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Multidimensional Reaction Screening for Photochemical Transformations as a Tool for Discovering New Chemotypes

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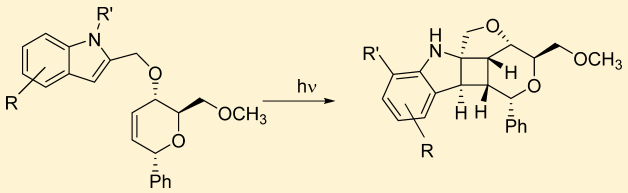
Supporting Information

ABSTRACT: We have developed an automated photochemical microfluidics platform that integrates a 1 kW high-pressure Hg vapor lamp and allows for analytical pulse flow or preparative continuous flow reactions. Herein, we will discuss the use of this platform toward the discovery of new chemotypes through multidimensional reaction screening. We will highlight the ability to discretely control wavelengths with optical filters, allowing for control of reaction outcomes.



INTRODUCTION

Photochemistry is among the most powerful complexity generating tools available to chemists.[1−3] Fundamentally groundbreaking reactions such as di-π-methane rearrangements[4] and arene olefin cycloadditions[5,6] have rarely been exceeded in their potential to construct molecular architecture, which would be unachievable in the absence of the reaction. However, traditional batch-mode photochemistry has a number of disadvantages that have hindered its implementation and development in traditional synthetic organic laboratories.[7,8] Typical batch reactor systems often suffer from poor UV penetration, long diffusion lengths, and poor temperature control. Furthermore, scale down and scale up of reactions is often difficult. While there have been a number of examples utilizing flow chemistry to increase the effectiveness of photochemistry,[9−16] we have focused our application on reaction screening and discovery of complex chemotypes. To this end, we have developed a microfluidic-based photochemistry platform capable of running pulse or continuous flow reactions, which is more suitable for high-throughput chemistry.[17]

In recent years, a number of exciting reaction discovery and development paradigms have been highlighted in the literature.[18−20] Examples such as multidimensional reaction screening developed in our laboratory,[22] McMillan's advent of enabled serendipity,[23] and Hartwig's use of mass spectrometry to analyze thousands of reaction mixtures[24] are a testament to the potential of screening reactions in parallel. Over the past several years, we have developed reaction screening techniques that take advantage of analytical reaction scale and microfluidics.[25,26] Herein, we report the expansion of our microfluidic platform to incorporate photo-optics for higher levels of wavelength control and its application to a multidimensional reaction screen.

RESULTS AND DISCUSSION

We have developed a photochemical microfluidic platform utilizing a 1 kW capillary mercury lamp and microreactor fabricated with Schott 8337, a UV transparent glass.[17] In an effort to advance the utility of photochemistry through expanded wavelength control, we designed a system that also incorporates photo-optical components (Figure 1). Specifically, a plano-concave lens focuses and collimates the beam, followed by a heat mirror that reflects IR wavelengths. Directly in front of the microfluidic device is positioned an exchangeable optical UV filter. A wide range of UV filters, both long-pass and band-pass, are commercially available.

One of the exciting applications of our photochemical platform is multidimensional reaction screening wherein multiple substrates are evaluated in photochemical reactions with varying wavelength, sensitizer, temperature, and solvent.[22] With this in mind, we selected a variety of substrates (14) that were part of the compound library collection in the CMLD-BU (Figure 2). The absorption spectrum of each compound indicated the presence of a chromophore that could potentially be excited under photochemical conditions. Along with four long-pass UV filters, we selected a series of sensitizers (matched with appropriate UV filters) with triplet energies ranging from 41 to 74 kcal/mol, as well as two electron-transfer sensitizers.

Two temperatures (room temperature and 60 °C) and two solvents (CH_3CN and THF) were also screened. Each reaction was performed on 100 μg scale at a concentration of 0.05 M. The sensitizers were utilized at 1.0 mol equiv. The residence time within the microfluidic device was 5 min (8 μL/min). The reactions were subsequently collected into a 96 well-plate and analyzed by UPLC/ELSD. Each reaction showing potential new products by UPLC analysis was scaled up using continuous flow and the same microfluidic device and photochemical

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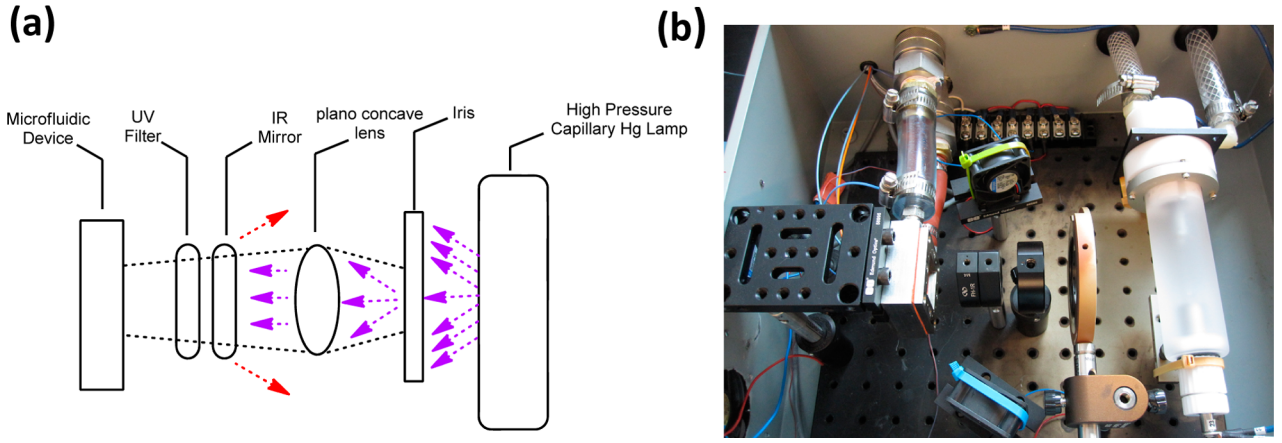


Figure 1. (a) Schematic diagram of photo-optical platform. (b) Photograph of the platform.

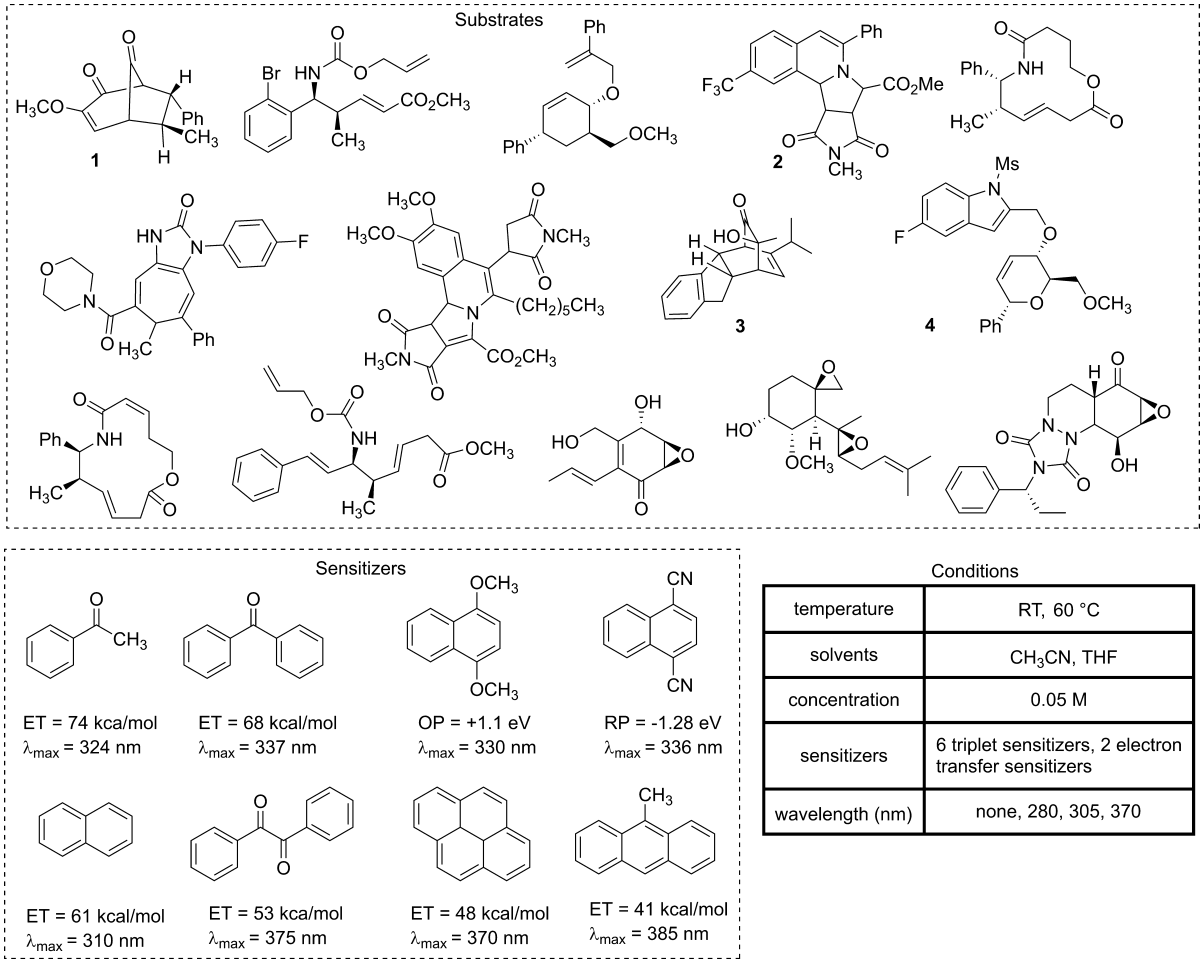
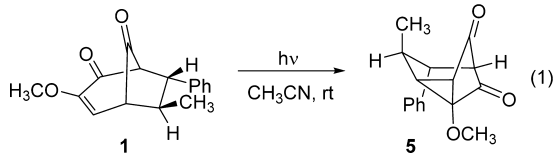


Figure 2. Multidimensional reaction screening parameters.

platform. The continuous flow reactions afforded appropriate amounts of material for structure elucidation. In total, we observed apparent reactivity with seven substrates. However, while we were able to reproduce reactions (as shown by the identical UPLC spectra), only four substrates afforded isolable products.[27]

The first reaction we observed in the screen involved bicyclo[3.2.1]octanoid scaffold **1**.[21] The reaction screen revealed multiple conditions leading to cyclopropane **5** via an oxa-di-π-methane rearrangement (eq 1).[28]



The reaction was facilitated by both direct excitation and triplet sensitization. Further optimization of the reaction revealed that reactions with a wavelength window of 340–

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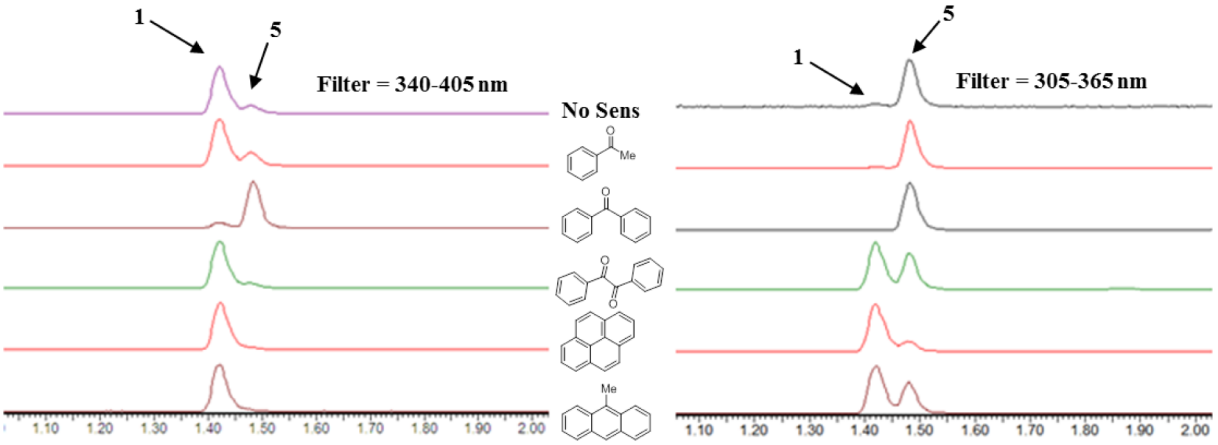
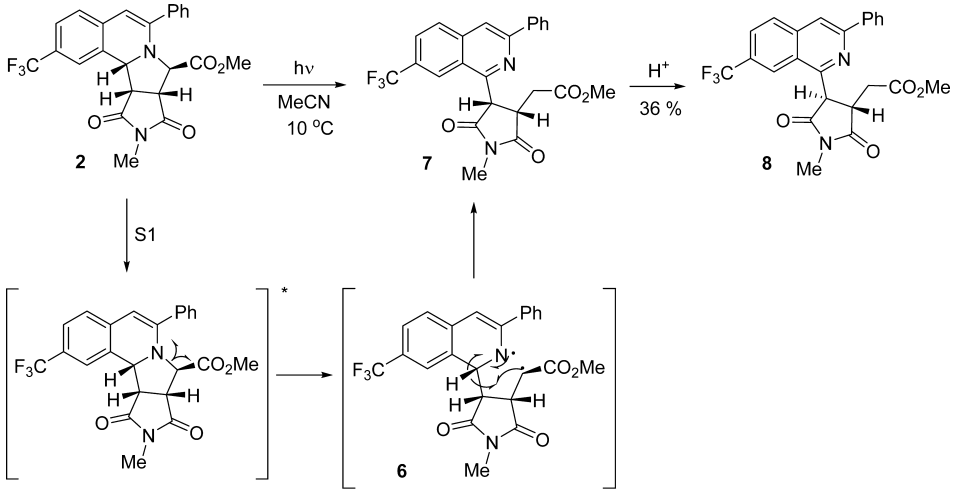


Figure 3. Reaction screen profile.

Scheme 1. Photofragmentation of 2



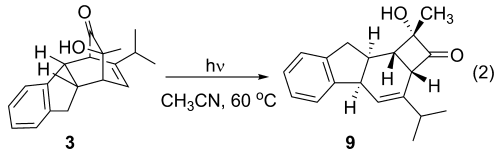
405 nm were not productive unless sensitized with benzophenone, which has a triplet energy of 68 kcal/mol and marginal absorption in the UV filter window (Figure 3).

However, when the reaction was carried out in absence of a sensitizer and a blue-shifted UV filter (305−365 nm), it proceeded to full conversion and was exceptionally clean. In this case, the reaction was fully quenched in the presence of sensitizers with triplet energies ranging from 41 to 53 kcal/mol. This reaction was further developed as described in a previous publication.[29]

The second reaction identified was a product derived from substrate **2** (Scheme 1). When heated in acetonitrile and irradiated at wavelengths >280 nm, **2** undergoes a homolytic C−N bond fragmentation leading to diradical intermediate **6** followed by a 1,4-hydride shift to form isoquinoline **7**, which rapidly isomerizes to diastereomer **8** during column chromatography.[30]

Although this is a simple reaction, it was notable that the original reaction conditions from the reaction screen resulted in incomplete conversion and significant decomposition. Utilizing the flexibility of the platform, we were able to optimize the transformation with a lower temperature and shorter residence time (10 °C and 3 min) and slightly longer UV wavelength (>295 nm).[27]

A third reaction was observed in the reaction screen utilizing tetracyclic scaffold **3**.[31] Elucidation of the purified material revealed cyclobutanone **9**, which is derived from a 1,3-acyl shift (eq 2).[32] The reaction screen profile revealed that utilizing a



(2)

UV filter >280 nm resulted in nearly complete conversion but significant decomposition by ^{1}H NMR (Figure 4a).[27] At wavelengths >305 nm, the reaction was significantly cleaner but had lower conversion. The reaction screen also revealed that the reaction was fully quenched by both acetophenone and benzophenone (triplet energies of 68 and 74 kcal/mol, respectively).

On the basis of data from the reaction screen, we carried out further optimization focused on wavelength variation. As summarized in Figure 4b, reactions focused on a chromophore at 255 nm resulted in no reaction. Significant loss of reactivity was observed at wavelengths >340 nm and no reactivity at wavelengths >370 nm. Notably, decomposition could be substantially avoided at wavelengths >320 nm.[27]

Utilizing the >300 nm UV filter, we evaluated longer residence times in order to drive the reaction to completion. However, this resulted in formation of a second product which

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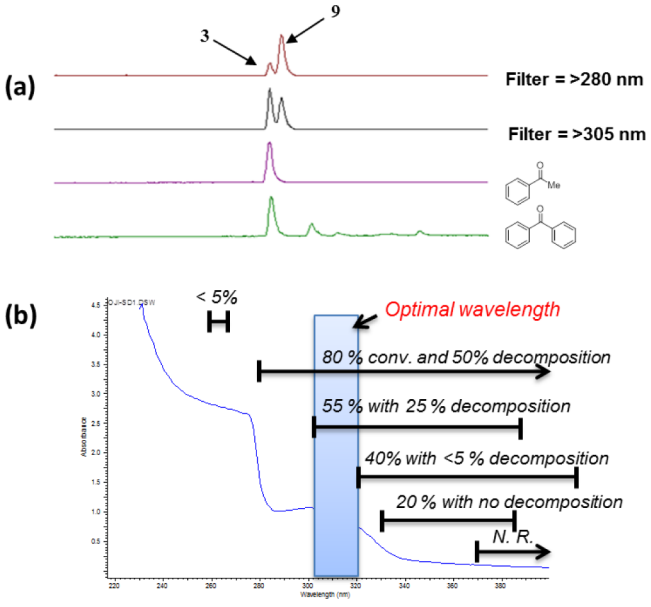
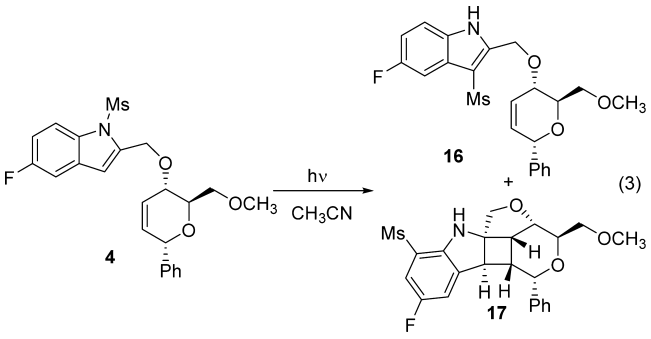


Figure 4. (a) Reaction screen profile. (b) Absorption spectrum of **3** with bars indicating that reactivity is wavelength dependent.

was determined to be tetrahydrofluorene **10** which was derived from a thermal decarbonylation.[33] Because cyclobutanone **9** is extremely unstable and difficult to purify, we took advantage of this transformation to afford a stable isolable product. Thus, microwave irradiation immediately following the photochemical transformation afforded ketone **10** as a 1:1 mixture of diastereomers in 27% yield (Scheme 2). We further evaluated the scope of this reaction as a one-pot, two-step procedure utilizing compounds **11**,[31] **13**,[34] and **15**.[34] Reaction of substrate **11** afforded ketone **12** (as a 1.5:1 mixture) in 43% yield, whereas cyclobutanone **14** could be isolated cleanly from **13** and did not decarbonylate under microwave radiations. Finally, ketol substrate **15** did not show any sign of reactivity under several photochemical conditions.

A fourth reaction was identified in the multidimensional reaction screen involving glycal-derived substrate **4** (eq 3).[35] Initial UPLC/ELSD analysis indicated a single major reaction product. However, upon scale-up and NMR analysis, it was apparent two products were present and, upon isolation and



elucidation, we determined that indole **16** and cyclobutane **17** were the major products. Indole **16** is derived from a simple photo-Fries[36−38] migration of the sulfonyl moiety to C3, while cyclobutane **17** may arise from an initial [2 + 2] cycloaddition followed by migration of the sulfonate to the indole C7.[39]

Close analysis of the reaction screening results and follow-up optimization suggested that the reaction pathways were wavelength dependent.[40−43] As illustrated in Figure 5, a UV

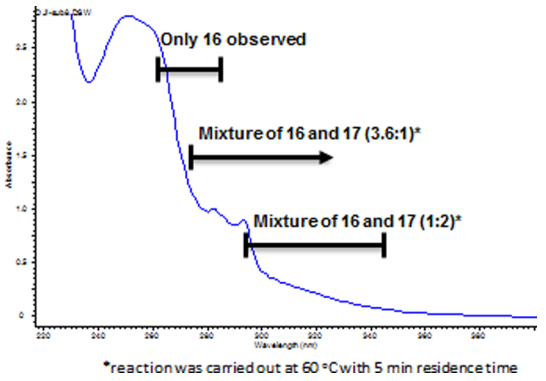
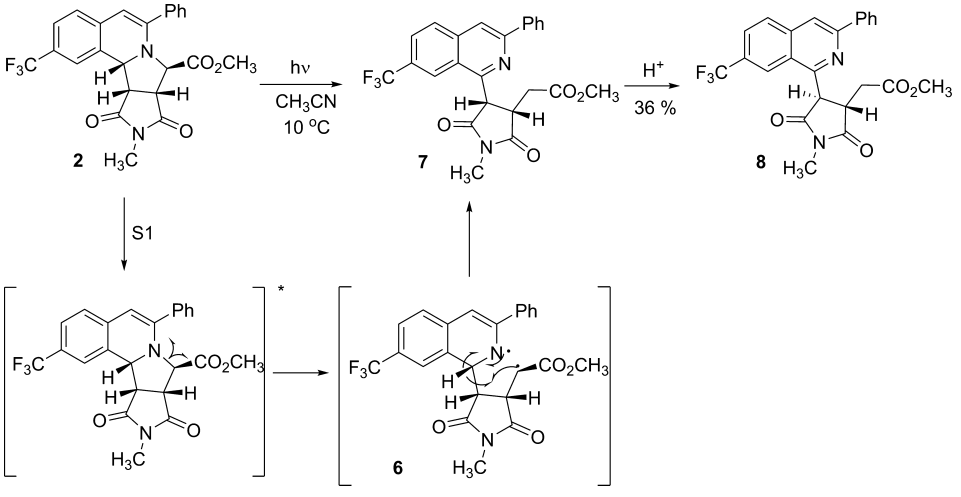


Figure 5. Absorption spectrum of **4** with bars indicating competing reactivity.

filter with a window of 260−300 nm resulted in the exclusive formation of photo-Fries product **16**. A slightly red-shifted UV filter (>275 nm) resulted in a mixture of **16** and **17** (favoring **16**), and a UV filter with a longer wavelength window of 290−340 nm favored formation of cyclobutane **17**.

Scheme 2. Reaction Scope of the 1,3-Acyl Shift Reaction



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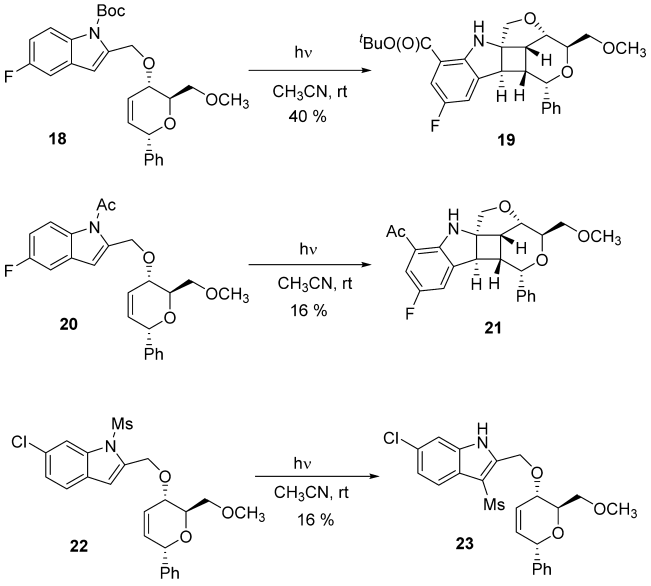
The reaction was further optimized by varying residence time and temperature. Thus, indole **16** could be isolated in 50% yield when the reaction was carried out at 60 °C with a 5 min residence time, and cyclobutane **17** could be isolated in 24% yield (no indole **16** was observed) when the reaction was carried out at room temperature with a 10 min residence time. Control experiments gave further support of divergent reaction pathways. Most notably, irradiation of **16** at various wavelengths and conditions did not result in formation of **17**.

It has been shown that indoles bearing *N*-acyl functionality can undergo [2 + 2] cycloadditions along with competing photo-Fries rearrangement.[36,38,39,44−50] However, if the Fries rearrangement occurs from a high energy singlet excited state, longer wavelengths may favor [2 + 2]-cycloaddition, which proceeds via a 1,4-diradical in the triplet excited state.[39] Indeed, irradiation of boc-protected **18** and acetate-protected **20** at 290−340 nm afforded only cyclobutanes **19** and **21** (Scheme 3). However, reactions at shorter wavelengths did not result in migration to C3 but only in decomposition. Indoles that were not acylated (N−H or N−CH_3) were unreactive under the photochemical reaction conditions. Changing the electronics of the indole ring with 5-chloro substitution (**22**) resulted in only the photo-Fries product (**23**) in low yield.

Scheme 3. Reaction Scope of the Competing Photo-Fries and [2 + 2] Reactions



In conclusion, we have successfully adapted a photochemical microfluidics platform for use in multidimensional reaction screening. By adding a photo-optics system, we are able to effectively control the wavelength of the reactions utilizing UV filters. Such control allows for introduction of irradiation wavelength as a screening variable as well as downstream optimization of reactions that are highly dependent on wavelength. Utilizing the platform in a multidimensional reaction screen, we were able to identify new chemotypes derived from photochemical transformations of complex scaffolds. Most notably, we identified complex chemotypes derived from an oxa-di-π-methane rearrangement of a bicyclo[3.2.1]octanoid scaffold, a 1,3-acyl shift of bicyclic ketol, and a wavelength-dependent photo-Fries/[2 + 2]-cycloaddition. The new scaffolds are currently being used to develop methodologies and access additional complex and unique molecules for use in high-throughput screening and medicinal chemistry programs.

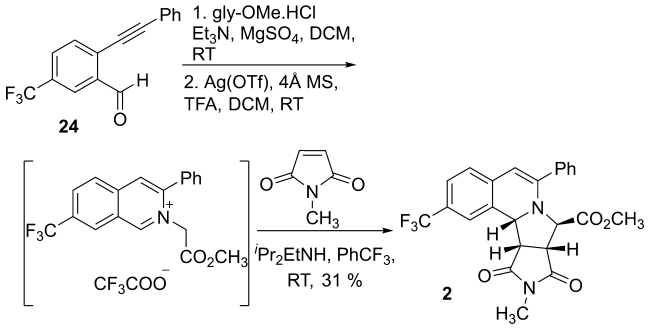
EXPERIMENTAL SECTION

General Experimental Information. All reactions were carried out in a flame-dried apparatus under an Ar atmosphere, unless otherwise noted. Solvents (methylene chloride, THF, and acetonitrile) were dried by passage through columns of neutral alumina. Diethylamine (Et_2NH) was degassed via the freeze−pump−thaw method immediately prior to its use. Flash chromatography was performed using silica gel (SiliaFlash P60, 230−400 mesh) purchased from Silicycle, or a flash chromatography system utilizing silica gel columns from Interchim. Analytical thin-layer chromatography was performed on 0.25 mm SiO_2 60 F-254 plates. TLC plates were analyzed using UV illumination and staining with basic $KMnO_4$ solution. NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature. Chemical shifts (δ) are reported in parts per million (ppm) relative to the solvent ($CDCl_3$ at 7.27 (77.0) ppm or C_6D_6 at 7.16 (128) ppm). Coupling constants (J) are reported in Hertz (Hz) with multiplicities denoted as br (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Infrared spectra values are reported in wavenumbers (cm^{-1}).

General Procedure for Analytical Reaction Screening. Stock solutions of substrate (0.1 M) and sensitizers (0.1 M) were prepared in CH_3CN or THF (anhydrous) while maintaining dry handling. The solutions were placed in a custom-designed 96-well aluminum holding block fitted with oven-dried glass sleeves. This was covered with an inert gas chamber and sealed. The block was attached to the microfluidics platform, and a slow, steady stream of argon was passed through the inert gas chamber. The system was fitted with the appropriate UV filter, and the parameters were set to achieve 5 min residence time at the chosen temperature. Individual reactions were collected into 96-well plates using optical detection. Each reaction was analyzed by UPLC/MS/ELSD (10−90% CH_3CN, 2 min). Reactions showing apparent reactivity were subsequently scaled up and isolated, using the system in continuous flow, for further characterization.

General Procedure for Continuous Flow (Scale-Up Reactions). The system was fitted with the appropriate optical filter and set at the appropriate temperature. A solution of substrate (1.0 equiv) in CH_3CN was loaded into a syringe and flowed through the device via a syringe pump set at the appropriate flow rate to obtain the desired residence time. The reactions were collected in a vial, concentrated in vacuo, and purified by flash chromatography.

Preparation of Isoquinoline 2.



Isoquinoline 2. Gly-OMe·HCl (0.084g, 0.666 mmol) was added to a solution of aldehyde **24**[51] (0.122 g, 0.444 mmol) in DCM (2.2 mL), followed by $MgSO_4$ (0.266 g, 2.22 mmol) and Et_3N (0.08 mL, 0.666 mmol). The reaction mixture was stirred at room temperature overnight. It was then concentrated in vacuo and dissolved in EtOAc (5 mL), filtered, and concentrated in vacuo. The resulting solid was dissolved in DCM (1.5 mL) and AgOTf (0.011 g, 0.044 mmol) was added, followed by molecular sieves (0.03 g) and TFA (0.04 mL, 0.489 mmol). The resulting mixture was stirred at room temperature for 1 h and filtered over a cotton plug. The filtrate was concentrated in vacuo to afford intermediate which was dissolved in $PhCF_3$ (4.4 mL) to be

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used directly in the next step. 1-Methyl-1*H*-pyrrole-2,5-dione (0.049 g, 0.444 mmol) was then added followed by Hunig's base (0.09 mL, 0.489 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated in vacuo. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded **2** as a white amorphous solid (0.063 g, 31%) over 3 steps: R_f = 0.58 (1:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 2956, 2924, 1708, 1435, 1329, 1118; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46−7.50 (m, 2H), 7.39−7.42 (m, 3H), 7.31 (bs, 1H), 7.04 (d, J = 7.6 Hz, 1H), 5.36 (s, 1H), 5.20 (d, J = 7.6 Hz, 1H), 4.91 (s, 1H), 3.86 (s, 3H), 3.74 (d, J = 7.6 Hz, 1H), 3.48 (t, J = 7.6 Hz, 1H), 2.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.3, 174.7, 170.4, 148.7, 136.1, 135.9, 132.1, 129.6, 129.2, 128.8, 127.8 (d, J_{C-F} = 32 Hz), 127.6, 126.0 (d, J_{C-F} = 4 Hz), 125.8, 125.0, 124.5 (d, J_{C-F} = 281 Hz), 124.3 (d, J_{C-F} = 4 Hz), 102.0, 67.1, 63.4, 53.6, 51.5, 46.5; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{24}H_{20}F_3N_2O_4$ 457.13785, found 457.1362.

(±)-Cyclopropane ***5***. (1) Prepared according to general continuous flow procedure using **1**[21] and benzophenone (1 equiv) in CH_3CN (0.05M) with a 340−405 nm band-pass filter and a 2 min residence time at room temperature. The reaction mixture was concentrated in vacuo to afford **5** (89%).[29] (2) Prepared according to general continuous flow procedure using **1** in CH_3CN (0.05M) with a 305−365 nm band-pass filter and a 2 min residence time at room temperature. The reaction mixture was concentrated in vacuo to afford **5** (70%).

Isoquinolines ***7*** *and* ***8***. Prepared according to the general continuous flow procedure using **2** (0.0143 g, 0.031 mmol) in CH_3CN (1.24 mL) with a 295 nm long pass filter and a 4 min residence time at 10 °C. The reaction mixture was concentrated in vacuo to afford **7**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.49 (s, 1H), 8.10 (s, 1H), 7.99−8.04 (m, 2H), 7.85−7.89 (m, 1H), 7.43−7.54 (m, 4H), 5.35 (d, J = 8.5 Hz, 1H), 3.91 (ddd, J = 11.0, 8.5, 4.0 Hz, 1H), 3.23 (s, 3H), 3.20 (s, 1H), 2.99 (dd, J = 18.0, 4.0 Hz, 1H), 2.25 (dd, J = 17.5, 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.4, 176.4, 171.8, 156.4, 151.7, 139.3, 137.8, 129.8, 129.7, 129.6, 129.5, 129.2, 129.2, 127.2, 126.9, 126.5 (d, J_{C-F} = 2 Hz), 125.8, 123.1(d, J_{C-F} = 4 Hz), 116.1, 51.9, 47.6, 42.3, 30.4, 25.7. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded **8** as an oil (0.0051 g, 36%): R_f = 0.71 (1:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 2958, 2924, 2852, 1703, 1635, 1436, 1329, 1294, 1122; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (s, 1H), 8.11 (m, 3H), 8.04 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 9.6 Hz, 1H), 7.44−7.54 (m, 4H), 5.01 (d, J = 5.6 Hz, 1H), 4.61 (q, J = 6.0 Hz, 1H), 3.64 (s, 3H), 3.14−3.20 (m, 1H), 3.12 (s, 1H), 2.87 (dd, J = 17.6, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.6, 175.4, 171.9, 155.2, 151.7, 139.4, 138.3, 129.7, 129.2, 128.8, 127.3, 126.5, 126.3, 124.1, 124.0, 116.5, 52.4, 50.1, 41.7, 33.2, 25.8; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{24}H_{20}F_3N_2O_4$ 457.1375, found 457.1373.

Tetrahydrofluorene ***10a*** *and* ***10b***. Prepared according to general continuous flow procedure using ketone **3**[30] (0.0014 g, 0.05 mmol) in CH_3CN (1 mL) with a 305−365 nm band-pass filter and a 10 min residence time at 60 °C. The reaction mixture was then transferred to a microwave flask and heated to 120 °C for 15 min in a CEM microwave. Purification by flash chromatography (15:1:1 hexanes/DCM/EtOAc) afforded a 1:1 mixture of **10a** and **10b**. **10a**: (0.002 g, 14%) as a yellow oil; R_f = 0.53 (15:1:1 hexanes/DCM/EtOAc); IR (thin film) ν (cm $^{-1}$) 2960, 2931, 1816, 1711, 1460, 1362, 755; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13−7.20 (m, 4H), 5.33 (d, J = 4.4 Hz, 1H), 3.87 (d, J = 4.4 Hz, 1H), 3.46 (q, J = 7.2 Hz, 1H), 3.07 (dd, J = 15.2, 8.0 Hz, 1H), 2.94−3.00 (m, 1H), 2.69 (dd, J = 15.2, 6.8 Hz, 1H), 2.38 (s, 3H), 2.34 (dd, J = 16.8, 7.2 Hz, 1H), 2.17−2.24 (m,1H), 2.10 (dd, J = 17.2, 6.0 Hz, 1H), 0.94 (d, J = 4.4 Hz, 3H), 0.91 (d, J = 5.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.4, 149.5, 147.9, 142.5, 126.8, 126.8, 125.0, 123.7, 113.3, 45.9, 42.2, 38.6, 37.7, 35.8, 29.3, 25.2, 21.3, 21.2; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{18}H_{23}O$ 255.1749, found 255.1773. **10b**: (0.0018 g, 13%) as a colorless oil; R_f = 0.5 (15:1: hexanes/DCM/EtOAc); IR (thin film) ν (cm $^{-1}$) 2960, 2927, 1709, 1665, 1459, 1353, 757; ^{1}H NMR (C_6D_6, 400 MHz) δ 7.04−7.12 (m, 4H), 5.29 (d, J = 4.0 Hz, 1H), 3.25 (q, J = 6.8 Hz, 1H), 2.82−2.92 (m, 2H), 2.68 (d, J = 4.4 Hz, 1H), 2.57 (dd, J = 14.4, 4.8 Hz, 1H), 2.19 (dd, J = 17.2, 7.6 Hz, 1H), 2.05 (sept, J = 7.2 Hz, 1H), 1.97 (dd, J = 16.8, 5.2 Hz, 1H), 1.78 (s, 3H), 0.87 (d, J = 6.4 Hz, 6H); ^{13}C NMR (C_6D_6, 100 MHz) δ 207.2, 148.1, 146.8, 143.1, 127.1, 127.1, 125.5, 123.8, 116.5, 54.0, 42.8, 39.1, 38.8, 35.9, 28.9, 28.2, 21.5, 21.4; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{18}H_{22}O$ 255.1749, found 255.1754.

Ketones ***12a*** *and* ***12b***. Prepared according to the general continuous flow procedure using ketone **11**[30] (0.0125 g, 0.053 mmol) in CH_3CN (1.1 mL) with a 305−365 nm band-pass filter and a 10 min residence time at 60 °C. The reaction mixture was then transferred to a microwave flask and heated to 120 °C for 15 min in a CEM microwave. Purification by flash chromatography (10:1 hexanes/EtOAc) afforded a 1:1 mixture of **12a** and **12b**. **12a**: (0.003 g, 26%) as a yellow oil; R_f = 0.52 (5:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 2961, 2872, 1707, 1665, 1063; ^{1}H NMR (C_6D_6, 400 MHz) δ 5.43 (d, J = 6.4 Hz, 1H), 4.32 (ddd, J = 7.8, 5.1, 3.1 Hz, 1H), 3.75 (dd, J = 6.4, 2.9 Hz, 1H), 3.68 (td, J = 8.4, 3.5 Hz, 1H), 3.31−3.37 (m, 1H), 2.58 (qd, J = 7.8, 3.1 Hz, 1H), 2.21 (dd, J = 16.8, 3.2 Hz, 1H), 2.00−2.08 (m, 2H), 1.92 (s, 3H), 1.57−1.64 (m, 1H), 1.26−1.26 (m, 1H), 0.86 (t, J = 6.8 Hz, 6H); ^{13}C NMR (C_6D_6, 100 MHz) δ 198.2, 150.2, 113.2, 77.5, 67.1, 46.2, 37.3, 36.0, 33.6, 30.7, 24.6, 21.2, 21.1; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{13}H_{21}O_2$ 209.1542, found 209.1547. **12b**: (0.002 g, 17%) as an oil: R_f = 0.47 (5:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 2962, 2873, 1708, 1673, 1355, 1057; ^{1}H NMR (CD_3CN, 500 MHz) δ 5.55 (d, J = 5.0 Hz, 1H), 4.07 (ddd, J = 6.6, 5.7, 3.8 Hz, 1H), 3.78 (td, J = 8.0, 4.7 Hz, 1H), 3.56 (dt, J = 8.5, 7.5 Hz, 1H), 3.05 (t, J = 4.5 Hz, 1H), 2.53 (quint., J = 7.0 Hz, 1H), 2.17−2.27 (m, 2H), 2.13 (s, 3H), 1.99−2.08 (m, 2H), 1.57 (dtd, J = 11.9, 7.7, 6.6 Hz, 1H), 0.99 (d, J = 3.0 Hz, 3H), 0.98 (d, J = 2.0 Hz, 3H); ^{13}C NMR (CD_3CN, 125 MHz) δ 209.5, 146.9, 116.5, 77.3, 67.1, 54.2, 38.4, 36.2, 33.6, 30.9, 29.1, 21.6, 21.6; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{13}H_{21}O_2$ 209.1542, found 209.1545.

Cyclobutanone ***14***. Prepared according to general continuous flow procedure using ketone **13**[33] (0.016 g, 0.055 mmol) in CH_3CN (2.3 mL), with a 290−340 nm band-pass filter and a 10 min residence time at 60 °C. Purification by flash chromatography (6:1 hexanes/EtOAc) afforded **14** (0.0044, 27%) as a colorless oil: R_f = 0.58 (3:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 3406, 2958, 2921, 1710, 1611, 1512, 1464, 1247, 1177; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.61−5.64 (m, 1H), 3.81 (s, 3H), 3.11−3.13 (m, 1H), 2.81−2.88 (m, 1H), 2.30 (sept., J = 6.4 Hz, 1H), 2.18−2.26 (m, 4H), 2.04−2.11 (m, 2H), 1.73 (ddd, J = 12.9, 11.3, 6.3 Hz, 1H), 1.06 (d, J = 4.4 Hz, 3H), 1.04 (d, J = 4.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.7, 158.2, 147.3, 138.8, 128.1, 115.5, 114.1, 114.1, 55.6, 49.3, 36.5, 35.7, 34.0, 31.2, 28.9, 21.9, 21.4; HRMS-ESI (m/z) [M-H_2O]$^+$ calcd for $C_{19}H_{22}O_2$ 283.1698, found 283.1706.

Indole ***16*** *and Cyclobutane* ***17***. Prepared according to the general continuous flow procedure using indole **4**[34] in CH_3CN (0.01M) and a 10 min residence time at room temperature. Purification using flash chromatography (2:1 to 1:2 hexanes/EtOAc) afforded a mixture of indole **16** and cyclobutane **17**. **16**: colorless oil; R_f = 0.33 (1:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 3286, 2925, 1723, 1488, 1454, 1433, 1305, 1282, 1135, 1111, 1087; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.07 (bs, 1H), 7.59 (dd, J = 9.2, 2.4 Hz, 1H), 7.36−7.46 (m, 5H), 7.28−7.29 (m, 1H), 7.02 (td, J = 9.0, 2.4 Hz, 1H), 6.19−6.26 (m, 2H), 5.31−5.34 (m, 2H), 5.16 (d, J = 15.9 Hz, 1H), 4.26 (dd, J = 7.2, 1.4 Hz, 1H), 3.80 (dt, J = 7.2, 4.8 Hz, 1H), 3.74 (dd, J = 10.5, 4. Hz, 1H), 3.62 (dd, J = 10.5, 5.0 Hz, 1H), 3.51 (s, 3H), 3.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.4 (d, J_{C-F} = 238 Hz), 143.5, 139.2, 131.1, 131.0, 128.8, 128.6, 128.5, 128.3, 126.4 (d, J_{C-F} = 11 Hz), 125.7, 112.9 (d, J_{C-F} = 10 Hz), 112.2 (d, J_{C-F} = 26 Hz), 109.9, 104.8 (d, J_{C-F} = 25 Hz), 74.5, 73.3, 73.1, 69.8, 63.0, 59.7, 45.5; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{23}H_{24}FNNaO_5S$ 468.1257, found 468.1269. **17**: colorless oil; R_f = 0.16 (1:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 3387, 2925, 2854, 1461, 1300, 1133; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33−7.44 (m, 6H), 6.97 (dd, J = 8.5, 3.0 Hz, 1H), 5.49 (ddd, J = 7.8, 2.6, 0.9 Hz, 1H), 5.01 (d, J = 4.0 Hz, 1H), 4.39 (t, J = 4.7 Hz, 1H), 4.15 (d, J = 7.9 Hz, 1H), 3.87 (d, J = 9.5 Hz, 1H), 3.69−3.73 (m, 3H), 3.49 (d, J = 9.2 Hz, 1H), 3.36 (s, 3H), 3.16−3.20 (m, 1H), 2.99 (s, 3H), 2.64 (ddd, J = 8.4, 6.9, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3 (d, J_{C-F} = 239 Hz), 147.5, 140.4, 137.5 (d, J_{C-F} = 8 Hz), 128.6, 127.6, 125.5, 118.0 (d, J_{C-F} = 25 Hz), 117.0 (d, J_{C-F} = 7

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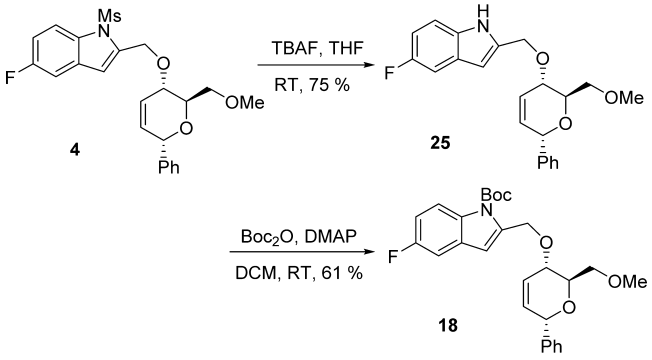
Hz), 111.4 (d, J_{C-F} = 26 Hz), 74.6, 74.3, 73.8, 72.5, 71.3, 70.0, 59.4, 44.3, 43.9, 43.0, 40.0; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{23}H_{25}FNO_5S$ 446.1437, found 446.1433.

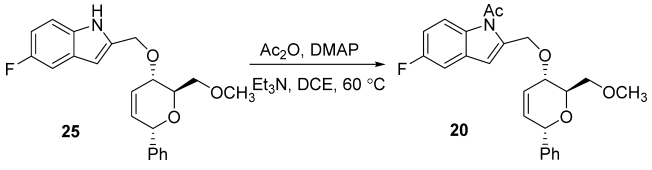
Preparation of Indole 18.



Indole ***25***. TBAF (0.54 mL, 0. 539 mmol, 1.0 M solution in THF) was added dropwise to a solution of indole **4** (0.12 g, 0.269 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature overnight. A saturated solution (5 mL) of NH_4Cl was then added. The mixture was extracted with EtOAc (3× 5 mL), washed with brine (2× 3 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded indole **25** (0.075 g, 75%) as a colorless oil: R_f = 0.65 (1:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 3316, 2922, 2853, 1486, 1452, 1318, 1169, 1078; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.69 (bs, 1H), 7.22−7.44 (m, 2H), 7.31−7.39 (m, 3H), 7.21−7.25 (m, 2H), 6.92 (td, J = 9.1, 2.6 Hz, 1H), 6.39 (d, J = 1.2 Hz, 1H), 6.11 (m, 1H), 5.30 (m, 1H), 4.85 (d, J = 12.8 Hz, 1H), 4.78 (d, J = 13.1 Hz, 1H), 4.22−4.24 (m, 1H), 3.69 (dt, J = 7.6, 3.8 Hz, 1H), 3.63 (dd, J = 10.4, 4.3 Hz, 1H), 3.51 (dd, J = 10.4, 3.4 Hz, 1H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.1(d, J_{C-F} = 232 Hz), 139.4, 137.5, 133.1, 130.2, 128.8 (d, J_{C-F} = 10 Hz), 128.7, 128.3, 126.8, 111.6 (d, J_{C-F} = 10 Hz), 110.5 (d, J_{C-F} = 26 Hz), 105.5 (d, J_{C-F} = 23 Hz), 101.6, 101.5, 74.4, 72.4, 70.9, 70.4, 64.5, 59.5; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{22}H_{23}FNO_3$ 368.1662, found 368.1658.

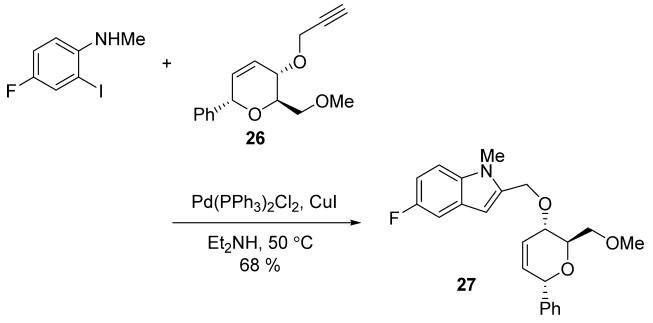
Indole ***18***. Boc_2O (0.036 g, 0.163 mmol) and DMAP (0.001 g, 0.008 mmol) were added to a solution of indole **25** (0.03 g, 0.082 mmol) in DCM (2 mL). The resulting mixture was stirred at room temperature for 30 min. H_2O (2 mL) was then added. The mixture was extracted with DCM (3× 5 mL), washed with brine (2× 3 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded indole **18** (0.023 g, 61%) as a yellow oil: R_f = 0.71 (1:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 2978, 2930, 1731, 1471, 1446, 1369, 1258, 1155, 1155, 1111; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (dd, J = 9.2, 4.6 Hz, 1H), 7.44−7.46 (m, 2H), 7.30−7.39 (m, 3H), 7.16 (dd, J = 8.5, 2.4 Hz, 1H), 6.99 (td, J = 9.0, 2.5 Hz, 1H), 6.63 (s, 1H), 6.10−6.19 (m, 2H), 5.31−5.34 (m, 1H), 5.05 (d, J = 14.3 Hz, 1H), 4.92 (d, J = 14.3 Hz, 1H), 4.26 (dd, J = 7.9, 1.5 Hz, 1H), 3.66−3.69 (m, 1H), 3.60 (dd, J = 10.4, 4.6 Hz, 1H), 3.52 (dd, J = 10.2, 2.6 Hz, 1H), 3.35−3.38 (m, 1H), 3.31 (s, 3H), 1.69 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.7, 158.3, 150.3, 149.2, 140.1, 139.7, 133.2, 130.2, 130.1, 129.9 128.7, 128.4, 128.2, 127.4, 116.7 (d, J_{C-F} = 9 Hz), 111.8 (d, J_{C-F} = 25 Hz), 108.5 (d, J_{C-F} = 4 Hz), 106.1 (d, J_{C-F} = 23 Hz), 84.7, 74.5, 72.0, 70.6, 70.5, 66.1, 59.5, 28.5; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{27}H_{30}FNNaO_5$ 490.2006, found 490.2004.

Preparation of Indole 20.



Indole ***20***. Ac_2O (0.04 mL, 0.441 mmol) and Et_3N (0.02 mL, 0.165 mmol) were added to a solution of indole **25** (0.0405 g, 0.11 mmol) and DMAP (0.003 g, 0.022 mmol) in DCE (0.5 mL). The resulting mixture was heated to 60 °C for 18 h. A saturated solution (1 mL) of NH_4Cl was then added. The mixture was extracted with EtOAc (3× 2 mL), washed with brine (2 × 3 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded indole **20** (0.03 g, 66%) as a yellow oil: R_f = 0.64 (1:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 2925, 2892, 1705, 1614, 1601, 1470, 1448, 1372, 1309, 1205, 1090; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (dd, J = 9.0, 4.3 Hz, 1H), 7.29−7.45 (m, 5H), 7.19 (dd, J = 8.6, 2.7 Hz, 1H), 7.04 (td, J = 9.1, 2.5 Hz, 1H), 6.69 (s, 1H), 6.10−6.13 (m, 2H), 5.31 (s, 1H), 5.03 (d, J = 14.5 Hz, 1H), 4.92 (d, J = 14.1 Hz, 1H), 4.27 (dd, J = 7.8, 2.0 Hz, 1H), 3.54−3.67 (m, 2H), 3.48 (dd, J = 10.2, 2.7 Hz, 1H), 3.29 (s, 3H), 2.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 159.3 (d, J_{C-F} = 223 Hz), 139.6, 133.6, 130.7, 130.2, 128.7, 128.3, 128.2, 126.9, 116.7(d, J_{C-F} = 11 Hz), 112.5 (d, J_{C-F} = 31 Hz), 111.2 (d, J_{C-F} = 4.5 Hz), 106.6 (d, J_{C-F} = 29 Hz), 74.5, 72.0, 70.6, 70.2, 65.9, 59.5, 26.8; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{24}H_{24}FNNaO_4$ 432.1587, found 432.1574.

Preparation of Indole 27.



Indole ***27***. 4-Fluoro-2-iodo-*N*-methylaniline (0.164 g, 0.652 mmol) was added dropwise to a solution of alkyne **26**[6] (0.252 g, 0.978 mmol), $Pd(PPh_3)_2Cl_2$ (0.023 g, 0.033 mmol), and CuI (0.006 g, 0.033 mmol) in Et_2NH (7 mL) at 50 °C. The resulting mixture was stirred at 50 °C for 2 h. The solution was then cooled to room temperature, and the solvent was evaporated. The resulting oil was dissolved in DCM and loaded on silica gel. Purification by flash chromatography (benzene then 4:1 hexanes/EtOAc) afforded **27** (0.169 g, 68%) as a brown oil: R_f = 0.71 (1:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 2916, 2849, 1515, 1488, 1451, 1315, 1265, 1166, 1076; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.45 (m, 6H), 7.02 (dd, J = 8.8, 2.9 Hz, 1H), 6.97 (td, J = 8.7, 2.9 Hz, 1H), 6.49 (dd, J = 9.0, 4.3 Hz, 1H), 6.12−6.22 (m, 2H), 5.32−5.34 (m, 1H), 4.55 (s, 2H), 4.33−4.36 (m, 1H), 3.63−3.68 (m, 2H), 3.52−3.56 (m, 1H), 3.35 (m, 3H), 2.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.2, 139.5, 130.4, 128.7, 128.6, 128.4, 128.4, 128.3, 128.2, 126.9, (d, J_{C-F} = 24 Hz), 117.4 (d, J_{C-F} = 22 Hz), 110.0 (d, J_{C-F} = 8 Hz), 91.9, 82.4, 74.4, 71.8, 70.5, 70.0, 59.6, 57.6, 31.0; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{23}H_{25}FNO_3$ 382.1818, found 382.1213.

Cyclobutane ***19***. Prepared according to general continuous flow procedure using indole **18** (0.015 g, 0.031 mmol) in CH_3CN (3.1 mL) with a 290−340 nm band-pass filter and a 10 min residence time at room temperature. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded indole **19** (0.0059 g, 40%) as a yellow oil: R_f = 0.71 (1:1 hexanes/EtOAc); IR (thin film) ν (cm $^{-1}$) 3429, 2971, 2930, 2881, 1707, 1479, 1452, 1369, 1260, 1140, 1089; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (bs, 1H), 7.38−7.43 (m, 4H), 7.33−7.37 (m, 1H), 6.71 (t, J = 7.8 Hz, 1H), 5.29 (dd, J = 8.1, 2.6 Hz, 1H), 5.00 (d, J = 4.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 1H), 4.06−4.15 (m, 2H), 3.70−3.75 (m, 3H), 3.60 (d, J = 7.0 Hz, 1H), 3.34−3.39 (m, 4H), 2.58 (td, J = 7.7, 4.1 Hz, 1H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.0, 159.9, 158.1, 151.9, 140.3, 128.6, 127.6, 125.6, 116.1 (d, J_{C-F} = 8 Hz), 113.7 (d, J_{C-F} = 22 Hz), 111.2 (d, J_{C-F} = 30 Hz), 81.5, 74.2, 73.6, 73.2, 72.4, 69.9, 59.4, 43.7, 39.9, 38.6, 28.8; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{27}H_{30}FNNaO_5$ 490.2006, found 490.2013.

Cyclobutane ***21***. Prepared according to the general continuous flow procedure using indole **20** (0.016 g, 0.038 mmol) in CH_3CN (0.01M, 3.8 mL) with a 290−340 nm band-pass filter and a 10 min residence time at room temperature. Purification using flash chromatography

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(2:1:1 hexanes/EtOAc/DCM) afforded indole **21** (0.0023 g, 16%) as a yellow oil: R_f = 0.35 (2:1:1 hexanes/EtOAc/DCM); IR (thin film) ν (cm^{-1}) 3403, 2923, 2853, 1737, 1462, 1127; ^1H NMR (C_6D_6, 500 MHz) δ 7.00−7.38 (m, 6H), 6.79 (dd, J = 10.1, 2.6 Hz, 1H), 5.72 (dd, J = 8.1, 2.4 Hz, 1H), 4.84 (d, J = 3.9 Hz, 1H), 4.40 (t, J = 4.6 Hz, 1H), 3.78 (d, J = 8.1 Hz, 1H), 3.67 (d, J = 6.8 Hz, 1H), 3.48 (d, J = 9.0 Hz, 1H), 3.23 (dd, J = 10.5, 4.4 Hz, 1H), 3.13 (dd, J = 10.5, 5.4 Hz, 1H), 2.89−2.90 (m, 4H), 2.63 (t, J = 7.5 Hz, 1H), 2.27 (td, J = 7.6, 3.9 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.5, 155.1, 153.2, 151.0, 140.6, 136.4 (d, J_{C-F} = 8 Hz), 128.6, 127.5, 125.6, 117.6 (d, J_{C-F} = 25 Hz), 114.3 (d, J_{C-F} = 6 Hz), 112.2 (d, J_{C-F} = 23 Hz), 105.3, 74.3, 73.8, 73.3, 72.7, 71.1, 70.0, 59.4, 44.1, 43.4, 39.7, 29.9; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{24}H_{25}FNO_4$ 410.1768, found 410.1762.

Indole ***23***. Prepared according to the general continuous flow procedure using indole **22**[34] (0.014 g, 0.03 mmol) in CH_3CN (3 mL) with a 305 nm long-pass filter and a 10 min residence time at room temperature. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded indole **23** (0.023 g, 16%) as a yellow oil: R_f = 0.38 (1:1 hexanes/EtOAc); IR (thin film) ν (cm^{-1}) 3335, 2925, 1722, 1681, 1449, 1420, 1302, 1146, 1125; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.13 (bs, 1H), 7.83 (d, J = 8.5 Hz, 3H), 7.36−7.46 (m, 6H), 7.34 (dd, J = 1.8, 0.6 Hz, 1H), 6.19−6.25 (m, 2H), 5.31−5.36 (m, 2H), 5.15 (d, J = 15.9 Hz, 1H), 4.24−4.26 (m, 1H), 3.77 (d, J = 7.9 Hz, 1H), 3.58 (d, J = 7.0 Hz, 1H), 3.49 (d, J = 7.0 Hz, 1H), 3.25 (dd, J = 10.5, 4.1 Hz, 1H), 3.13 (dd, J = 10.5, 5.0 Hz, 1H), 2.92 (s, 3H), 2.50 (t, J = 7.8 Hz, 1H), 2.30 (s, 3H), 2.10 (ddd, J = 8.5, 6.6, 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.8, 139.1, 131.0, 129.7, 128.8, 128.5, 128.3, 125.7, 124.2, 123.4, 120.3, 111.9, 110.0, 74.5, 73.4, 73.2, 69.7, 62.9, 59.8, 53.7, 45.7, 31.2; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{23}H_{24}ClNNaO_5S$ 484.0961, found 484.0965.

■ ASSOCIATED CONTENT

Supporting Information

Reaction screen UPLC profiles and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052.
(2) Bach, T.; Hehn, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1000.
(3) Hoffmann, N. *Photochem. Photobiol. Sci.* **2012**, *11*, 1613.
(4) Rao, V. J.; Griesbeck, A. G. *Mol. Supramol. Photochem.* **2005**, *12*, 161.
(5) Hoffmann, N. *Synthesis* **2004**, *4*, 481.
(6) Streit, U.; Bochet, C. G. *Beilstein J. Org. Chem.* **2011**, *7*, 525.
(7) Braun, A. M.; Maurette, M.-T.; Oliveros, E. *Photochemical Technology*; Wiley: Chichester, West Sussex, England, 1991.
(8) Roberts, R.; Ouellette, R. P.; Muradaz, M. M.; Cozzens, R. F.; Cheremisinoff, P. N. *Applications of Photochemistry*; Technomic Publishing Co., Inc.: Lancaster, PA, 1984.
(9) Hook, B. D. A.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M. B.; Booker-Milburn, K. I. *J. Org. Chem.* **2005**, *70*, 7558.
(10) Sakeda, K.; Wakabayashi, K.; Matsushita, Y.; Ichimura, T.; Suzuki, T.; Wada, T.; Inoue, Y. *J. Photochem. Photobiol., A* **2007**, *192*, 166.
(11) Coyle, E. E.; Oelgemöller, M. *Photochem. Photobiol. Sci.* **2008**, *7*, 1313−1322.
(12) Matsushita, Y.; Ichimura, T.; Ohba, N.; Kumada, S.; Sakeda, K.; Suzuki, T.; Tanibata, H.; Murata, T. *Pure Appl. Chem.* **2007**, *79*, 1959.
(13) Oelgmöller, M.; Shvydkiv, O. *Molecules* **2011**, *16*, 7522.
(14) Oelgmöller, M. *Chem. Eng. Technol.* **2012**, *35*, 1144.
(15) Yavoraskyy, A.; Shvydkvi, O.; Hoffmann, N.; Nolan, K.; Oelgmöller, M. *Org. Lett.* **2012**, *14*, 4342.
(16) Hang, Y.; Blackman, M. L.; Leduc, A. B.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2013**, *52*, 4251.
(17) Pimparkar, K.; Yen, B.; Goodell, J. R.; Martin, V. I.; Lee, W.-H.; Porco, J. A., Jr.; Beeler, A. B.; Jensen, K. J. *J. Flow Chem.* **2011**, *2*, 53.
(18) McDougal, N. T.; Virgil, S. C.; Stoltz, B. M. *Synlett* **2010**, *11*, 1712−1716.
(19) Kanan, M. W.; Rozenman, M. M.; Sakurai, K.; Snyder, T. M.; Liu, D. R. *Nature* **2004**, *431*, 545−549.
(20) Lichtor, P. A.; Miller, S. J. *ACS Comb. Sci.* **2011**, *13*, 321−326.
(21) Montavon, T. J.; Li, J.; Cabrera-Pardo, J. R.; Mrksich, M.; Kozmin, S. A. *Nat. Chem.* **2012**, *4*, 45−51.
(22) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413.
(23) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114.
(24) Robbins, D. W.; Hartwig, J. F. *Science* **2011**, *333*, 1423.25.
(25) Goodell, J. R.; McMullen, J. P.; Zaborenko, N.; Maloney, J. R.; Ho, C.; Jensen, K. F.; Porco, J. A., Jr.; Beeler, A. B. *J. Org. Chem.* **2009**, *74*, 6169.
(26) Goodell, J. R.; Leng, B.; Snyder, T. K.; Beeler, A. B.; Porco, J. A., Jr. *Synthesis* **2010**, *13*, 2254.
(27) See Supporting Information for complete details.
(28) Armesto, D.; Ortiz, M. J.; Agarrabeitia, A. R. *Mol. Supramol. Photochem.* **2005**, *12*, 189.
(29) Goodell, J. R.; Poole, J. L.; Beeler, A. B.; Aubé, J.; Porco, J. A., Jr. *J. Org. Chem.* **2011**, *76*, 9792.
(30) Izzo, P. T.; Kende, A. S. *Tetrahedron Lett.* **1966**, *46*, 5731.
(31) Dong, S.; Hamel, E.; Bai, R.; Covell, D. G.; Beutler, J. A.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2009**, *48*, 1494.
(32) Singh, V. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press LLC: Boca Raton, FL, 2004; vol. *79*, p 1.
(33) Arjona, O.; Medel, R.; Plumet, J.; Rojas, J. K. *Rev. Soc. Quim. Mex.* **2003**, *47*, 227.
(34) Dong, S.; Cahill, K. J.; Kang, M.-I.; Colburn, N. H.; Henrich, C. J.; Wilson, J. A.; Beutler, J. A.; Johnson, R. P.; Porco, J. A., Jr. *J. Org. Chem.* **2011**, *76*, 8944.
(35) Medeiros, M. R.; Schaus, S. E.; Porco, J. A., Jr. *Org. Lett.* **2011**, *13*, 4012.
(36) Wheedon, A. The Photochemistry of Indoles. In *Advances in Photochemistry*; Neckers, D. C., Volman, D. H., Von Bünau, G., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2007; vol. *22*, p 229.
(37) Somei, M.; Natsume, M. *Tetrahedron Lett.* **1973**, *27*, 2451.
(38) Chakrabarti, A.; Biswas, G. K.; Chakraborty, D. P. *Tetrahedron* **1989**, *16*, 5059.
(39) It is unclear which event occurs first and mechanism studies to date have been inconclusive.
(40) Dauban, W. G.; Hecht, S. *J. Org. Chem.* **1998**, *63*, 6102.
(41) Bogdanova, A.; Popik, V. V. *J. Am. Chem. Soc.* **2003**, *125*, 14153.
(42) Bochet, C. G. *Synlett* **2004**, *13*, 2268.
(43) Inui, H.; Murata, S. *J. Am. Chem. Soc.* **2005**, *127*, 2628.
(44) Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 405.
(45) Hastings, D. J.; Weedon, A. C. *Can. J. Chem.* **1991**, *69*, 1171.
(46) Disanayaka, B. W.; Weedon, A. C. *Can. J. Chem.* **1990**, *68*, 1685.
(47) Oldroyd, D. L.; Weedon, A. C. *J. Photochem. Photobiol., A* **1991**, *57*, 207.
(48) Weedon, A. C.; Zhang, B. *Synthesis* **1992**, 95.
(49) Oldroyd, D. L.; Weedon, A. C. *J. Org. Chem.* **1994**, *59*, 1333.

(50) Andrew, D.; Hastings, D. J.; Oldroyd, D. L.; Rudolph, A.; Weedon, A. C.; Wong, D. F.; Zhang, B. *Pure Appl. Chem.* **1992**, *64*, 1327.
(51) Patil, N. T.; Mutyala, A. K.; Lakshmi, P. G. V. V; Raju, P. V. K.; Sridhar, B. *Eur. J. Org. Chem.* **2010**, 1999−2007.