Continuous Flow Synthesis of Fullerene Derivatives

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Supporting Information

ABSTRACT: Various fullerene-based electron acceptor materials for organic photovoltaic applications were prepared via [3] + 2 and [4 + 2] cycloadditions using a continuous flow approach. The 1,3-dipolar cycloaddition of the tosylhydrazone precursor and the Diels-Alder cycloaddition of indene to either C_{60} or C_{70} under conventional batch reaction conditions were translated to the continuous flow process. By varying the residence time, temperature, and equivalents of cycloaddition



reagent, significant improvements in yields and reaction times were achieved over conventional batch processes.

 \mathbf{F} ullerene is one of the most widely studied *n*-type organic semiconductor materials. Buckminsterfullerene (C₆₀) can reversibly accept six electrons, and electron mobility on the order of 1 $\text{cm}^2/(\text{V s})$ has been measured.¹⁻⁶ Derivatives of fullerenes (C₆₀ and C₇₀) have been used extensively in donor-acceptor bulk heterojunction (BHJ) solar cells due to their remarkable electronic properties and solution processability.^{7–12} In fact, state-of-the-art BHJ devices typically consist of a polymeric donor material and fullerene derivatives as acceptors.^{13,14} One of the main advantages of BHJ solar cells is the possibility of cheap and fast device fabrication by employing reel-to-reel printing techniques. However, a large quantity of material is required to optimize the performance of printed devices.

There are numerous methods for the functionalization of fullerenes. The most popular reactions are cyclopropanations, 1,3dipolar cycloadditions, and Diels-Alder cycloadditions.¹⁵⁻¹⁹ While these are relatively simple single-step reactions, the reaction scale is seriously restricted by the amount of solvent required to fully dissolve the fullerene starting material. The solubility of C₆₀ in toluene is only 2.8 mg/mL at 25 °C with solubility increasing to 24 mg/mL in o-dichlororbenzene (o-DCB).²⁰ Continuous flow synthetic methods offer a solution to this problem. The advantages of continuous flow reactions include superior heat transfer and reagent control, fully contained and closed reactor system allowing for safe handling of hazardous reagents and high pressure reactions, ultimate reproducibility owing to precise control of parameters, and most importantly, scalability.²¹⁻²⁶ A very recent publication showed the possibility to synthesize a fullerene derivative using continuous flow methods on microfluidic chips.²⁷ However, only small scale production was examined with maximum output of 6 mg of crude product per hour. The objective of this study is to apply continuous flow methods to the synthesis of four fullerene derivatives that are currently setting the benchmark in BHJ solar cell performance. Comparison between the conventional batch reaction and the continuous flow process will be made in the context of reaction time, conversion and product purity.

The continuous flow reactions were performed on a commercially available flow reactor (Vaportec,²⁸ see Experimental Section for details). The reactor setup consisted of polymeric or stainless steel tubing (10 or 12 mL internal volume) and a HPLC pump (R2+ module, Vaportec), a 2 mL loop attached to a 6-way valve, and a backpressure regulator (BPR) fitted to the reactor outflow. A representative reaction procedure for small scale optimization studies is carried out by loading the sample loop containing the fullerene substrate, cycloaddition precursor and base, if necessary (Scheme 1A). For large scale synthesis, a single flow channel was used to deliver either solvent or stock solution (Scheme 1B). The effect of residence time, temperature, irradiation, and equivalents of reactants on the yield was evaluated via HPLC analysis of product mixtures (Figure 1).

The synthesis of the most commonly used fullerene acceptor in organic electronics, phenyl-C₆₁-butyric acid methyl ester 3 (PC₆₁BM) and its C₇₀ analogue, phenyl-C₇₁-butyric acid methyl ester 6 ($PC_{71}BM$), was performed under continuous flow conditions. The primary challenge in translating conventional batch reactions to continuous flow methods is the solubility of reactants and products. The synthesis of PC₆₁BM 3 is essentially a one-pot reaction with three steps (Scheme 2).^{29,30} In the first step, the diazo intermediate 4 is generated by the reaction of tosylhydrazone 1 with sodium methoxide in the presence of pyridine. 1,3-Dipolar cycloaddition of intermediate 4 to the C_{60} followed by N₂ liberation gives a mixture of two isomers of $PC_{61}BM$, the open-cage [5,6]fulleroid and close-cage [6,6]isomer. The mixture can then be thermally isomerized to give exclusively the close-cage [6,6] isomer.

In the conventional batch process, tosylhydrazone 1 and sodium methoxide are suspended in pyridine to give the diazo intermediate 4. This is not easily translated to the continuous flow process in which reactants should be fully dissolved in the reaction solvent, o-DCB. 2,2,6,6-Tetramethylpiperidine 2 (TMP) proved to be a good

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^{*a*} Reaction setup for the (A) small scale optimization and (B) large scale fullerene functionalization via 1,3-dipolar cycloaddition.

alternative to sodium methoxide. By mixing 1 with TMP in *o*-DCB, intermediate 4 was generated *in situ* in the tube reactor (Scheme 1A). Intermediate 4 then reacted with C₆₀ and eventually led to $PC_{61}BM$ on heating. Initial small-scale optimization experiments for the synthesis of $PC_{61}BM$ used 2 equiv of tosylhydrazone 1 with reaction temperatures up to 150 °C and gave relatively low yields and multiadducts as the main impurity (Table 1, entries 1, 2). Additionally, ¹H NMR analysis showed that the monoadduct fraction consisted of a mixture of isomers that can be thermally isomerized to produced the desired [6,6]isomer (Figure SI-9 in Supporting Information).²⁹

In the presence of stoichiometric quantities of 1, the amount of multiadducts was effectively reduced (Table 1, entry 3), whereas the increase of the reaction temperature and residence times were translated into moderate yields and direct thermolysis to the [6,6] isomer (Table 1, entry 4, Figure 1A). The continuous flow approach showed a notably improved yield of 59% PC₆₁BM (94% based on converted C₆₀) in comparison with the reported 35% yield (83% based on converted C₆₀)²⁹ via the one-pot batch synthesis.

The large scale continuous flow synthesis of $PC_{61}BM$ 3 was performed with a modified reactor configuration to allow a continuous feed of reactants from a stock solution reservoir (Scheme 1B). It is important to note that the anomalous solubility behavior of C_{60} must be taken into account in large scale continuous flow reactions.³¹ The fact that the solubility of C₆₀ decreases (by as much as 2/3) with increasing temperature can have significant impact on the progress of the flow reaction. As the stock solutions were made with near saturated room temperature concentrations of C_{60} (28 mM), precipitation of C_{60} in the tube reactor at temperature exceeding 150 °C is likely.³² To overcome this problem, the reaction temperature was increased gradually from 70 °C³³ (10 mL internal volume) to 150 °C (20 mL internal volume) and 250 °C (10 mL internal volume). Additionally, the reduction of the residence time from 100 min (Table 1, entry 4) to 80 and 40 min yielded 48% and 39% conversion, respectively. Reducing the reaction time to less than 1 h compromises the reaction yield by 20%, while increasing the throughput by 2.5 times. For instance, our equipment allowed a continuous flow production of 2.6 g (35% isolated yield after column chromatography) of PC₆₁BM in 8 h.

Next, we turned our attention to the preparation of the C_{70} analogue, PC₇₁BM **6**.³⁴ As for PC₆₁BM, the batch synthesis of



Figure 1. HPLC traces of the crude products from the continuous flow synthesis of (A) $PC_{61}BM$, (B) $PC_{71}BM$, (C) $IC_{60}BA$ (mixture of regioisomers), and (D) $IC_{70}BA$ (mixture of regioisomers). ICMA: indene-fullerene monoaduct. A normal phase silica gel column (Rainin Dynamax 60 Å Si-83-101-C) was used with toluene (detection at 330 nm) and toluene/hexane (10:1) (detection at 313 nm) as eluents at 1 mL/min for the PCBM and indene derivatives, respectively.

 $PC_{71}BM$ is a one-pot reaction with 3 steps (Scheme 2). The difference between the two reaction sequences lies in the final step where irradiation is the preferred method for the isomerization of [5,6] to [6,6] isomers of $PC_{71}BM$. It is important to note here that although isomerization by irradiation does reduce the number of regioisomers in the $PC_{71}BM$ product mixture, the monoadduct fraction still consists of three major isomers that are inseparable by conventional chromatography methods.³⁴ Using TMP as base, we found that reaction of 2 equiv of tosylhydrazone I with C_{70} delivered the product mixture in 42% yield after relatively short irradiation times in continuous flow (Table 1, entry 5). HPLC analysis of the relative product ratios in the reaction with equimolar amounts of tosylhydrazone showed moderated conversions (49%) after 60 min reaction times and 94% yield based on converted C_{70} (Table 1, entry 6 and Figure 1B).

Recently, Diels—Alder adducts of indene with fullerenes have been successfully used to improve polymer/fullerene bulk heterojunction (BHJ) solar cell device performance. Both indene- C_{60} bisadduct 9 (IC₆₀BA)^{35,36} and indene-C₇₀ bisadduct 10 (IC₇₀BA)³⁷ are attractive fullerene acceptor materials for two main reasons. First, the LUMO energy levels of IC₆₀BA and IC₇₀BA are elevated compared with their PCBM counterparts leading to a larger open circuit voltage in BHJ devices with donor polymers. Second, the synthesis involves only two reactants: the Diels—Alder cycloaddition of indene and fullerene (Scheme 3A). By using 1,2,4-trichlorobenzene as solvent, the yield of the reported batch reaction is 34% for IC₆₀BA.³⁵ For IC₇₀BA, a high molar ratio of indene to C_{70} in combination with long reaction times were shown to be necessary for good conversions (58%).³⁷ It is important to note that both bisadducts of C_{60} and C_{70} consist of complex mixtures of regioisomers as can be observed in the HPLC analyses (Figure 1C and D).

One of the advantageous features of continuous flow reactions is the ability to perform reaction under pressure with superheated solvents. This means the high temperatures required for the Diels–Alder addition of indene to fullerenes should translate well to continuous flow methods. Indene is thermally converted to isoindene in the tube reactor, which then reacts with C_{60} or C_{70} via Diels–Alder cycloaddition (Scheme 3B). The experiments were conducted with 20 to 36 equivalents of the indene under superheated conditions at 220 °C in a stainless steel reactor with *o*-DCB as a solvent. IC₆₀BA and IC₇₀BA were both successfully prepared in less than 2 h in 54% and 49% yield, respectively (Table 1, entries 7 and 8, Figures 1C and D) achieving comparable to significantly improved yields over the batch process.

In summary, effective procedures were developed for the preparation of fullerenes derivatives via [3 + 2] and [4 + 2] cycloaddition reactions using a continuous flow approach. Electron acceptor materials PC₆₁BM, PC₇₁BM, IC₆₀BA, and IC₇₀BA were produced in maximum reaction times of 100 min, whereas fullerene derivatization in batch frequently requires several hours to days under reflux conditions. The described results, in the case of PC₆₁BM, translate to continuous material production of up to

Scheme 2. Synthesis of Phenyl-C₆₁-butyric Acid Methyl Ester ($PC_{61}BM$) and Its C₇₀ analogue ($PC_{71}BM$) under Conventional Batch Reaction Conditions



Table 1. Optimization for the Cycloadditions of C₆₀ and C₇₀ with Diazo Intermediate 4 and with Indene under Flow Conditions

| entry | fullerene | reagent | diene/dipole precursor (equiv) | conditions ^{b} (°C) | residence time (min) [lit., h] | yield $(\%)^c$ [lit.] | converted fullerenes (%) |
|-------|-----------------|---------|--------------------------------|---|--------------------------------|---------------------------------------|--------------------------|
| 1 | C ₆₀ | 1^{a} | 2 | 130 | 100 | 45 | 47 |
| 2 | C ₆₀ | 1^{a} | 2 | 150 | 50 | 42 | 45 |
| 3 | C ₆₀ | 1^{a} | 1 | 150 | 50 | 53 | 80 |
| 4 | C ₆₀ | 1^{a} | 1 | 180 | $100 [24 - 29^d]$ | 59 [35 ^{<i>d</i>,<i>e</i>}] | 94 |
| 5 | C ₇₀ | 1^{a} | 2 | $h\nu$ | 60 | 42 | 45 |
| 6 | C ₇₀ | 1^{a} | 1 | $h\nu$ | 60 | 49 [59 ^{e,f}] | 94 |
| 7 | C ₆₀ | indene | 20 | 220 | $100[12^g]$ | 54 [34 ^g] | 56 |
| 8 | C ₇₀ | indene | 36 | 220 | $100 [12-72^{h}]$ | 49 [8-58 ^h] | 52 |

^{*a*} Five equivalents of TMP were used to activate tosylhydrazone 1. ^{*b*} Degassed *o*-DCB as solvent. ^{*c*} Yield determined via HPLC. ^{*d*} The authors isolated intentionally the open cage fulleroid, performing the cycloaddition and N₂ extrusion at 65–70 °C for 22 h. Isomerization was induced thermally within 2–7 h.²⁹ ^{*c*} Reported isolated yield of one-pot reaction procedures using sodium methoxide as a base. ^{*f*} Reference 34. ^{*g*} Isolated yield using 1,2,4-trichlorobenzene as a solvent.^{35 h} Reference 37.

approximately 15 g/day with one benchtop continuous flow reactor. 38

EXPERIMENTAL SECTION

General Experimental. The benzoyl propionic acid methyl ester and the corresponding *p*-tosylhydrazone of methyl benzoylbutyrate were prepared using standard procedures.²⁹ Commercial reagents were used as purchased without further purification. C_{60} (99.5%) and C_{70} (95%) were bought from Nano-C and BuckyUSA, respectively.

The continuous flow experiments were conducted using a Vaportec R2+R4 unit.²⁸ All solutions were degassed and reactions were performed under anaerobic conditions. Polytetrafluoroethylene PTFE (12 mL internal volume), perfluoroalkoxy PFA (10 mL internal volume), or stainless steel (10 mL internal volume) tubing material was used in the

reactor setups. The Vaportec R4-pumping module was operated in the small scale fluid connection mode with manual loaded sample loops. The reactants were channeled into the tube reactor by pumping solvent from a reservoir at 0.1 or 0.2 mL/min (equivalent to residence times of between 50 and 100 min depending on the internal volume of the reactor). All reactions were performed either thermally (R4-module, Vaportec) or photochemically, in *o*-dichlorobenzene (*o*-DCB), at a concentration range of 22 to 28 mM (based on fullerene component) and under approximately 6–19 bar system pressure (Scheme SI-1 in Supporting Information).

 11 H and 13 C NMR measurements were and carried out from CDCl₃ solutions on either 400 or 500 MHz instruments. The 1 H and 13 C NMR spectrum of the fullerene derivatives are provided in the Supporting Information. HPLC analysis was carried out using a standard HPLC system with a UV–vis detector. A Rainin Dynamax 60 Å (Si-83–101-C)

Scheme 3. Synthesis of Indene- C_{60} Bisadduct (IC₆₀BA) and Indene- C_{70} Bisadduct (IC₇₀BA) under (A) Conventional Batch Reaction and (B) Continuous Flow Conditions



analytical HPLC column was used. The product ratios and yields are based on the percental area from the signal integrations of the HPLC trace (detection at 330 and 313 nm). Analytical and large scale material purification was performed following standard chromatographic purification methods on silica gel. MALDI-TOF (matrix-assisted laser desorption ionization time-of-flight) mass spectra were obtained in positive-ion mode with *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile as the matrix.

Functionalization of Fullerenes via 1,3-Dipolar Cycloadddtion under Continuous Flow. Synthesis of PC₆₁BM 3. A degassed solution of C_{60} (40 mg, 5.5 × 10⁻² mmol), *p*-tosylhydrazone of methyl benzoylbutyrate (21 mg, 1 equiv), and 2,2,6,6-tetramethylpiperidine (50 μ L, 0.3 mmol) in 2 mL of *o*-DCB was pumped through a preheated reactor (at 135 °C, 150 or 180 °C) using a HPLC pump at the corresponding flow rate. An analytical sample was diluted with toluene, washed with water, and dried with magnesium sulfate, and the yield was determined by analytical HPLC. In a representative large scale experiment one R4-reactor modules with four temperature controllable zones was used: one reactor at 70 °C (10 mL internal volume), two reactors at 150 °C (20 mL internal volume), followed by telescopic isomerization in one reactor at 250 °C (10 mL internal volume) at 1 mL/min flow rate (residence time = 40 min, BPR = 250 psi). Therefore, 6 g (8.33 mmol) of C_{60} , 3.18 g (8.5 mmol) of *p*-tosylhydrazone of methyl benzoylbutyrate, and 2,2,6,6-tetramethylpiperidine (5.7 mL, 34.3 mmol) were dissolved in 360 mL of o-DCB and pumped through the reactor. The collected solution at the reactor outlet was concentrated under reduced pressure and purified by column chromatography with toluene as eluent to afford PC₆₁BM (2.67 g, 2.93 mmol, 35%). HPLC (min., 330 nm, 100% toluene, 1 mL/min) PC₆₁BM: 7.5. ¹H NMR (CDCl₃, 500 MHz) δ ppm: 7.94 (d, 2 H, J = 8 Hz), 7.56 (t, 2 H, J = 7.5 Hz), 7.48 (t, 1 H, J = 7.4 Hz),3.69 (s, 3 H), 2.92 (m, 2 H), 2.54 (t, 2 H, J = 7.4 Hz), 2.2 (m, 2 H). ¹³C NMR (CDCl₃, 500 MHz) δ ppm: 173.5, 148.8, 147.8, 145.2, 145.1 (2), 144.8, 144.7, 144.4, 144.0, 143.8, 143.0 (2), 142.9, 142.2 (2), 142.1 (2), 141.0, 138.0, 137.6, 136.7, 132.1, 128.4, 128.3, 79.9, 51.9, 51.7, 33.9, 33.7, 22.4. MS-MALDI (m/z): calcd for C₇₂H₁₄O₂, 910.10; found M⁺, 910.10.

Synthesis of $PC_{71}BM$ **6**. A degassed solution of C_{70} (40 mg, 4.8 × 10⁻² mmol), *p*-tosylhydrazone of methyl benzoylbutyrate (20 mg, 1.1 equiv), and tetramethylpiperidine (40 μ L, 0.2 mmol) in 2 mL of *o*-DCB was pumped through a tube reactor using a HPLC pump at the corresponding flow rates and irradiated with a white halogen lamp. An analytical sample was diluted with toluene, washed with water, and dried with magnesium sulfate, and the yield was determined by analytical HPLC. HPLC (min., 330 nm, 100% toluene, 1 mL/min) PC₇₁BM: 6.5. ¹H NMR (CDCl₃, 500 MHz) δ ppm: 7.2–7.95 (m, 5 H); 3.52, 3.69 (major isomer), 3.76 (s, 3H, ratio 1:10:1); 2.41–2.94 (m, 4 H); 1.79–2.24 (m, 2 H). ¹³C NMR (CDCl₃, 500 MHz) δ ppm: 173.3, 156.0, 155.3, 152–138 (forest of peaks belonging to sp² carbons on the fullerene cage, Figure SI-13 in Supporting Information), 131.6, 130.8, 128.6, 128.3, 72.9, 69.9, 51.8, 36.0, 34.2, 33.9, 21.8. MS-MALDI (*m*/*z*): calcd for $C_{82}H_{14}O_2$, 1030.10; found M⁺, 1030.10.

Functionalization of Fullerenes via Diels–Alder Cycloadddtion under Continuous Flow. Synthesis of $I_{60}BA$ **9**. A degassed solution of C₆₀ (40 mg, 5.5 × 10⁻² mmol) and indene (130 μ L, 1.1 mmol, 20 equiv) in 2 mL of *o*-DCB was pumped through a preheated reactor (220 °C) at 100 μ L/min. An analytical sample was diluted with toluene/hexane (1:10), and the yield was determined by analytical HPLC. After precipitation from ethanol, 40 mg of crude product was purified by column chromatography (30% toluene in hexane). HPLC (min, 313 nm, toluene/hexane (1:10) 1 mL/min) IC₆₀BA: 16–28. ¹H NMR (CDCl₃, 500 MHz) δ ppm: 7.91–7.20 (m, 8H), 2.57–4.44 (m, 4H), 48.08–3.22 (m, 2H), 3.06–2.49 (m, 2H). ¹³C NMR (CDCl₃, 500 MHz) δ ppm: 161–136 (forest of peaks belonging to sp² carbons on the fullerene cage, Figure SI-15 in Supporting Information), 127, 124 (sp² carbons on the indene addend), 74, 57, 46 (sp³ on the indene addend). MS-MALDI (*m*/ *z*): calcd for C₇₈H₁₆, 952.13; found M⁺, 952.18.

Synthesis of $IC_{70}BA$ **10**. C_{70} (40 mg, 4.7×10^{-2} mmol) and indene (200 μ L, 36 equiv) were reacted following the procedure described for IC₆₀BA **5**. HPLC (min, 313 nm, toluene/hexane (1:10) 1 mL/min) IC₇₀BA: 30–49. ¹H NMR (CDCl₃, 500 MHz) δ ppm: 7.73–7.24 (m, 8H), 4.79–4.45 (m, 2H), 4.33–4.14 (m, 2H), 2.92–2.70 (m, 2H),

2.50–2.37 (m, 2H). 13 C NMR (CDCl₃, 400 MHz) δ ppm: 162–129 (forest of peaks belonging to sp² carbons on the fullerene cage, Figure SI-18 in Supporting Information), 127, 124 (sp² carbons on the indene addend), 68.2, 67.4, 58.0, 55.9, 46, 38.7 (sp³ on the indene addend). MS-MALDI (*m*/*z*): calcd for C₈₈H₁₆, 1072.13; found M⁺, 1072.13.

ASSOCIATED CONTENT

Supporting Information. HPLC-elugrams and NMR spectra of the fullerene derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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