A Capture-and-Release Catalytic Flow System

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Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

Supported transition-metal catalysts offer the promise of catalyst reuse in order to make chemical transformations more environmentally friendly and less expensive; however, catalysts that are supported on insoluble scaffolds often exhibit significantly reduced selectivities and rates. A capture/release strategy that unites the benefits of heterogeneous and homogeneous catalysis would overcome these current shortcomings. Herein, we report on a novel capture-and-release flow system that takes advantage of a non-covalent pyrene–single wall nanotube (SWNT) interaction. We demonstrate that a Pd complex containing one or two pyrene arms is captured and released from a SWNT column at different rates and can be utilized for the homogeneous catalysis of *Suzuki* and *Heck* reactions.

Introduction. – Flow reactors offer certain advantages over traditional batch reactors including rapid heat transfer, controlled mixing, and serial reactions resulting in faster, safer, and cleaner processes [1]. Many catalytic reactions have been conducted continuously using homogeneous, supported, solid, and solid-to-solution catalysis [2]. Though many of these reactions provide excellent yields, selectivities, and productivities, a major challenge remains. While reactions using homogenous catalysts tend to offer rapid rates and improved selectivity, catalyst recycling is difficult. Supported catalysts, on the other hand, are easily recycled but typically show reduced activity and selectivity [3].

We set out to combine the advantages of homogeneous and heterogeneous catalysts by implementing a catch-and-release system where 'captured' catalysts are 'released' into a homogeneous reaction stream. An inert capture mechanism would, in our opinion, enable the widest range of chemistry, so accordingly we selected a pyrene–nanotube interaction to provide the desired properties. *Dai* and co-workers were the first to demonstrate that pyrene could be used to non-covalently functionalize single wall nanotubes (SWNTs) [4], and a number of researchers have utilized this novel interaction [5]. A wide range of hydrocarbons bind to supported SWNTs, whereby pyrene exhibits one of the strongest hydrocarbon–SWNT interactions [6]. Recently, pyrene–SWNT conjugates were used to produce supported catalysts [7] and a batch catch-release system [8].

Herein, we report on a flow 'capture-and-release' approach where we unite homogenous and supported catalysis (*Fig. 1*). We show that complexes **3** and **4**

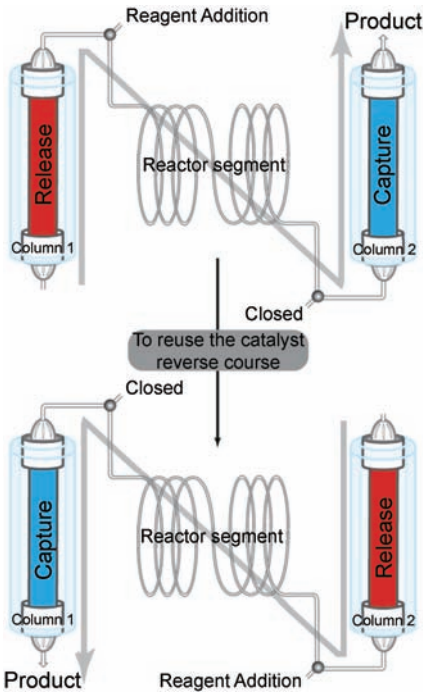
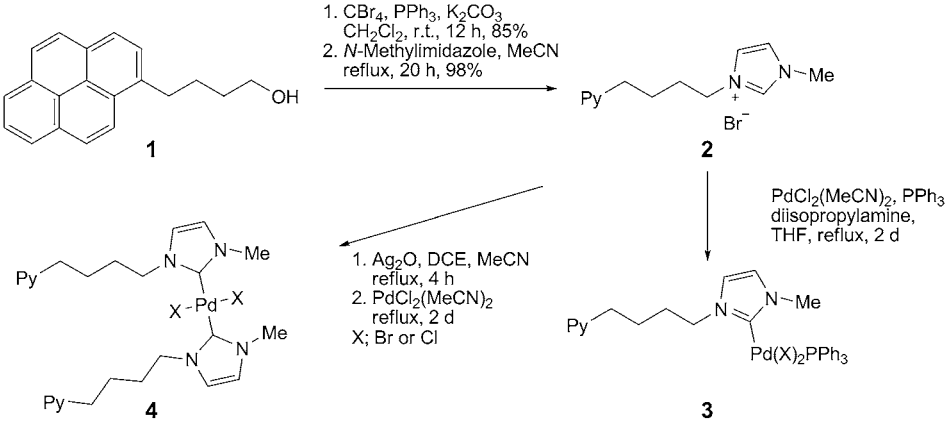


Fig. 1. *Catch-release catalytic flow system set-up*

(*Scheme 1*) can bind to a column containing SWNTs, and that this captured complex can be released at elevated temperatures. Complexes **3** and **4** are used in the capture-and-release format, thermally releasing the complexes from their support into a homogeneous reactor domain. After use, the complexes are captured on a cooler

Scheme 1. *Synthesis of Pd–NHC Complexes* **3** *and* **4** (DCE = 1,2-dichloroethane; Py = pyren-3-yl)



SWNT column. Catalyst reuse is demonstrated by running the system in reverse (*Fig. 1*).

Results and Discussion. – A catalyst system where the same complex was appended to one or two pyrene rings was prepared so that the relationship between pyrene–SWNT binding and release could be evaluated. Complexes **3** and **4** were prepared by converting 4-(pyren-1-yl)butan-1-ol to the bromide by action of CBr_4 and PPh_3 [9], followed by displacement with 1-methyl-1*H*-imidazole yielding the imidazolium salt **2** (*Scheme 1*) [10]. Complex **3** was prepared by combining 1 equiv. of **2** with $[PdCl_2(MeCN)_2]$, and complex **4** was prepared by combining excess **2** with $[PdCl_2(MeCN)_2]$ in the presence of excess Ag_2O.

Complexes **3** and **4** were loaded on separate 450-mg SWNT columns using DMF as the loading solvent at room temperature. UV Spectra of the filtrate during the loading phase revealed no evidence of **3** or **4**, indicating that 100% of the complexes were captured on the SWNT-packed bed. The column temperature was raised to 100°, and **3** and **4** were eluted with DMF. Elution was monitored as a function of time, and the concentrations of **3** and **4** were determined by UV/VIS spectroscopy. *Fig. 2* shows the elution profiles as function of molarity (mmol) *vs.* eluent volume (ml) at a flow rate of 50 µl/min. Peak molarities of **3** and **4** were observed at volumes of 3 and 8 ml, respectively. When the eluted fractions were concentrated, the recovered mass corresponded to quantitative release of both complexes. Two conclusions were drawn based on these observations: *1*) both mono- and dipyrene species were caught and released even when carrying a large payload; and *2*) the single-pyrene complex **3** binds less strongly than the double-pyrene complex **4**, supporting recent reports demonstrating that tripyrene complexes bind to graphene more avidly than mono-pyrene complexes [11]. These results are not surprising considering that π–π interactions depend strongly on the surface area [12].

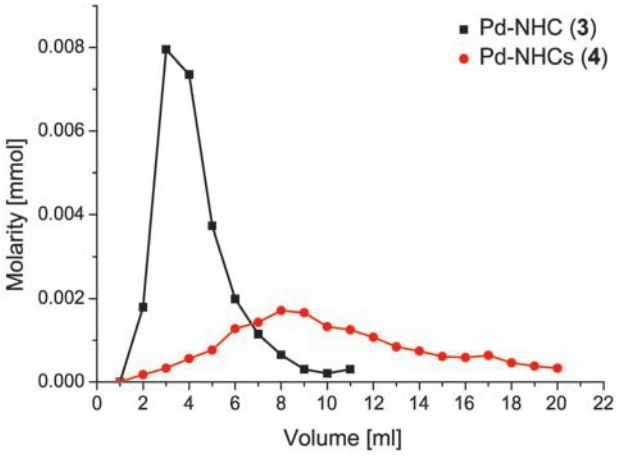


Fig. 2. *Desorption speed of Pd-NHC complexes at 100°*

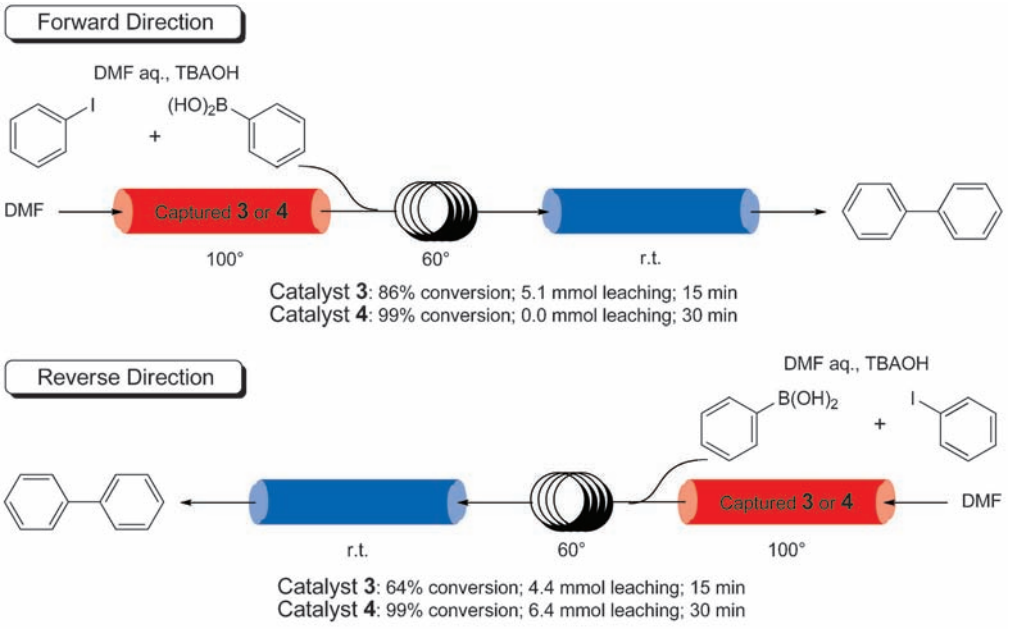
We moved to the next stage by creating a capture-and-release catalytic flow system (*Fig. 1*). The process is characterized by: *1*) a release column, *2*) a reactor segment, and *3*) a capture column. The flow in the system can be run in both directions. Both the capture-and-release columns are filled with SWNTs, and only the flow direction and temperature differ between the two columns. The system also features input valves where starting materials can be introduced. Both columns and reactor temperature can be independently controlled. Though in principle this capture-and-release set-up could be used to perform many different types of reactions, we showcased the system using two cross-coupling reactions.

The Pd cross-coupling experiments were initiated by first adsorbing **3** or **4** to the SWNT release column (*Fig. 1*). The reaction was started by heating the release column to 100° and the reactor coil to 60°, as well as placing a cooling bath (4°) on the output of the reactor coil leading to the room-temperature capture coil. DMF was then passed through the heated release column, and the effluent was combined with reagents entering *via* a T-mixer. The released catalyst/reagent mixture entered the reactor segment. Using the release data (*Fig. 2*), we combined catalyst release stream and substrate stream only after the catalyst reached the maximum release rate (2 ml for **3**; 5 ml for **4**), thereby, eliminating problems with large changes in catalyst loading. The reactions chosen function effectively at very low catalyst loadings and thus by design saturated the system in catalyst. Upon exiting the reactor coil, the pyrene-bound catalyst was captured and the products and unreacted starting materials exited out the top of the capture column. We performed both *Suzuki* and *Heck* couplings to examine the activity of **3** and **4**.

The *Suzuki* reaction was carried out by injecting PhI (1.0 equiv.), $PhB(OH)_2$ (1.5 equiv.), and aq. Bu_4NOH (TBAOH; 2.0 equiv.) as a 0.1M solution in DMF into the release stream at a flow rate of 50 or 25 µl/min (*Scheme 2*). Both solutions were mixed in a polytetrafluoroethylene (PTFE) tube reactor (1.5 ml volume, heated at 100°) *via* a T-mixer. These conditions were used with both **3** and **4**, and with residence times of 15 and 30 min, respectively. The reactor output flowed into the capture column, and the product effluent out the top of the column was collected and analyzed with HPLC (*Fig. 1*).

After the first cycle, the system was reversed, and a second reaction cycle was performed. The *Suzuki* reaction was successful using both catalysts **3** and **4**. Complex **4** exhibited the best overall performance using a 30 min residence time. As shown in *Scheme 2* (forward and reverse), catalyst **4** provides 99% conversion with no detectable leaching in the forward direction, and 99% conversion on the reverse reaction with 21% leaching on the reverse reaction. The reaction with complex **3** for longer periods (30 min; data not shown) resulted in higher leaching (injected 50 mmol and 14.4 mmol leached – 28%). These observations indicate that the single pyrene is not captured as well as the dual pyrene case. The greater leaching observed for **4** in the reverse reaction might be due to competition between 1,1′-biphenyl product and **4** for SWNT binding sites [6]. We determined the retention efficiency of 1,1′-biphenyl on the column and found that 1,1′-biphenyl is not retained on the column, but this observation does not rule out that the presence of 1,1′-biphenyl can inhibit the binding of **4** to the SWNT bed. We also determined in separate experiments that the NMR conversions correspond well to isolated yields.

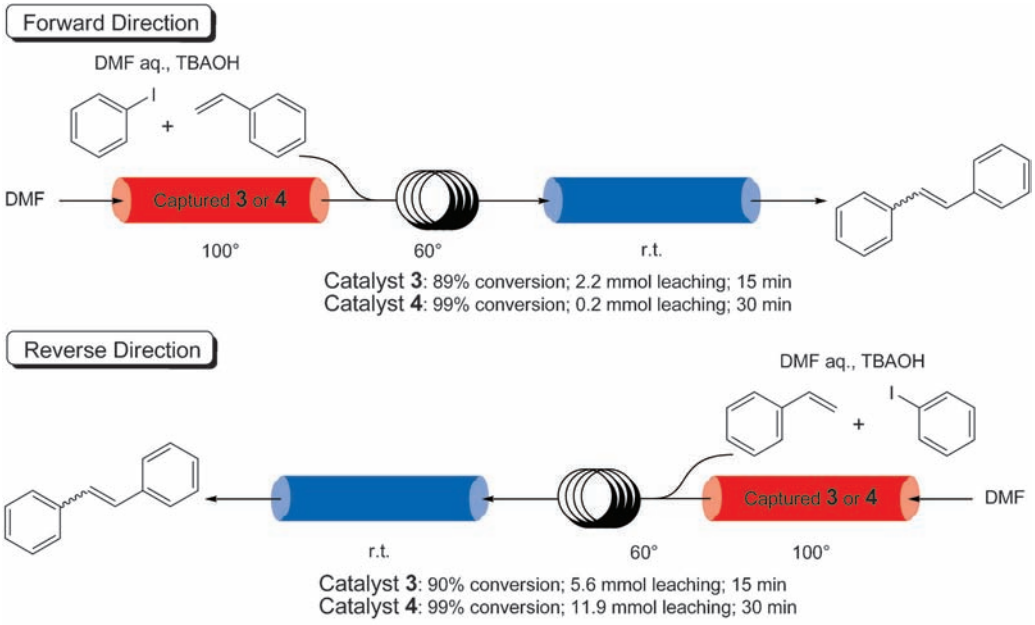
Scheme 2. *Capture-and-Release Continuous-Flow* Suzuki *Reaction Using Complexes* **3** *and* **4**



Applying a similar set of conditions, we also performed a *Heck* reaction using the capture-and-release system. Both complexes **3** and **4** exhibited high conversions in the forward and reverse directions (*Scheme 3*). Interestingly, less leaching was observed using the single-pyrene complex **3**. We propose that these data indicate a complex relationship between pyrene–SWNT, pyrene–product, and product–SWNT interaction. Furthermore, we predict that these interactions will change as a function of solvent. In future experiments, the impact of solvent polarity on release, capture, and leaching will be explored.

Conclusions. – We demonstrated that pyrene-appended Pd complexes **3** and **4** are captured from a DMF solution at room temperature, and that these complexes are released on heating. The number of pyrenes present impacts the shape and rate of release. Once released, these complexes catalyze both *Suzuki* and *Heck* reactions. Once the reaction is complete, complexes **3** and **4** are captured by a SWNT column kept at room temperature. The system can be reversed and complexes re-released to perform a subsequent reaction. The capture efficiency of the complexes is not 100% and depends on the cycle. The non-covalent interactions within the system appear to be complex and may suggest that the complexes decompose such that ligandless Pd may play a role [13]. While questions remain to be answered, we predict that capture-and-release systems exploiting the concept disclosed here will become an important method to marry the best of homogeneous and heterogeneous catalysis.

Scheme 3. *Capture-and-Release Continuous-Flow* Heck *Reaction Using Complexes* **3** *and* **4**

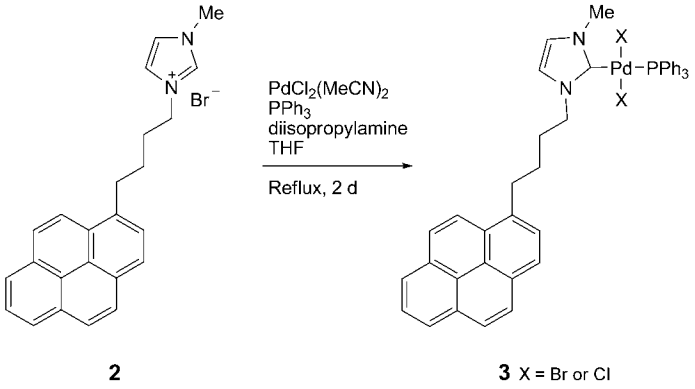


Experimental Part

1. *General.* All chemicals were reagent grade and used as supplied except where noted. PTFE, Polytetrafluoroethylene; ETFE, ethylene tetrafluoroethylene. SWNT were purchased from *HELIX Material Solutions Inc*. High-Purity Single Wall Carbon Nanotube Part No. SWNT-12900002-00, Lot No. BSCA06310099. Anal. TLC: Kieselgel *60* F_{254} glass plates precoated with a 0.25-mm thickness of silica gel (SiO_2); visualization with UV light. Conversion was assigned by HPLC (*Agilent Technologies 1200 Series*) analysis recorded at 230 nm at a flow of 1.0 ml/min on *C-8* column (*Macherey-Nagel*, *EC 250/4.6 Nucleosil 100-5 C-8*). Column chromatography (CC): *Biotage SP1-B2C0* silica gel (*Fluka Kieselgel 60*, 230–400 mesh). UV Spectra: *SHIMADZU* Spectrometer *UVmini-1240* at ambient temp. ^{1}H- and ^{13}C-NMR spectra: *Varian 600* spectrometer, at ambient temp. The H-atom signal of residual non-deuterated solvent (δ 7.26 ppm for $CDCl_3$, 2.50 ppm for (D_6)DMSO) was used as an internal reference for ^{1}H spectra; data are reported as follows: chemical shifts, δ, ppm, coupling constants, J, in Hz. ^{13}C-NMR Spectra: *Varian 600-MR* spectrometer (at 150 MHz) at ambient temp.; chemical shifts, δ, in ppm; the C-atom signal of deuterated solvent (δ 77.2 ppm for $CDCl_3$, 39.5 ppm for DMSO) was used as an internal reference for ^{13}C-NMR spectra. HR-MS: with EI-MS (*Varian MAT*, *MAT711*) and ESI-TOF (*Agilent Technologies*, *Agilent 6210 ESI-TOF*) at the Freie Universität Berlin, Mass Spectrometry Core Facility.

2. *New Compounds.* 2.1. *Synthesis of Dichloro(2,3-dihydro-1-methyl-3-[4-(pyren-1-yl)butyl]-1*H*-imidazol-2-yl)triphenylphosphinopalladium(IV)* (**3**; *Scheme 4*). A soln. of **2** [9] (323 mg, 0.77 mmol), bis(MeCN)palladium(II) chloride (100 mg, 0.39 mmol), PPh_3 (101 mg, 0.39 mmol), and ^{i}Pr$_2$NH (270 µl, 1.92 mmol) in 1,2-dichloroethane (DCE)/MeCN 1:1 (20 ml) was stirred at 80° for 48 h. After cooling to r.t., the soln. was evaporated *in vacuo* to give a residue that was purified by CC (SiO_2; $CHCl_3$ to $CHCl_3$/MeOH: 100:1 to 20:1) to give **3** (286 mg, 48%). Pale-yellow powder. ^{1}H-NMR (600 MHz, (D_6)DMSO): 8.28 (*m*, 3 H); 8.23 (*d*, J = 7.3, 1 H); 8.21 (*d*, J = 9.0, 1 H); 8.15 (*d*, J = 9.0, 1 H); 8.13 (*d*, J = 9.0, 1 H); 8.07 (*d*, J = 7.6, 1 H); 8.06 (*d*, J = 7.6, 1 H); 7.93 (*d*, J = 7.8, 1 H); 7.52 (*m*, 8 H); 7.41 (*m*, 5 H); 7.05 (*d*, J = 1.9,

Scheme 4

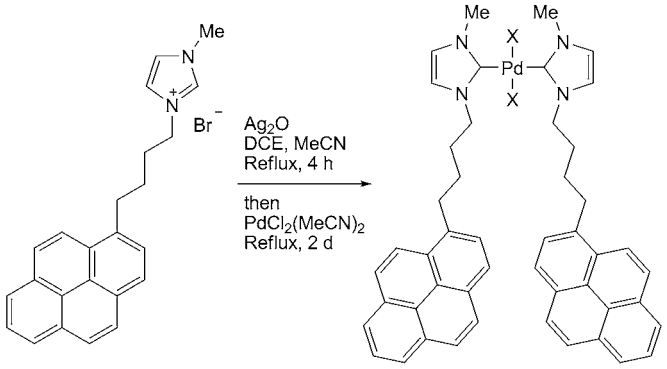


2 **3** X = Br or Cl

1 H); 7.01 (*d*, *J* = 1.9, 1 H); 4.09 (*m*, 1 H); 3.74 (*m*, 1 H); 3.54 (br. *s*, 3 H); 3.28 (*m*, 2 H); 2.00 (*m*, 1 H); 1.88 (*m*, 1 H); 1.74 (*m*, 2 H). ^{13}C-NMR (150 MHz, (D_6)DMSO): 157.9; 136.4; 133.7 (2 C); 131.1; 130.4; 129.3; 128.6; 128.5; 128.0; 127.4 (2 C); 127.3; 126.5; 126.1; 125.0; 124.9; 124.8; 124.2; 124.1; 123.4; 48.6; 35.8; 32.2; 29.5; 28.4. HR-ESI-MS: 741.1484 ($[M - H - Cl]^+$, $C_{42}H_{37}ClN_2PPd^+$; calc. 741.1418), 785.0977 ($[M - H - Br]^+$, $C_{42}H_{37}BrN_2PPd^+$; calc. 785.0913).

2.2. *Synthesis of Dichlorobis{2,3-dihydro-1-methyl-3-[4-(pyren-1-yl)butyl]-1*H*-imidazol-2-yl}palladium(IV)* (**4**; *Scheme 5*). A soln. of **2** (313 mg, 0.75 mmol) and Ag_2O (190 mg, 0.82 mmol) in DCE/MeCN 1:1 (20 ml) was stirred at 80° for 3 h. [$PdCl_2(MeCN)_2$] (213 mg, 0.82 mmol) was added into the mixture and stirred for 48 h. After cooling to r.t., the soln. was evaporated *in vacuo* to give a residue that was purified by CC (SiO_2; $CHCl_3$/MeOH 100:0 to 20:1) to give **4** (363 mg, 57%). Pale-yellow powder. The ^{1}H-NMR spectrum of **4** exhibited a second set of signals, which corresponds to the atropisomer that has been reported for similar compounds [14]. Major A: ^{1}H-NMR (600 MHz, $CDCl_3$): 8.03 (*m*, 18 H); 6.71 (*m*, 4 H); 4.47 (*m*, 4 H); 4.19 (*s*, 6 H); 3.24 (*m*, 4 H); 2.21 (*m*, 4 H); 1.84 (*m*, 4 H). Major B: ^{1}H-NMR (600 MHz, $CDCl_3$): 8.03 (*m*, 18 H); 7.65 (*m*, 4 H); 4.56 (*m*, 4 H); 4.02 (*s*, 6 H); 3.47 (*m*, 4 H); 2.38 (*m*, 4 H); 2.05 (*m*, 4 H). HR-ESI-MS: 817.2340 ($[M - 2\,H - Cl]^+$, $C_{48}H_{44}ClN_4Pd^+$; calc. 817.2289), 861.1845 ($[M - 2\,H - Br]^+$, $C_{48}H_{44}BrN_4Pd^+$; calc. 861.1784).

Scheme 5



2 **4** X = Br or Cl

2.4. *Catalyst Loading and Release.* We used the capture-and-release system (*Fig. 3*). A soln. of Pd–NHC (N-heterocyclic carbene) complexes (**3**, 0.05M; **4**, 0.03M) in DMF (0.5 ml) at a flow rate of 50 µl/min was introduced into the glass column which was packed with SWNT (450 mg). Release was measured by passing DMF (5.0 ml; flow rate, of 50 µl/min) through the system using syringe pump. Fractions (1.0 ml) were collected and analyzed by UV/VIS spectroscopy.

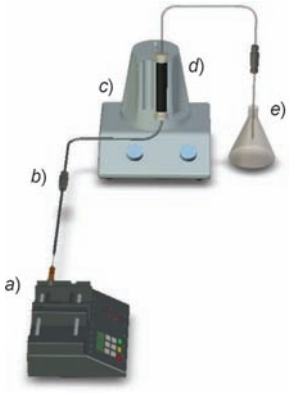


Fig. 3. *System for capture-and-release measurements.* The system is composed of: *a*) syringe pump, *b*) check-valve, *c*) *Syrris FRX Flow* System, *d*) *Omnifit* glass column, *e*) collection flask.

2.5. *Capture-and-Release Catalytic Reaction System.* The flow system is composed of: *a*) syringe pump I, *b*) syringe pump II, *c*) check-valve, *d*) *Syrris FRX Flow* system, *e*) *Omnifit* glass column I, *f*) ETFE T-mixer, *g*) oil bath, *h*) PTFE tubing reactor (1.5 ml or 3.0 ml), *i*) Omnifit glass column II, and *j*) collection flask (*Fig. 4*).

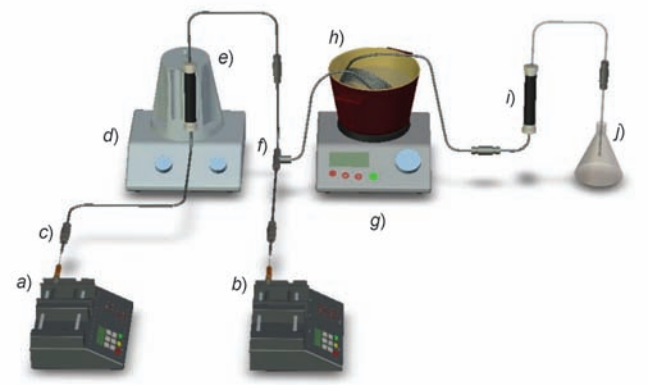


Fig. 4. *System for* Suzuki *and* Heck *reactions*

2.6. Suzuki *Reaction Using* **3** *at 30-min Residence Time.* After loading **3**, the glass column on a *Syrris FRX* flow system was heated to 100° and flushed with DMF (12.0 ml; flow rate of 50 µl/min) using syringe pump I. After DMF (5.5 ml, flow rate of 50 µl/min) was introduced into column I, a 0.1M soln. of PhI (1 equiv.), $PhB(OH)_2$ (1.5 equiv.), and aq. Bu_4NOH (2 equiv.) in DMF (0.2 ml) were injected using syringe pump II. In this fashion, starting materials were mixed with the highest concentration of **3** *via* T-

mixer. Then, DMF (6.3 ml) was injected to the system using syringe pump II. Both reagents were mixed in a PTFE tubing reactor (volume 3.0 ml).

The output soln. was collected in a flask, and the crude soln. was directly analyzed by HPLC. Conversion was estimated from HPLC spectra using a calibration curve. HPLC was performed at 230 nm at a flow of 1.0 ml/min; eluents *A* (H_2O) and *B* (MeCN) were used in the isocratic mode (60% *B* in 15 min). The retention time (t_R) of PhI is 6.24 and 1,1′-biphenyl is 6.77 min.

^{1}H-NMR (600 MHz, $CDCl_3$): 7.60 (*m*, 4 H); 7.44 (*m*, 4 H); 7.38 (*m*, 2 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 141.4; 128.9; 127.4; 127.3. HR-EI-MS: 154.0789 (M^+, $C_{12}H_{10}^+$; calc. 154.0783).

2.7. Suzuki *Reaction Using* **3** *in 15-min Residence Time.* After loading **3**, the glass column on a *Syrris FRX Flow* system was heated to 100° and flushed with DMF (11.5 ml; flow rate, 50 µl/min) using syringe pump I. After DMF (5.5 ml; flow rate, 50 µl/min) was introduced into column I, a 0.1M soln. of PhI (1 equiv.), $PhB(OH)_2$ (1.5 equiv.), and aq. Bu_4NOH (2 equiv.) in DMF (0.2 ml) were injected using syringe pump II. In this fashion, starting materials were mixed with the highest concentration of **3** *via* T-mixer. Then, DMF (5.8 ml) was injected to the system using syringe pump II. Both reagents were mixed in a PTFE tubing reactor (volume 3.0 ml).

The output soln. was collected in a flask and the crude soln. was directly analyzed by HPLC. The conversion was estimated from HPLC spectra based on a calibration curve. HPLC was performed at 230 nm at a flow of 1 ml/min on *C-8* column; eluents *A* (H_2O) and *B* (MeCN) were used in isocratic mode (60% *B* in 15 min). The t_R (PhI) 6.24 and t_R (1,1′-biphenyl) 6.77 min.

2.8. Suzuki *Reaction Using* **4** *in 30-min Residence Time.* After loading **4**, the glass column on a *Syrris FRX Flow* system was heated to 100° and flushed with DMF (7.0 ml; flow rate, 50 µl/min) using syringe pump I. After DMF (0.5 ml, flow rate of 50 µl/min) was introduced into column I, a 0.1M soln. of PhI (1 equiv.), $PhB(OH)_2$ (1.5 equiv.), and aq. Bu_4NOH (2 equiv.) in DMF (0.2 ml) were injected using syringe pump II. In this fashion, starting materials were mixed with the highest concentration of **4** *via* T-mixer. DMF (6.3 ml) was then injected to the system using syringe pump II. Both reagents were mixed in a PTFE tube reactor (volume 3.0 ml).

The output soln. was collected in a flask, and the crude soln. was directly analyzed by HPLC. The conversion was estimated from HPLC spectra using a calibration curve. HPLC was performed at 230 nm at a flow of 1.0 ml/min on *C-8* column; eluents *A* (H_2O) and *B* (MeCN) were used in isocratic (60% *B* in 15 min). t_R (PhI) 6.24 and t_R (1,1′-biphenyl) 6.77 min.

2.9. Suzuki *Reaction Using* **4** *in 15-min Residence Time.* After loading **4**, the glass column on a *Syrris FRX Flow* system was heated to 100° and flushed with DMF (6.5 ml; flow rate, 50 µl/min) using syringe pump I. After DMF (0.5 ml, flow rate of 50 µl/min) was introduced into column I, a 0.1M soln. of PhI (1 equiv.), $PhB(OH)_2$ (1.5 equiv.), and aq. Bu_4NOH (2 equiv.) in DMF (0.2 ml) were injected using syringe pump II. In this fashion, starting materials were mixed with the highest concentration of **4** *via* T-mixer. DMF (5.8 ml) was then injected to the system using syringe pump II. Both reagents were mixed in a PTFE tubing reactor (volume 1.5 ml).

The output soln. was collected in a flask, and the crude soln. was directly analyzed by HPLC. The conversion was estimated from HPLC spectra using a calibration curve. HPLC was conducted at 230 nm at a flow of 1 ml/min on *C-8* column; eluents *A* (H_2O) and *B* (MeCN) were used in isocratic (60% *B* in 15 min). t_R (PhI) 6.24 and t_R (1,1′-biphenyl) 6.77 min.

2.10. Heck *Reaction Using* **3** *at 30-min Residence Time.* After loading **3**, the glass column on a *Syrris FRX Flow* system was heated to 100° and was flushed with DMF (12.0 ml; flow rate, 50 µl/min) using syringe pump I. After DMF (5.5 ml, flow rate of 50 µl/min) was introduced into column I, a 0.1M soln. of PhI (1 equiv.), styrene (1.5 equiv.), and aq. Bu_4NOH (2 equiv.) in DMF (0.2 ml) were injected using syringe pump II. In this fashion, starting materials were mixed with the highest concentration of **3** *via* T-mixer. DMF (6.3 ml) was then injected to the system using syringe pump II. Both reagents were mixed in a PTFE tubing reactor (volume 3.0 ml).

The output soln. was collected in a flask, and the crude soln. was directly analyzed by HPLC. Conversion was estimated from HPLC spectra by calibration curve. HPLC was performed at 230 and 280 nm at a flow of 1 ml/min on *C-8* Column; eluents *A* (H_2O) and *B* (MeCN) were used in isocratic (55% *B* in 15 min). t_R (styrene) 6.74 and t_R (1,1′-biphenyl) 7.36 min at 230 nm; t_R (stilbene) 10.90 min at 280 nm.

^{1}H-NMR (600 MHz, $CDCl_3$): 7.67 (*m*, 4 H); 7.51 (*m*, 4 H); 7.40 (*m*, 4 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 137.5; 128.9; 128.8; 127.8; 126.7. HR-EI-MS: 180.0943 (M^+, $C_{14}H_{12}^+$; calc. 180.0939).

2.11. Heck *Reaction Using* **3** *in 15-min Residence Time.* After loading **3**, the glass column on a *Syrris FRX Flow* system was heated to 100° and flushed with DMF (11.5 ml; flow rate, 50 µl/min) using syringe pump I. After DMF (5.5 ml, flow rate of 50 µl/min) was introduced into column I, a 0.1M soln. of PhI (1 equiv.), styrene (1.5 equiv.), and aq. Bu_4NOH (2 equiv.) in DMF (0.2 ml) were injected using syringe pump II. In this fashion, starting materials were mixed with the highest concentration of **3** *via* T-mixer. Then, DMF (5.8 ml) was injected to the system using syringe pump II. Both reagents were mixed in a PTFE tubing reactor (volume 3.0 ml).

The output soln. was collected in a flask, and the crude soln. was directly analyzed by HPLC. The conversion was estimated from HPLC spectra by calibration curve. HPLC was performed at 230 and 280 nm at a flow of 1 ml/min on *C-8* column; eluents *A* (H_2O) and *B* (MeCN) were used in isocratic (55% *B* in 15 min). t_R (styrene) 6.74 and t_R (1,1′-biphenyl) 7.36 min at 230 nm; t_R (stilbene) 10.90 min at 280 nm.

2.12. Suzuki *Reaction Using* **4** *in 30-min Residence Time.* After loading **4**, the glass column on a *Syrris FRX Flow* system was heated to 100° and flushed with DMF (7.0 ml; flow rate, 50 µl/min) using syringe pump I. After DMF (0.5 ml; flow rate, 50 µl/min) was introduced into column I, a 0.1M soln. of PhI (1 equiv.), styrene (1.5 equiv.), and aq. Bu_4NOH (2 equiv.) in DMF (0.2 ml) were injected using syringe pump II. In this fashion, starting materials were mixed with the highest concentration of **4** *via* T-mixer. DMF (6.3 ml) was then injected to the system using syringe pump II. Both reagents were mixed in a PTFE tube reactor (volume 3.0 ml).

The output soln. was collected in a flask, and the crude soln. was directly analyzed by HPLC. The conversion was estimated from HPLC spectra by calibration curve. HPLC was conducted at 230 and 280 nm at a flow of 1 ml/min on *C-8* column; eluents *A* (H_2O) and *B* (MeCN) were used in isocratic (55% *B* in 15 min). t_R (styrene) 6.74 and t_R (1,1′-biphenyl) 7.36 min at 230 nm; t_R (stilbene) 10.90 min at 280 nm.

2.13. Suzuki *Reaction Using* **4** *in 15-min Residence Time.* After loading **4**, the glass column on a *Syrris FRX Flow* system was heated to 100° and flushed with DMF (6.5 ml; flow rate, 50 µl/min) using syringe pump I. After DMF (0.5 ml, flow rate of 50 µl/min) was introduced into column I, a 0.1M soln. of PhI (1 equiv.), styrene (1.5 equiv.), and aq. Bu_4NOH (2 equiv.) in DMF (0.2 ml) were injected using syringe pump II. In this fashion, starting materials were mixed with the highest concentration of **4** *via* T-mixer. Then, DMF (5.8 ml) was injected to the system using syringe pump II. Both reagents were mixed in a PTFE tubing reactor (volume 1.5 ml).

The output soln. was collected in a flask, and the crude soln. was directly analyzed by HPLC. The conversion was estimated from HPLC spectra by calibration curve. HPLC were recorded at 230 and 280 nm at a flow of 1 ml/min on *C-8* column; eluents *A* (H_2O) and *B* (MeCN) were used in isocratic (55% *B* in 15 min). t_R (styrene) 6.74 and t_R (1,1′-biphenyl) 7.36 min at 230 nm; t_R (stilbene) 10.90 min at 280 nm.

REFERENCES

[1] R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem., Int. Ed.* **2011**, *50*, 7502; B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300; K. Mennecke, W. Solodenko, A. Kirschning, *Synthesis* **2008**, 1589; G. Nan, F. Ren, M. Luo, *Beilstein J. Org. Chem.* **2010**, *6*, 70; K. Mennecke, A. Kirschning, *Beilstein J. Org. Chem.* **2009**, *5*, 21; N. Nikbin, M. Ladlow, S. V. Ley, *Org. Process Res. Dev.* **2007**, *11*, 458; C. Wiles, P. Watts, *Eur. J. Org. Chem.* **2008**, *10*, 1655; I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Chem. – Eur. J.* **2006**, *12*, 4407; N. T. S. Phan, J. Khan, P. Styring, *Tetrahedron* **2005**, *61*, 12065; 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; N. Nikbin, P. Watts, *Org. Process Res. Dev.* **2004**, *8*, 942; W. Solodenko, H. Wen, S. Leue, F. Stuhlmann, G. Sourkouni-Argirusi, G. Jas, H. Schönfeld, U. Kunz, A. Kirschning, *Eur. J. Org. Chem.* **2004**, 3601; P. He, S. J. Haswell, P. D. I. Fletcher, *Appl. Catal., A* **2004**, *274*, 111.

[2] A. Bogdan, D. T. McQuade, *Beilstein J. Org. Chem.* **2009**, *5*, 17; A. R. Bogdan, B. P. Mason, K. T. Sylvester, D. T. McQuade, *Angew. Chem., Int. Ed.* **2007**, *46*, 1698; F. R. Bou-Hamdan, P. H. Seeberger, *Chem. Sci.* **2012**, *3*, 1612; T. Chinnusamy, S. S. Yudha, M. Hager, P. Kreitmeier, O. Reiser, *ChemSusChem* **2012**, *5*, 247; T. N. Glasnov, S. Findenig, C. O. Kappe, *Chem. – Eur. J.* **2009**, *15*, 1001; M. Irfan, T. N. Glasnov, C. O. Kappe, *ChemSusChem* **2011**, *4*, 300; A. Kirschning, G. Jas, *Immob. Catal.* **2004**, *242*, 209; X. Y. Mak, P. Laurino, P. H. Seeberger, *Beilstein J. Org. Chem.* **2009**, *5*, 19; J. A. Moulijn, M. T. Kreutzer, T. A. Nijhuis, F. Kapteijn, in Advances in Catalysis, Vol. 54, Chapt. 5, Eds. B. C. Gates, H. Knozinger, 2011, pp. 249 – 327; A. Odedra, P. H. Seeberger, *Angew. Chem., Int. Ed.* **2009**, *48*, 2699; S. M. Opalka, A. R. Longstreet, D. T. McQuade, *Beilstein J. Org. Chem.* **2011**, *7*, 1671; D. A. Snyder, C. Noti, P. H. Seeberger, F. Schael, T. Bieber, G. Rimmel, W. Ehrfeld, *Helv. Chim. Acta* **2005**, *88*, 1.

[3] F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367; S. Kobayashi, R. Akiyama, *Chem. Commun.* **2003**, 449; P. McMorn, G. J. Hutchings, *Chem. Soc. Rev.* **2004**, *33*, 108; J. R. Severn, J. C. Chadwick, R. Duchateau, N. Friederichs, *Chem. Rev.* **2005**, *105*, 4073; I. F. J. Vankelecom, *Chem. Rev.* **2002**, *102*, 3779.

[4] R. J. Chen, Y. Zhang, D. Wang, H. Dai, *J. Am. Chem. Soc.* **2001**, *123*, 3838.

[5] K. Besteman, J.-O Lee, F. G. M. Wiertz, H. A. Heering, C. Dekker, *Nano Lett.* **2003**, *3*, 727; L. Qu, R. B. Martin, W. Huang, K. Fu, D. Zweifel, Y. Lin, Y.-P. Sun, C. E. Bunker, B. A. Harruff, J. R. Gord, L. F. Allard, *J. Chem. Phys.* **2002**, *117*, 8089; H. G. Sudibya, J. Ma, X. Dong, S. Ng, L.-J. Li, X.-W. Liu, P. Chen, *Angew. Chem., Int. Ed.* **2009**, *48*, 2723; P. Wu, X. Chen, N. Hu, U. C. Tam, O. Blixt, A. Zettl, C. R. Bertozzi, *Angew. Chem., Int. Ed.* **2008**, *47*, 5022.

[6] J. Yoo, H. Ozawa, T. Fujigaya, N. Nakashima, *Nanoscale* **2011**, *3*, 2517.

[7] F. J. Gómez, R. J. Chen, D. Wang, R. M. Waymouth, H. Dai, *Chem. Commun.* **2003**, 190.

[8] G. Liu, B. Wu, J. Zhang, X. Wang, M. Shao, J. Wang, *Inorg. Chem.* **2009**, *48*, 2383; F. Li, B. Zhang, X. Li, Y. Jiang, L. Chen, Y. Li, L. Sun, *Angew. Chem., Int. Ed.* **2011**, *50*, 12276.

[9] A. J. Lampkins, E. J. O'Neil, B. D. Smith, *J. Org. Chem.* **2008**, *73*, 6053; S. Wittmann, A. Schätz, R. N. Grass, W. J. Stark, O. Reiser, *Angew. Chem., Int. Ed.* **2010**, *49*, 1867.

[10] E. A. B. Kantchev, C. J. O'Brien, Organ, *Angew. Chem., Int. Ed.* **2007**, *46*, 2768; W. A. Herrmann, V. P. W. Böhm, C. W. K. Gstöttmayr, M. Grosche, C.-P. Reisinger, T. Weskamp, *J. Organomet. Chem.* **2001**, *617 – 618*, 616.

[11] J. A. Mann, J. Rodrígues-López, H. D. Abruña, W. R. Dichtel, *J. Am. Chem.* **2011**, *133*, 17614.

[12] C. R. Martinez, B. L. Iverson, *Chem. Sci.* **2012**, *3*, 2191.

[13] S. J. Broadwater, D. T. McQuade, *J. Org. Chem.* **2006**, *71*, 2131.

[14] R. Kamisue, S. Sakaguchi, *J. Organomet. Chem.* **2011**, *696*, 1910.

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