Supporting Information

Batch to Flow Deoxygenation Using Visible Light Photoredox Catalysis

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General Information

Chemicals were either used as received or purified according to *Purification of Common Laboratory Chemicals*. All reactions were performed using common anhydrous, inert atmosphere techniques. Reactions were monitored by TLC and visualized by a dual short wave/long wave UV lamp and stained with an ethanolic solution of potassium permanganate or *p*-anisaldehyde. Column flash chromatography was performed using 230-400 mesh silica gel. NMR spectra were recorded on Varian Unity Plus 400 and Varian Mercury 500 spectrometers. Chemical shifts for ^{1}H NMR were reported as δ, parts per million, relative to the signal of $CHCl_3$ at 7.26 ppm. Chemical shifts for ^{13}C NMR were reported as δ, parts per million, relative to the $CDCl_3$ triplet at 77.0 ppm. Proton and carbon assignments were established using spectral data of similar compounds. The abbreviations s, br. s, d, dd, br. d, ddd, t, q, br. q, qi, m, and br. m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, quintet, multiplet and broad multiplet, respectively. IR spectra were recorded on an Avatar 360 FT-IR spectrometer. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the Boston University in Boston, MA on a Waters Q-Tof API-US with ESI high resolution mass spectrometer. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg).

Reaction Apparatus

A photograph of the assembled photoreactor is shown in Figure S-1. The LED assembly (5.88 W) consists of 7 prearranged Luxeon Rebel high power LEDs (royal blue color, λ_{max} = 447.5 nm) (http://www.luxeonstar.com/Royal-Blue-447-5nm-7-LED-40mm-Round-Assembly-p/sr-02-r0425.htm). This is mounted to a heat sink to dissipate any heat generated by the LEDs (http://www.luxeonstar.com/60mm-Round-Alpha-Heat-Sink-p/cn60-45b.htm) and powered by a 24V power supply (http://www.ledsupply.com/24vdc17a.php). To support the tubing, three flint glass test tubes were supported at both ends by small pieces of cardboard. The PFA Tubing (IDEX Health and Science, Part # 1514L) is wrapped around and between the tubes so that a total volume of 1.34 mL is placed on the test tubes. This is done so that the total length of the coils does not exceed the size of the LED apparatus (4.0 cm). The tubing is secured in place by a small piece of tape. The coiled tubing is then suspended approximately 2 cm above the LED apparatus.

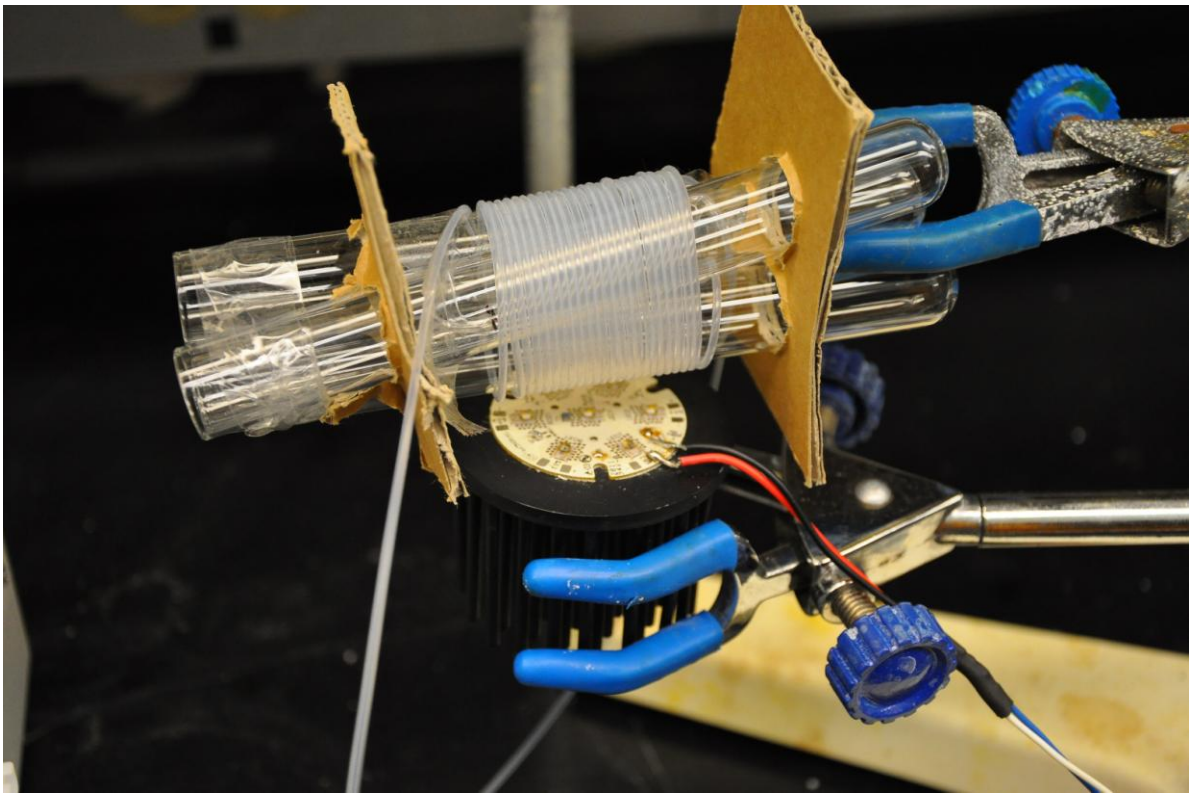


Figure S-1: Close up picture of photoreactor

The photoreactor tubing is the connected to the peristaltic pump tubing (IDEX Health and Science, Part # SC0717) by means of a conical adapter (IDEX Health and Science, Part # P-797) which contains the appropriate female nut, ferrule and washer. Likewise another short piece of PFA tubing, for delivery of the reaction mixture, was connected to the other end of the peristaltic pump tubing and fitted with a 20 gauge needle to pierce the septum of the reaction flask. Figure S-2 depicts the assembled reactor. During the operation of the flow reactor a sheet of aluminum foil is placed around the reaction apparatus due to the brightness of the LEDs.

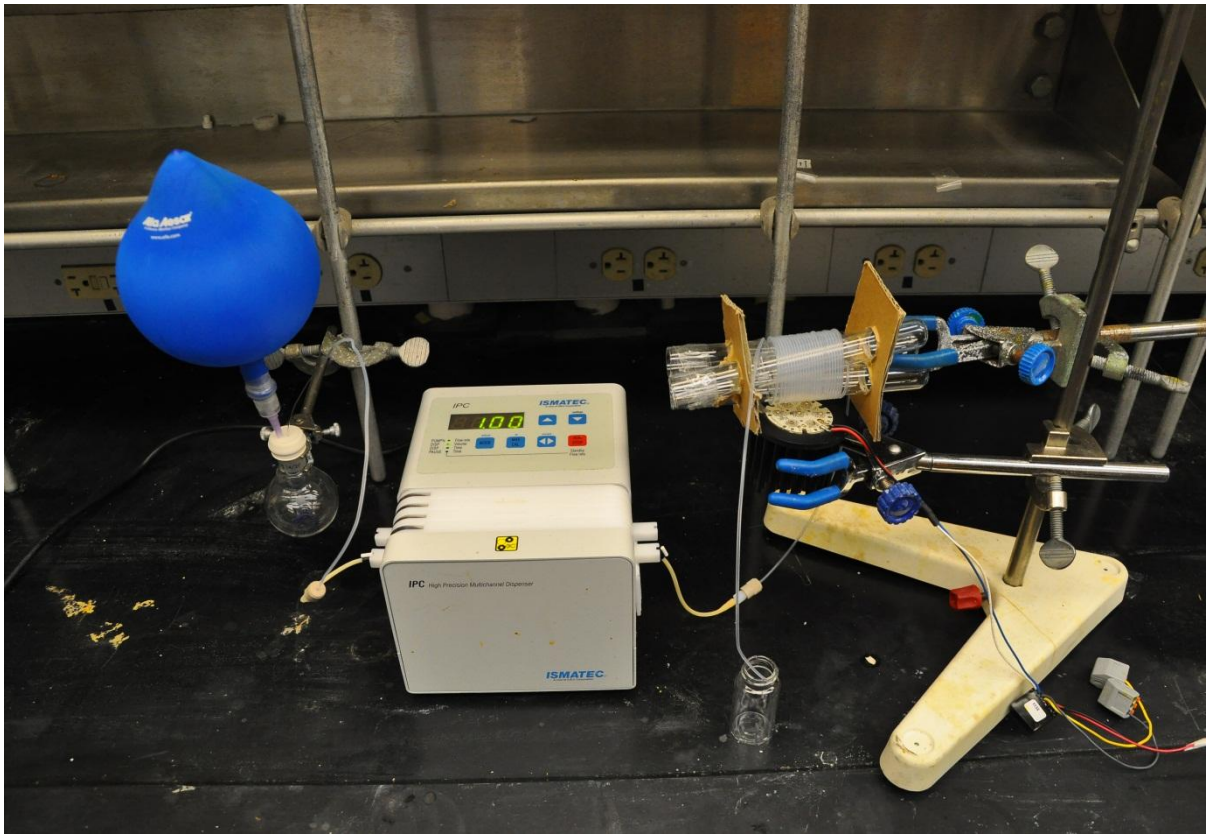


Figure S-2: Assembled photochemical flow reactor

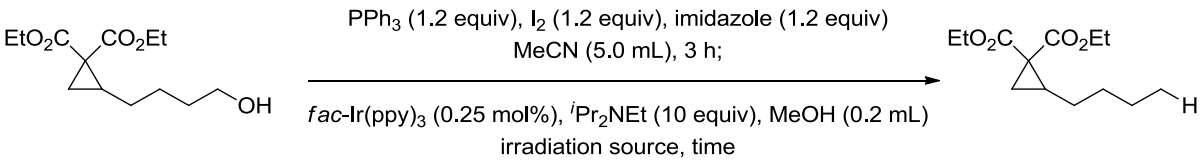
General Procedure A

A flame dried 10 mL round bottom flask with a rubber septum and magnetic stir bar was charged with the corresponding alkyl alcohol (1.0 mmol, 1.0 equiv), MeCN (5.0 mL), triphenylphosphine (1.2 mmol, 1.2 equiv), and imidazole (1.2 mmol, 1.2 equiv). The reaction mixture is cooled in an ice bath to 0 ºC and iodine (1.2 mmol, 1.2 equiv) is added in portions. After 0.5 h, the reaction is removed from the ice bath and stirred at room temperature until the alcohol is fully consumed (as judged by TLC analysis). *N*,*N*-Diisopropylethylamine (10 mmol, 10 equiv), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (0.0025 mmol, 0.0025 equiv) are added to the reaction mixture and stirred until a homogenous solution is formed. The reaction mixture is then pumped through the photoreactor at a flow rate to achieve a residence time of 18 min. The solvent was removed from the crude mixture *in vacuo* and was dissolved in a minimal amount of EtOAc before being passed through a bed of silica gel and eluted with diethyl ether. The filtrate was concentrated and the crude product was purified by chromatography on silica gel, using the solvent system indicated, to afford the desired product.

General Procedure B

A flame dried 10 mL round bottom flask with a rubber septum and magnetic stir bar was charged with the corresponding alkyl alcohol (1.0 mmol, 1.0 equiv), MeCN (5.0 mL), triphenylphosphine (1.5 mmol, 1.5 equiv), and imidazole (2.0 mmol, 2.0 equiv). The reaction mixture is cooled in an ice bath to 0 ºC and iodine (1.5 mmol, 1.5 equiv) is added in portions. After 0.5 h, the reaction is removed from the ice bath and stirred at room temperature until the alcohol is fully consumed (as judged by TLC analysis). *N*,*N*-Diisopropylethylamine (10 mmol, 10 equiv), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (0.0025 mmol, 0.0025 equiv) are added to the reaction mixture and stirred until a homogenous solution is formed. The reaction mixture is then pumped through the photoreactor at a flow rate to achieve a residence time of 18 min. The solvent was removed from the crude mixture *in vacuo* and was dissolved in a minimal amount of EtOAc before being passed through a bed of silica gel and eluted with diethyl ether. The filtrate was concentrated and the crude product was purified by chromatography on silica gel, using the solvent system indicated, to afford the desired product.

Comparison Studies

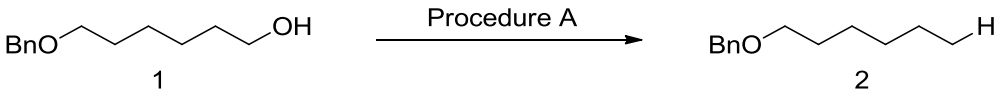


Entry[a]	Irradiation Source	Description	Time(h)	^{1}H NMR yield
1	1W LED strip	Batch reaction	60	100
2	5.88W LED puck	Batch reaction	12	100
3[b]	5.88W LED puck	Batch to flow (t_R = 18 min) with silver mirrored Erlenmeyer flask	3.5	100
4[b]	5.88W LED puck	Batch to flow (t_R = 18 min) without silver mirrored Erlenmeyer flask	3.5	100
5[b]	5.88W LED puck	Batch to flow (t_R = 18 min) with silver mirror	3.5	100
6[b]	5.88W LED puck	Batch to flow (t_R = 9 min) with silver mirrored Erlenmeyer flask	1.8	58
7[b]	5.88W LED puck	Batch to flow (t_R = 9 min) without silver mirrored Erlenmeyer flask	1.8	52
8[b]	5.88W LED puck	Batch to flow (t_R = 9 min) with silver mirror	1.8	60

[a]All reactions run on 1 mmol scale of alcohol; [b]Reaction time refers to the total time to flow the reaction mixture through the flow reactor.

Utilizing the flow reactor for the second step of the one pot deoxygenation protocol leads to a significant decrease in reaction time due to the stronger irradiation source (entry 2), the more efficient light irradiation, and the more efficient mixing of reaction components in a flow reactor (entries 3 – 8). In addition, the presence of a silver mirror placed above the reactor shows a small increase of reaction efficiency (entries 6 – 8), although this is irrelevant for the conditions described in this communication (entries 3 – 5).

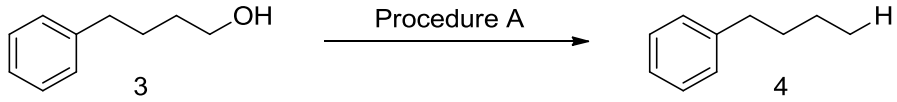
Compound Characterization



Benzyl hexyl ether: According to General Procedure A, **1**[1] (0.21 g, 1.0 mmol), triphenylphosphine (0.32 g, 1.2 mmol), imidazole (82 mg, 1.2 mmol), and iodine (0.30 g, 1.2 mmol) in MeCN (5.0 mL) was stirred overnight. After full consumption of the alcohol *N*,*N*-Diisopropylethylamine (1.7 mL, 10 mmol), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol) are added and the reaction mixture is pumped through the photoreactor at a flow rate to achieve a residence time of 18 min which afforded **2**[2] (0.17 g, 88%) as a colorless oil after purification by chromatography on SiO_2 (98:2, petroleum ether/EtOAc).

R_f (EtOAc/hexane 1:19): 0.50;

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 – 7.26 (m, 5H), 4.51 (s, 2H), 3.48 (t, J = 6.7 Hz, 2H), 1.67 – 1.58 (m, 2H), 1.42 – 1.25 (m, 6H), 0.90 (t, J = 6.7 Hz, 3H).

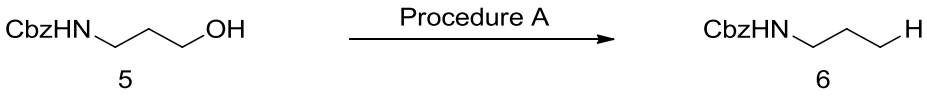


Butylbenzene: According to General Procedure A, **3**[3] (0.15 g, 1.0 mmol), triphenylphosphine (0.32 g, 1.2 mmol), imidazole (82 mg, 1.2 mmol), and iodine (0.30 g, 1.2 mmol) in MeCN (5.0 mL) was stirred overnight. After full consumption of the alcohol *N*,*N*-Diisopropylethylamine (1.7 mL, 10 mmol), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol) are added and the reaction mixture is pumped through the photoreactor at a flow rate to achieve a residence time of 18 min which afforded **4**[4] (99 mg, 74%) as a colorless oil after purification by chromatography on SiO_2 (petroleum ether).

R_f (hexanes): 0.54;

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 – 7.29 (m, 2H), 7.23 – 7.18 (m, 3H), 2.65 (t, J = 8.0 Hz, 2H), 1.68 – 1.60 (m, 2H), 1.44 – 1.36 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H).

[1] Characterization and preparation of substrate **1** is reported in R. S. Narayan and B. Borhan, *J. Org. Chem.* **2006**, *71*, 1416-1429.
[2] Q. Chu, M. M. Brahmi, A. Solovyev, S.-H. Ueng,D. P. Curran, M. Malacria, L. Fensterbank and E. Lacóte, *Chem. Eur. J.* **2009**, *15*, 12937-12940.
[3] Commercially available from Sigma Aldrich.
[4] F. Alonso, P. Riente and M. Yus, *Tetrahedron* **2009**, *65*, 10637-10643.

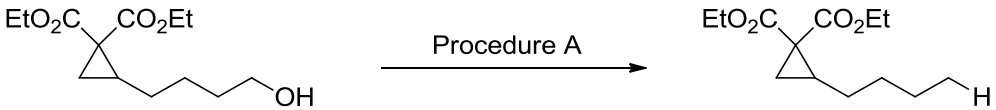


5 6

Benzyl propylcarbamate: According to General Procedure A, **5**[5] (0.20 g, 1.0 mmol), triphenylphosphine (0.32 g, 1.2 mmol), imidazole (82 mg, 1.2 mmol), and iodine (0.30 g, 1.2 mmol) in MeCN (5.0 mL) was stirred overnight. After full consumption of the alcohol *N*,*N*-Diisopropylethylamine (1.7 mL, 10 mmol), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol) are added and the reaction mixture is pumped through the photoreactor at a flow rate to achieve a residence time of 18 min which afforded **6**[6] (0.16 g, 81%) as a colorless oil after purification by chromatography on SiO_2 (95:5, hexanes/EtOAc).

R_f (EtOAc/hexane 1:4): 0.42;

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 – 7.30 (m, 5H), 5.10 (s, 2H), 3.21 – 3.13 (m, 2H), 1.60 – 1.48 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H).



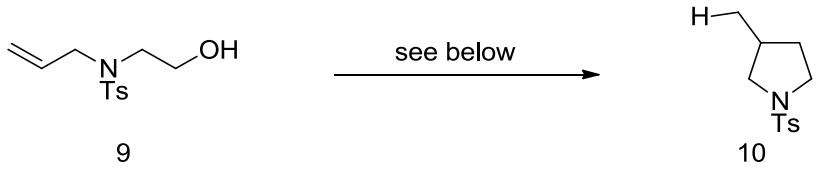
7 8

Diethyl 2-butylcyclopropane-1,1-dicarboxylate: According to General Procedure A, **7**[7] (0.26 g, 1.0 mmol), triphenylphosphine (0.32 g, 1.2 mmol), imidazole (82 mg, 1.2 mmol), and iodine (0.30 g, 1.2 mmol) in MeCN (5.0 mL) was stirred overnight. After full consumption of the alcohol *N*,*N*-Diisopropylethylamine (1.7 mL, 10 mmol), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol) are added and the reaction mixture is pumped through the photoreactor at a flow rate to achieve a residence time of 18 min which afforded **8**[8] (0.21 g, 87%) as a colorless oil after purification by chromatography on SiO_2 (95:5, hexanes/EtOAc).

R_f (EtOAc/hexanes 1:9): 0.50;

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.31 – 4.09 (m, 4H), 1.93 – 1.84 (m, 1H), 1.53 – 1.14 (m, 14H), 0.89 (t, J = 7.1 Hz, 3H).

[5] Characterization and preparation of substrate **5** is reported in K. S. Babu, V. R. S. Rao, R. R. Rao, S. S. Babu, J. M. Rao, *Can. J. Chem.* **2009**, *87*, 393-396.
[6] K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron* **2000**, *56*, 8433-8441.
[7] Characterization and preparation of substrate **7** is reported in J. D. Nguyen, J. W. Tucker, M. D. Konieczynska and C. R. J. Stephenson, *J. Am. Chem. Soc.* **2011**, *133*, 4160-4163.
[8] X. He, G. Qiu, J. Yang, Y. Xiao, Z. Wu, G. Qiu and X. Hu, *Eur. J. Med. Chem.* **2010**, *45*, 3818-3830.

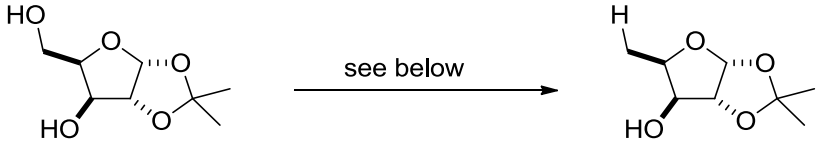


9 10

3-Methyl-1-tosylpyrrolidine: A flame dried 10 mL round bottom flask with a rubber septum and magnetic stir bar was charged with the **9**[9] (0.26 g, 1.0 mmol), MeCN (6.0 mL), triphenylphosphine (0.48 g, 1.8 mmol), and imidazole (0.12 g, 1.8 mmol). The reaction mixture is cooled in an ice bath to 0 ºC and iodine (0.46 g, 1.8 mmol) is added in portions. After 0.5 h, the reaction is removed from the ice bath and stirred at room temperature until the alcohol is fully consumed (as judged by TLC analysis). *N*,*N*-Diisopropylethylamine (1.7 mL, 10 mmol), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (3.2 mg, 0.0050 mmol) are added to the reaction mixture and stirred until a homogenous solution is formed. The reaction mixture is then pumped through the photoreactor at a flow rate to achieve a residence time of 18 min. The solvent was removed from the crude mixture *in vacuo* and was dissolved in a minimal amount of EtOAc before being passed through a bed of silica gel and eluted with diethyl ether. The filtrate was concentrated and the crude product was purified by chromatography on silica gel (96:4, petroleum ether/EtOAc) to afford **10**[10] (0.20 g, 85%) as a colorless solid.

R_f (EtOAc/hexane 1:9): 0.47;

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 3.43 (dd, *J* = 9.5, 7.1 Hz, 1H), 3.35 (ddd, *J* = 9.8, 8.3, 4.2 Hz, 1H), 3.27−3.19 (m, 1H), 2.76 (dd, *J* = 9.7, 7.7 Hz, 1H), 2.44 (s, 3H), 2.19−2.07 (m, 1H), 1.96−1.86 (m, 1H), 1.42−1.31 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H).



11 12

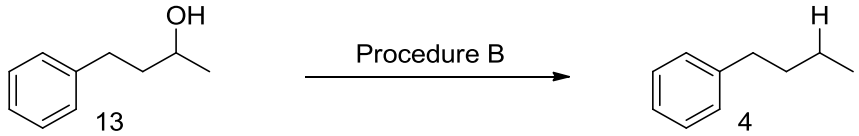
1,2-*O*-Isopropylidene-5-deoxy-α-D-xylofuranose: A flame dried 10 mL round bottom flask with a rubber septum and magnetic stir bar was charged with the **11**[3] (0.19 g, 1.0 mmol), MeCN (7.0 mL), triphenylphosphine (0.66 g, 2.5 mmol), imidazole (0.34 g, 5.0 mmol), and iodine (0.63 g, 2.5 mmol) is added in portions. The reaction is stirred at 50 ºC until the alcohol is fully consumed (as judged by TLC analysis). *N*,*N*-Diisopropylethylamine (1.7 mL, 10 mmol), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol) are added to the reaction mixture and stirred until a homogenous solution is formed. The reaction mixture is then pumped through the photoreactor at a flow rate to achieve a residence time of 18 min. The solvent was removed

[9] Characterization and preparation of substrate **9** is reported in M. Poornachandran and R. Raghunathan, *Tetrahedron* **2008**, *64*, 6461-6474.
[10] S.-H. Ueng, L. Fensterbank, E. Lacôte, M. Malacria and D. P. Curran, *Org. Biomol. Chem.* **2011**, *9*, 3415-3420.

from the crude mixture *in vacuo* and was dissolved in a minimal amount of EtOAc before being passed through a bed of silica gel and eluted with diethyl ether. The filtrate was concentrated and the crude product was purified by chromatography on silica gel (70:30, hexanes/EtOAc) to afford **12**[11] (0.12 g, 70%) as a colorless solid.

R_f (EtOAc/hexane 2:3): 0.37;

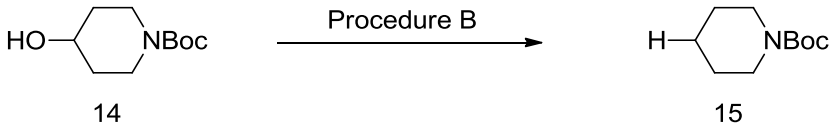
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.90 (d, *J* = 4.0 Hz, 1H), 4.53 (d, *J* = 4.0 Hz, 1H), 4.36 – 4.30 (m, 1H), 4.00 (d, *J* = 2.4 Hz, 1H), 1.65 − 1.57 (br s, 1H), 1.51 (s, 3H), 1.33−1.30 (m, 6H).



Butylbenzene: According to General Procedure B, **13**[3] (0.15 g, 1.0 mmol), triphenylphosphine (0.39 g, 1.5 mmol), imidazole (0.14 g, 2.0 mmol), and iodine (0.38 g, 1.5 mmol) in MeCN (5.0 mL) was stirred overnight. After full consumption of the alcohol *N*,*N*-Diisopropylethylamine (1.7 mL, 10 mmol), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol) are added and the reaction mixture is pumped through the photoreactor at a flow rate to achieve a residence time of 18 min which afforded **4**[4] (0.10 g, 78%) as a colorless oil after purification by chromatography on SiO_2 (petroleum ether).

R_f (hexanes): 0.54;

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 – 7.29 (m, 2H), 7.23 – 7.18 (m, 3H), 2.65 (t, *J* = 8.0 Hz, 2H), 1.68 – 1.60 (m, 2H), 1.44 – 1.36 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

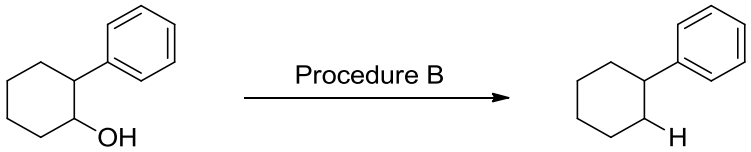


***tert*-Butyl piperidine-1-carboxylate**: According to General Procedure B, **14**[3] (0.20 g, 1.0 mmol), triphenylphosphine (0.39 g, 1.5 mmol), imidazole (0.14 g, 2.0 mmol), and iodine (0.38 g, 1.5 mmol) in MeCN (5.0 mL) was stirred overnight. After full consumption of the alcohol *N*,*N*-Diisopropylethylamine (1.7 mL, 10 mmol), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol) are added and the reaction mixture is pumped through the photoreactor at a flow rate to achieve a residence time of 18 min which afforded **15**[12] (0.14 g, 76%) as a colorless oil after purification by chromatography on SiO_2 (95:5, hexanes/EtOAc).

R_f (EtOAc/hexane 1:9): 0.32;

[11] H. S. Park, H. Y. Lee and Y. H. Kim, *Org. Lett.* **2005**, *7*, 3187-3190.
[12] G. Barker, P. O'Brien and K. R. Campos, *Org. Lett.* **2010**, *12*, 4176-4179.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.37 – 3.33 (m, 4H), 1.59 – 1.53 (m, 2H), 1.53 – 1.46 (m, 4H), 1.45 (s, 9H).

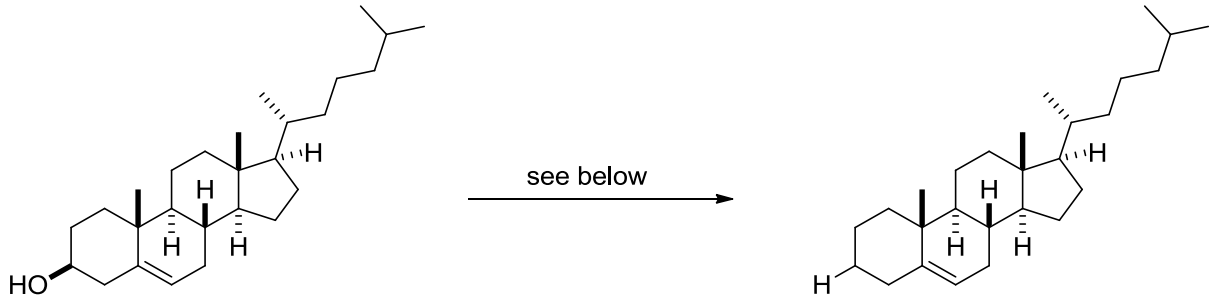


16 17

Cyclohexylbenzene: According to General Procedure B, **16**[13] (0.18 g, 1.0 mmol), triphenylphosphine (0.39 g, 1.5 mmol), imidazole (0.14 g, 2.0 mmol), and iodine (0.38 g, 1.5 mmol) in MeCN (5.0 mL) was stirred overnight. After full consumption of the alcohol *N*,*N*-Diisopropylethylamine (1.7 mL, 10 mmol), methanol (0.2 mL), and *fac*-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol) are added and the reaction mixture is pumped through the photoreactor at a flow rate to achieve a residence time of 18 min which afforded **17**[14] (0.11 g, 67%) as a colorless oil after purification by chromatography on SiO_2 (petroleum ether).

R_f(hexanes): 0.51;

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.29 (m, 2H), 7.26 – 7.18 (m, 3H), 2.57 – 2.48 (m, 1H), 1.96 – 1.82 (m, 4H), 1.82 – 1.75 (m, 1H), 1.51 – 1.37 (m, 4H), 1.34 – 1.23 (m, 1H).



18 19

Cholest-5-ene: A flame dried 10 mL round bottom flask with a rubber septum and magnetic stir bar was charged with the **18**[3] (0.39 g, 1.0 mmol), toluene (2.0 mL), MeCN (4.0 mL), triphenylphosphine (0.39 g, 1.5 mmol), and imidazole (0.14 g, 2.0 mmol). The reaction mixture is cooled in an ice bath to 0 ºC and iodine (0.38 g, 1.5 mmol) is added in portions. After 0.5 h, the reaction is removed from the ice bath and stirred at room temperature until the alcohol is fully consumed (as judged by TLC analysis). *N*,*N*-Diisopropylethylamine (2.6 mL, 15 mmol), methanol (0.5 mL), and *fac*-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol) are added to the reaction mixture and stirred until a homogenous solution is formed. The reaction mixture is then pumped through

[13] Characterization and preparation of substrate **16** is reported in R. Balamurugan and V. Gulda, *Org. Lett.* **2009**, *11*, 3116-3119.
[14] D. A. Powell and G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 7788-7789.

the photoreactor at a flow rate to achieve a residence time of 38 min. The solvent was removed from the crude mixture *in vacuo* and was dissolved in a minimal amount of EtOAc before being passed through a bed of silica gel and eluted with diethyl ether. The filtrate was concentrated and the crude product was purified by chromatography on silica gel (petroleum ether) to afford **19**[15] (0.27 g, 72%) as a colorless solid.

R_f (hexanes): 0.73;

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.27 (br dt, J = 5.2, 1.6 Hz, 1H), 2.29 – 2.18 (m, 1H), 2.03 – 1.91 (m, 3H), 1.87 – 1.78 (m, 2H), 1.76 – 1.69 (m, 1H), 1.00 (s, 3H), 1.62 – 0.92 (m, 23H), 0.92 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 1.6 Hz, 3H), 0.86 (d, J = 2.0 Hz, 3H), 0.68 (s, 3H).

[15] W. R. Bowman, S. L. Krintel and M. B. Schilling, *Org. Biomol. Chem.* **2004**, *2*, 585-592.