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A Sustainable 1-Pot, 3-Step Synthesis of Boscalid Using Part per Million Level Pd Catalysis in Water

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Supporting Information

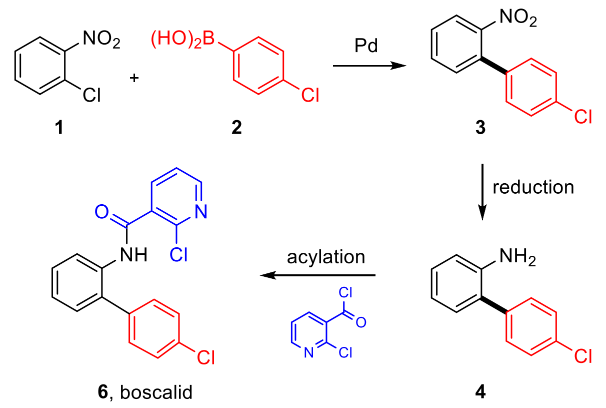
ABSTRACT: Boscalid is an active ingredient in several fungicides marketed by the BASF. Literature approaches use multipot processes, organic solvents, and unsustainable levels of palladium catalysis. Herein is disclosed a 1-pot, 3-step route using nanomicelles in water as the reaction medium and a very low loading (700 ppm or 0.07 mol %) of costly and endangered Pd. The sequence developed involves an initial Suzuki−Miyaura cross-coupling, the product from which is not isolated. The second step relies on a carbonyl iron powder (CIP) reduction of the aryl nitro group, followed by the third and final step involving an acylation with the required 2-chloronicotinyl chloride. The overall isolated yield for these three steps is 83%.

KEYWORDS: *boscalid, 1-pot synthesis, Suzuki−Miyaura coupling, chemistry in water*

INTRODUCTION

Boscalid[1] is an active ingredient found in several fungicides (Emerald, Endura, and Pristine) marketed by the BASF beginning in 2003.[2] Currently, it is produced in excess of 1000 MTs per year,[3] being used to prevent gray/blue mold produced due to *Botrytis cinerea* and *Penicillium expansum* in plants.[4] One common synthetic approach to boscalid is shown in Scheme 1. In the patented route by the BASF, although complete details about the process are lacking, the sequence involved (1) a Pd(0)-catalyzed Suzuki−Miyaura (SM) coupling, (2) reduction of the nitrobiaryl intermediate, and (3) an amide bond construction. A few new routes have appeared recently,[5] including one utilizing flow chemistry;[6] however, all involve use of organic solvents, high catalyst loadings, and especially high temperatures. Moreover, selective nitro group reduction in the presence of an aryl chloride required expensive Pt/C under high pressure of hydrogen.[5,6] Dunst and Knochel used an alternative approach to replace the Suzuki−Miyaura (SM) reaction by a Kumada-type coupling leading to the desired biarylamine in 70% yield with 1 mol % of a Pd catalyst.[7] In short, none of these methods offer an environmentally sustainable, benign approach. In recent years, an awareness of green processes, metrics such as PMI[8] and E Factors,[9] and attention to waste creation and its proper handling have increased dramatically, in part due to environmental policies.[10] Our contributions have focused in large measure on reducing, if not completely removing, organic solvents as currently used for chemical reactions.[11] In addition, real prospects now exist for reducing use of endangered Pd-catalyst loadings to ppm levels for key Suzuki−Miyaura cross couplings, among other Pd-catalyzed processes,[12] thereby significantly reducing the cost of this precious metal catalysis.[13]

Scheme 1. Synthetic Pathway toward Boscalid



RESULTS AND DISCUSSION

Initially, optimization of the SM coupling was studied using Pd catalysts based on either PPh_3 or SPhos ligands (Table 1). Stirring 2-chloronitrobenzene **1** with boronic acid **2** using $Pd(OAc)_2/PPh_3$ (1:2; 0.5 mol %, or 5000 ppm Pd), as catalyst under aqueous micellar conditions at 45 °C led to 54% conversion to the desired biaryl product **3** (entry 1). Increasing the temperature to 55 °C did not increase the extent of conversion (entry 2). Also, increasing the ratio of Pd/L to 1:4 did not significantly change the outcome of this coupling (entry 3). Raising the temperature further to 70 °C increased the yield (entry 4); however, the extent of completion even after simultaneously increasing the Pd loading (entry 5) was not satisfactory. In efforts to minimize the amount of Pd required, the ligand was then switched to SPhos. In this case, reaction was complete using 5000 ppm Pd at 45 °C (entry 6).

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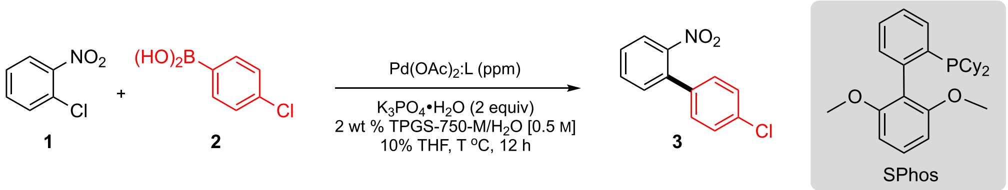
Table 1. Catalyst Screening for SM Couplings[a]

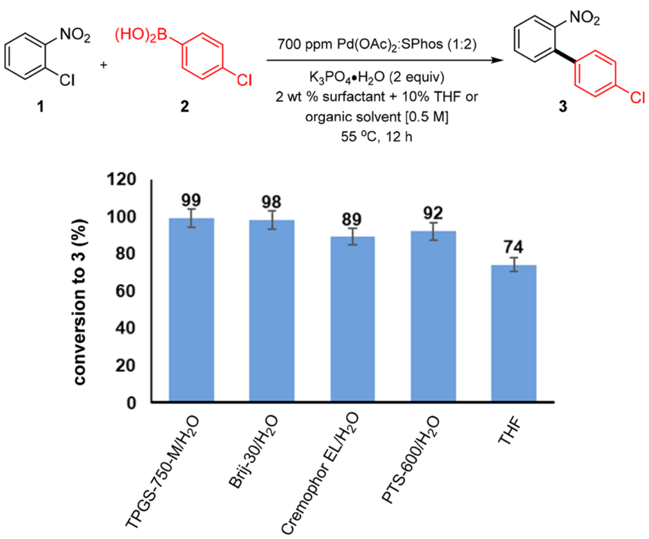


entry	Pd/L (ppm)	T (°C)	conv. to **3** (%)[b]
1	$Pd(OAc)_2/PPh_3$ (5000:10000)	45	54
2	$Pd(OAc)_2/PPh_3$ (5000:10000)	55	60
3	$Pd(OAc)_2/PPh_3$ (5000:20000)	45	56
4	$Pd(OAc)_2/PPh_3$ (5000:20000)	70	72
5	$Pd(OAc)_2/PPh_3$ (7000:28000)	70	73
6	$Pd(OAc)_2$/SPhos (5000:8000)	45	100
7	**$Pd(OAc)_2$/SPhos**(700:1400)	**55**	**100**
8	$Pd(OAc)_2$/SPhos (500:1000)	55	73
9	$Pd(OAc)_2$/SPhos (300:600)	55	57
10	$Pd(OAc)_2$/SPhos (400:800)	65	100[c]

[a] Reaction conditions: 0.5 mmol of **1**, 0.55 mmol of **2**, 1 mmol of $K_3PO_4 \cdot H_2O$, and Pd/L catalyst were stirred in 1 mL of 2 wt % TPGS-750-M/H_2O−THF (9:1) for 12 h at the given temperature. [b] Conversion determined by GC-MS. [c] 22 h.

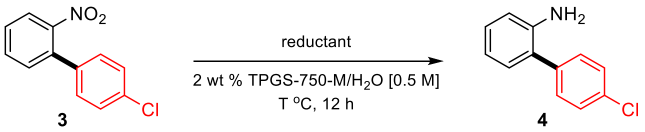
Further lowering the catalyst loading to only 700 ppm of Pd in combination with 1400 ppm of SPhos sufficed to arrive at quantitative conversion, in this case achieved by increasing the reaction temperature to 55 °C (entry 7). Further lowering of the Pd loading to 300−500 ppm under these reaction conditions reduced the conversion to product to only 57−73% (entries 8 and 9). Nonetheless, with another ten degree temperature rise to 65 °C, the Pd loading could be reduced to 400 ppm while maintaining a 100% conversion to product (entry 10). Screening of surfactants in the presence of 10% THF as cosolvent suggested that both TPGS-750-M and Brij-30 are interchangeable; each led to excellent conversion (Scheme 2). By contrast, the same coupling run under otherwise identical conditions, but using pure THF as reaction medium, gave an inferior result compared to the aqueous micellar system.

Scheme 2. Reaction Medium Screening for SM Coupling of 1 + 2



We next focused on optimization of the nitro group reduction, screening a wide variety of reducing agents using the same aqueous micellar system (Table 2). The most commonly used reagent, Pd/C, along with a balloon of hydrogen at 45 °C, led to full conversion but resulted in only a 44% yield of the isolated product, along with dechlorination (of the reduced product) as the major, undesired product (51%; entry 1). An attempt to replace Pd/C with Pt/C, using a hydrogen balloon, led to 68% of the isolated product along with the formation of an unknown impurity. Similar results were obtained when Fe/ppm Pd + Ni nanoparticles were used (entry 3).[14] In this case, the desired product was isolated in 70% yield, along with 25% dechlorinated material. Ultimately, carbonyl iron powder (CIP) together with NH_4Cl at 45 °C afforded an 85% yield of the desired aniline with some starting material recovered (entry 5).[15]

Table 2. Optimization of Nitro Group Reduction[a]

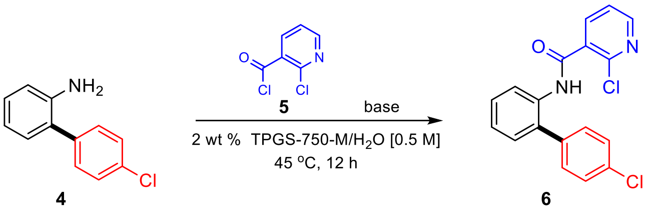


entry	reductant	T (°C)	conv. to **4** (%)[b]
1	1 mol % Pd/C, H_2 balloon	45	44[c]
2	0.5 mol % Pt/C, H_2 balloon	45	(68)[d,f]
3	Fe/ppm Pd + Ni NPs, $NaBH_4$ (3 equiv)	rt	70[e]
4	CIP (5 equiv), NH_4Cl (3 equiv)	rt	50
5	**CIP (5 equiv), NH_4Cl (3 equiv)**	**45**	**89 (85)**[f]

[a] Reaction conditions: 0.5 mmol of **3**, stirred along with the reducing system in 1 mL of 2 wt % TPGS-750-M/H_2O at a given temperature. [b] Conversion determined by GC-MS. [c] 1 wt % Pd/C was used, dechlorinated product obtained (51%). [d] 5 wt % Pt/C was used. [e] Dechlorinated product obtained (25%). [f] Isolated yield in parentheses.

The last step in the synthesis, acylation of the aniline **4**, was optimized leading to quantitative conversion of **4** to **6** (Table 3). Thus, while Hünig's base (i-Pr_2NEt) led to complete

Table 3. Final Step: Amide Formation[a]

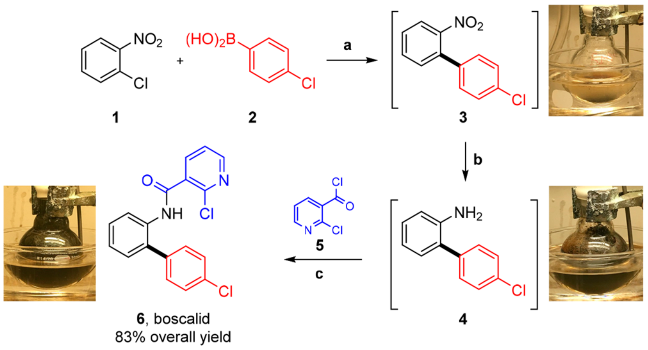


entry	base	conv. to 6 (%)[b]
1	Et$_3$N (2 equiv)	65
2	***i*-Pr$_2$NEt (2 equiv)**	**100 (97)**[c]
3	pyridine (2 equiv)	68
4	none	28

[a]Reaction conditions: 0.5 mmol of **4**, 0.75 mmol of **5**, and 1.0 mmol of base were stirred for 12 h in 1 mL of 2 wt % TPGS-750-M/H$_2$O at 45 °C. [b]Conversion determined by GC-MS. [c]Isolated yields in parentheses.

conversion (entry 2), other bases such as triethylamine (entry 1) and pyridine (entry 3) gave far lower levels of product formation. In the absence of base, the reaction was especially slow (entry 4).

Scheme 3. Gram Scale 1-Pot Synthesis of Boscalid[a]



[a]Reaction conditions: (a) 5 mmol of **1**, 5.5 mmol of **2**, 10 mmol of K$_3$PO$_4$·H$_2$O, Pd(OAc)$_2$/SPhos (700:1400 ppm), 10 mL of 2 wt % TPGS-750-M/H$_2$O−THF (9:1), 55 °C, 12 h; (b) CIP (5 equiv), NH$_4$Cl (3 equiv), 45 °C, 12 h; (c) 2.0 equiv of *i*-Pr$_2$NEt, 1.5 equiv of **5**, 45 °C, 16 h.

Once optimization conditions associated with each step had been determined, the feasibility of this sequence being conducted in water on a larger 5 mmol scale was examined, all in a single reaction vessel (Scheme 3). Initial SM coupling went smoothly, leading with quantitative conversion to biaryl **3** (confirmed with GC-MS). Without workup or isolation, reduction to amine **4** followed via addition of CIP, which was complete in 12 h. The newly formed amine was treated directly with 2-chloronicotinyl chloride **5** in the presence of Hünig's base. Upon full conversion, 1.42 g of boscalid could be isolated (83% overall yield).

■ CONCLUSION

In summary, an overall high yielding, 1-pot, environmentally responsible synthesis of boscalid, a widely used fungicide, has been demonstrated. Each of the three steps can be carried out in water containing nanomicelles as reaction medium. The key Suzuki−Miyaura coupling requires only 700 ppm (0.07 mol %) Pd in the presence of a commercially available ligand (SPhos, 1400 ppm or 0.14 mol %). This sequence is representative of the potential for chemistry in water using nanoparticle technology to significantly reduce not only the cost but simultaneously waste creation, two issues typically associated with traditional syntheses in organic solvents.

■ EXPERIMENTAL SECTION

A solution of 2 wt % surfactant/H$_2$O was prepared by dissolving the desired surfactant in degassed HPLC grade water and was stored under argon. TPGS was made as previously described.[16] All commercially available reagents were used without further purification. THF was taken from an Innovative Technologies Solvent Purification System (SPS) and used immediately. Thin layer chromatography (TLC) was done using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). Flash chromatography was done in glass columns using Silica Gel 60 (EMD, 40−63 μm). ^{1}H and ^{13}C NMR were recorded at 23 °C on a Varian Unity Inova 500 MHz spectrometer in CDCl$_3$ with residual CHCl$_3$ (^{1}H = 7.26 ppm, ^{13}C = 77.20 ppm) as internal standard. Chemical shifts are reported in parts per million (ppm).

The Stock Solution for ppm Pd Use. In a 2-dram vial, 3.9 mg of Pd(OAc)$_2$ and 14.4 mg of ligand (SPhos) were added. The vial was capped with a rubber septum and evacuated and then backfilled with argon (repeated 3 times), and 5.0 mL of degassed THF was added under positive argon flow. The amount of THF was manipulated so that it served as 10% cosolvent for the reaction scale used in Suzuki−Miyaura coupling (*vide infra*), for example, for 0.5 mmol scale reaction 0.079 mg of Pd(OAc)$_2$ and 0.29 mg of SPhos in 100 μL of THF, which corresponds to 700 ppm Pd/0.5 mmol scale reaction.

Procedure for Suzuki−Miyaura Coupling. In a 1-dram vial containing a Teflon-coated stir bar, 78.8 mg (0.50 mmol) of 2-chloronitrobenzene **1**, 86.0 mg (0.55 mmol) of 4-chlorophenylboronic acid **2**, and 230.3 mg (1.0 mmol) of K$_3$PO$_4$·H$_2$O were added, and the vial was evacuated and backfilled with argon (this process was repeated three times). Finally, 100 μL of the above stock solution, corresponding to 700 ppm Pd (0.07 mol %), and 0.9 mL of 2 wt % aqueous surfactant solution were added under argon. The vial was quickly screw capped and then stirred at 55 °C until completion (as monitored on TLC or GC-MS). The reaction mixture was absorbed on silica and purified by flash column using a hexanes/EtOAc (9:1) gradient to obtain the desired product (114.2 mg; 98%) as light yellow oil.

Procedure for Nitro Reduction Using CIP and NH$_4$Cl. In a 1-dram vial with Teflon-coated stir bar were added 116.5 mg of nitrobiphenyl **3** (0.5 mmol, 1.0 equiv), 139.6 mg of carbonyl Fe powder (CIP; 2.5 mmol, 5.0 equiv), and 80.4 mg of NH$_4$Cl (1.5 mmol, 3.0 equiv). To this vial, 1.0 mL of 2 wt % TPGS-750-M/H$_2$O was added, and the vial was capped and stirred vigorously at 45 °C for 12 h. The contents of the reaction mixture were then directly absorbed on silica and purified by flash column using a hexanes/EtOAc (9:1) gradient to obtain the desired product as yellow oil (86.23 mg; 85%), which solidified on cooling.

Procedure for Amide Construction. In a 1-dram vial with Teflon-coated stir bar were added 101.5 mg of aminobiphenyl **4** (0.5 mmol, 1.0 equiv), 174.7 μL of *i*-Pr$_2$NEt (1.0 mmol, 2.0 equiv), and 1.0 mL of 2 wt % TPGS-750-M/H$_2$O. The reaction mixture was stirred gently at rt before addition of 131.2 mg of 2-chloronicotinyl chloride **5**

(0.75 mmol, 1.5 equiv). The reaction mixture was then stirred vigorously at 45 °C until complete conversion of the amine to the amide was observed by TLC. The contents of the reaction mixture were directly absorbed on silica and purified by flash column using hexanes/EtOAc (9:1 to 1:9) gradient to obtain the desired product as a white powder (165.9 mg; 97%).

Procedure for 1-Pot, Large-Scale Synthesis of Boscalid in Water. In a 25 mL round-bottom flask were added 0.79 g (5.0 mmol) of 2-chloronitrobenzene **1**, 0.86 g (5.5 mmol) of 4-chlorophenylboronic acid **2**, and 2.30 g (10 mmol) of $K_3PO_4 \cdot H_2O$, and the flask was evacuated and backfilled with argon (this process was repeated three times). Finally, 1.0 mL from the stock solution containing 700 ppm of Pd was added before adding 9.0 mL of 2 wt % TPGS-750-M/H_2O. The reaction mixture was stirred vigorously at 55 °C for 15 h under argon. The reaction mixture was cooled to rt, and 1.34 g of carbonyl Fe powder (CIP; 25 mmol, 5.0 equiv) and 0.81 g of NH_4Cl (15 mmol, 3.0 equiv) were added. The reaction flask was placed again in an oil bath and heated at 45 °C for 12 h. The flask was then cooled to rt, and 1.8 mL of *i*-Pr_2NEt (10.0 mmol, 2.0 equiv) and 0.44 g of 2-chloronitotinyl chloride (2.5 mmol, 0.5 equiv) was added at one time. It was then heated at 45 °C for 2 h. A second portion, 0.44 g (2.5 mmol, 0.5 equiv), of 2-chloronicotinyl chloride was added all at once, and stirring was then continued for another 2 h, after which the final portion, 0.44 g (0.5 equiv), of 2-chloronicotinyl chloride was added, again all at one time. The reaction was allowed to stir at 45 °C for 12 h (total 16 h reaction time), and upon completion (monitored on TLC), the reaction mixture was extracted with EtOAc (4 × 10 mL). The organic layer was evaporated, and the material was further purified using flash chromatography to afford 1.42 g of boscalid **6** (83% overall yield). Boscalid could also be recrystallized by a known literature method.[1a] Spectral data for the isolated material matched that in the literature.[5]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.9b00455.

Compound characterization data and NMR spectra for **3**, **4**, and **6** (PDF)

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Notes

The authors declare no competing financial interest.

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