Flow reactor synthesis of unsymmetrically substituted \( p \)-terphenyls using sequentially selective Suzuki cross-coupling protocols

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ABSTRACT

Synthetic procedures, based on integrated flow chemical methods, have been developed for the sequential chemo-selective Suzuki–Miyaura cross-coupling of 1,4-dibromo-2-nitrobenzene (1) with various arylboronic acids. The first Suzuki coupling step used a phosphine-(ligand)-free palladium catalyst at room temperature and gave regio-selective coupling of (1) at the ortho-position to the nitro group. The bromo-biaryl product was then directly subjected in situ to a second coupling step, using different arylboronic acids, as a continuous in-flow operation. Based on this methodology, a number of unsymmetrically substituted \( p \)-terphenyl compounds were synthesized in excellent overall yields. This approach provides a convenient route to this class of compounds, and is suited for the generation of targeted chemical libraries, or the synthesis of precursors of biologically active natural product analogues that contain the \( p \)-terphenyl core. During the first coupling step, dimerization at low levels of the bromo-biaryl intermediate occurred, leading to formation of quaterphenyl compounds.

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1. Introduction

The Suzuki–Miyaura palladium-catalyzed cross-coupling reaction between an aryl-boronic acid and an aryl halide is one of the most important and versatile synthetic transformations available for the preparation of bis-aryl compounds (1). The reaction has found many applications with mono-halogenated arenes, leading to the synthesis of symmetrical bis-aryl and bis-naphthylmethanes (2), as well as more complex structures such as helical ortho-polyphenylene oligomers or boron-substituted poly-arenes (3–6). In comparison, application of sequentially selective, double-Suzuki–Miyaura coupling reactions with di-halogenated arenes to form asymmetric \( p \)-terphenyl products in one pot reactions has, however, received relatively little attention. Regio-selective cross-coupling has been reported for a wide range of polyhalogenated heteroaromatic substrates, including pyridines and pyrroles (7) with region-selective Suzuki poly-coupling affording an elegant route to the pyrrole core of the lamellarins (8). Typically, the synthesis of unsymmetrical terphenyls has been carried out by either stepwise Pd- or Ni-catalyzed coupling of bromobenzene-sulfonates with arylboronic acids and aryl-magnesium bromides (9), or by sequential Pd-catalyzed Negishi cross-coupling reactions of arylzinc reagents with iodo-aryl nonaflates (10) or zinc phenoxides with aryl triflates (11). However, the reactivities of the organometallic reagents employed in these previous syntheses often are incompatible with electrophilic functionalities present in some starting materials (4). If efficient syntheses are to proceed with these procedures, anhydrous reaction conditions are also essential, and purification of the bis-aryl intermediates by column chromatography is frequently needed.

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In Nature terphenyl compounds occur widely, often as p-terphenyl derivatives (12). These compounds exhibit a broad range of biological properties, including antimicrobial, immuno-suppressant, neuro-protective, S-lipoxygenase inhibitory, anti-coagulant and antithrombotic activities (5, 12–15). In addition, different chemo-protective, cytotoxic and anti-proliferative effects have been documented with a variety of transformed or cancerous cell lines, such as HeLa, HepG2, HCT116 or Caco2 cells in culture (16, 17). As such, p-terphenyl derivatives are attractive targets for medicinal chemists in the search for new therapeutic drug leads. Besides their use in biology and medicine, terphenyl and poly-phenyl compounds have found other important applications, as liquid crystals and fluorescent optoelectronic compounds (18). Functionalized terphenyls, based on di- or tri-amino-1,1′:3′,1′′-terphenyls, have, for example, been used in charge transporting/ charge generating agents (19, 20), metal organic frameworks (21), conducting polymers (22, 23), and light emitting diodes (24), whilst the photo-physical properties of o-, m-, and p-terphenyl compounds have been exploited in organic liquid-crystalline materials and organic electroluminescent (OEL) devices by taking advantage of the different organizational arrangements of the aromatic rings in the two dimensional plane (18, 25).

Herein, we describe a procedure based on a flow reactor format for the practical, high-yielding chemical synthesis of unsymmetrical p-terphenyls via sequential regio-selective Suzuki–Miyaura (SM) methods. As is the case with other synthetic applications of flow technologies, it was envisaged that this approach would have broad scope, since the aryl precursors are widely available; the reagents are generally easy to handle and air or moisture compatible, and many types of substituent groups can be accommodated. Due to better control over system residency, reagent mixing and thermal effects, it was also anticipated that these procedures would offer the benefit of increased regio-selectivity at the first arylation stage. Hitherto, in batch procedures mono-arylation of di-iodo- and di-bromo-arenes has been shown to be highly sensitive to the reaction conditions (26, 27), whilst reactions with bromiiodobenzenes typically have led to complex mixtures of mono- and di-arylated products (28). The opportunity was thus taken in this current work to better exploit under flow conditions differences in the reactivity of the C1 and C4 positions (ortho and meta to the nitro group respectively) of the 1,4-di-bromo-2-nitro-benzene substrate and allow the successive regio-selective introduction of two different substituents to a substituted benzene ring in a highly convergent and flexible manner. From green chemical perspectives, this approach targets the rapid generation of precursors of numerous bioactive natural products and polymeric materials that contain the p-terphenyl scaffold generated from 2-substituted dibromonitrobenzenes.

2. Results and discussion

In recent years, flow chemistry has emerged as an enabling technology, allowing access to novel and more sustainable manufacturing processes (29). Where necessary, reactions can be performed under high temperature and pressure conditions, often above the boiling point of the carrier solvents used. Favourable attributes also include excellent control over reaction parameters, i.e. more efficient control of local heating and temperature profiles during the reaction, leading to enhanced mass transfer, thereby often resulting in improved selectivity and yield (30,31). This approach, in principle, also permits the integration of several steps into a single streamlined process, thus potentially shortening the synthesis time for structurally more complex compounds (32). Continuous manufacturing with flow reactors can also contribute to the adoption of more sustainable green chemical practices, with hazardous compounds better contained and, in many cases, the amounts of these and other chemicals, including waste, significantly reduced (33).

In preliminary experiments, we were able to demonstrate that in flow format, phosphine ligand-free Suzuki reactions could be carried out with low catalyst loadings using palladium acetate as catalyst and water as co-solvent. Under these conditions, rapid coupling reactions were observed and phosphine-related side reactions such as aryl-aryl exchange eliminated, avoiding constraints reported for batch synthesis (34–39). Adaptation of similar flow chemical procedures to double coupling of 1,4-dibromo-2-nitrobenzene (1) using ethanol as a co-solvent led to further improvements in regio-selectivity and higher yields compared to the corresponding one-pot double Suzuki couplings carried out in the batch mode. For example, with one-pot batch conditions the cross-coupling of 1,4-dibromo-2-nitrobenzene (1) with 4-methoxyphenylboronic acid (2), catalyzed by phosphate-free Pd(OAc)2 exhibited strong temperature and solvent effects with the ratios of the mono-coupled product to the bis-coupled product varying between 1:5:1 and 15:1 depending on the chosen temperature and solvent (40).

In Suzuki couplings, the rate determining step is often considered to involve irreversible oxidative addition of the incoming aryl moiety (41). The electronic preference for this oxidative addition has been reported to parallel nucleophilic aromatic substitution (NAS) reactions with
polyhaloaromatics, which in turn reflects the degree of electron deficiency of the carbon bearing the halogen leaving group (42). Preferential oxidative addition at the C-3 position for arylation of 2,3-dibromo-2-alkenoates with palladium catalysts bearing phosphine ligands has been reported to result from a combination of steric and electronic effects (43, 44). By analogy in the present work with phosphine-(ligand)-free palladium catalysis, 1,4-dibromo-2-nitrobenzene (1) was expected to undergo regio-selective Suzuki coupling at the more electron deficient C1 position (ortho to the nitro group) compared to the C4 position (meta to the nitro group). After the first coupling, the residual 4-bromo group would be available for a second coupling step with a different arylboronic acid. Selective coupling of (1) with a suitable arylboronic acid, such as 4-methoxyphenylboronic acid (2), was anticipated to predominately give the biaryl (3) with minimal formation of the bis-product (4) or dimer (5) (Scheme 1) under flow synthetic conditions.

Firstly, the effect of reaction temperature was examined using 1,4-dibromo-2-nitrobenzene (1) as the substrate using a “Polar Bear” Flow reactor (Table 1). In this way, reaction selectivity could be optimized using temperature at the first coupling reaction stage. Moreover, in this format, the solubilities of the reagents and final products could be easily controlled and the propensity of the substrate to undergo oxidative additions at competing sites (leading to unwanted byproducts) at higher temperatures determined (Scheme 1). The results confirmed that selectivity fell drastically at higher temperature, although the level of conversion essentially remained constant. The highest conversion of 93% was achieved at 25°C with highest mono-selectivity for (3) of 74% and with low dimerization of the coupling product to give (5) (Table 1, entry 2). As also evident from Table 1, formation of the dimer (5) increased from 2% at 0°C or 25°C to 7% at 70°C, consistent with dimer formation being associated with higher activation energy and assisted by the higher temperatures.

In order to demonstrate the suitability of the Pd(OAc)2 catalyst for sequentially selective double Suzuki coupling procedures in in-flow systems, additional experiments were carried out at three different catalyst loadings with the same substrate (Scheme 2, Table 2). For these experiments, the reagents were continuously fed into the flow reactor for the same fixed time using the general conditions described in the Experimental Section with catalyst loadings of 2, 4 and 7 mol%. Conversion and selectivity were confirmed from 1H NMR data of the crude products after work-up. As evident from Table 2, 2 or 4 mol% catalyst loadings gave similar conversions and selectivities, whilst 7 mol% gave relatively higher conversion. Although lower catalyst loadings gave good conversion and selectivity for the first coupling step, 7 mol% catalyst was chosen for the in-flow double Suzuki coupling procedure to allow maximal conversion and selectivity to be achieved in the first

\[ \text{Scheme 1. Cross-coupling of 1,4-dibromo-2-nitrobenzene (1) carried out under Suzuki reaction conditions with 4-methoxyphenylboronic acid (2) catalyzed by the phosphine ligand-free Pd(OAc)\textsubscript{2}.} \]

\[ \text{Table 1. Effect of temperature on cross-coupling of (1) and (2) catalyzed by the ligand-free Pd(OAc)\textsubscript{2} using an integrated Flow Reactor System.} \]

| Entry | Temperature °C | Conversion (%)b | Products (%)b | Starting (1) | Mono (3) | Bis (4) | Dimer (5) |
|-------|---------------|----------------|--------------|-------------|----------|--------|---------|
| 1     | 0             | 86             | 14           | 65          | 19       | 2      |
| 2     | 25            | 93             | 7            | 74          | 17       | 2      |
| 3     | 70            | 90             | 10           | 49          | 34       | 7      |

\[ a\text{A solution containing (1), (2) and Bu\textsubscript{4}NOAc (mole equivalents ratio 1: 1.5: 2) in EtOH (2 mL) was mixed with a solution of Pd(OAc)\textsubscript{2} (7 mol%) in an equal volume of a 2:1 mixture of EtOH/THF using a T-piece connector and the resulting solution then passed through a flow coil (14 mL) heated at the specified temperatures using a syringe pump at a combined flow rate of 0.1 mL/min. With this system, a residence time of 70 min was found to be not long enough for full conversion.} \]

\[ b\text{Yields of the mono-, bis- and dimer products were determined from } ^1\text{H NMR data by integration of the aromatic proton adjacent to the NO_2 group for each compound in the crude reaction mixture (chemical shifts (ppm) for doublets at } \delta \text{ for (1), } \delta \text{ for (3), } \delta \text{ for (4) and } \delta \text{ for (5).} \]

\[ \text{Table 2. Effect of catalyst loadings on cross-coupling of (1) and (2) catalyzed by the ligand-free Pd(OAc)\textsubscript{2} using an integrated Flow Reactor System.} \]

| Catalyst Loading | Conversion (%) | Products (%) | Starting (1) | Mono (3) | Bis (4) | Dimer (5) |
|------------------|---------------|--------------|-------------|----------|--------|---------|
| 2 mol%           | 86            | 14           | 65          | 19       | 2      |
| 4 mol%           | 93            | 7            | 74          | 17       | 2      |
| 7 mol%           | 90            | 10           | 49          | 34       | 7      |

\[ a\text{A solution containing (1), (2) and Bu\textsubscript{4}NOAc (mole equivalents ratio 1: 1.5: 2) in EtOH (2 mL) was mixed with a solution of Pd(OAc)\textsubscript{2} (7 mol%) in an equal volume of a 2:1 mixture of EtOH/THF using a T-piece connector and the resulting solution then passed through a flow coil (14 mL) heated at the specified temperatures using a syringe pump at a combined flow rate of 0.1 mL/min. With this system, a residence time of 70 min was found to be not long enough for full conversion.} \]

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coupling step and also to ensure that an excess Pd (OAc)$_2$ remained in the flow system for the second coupling reaction.

Based on these experiments, which documented the level of regio-selectivity for Suzuki coupling reactions with a substituted dibromobenzene under in-flow conditions, these continuous flow processes were extended to multiple sequentially selective transformations, leading to unsymmetrical $p$-terphenyls. Besides its flexibility, this approach was also expected to provide economic advantages when cost outlays for the catalyst, solvent, purification of precursor materials, and time are taken into account. Regio-selective double cross-coupling reactions were thus explored, recognizing that studies devoted to the poly-coupling of halogenated nitrobenzene electrophiles with different boronic acids in the same pot are relatively uncommon in the scientific literature (3–5).

Our results confirmed that Pd(OAc)$_2$, without the need for a phosphine ligand or a nano-material support, such as carbon, was able to catalyze two different cross-couplings sequentially under in-flow conditions, forming two new carbon–carbon bonds (Scheme 3). The solvent system, EtOH:THF (2:1) was found to be suitable for these reactions, conferring good solubility for the catalyst, reagents and the products. As a consequence, the first cross-coupling, e.g. at the 2-position of (1) was run at 25°C for better conversion and selectivity (for a 140 min residence time at a combined flow rate of 0.1 mL/min for a 14 mL reactor), whereas, the second cross-coupling step was carried out at 70°C (for a 70 min residence time at a combined flow rate of 0.2 mL/min).

As highlighted in Table 3, the developed protocol resulted in an efficient in-flow ligand-less double Suzuki coupling of 1,4-dibromo-2-nitrobenzene (1) with up to 78% yield of the double coupling product was obtained. Depending on the reactivity of the second boronic acid, significant amounts (ca. 20%–25%) of products (4) and (5) derived from the initially formed mono-coupled product (3) could be isolated. However, implementation of simple rate enhancement steps at the stage of the second coupling procedure, such as an increase in temperature or longer residence time as practical process intensification steps, could shift the reaction towards the double coupling product (7). Previous double Suzuki coupling carried out under batch conditions led to higher yields of (7), with only mono-coupled product

Table 2. Effect of catalyst loading on cross-coupling of (1) and (2) catalyzed by ligand-free Pd(OAc)$_2$ in a Flow Reactor system.

| Entry | Catalyst mol% | Conversion (%) | Mono (3): Bis (4) product |
|-------|---------------|---------------|--------------------------|
| 1     | 2             | 84            | 3.8:1                     |
| 2     | 4             | 86            | 3.7:1                     |
| 3     | 7             | 93            | 4.4:1                     |

*aAll couplings were carried out at the specified catalyst loading (mol%Pd(OAc)$_2$) with 1.5 mol equivalents of (2) and 2 mol equivalents of Bu$_4$NOAc in EtOH/THF (2:1), at a flow rate of 0.1 mL/min at 25°C. The conversion yields and monomer to bis product ratios were determined by integration of the $^1$H NMR data for the crude reaction mixture (see footnote (b) to Table 1).*
(3) isolated (in reactions with (6c) and (6d)) (40). These batch reactions, however, needed to be carried out under quite different conditions to achieve site selectivity, namely 0°C for the initial coupling, 25°C for the second coupling and THF:H2O (1:1) as the solvent.

Dong and Hu(26a) have reported selective double-SM coupling (up to 99:1 double vs. mono-coupling) of different dihalobenzenes in batch mode using equimolar amounts of o- or p-tolylboronic acid, or p-methoxyphenylboronic acid and t-Bu3P (10 mol%) with 2.5 mol %Pd2(dba)3. Selectivity for the first coupling was dependent on the choice of ligand, with PPh3, for example, giving low conversion to mainly the mono-adduct (92:8), whilst t-Bu3P gave mainly the di-adduct. Since the ratio of dihalo-benzene to arylboronic acid used in these experiments was 1:1, only a maximum of 50% of the dihalobenzene starting compound could be converted. These authors proposed that under these batch conditions the selectivity arose via a preferential oxidative addition pathway. In this mechanism, the Pd(0), released from the first reductive elimination, preferentially reacts in a subsequent oxidative addition reaction with the already-formed coupling product rather than with the unreacted dihalobenzene starting compound.

Here, we propose that the ligand-free Pd-catalyzed, double-SM cross-coupling reaction proceeds by sequential steps of the oxidative addition, trans-metalation and reductive elimination as a catalytic cycle that is governed by the electronic influence of the nitro group at the neighboring halogen of the halo arene (1), (Figure 1). The strongly electron withdrawing nature of the NO2 group promotes the oxidative addition at the o-position rather than the m-position of (1), leading to o-substituted mono coupling product (3) via the intermediates (8) and then (9). In accordance with the generally accepted mechanism for monoauration of dihaloarenes via Suzuki cross-coupling reactions,(26) and the proposal of Moreno-Mañas and co-workers(26c) for the formation of Pd(0) from Pd(OAc)2, the Pd(0) catalyst regenerated by reductive elimination of (3) from the complex (9) was expected to interact preferentially in a second cycle with the dihalo-nitrobenzene starting material (1) rather than interacting with the already-formed product (3). Once the dihalonitrobenzene starting material (1) has been depleted in the first low temperature phase of the two-stage reaction and the temperature is increased, the less reactive (3) now adds oxidatively to the Pd(0) catalyst to give the intermediate complex, 10. Transmetalation followed by reductive elimination leads to the p-terphenyls (7a–7d) via the intermediate complex (11) and regenerates the Pd(II) to complete the cycle.

During the first coupling reaction, formation of a dimerization product derived from the biaryl intermediate (3) was observed. Thus, reaction of 1,4-dibromo-2-nitro-benzene (1) with 4-methoxyphenylboronic acid (2) under the reaction conditions led to formation of 4,4”’-dimethoxy-2’,3”’-dinitro-1,1’4’,1”’-quarter-}

### Table 3. Preparation of terphenyls (7) by sequentially selective Suzuki coupling catalyzed by ligand-free Pd(OAc)2 in a Flow Reactor system*a.

| Entry | Boronic acid (6) | Bis-product (4) | Dimer (5) | Product (7) |
|-------|-----------------|----------------|-----------|-------------|
| 1     | (HO)2B-Cl       | 15%            | 10%       |             |
| 2     | (HO)2B-OMe      | 10%            | 11%       |             |
| 3     | (HO)2B-OH       | 13%            | 6%        |             |
| 4     | (HO)2B-OH       | 16%            | 9%        |             |

*First coupling was carried out at 25°C with 7 mol% Pd(OAc)2 and 3 mol equivalents of Bu4NOAc in EtOH/THF (3:1); the second coupling was carried out at 70°C, under-flow conditions. aIsolated yield.
phenyl \( (5) \) in 2\%-7\% yield (Table 1), indicating that the “in-flow” reaction can lead to the formation of a quaterphenyl product via a dimerization pathway. Based on previous reports \((45, 46)\) and the results from this investigation, a \(\text{Pd}(0)/\text{Pd}(II)\) mechanism for the homo-coupling reaction can be proposed (Figure 2). In this mechanism, initial electrophilic palladation occurs at the C4-position of 4-bromo-4\'-methoxy-2-nitro-1,1\'-bi-phenyl \( (3) \). The intermediate \((12) \) then undergoes trans-metalation with a second unit of 4-bromo-4\'-methoxy-2-nitro-1,1\'-biphenyl \( (3) \) to form the intermediate \((13) \). Reductive elimination regenerates the \(\text{Pd}(II)\) to complete the cycle and release the quaterphenyl, \( (5) \).

Due to the low yield of the quaterphenyl \( (5) \) with the in-flow process, good quality crystals needed for the determination of its X-ray crystallographic structure were not readily available. This limitation prompted a search for a suitable alternative method for its synthesis. Single coupling under flow reactor conditions at a very low flow rate to increase the residence time did not significantly increase the yield of \( (5) \). Attempted syntheses based on batch process methods for 7 days at ambient temperature also did not increase the yield of \( (5) \). Batch process methods in flasks at more elevated
temperatures lead to a moderate increase in yield (53% at 100°C), but increasing the temperature beyond 100°C resulted in polymerized products. Finally, the highest yields of (5) were achieved using microwave irradiation conditions at 150°C for 30 min, which gave (5) in 84% yield after column chromatographic purification. The simplicity of the $^1$H and $^{13}$C NMR spectra of compound (5) is consistent with its symmetrical structure.

The $^1$H NMR spectrum shows a doublet at δ 6.99 ppm and a δ doublet at 7.30 ppm for the protons in the para-disubstituted ring and one set of 3 peaks for the 3 protons in the ring bearing the nitro group. Similarly, the $^{13}$C NMR spectrum showed only one set of 11 peaks, consistent with the proposed dimeric structure. High resolution mass spectroscopy confirmed a molecular ion peak at m/z 456.1316, consistent with the calculated monoisotopic mass for the dimer, (5). Single crystals of the $p$-quaterphenyl (5) were obtained by recrystallization of the product from THF/EtOH. The X-ray crystallographic structure of the $p$-quaterphenyl (Figure 4(a,b)) validates a process of dimerization of the biaryl intermediary compound, (3). The crystal structure (Figure 4(a)) also shows that the two nitro groups in
the dimer are oriented in opposite directions in relation to the biphenyl bond, as expected due to steric effects.

3. Conclusions
From green chemistry perspectives, continuous synthetic methodologies in a flow format that involve the use of low loadings of a ligand-free catalyst, low energy consumption and the use of benign solvents are highly desirable. Since the yield for batch processes even at small laboratory scales can vary considerably and potential hazards associated with scaling up can increase significantly, an alternative flow chemistry method was sought. The outcomes are the benefits of higher reproducibility due to better control over heat and mass transfer provided by the micro-mixing in the flow system. Potentially, at larger (process) scales further increases in productivity could be realized through automation and improved safety profiles in the handling of toxic or hazardous reagents (47, 48).

This study has investigated the regio-selective generation by flow chemical synthetic methods of compounds containing an unsymmetrical p-terphenyl architecture. The utility of using a double Suzuki cross-coupling protocol within a flow chemistry format for the synthesis of unsymmetrical p-terphenyls using a ligand-free, yet, robust palladium catalyst has been documented. These flow reactor methods allowed selective monoarylation of a dibromonitroarene with arylboronic acids to give bromobiaryl precursors endowed with good ortho-chemoselectivity, followed by subsequent double cross-coupling to provide in-flow a “one pot” practical protocol for preparing unsymmetrically substituted p-terphenyls. The availability of low cost starting materials and a stable, ligand-less catalyst, convenient in-flow process control and air/moisture tolerance make the described synthetic methods very useful from a green chemical viewpoint. Finally, the simplicity of the reactions and flow chemistry work tasks suggests further adaptations of this methodology for the generation of structurally more diverse combinatorial terphenyl or triphenylene libraries should be feasible.

4. Materials and methods
4.1. General
All reagents and solvents were purchased from Sigma-Aldrich, Acros Organics or Alfa Aesar and used without further purification. TLC was performed on Merck silica gel 60F254 precoated aluminum plates. The components were visualized by fluorescence under 254 nm ultraviolet irradiation or by exposure to a variety of development/charring reagents where necessary. Flash chromatography was performed on a FlashMaster II using Merck silica gel 60, 0.040–0.063 mm, (230–400 mesh) for normal phase chromatography and Grace Vydac C18 silica gel (Davisil), 35–70 μm for reverse phase chromatography using automated gradient elution mode. Melting points were determined using a Stuart melting point apparatus (SMP3) with a digital thermometer and are uncorrected.

1H and 13C NMR spectra were recorded on a Bruker DPX-300 spectrometer (300 MHz 1H, 75 MHz 13C) and a Bruker DPX-400 spectrometer (400 MHz 1H, 100.6 MHz 13C). The 1H n.m.r. spectra refer to solutions in deuterated solvents. The residual solvent peaks were used as an internal reference, except CDCl3 where tetramethylsilane (TMS) was used as the internal standard (δ 0.00 ppm).

Low resolution electrospray ionization mass spectra (ESI) were recorded on a Micromass Platform II API QMS Electrospray mass spectrometer with cone voltage at 25 V as solutions in MeOH unless otherwise indicated. High resolution electrospray ionization mass spectra (HRMS) (ESI) were recorded with an Agilent 6220 Accurate Mass TOF LC/MS spectrometer in positive (ESI+) mode except for phenol (7c) which was analysed in negative (ESI-) mode. High resolution electron impact mass spectra (HRMS) (EI) were recorded with a Thermo Scientific MAT95XK spectrometer.

Flow reactions were carried out using a Polar Bear Plus Flow Synthesizer (Cambridge Reactor Design). Microwave reactions were carried out using a CEM Discovery S-class microwave reactor fitted with an Explorer 48 automation deck and Synergy control software (A.i.Scientific Pty Ltd).

4.2. General flow chemical procedures
4.2.1. Single coupling reactions
Using a Fusion 200 Touch Syringe Pump, a solution of 1,4-dibromo-2-nitrobenzene (1) (70 mg, 0.25 mmol), 4-methoxynaphthalene (2) (57 mg, 0.38 m mol) and tetrabutyl-ammonium acetate (151 mg, 0.5 mmol) in absolute EtOH (2 mL) was loaded into a 10 mL Normject syringe in Line A. A solution of Pd(OAc)2 (7 mol%) in absolute EtOH/THF 2:1 (2 mL) was loaded into a second syringe in Line B. Sample lines were joined via a T-piece and the mixed stream allowed to flow into a 14 mL coil of PFA tubing on a Polar Bear reactor held at 25°C. The liquid stream was pumped at a combined flow rate of 0.1 mL/min (residence time: 140 min) and collected in a conical flask containing H2O as a
quenching medium, extracted with CH$_2$Cl$_2$, washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The PFA tubing was thoroughly flushed with MeOH to remove any traces of Pd black formed during reactions.

### 4.2.2. Double coupling reactions

Using a Fusion 200 Touch Syringe Pump, a solution of 1,4-dibromo-2-nitrobenzene (1) (140 mg, 0.55 mmol), 4-methoxyphenylboronic acid (2) (114 mg, 0.75 mmol) and tetrabutyl-ammonium acetate (453 mg, 1.5 mmol) in absolute EtOH (4 mL) was loaded into a 10 mL Normject syringe in Line A. A solution of Pd(OAc)$_2$ (7 mol%) and K$_2$CO$_3$ (7.4 g, 53.4 mmol) in DMF (30 mL) was pumped at a combined flow rate of 0.1 mL/min (residence time: 140 min) and mixed with the 2nd stream of boronic acid (6) (2 equiv.) at a flow rate of 0.1 mL/min via a T-piece and the mixed stream flowed into a 14 mL coil of PFA tubing on a Polar Bear reactor held at 70°C. The liquid stream was pumped at a combined flow rate of 0.2 mL/min (residence time: 70 min) and collected in a conical flask containing H$_2$O as a quenching medium. The reaction mixture was extracted with CH$_2$Cl$_2$, washed with H$_2$O (10 mL) at ambient temperature for 2 h. Workup and column chromatography on silica using 10% EtOAc/hexane gave the biphenyl (7g) as a yellow solid in 75% yield. HRMS (ESI) m/z [M + Na]$^+$ calcd for C$_{19}$H$_{14}$ClNNaO$_3$: 362.0560, found 362.0555.

### 4.4. Synthesis of 4′-chloro-4-methoxy-2-nitro-1,1′:4′,1″-terphenyl (7d)

Compound (7d) was prepared by the above procedures. Yield, 61%; m.p. 132.7°C; $^1$H NMR (CDCl$_3$) δ 3.85 (s, 3H), 6.97 (d, 2H, J = 8.8 Hz), 7.28 (d, 2H, J = 8.8 Hz), 7.36 (br. dd, 1H, J = 7.8, 1.9 Hz), 7.41 (br. s, 1H), 7.45 (d, 1H, J = 8.0 Hz), 7.78 (dd, 1H, J = 8.0, 1.9 Hz), 7.99 (d, 1H, J = 1.9 Hz); $^{13}$C NMR (CDCl$_3$) δ 19.7, 20.1, 55.5, 114.5 (2x), 122.4, 124.5, 128.4, 129.4 (2x), 129.5, 130.4, 130.6, 132.4, 134.2, 136.1, 137.4, 137.7, 141.4, 149.9, 159.9; HRMS (ESI) m/z [M + Na]$^+$ calcd for C$_{19}$H$_{14}$ClNNaO$_3$: 362.0560, found 362.0555.
4.5. Synthesis of 4,4″-dimethoxy-2',3'-dinitro-1,1″:4,1″:4',1″″:4″″-quaterphenyl (5)

To a 10 mL microwave vial with a stir bar and rubber septum were added 4-bromo-4'-methoxy-2-nitro-1',1″-biphenyl (3) (40 mg, 0.13 mmol), Pd(OAc)₂ (5 mg, 17 mol %), tetraphenylammonium acetate (140 mg, 0.46 mmol) and DMF (2 mL). The resulting mixture was microwaved using the CEM Discover reactor for 30 min at 150°C before quenching with water (10 mL). The mixture was extracted with CH₂Cl₂, washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc, 3:1) to give 4,4″-dimethoxy-2',3'-dinitro-1,1″:4,1″:4',1″″:4″″-quaterphenyl (5) (25 mg, 84% yield) as a yellow solid; m.p. 226°C; ¹H NMR (CDCl₃) δ 3.87 (s, 2x 3H), 6.99 (d, 2x 2H, J = 8.8 Hz), 7.30 (d, 2x 2H, J = 8.7 Hz), 7.57 (d, 2x 1H, J = 8.0 Hz), 7.85 (dd, 2x 1H, J = 8.0, 2.0 Hz), 8.1 (d, 2x 1H, J = 1.9 Hz); ¹³C NMR (CDCl₃) δ 55.6 (2x), 114.6 (4x), 122.6 (2x), 128.9 (2x), 129.4 (4x), 130.5 (2x), 133.0 (2x), 135.9 (2x), 138.4 (2x), 150.1 (2x), 160.2 (2x); HRMS (EI): m/z [M] calcd for C₂₆H₂₃N₂O₆: 456.1321, found 456.1316.

4.6 X-ray crystal structure Determinations

A yellow plate-like crystal of (5) was covered in a viscous oil and mounted onto an OXFORD Gemini Ultra CCD diffractometer and cooled to 173 K. Data were collected with MoKα radiation, λ = 0.71073 Å to 2θmax, 50° yielding 21170 reflections, these merging to 3731 unique data (Rint = 0.077) with 2697 having l > 2σ(l) considered observed, after an empirical absorption correction. The CrysAlisPro v 1.171.35.15 (Agilent Technologies, 2012) (57) software package was used for the data collection and data reduction. The structure was solved by conventional methods and refined by full matrix least squares on F² (SHELX97) (52) with anisotropic thermal parameter forms for all non-hydrogen atoms. Hydrogen atoms were placed in calculated positions using a riding model. The data were treated a pseudo-merohedral twin (twins matrix 0 0 1 0 −1 0 1 0 0, twin ratio 0.47) using the SHELX TWIN command. Significant residual electron density peaks (ca. 0.97 e Å⁻³) were presumed to arise through inadequacies of the twin model.

4.7. Crystal and refinement data

Crystals of (5) exhibited the following characteristics: C₂₆H₂₀N₂O₆. M = 456.44. Monoclinic, P2₁/c, a = 13.580(3); b = 12.5335(13); c = 13.586(2) Å; β = 112.90(2)°. V = 2130.1 (6) Å³. Z = 4. ρcalc = 1.423 g cm⁻³, μ(MoKα) 0.102 mm⁻¹. Ntotal = 21170 (Rint = 0.077), N = 3731, Nᵢ (l > 2σ(l)) 2697.

R1 0.101, wR2 = 0.240 (l > 2σ(l)); R1 = 0.129, wR2 = 0.275 (all data). GoF = 1.044. Δεmin,max = −0.34, 0.89 e Å⁻³.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Notes on contributors

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[47] Appendix A

CCDC 1510141 contains the supplementary crystallographic data for (5). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.