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Continuous flow synthesis of *meta*-substituted phenol derivatives

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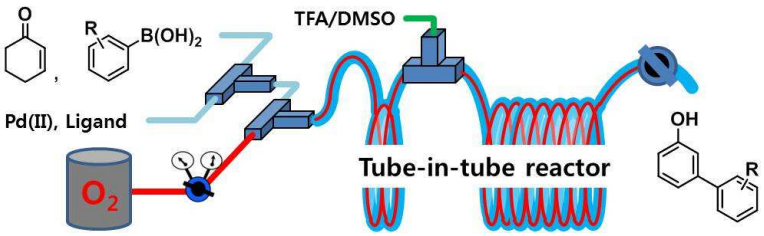
Table of Contents Graphic



ABSTRACT. Two complementary microreactor technologies for the study of biphasic gas-liquid reactions and preparation of *meta*-substituted phenol derivatives were developed. The first capillary microreactor composed of a T-junction and simple capillary enabled oxidative Heck/dehydrogenation in microgram-scale with shortened reaction time; the total sequence time of oxidative Heck/dehydrogenation reactions was optimized from 2160 min in a traditional batch system to 130 min in the microchemical system. Moreover, the second tube-in-tube microreactor composed of a gas-permeable inner tube and gas-nonpermeable outer tube successfully performed a gram-scale synthesis under the optimized safe and economic condition which was established from the first microgram-scale study. The two microreactors have great potential for exploring the reactions involving gaseous and liquid reagents.

KEYWORDS. Biphasic catalysis, Gas-liquid reaction, Microreactors, Phenols, Dehydrogenation

INTRODUCTION

Because of the enormous potential of phenol derivatives as the building blocks for the synthesis of bioactive natural products and conducting polymers, diverse methods have been developed for their preparation.[1] Electrophilic aromatic substitution is one of the most versatile methods; however, the strong *ortho/para*-directing effect of hydroxyl group hinders the preparation of *meta*-substituted phenol derivatives. In recent years, Stahl and coworkers reported the preparation of phenol derivatives by oxidative Heck/dehydrogenation reactions;[2] however, the reactions suffer from prolonged reaction time up to several days, thus requiring further optimization of reaction conditions including solvent, pressure, and temperature. Moreover, the restricted contact between gaseous oxygen and liquid reagents lowers the feasibility for practical scale-up. This contact area per reaction volume significantly decreases with increasing reaction volume, and as a result, the scaled-up process for their industrial applications would be inefficient.

Microchemical technologies have presented new concepts and several attractive possibilities as they have been applied to various standard organic reactions and new chemistries,[3] and biphasic gas–liquid reactions are particularly challenging. A number of reactor configurations including the segmented flow microreactor, the packed-bed microreactor, the falling film microreactor, and dual channel microreactor have been reported. Increased surface-to-volume ratio in the microchemical systems allows greater mass transfer.[4] Recently, tube-in-tube design has received much attention as a convenient method for gas-liquid reactions, because Teflon AF-2400 tubing can maintain high permeability to a range of gases while remaining impermeable to liquids. Continuous flow processing in the tube-in-tube microreactor have been applied to various reactions such as ozonolysis, carboxylation, Heck vinylation, hydroformylation, Heck-Heck

sequence, Glaser-Hay coupling, oxidative nitro-Mannich reaction, Paal-Knorr pyrrole synthesis, iso(thio)ureas synthesis, Wacker oxidation, hydrogenation, oxazolidinone synthesis, diazomethane generation, amitripyline synthesis, aromatic hydroxylation, biocatalytic production of catechols, and photooxygenation.[5] However, performances in the tube-in-tube reactor often show wasteful consumption of reagents, which would be the only drawback compared to the previous microchemical gas–liquid approaches. The working volume in the tube in tube microreactor is consistent due to separation between gas channel and liquid channel, while the working volume in capillary microreactor can be regulated by changing the amounts of injected gas and liquids.

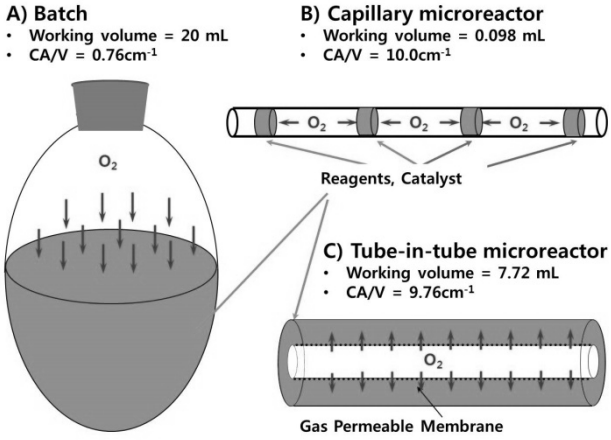


Figure 1. Comparative illustration of contacting modes between gas and liquid phases in two microreactors and batch system. The detailed calcurations for contact area to volume ratio (CA/V) and working volume are described in the supporting information.

Herein, we describe two complementary microreactors for the study of gas–liquid binary reactions and preparation of *meta*-substituted phenol derivatives (Figure 1). The first capillary microreactor (working volume: 0.098mL), composed of a T-junction and simple capillary, is

very useful for repeated oxidative Heck/dehydrogenation reactions, which depend on several parameters including solvent, temperature, and pressure. Multiple reaction conditions could be easily screened in a short time with the consumption of reagents in microgram-scale. The second tube-in-tube microreactor (working volume: 7.72mL), composed of a gas-permeable inner tube and gas-nonpermeable outer tube, enables gram-scale reactions under the optimized safe and economic reaction conditions for the first microgram-scale study. Both capillary and tube-in-tube microreactors guarantee the sufficient mass transfer of gaseous oxygen into the solution phase.

RESULTS AND DISCUSSION

The oxidative Heck reaction in the microreactors.

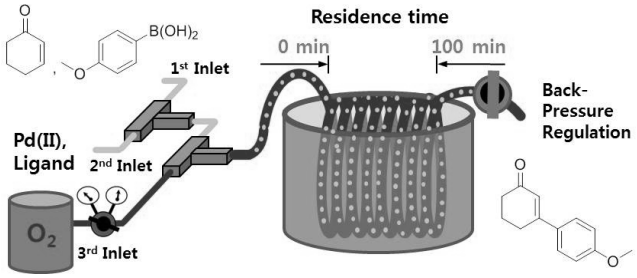


Figure 2. Schematic of the oxidative Heck reaction of cyclohex-2-enone and 4-methoxyphenylboronic acid in the capillary microreactor.

Palladium (Pd) catalyst has widely been used for microchemical reaction. Heterogeneous Pd catalysts immobilized on microchannel surface or homogeneous catalysts are highly efficient in hydrogenation, Suzuki-Miyaura, Sonogashira, Heck reaction, and other reactions.[6] Initially for

the oxidative Heck reaction, a segmented mode of gas bubbles and liquid slugs were utilized in the simple capillary microreactor (Figure 2). The mode has the advantages of a simple set up and broad choice of capillary materials for better chemical stability and mechanical strength even at high temperatures and pressures. Importantly, the wasteful consumption of reagents and labor could be minimized in the repeated screenings.

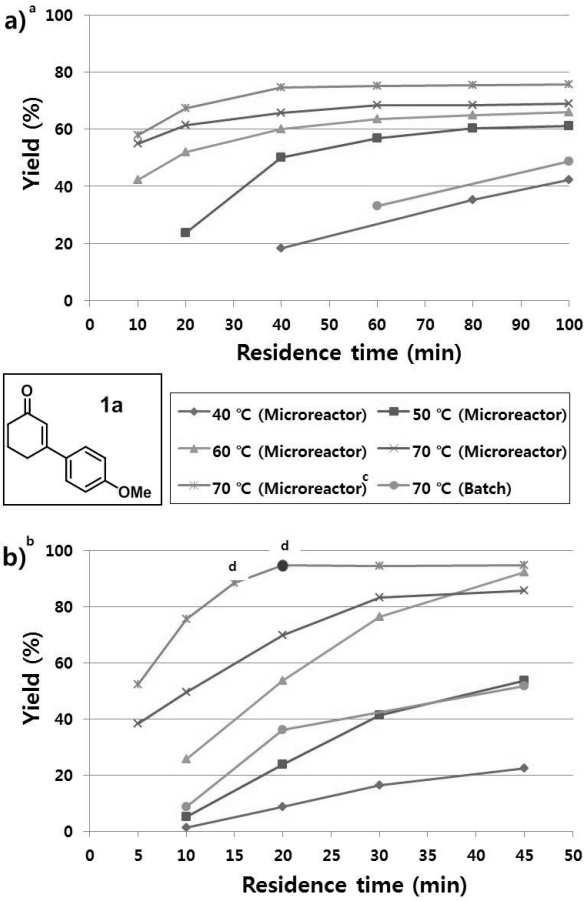


Figure 3. Microgram-scale reactions of cyclohex-2-enone with 4-methoxyphenylboronic acid in the capillary microreactor. [a]Standard reaction conditions: NMP (0.4 mL), cyclohex-2-enone (3 equiv), 4-methoxyphenylboronic acid (1.0 mmol), $Pd(OAc)_2$ (5 mol%), and dmphen (2,9-dimethyl-1,10-phenanthroline, 5 mol%), 1.3 atm oxygen, capillary (inner diameter = 0.6 mm, length = 5 m). [b]Standard reaction conditions: NMP (0.4 mL), cyclohex-2-enone (3 equiv), 4-methoxyphenylboronic acid (1.0 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (5 mol%), and 6,6′-dimethyl-2,2′-bipyridyl (5 mol%), 1.3 atm oxygen, PTFE capillary (inner diameter = 0.6 mL, length = 5 m). The **1a** yields in a) and b) were determined by ^{1}H NMR analysis. [c]1.6 atm oxygen. [d]No significant variations over 1.6 (2.5, 3.5, and 5.0) atm oxygen.

First, we investigated reaction parameters in the synthesis of **1a** through the microgram-scale reactions (Figure 3). An NMP solution of 4-methoxyphenylboronic boronic acid (1 mmol) and cyclohex-2-enone (3 mmol) was placed in the first inlet. An NMP solution of a Pd(II) complex prepared from 5 mol% $Pd(CH_3CN)_4(BF_4)_2$ and 5 mol% 6,6′-dimethyl-2,2′-bipyridyl was placed in the second inlet, and oxygen gas was placed in the third inlet. The injection rates of the reagents and catalyst were varied in the range 1.0–2.0 μL/min, and the pressure of oxygen gas was regulated in the range 1.3–5.0 atm. The reaction was terminated by dipping the reaction tube into an ice bath at 0 °C, and the droplets collected from different positions were analyzed using GC-MS/^{1}H NMR instruments. The reactions conducted under dried air or nitrogen instead of oxygen led to poor results (14% and 4% yields, respectively) and a significant amount of black precipitation, as expected.[7] Although the reactions in DMF showed very similar results to those conducted in NMP, the reactions conducted in THF or ACN (acetonitrile) were very troublesome due to the lack of solubility of the 4-methoxyphenylboronic acid and other additives. The microchemical reactions were carried out over a range of temperatures from 40 °C to 120 °C.

The yields in the range 40–70 °C increased with increasing reaction temperature for both $Pd(CH_3CN)_4(BF_4)_2$ and $Pd(OAc)_2$; however, the yields over 70 °C did not deviate from that of 70 °C (94.7% yield) and significant amount of black precipitation was observed in the microchannel over 120 °C. The precipitation frequently blocked the microchannel, which was a more serious problem in the second oxidative dehydrogenation. The oxygen pressure in the microchemical system was one of the key parameters; it was much more important above 50 °C. The results can be attributed to the oxygen concentration in the solution phase. The nature of the catalyst was also important because the combination of $Pd(CH_3CN)_4(BF_4)_2$ and 6,6′-dimethyl-2,2′-bipyridyl was found to be superior for both conversion and selectivity. The combination resulted in an excellent yield of the product (95%, 20 min) at 70 °C, while the combination of $Pd(OAc)_2$ and 2,9-dimethyl-1,10-phenanthroline afforded only moderate yields (67%, 20 min; 76 %, 100 min) at the same temperature. The results obtained from a batch system were compared; the batch reaction only afforded 20% yield (20 min) at 70 °C and 90% yield (360 min) at 50 °C due to insufficient oxygen caused by limited contact between oxygen and the reactants. Thus, the capillary microreactor was suitable for the simple and facile variation of the parameters and saved time and reagents significantly.

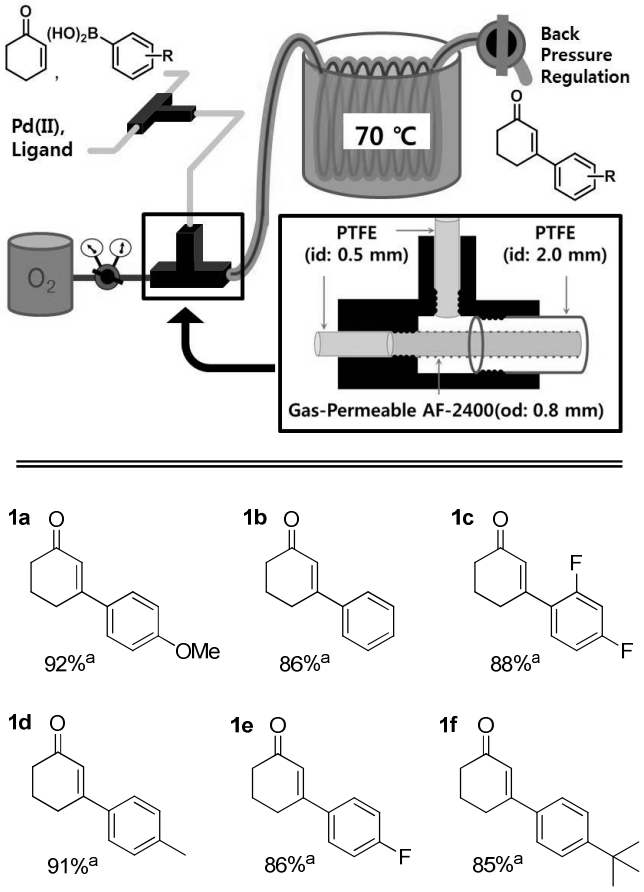


Figure 4. Schematic of the oxidative Heck reaction of cyclohex-2-enone and arylboronic acids in the tube-in-tube microreactor. Standard reaction conditions: NMP (2.4 mL), cyclohex-2-enone (9 mmol, 865 mg), arylboronic acid (3 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (5 mol%), and 6,6′-dimethyl-2,2′-bipyridyl (5 mol%), 1.6 atm oxygen, 70 °C, inner tube (AF-2400, outer diameter = 0.6 mm, length = 2 m), outer tube (PTFE, inner diameter = 1.5 mm, length = 2 m). [a]Isolated yield.

Based on the optimized reaction conditions for the first capillary microreactor, we configured the second tube-in-tube microreactor composed of a gas-permeable inner tube (AF-2400, DuPont) and gas-nonpermeable outer tube (Figure 4).[8] The first and second inlets were connected into the outer tube, and the third inlet was connected into the inner tube. An NMP

solution (1.2 mL) of 4-methoxyphenylboronic acid (3 mmol) and cyclohex-2-enone (9 mmol) was placed in the first inlet. An NMP solution (1.2 mL) of a Pd(II) complex prepared from 5 mol% $Pd(CH_3CN)_4(BF_4)_2$ and 5 mol% 6,6′-dimethyl-2,2′-bipyridyl was placed in the second inlet, and oxygen gas at 5.0 atm was placed in the third inlet. The injection rates were varied in the range 500–1000 μL/min, and bubble formation in tube-in-tube microreactor should be suppressed to obtain consistent results. The oxidative Heck reaction in the tube-in-tube microreactor afforded the desired product 1a in an excellent isolated yield (92%), which was almost similar to that of the capillary microreactor (95% NMR yield). To further explore the established tube-in-tube microreactor, we tested five reactions of cyclohex-2-enone with arylboronic acids. The reactions of phenylboronic acid and 2,4-difluorophenylboronic acid afforded the corresponding products, **1b** (86% isolated yield) and **1c** (88% isolated yield), respectively. The reactions of 4-tolylboronic acid, 4-fluorophenylboronic acid, and 4-(methoxycarbonyl)phenyl-boronic acid afforded the corresponding products, **1d** (91% isolated yield), **1e** (86% isolated yield), and **1f** (85% isolated yield), respectively.

The oxidative dehydrogenation in the microreactors

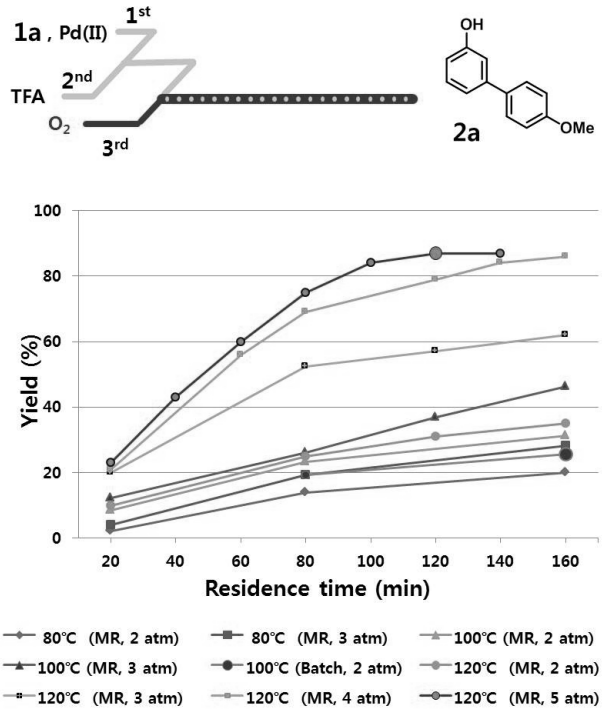


Figure 5. Schematic of the microchemical oxidative dehydrogenation. Standard reaction conditions: The reaction solution (0.8 mL) collected from the oxidative Heck reaction in the tube-in-tube microreactor; 5% TFA in DMSO, 2 mL. The overall yield after the first oxidative Heck reaction in the tube-in-tube microreactor and the second oxidative dehydrogenation in the capillary microreactor was determined by ^{1}H NMR analysis.

We attempted the oxidative dehydrogenation in the capillary microreactor (Figure 5). The solution collected from the tube-in-tube reaction of 4-methoxyphenylboronic acid and cyclohex-2-enone was placed in the first inlet. 5% TFA (trifluoroacetic acid) in DMSO was placed in the second inlet, and oxygen gas was placed in the third inlet. The synthesis of 4′-methoxybiphenyl-

3-ol **2a** progressed very slowly at 60 °C; however, the rate of the reaction increased with an elevated reaction temperature. We also regulated the pressure, which was not investigated in the previous study.[2] The reaction at 5.0 atm and 120 °C completed after 120 min (85% yield). The low oxygen concentration in the solution phase may have caused the long reaction time in the low-pressure and batch reactions, which was closely related to the precipitation of Pd(0). Consequently, higher pressure was much more important in the reaction conducted at elevated temperatures. Additionally, the microchemical reactions under different pressures were easily conducted, the high-pressure reaction in traditional batch system requires a special reactor that suffers from somewhat difficult handling and high reagent consumption (>100 times). The reactions conducted over 120 °C were suffered from heavy precipitation of palladium black.

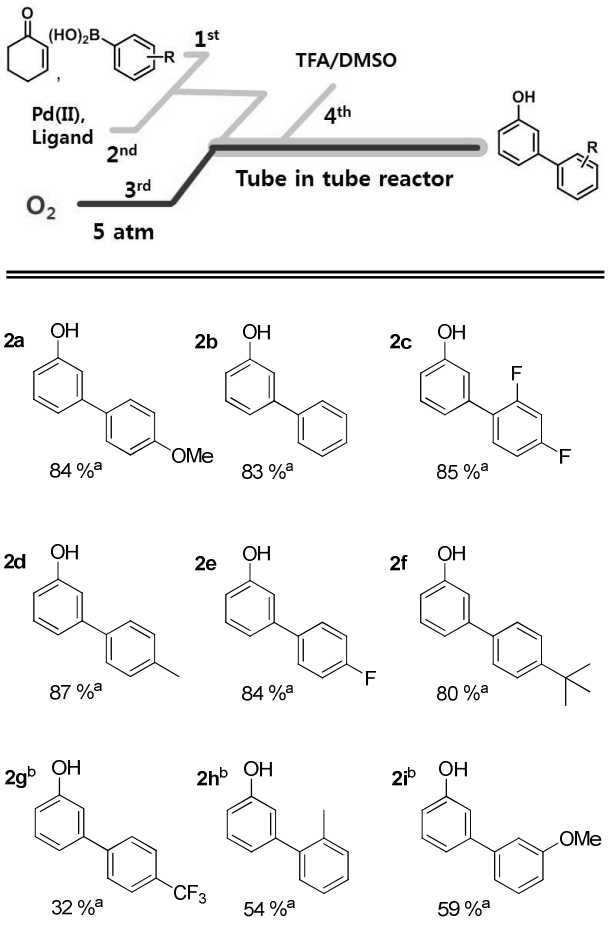
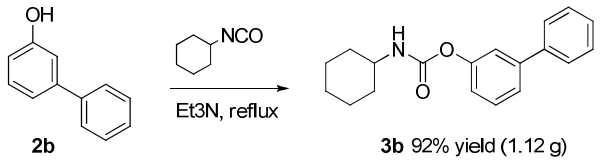


Figure 6. Continuous flow synthesis of *meta*-substituted phenol derivatives in the tube-in-tube microreactor. Standard reaction conditions: NMP (1.6 mL) of cyclohex-2-enone (15 mmol, 1.43 g) and arylboronic acid (5 mmol), NMP (1.6 mL) of $Pd(CH_3CN)_4(BF_4)_2$ (5 mol%) and 6,6′-dimethyl-2,2′-bipyridyl (5 mol%), 5 atm oxygen, 5% TFA (trifluoroacetic acid) in DMSO (8 mL), 120 °C, residence time of 130 min, inner tube (AF-2400, outer diameter = 0.6 mm, length = 2 m), outer tube (PTFE, inner diameter = 1.5 mm, length = 2 m). [a] Isolated yield. [b] Residence time of 180 min and cyclohex-2-enone of 25 mmol.

With optimized reaction conditions, we attempted the gram-scale oxidative Heck/dehydrogenation sequences in the tube-in-tube microreactor (Figure 6). To our delight, the system functioned well at the same pressure and temperature for the oxidative Heck/dehydrogenation. The oxidative Heck reaction at 5.0 atm and 120 °C showed a similar result for the reaction under the optimized conditions, 1.6 atm and 70 °C. The sequences were completed within 130 min, and the isolated yield of 4′-methylbiphenyl-3-ol **2d** increased to 87%. The products, 4′-methoxybiphenyl-3-ol **2a** (837 mg, 84% isolated yield) and biphenyl-3-ol **2b** (705 mg, 83% isolated yield), could be synthesized. Three more phenol derivatives were synthesized in good isolated yields (2′,4′-difluorobiphenyl-3-ol **2c**: 85%, 4′-fluorobiphenyl-3-ol **2e**: 84%, and methyl 3′-hydroxybiphenyl-4-carboxylate **2f**: 80%). However, there was a limitation in the synthesis of 4'-(trifluoromethyl)biphenyl-3-ol **2g** (32 % isolated yield, 65 % conversion), 2'-methylbiphenyl-3-ol **2h** (54 % isolated yield, 75 % conversion), and 3'-methoxybiphenyl-3-ol **2i** (59 % isolated yield, 81 % conversion). Even though we increased the residence time (180 min) and the amount of cyclohex-2-enone (5 equiv.), the conversions were significantly lowered due to the low reactivity of the boronic acids in the first oxidative Heck reaction. We tried to increase the conversions with the longer residence time (over 180 min) and the harsher reaction temperature (over 120 ^{o}C), but a black precipitation frequently blocked the microchannel under such reaction conditions.

To demonstrate the utility of the gram-scale synthesis in the tube-in-tube microreactor, biphenyl-3-ol **2b** (705 mg) was reacted with cyclohexyl isocyanate (778 mg, 1.5 equiv) to afford cyclohexylcarbamic acid biphenyl-3-yl ester **3b** (URB524, 92% isolated yield, 1.12g), which inhibited the fatty acid amide hydrolase (FAAH) activity in rat brain membranes (Scheme 1).[9]

Scheme 1. Gram-scale synthesis of URB524.



CONCLUSION

The total sequence time of oxidative Heck/dehydrogenation was optimized from 36 h in a traditional batch system to 130 min in the microchemical systems. The working volume in capillary microreactor can be regulated by changing the amounts of injected gas and liquids, and it enabled the microgram-scale study without the wasteful reagent consumption. The tube-in-tube microreactor successfully performed the gram-scale synthesis under the optimized conditions. In addition, the operations with capillary microreactor were very easy, but bubble formation in tube-in-tube microreactor should be suppressed to obtain consistent results.

EXPERIMENTAL SECTION

General information

Thin-layer chromatography (TLC) was performed using 60 mesh silica gel plates visualized with short-wavelength UV light (254 nm). Silica gel 60 (230~400 mesh) was used for column chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Advance 300 and Bruker Advance 600. Proton chemical shifts are reported in ppm (δ) relative to TMS with the solvent resonance employed as the internal standard ($CDCl_3$, δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet and doublet dt = doublet and triplet, m = multiplet), coupling constants (Hz) and integration. Carbon chemical shifts are reported in ppm from TMS with the solvent resonance as the internal

standard ($CDCl_3$ δ = 77.0 ppm). PTFE tubing and static mixing tees were purchased from UPCHURCH, USA.

General description of the microreactor mediated oxidative Heck reaction

NMP(N-methyl-2-pyrollidine) solution(0.4 mL) of aryl boronic acid (1.0 mmol) and cyclohex-2-enone (3.0 mmol) was placed in the first inlet. NMP solution(0.4 mL) of a Pd(II) complex prepared with 0.05 mmol $Pd(CH_3CN)_4(BF4)_2$ and 0.05 mmol 6,6'-dimethyl-2,2'-bipyridyl was placed in the second inlet, oxygen gas was placed in the third inlet. The reaction streams were introduced to the three-inlets of the microreactor, the injection rates of reagent and catalyst varied from 1.0 to 2.0 μL/min, and pressure of oxygen gas was varied from 1.3 to 1.6 atm. The reaction result was collected through a backpressure regulator, reaction yield was measured through the ^{1}H NMR analysis using an external capillary standard.

General description of the microreactor mediated oxidative dehydrogenation reaction

0.8 mL NMP solution of the oxidative Heck reaction was placed in a syringe, and 2.0 mL of a DMSO solution containing 5% CF_3CO_2H was placed in another syringe. Oxygen gas was placed in the third inlet. The reaction streams were introduced to the three inlets of the microreactor, the injection speeds were varied from 0.5 to 2.0 μL/min, and the pressure of the oxygen gas was varied from 1.6 to 2.0 atm. The product was collected through a backpressure regulator, and reaction yield was measured through the ^{1}H NMR analysis using an external capillary standard.

Characterization of the compounds

*3-(4-methoxyphenyl)cyclohex-2-enone (**1a**)*. The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 4) in 92% yield (559 mg, yellow solid (m.p.: 81-83^{o}C)). Experimental data were in accordance with those reported in the previous literature.[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54(d, *J* = 8.82 Hz, 2H), 6.95 (d, *J* = 8.89 Hz, 2H), 6.41 (s, 1H), 3.86 (s, 3H), 2.76 (t, *J* = 5.46 Hz, 2H), 2.48 (t, *J* = 6.97 Hz, 2H), 2.20-2.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.78, 161.26, 159.05, 130.86, 127.61, 123.74, 114.17, 55.37, 37.19, 27.89, 22.78.

*3-phenylcyclohex-2-enone (**1b**)*. The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 3) in 86% yield (445 mg, colorless crystals solid (m.p.: 58-60^{o}C)). Experimental data were in accordance with those reported in the previous literature.[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.52 (dd, *J* = 5.44 Hz, 2.28 Hz, 2H), 7.41-7.42(m, 3H), 6.43(s, 1H), 2.78 (t, *J* = 5.7 Hz, 2H), 2.49 (t, *J* = 6.75 Hz, 2H), 2.20-2.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.82, 159.79, 138.80, 129.97, 128.75, 126.07, 125.43, 37.26, 28.11, 22.82.

*3-(2,4-difluorophenyl)cyclohex-2-enone (**1c**)*. The yellowish liquid was isolated after column chromatography (EtOAc : Hexane = 1 : 3) in 88% yield (549 mg, yellow oil). Experimental data were in accordance with those reported in the previous literature.[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.22 (m, 1H), 6.96-6.80 (m, 2H), 6.27 (s, 1H), 2.75 (t, *J* = 5.85 Hz, 2H), 2.52 (t, *J* = 6.98 Hz, 2H), 2.20-2.12 (m, *J* = 6.4, 2H); ^{13}C NMR (75 MHz, $CDCl_3$). δ 199.38, 163.43 (J_{CF} = 251.34 Hz), 160.17 (J_{CF} = 253.21 Hz), 156.00, 129.94, 129.88, 124.06 (J_{CF} = 13.56 Hz), 111.83 (J_{CF} = 20.8 Hz), 104.82 (J_{CF} = 25.42 Hz), 37.33, 29.59, 23.08; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{10}F_2ONa$ 231.0597; Found 231.0582.

*3-p-tolylcyclohex-2-enone (**1d**)*. The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 3) in 91% yield (509 mg, yellow oil). Experimental data were in accordance with those reported in the previous literature.[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 7.99 Hz, 2H), 6.43 (s, 1H), 2.77 (t, J = 5.41 Hz, 2H), 2.49 (t, J = 7.1 Hz, 2H), 2.39 (s, 3H), 2.20-2.11 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.02, 159.75, 140.42, 135.85, 129.52, 126.08, 124.71, 37.32, 28.04, 22.85, 21.35.

*3-(4-fluorophenyl)cyclohex-2-enone (**1e**)*. The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 3) in 86% yield (491 mg, colorless oil). Experimental

data were in accordance with those reported in the previous literature.[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.47 (dd, J = 5.18 Hz, 2H), 7.12 (t, J = 8.87 Hz, 2H), 6.39 (s, 1H), 2.77 (t, J = 5.54 Hz, 2H), 2.50 (t, J = 7.70 Hz, 2H), 2.17 (q, J = 6.12 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.68, 163.8 (J_{CF} = 250.77 Hz), 158.43, 134.88, 128,05, 128.00, 125.31, 115.91, 115.77, 37.16, 28.15, 22.76.

3-(4-tert-butylphenyl)cyclohex-2-enone ***(1f)***. The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 3) in 85% yield (582 mg, off-white crystalline solid (m.p.: 47.5-49.5 ^{o}C)). Experimental data were in accordance with those reported in the previous literature.[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.70 Hz, 2H), 7.47 (d, J = 8.70 Hz, 2H), 6.46 (s, 1H), 2.80 (t, J = 5.60 Hz, 2H), 2.51 (t, J = 7.13 Hz, 2H), 2.17 (q, J = 6.37 Hz, 2H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.02, 159.60, 153.57, 136.74, 125.92, 125.76, 124.75, 37.31, 34.82, 31.19, 27.97, 22.84.

4'-methoxybiphenyl-3-ol ***(2a)***. The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 6) in 84% yield (837 mg, white powder (m.p.: 117^{o}C)). Experimental data were in accordance with those reported in the previous literature.[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.66 Hz, 2H), 7.30 (t, J = 7.76 Hz, 1H), 7.15 (d, J = 7.53 Hz, 1H), 7.05 (s, 1H), 6.99 (d, J = 8.67 Hz, 2H), 6.80 (dd, J = 7.71 Hz, 1.94 Hz, 1H), 4.94 (bs, OH), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.32, 155.87, 142.64, 133.32, 129.91, 128.11, 119.36, 114.22, 113.68, 113.60, 55.36.

biphenyl-3-ol ***(2b)***. The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 6) in 83% yield (705 mg, white solid (m.p.: 73-74^{o}C)). Experimental data were in accordance with those reported in the previous literature.[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 6.98 Hz, 1.52 Hz, 2H), 7.46 (t, *J* = 6.98 Hz, 2H), 7.31-7.39 (m, 2H), 7.20 (d, *J* = 7.71 Hz, 1H), 7.09 (s, 1H), 6.84 (dd, *J* = 8.18Hz, 1.79 Hz, 1H), 4.75 (bs, OH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.86, 143.04, 140.76, 130.01, 128.77, 127.52, 127.15, 119.83, 114.18, 114.12.

2',4'-difluorobiphenyl-3-ol ***(2c)***. The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 7) in 85% yield (876 mg, yellow oil). Experimental data were in accordance with those reported in the previous literature.[3] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (q, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.02 (s, 1H), 6.99-6.92 (m, 2H), 6.89 (dd, *J* = 7.9 Hz, 1.83 Hz), 4.78(bs, OH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.37(J_{CF} = 249.43 Hz),

159.72(J_{CF} = 250.61 Hz), 155.52, 136.57, 131.39, 129.78, 124.86 (J_{CF} = 13.48 Hz), 121.53, 115.94, 114.75, 111.56 (J_{CF} = 20.28 Hz), 104.40 (J_{CF} = 24.75 Hz).

*4'-methylbiphenyl-3-ol (**2d**).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 4) in 87% yield (801 mg, white solid (m.p.: 75.2-75.3^{o}C)). Experimental data were in accordance with those reported in the previous literature.[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.09 Hz, 2H), 7.37 (t, *J* = 8.05 Hz, 1H), 7.29 (d, *J* = 7.77 Hz, 2H), 7.23 (d, *J* = 7.89, 1H), 7.10 (s, 1H), 6.83 (dd, *J* = 7.89, 1.7 Hz, 1H), 5.28 (bs, OH), 2.44 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 155.82, 143.00, 137.88, 137.32, 129.98, 129.50, 126.97, 119.66, 113.99, 113.97, 21.10.

*4'-fluorobiphenyl-3-ol (**2e**).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 6) in 84% yield (792 mg, amorphous solid (m.p.: 78-79^{o}C)). Experimental data were in accordance with those reported in the previous literature.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.52 (dd, J = 5.66 Hz, 8.48Hz, 2H), 7.33 (t, *J* = 7.91 Hz, 1H), 7.17-7.11 (m, 3H), 7.04 (s, 1H), 6.86 (dd, *J* = 7.79, 2.03 Hz, 1H), 4.89 (bs, OH); ^{13}C NMR(150 MHz, $CDCl_3$) δ 162.57 (J_{CF} = 246.06 Hz), 155.95, 142.04, 136.88, 130.07, 128.70, 128.65, 119.61, 115.69, 115.56, 114.21, 114.02.

*4'-tert-butylbiphenyl-3-ol (**2f**).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 6) in 80% yield (906 mg, yellow solid (m.p.:89.5^{o}C)). Experimental data were in accordance with those reported in the previous literature.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.29 Hz, 2H), 7.47 (d, *J* = 8.11 Hz, 2H), 7.32 (t, *J* = 7.92 Hz, 1H), 7.20 (d, *J* = 7.91 Hz 1H), 7.08 (s, 1H), 6.84 (d, *J* = 7.90, 1H), 4.79 (bs, OH), 1.38 (s, 9H); ^{13}C NMR(150 MHz, $CDCl_3$) δ 155.79, 150.56, 142.88, 137.80, 129.93, 126.75, 125.72, 119.68, 113.92, 113.91, 34.56, 31.37.

*4'-(trifluoromethyl)biphenyl-3-ol (**2g**).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 6) in 32% yield (381 mg, colorless needles (m.p.: 73-75^{o}C)). Experimental data were in accordance with those reported in the previous literature.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 4H), 7.37 (t, J = 7.79Hz, 1H), 7.20 (d, J = 7.79Hz, 1H), 7.09(s, 1H), 6.90 (dd, 7.79Hz, 1.95Hz, 1H), 4.86 (bs, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.00, 144.26, 141.54, 130.24, 127.40, 125.70 (J_{CF} = 3.42 Hz), 119.90, 115.11, 114.24.

*2'-methylbiphenyl-3-ol (**2h**).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 4) in 54% yield (497 mg, colourless oil). Experimental data were in accordance with those reported in the previous literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H),

6.92 (d, J = 7.15Hz, 1H), 6.85-6.82 (m, 2H), 4.80 (bs, OH), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.19, 143.72, 141.48, 135.29, 130.29, 129.58, 129.28, 127.35, 125.71, 121.91, 116.20, 113.70, 20.38.

*3'-methoxybiphenyl-3-ol (**2i**).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 4) in 59% yield (590 mg, brown oil). Experimental data were in accordance with those reported in the previous literature.[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (m, 2H), 7.20-7.08 (m, 4H), 6.93 (dd, J = 8.41 Hz, 2.4 Hz, 1H), 6.85 (dd, J = 8 Hz, 2 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.93, 155.82, 142.91, 142.29, 129.95, 129.74, 119.83, 119.65, 114.34, 114.16, 113.00, 112.85, 55.32.

*biphenyl-3-yl cyclohexylcarbamate (**3b**).* The compound was isolated after column chromatography (EtOAc : hexane = 1 : 3) in 92% yield (1.12 g, white crystals (m.p.: 141-143 ^{o}C)) Experimental data were in accordance with those reported in the previous literature.[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.04 (m, 9H), 4.86 (m, 1H), 3.52 (m, 1H), 1.97-1.13(m, 10H); ^{13}C NMR(150 MHz, $CDCl_3$) δ 153.65, 151.48, 142.63, 140.42, 129.52, 128.75, 127.51, 127.22, 123.94, 120.41, 50.18, 33.31, 25.48, 24.78.

ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H NMR and ^{13}C NMR spectra for isolated products. This material is available free of charge *via* the internet at http://pubs.acs.org.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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REFERENCES

1. Selected examples, (a) Hoarau, C.; Pettus, T. R. R. *Synlett* **2003**, 127–137. (b) Dewick, P. M. *Medicinal Natural Products: A* Biosynthetic Approach, Wiley-VCH, Weinheim, **2011**. (c) He, Z.; Jamison, T. F. *Angew. Chem., Int. Ed*. **2014**, *53*, 3353–3357. (d) Dai, H.-X.; Li, G.; Zhang, X.-G.; Stepan, A. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 7567–7571.

2. (a) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209–213. (b) Izawa, Y.; Zheng, C.; Stahl. S. S. *Angew. Chem., Int. Ed*. **2013**, *52*, 3672–3675.

3. Selected examples, (a) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300–2318. (b) Whitesides, G. M. *Nature*, **2006**, *442*, 368–373. (c) Park, C. P.; Kim, D.-P. *Angew. Chem. Int. Ed.* **2010**, *49*, 6825–6829. (d) Park, J. H.; Park, C. Y.; Song. H. S.; Huh, Y. S.; Kim, G. H.; Park, C. P. *Org. Lett.* **2013**, 15, 752–755. (e) Wiles, C.; Watts, P.; Haswell, S. J. *Lab Chip* **2007**, *7*, 322–330. (f) Baxendale, I. R.; Ley, S. V.; Mansfield, A. C.; Smith, C. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 4017–4021. (g) Kobayashi, J.; Mori, Y.; Okamoto, K.; Akiyama, R.; Ueno, M.; Kitamori, T.; Kobayashi, S.; *Science* **2004**, *304*, 1305–1308. (h) Nagaki, A.; Kim, H,; Yoshida, J. *Angew. Chem. Int. Ed*., **2009**, *48*, 8063–8065. (i) Fukuyama, T.; Tokoki, T.; Ryu, I. *Org. Lett.*, **2014**, *16*, 5632–5635. (j) Maurya, R. A.; Hoang, P.

H.; Kim, D.-P. *Lab Chip* **2012**, *12*, 65–68. (k) Biswas, K. G.; Patra, R.; Das, G. Ray, S.; Basu, J. K. *Chem. Eng. J.* **2015**, *262*, 436–446. (l) Deng, Q.; Shen, R.; Zhao, Z.; Yan, M.; Zhang, L. *Chem. Eng. J.* **2015**, *262*, 1168–1174. (m) Frost, C. G.; Mutton, L. *Green Chem*. **2010**, *12*, 1687–1703. (n) Noël, T.; Buchwald, S. L. *Chem. Soc. Rev*. **2011**, *40*, 5010–5029.

4. Selected exemples, (a) Kobayashi, J.; Mori, Y.; Kobayashi, S. *Adv. Synth. Catal*. **2005**, *347*, 1889–1892. (b) Wang, N.; Matsumoto, T.; Ueno, M.; Miyamura, H.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 4744–4746. (c) Shore, G.; Morin, S.; Organ, M. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2761–2766. (d) Jähnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Haverkamp, V.; Löwe, H.; Wille, C.; Guber, A. *J. Fluorine Chem.* **2000**, *105*, 117–128. (e) Yeong, K. K.; Gavriilidis, A.; Zapf, R.; Hessel, V. *Chem. Eng. Sci.* **2004**, *59*, 3491–3494. (f) Park, C. P.; Kim, D.-P. *J. Am. Chem. Soc*. **2010**, *132*, 10102–10106. (g) Miller, P. W.; Long, N. J.; de Mello, A. J.; Vilar, R.; Audrain, H.; Bender, D.; Passchier, J.; Gee, A. *Angew. Chem., Int. Ed*. **2007**, *46*, 2875–2878. (h) Rahman, M. T.; Fukuyama, T.; Kamata, N.; Sato, M.; Ryu, I. *Chem. Commun*. **2006**, *21*, 2236–2238. (i) Rebrov, E. V.; Klinger, E. A.; Berenguer-Murcia, A.; Sulman, E. M.; Schouten, J. C. *Org. Process Res. Dev*. **2009**, *13*, 991–998. (j) Straathof, N. J. W.; Tegelbeckers, B. J. P.; Hessel, V.; Wang, X.; Noël, T. *Chem. Sci.* **2014**, *5*, 4768–4773. (k) Straathof, N. J. W.; Gemoets, H. P. L; Wang, X.; Schouten, J. C.; Hessel, V.; Noël, T. *ChemSusChem* **2014**, *7*, 1612–1617. (l) Gemoets, H. P. L.; Hessel, V.; Noël, T. *Org. Lett.* **2014**, *16*, 5800–5803. (m) Talla, A.; Driessen, B.; Straathof, N. J. W.; Milroy, L.-G. Brunsveld, L.; Hessel, V.; Noël, T. *Adv. Synth. Catal.* **2015**, DOI: 10.1002/adsc.201401010.

5. (a) Yang, L; Jensen, K. F. *Org. Process Res. Dev*. **2013**, *17*, 927–933. (b) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. *Acc. Chem. Res.* **2015**. *48*. 349–362. (c) Cranwell, P. B.; O'Brien, M.; Browne, D. L.; Koos, P.; Polyzos, A.; Peña-López, M.; Ley, S. V. *Org. Biomol.*

Chem. **2012**, *10*, 5774–5779. (d) Tomaszewski, B.; Lloyd, R. C.; Warr, A. J.; Buehler, K.; Schmid, A. *ChemCatChem* **2014**, *6*, 2567–2576. (e) Buba, A. E.; Koch, S.; Kunz, H.; Lowe, H. *Eur. J. Org. Chem*. **2013**, 4509–4513. (f) Tomaszewski, B.; Schmid, A.; Buehler, K. *Org. Process Res. Dev*. **2014**, *18*, 1516–1526. (g) Park, C. Y.; Kim, Y. J.; Lim, H. J.; Park, J. H.; Kim, M. J.; Seo, S. W.; Park, C. P. *RSC Adv.*, **2015**, *5*, 4233–4237.

6. Selected exemples, (a) Kawanami, H.; Matsushima, K.; Sato, M.; Ikushima, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5129–5132. (b) Shore, G.; Morin, S.; Organ, M. G. *Angew. Chem., Int. Ed*. **2006**, *45*, 2761–2766. (c) Yamada, Y. M. A.; Watanabe, T.; Torii, K.; Uozumi, Y. *Chem. Commun.* **2009**, 5594–5596.

7. (a) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc*., **2006**, *128*, 16384–16393. (b) Yoo, K. S.; Park, C. P.; Yoon, C. H.; Sakaguchi, S.; O'Neill, J.; Jung, K. W. *Org. Lett*., **2007**, *9*, 3933–3935.

8. (a) Fukuyama, T.; Totoki, T.; Ryu, I. *Green Chem*. **2014**, *16*, 2042–2050. (b) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett*. **2010**, *12*, 1596–1598. (c) Polyzos, A.; O'Brien, M.; Petersen, T. P.; Baxendale, I. R.; Ley, S. V. *Angew. Chem., Int. Ed*. **2011**, *5*, 1190–1193.

9. (a) Mor, M.; Lodola, A.; Rivara, S.; Vacondio, F.; Duranti, A.; Tontini, A.; Sanchini, S.; Piersanti, G.; Clapper, J. R.; King, A. R.; Tarzia, G.; Piomelli, D. *J Med Chem.* **2009**, 51, 3487–3498. (b) Tarzia, G.; Duranti, A.; Tontini, A.; Piersanti, G.; Mor, M.; Rivara, S.; Plazzi, P. V.; Park, C, Kathuria, S.; Piomelli, D. *J. Med. Chem*. **2003**, *46*, 2352–2360.