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Improved Suzuki–Miyaura Reactions of Aryldiazonium Salts with Boronic Acids by Tuning Palladium on Charcoal Catalyst Properties

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Abstract: An improved Suzuki–Miyaura cross-coupling reaction of aryldiazonium tetrafluoroborates with boronic acids catalyzed by a highly active palladium catalyst supported on charcoal is described as an extremely practical and efficient protocol. A properties-activity study of various catalysts clearly established that the optimal catalytic activity was obtained with palladium nanoparticles having a low oxidation degree and uniformly dispersed on the charcoal. The optimized reaction conditions allow the cross-coupling to proceed at room temperature without any base and ligand in technical grade methanol. Although the catalyst could not be recycled, the low palladium contamination of the solvent and product after a simple filtration of the palladium on charcoal (Pd/C) renders the present protocol competitive and safer for the environment compared to more conventional homogeneous conditions. We have highlighted the efficiency of this novel protocol by a short synthesis of the fungicide Boscalid®.

Keywords: aryldiazonium tetrafluoroborates; palladium on activated charcoal; practical cross-coupling; sustainable chemistry; Suzuki–Miyaura reaction

Introduction

Palladium-catalyzed cross-coupling reactions have profoundly impacted the development of organic chemistry these last decades.[1] The Suzuki–Miyaura cross-coupling reaction is probably one of the most relevant palladium-mediated methods for C−C bond formation that allows the coupling of aryl and vinyl halides with boron compounds.[2] The pioneering studies of Suzuki and Miyaura[3] have been followed by an impressive amount of work from laboratories all around the world which has led to highly efficient procedures.[4]

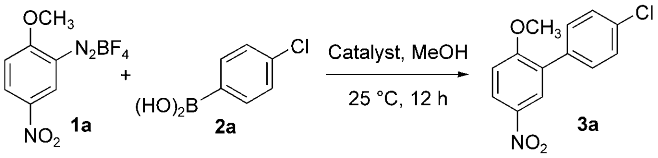
On the other hand, the progress of modern sustainable chemistry has become a major concern to solve many environmental issues we must face. In this context, we recently started a program aimed at the development of easy-to-handle palladium-catalyzed reactions.[5] Our approach is based on the use of robust and inexpensive heterogeneous catalysts employing non-anhydrous and non-degassed conditions. We also revisited the chemistry of aryldiazonium salts as highly reactive aryl halide surrogates.[6] For instance, we recently published an easy to handle protocol for the cross-coupling reactions of boronic acids with aryldiazonium salts catalyzed by Pd(0)/C.[5d] The procedure allows selective and fast reactions (5–30 min) under ligandless and base-free conditions in technical grade methanol at 50 °C. However, the cross-coupling worked best with a rather high loading (5 mol% Pd) of a not well-defined commercially available palladium catalyst. Considering that a fine-tuning of catalyst properties could considerably improve the catalytic efficiency and thereby solve the loading issues, we engaged in a property-activity relationship study of various Pd/C catalysts.[7]

In this paper we established that the properties of Pd/C catalysts dramatically influence the reaction outcome. Our newly designed protocol allows cross-coupling at 25 °C under ligandless and base-free conditions with loading as low as 0.1–0.9 mol% Pd.

Results and Discussion

In this study we examined four catalysts differing by their oxidation degree [i.e., Pd(0) or Pd(II)] and the Pd distribution over charcoal (i.e., eggshell or uniform). An eggshell distribution means that palladium nanoparticles are distributed close to the surface of the charcoal. A uniform distribution means that palladium nanoparticles are homogeneously dispersed in

Table 1. Optimization studies.



Entry	Equiv.		Dilution [M][a]	Catalyst[b]	Pd [mol%]	Yield [%][c]
	1a	2a				
1	1.5	1	0.10	Cat. A	1	95
2	1.5	1	0.10	Cat. B	1	94
3	1.5	1	0.10	Cat. C	1	83
4	1.5	1	0.10	Cat. D	1	94
5	1.5	1	0.10	Cat. A	0.5	94
6	1.5	1	0.10	Cat. B	0.5	94
7	1.5	1	0.10	Cat. C	0.5	68
8	1.5	1	0.10	Cat. D	0.5	92
9	**1.5**	**1**	**0.10**	**Cat. A**	**0.1**	**94**
10	1.5	1	0.10	Cat. B	0.1	54
11	1.5	1	0.10	Cat. C	0.1	21
12	1.5	1	0.10	Cat. D	0.1	53
13	1.2	1	0.10	Cat. A	0.1	82

[a] Concentration of the diazonium salt.

[b] Cat. A: Pd(0)/C-uniform; Cat. B: Pd(0)/C-eggshell; Cat. C: Pd(II)/C-uniform; Cat. D: Pd(II)/C-eggshell.

[c] Yields are an average of at least two runs

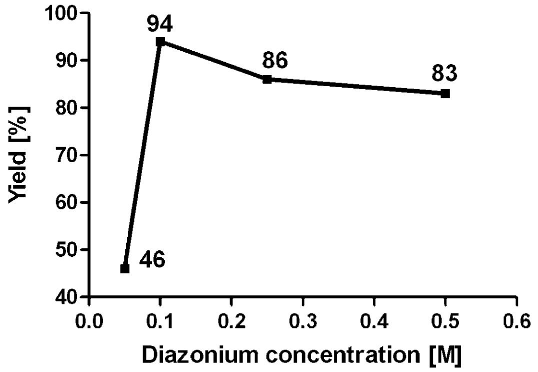


Figure 1. Cross-coupling reaction of diazonium salt **1a** with 4-chlorophenylboronic acid **2a** catalyzed by 0.1 mol% Pd (catalyst A) in MeOH (25 °C, 12 h) at various concentrations.

the charcoal. The support has a BET surface area of approximately 800 $m^2 g^{-1}$. In addition, all the catalysts were ligandless and were selected at a constant loading (i.e., 5 wt.% Pd on charcoal) and with 50% water content for safety issues.[8]

As reported in Table 1, our preliminary studies led us to consider the Pd/C-catalyzed cross-coupling of 2-methoxy-3-nitrobenzenediazonium tetrafluoroborate **1a** and 4-chlorobenzeneboronic acid **2a** in undistilled technical grade MeOH at 25 °C under air and with no external additives (base and ligand). Interestingly, the four catalysts studied (catalysts A–D) were all active for this cross-coupling with 1 mol% Pd although catalyst C was slightly less active. In contrasting, lowering the loading to 0.1 mol% Pd significantly highlighted the performance of catalyst A in comparison to the other three catalysts B–D (entry 9 *versus* entries 10–12). From those preliminary studies it was clear that the optimal catalytic activity was obtained with palladium nanoparticles having a low oxidation [Pd(0)] degree and uniformly dispersed on the charcoal. We also experienced that for most cross-couplings studied in this work, it was preferable to use 1.5 equivalents of the diazonium salt. Lowering the quantity of diazonium salts to 1.2 equivalents could slightly alter the yield due to de-diazotization pathways (entry 13).

The impact of the diazonium salt concentration on the yield of the cross-coupling leading to **3a** was also studied (Figure 1). From that work, we noticed that the reaction was best conducted with a diazonium salt concentration in the range of 0.1–0.2 M. Indeed, the yield drops drastically to 46% with more diluted conditions (0.05 M) while concentrated solutions were less damaging. It has been observed that more diluted conditions favour the de-diazotization pathway leading to unwanted by-products.

With the carefully optimized conditions in hand, we compared catalysts A–D with different heterogeneous and homogeneous palladium sources (Figure 2). Impressively, catalyst A showed a significantly high catalytic activity that overpassed all other catalysts tested in this study. Catalyst A gave **3a** with even higher yield than $Pd(OAc)_2$ (catalyst G), the widely used homogeneous catalyst for such cross-coupling reactions.[7]

With the realization of an optimized protocol, the scope and limitations of this cross-coupling were investigated (Table 2). A variety of substituted biphenyls was efficiently prepared under mild conditions with a low loading of palladium. All aryldiazonium tetrafluoroborates were easily accessed by reacting

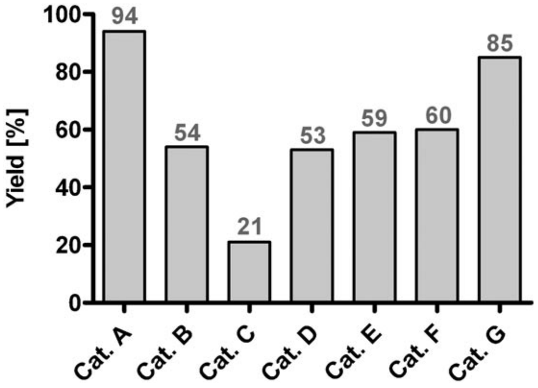
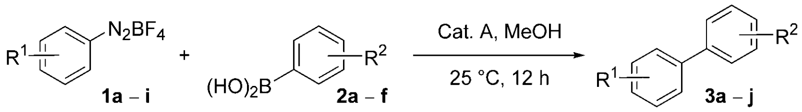
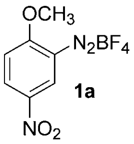
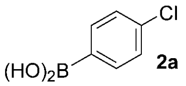
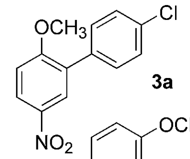
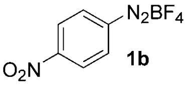
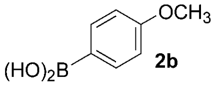
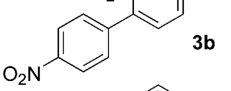
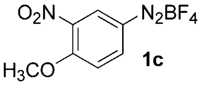
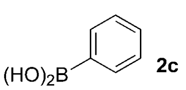
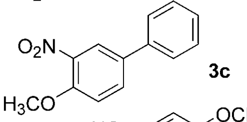
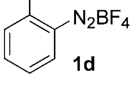
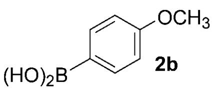
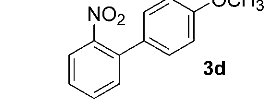
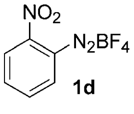
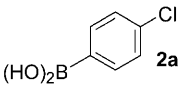
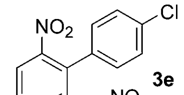
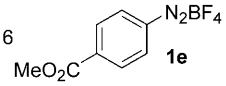
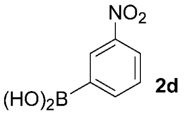
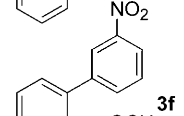
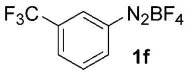
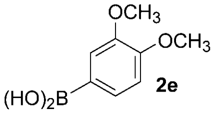
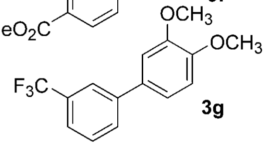
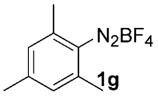
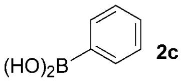
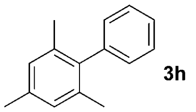
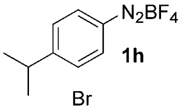
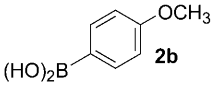
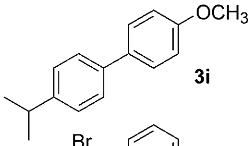
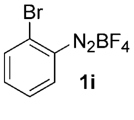
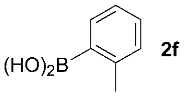
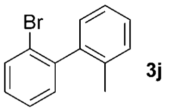


Figure 2. Cross-coupling reaction of diazonium salt **1a** with 4-chlorophenylboronic acid **2a** catalyzed by 0.1 mol% Pd (catalysts A–G) in MeOH at 25 °C for 12 h. Cat. E: Pd/C (catalyst used in refer.[6a]), Cat. F: $Pd(0)/BaCO_3$, Cat. G: Pd-$(OAc)_2$

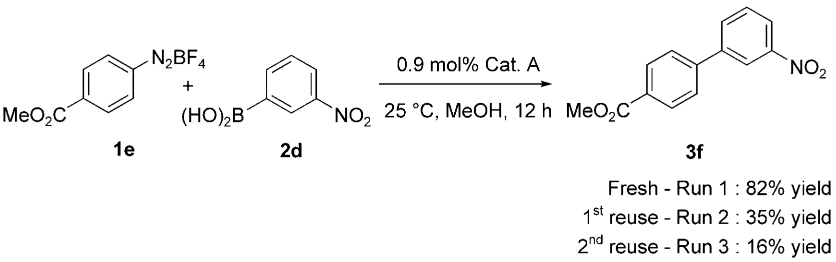
Table 2. Scope of the cross-coupling.



Entry	Diazonium salts	Boronic acid	Biphenyl	Cat. A [mol %]	Yield [%][a]
1	 1a	 2a	 3a	0.10	94
2	 1b	 2b	 3b	0.25	84
3	 1c	 2c	 3c	0.10	97
4	 1d	 2b	 3d	0.25	62
5	 1d	 2a	 3e	0.25	95
6	 1e	 2d	 3f	0.90	82
7	 1f	 2e	 3g	0.25	86
8	 1g	 2c	 3h	0.50	--[b]
9	 1h	 2b	 3i	0.25	78
10	 1i	 2f	 3j	0.25	77

[a] Yields are an average of two runs.
[b] No reaction.

the corresponding anilines with sodium nitrite and tetrafluoroboric acid.[9] Importantly, the prepared aryldiazonium tetrafluoroborates showed excellent stability over years when stored at −20 °C. Diazonium electrophiles compete favourably with less reactive and more expensive halogenated electrophiles as exemplified by reported industrial applications.[10] To our delight, the use of 2-nitrobenzenediazonium salt **1d** and 4-nitrobenzenediazonium salt **1e** as coupling partners was not prohibitive for the success of the reaction. Indeed, it has been reported that 2-nitrobenzenediazonium salts failed to participate in the Suzuki reaction with arylboronic acids with 10 mol% $Pd(OAc)_2$ in methanol.[6f] This failure has been ascribed to the high redox potentials and a preference for homolytic de-diazonization pathways. However, recent reports overcome this failure by the use of a C_2-symmetrical thiourea as ligand,[11] non-protic con-



Scheme 1.

ditions[6k] or other sources of palladium.[5b] The methodology is tolerant to a variety of electronically different substituents. Importantly, *ortho-* and especially *ortho*,*ortho'*-disubstitued biphenyls can be prepared in good yields while still maintaining the low loading of the catalyst (entry 10). These results are in sharp contrast with few reports that describe the inability of diazonium salts to participate in such cross-couplings.[6e,f] It should be noted that mesityldiazonium salt **1g** remained reluctant to participate in the cross-coupling as already observed by Genêt et al.[6b]

We further explored the catalyst recycling for the preparation of biphenyl **3f** (Scheme 1). Unfortunately, after the first run, the reused catalyst showed a strong deactivation leading to a modest yield of compound **3f**.

The inability to recycle the catalyst could not be attributed to a lower loading of palladium nanoparticles on the charcoal since only 3% of soluble palladium species (based on 100% introduced) remained in the solution at the end of the reaction as indicated by ICP-MS analyses. For a deeper understanding of the deactivation during the recycling process we investigated the catalyst evolution by transmission electron microscopy (TEM). As shown in Figure 3, a significant increase of the average of particle size from 20 nm to 120 nm occurred during the reaction and was correlated with the strong deactivation of the catalyst. This observation supports a homogeneous mechanism where catalytically active palladium nanoparticles are leached from the support and latter re-precipitated onto the charcoal at the end of the catalytic cycle as already observed by other groups.[12] However, the extremely mild conditions (25 °C) used in this study ruled out a temperature-induced leaching that could most likely occur during the oxidative addition of the diazonium salt.

The power of our protocol was then highlighted by a short and highly efficient synthesis of Boscalid® **5** a new fungicide marketed by BASF company

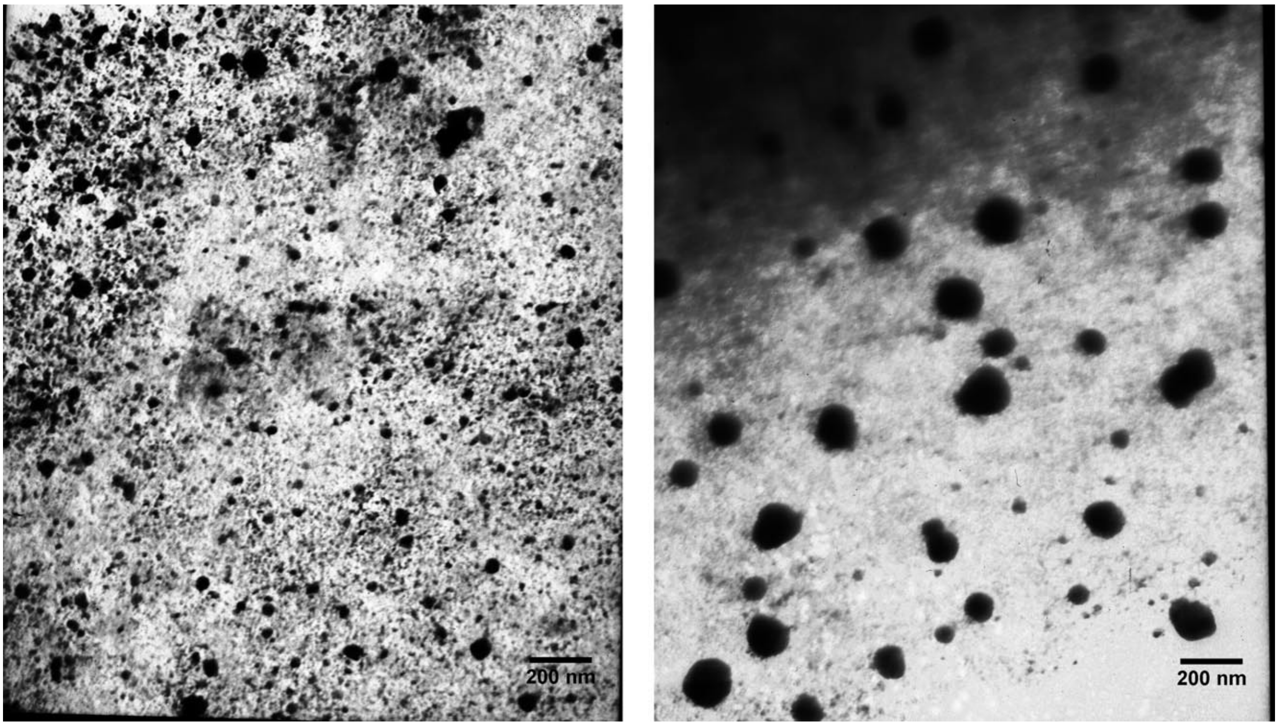
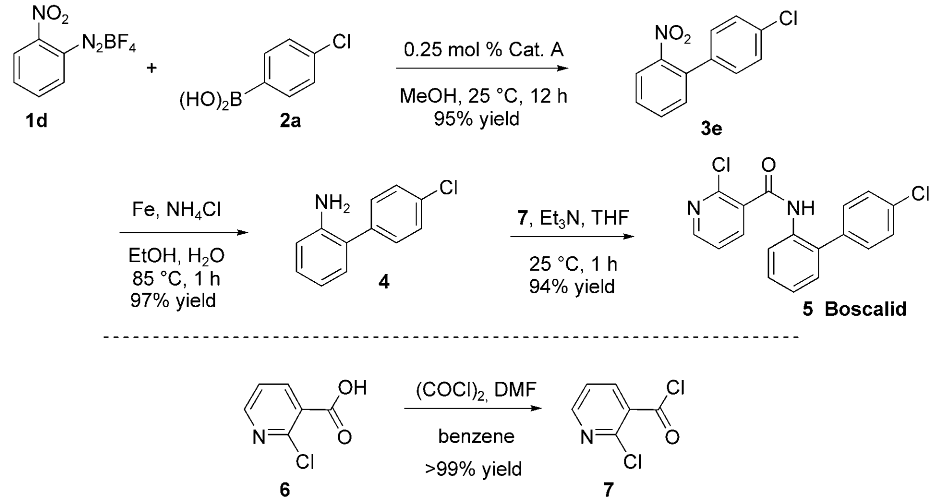


Figure 3. TEM images of the fresh catalyst A (*left*) and the reused catalyst A (*right*) at the same magnification.



Scheme 2. Short synthesis of Boscalid®.

(Scheme 2). Boscalid® **5** is used to control a range of plant pathogens in broadacre and horticultural crops. Although the patent application does not fully describe its synthesis,[13] Boscalid® **5** is currently one of the largest industrial applications of the Suzuki–Miyaura reaction (*ca.* 1000 tons/year).[14] Spivey et al. reported a synthesis of the fungicide based on a Pd-catalyzed reaction of an arylgermane to form the biphenyl core.[15] Very recently, Heinreich et al. reported a novel synthesis of Boscalid based on a original free-radical biaryl cross-coupling.[16]

As pointed out before, the cross-coupling of 2-nitrobezenediazonium tetrafluoroborate **1d** with 4-chlorobenzeneboronic acid **2a** gave a high yield of **3e** (95%) under extremely mild conditions (25 °C). A practical and particularly efficient iron-mediated reduction of the nitro group furnished **4** in 97% yield. Targeted Boscalid® **5** was finally obtained from the coupling of biphenylamine **4** with nicotinoyl chloride **7** (prepared from commercially available 2-chloronicotinic acid **6**). The three-steps synthesis proceeds with an exceptional 87% overall yield and could potentially be carried out on a larger scale.

Conclusions

In summary, we have developed a practical, efficient and general protocol for the cross-coupling of aryldiazonium tetrafluoroborate salts with boronic acids catalyzed by a well-defined Pd/C catalyst. The method has a wide substrate scope and provides biphenyls under particularly mild conditions without any additional additives (base and ligand). A short and efficient synthesis of the antifungal Boscalid® supports the usefulness of our protocol. We anticipated that this methodology could be of interest for medicinal, as well as, process chemists.

Experimental Section

General Remarks

Chemical shifts from proton and carbon NMR spectra are reported in ppm relative to the $CDCl_3$ peak at 7.26 ppm (^1H) or 77.0 ppm (^{13}C). Infrared (IR) spectra were recorded as neat samples on NaCl plates or with KBr pellets. The transmission electron microscopy (TEM) images have been performed with a Hitachi H-600 microscope. The catalysts were dispersed into methanol and samples of the solution have been taken and air-dried onto standard Formar/carbon-coated copper support grids. The micrographs of this work have been realised with the same magnification.

Yields refer to isolated material determined to be pure by NMR spectroscopy and thin layer chromatography (TLC), unless specified otherwise in the text. Diazonium salts used in this study were all known and prepared as described in the literature. Pd/C catalysts were commercially available from Evonik Degussa GmbH, Business Line Catalysts. An eggshell distribution means that palladium nanoparticles are distributed close to the surface of the charcoal. A uniform distribution means that palladium nanoparticles are homogeneously dispersed in the charcoal.

General Procedure for the Preparation of Biphenyl

To a solution of diazonium salt (1.5 mmol) in MeOH (15 mL) were added $ArB(OH)_2$ (1 mmol) and 5% Pd(0)/C (0.1–0.9 mol%, see Table 2). The resulting mixture was stirred for 12 h at 25 °C and then filtered and concentrated under reduced pressure. The crude was purified by flash chromatography to give the corresponding cross-coupled product.

4-Chloro-2′-methoxy-3′-nitrobiphenyl (3a): Purification by flash chromatography (10% EtOAc-petroleum ether) gave a white solid; mp 127 °C [Lit.[17] 120–122 °C]. IR (KBr): $\nu =$ 1584, 1615, 2844, 2922, 2980, 3090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 3.94$ (s, 3H), 7.04 (d, 1H, $J = 7.5$ Hz), 7.40–7.48 (m, 4H), 8.19 (d, 1H, $J = 2.2$ Hz), 8.25 (dd, 1H, $J = 2.2$, 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 56.3$, 110.8, 125.1, 126.1, 128.5, 130.1, 130.7, 134.1, 134.5, 141.5, 161.3; MS (EI):

m/z = 265 (M, ^{35}Cl), 265 (M, ^{37}Cl), 264 (M + H$^+$, ^{35}Cl), 266 (M + H$^+$, ^{37}Cl).

4-Methoxy-4′-nitrobiphenyl (3b): Purification by flash chromatography (5% EtOAc-petroleum ether) gave a yellow solid; mp 106 °C [Lit.[18] 107–108 °C]. IR (KBr): ν = 2930, 2968, 3052 cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 3.88 (s, 3H), 7.02 (dt, 2H, *J* = 3.1, 8.9 Hz), 7.58 (dt, 2H, *J* = 3.1, 8.9 Hz), 7.69 (dt, 2H, *J* = 2.4, 9.2 Hz), 8.27 (dt, 2H, *J* = 2.4, 9.2 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 55.4, 114.6, 124.1, 127.0, 128.5, 131.0, 146.5, 147.2, 160.4; MS (EI): *m/z* = 229 (M).

2-Methoxy-4-nitrobiphenyl (3c): Purification by flash chromatography (10% EtOAc-petroleum ether) followed by recrystallization (Et$_2$O-petroleum ether) gave a pale yellow solid; mp 90 °C [Lit.[19] 90–91 °C]. IR (KBr): ν = 1625, 2949, 3014, 3064, cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 4.00 (s, 3H), 7.17 (d, 1H, *J* = 8.9 Hz), 7.35–7.49 (m, 3H), 7.53–7.57 (m, 2H), 7.77 (dd, 1H, *J* = 2.5, 8.9 Hz), 8.09 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 56.6, 113.9, 124.0, 126.7, 127.8, 129.0, 132.5, 133.8, 138.3, 152.2; MS (EI): *m/z* = 229 (M).

4-Methoxy-2′-nitrobiphenyl (3d): Purification by flash chromatography (5% EtOAc-petroleum ether) gave a yellow solid; mp 62 °C [Lit.[20] 62–64 °C]. IR (KBr): ν = 1611, 2844, 2920, 3010 cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 3.85 (s, 3H), 6.96 (dt, 2H, *J* = 3.1, 8.8 Hz), 7.26 (dt, 2H, *J* = 2.8, 8.9 Hz), 7.41–7.48 (m, 2H), 7.56–7.62 (m, 1H), 7.80 (dd, 1H, *J* = 1.8, 8.6 Hz). ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 55.3, 114.2, 124.0, 127.7, 129.1, 129.4, 131.9, 132.1, 135.8, 149.4, 159.7; MS (EI): *m/z* = 229 (M).

4-Chloro-2′-nitrobiphenyl (3e): Purification by flash chromatography (5% EtOAc-petroleum ether) gave a yellow solid; mp 64 °C [Lit.[21] 61 °C]. IR (KBr): ν = 1530, 1609, 2866, 3068 cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 7.25 (dm, 2H, *J* = 8.7 Hz), 7.41 (dm, 2H, *J* = 8.7 Hz), 7.51 (app dt, 1H, *J* = 1.6, 8.1 Hz), 7.62 (app dt, 1H, *J* = 1.4, 7.5 Hz), 7.88 (dd, 1H, *J* = 1.2, 7.9 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 124.2, 128.5, 128.9, 129.2, 131.8, 132.5, 134.4, 135.2, 149.0; MS (EI): *m/z* = 233 (M, ^{35}Cl), 235 (M, ^{37}Cl), 197 (M–Cl).

4-Carboxymethyl-2′-nitrobiphenyl (3f): Purification by flash chromatography (10% EtOAc-petroleum ether) gave a white solid; mp 144 °C [Lit.[22] 145–147 °C]. IR (KBr): ν = 1609, 1718, 2952, 3002, 3072 cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 3.95 (s, 3H), 7.61–7.66 (m, 1H), 7.68 (d, 2H, *J* = 8.3 Hz), 7.92–7.95 (m, 1H), 8.14 (d, 2H, *J* = 8.3 Hz), 8.21–8.25 (m, 1H), 8.46 (app t, 1H, *J* = 2.0 Hz); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 50.2, 122.0, 122.8, 127.1, 129.9, 130.1, 130.4, 133.1, 141.6, 142.8, 148.7, 166.5; MS (EI): *m/z* = 257 (M), 226 (M–OCH$_3$).

3,4-Dimethoxy-3′-trifluoromethylbiphenyl (3g): Purification by flash chromatography (10% EtOAc-petroleum ether) gave a pale yellow oil. IR (neat): ν = 2838, 2939, 3002 cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 3.94 (s, 3H), 3.97 (s, 3H), 6.97 (d, 1H, *J* = 6.9 Hz), 7.09 (d, 1H, *J* = 1.9 Hz), 7.16 (dd, 1H, *J* = 1.6, 6.9 Hz), 7.50–7.58 (m, 2H), 7.73 (d, 1H, *J* = 6.0 Hz), 7.79 (s, 1H); MS (EI): *m/z* = 282 (M); HR-MS (electrospray): *m/z* = 305.0768, calcd. for C$_{15}$H$_{13}$O$_2$F$_3$Na (M + Na$^+$): 305.0765.

4-Methoxy-4′-isopropylbiphenyl (3i): Purification by flash chromatography (2% EtOAc-petroleum ether) gave a white solid; mp 95 °C. IR (KBr): ν = 1497, 1605, 2834, 2868, 2961, 2996, 3028 cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 1.33 (d, 6H, *J* = 6.9 Hz), 2.99 (sep, 1H, *J* = 7.3 Hz), 3.87 (s, 3H), 7.00 (d, 2H, *J* = 8.5 Hz), 7.32 (d, 2H, *J* = 8.1 Hz), 7.51–7.58 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 24.0, 33.7, 55.3, 114.1, 126.6, 126.8, 127.0, 133.7, 138.3, 147.3, 158.9; HR-MS (electrospray): *m/z* = 249.1252, calcd. for C$_{16}$H$_{18}$ONa (M + Na$^+$): 249.1250.

2-Bromo-2′-methylbiphenyl (3j): Purification by flash chromatography (100% petroleum ether) gave a colorless oil. IR (neat): ν = 1465, 2922, 3018, 3057 cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 2.12 (s, 3H), 7.11–7.15 (m, 1H), 7.19–7.40 (m, 6H), 7.64–7.69 (m, 1H); ^{13}C NMR (CDCl$_3$, 62.5 MHz): δ = 19.8, 123.7, 125.5, 127.2, 127.9, 128.7, 129.2, 129.8, 130.8, 132.5, 135.9, 141.1, 142.6; MS (EI): *m/z* = 248 (M, ^{81}Br), 246 (M, ^{79}Br).

2-Amino-4′-Chlorobiphenyl (4)

To a solution of 4-chloro-2′-nitrobiphenyl **3e** (211 mg, 0.91 mmol) in EtOH (3 mL) was added Fe powder (154 mg, 2.75 mmol), NH$_4$Cl (29 mg, 0.54 mmol) and H$_2$O (1 mL). The resulting mixture was stirred for 1 h at 85 °C, then, cooled to room temperature, extracted with CH$_2$Cl$_2$ (3 ×) and dried over MgSO$_4$. Filtration over a microfilter (0.45 μm) and concentration under reduced pressure gave **4** as a pale yellow solid which was used in the next step without further purification; yiled: 176 mg (96%); mp 45 °C. IR (KBr): ν = 1482, 1615, 2925, 3028, 3063, 3376, 3462 cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 3.70 (br s, 2H), 6.77 (dm, 1H, *J* = 7.9 Hz), 6.84 (dt, 1H, *J* = 1.2, 7.5 Hz), 7.10 (dm, 1H, *J* = 7.5 Hz), 7.17–7.21 (m, 1H), 7.42 (s, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 124.2, 128.5, 128.9, 129.2, 131.8, 132.5, 134.4, 135.2, 149.0; MS (EI): *m/z* = 203 (M, ^{35}Cl), 205 (M, ^{37}Cl), 168 (M–HCl).

Boscalid® (5)

A solution of chloronicotinic acid (210 mg, 1.34 mmol) in benzene (7 mL) was treated with (COCl)$_2$ (0.23 mL, 2.68 mmol) and two drops of DMF. After 1 h of stirring at room temperature, the resulting mixture was concentrated under reduced pressure and dissolved in THF (5 mL). To this mixture was added a solution of aniline (170 mg, 0.84 mmol) in THF (5 mL) followed by Et$_3$N (0.23 mL, 1.68 mmol). The reaction mixture was stirred for 1 h at room temperature and concentrated under vacuum. Purification by flash chromatography (40% EtOAc-petroleum ether) gave **5** as a white solid; yield: 270 mg (94%); mp 143 °C. IR (KBr): ν = 1652, 2850, 3023, 3171, 3254, 3288 cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 7.28–7.48 (m, 8H), 8.10 (dd, 1H, *J* = 2.0, 7.7 Hz), 8.17 (br s, 1H), 8.39 (d, 1H, *J* = 8.7 Hz), 8.42 (dd, 1H, *J* = 2.0, 4.8 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 122.1, 122.8, 125.3, 128.8, 129.2, 130.2, 130.7, 131.0, 132.2, 134.2, 134.4, 136.2, 140.0, 146.6, 151.2, 162.5; HR-MS (electrospray): *m/z* = 365.0202, calcd. for C$_{18}$H$_{12}$N$_2$ONaCl$_2$ (M + Na$^+$): 365.0218.

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