying reagent addition times and duration of stirring at $-95\text{ }^{\circ}\text{C}$ on yield^a

addition time [min] (additional stirring time [min])	ZnCl ₂ addition time [min] (additional stirring time [min])	yield of 1 [%]
45 (15)	45 (60)	79
45 (120)	45 (60)	47
45 (180)	45 (60)	36
5 (5)	5 (60)	78

^a Compound **8** was formed as main byproduct in all cases.

plant reaction can be much longer than on a laboratory scale. Therefore, the stability of **16** during its generation and during additional stirring at $-95\text{ }^{\circ}\text{C}$ was investigated (Table 1). Even at $-95\text{ }^{\circ}\text{C}$, the aryllithium intermediate **16** proved to be unstable on prolonged (120 min) stirring, leading to lower yields for the Negishi coupling. Accordingly, fast addition of HexLi was necessary, after which the mixture was stirred at $-95\text{ }^{\circ}\text{C}$ until the formation of **16** was complete.

Initial Pd-catalysed couplings of the arylzinc intermediate **17** with the aryl bromide **5** gave modest yields (ca. 40%) of the desired product **1**. The bromide **20** (Figure 2) was isolated as byproduct, along with high amounts of other insoluble byproducts. The byproduct **20** arises from α -lithiation of **9** by HexLi, which competes with the desired lithium–bromine exchange reaction to form aryllithium **16**. The bromide **20** can also participate in a Negishi coupling with the arylzinc intermediate **17**, leading to poorly soluble polyaromatic byproducts.

The Negishi coupling yielded **1**, which was still contaminated with remarkably high amounts of palladium (300–800 ppm) after chromatography and crystallisation. This might be attributed to a strong complexation of **1** with Pd(0), which could change the properties of the Pd(0) catalyst if it occurred during the reaction. The 4-(4-methoxyphenyl)pyridine substructure is probably a good ligand for Pd(0), since 4-methoxypyridines and 4-aminopyridines are well-known to ligate palladium. This complexation may account for the initial slow reaction rates and low yields of the Negishi coupling. Experimental results supported this hypothesis. When a solution of the complex **18** (Scheme 4), preformed from the bromide **5** and Pd(PPh₃)₄, was added to a solution of the arylzinc intermediate **17**, the coupling reaction was faster and the yield increased, as compared to a process using the sequential addition of **5** followed by the

(48) Prikoszovich, W. Results presented at the *International Symposium on Process Development Chemistry*; organised by Chirex, Amelia Islands, April 19–21, 1999.

Table 2. Comparison of selected reaction parameters of the Negishi coupling: research synthesis versus optimised scale-up synthesis

parameter	research synthesis	scale-up synthesis
concentration of 9 [m/m]	5.6%	2.7%
molar ratio of 9 : 5	1:1	1:1
equivalents of HexLi	1.4	1.3
initial temperature	−95 °C	−95 °C
HexLi and additional stirring	60 min.	15 min
equivalents of ZnCl ₂	1.4	1.2
ZnCl ₂ and additional stirring	15 min	60 min
mol % of Pd (Ph ₃ P) ₄ catalyst	8%	0.8%
temperature for coupling	0–22 °C	0–22 °C
reaction time for coupling	16 h	1 h
yield of PDE472 (1)	38%	79%

catalyst, Pd(Ph₃P)₄. By this procedure, the quantity of catalyst could also be reduced by a factor of 10.

Applying all of the above improvements, the yield of the Negishi coupling was increased from 38% to 79%. A direct comparison of the reaction parameters for the Negishi coupling (research versus optimised scale-up synthesis) is listed in Table 2. The optimised Negishi coupling was successfully scaled up by a factor of 500 to produce 4.5 kg of PDE472 (**1**), in the pilot plant.

2.2.3. Palladium Removal from the Drug Substance.

Removal of trace amounts of palladium from drug substances is a general problem, since a Pd content of less than 2 ppm is usually desirable. High palladium content is a particular problem, when the last step in the synthesis is catalysed by the metal and where the drug substance is a good ligand for Pd(0). A number of methods for the removal of palladium impurities from organic substances have been reported,^{49,50} with one of the most efficient being the precipitation of palladium from solutions using trimercaptotriazine.⁴⁹

To address the high palladium content in PDE472 (**1**), different crystallised salts were examined. These included the hemi-sulfate, hydrochloride, dihydrogen phosphate, hemi-tartrate, hemi-fumarate, and hemi-maleate. The hemi-maleate salt, prepared in 97% yield by treating **1** with 2 equiv of maleic acid, possessed a very low palladium content (10–30 ppm), compared to that of the free base (100–800 ppm) and to other salts. The residual palladium content of the drug substance was finally reduced to <0.5 ppm, by converting the hemi-maleate salt back to the free base with aqueous sodium carbonate (5%) in methyl acetate, treating the organic phase with active charcoal and recrystallization from acetone, to afford **1** in 94% recovery. Thus, the preparation of a hemi-maleate salt and subsequent regeneration of the free base proved to be an effective method for palladium removal from PDE472 (**1**) and may have applications for removal of palladium impurities also from other heterocyclic bases.

PDE472 (**1**) is apparently a good ligand not only for Pd(0) but also for Ni(0). When the Negishi coupling was carried out in a hastelloy-steel reactor, the Ni content of the product

increased to about 23 ppm, although the Ni content of all starting materials was <2 ppm. Obviously, compound **1** was able to complex and solubilise nickel traces from the surface of the reactor vessel. This problem was circumvented by using a glass-lined steel (enamel) reactor in place of the hastelloy-steel reactor.

3. Conclusions

The Negishi coupling has successfully been scaled-up from laboratory- to pilot-plant scale for the preparation of the phase 1 batch of PDE472 (**1**). For this purpose, the interplay between important reaction parameters such as temperature, stoichiometry of reagents, reaction time, addition time of the reagents, and also the stability of particular intermediates had to be investigated. As a result, the reaction conditions were optimised and the yield was improved. Residual palladium impurities were removed from the aromatic nitrogen heterocycle **1** by purification over a hemi-maleate salt.

4. Experimental Section

Reagents and solvents were obtained from commercial sources and used as received. Hexyllithium was obtained from Chemetall, Germany. All reactions were carried out under an atmosphere of nitrogen unless otherwise stated. Temperatures were internally measured unless otherwise stated. Chromatography was performed using silica gel (E. Merck, Grade 60, particle size 0.040–0.063 mm, 230–400 mesh ASTM) with the eluent indicated. Melting points were determined on a Leitz Kofler hot-stage apparatus and are uncorrected. Proton NMR spectra were recorded at 300 K and 500 MHz (Bruker DRX500) using deuterated DMSO as internal standard. Chemical shifts (δ) are given in ppm. Chemical analyses, indicated by the symbols of the elements, were performed by the CTA-Analytical Services, Novartis. For the analysis of the metal impurities mentioned in this work (Fe, Ni, Pd), X-ray fluorescence methods were used (Solvias AG, Basel).

4.1. Research Synthesis Procedures. 4-Bromo-2-nitrobenzenamine (3). *Method 1.* NBS (79 g, 0.44 mol) was added over 30 min to a stirred solution of **2** (60 g, 0.45 mol) in HOAc at 55 °C. The mixture was stirred for 3 h at 40–50 °C and then poured into ice–water (5 L). The product was filtered, washed with cold water, and recrystallised from EtOH–water to give **3** (86 g, 91%) as an orange crystalline solid, mp 108–110 °C (lit.⁵¹ 109–110 °C).

Method 2. Anhydrous sodium acetate (65.6 g, 0.80 mol) was added to a stirred suspension of **2** (110.5 g, 0.8 mol) in HOAc (320 mL) at 10 °C. The mixture was stirred for 45 min and then treated dropwise with a solution of bromine (121.6 g, 0.76 mol) in HOAc (200 mL), during which time the temperature was maintained at 20 °C. The mixture was stirred for a further 30 min at 20 °C, treated with water (800 mL at 20 °C), and stirred for a further 60 min. The product was filtered, washed with cold water (2 × 250 mL), dried, and recrystallised from EtOH to give **3** (137 g, 79%) as an orange-brown crystalline solid, mp 106–108 °C (lit.⁵¹ 109–110 °C).

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5-Bromo-2,1,3-benzoxadiazole-3-oxide (4). A stirred solution of KOH (28.6 g, 0.51 mol) in EtOH (300 mL) at 47 °C was treated in portions with **3** (68.7 g, 0.32 mol) such that the temperature remained stable and then was heated at 65 °C for 2 h. The deep-red reaction mixture was then cooled to 2 °C, treated dropwise with an aqueous solution of sodium hypochlorite (600 mL of 15%), and stirred for 90 min at <5 °C, followed by 18 h at 10–20 °C. The product was filtered off, washed with water (2 × 500 mL), and dried in vacuo to give **4** (67 g, 98%) as red powder, mp 63–66 °C (lit.²⁰ 69 °C).

5-Bromo-2,1,3-benzoxadiazole (5). A stirred solution of triphenylphosphine (23.6 g, 0.872 mol) in xylene (230 mL) at 140 °C under an argon atmosphere was treated dropwise with a solution of **4** (17.1 g, 0.079 mol) in xylene (40 mL) during 1 h. The mixture was stirred for a further 3 h at 140 °C after which the solvent was evaporated off under reduced pressure. The resulting residue was purified by column chromatography (5% methyl *tert*-butyl ether in cyclohexane), recrystallised from pentane, and sublimed (56 °C, 20 mmHg) to give **5** (8.6 g, 55%) as colorless needles, mp 72–75 °C (subl.; lit.²¹ 75 °C); ¹H NMR (DMSO-*d*₆): 7.72 (m, 1H), 8.07 (dd, *J* = 9.4, 0.9 Hz, 1H) and 8.52 (m, 1H).

2,1,3-Benzoxadiazol-5-yl-boronic Acid (6). A solution of *n*-BuLi in hexane (20 mL of 2.5 M, 50 mmol) was added over 5 min to a stirred solution of **5** (7.90 g, 40 mmol) and triethylborate (8.44 mL, 50 mmol) in dry THF (200 mL) at –90 °C under an argon atmosphere. The mixture was stirred for 15 min at –80 °C, then added to a saturated aqueous solution of ammonium chloride (300 mL), and extracted with EtOAc (2 × 80 mL). The combined extracts were washed with a saturated aqueous solution of ammonium chloride (80 mL), dried (Na₂SO₄) and filtered, and the solvent was evaporated off under reduced pressure to give a residue which was purified by chromatography (40% EtOAc in cyclohexane) to give **6** (2.2 g, 34%) as a pink crystalline solid, mp > 300 °C; ¹H NMR (DMSO-*d*₆ + D₂O): 7.85 (dd, *J* = 9.1, 1.2 Hz, 1H), 7.94 (dd, *J* = 9.1, *J* = 1.2 Hz, 1H) and 8.38 (d, *J* = 1.2 Hz, 1H).

Tris-(4-methoxyphenyl)boroxin (11). A solution of 4-methoxyphenylmagnesium bromide, prepared from 4-bromoanisole (**10**, 37.4 g, 0.20 mol) and magnesium (5.6 g, 0.23 mol) in dry THF (200 mL) was filtered and added dropwise to a stirred solution of triethylborate (38.8 mL, 0.23 mol) in dry THF (200 mL) at –60 °C, under an argon atmosphere. The mixture was then stirred for 30 min at –60 °C and then allowed to warm to 0 °C over 60 min. The mixture was washed with a saturated aqueous solution of ammonium chloride (2 × 100 mL) and dried (Na₂SO₄), and the solvent was evaporated off under reduced pressure to yield the crude product which was recrystallised from EtOAc–hexane to give **11** (18 g, 59%) as a colorless crystalline solid, mp 209–211 °C (lit.⁵² 213 °C).

4-(4-Methoxyphenyl)pyridine (8). *Suzuki Method.* A stirred mixture of **11** (13.4 g, 33 mmol), 4-bromopyridine hydrochloride (**7**, 21.4 g, 110 mmol), tri-*o*-tolylphosphine (3.04 g, 10 mmol), palladium (II) acetate (1.12 g, 5 mmol),

K₂CO₃ (34.6 g, 250 mmol), and water (200 mL) in dimethoxyethane (400 mL) was heated at 80 °C for 7 h. The mixture was then treated with a saturated aqueous solution of ammonium chloride (200 mL) and extracted with EtOAc (4 × 200 mL). The combined extracts were then extracted with hydrochloric acid (3 × 200 mL of 2 M). The combined acid extracts were basified (pH 10) with aqueous NaOH (5 M) and extracted with methyl *tert*-butyl ether (5 × 200 mL). The combined extracts were dried (Na₂SO₄) and filtered, and the solvent was evaporated off under reduced pressure to yield the crude product which was recrystallised from methyl *tert*-butyl ether–hexane to give **8** (15.6 g, 84%) as a colorless crystalline solid, mp 94–96 °C (lit.⁵³ 95–96 °C).

Grignard Method. A solution of 4-methoxyphenylmagnesium bromide, prepared from 4-bromoanisole (**10**, 150 g, 0.80 mol) and magnesium (20 g, 0.83 mol) in dry THF (300 mL) was filtered, cooled to –10 °C, and added cautiously to a stirred mixture of bis(triphenylphosphine)nickel (II) chloride²³ (1.5 g, 2.25 mmol) and 4-bromopyridine hydrochloride (**7**, 65 g, 0.334 mol) in dry THF (300 mL) at 10 °C, under an argon atmosphere. After 50% of the Grignard reagent had been added, a vigorous, exothermic reaction set in, and the temperature of the mixture was maintained between 50 and 60 °C throughout the rest of the addition by employing an ice–MeOH cooling bath. The mixture was then stirred for 60 min at 50 °C, after which the solvent was evaporated off under reduced pressure to yield a residue, which was treated with methyl *tert*-butyl ether (500 mL) and extracted with HCl (3 × 300 mL of 5M). The combined extracts were washed (methyl *tert*-butyl ether), basified (aqueous NaOH) and extracted with methyl *tert*-butyl ether (4 × 300 mL). The combined extracts were dried (Na₂SO₄), and the solvent was evaporated off under reduced pressure to yield the crude product which was purified by recrystallisation from methyl *tert*-butyl ether–cyclohexane to give **8** (50 g, 93%) as a colorless crystalline solid, mp 94–96 °C (lit.⁵³ 95–96 °C).

Chromatography (silica gel; 20% EtOAc in hexane) of the mother liquors followed by recrystallisation from methyl *tert*-butyl ether afforded 2,4-bis(4-methoxyphenyl)pyridine (0.25 g, 0.5%) as a colorless crystalline solid, mp 153–156 °C (lit.⁵⁴ 152–153 °C).

4-(3-Bromo-4-methoxyphenyl)pyridine (9). Bromine (28.1 g, 176 mmol) was added to a stirred solution of **8** (14.8 g, 80 mmol) in HOAc (400 mL) and heated at 60 °C for 72 h. The orange suspension was then evaporated to dryness under reduced pressure, and the residue was treated with aqueous ammonia (400 mL of 6 M) and extracted with EtOAc (4 × 200 mL). The combined extracts were dried (Na₂SO₄) and filtered, and the solvent was evaporated off under reduced pressure to yield the crude product which was purified by chromatography (methyl *tert*-butyl ether) and recrystallised from ether–cyclohexane to give **9** (20.2 g, 96%) as a pale-yellow crystalline solid, mp 82–84 °C. ¹H NMR (DMSO-*d*₆): 3.92 (s, 3H), 7.25 (d, *J* = 8.9 Hz, 1H), 7.79 (d, *J* = 6.2 Hz, 2H), 7.83 (dd, *J* = 9.4, 1.3 Hz, 1H),

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7.93 (s, 1H), 7.94 (dd, $J = 9.3, 2.4$ Hz, 1H), 8.06 (dd, $J = 9.4, 1.0$ Hz, 1H), 8.21 (d, $J = 1.2$ Hz, 1H) and 8.60 (d, $J = 6.2$ Hz, 2H). Anal. Calcd for $C_{12}H_{10}NOBr$: C, 54.57; H, 3.82; N, 5.30; Br, 30.25. Found: C, 54.58; H, 3.90; N, 5.32; Br, 30.1.

5-[2-Methoxy-5-(4-pyridinyl)phenyl]-2,1,3-benzoxadiazole (1). *Suzuki Method.* A stirred mixture of **9** (1.43 g, 5.4 mmol), **6** (1.10 g, 6.7 mmol), tri-*o*-tolylphosphine (0.164 g, 0.54 mmol), palladium (II) acetate (0.061 g, 0.27 mmol), Na_2CO_3 (1.73 g, 16.2 mmol), and water (16 mL) in DMF (56 mL) was heated at 60 °C for 5 h. The mixture was then treated with water (100 mL) and extracted with EtOAc (3 × 80 mL). The combined extracts were washed (saturated NaCl), dried (Na_2SO_4) and filtered, and the solvent was evaporated off under reduced pressure to yield the crude product which was purified by chromatography (EtOAc) and recrystallised from acetone–methyl *tert*-butyl ether to give **1** (0.56 g, 34%) as a colorless needles, mp 206–207 °C; 1H NMR (DMSO- d_6): 3.89 (s, 3H), 7.34 (d, $J = 8.9$ Hz, 1H), 7.79 (d, $J = 6.2$ Hz, 2H), 7.83 (dd, $J = 9.4, 1.3$ Hz, 1H), 7.93 (s, 1H), 7.94 (dd, $J = 9.3, 2.4$ Hz, 1H), 8.06 (dd, $J = 9.4, 1.0$ Hz, 1H), 8.21 (d, $J = 1.2$ Hz, 1H) and 8.60 (d, $J = 6.2$ Hz, 2H). Anal. Calcd for $C_{18}H_{13}N_3O_2 \cdot 0.2 H_2O$: C, 70.44; H, 4.40; N, 13.69. Found: C, 70.46; H, 4.41; N, 13.67.

Negishi Method. A solution of *n*-BuLi in hexane (8.8 mL of 2.5 M, 22 mmol) was added to a stirred solution of **9** (5.28 g, 20 mmol) in a mixture of dry THF (100 mL) and pentane (10 mL, to prevent crystallization of solvent) at –100 °C under an argon atmosphere. The yellow suspension was stirred for 30 min at –90 °C, treated with a solution of $ZnCl_2$ in THF (46 mL of 0.5 M, 23 mmol), and allowed to warm to 0 °C over 60 min. Tetrakis(triphenylphosphine)palladium (2.0 g, 1.7 mmol) was then added to the brown suspension, which was stirred for 5 min, treated with **5** (3.80 g, 20 mmol), and stirred at 20 °C for 3 h. The resulting mixture was treated with a saturated aqueous solution of ammonium chloride (250 mL) and extracted with EtOAc (2 × 100 mL). The combined extracts were washed (25% aqueous NH_3), dried (Na_2SO_4) and filtered, and the solvent was evaporated off under reduced pressure to yield the crude product which was recrystallised from acetone–methyl *tert*-butyl ether to give **1** (2.3 g, 38%) as colorless needles, mp 206–208 °C.

2-Methoxy-5-(4-pyridinyl)phenylboronic Acid (12). A solution of *n*-BuLi in hexane (15 mL of 2.5 M, 37.5 mmol) was added to a stirred solution of **9** (7.92 g, 30 mmol) and triethylborate (6.34 mL, 37.5 mmol) in dry THF (150 mL) at –85 °C under an argon atmosphere. The mixture was stirred for 15 min at –80 °C, then treated with a saturated aqueous solution of ammonium chloride (200 mL), and extracted with a mixture of 10% EtOH in EtOAc (2 × 120 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the solvent was evaporated off under reduced pressure to yield the crude product which was purified by recrystallization from EtOAc–hexane to give **12** (6.1 g, 89%) as a cream crystalline solid, mp 196–200 °C; 1H NMR (DMSO- d_6): 3.88 (s, 3H), 7.13 (d, $J = 8.7$ Hz, 1H), 7.68 (d, $J = 6.1$ Hz, 2H), 7.88 (s, 1H), 7.85 (dd, $J = 8.7, 2.4$ Hz, 1H), 7.97 (d, $J = 2.4$ Hz, 1H) and 8.60 (d, $J = 6.1$ Hz, 2H).

Anal. Calcd for $C_{12}H_{12}BNO_3$: C, 62.93; H, 5.28; N, 6.12. Found: C, 62.53; H, 5.29; N, 6.16.

4.2. Procedures for Pilot-Plant Syntheses. 4-Bromo-2-nitrobenzenamine (3). A suspension of NBS (119 g, 0.67 mol) in HOAc (400 mL) was prepared at 20–25 °C and transferred from reactor to reactor into a solution of 2-nitroaniline (**2**, 90 g, 0.65 mol) in HOAc (530 mL) at 60 °C at such a rate to maintain the temperature in the range 60–65 °C. After rinsing with HOAc (44 mL) the reaction mixture was kept at 60–65 °C until the reaction was complete (3–5 h). A volume of HOAc (345 mL) was then distilled from the reaction mixture at 50–60 °C under reduced pressure. Crystallization was induced by gradual addition of water (975 mL) and by maintaining the temperature at 40 °C. The resulting suspension was slowly cooled to 5 °C, filtered, washed with water (176 mL), and dried at 35–50 °C under reduced pressure to give **3** (133 g, 94%) as an orange-red solid. On larger scale (210-fold) the product was converted to **4** without drying on the basis of the calculated dry weight.

5-Bromo-2,1,3-benzoxadiazole-3-oxide (4). Aqueous KOH (164 g of 50%, 1.3 mol) was added over 15 min to a suspension of **3** (240 g, 1.11 mol) in water (180 mL) and *tert*-butyl alcohol (306 mL) at 25 °C. An aqueous sodium hypochlorite solution (796 g of 12%, 1.12 mol) was added slowly (60 min) to maintain the temperature at 27 °C. After the addition, the mixture was warmed to 30 °C, stirred for 5 h, and then treated with aqueous sodium thiosulfate solution (100 mL of 10%) at 15 °C. The mixture was cooled to 10 °C, and the yellow solids were filtered, washed with cold water (300 mL), and dried under reduced pressure at 40–50 °C to give **4** (226 g, 95%). For safety considerations on larger scale (420-fold) the water-wet product (average dry mass 83%, Fe content < 2 ppm) was used for the production of **5** on the basis of the calculated dry weight.

5-Bromo-2,1,3-benzoxadiazole (5). Triethyl phosphite (93 g, 0.56 mol) was added to a solution of **4** (107.5 g, 0.5 mol) in EtOH (1080 mL) at 70 °C over 60 min, so that the temperature did not exceed 75 °C. After another 60 min at 75 °C, a volume of EtOH (670 mL) was distilled from the reaction mixture under reduced pressure at 35 °C. Water (400 mL) was slowly added over 60 min at 35 °C, and the resulting mixture was cooled to 10 °C. The crude product was filtered, washed with water–ethanol (240 mL, 3:1, v/v), dried at 40 °C under reduced pressure, and recrystallised from hexane (415 mL) to yield **5** (77 g, 77%; HPLC assay > 99%).

(*E,Z*)-3-Bromo-hexa-2,4-dienedinitrile (**13**; ca. 0.8% based on **4**) was isolated as a minor side product from the concentrated mother liquor by chromatography on silica gel using toluene (R_f : 0.32) as eluent. 1H NMR (δ $CDCl_3$; 200 MHz): 5.82 (d, $J = 10.5$ Hz, 1H), 6.15 (s, 1H), 7.19 (d, $J = 10.5$ Hz, 1H). IR (KBr): 3440, 3207, 3067, 3040, 2924, 2853, 2218, 1929w, 1740w, 1551, 1534, 1464, 1397, 1098, 993, 835, 778 cm^{-1} . MS (EI): m/z 184 (M + H), 182, 103, 76, 75, 63.

4-(4-Methoxyphenyl)pyridine (11). (a) An aliquot (10 mL) of a solution of 4-bromoanisole (**9**, 80 g, 0.43 mol) in toluene (60 mL) was added to Mg turnings (11.1 g, 0.46

mol) and iodine (0.1 g) in THF (160 mL) at 35 °C. After the reaction had initiated, the remainder of the solution of **9** was added at such a rate to maintain the temperature in the range of 35–45 °C. After a further 3 h at 45 °C the mixture was cooled to 25 °C and used without filtration for the coupling step.

(b) Aqueous 30% NaOH solution (ca. 55 g, 0.42 mol) was added to a stirred mixture of 4-chloropyridine hydrochloride (**15**; 60 g, 0.40 mol) in toluene (200 mL) and water (220 mL) at 0 °C, at such a rate to maintain a temperature <5 °C and to adjust pH ca. 9. After another 10 min the layers were separated, and the organic layer was heated under reflux (250–100 mbar, 50 °C) using a water trap to azeotropically remove the residual water (<0.05% water by Karl Fischer titration). [Safety remark: The solution may be stored overnight at 0 °C under nitrogen. Removal of toluene by distillation may lead to a strongly exothermic autopolymerization of the free base of **15**, accompanied by material loss due to codistillation of the base with toluene].

(c) NiCl₂(dppp) (0.3 g, 0.56 mmol) was added to the dried base solution of **15** in toluene (prepared in b) at 25 °C. A portion (approximately 20 mL) of the 4-methoxyphenylmagnesium bromide solution (prepared in a) was then transferred from reactor to reactor, at such a rate as to keep the initially exothermic reaction <30 °C. After a delay of 15 min the temperature was raised to 35 °C, and the remainder of the 4-methoxyphenylmagnesium bromide solution was transferred slowly (60 min) to maintain a 35–45 °C temperature. The feed reactor and transfer line were rinsed with toluene (20 mL). After a further 3 h at 45 °C the reaction was complete, and the mixture cooled to 25 °C.

(d) A solution of citric acid (70 g) in water (140 mL) and hydrochloric acid (19 mL of 36%) was prepared and the reaction mixture from the coupling reaction (described in c) was added over 1 h, so that the temperature remained < 25 °C. [Safety remark: Residual magnesium liberates hydrogen.] For rinsing, toluene (60 mL), water (140 mL), and hydrochloric acid (19 mL of 36%) were mixed in the coupling reactor and transferred into the hydrolysis mixture. The hydrolysed mixture was heated to 30 °C, and the layers were separated. The water layer, containing the hydrochloride of **8**, was washed with toluene (60 mL) at 30 °C and then cooled to 25 °C to give a suspension. Toluene was added (300 mL), and pH 9–10 was adjusted with aqueous NaOH (150 mL of 30%). The layers were separated, and the toluene phase was evaporated to dryness at 45 °C under reduced pressure to yield crude **8** (55 g, 74% based on **15**; Ni content < 20 ppm). On larger scale (675-fold) this residue was brominated directly to **9**.

4-(3-Bromo-4-methoxyphenyl)pyridine (9). Bromine (76 g, 0.48 mol) was added over 60 min to a solution of **8** (40 g, 0.22 mol) in HOAc (480 mL) at 60 °C, and the reaction mixture was heated for 18–24 h. Aqueous sodium sulfite solution (330 mL of 10%) was added over 30 min at 25 °C, and the temperature was raised to 45 °C. The solvent was distilled off under reduced pressure, and the residue was dissolved in a mixture of water (400 mL) and toluene (280 mL). At 20 °C the mixture was basified to pH 8.5 with

aqueous NH₃ (50 mL of 30%). The toluene layer was separated and dried by azeotropic distillation under reduced pressure at 45 °C using a water trap. Toluene (190 mL) was distilled off under reduced pressure at 45 °C, and the concentrated solution was treated with bentonite clay (4–16 g), diluted with hot (55 °C) hexane (160 mL), and filtered. Crystallization was induced by seeding at 35 °C. Hexane (400 mL) was added at 35 °C over 60 min, and after gradual cooling to –5 °C, the solids were filtered, washed with a cold hexane–toluene mixture (50 mL, 4:1, v/v), and dried under reduced pressure at 60 °C to yield **9** (43 g, 75%). (HPLC assay 99.7%; Ni content < 3 ppm).

5-[2-Methoxy-5-(4-pyridinyl)phenyl]-2,1,3-benzoxadiazole (1). A solution of **9** (10.8 g, 40.9 mmol) in THF (400 mL) and pentane (60 mL) was cooled to –95 °C. A solution of HexLi in hexane (15.2 g of 32.3%, 53.4 mmol) was slowly added to the solution over 45 min, while maintaining the temperature between –94 and –96 °C. The resulting suspension was stirred for 15 min at –96 °C and then treated over 45 min with a solution of ZnCl₂ (6.72 g, 49.3 mmol) in THF (200 mL). The mixture was then allowed to warm to 0 °C over 45 min and then stirred at 0 °C for 1 h, to give a suspension of the arylzinc compound **17**. In a separate reactor, **5** (8.16 g, 40.9 mmol) was dissolved in THF (120 mL), and Pd(Ph₃P)₄ was added to form the palladium complex **18**. This solution was added to the suspension of the arylzinc compound **17** at 0 °C, and the reaction mixture was stirred for 15 min at 0 °C and for 1 h at 22 °C. The reaction was quenched with HOAc (6.1 mL), diluted with MeOAc (200 mL), washed with brine (200 mL), aqueous NH₃ (400 mL of 2.5%), and brine (200 mL), and then concentrated to a 600-mL volume by distillation. The solution was filtered through silica (100 g), and the residual product was eluted from silica with acetone (650 mL). The combined fractions were evaporated to dryness under reduced pressure, and the residue was dissolved in hot acetone (700 mL) to give a clear solution. The solution was concentrated to 280 mL, cooled to 25 °C, stirred for 2 h, and then cooled to 0 °C. The crystalline product was filtered off, washed with acetone (80 mL), and dried in vacuo at 50 °C to give **1** (9.8 g, 79%) as colorless needles. This procedure was scaled up 500-fold in a pilot plant to produce 4.5 kg of **1** (72.5% yield).

5-[2-Methoxy-5-(4-pyridinyl)phenyl]-2,1,3-benzoxadiazole, Hemi-maleate Salt (1 Hemi-maleate). A suspension of **1** (16.25 g, 53.6 mmol, 350 ppm Pd) in THF (1530 mL) was heated to 67 °C and stirred under reflux to give a clear solution. A preformed solution of maleic acid (13 g, 112 mmol) in THF (170 mL) was added dropwise over 20 min to the solution of **1** at 67 °C. The mixture was stirred for 15 min and then cooled to 22 °C over 2 h. The hemi-maleate salt started to crystallise at ca. 62 °C. The suspension was stirred for 18 h at 20–22 °C, and the product was filtered, washed with ice-cold THF (3 × 250 mL), and dried in vacuo at 55 °C to obtain the hemi-maleate salt of **1** (22.0 g, 98%) as a beige, crystalline solid, mp 200 °C dec. Pd: 27 ppm. ¹H NMR (DMSO-*d*₆): 3.93 (s, 3H), 6.23 (s, 2H), 7.38 (d, *J* = 9 Hz, 1H), 7.855 (dd, *J* = 10 and 1 Hz, 1H), 7.98 (d, *J* = 6.5 Hz, 2H), 8.01 (s, 1H), 8.026 (dd, *J* = 9 and 2.5 Hz, 1H),

8.09 (d, $J = 9.5$ Hz, 1H), 8.24 (s, 1H), 8.70 (d, $J = 6.5$ Hz, 2H). Anal. Calcd for $C_{22}H_{17}N_3O_6$: C, 63.01; H, 4.09; N, 10.02. Found: C, 62.68; H, 4.06; N, 10.00.

6-Hexyl-2,1,3-benzoxadiazole (19). Compound **19** was isolated as a colourless liquid from the mother liquor of compound **1** by column chromatography on silica gel using hexane/toluene (4:1) as eluent. R_f : 0.72 (ethyl acetate/hexanes 4:1). 1H NMR ($CDCl_3$; 400 MHz): 0.88 (t, $J = 6.9$ Hz, 3H), 1.23–1.42 (m, 6H), 1.66 (m, 2H), 2.69 (t, $J = 7.6$ Hz, 2H), 7.26 (d, $J = 9.3$ Hz, 1H), 7.51 (s, 1H), 7.71 (d, $J = 9.3$ Hz, 1H), IR (film): 2956, 2930, 2858, 1634w, 1539, 1522w, 1468, 1378w, 1009, 881, 852w, 803, 745w, 638w. MS (EI): m/z 204 (M^+), 134 (100%), 117, 103, 76.

5-[3-Bromo-2-methoxy-5-(4-pyridinyl)phenyl]-2,1,3-benzoxadiazole (20). Compound **20** was isolated as a white solid from the mother liquor of compound **1** by column chromatography on silica gel using ethyl acetate/hexane (4:1) as eluent. R_f : 0.29 (ethyl acetate/hexane 4:1). 1H NMR ($CDCl_3$; 400 MHz): 3.62 (s, 3H), 7.50 (d, $J = 6$ Hz, 2H),

7.62 (d, $J = 2.2$ Hz, 1H), 7.71 (d, $J = 9.3$ Hz, 1H), 7.92 (d, $J = 9.3$ Hz, 1H), 7.93 (s, 1H), 8.01 (s, 1H), 8.70 (d, $J = 6.0$ Hz, 2H). ^{13}C ($CDCl_3$; 400 MHz): 61 (3C), 115.0, 115.5, 119.0, 121(2C), 128.0, 133.50, 134.0, 141.0, 146.0, 148.0, 149.5, 150.5 (2C), 155.5. IR (KBr): 1598, 1535, 1463, 1424, 1407, 1313, 1296, 1253, 1224, 989, 877, 814, 796, 750, 647 cm^{-1} . MS (EI): m/z 384 and 382 (MH^+ , 100%), 365, 353, 328, 321, 301, 270.

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