DOI: 10.1002/adsc.201000646

Toward a Continuous-Flow Synthesis of Boscalid®

Toma N. Glasnov[a] and C. Oliver Kappe[a,*]

[a] Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of Chemistry, Karl-Franzens University Graz, Heinrichstrasse 28, A-8010 Graz, Austria
Fax: (+43)-316-380-9840; phone: (+43)-316-380-5352; e-mail: oliver.kappe@uni-graz.at

Received: August 18, 2010; Published online: November 9, 2010

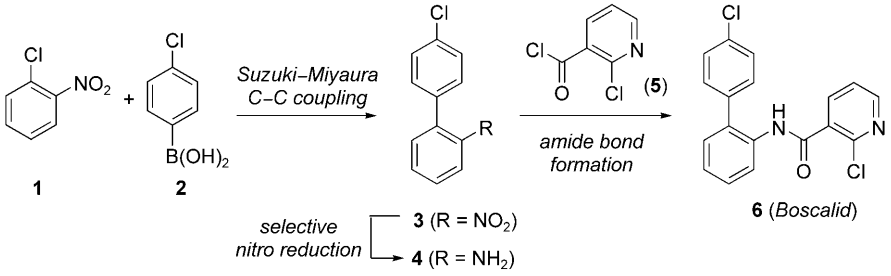
Abstract: A two-step continuous-flow protocol for the synthesis of 2-amino-4′-chlorobiphenyl, a key intermediate for the industrial preparation of the fungicide Boscalid® is described. Initial tetrakis(triphenylphosphine)palladium-catalyzed high-temperature Suzuki–Miyaura cross-coupling of 1-chloro-2-nitrobenzene with 4-chlorophenylboronic acid in a microtubular flow reactor at 160 °C using the *tert*-butanol/water/potassium *tert*-butoxide solvent/base system provides 4′-chloro-2-nitrobiphenyl in high yield. After in-line scavenging of palladium metal with the aid of a thiourea-based resin, subsequent heterogeneous catalytic hydrogenation is performed over platinum-on-charcoal in a dedicated continuous-flow hydrogenation device. The overall two-step homogeneous/heterogeneous catalytic process can be performed in a single operation providing the desired 2-amino-4′-chlorobiphenyl in good overall yield and high selectivity.

Keywords: cross-coupling; flow chemistry; heterogeneous catalysis; homogeneous catalysis; hydrogenation; microwave chemistry

Introduction

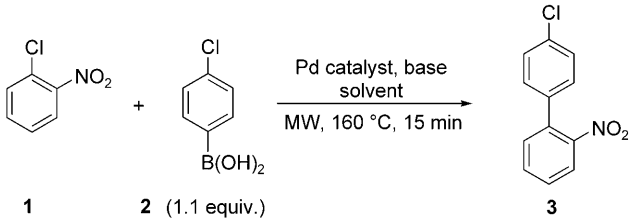
Boscalid® (**6**) is an important fungicide belonging to the class of succinate dehydrogenase inhibitors that enables the efficient control of ascomycetes on various fruits and vegetables.[1] Introduced into the market by BASF in 2003, the current total production volume of this fungicide is more than 1000 tons/year.[2] Although not described in full detail in the relevant patent literature,[3] the industrial synthesis of Boscalid® outlined in Scheme 1 relies on the Pd(0)-catalyzed Suzuki–Miyaura cross-coupling of 1-chloro-2-nitrobenzene (**1**) with 4-chlorophenylboronic acid (**2**). The obtained 4′-chloro-2-nitrobiphenyl intermediate (**3**) can then be selectively reduced to the corresponding aniline **4**, thus preserving the halogen functionality, which plays an important role for fungicidal activity.[1] In the final step, aniline **4** is reacted with 2-chloronicotinoyl chloride (**5**) to produce Boscalid® (**6**). The key Pd(0)-catalyzed carbon-carbon cross-coupling step leading to biaryl **3** is currently one of the largest known industrial applications of the Suzuki–Miyaura reaction.[2,4]

In the past few years, the use of microreactors and continuous-flow technology in general has become increasingly popular in synthetic organic chemistry.[5,6] Because of the high surface-to-volume ratio in microreactors, heat transfer is very efficient and reaction temperatures in microreactors can be changed efficiently by application or removal of heat. Enhanced mass transfer characteristics and the ability to efficiently optimize reaction conditions by control of residence time add value to the technology. In addition, process intensification can readily be achieved by operating in a high-temperature/high-pressure regime.[7] A particularly attractive feature of microreaction technology is the ease with which reaction conditions



Scheme 1. Industrial synthesis of Boscalid®.[3]

Table 1. Reaction optimization for the microwave-assisted Pd-catalyzed Suzuki–Miyaura coupling of 1-chloro-2-nitrobenzene (**1**) with 4-chlorophenylboronic acid (**2**).[a]



1 **2** (1.1 equiv.) **3**

Entry	Catalyst [mol%]	Base [equiv.]	Additive [equiv.]	Solvent [v/v]	Product distribution 1/**3**/D [%][b]
1	$Pd(OAc)_2$ [1.0]	K_3PO_4, [3]	TBAB [0.1]	DMF:H_2O, [1:1]	22/**53**/25
2	$Pd(OAc)_2$ [1.0]	(i-Pr)$_2$NEt, [1.5]	TBAB [0.1]	DMF:H_2O, [1:1]	97/**0**/3
3	$Pd(OAc)_2$ [1.0]	KOH, [1.5]	–	DMF:H_2O, [6:1]	31/**50**/19
4	$Pd(OAc)_2$ [5.0]	KOH, [1.5]	TBAB [0.5]	THF:H_2O, [6:1]	26/**58**/16
5	$PdCl_2$ [0.15]	NaOH [2.0]	PPh_3 [0.006]	THF:H_2O, [3:1]	100/**0**/0
7	Pd/C [0.25]	NaOH [2.0]	PPh_3 [0.01]	THF/H_2O [1:1]	64/**36**/0
8	Pd/C [0.5]	NaOH [2.0]	PPh_3 [0.02]	THF/H_2O [1:1]	8/**90**/2
9	$Pd(PPh_3)_4$ [0.5]	KOH [1.3]	–	THF/H_2O [6:1]	0/**89**/11
10[c]	$Pd(PPh_3)_4$ [0.25]	NaOH [1.3]	TBAB [0.025]	THF/H_2O [1:1]	0/**99**/1
11[c]	$Pd(PPh_3)_4$ [0.25]	NaOH [1.3]	–	THF/H_2O [1:1]	0/**99**/1
12	$Pd(PPh_3)_4$ [0.25]	NaOEt [2]	–	EtOH	0/**99**/1
13	$Pd(PPh_3)_4$ [0.25]	K-t-OBu [1.3]	–	t-BuOH	0/**98**/2
14[c]	$Pd(PPh_3)_4$ [0.25]	K-t-OBu [1.3]	–	t-BuOH/H_2O [4:1]	0/**99**/1

[a] *General reaction conditions:* 0.2 mmol 1-chloro-2-nitrobenzene (**1**), 0.22 mmol (1.1 equiv.) 4-chlorophenylboronic acid (**2**), 2 mL of solvent, sealed vessel single-mode microwave irradiation (Monowave 300, Anton Paar GmbH). See the Experimental Section for further information.

[b] Product distribution refers to relative peak area (%) ratios of crude GC-MS traces: starting material **1**/product **3**/dehalogenated product (nitrobenzene).

[c] Only these protocols were sufficiently homogeneous to be transferred to a flow process.

can be scaled through the operation of multiple systems in parallel or other techniques, thereby readily achieving production scale capabilities.[8]

With this background in mind we herewith describe a continuous-flow protocol for the generation of the key Boscalid® intermediate 2-amino-4′-chlorobiphenyl (**4**, Scheme 1) employing a combination of two process intensified microreactor steps.

Results and Discussion

Although in recent years a number of alternative transition metal-catalyzed cross-coupling protocols for the synthesis of the initial 4′-chloro-2-nitrobiphenyl intermediate **3** have been disclosed in the literature,[9–14] our continuous-flow route toward Boscalid® is based on the original Suzuki–Miyaura BASF strategy (Scheme 1) as this appeared to be the most practical and economical route. Following the "microwave-to-flow" optimization paradigm,[15,16] all three reaction steps were first investigated on a small scale using sealed vessel batch microwave heating as a process intensification method in order to derive at the shortest possible reaction times, a prerequisite for achieving high throughput in continuous-flow synthesis.[7,8]

The starting point for our studies involved the adaptation of the originally disclosed[3] Suzuki–Miyaura cross-coupling of 1-chloro-2-nitrobenzene (**1**) with 4-chlorophenylboronic acid (**2**) to 4′-chloro-2-nitrobiphenyl (**3**) into a high-speed microwave protocol. The most favourable reaction conditions for this cross-coupling described in the patent literature utilize either a combination of a Pd(II) salt and phosphine ligand [PPh_3, (t-Bu)$_3$P], or $Pd(PPh_3)_4$ complex as transition metal catalyst (catalyst loading 0.15–3.5 mol%).[3] In a typical coupling experiment either THF, DME or toluene is used as solvent in combination with aqueous NaOH or Na_2CO_3 as base.[3] Reported reaction times to achieve complete conversion for this Suzuki–Miyaura cross-coupling are between 8 and 18 h at 65–100 °C, clearly unsuitable for continuous-flow processing where reaction times (=residence times) of a few minutes are generally desired.[5–8]

In our hands, performing the Suzuki–Miyaura cross-coupling under controlled microwave conditions in a dedicated single-mode reactor with accurate internal temperature control (Monowave 300, Anton Paar GmbH) proceded very well.[17] For most of the evaluated catalyst systems [in particular for

$Pd(PPh_3)_4$], solvents and additive combinations, high conversions were achieved employing 1.1 equivalents of the boronic acid and selecting 160 °C as the reaction temperature and 15 min as reaction time (Table 1).[18] Lower reaction temperatures or shorter times led to a slower cross-coupling, less attractive for subsequent flow processing, whereas higher temperatures produced more undesired side products. Special attention was paid to the selection of a proper base for this transformation, keeping the general requirement for homogeneous reaction conditions in the continuous-flow process in mind.[5–8] Various organic and inorganic bases such as $(i\text{-Pr})_2NEt$, K_2CO_3, Cs_2CO_3, NaOMe, NaOEt and *t*-BuOK were tested and compared to the originally reported NaOH and Na_2CO_3.[3] Similarly, different solvents including MeOH, EtOH, *n*-BuOH, *t*-BuOH, DMF, DME and solvent mixtures containing varying amounts of water were also evaluated as possible reaction media. Different sources of catalytic Pd such as $PdCl_2$ and $Pd(OAc)_2$ were also examined. From this reagent matrix we were able to identify the two optimal sets of conditions which worked particularly well under batch microwave conditions and fulfilled the criteria of short reaction times and reaction homogeneity throughout the overall process: (i) THF/H_2O (1:1) as a solvent mixture, 0.25 mol% $Pd(PPh_3)_4$ as a catalyst and 1.3 equivalents of NaOH as a base; or (ii) *t*-BuOH/H_2O (4:1) as a solvent mixture, 0.25 mol% $Pd(PPh_3)_4$ as a catalyst and 1.3 equivalents of *t*-BuOK as a base (see Table 1, entries 11 and 14). Utilizing these conditions, the Suzuki–Miyaura cross-couplings were remarkably clean in the concentration range of 0.1–1.0 M with only minute amounts of dehalogenated side product (nitrobenzene, traces) being observable by GC-MS analysis of the crude reaction mixture. Employing a reaction temperature of 160 °C (~10 bar) and a reaction time of 15 min, full conversion was observed for both protocols, providing 4′-chloro-2-nitrobiphenyl (**1**) in 91% isolated yield after chromatographic purification.

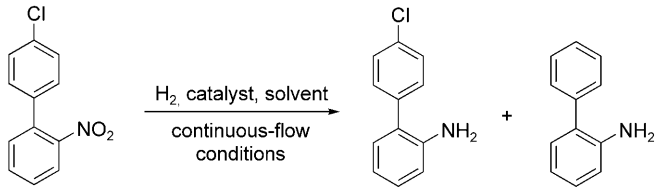
Continuous-flow experimentation was performed in a high-temperature, high-pressure microtubular flow unit that can be used for processing homogeneous reaction mixtures (X-Cube Flash, Thales Nanotechnology Inc.).[19] The reactor uses stainless steel coils (i.d. 1000 μm) of variable length (4, 8, and 16 mL volume) that can be directly heated across their full length by electric resistance heating to temperatures up to 350 °C. The reaction mixture is introduced to the reactor block containing the steel coils and a heat exchanger *via* one or more standard HPLC pumps (flow rate: 0.01–10.0 mL min^{-1}). The system pressure valve sets and stabilizes the set pressure value between a pressure range of 50–180 bar. Before moving to a flow format we ensured that the rate enhancements seen for the Suzuki–Miyaura cross-coupling **1**+**2**→**3** comparing conventional heating (65–100 °C, 8–22 h)[3] with microwave heating (160 °C, 15 min, Table 1) were in fact only due to a thermal effect and not to a direct involvement of the electromagnetic field, and therefore could be mimicked in a conventionally heated flow system. For this purpose the two optimized sets of conditions (Table 1, entries 11 and 14) were repeated in the microwave batch reactor employing a reaction vessel made out of strongly microwave absorbing silicon carbide. This technology allows separation of thermal from electromagnetic field effects.[20] As expected, the results using genuine microwave dielectric heating and heating by conduction in the silicon carbide vessel were identical.

Employing the flow reactor system we initially attempted to perform the Suzuki–Miyaura reaction following the THF/H_2O conditions (Table 1, entry 11). Using the 16 mL reaction coil, a flow speed of 1 mL min^{-1} and 160 °C coil temperature were selected (=16 min residence time) in order to attain comparable conditions to the microwave experiments (160 °C, 15 min reaction time).[16] Although flow processing of the reaction mixture (0.1 M concentration) was successfully performed through the reactor, only minor amounts of the desired biaryl product **3** were detected (<5%, GC-MS) and most of the starting materials were recovered from the reaction mixture. Careful reevaluation of the initial microwave batch experiments showed that while the initial THF/H_2O reaction mixture was completely homogeneous, after microwave processing two clearly separated phases had developed. We speculated that while in the batch microwave runs using intense magnetic stirring this was not a problem, the laminar flow regime likely experienced in a tubular/coil flow reactor may lead to inefficient mixing of reaction components (starting materials, base, catalyst) dissolved in the two phases and thus to a low conversion. Gratifyingly, by adding 0.025 equivalent (2.5 mol%) of tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst this issue was resolved and under these modified conditions full and clean conversion in both the microwave run (Table 1, entry 10) and the flow experiment was observed, with a 90% isolated yield of 4′-chloro-2-nitrobiphenyl (**3**) being produced from the flow reactor.

When using the *t*-BuOH/H_2O conditions (Table 1, entry 14) no TBAB addition was required since the reaction mixture did not show any phase separation and flow processing at 160 °C (16 min residence time) resulted in full conversion providing 89% isolated yield of the target 4′-chloro-2-nitrobiphenyl (**3**). The high-temperature continuous-flow conditions introduced herein for the Suzuki–Miyaura cross-coupling involving an aryl chloride compare favourably with the throughput achieved in previous continuous-flow Suzuki–Miyaura reactions.[21,22]

For the selective reduction of the nitro group in 4′-chloro-2-nitrobiphenyl (**3**) we have envisaged a heterogeneous transition metal-catalyzed hydrogenation protocol as these methods generally can be easily transformed into a scalable continuous-flow process employing a fixed-bed catalyst reactor.[23] To the best of our knowledge, in the context of the synthesis of Boscalid® such an approach has never been considered, and most of the published methods employ more traditional reducing agents such as $SnCl_2$[10,12] or Fe/NH_4Cl.[13] Following the "microwave-to-flow" optimization regime, initial experiments were carried out in a batch microwave reactor. Although it is possible to perform hydrogenations with molecular hydrogen under pressure using controlled microwave conditions,[24] we considered a catalytic transfer hydrogenation protocol for safety and convenience reasons, not requiring a specialized microwave apparatus that allows pre-pressurization of the sealed reaction vial with hydrogen gas. For the nitro group reduction in 4′-chloro-2-nitrobiphenyl (**3**), cyclohexene was found to be a hydrogen donor of appropriate reactivity, not necessitating the use of more reactive 1,4-cyclohexadiene or 1-methyl-1-cyclohexene which have recently been reported for microwave-assisted catalytic transfer hydrogenations.[25] Previous studies from our group have found that microwave-assisted transfer hydrogenations of aromatic nitro compounds can be effectively carried out using Pd/C as a catalyst under microwave conditions at 160 °C (EtOH, cyclohexene) providing the corresponding anilines in high yields after only 2 min reaction time.[26] However, in the case of 4′-chloro-2-nitrobiphenyl (**3**), the use 1 mol% of a standard 10% (w/w) Pd/C catalyst led to a significant over reduction, producing ~25% (GC-MS) of the undesired 2-aminobiphenyl by-product (**7**, see Table 2) in addition to the target Boscalid® intermediate 2-amino-4′-chlorobiphenyl (**4**). Gratifyingly, using 1 mol% of a 5% (w/w) Pt/C catalyst[27] and 5 equivalents of cyclohexene at 150 °C in EtOH, clean and complete reduction of the nitro group was obtained providing 2-amino-4′-chlorobiphenyl (**4**) within 30 min in 81% isolated yield after solvent removal and subsequent flash chromatography. Under these conditions only trace amounts of the dehalogenated 2-aminobiphenyl product (**7**) were observed (GC-MS, <1%). The use of different solvents like MeOH, THF/H_2O (1:1) or *t*-$BuOH/H_2O$ (4:1) did not have any significant effect on the reaction outcome.

Table 2. Reaction optimization for the continuous flow hydrogenation of 4′-chloro-2-nitrobiphenyl (**3**).[a]



3 **4** **7**

Entry	Catalyst [w/w%]	Solvent, concentration [M]	Temp. [°C]/ Pressure [bar][b]	Flow rate [mL min^{-1}]	Product distribution 3/**4**/7 [%][c]
1	Pd/C, 10	MeOH, 0.1	40/50	1.0	0/**25**/75
2	RaNi	MeOH, 0.1	40/50	1.0	7/**43**/50
3	RaNi	MeOH, 0.1	40/50	1.5	14/**64**/22
4	Pt/C, 10	MeOH, 0.1	40/50	3.0	0/**99**/1
5	Pt/C, 10	MeOH, 0.2	40/50	1.0	0/**99**/1
6	Pt/C, 10	THF/H_2O 1:1, 0.1	40/50	1.0	0/**91**/9
7	Pt/C, 10	*t*-$BuOH/H_2O$ 4:1, 0.05	75/atm	1.0	0/**48**/23[d]
8	Pt/C, 10	*t*-$BuOH/H_2O$ 4:1, 0.05	60/atm	1.0	0/**80**/20
9	Pt/C, 10	*t*-$BuOH/H_2O$ 4:1, 0.05	45/atm	1.0	0/**94**/6
10	Pt/C, 10	*t*-$BuOH/H_2O$ 4:1, 0.05	30/atm	1.0	0/**99**/1
11	Pt/C, 10	*t*-$BuOH/H_2O$ 4:1, 0.1	30/atm	1.0	0/**99**/1

[a] *General reaction conditions:* H-Cube, substrate **3** dissolved in 2 mL of solvent were pumped at the given flow rate through the reactor, 30×4 mm i.d. catalyst cartridge, ~150 mg catalyst. For further details, see the Experimental Section.

[b] atm = full-H_2 mode: the instrument is working at atmospheric pressure, applying all of the generated H_2 from the electrolysis cell to the processed reaction mixture; 50 bar = controlled-H_2 mode: the instrument is maintaining the selected H_2 pressure using only a part of the generated H_2.

[c] Product distribution refers to relative peak area (%) ratios of crude GC-MS traces: starting material **3**/product **4**/over-reduced product **7**.

[d] The remaining ~30% consists of a mixture of hydrogenation products where one or both of the aromatic rings in the biphenyl skeleton were fully reduced (GC-MS).

Before moving to a flow format we confirmed that the use of microwave irradiation did not produce selective heating phenomena on the Pt/C catalyst[24] applying the silicon carbide reaction vial procedure,[20] and that therefore the results achieved in the microwave reactor were of purely thermal origin. Hydrogenations under continuous flow conditions were performed in a high pressure hydrogenator enabling heterogeneous hydrogenations at temperatures up to 100 °C and 100 bar of hydrogen pressure in continuous-flow mode (H-Cube, Thales Nanotechnology Inc.).[28] The pre-packed, replaceable cartridge of the heterogeneous catalyst (30×4 mm i.d., *circa* 100–200 mg catalyst/cartridge) contained in the system, allows a uniform substrate flow (mixed with hydrogen) without catalyst leaching, circumventing the need to filter the catalyst from the substrate after the hydrogenation process is completed. The substrate/hydrogen mixture flows through the packed catalyst bed, leading to a very high ratio between the active area catalyst and the amount of hydrogen and substrate.[28] The flow hydrogenation of 4′-chloro-2-nitrobiphenyl (**3**) was initially performed in MeOH solution using catalyst cartridges filled with Pd/C, RaNi and Pt/C. As can be seen from the data presented in Table 2, only the use of Pt/C – similar to the transfer hydrogenation experiments described above – provided a high selectivity for nitro group reduction. For example, selective hydrogenation (~99% selectivity) over a standard Pt/C catalyst (10% w/w) was obtained by using a 0.1 M stock solution at a flow rate of 3 mL min^{-1} at 40 °C under 50 bar hydrogen pressure (Table 2, entry 4). Based on the measured dead volume of around 140 μL of the catalyst cartridge (30×4 mm i.d., 150 mg Pt/C), a residence time of less than 3 s for hydrogenation over the catalyst can be calculated by applying a 3.0 mL min^{-1} flow rate (the residence time in the complete H-Cube system is around 50 s at this flow rate). Having the eventual combination of the Suzuki–Miyaura cross-coupling and the hydrogenation step in mind (see below), flow hydrogenation experiments were also performed with THF/H_2O or *t*-BuOH/H_2O as solvent mixtures, resulting in similar high selectivities under carefully optimized conditions. Notably, lower temperatures provided higher selectivities for the desired nitro group reduction (Table 2, compare entries 7–11). Too high hydrogenation temperatures in combination with the Pt/C catalyst produced hydrogenation products where in addition to functional group hydrogenation one or both of the aromatic rings in the biphenyl skeleton were fully reduced (Table 2, entry 7). Utilizing the optimized conditions however (Table 2, entry 11), a 10-mL experiment delivered 93% (>96% purity, GC-MS) crude yield of the desired 2-amino-4′-chlorobiphenyl product (**4**).

The final step in the Boscalid® synthesis requires the formation of a standard amide bond (Scheme 1). In agreement with the literature,[3,13] we find that this amide coupling can be readily performed at room temperature using commercially available 2-chloronicotinoyl chloride (**5**) in the presence of a base (Et_3N, THF) providing Boscalid® in 89% yield within 10 min. Although it is evident that process intensification is not required for this last step we nevertheless have evaluated a direct microwave-assisted amidation protocol[26] that involves heating 2-amino-4′-chlorobiphenyl (**4**) with 2-chloronicotinic acid in MeCN in the presence of 1 equivalent of PCl_3. Microwave heating at 150 °C for 10 min provided Boscalid® in 87% yield after chromatographic purification.

Our ultimate goal in this project was to merge the Suzuki–Miyaura cross-coupling and the hydrogenation in a two-step flow process to generate the key Boscalid® intermediate 2-amino-4′-chlorobiphenyl (**4**) in a single synthetic operation. Performing multi-step continuous-flow syntheses is considerable more challenging than carrying out individual transformations in flow since all substrates (including concentration levels), reagents, catalysts, additives, and the solvents used in the first step must be compatible with all the subsequent reaction steps.[29] In addition, if an uninterrupted line of flow systems is employed, the flow rates and back pressures also have to be adjusted accordingly. In our initial experiments, the reaction mixture (0.1 M concentration) resulting from the optimized Suzuki–Miyaura cross-coupling flow process using *t*-BuOH/H_2O (4:1) as reaction medium (see above) was flowed into the H-Cube hydrogenator using Pt/C as a catalyst and flow conditions similar to those described in Table 2, entry 10, providing a 95% overall conversion. Disappointingly, the desired 2-amino-4′-chlorobiphenyl product (**4**) was contaminated with ~12% of the over-reduced 2-aminobiphenyl (**7**). This drop in selectivity can be rationalized by Pd metal used as homogeneous catalyst for the Suzuki–Miyaura cross-coupling in step 1 entering the hydrogenation apparatus and contaminating the heterogeneous Pt/C catalyst cartridge.[30] In order to eliminate this problem Pd metal was scavenged in-line using a macroporous Quadrapure™ TU (thiourea) resin cartridge[31] housed in an X-Cube flow reactor (Thales Nanotechnology Inc.)[32] placed between the X-Cube Flash and the H-Cube flow devices (Figure 1). Using this experimental configuration the formation of over-hydrogenated side product **7** was reduced to <1% utilizing appropriate hydrogenation conditions (Figure 1). The desired key intermediate in the Boscalid® synthesis, 2-amino-4′-chlorobiphenyl (**4**), could therefore be obtained in 77% overall yield (after chromatography, 90% crude yield) in a single operation combining a Pd-catalyzed Suzuki–Miyaura

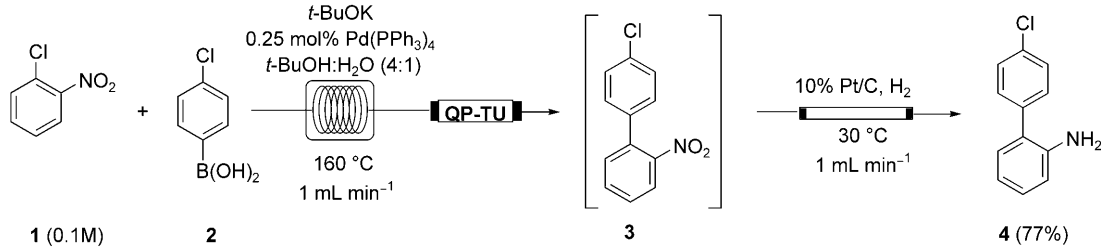


Figure 1. Schematic diagram and reaction conditions for the two-step continuous-flow synthesis of 2-amino-4-chlorobiphenyl (**4**).

cross-coupling reaction with a Pt-catalyzed selective heterogeneous hydrogenation step.

Conclusions

In summary, we have developed a two-step continuous-flow process for the preparation of 2-amino-4′-chlorobiphenyl (**4**), an important intermediate in the synthesis of the fungicide Boscalid® (**6**), currently produced in more than 1000 tons/year quantity. Our method is based on a Pd(0)-catalyzed high-temperature flow Suzuki–Miyaura cross-coupling transformation constructing the central biaryl unit in 4′-chloro-2-nitrobiphenyl (**3**), coupled with a highly chemoselective heterogeneous Pt/C-catalyzed nitro group reduction to produce the target aniline structure **4**. Key to the success of this method is a change of transition metal from Pd (homogeneous) to Pt (heterogeneous) in order to achieve complete selectivity for nitro group reduction leaving the chlorine functionality in 2-amino-4′-chlorobiphenyl (**4**) intact. Although the current protocol using laboratory-scale flow reactors does not allow the preparation of large product quantities, a first proof-of-concept for the continuous-flow manufacturing of this important target structure has been established. Future work will focus on improved methods for the scavenging and recovery of the Pd catalyst employed in the Suzuki–Miyaura cross-coupling and on developing engineering solutions for allowing this flow protocol to be performed on a production scale.

Experimental Section

General Remarks

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. GC/MS (FOCUS-GC/DSQ II MS, ThermoFisher) monitoring was based on electron impact ionization (70 eV) using a HP/5MS column (30 m × 0.250 mm × 0.025 μm). After 1 min at 50 °C the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 1 min. The carrier gas was helium and the flow rate 1.0 mL min^{-1} in constant-flow mode. The identity of the peaks in the chromatograms was confirmed by computerized comparison with the NIST library. Low-resolution mass spectra were obtained on a Shimadzu LCMS-QP2020 instrument using electrospray ionization (ESI) in positive or negative mode. The pre-analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 25 °C using a mobile phase A [water/acetonitrile 90:10 (v/v) + 0.1% TFA] and B (MeCN + 0.1% TFA) at a flow rate of 0.6 mL min^{-1}. The following gradient was applied: linear increase from solution 30% B to 100% B in 15 min, hold at 100% solution B for 2 min. All chemicals, solvents, catalysts and ligands were obtained from Aldrich Chem. Co. or Acros Organics and were used without any further purification. Microwave irradiation experiments were carried out in a Monowave 300 (Anton Paar GmbH, Graz, Austria) in Pyrex or SiC microwave process vials using standard procedures.[17,20] Reaction times refer to hold times at the temperature indicated, not to total irradiation times. The temperature was measured using an internal fiber-optic temperature sensor. The flow chemistry examples described herein were performed using X-Cube Flash, H-Cube or X-Cube flow reactors (ThalesNano Nanotechnology Inc.) according to established principles.[19,28,32] The synthesized compounds were purified using an automated chromatography system (SP1™, Biotage) using cartridges packed with KP-SIL, 60 Å (40–63 μm particle size) and ethyl acetate (or ethyl acetate containing 0.5% Et_3N for the purification of aniline **4**)/petroleum ether mixtures as eluent. All products synthesized in this study are known in the literature and have been identified and characterized by melting point, ^{1}H NMR and MS analysis.

4′-Chloro-2-nitrobiphenyl (3)

Batch Microwave Conditions (Table 1, entry 14): To a stirred mixture of 1-chloro-2-nitrobenzene (**1**) (32 mg, 0.2 mmol, 0.1 M), 4-chlorophenylboronic acid (**2**) (35 mg, 0.22 mmol, 1.1 equiv.), *t*-BuOK (30 mg, 0.26 mmol, 1.3 equiv.) and *t*-BuOH/H_2O (4:1) (1 mL) in a 10 mL Pyrex microwave vial, 1 mL of a 0.0005 M stock solution of $Pd(PPh_3)_4$ in *t*-BuOH/H_2O (4:1) (0.6 mg, 0.25 mol%) was added. The reaction mixture was stirred for 30 s, capped with a Teflon septum and subjected to microwave heating for 15 min (hold time) at 160 °C and subsequently cooled to 50 °C. The resulting reaction mixture was concentrated under reduced pressure and the residue purified by flash

chromatography to afford 4′-chloro-2-nitrobiphenyl (**3**) as a yellowish oil, which upon standing provided brown crystals; yield: 43 mg (91%): mp 61–63 °C, lit.[11c,13] m 60–62 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta = 7.27$ (dm, 2H, $J =$ 8.5 Hz), 7.42 (dm, 3H, $J = 8.5$ Hz), 7.52 (dt, 1H, $J = 1.5$ and 7.8 Hz), 7.65 (dt, 1H, $J = 1.5$ and 7.8 Hz), 7.90 (dd, 1H, $J =$ 1.2 and 8.1 Hz); MS (pos. ESI): $m/z = 233$ (M^+), 279 ($M^+ +$ HCO_2H).

For preparative purposes, the reaction was also performed equally efficiently at 1.0 M concentration providing biaryl **3** on a gram scale. The results achieved in a SiC reaction vial (0.1 M concentration) under otherwise identical conditions[20] provided identical results compared to the Pyrex run with respect to the GC-MS crude reaction profiles.

Continuous-Flow Processing: To a stirred mixture of 1-chloro-2-nitrobenzene (**1**) (64 mg, 0.4 mmol, 0.1 M), 4-chlorophenylboronic acid (**2**) (70 mg, 0.44 mmol, 1.1 equiv.), *t*-BuOK (60 mg, 0.52 mmol, 1.3 equiv.) and *t*-BuOH/H_2O (4:1) (3 mL) in a 5 mL glass vial, 1 mL of a 0.001 M stock solution of $Pd(PPh_3)_4$ in *t*-BuOH/H_2O (4:1) (1.17 mg, 0.25 mol%) was added. The reaction mixture was stirred for 30 s. At the same time the X-cube Flash reactor was equipped with a stainless steel reaction coil (16 mL volume, 16 min residence time at 1 mL min^{-1} flow rate). The reaction parameters temperature (160 °C), 1 mL min^{-1} flow rate and pressure (75 bar) were selected on the flow reactor, and processing was started, whereby initially only solvent *t*-BuOH/H_2O (4:1) was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the inlet tube was switched from the solvent flask to the 5-mL glass vial containing the freshly prepared reaction mixture. After processing through the flow reactor, the inlet tube was dipped back into the flask containing solvent and processed for an additional 10 min, thus washing from the system any remaining reaction mixture. The reaction was concentrated under vacuum and the product was isolated as described above in 89% yield identical in all respects with a sample prepared under microwave conditions.

Synthesis 2-Amino-4′-chlorobiphenyl (4)

Batch Microwave Conditions: To a stirred mixture of 4′-chloro-2-nitrobiphenyl (**3**) (515 mg, 2.2 mmol) and *t*-BuOH/H_2O (4:1) (3 mL) in a 10-mL Pyrex microwave vial, cyclohexene (905 mg, 11 mmol, 5 equiv., 1.12 mL) was added, immediately followed by 10% (w/w) Pt/C (86 mg, 0.022 mmol, 1 mol%). The reaction mixture was stirred for 10 s, capped with a Teflon septum and subjected to microwave heating for 30 min (hold time) at 150 °C and subsequently cooled to 50 °C. The resulting reaction mixture was concentrated under reduced pressure and the residue purified by flash chromatography to afford 2-amino-4′-chlorobiphenyl (**4**) as an oil, which upon standing provided pale yellow crystals; yield: 364 mg (81%); mp 45–47 °C, lit.[33] m 47–48 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta = 3.43$ (br s, 2H), 6.50 (dd, 1H, $J = 0.7$ and 7.9 Hz), 6.57 (dt, 1H, $J = 1.1$ and 7.5 Hz), 6.84 (dd, 1H, $J = 1.3$ and 7.6 Hz), 6.82–6.94 (m, 1H), 7.15 (s, 4H); MS (pos. ESI): $m/z = 204$ (M^+), 245 ($M^+ + CH_3CN$), 286 ($M^+ + 2\,CH_3CN$).

The results achieved in a SiC reaction vial under otherwise identical conditions[20] provided identical results with respect to the GC-MS crude reaction profile.

Continuous Flow Processing (Table 2, entry 11): A 10 mL stock solution of 4′-chloro-2-nitrobiphenyl (**3**) with a 0.1 M concentration in *t*-BuOH/H_2O (4:1) was prepared in a glass vial. The reaction parameters (Full-H_2 mode, 30 °C and 1 mL min^{-1} flow rate) were selected on the H-Cube hydrogenator. The instrument was fitted with a 30 mm 10% Pt/C CatCart and the processing was started, whereby initially only pure solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the sample inlet line was switched to the vial containing the substrate. A total reaction volume of 15 mL was collected and the cartridge subsequently washed with pure solvent for 5 min to remove any substrate/product still adsorbed on the catalyst. Evaporation of the solvent affords 2-amino-4′-chlorobiphenyl (**4**) as oil (93% crude yield), which was purified by flash chromatography to provide a pale yellow solid, identical in all respects with a sample prepared under microwave conditions; yield: 161 mg (78%).

2-Chloro-*N*-(4′-chlorobiphenyl-2-yl)nicotinamide (6) (*Boscalid®*)

To a stirred mixture of freshly distilled 2-amino-4′-chlorobiphenyl (**4**) (100 mg, 0.5 mmol) and acetonitrile (2 mL) in a 5-mL Pyrex microwave vial, 2-chloronicotinic acid (85 mg, 0.54 mmol, 1.1 equiv.) was added, followed by dropwise addition of PCl_3 (135 mg, 86 μL, 1 mmol, 2 equiv.). The suspension was stirred for 10 s before being subjected to microwave heating for 10 min (hold time) at 150 °C. After cooling to ambient conditions and evaporation of solvent the residue was purified by flash chromatography to afford 2-chloro-*N*-(4′-chlorobiphenyl-2-yl)nicotinamide (**6**) (*Boscalid®*) as a white solid; yield: 146 mg (87%); mp 142–144 °C, lit.[13] mp 143 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta = 7.28$–7.51 (m, 8H), 8.17 (d, 2H, $J = 6.0$ Hz), 8.43–8.49 (m, 2H); MS (pos. ESI): $m/z = 343$ (M^+), 284 ($M^+ + CH_3CN$).

Alternatively, N-(4′-chlorobiphenyl-2-yl)nicotinamide (**6**) was obtained by reacting solution of a freshly distilled 2-amino-4′-chlorobiphenyl (**4**) (100 mg, 0.5 mmol) in 2 mL of CH_2Cl_2 with 2-chloronicotinoyl chloride (89 mg, 1.02 equiv) in the presence of Et_3N (127 mg, 163 μL, 1 mmol, 2 equiv.) at 25 °C for 10 min. After the removal of solvent under reduced pressure, the residue was purified as described above to afford 2-chloro-*N*-(4′-chlorobiphenyl-2-yl)nicotinamide (**6**) (*Boscalid®*) as a white solid; yield: 149 mg (89%).

Two-step Flow Protocol (Figure 1): To a stirred mixture of 1-chloro-2-nitrobenzene (**1**) (64 mg, 0.4 mmol, 0.1 M), 4-chlorophenylboronic acid (**2**) (70 mg, 0.44 mmol, 1.1 equiv.), *t*-BuOK (60 mg, 0.52 mmol, 1.3 equiv.) and *t*-BuOH/H_2O (4:1) (3 mL) in a 5-mL glass vial, 1 mL of a 0.001 M stock solution of $Pd(PPh_3)_4$ in *t*-BuOH/H_2O (4:1) (1.17 mg, 0.25 mol%) was added. The X-Cube Flash reactor was equipped with a stainless steel reaction coil (16 mL volume, 16 min residence time at 1 mL min^{-1} flow rate). The reaction parameters temperature (160 °C), 1 mL min^{-1} flow rate and pressure (75 bar) were selected on the flow reactor, and processing was started, whereby only solvent *t*-BuOH/H_2O (4:1) was pumped through the system until the instrument

had achieved the desired reaction parameters and stable processing was achieved. The outlet of the X-Cube flash was connected to the CatCart holder on the X-Cube reactor, equipped with a Quadrapure-TU cartridge (70×4 mm i.d., ~122 mg loading), able to remove the residual Pd form the C–C coupling step. The reaction parameters for the selective nitro reduction (Full-H_2 mode, 30 °C, 1 mL min^{-1} flow rate) were at the same time selected on the H-Cube hydrogenator. The instrument was fitted with a 10% (w/w) Pt/C CatCart (30×4 mm i.d., 150 mg Pt/C) and the processing was started, whereby initially only pure solvent *t*-BuOH/H_2O (4:1) was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the sample inlet line of the H-Cube was switched to a vial containing 1 mL of the solvent and at the same time the outlet of the X-Cube was inserted. At that time the inlet tube of the X-Cube Flash instrument was switched from the solvent flask to the 5-mL glass vial containing the 4 mL aliquot sample of the freshly prepared reaction mixture. The whole reaction process through the X-Cube Flash, X-Cube and H-Cube instruments was continued for 30 min–20 min reaction time plus an additional 10 min washing with pure solvent thus washing from the system any remaining reaction mixture. A total reaction volume of 30 mL was collected. Evaporation of the solvent affords 2-amino-4′-chlorobiphenyl (**4**) as an oil (90% crude yield; 96% purity by GC-MS). Purification by flash chromatography provided 63 mg (77%) of analytically pure product identical in all respects to the samples prepared via the methods described above.

Acknowledgements

This work was supported by a grant from the Christian Doppler Research Society (CDG).

References

[1] a) K.-H. Kuck, U. Gisi, in: *Modern Crop Protection Compounds*, Vol. 2, (Eds.: W. Krämer, U. Schrimer), Wiley-VCH, Weinheim, **2007**, pp 415–432; b) F. Earley, in: *Modern Crop Protection Compounds*, Vol. 2, (Eds.: W. Krämer, U. Schrimer), Wiley-VCH, Weinheim, **2007**, pp 433–538.

[2] C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027.

[3] a) K. Eicken, N. Goetz, A. Harreus, E. Ammermann, G. Lorenz, H. Rang, (BASF AG, Ludwigshafen), European Patent EP0545099, **1993**; b) K. Eicken, H. Rang, A. Harreus, N. Goetz, E. Ammermann, G. Lorenz, S. Strathmann, (BASF AG, Ludwigshafen), German Patent DE19531813, **1997**; *Chem. Abstr.* **1997**, *126*, 264007; c) K. Eicken, M. Rack, F. Wetterich, E. Ammermann, G. Lorenz, S. Strathmann, (BASF AG, Ludwigshafen), German Patent DE 19735224, **1999**; *Chem. Abstr.* **1999**, *130*, 182464; d) K. Eicken, M. Rack, F. Wetterich, E. Ammermann, G. Hardt, M. Rack, P. Schäfer, (BASF AG, Ludwigshafen), WO Patent 97/33846, **1997**; e) S. Engel, T. Oberding, (BASF AG, Ludwigshafen), WO Patent 2006/092429, **2006**.

[4] A. M. Rouhi, *Chem. Eng. News* **2004**, *82* (36), 49.

[5] For recent selected reviews on continuous flow/microreactor chemistry, see: a) K. Geyer, T. Gustafson, P. H. Seeberger, *Synlett* **2009**, 2382; b) R. L. Hartman, K. F. Jensen, *Lab Chip* **2009**, *9*, 2495; c) C. Wiles, P. Watts, *Eur. J. Org. Chem.* **2008**, 1655; d) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151; e) B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733; f) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300; g) I. R. Baxendale, J. J. Hayward, S. V. Ley, G. K. Tranmer, *ChemMedChem* **2007**, *2*, 768.

[6] a) *Microreactors in Organic Synthesis and Catalysis*, (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2008**; b) *Handbook of Micro Reactors*, (Eds.: V. Hessel, J. C. Schouten, A. Renken, Y. Wang, J.-i. Yoshida), Wiley-VCH, Weinheim, **2009**; c) J.-I. Yoshida, *Flash Chemistry – Fast Organic Synthesis in Microsystems*, Wiley-VCH, Weinheim, **2008**; d) *Chemical Reactions and Processes under Flow Conditions*, (Eds.: S. V. Luis, E. Garcia-Verduqo), Royal Soceity of Chemistry, Cambridge, **2010**.

[7] T. Razzaq, C. O. Kappe, *Chem. Asian J.* **2010**, *5*, 1274.

[8] a) D. M. Roberge, M. Gottsponer, M. Eyholzer, N. Kockmann, *Chem. Today* **2009**, *27* (4), 8; b) D. M. Roberge, B. Zimmermann, F. Rainone, M. Gottsponer, M. Eyholzer, N. Kockmann, *Org. Process Res. Dev.* **2008**, *12*, 905; c) H. Pennemann, P. Watts, S. J. Haswell, V. Hessel, H. Löwe, *Org. Process Res. Dev.* **2004**, *8*, 422; d) X. Zhang, S. Stefanick, F. J. Villani, *Org. Process Res. Dev.* **2004**, *8*, 455; e) V. Hessel, S. Hardt, H. Löwe, *Micro Chemical Process Engineering*, Wiley-VCH, Weinheim, **2004**.

[9] P. Appukkuttan, E. Van der Eycken, W. Dehaen, *Synlett* **2005**, 127.

[10] A. C. Spivey, C.-C. Tseng, J. P. Hannah, C. J. G. Gripton, P. de Fraine, N. J. Parr, J. J. Scicinski, *Chem. Commun.* **2007**, 2926.

[11] a) L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 663; b) L. J. Gooßen, B. Zimmermann, C. Linder, N. Rodríguez, P. P. Lange, J. Hartung, *Adv. Synth. Catal.* **2009**, *351*, 2667; c) L. J. Gooßen, C. Linder, N. Rodriguez, P. P. Lange, *Chem. Eur. J.* **2009**, *15*, 9336.

[12] a) L. Caron, L.-C. Campeau, K. Fagnou, *Org. Lett.* **2008**, *10*, 4533; b) R. Dey, B. Sreedhar, B. C. Ranu, *Tetrahedron* **2010**, *66*, 2301.

[13] F.-X. Felpin, E. Fouquet, C. Zakri, *Adv. Synth. Catal.* **2009**, *351*, 649.

[14] For a non-transition metal-catalyzed free radical process, see: A. Wetzel, V. Ehrhardt, M. R. Heinrich, *Angew. Chem.* **2008**, *120*, 9270; *Angew. Chem. Int. Ed.* **2008**, *47*, 9130.

[15] a) T Gustafsson, F. Pontén, P. H. Seeberger, *Chem. Commun.* **2008**, 1100; b) M. W. Bedore, N. Zaborenko, K. F. Jensen, T. F. Jamison, *Org. Process Res. Dev.* **2010**, *14*, 432.

[16] a) T. Razzaq, T. N. Glasnov, C. O. Kappe, *Eur. J. Org. Chem.* **2009**, 1321; b) T. N. Glasnov, S. Findenig, C. O. Kappe, *Chem. Eur. J.* **2009**, *15*, 1001; c) M. Fuchs, W. Goessler, C. Pilger, C. O. Kappe, *Adv. Synth. Catal.* **2010**, *352*, 323; d) M. Damm, T. N. Glasnov, C. O.

Kappe, *Org. Process Res. Dev.* **2010**, *14*, 215; e) B. Gutmann, J.-P. Roduit, D. Roberge, C. O. Kappe, *Angew. Chem.* **2010**, *122*, 7255; *Angew. Chem. Int. Ed.* **2010**, *49*, 7101.

[17] For a detailed description of this microwave reactor and a discussion on the importance of internal temperature monitoring in microwave chemistry, see: D. Obermayer, C. O. Kappe, *Org. Biomol. Chem.* **2010**, *8*, 114.

[18] For general reviews on microwave-assisted Suzuki–Miyaura and related transition metal-catalyzed transformations, see: a) C. O. Kappe, D. Dallinger, *Mol. Diversity* **2009**, *13*, 71; b) B. K. Singh, N. Kaval, S. Tomar, E. Van der Eycken, V. S. Parmar, *Org. Process Res. Dev.* **2008**, *12*, 468; c) P. Appukkattan, E. Van der Eycken, *Eur. J. Org. Chem.* **2008**, 1133; d) P. Nilsson, K. Olofsson, M. Larhed, *Top. Curr. Chem.* **2006**, *266*, 103; e) N. E. Leadbeater, *Chem. Commun.* **2005**, *23*, 2881; f) M. Larhed, C. Moberg, A. Hallberg, *Acc. Chem. Res.* **2002**, *35*, 717.

[19] For a detailed description of this reactor, see: T. Razzaq, T. N. Glasnov, C. O. Kappe, *Chem. Eng. Technol.* **2009**, *32*, 1702.

[20] a) D. Obermayer, B. Gutmann, C. O. Kappe, *Angew. Chem.* **2009**, *121*, 8471; *Angew. Chem. Int. Ed.* **2009**, *48*, 8321; b) B. Gutmann, D. Obermayer, B. Reichart, B. Prekodravac, M. Irfan, J. M. Kremsner, C. O. Kappe, *Chem. Eur. J.* **2010**, *16*, 12182.

[21] For examples of continuous flow Suzuki–Miyaura cross-couplings using heterogeneous Pd catalysts, see: a) H. Ping, S. J. Haswell, P. D. I. Fletcher, *Appl. Catal. A: Gen.* **2004**, *274*, 111; b) W. Solodenko, H. L. Wen, S. Leue, F. Stuhlmann, G. Sourkouni-Argirusi, G. Jas, H. Schonfeld, U. Kunz, A. Kirschning, *Eur. J. Org. Chem.* **2004**, 3601; c) C. K. Y. Lee, A. B. Holmes, S. V. Ley, I. F. McConvey, B. Al-Duri, G. A. Leeke, R. C. D. Santos, J. P. K. Seville, *Chem. Commun.* **2005**, 2175; d) I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Chem. Eur. J.* **2006**, *12*, 4407; e) N. Karbass, V. Sans, E. Garcia-Verdugo, M. I. Burguete, S. V. Luis, *Chem. Commun.* **2006**, 3095; f) W. Solodenko, K. Mennecke, C. Vogt, S. Gruhl, A. Kirschning, *Synthesis* **2006**, 1873; g) G. A. Leeke, R. C. D. Santos, B. Al-Duri, J. P. K. Seville, C. J. Smith, C. K. Y. Lee, A. B. Holmes, I. F. McConvey, *Org. Process Res. Dev.* **2007**, *11*, 144; h) S. Ceylan, C. Friese, C. Lammel, K. Mazac, A. Kirschning, *Angew. Chem.* **2008**, *120*, 9083; *Angew. Chem. Int. Ed.* **2008**, *47*, 8950; i) U. Schön, M. Josef, E. Simone, A. Kirschning, *Tetrahedron Lett.* **2008**, *49*, 3204; j) A. Gomann, J. A. Deverell, K. F. Munting, R. C. Jones, T. Rodemann, A. J. Canty, J. A. Smith, R. M. Guijt, *Tetrahedron* **2009**, *65*, 1450; k) M. V. Gomez, H. H. J. Verputten, A. Diaz-Ortiz, A. Moreno, A. de La Hoz, A. H. Velders, *Chem. Commun.* **2010**, *46*, 4514.

[22] For examples of continuous flow Suzuki–Miyaura cross-couplings using homogeneous Pd catalysts, see: a) N. S. Wilson, C. R. Sarko, G. P. Roth, *Org. Process Res. Dev.* **2004**, *8*, 535; b) E. Comer, M. G. Organ, *J. Am. Chem. Soc.* **2005**, *127*, 8160; c) O. Benali, M. Deal, E. Farrant, D. Tapolczay, R. Wheeler, *Org. Process Res. Dev.* **2008**, *12*, 1007; d) J. Jin, M.-M. Min, J-X. Li, *Synlett* **2009**, 2534.

[23] a) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, Wiley-Interscience, **2001**; b) P. N. Rylander, *Hydrogenation Methods*, Academic Press, New York, **1990**; c) P. N. Rylander, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, **1979**.

[24] M. Irfan, M. Fuchs, T. N. Glasnov, C. O. Kappe, *Chem. Eur. J.* **2009**, *15*, 11608, and references cited therein.

[25] a) J. F. Quinn, D. A. Razzano, K. C. Golden, B. T. Gregg, *Tetrahedron Lett.* **2008**, *49*, 6137; b) N. Chapman, B. Conway, F. O'Grady, M. D. Wall, *Synlett* **2006**, 1043.

[26] T. N. Glasnov, K. Groschner, C. O. Kappe, *ChemMedChem* **2009**, *4*, 1816.

[27] J. F. Quinn, C. E. Bryant, K. C. Golden, B. T. Gregg, *Tetrahedron Lett.* **2010**, *51*, 786.

[28] For a more detailed description, see: M. Irfan, E. Petricci, T. N. Glasnov, M. Taddei, C. O. Kappe, *Eur. J. Org. Chem.* **2009**, 1327, and references cited therein.

[29] For examples of multistep continuous flow synthesis, see: a) I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer, *Chem. Commun.* **2006**, 2566; b) H. R. Sahoo, J. G. Kralji, K. F. Jensen, *Angew. Chem.* **2007**, *119*, 5806; *Angew. Chem. Int. Ed.* **2007**, *46*, 5704; c) T. Gustafsson, F. Ponten, P. H. Seeberger, *Chem. Commun.* **2008**, 1100; d) D. Grant, R. Dahl, N. D. P. Cosford, *J. Org. Chem.* **2008**, *73*, 7219; e) T. P. Petersen, A. Ritze'n, T. Ulven, *Org. Lett.* **2009**, *11*, 5134; f) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem.* **2009**, *121*, 4077; *Angew. Chem. Int. Ed.* **2009**, *48*, 4017; g) A. Herath, R. Dahl, N. D. P. Cosford, *Org. Lett.* **2010**, *12*, 412; h) I. R. Baxendale, S. C. Schou, J. Sedelmeier, S. V. Ley, *Chem. Eur. J.* **2010**, *16*, 89.

[30] Although it is tempting to speculate that use of a heterogeneous Pd catalyst for the continuous flow Suzuki–Miyaura cross-coupling in step 1 (see ref.[21] for examples) may eliminate these contamination problems, the fact that this transition metal-catalyzed process is mechanistically homogeneous in nature will mean that most likely significant amounts of Pd metal will ultimately leach under continuous-flow conditions and therefore will not prevent contamination issues in the subsequent heterogeneous Pt-catalyzed hydrogenation step (see refs.[16b,c] for similar observations made with related transition metal-catalyzed processes).

[31] A. Hinchcliffe, C. Hughes, D. A. Pears, M. R. Pitts, *Org. Process Res. Dev.* **2007**, *11*, 477.

[32] For a detailed description of the X-Cube reactor, see: a) C. Csajági, B. Borcsek, K. Niesz, I. Kovács, Z. Székelyhidi, Z. Bajkó, L. Ürge, F. Darvas, *Org. Lett.* **2008**, *10*, 1589; b) see also refs.[16b,c]

[33] E. H. Huntress, M. K. Seikel, *J. Am. Chem. Soc.* **1939**, *61*, 816.

