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Dehydrogenative Transformations of Imines Using a Heterogeneous Photocatalyst

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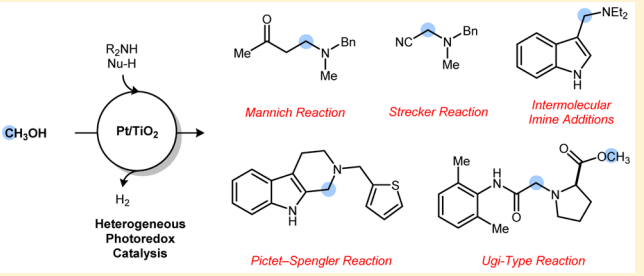
Supporting Information

ABSTRACT: Heterogeneous semiconductors are underexploited as photoredox catalysts in organic synthesis relative to their homogeneous, molecular counterparts. Here, we report the use of metal/TiO_2 particles as catalysts for light-induced dehydrogenative imine transformations. The highly oxophilic nature of the TiO_2 surface promotes the selective binding and dehydrogenation of alcohols in the presence of other oxidizable and Lewis basic functional groups. This feature enables the clean photogeneration of aldehyde equivalents that can be utilized in multicomponent couplings.



Photoredox catalysis has emerged as a powerful platform for introducing kinetically facile single-electron pathways into a broad range of organic transformations.[1] The most common photosensitizers being used in current methods are molecular transition-metal complexes or organic dyes that act as single-electron donors or acceptors in their excited state. Because these photosensitizers generally function by outersphere electron transfer,[2] designing a viable catalytic process requires carefully balancing the redox potentials of each starting material, reaction intermediate, and product. In comparison to their molecular counterparts, heterogeneous semiconductors, extensively studied in energy catalysis,[3] have seen significantly less use in organic synthesis. In principle, the ability to exploit specific interactions between surface sites and organic substrates may provide complementary tools to build selectivity into photoredox reactions.

TiO_2 is a large band gap semiconducting material. Upon excitation with UV light, TiO_2 is capable of delivering oxidizing equivalents at 3.0 V vs NHE, a potential that is sufficiently oxidizing to generate hydroxyl radicals from water.[4] Because of its potent oxidizing power, TiO_2 has garnered interest as a photocatalyst for water or air purification, where the complete degradation of all organic contaminants to CO_2 is desired.[5] Recently, the oxophilic nature of the TiO_2 surface has been exploited to bind alcohol substrates and enable their mild dehydrogenation under less energetic visible/near-UV light illumination.[6] When coupled with an efficient proton reduction catalyst, such as Pt metal, the reaction can be conducted under strictly anaerobic conditions, generating H_2 as the sole stoichiometric byproduct.[7] This approach presents an attractive alternative to dark transition-metal catalyzed alcohol dehydrogenation methods, which often require high temperatures and/or the use of stoichiometric oxidants.[8,9]

Metal/TiO_2-mediated alcohol dehydrogenations have been predominantly studied from the perspective of renewable H_2 generation;[3,7] however, there is significant underexplored potential for their application in more complex organic transformations.[10] Realizing this goal would require establishing the compatibility of these large band gap semiconductors with redox-sensitive functional groups. Here, we report our initial efforts to explore these concepts in a series of multicomponent imine transformations (Figure 1). Light-induced, dehydrogenative variants of the Pictet–Spengler cyclization, the Strecker reaction, the Mannich reaction, and Ugi-type couplings are described.

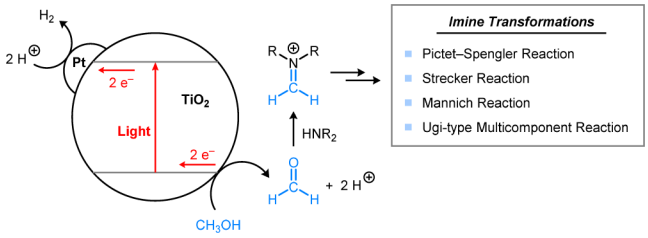


Figure 1. A photocatalytic scheme for dehydrogenative imine transformations using a Pt/TiO_2 catalyst.

We initiated our studies by preparing known platinized TiO_2 materials by photodepositing H_2PtCl_6 (0.5 wt % Pt) onto P25 TiO_2 using *i*-PrOH as a sacrificial reductant.[11] This relatively straightforward catalyst preparation avoids the need for high-temperature calcination, which is a commonly employed alternative procedure described in the literature.[12] The Pictet–Spengler cyclization of tryptamine substrate **1** served as an appropriate venue to test the compatibility of photocatalytic alcohol dehydrogenation with oxidizable functional groups, including a secondary amine and an electron-rich

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heterocycle. It is noteworthy in this context that **1** undergoes electrochemical degradation at 1.2 V vs NHE (see Supporting Information for CV data), which is significantly less positive than the valence band potential of TiO_2. Consequently, when solutions of **1** in MeOH were combined with Pt/TiO_2 and irradiated under a high-energy, 254 nm light source, rapid decomposition was observed, forming an intractable mixture of products (Figure 2a).

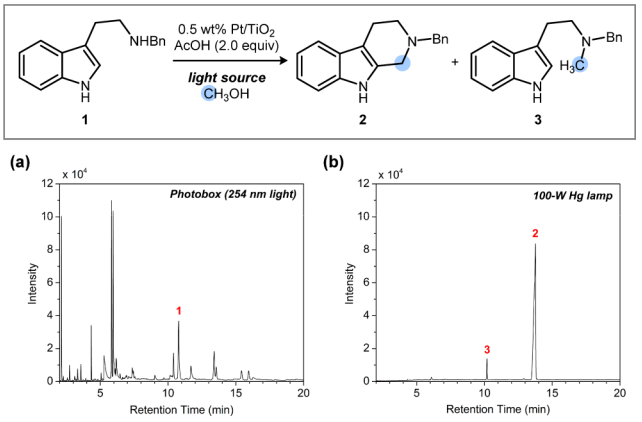


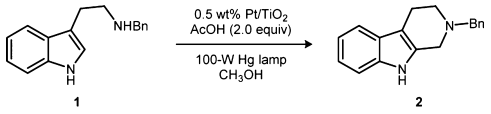
Figure 2. Gas chromatography data for photocatalytic dehydrogenative Pictet–Spengler cyclizations conducted using (a) a 254 nm light source in a photobox or (b) a 100-W Hg lamp.

Aliphatic alcohols, such as MeOH, coordinate to the Lewis acidic TiO_2 surface, creating higher energy donor levels that can be excited using less energetic photons. Accordingly, when the same reaction shown in Figure 2 is illuminated with a 100-W Hg lamp (Figure 2b), MeOH dehydrogenation proceeds cleanly to form formaldehyde equivalents that are incorporated into the tetrahydro-β-carboline product **2** (90% isolated yield). The *N*-methylated product **3** is observed as a minor side product (6% yield). The formation of H_2 as a stoichiometric byproduct was confirmed by mass analysis of the headspace gas. Additionally, when CD_3OD was used in place of CH_3OH, deuterium was incorporated into product **2**, and D_2 gas was evolved.

Key control experiments conducted during our optimization studies are collected in Table 1. No conversion of starting material is observed when the reaction is conducted in the dark (entry 2), when a 500 nm cutoff filter is applied to the light source (entry 3), or when the TiO_2 photocatalyst is omitted (entries 4 or 5). The use of quartz over standard borosilicate glassware resulted in a modest decrease in the yield of **2**, consistent with a beneficial effect associated with filtering out <300 nm light (entry 6). Under aerobic conditions, significant product formation is observed but the yield is diminished due to competing degradation processes (entry 7). The presence of AcOH positively impacts yield (entry 8), and the use of a stronger acid, such as HCl, causes a precipitous decrease in the formation of **2** (entry 9). Bare TiO_2 without Pt deposition is a significantly less effective catalyst (entry 10). Finally, attempts to platinize TiO_2 *in situ* under the standard reaction conditions led to a decrease in the yield of the desired product (entry 11).

With a set of optimized conditions in hand, we next evaluated modifications to the catalyst by photodepositing other noble metals onto TiO_2. The metal dopants shown in Table 2 were selected based on their prior use in related alcohol oxidation[6a,13] and water splitting reactions.[14] TiO_2 deposited

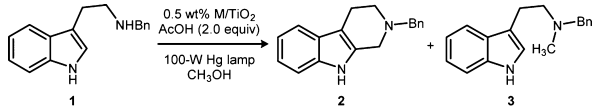
Table 1. Reaction Optimization Studies and Control Experiments



entry	modifications from standard conditions	conversion (%)	yield **2** (%)
1	none[a]	>99	90
2	in the dark	0	0
3	100-W Hg lamp with a 500 nm cutoff filter	0	0
4	no Pt/TiO_2	0	0
5	H_2PtCl_6 instead of Pt/TiO_2	0	0
6	quartz instead of borosilicate glassware	>99	74
7	under air instead of an N_2 atmosphere	>99	52
8	no AcOH	92	44
9	HCl instead of AcOH	70	3
10	nonplatinized TiO_2	94	39
11	H_2PtCl_6 + TiO_2 (*in situ* platinization)	>99	66

[a]Reactions were conducted on a 0.2 mmol scale of **1** using AcOH (2.0 equiv) and 0.5 wt % Pt/TiO_2 (5.0 mg) in MeOH (3 mL). Reactions were run in borosilicate glassware under an N_2 atmosphere for 15 h at room temperature under a 100-W Hg lamp.

Table 2. Screen of Metal Dopants[a]



entry	metal dopant	conversion (%)	yield **2** (%)	yield **3** (%)
1	Pt	>99	90	6
2	Au	38	33	1
3	Ag	64	51	4
4	Pd	>99	48	45
5	Pd[b]	>99	56	40

[a]Reactions were conducted under the standard conditions shown in Table 1. [b]Using CD_3OD instead of CH_3OH.

with Ag or Au nanoparticles (entries 2 and 3) proved to be selective catalysts but afforded slower rates than the Pt analogue. Interestingly, the Pd/TiO_2 catalyst effected the rapid consumption of starting material but formed increased amounts of the *N*-methylated side product **3** (entry 4).[15] We reasoned that the deposited Pd nanoparticles may be more effective at hydrogenating the putative iminium ion intermediate prior to cyclization. Using CD_3OD, the *N*-Me group is fully deuterated, confirming the source of the H atom equivalents. Additionally, a decrease in the fraction of the *N*-Me product **3** is observed with CD_3OD, suggesting that there is a significant primary KIE associated with the selectivity-determining step (entry 5).

The substrate scope (Figure 3) for the dehydrogenative Pictet–Spengler cyclization was explored under the optimized conditions shown in Table 1. A variety of common functional groups were found to be tolerated, including halides, alkenes, ethers, alcohols, esters, and trifluoromethyl substituents. Additionally, both electron-deficient (**7** and **9**) and electron-rich (**8**) ring systems were unaffected by the photocatalyst. Of particular note, *N*-PMB groups (**5**), which are typically deprotected under oxidative conditions, remained intact during the reaction. Due to the large excess of MeOH, which is being

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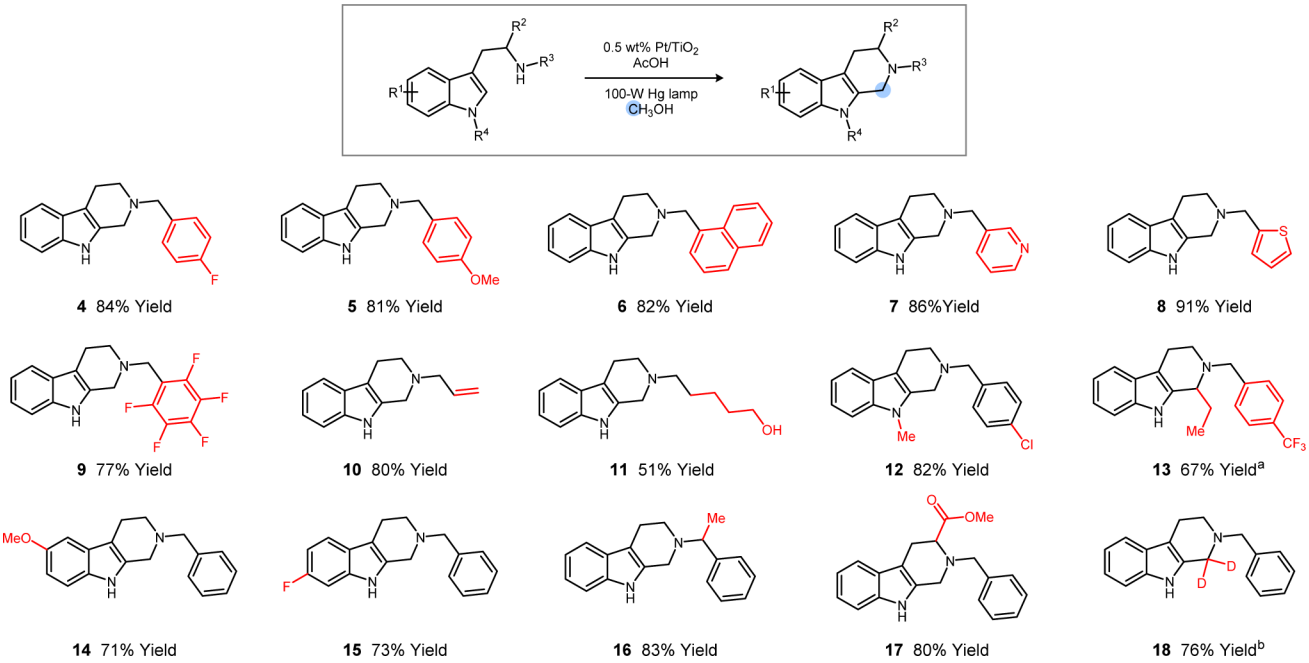

Figure 3. Substrate scope for the photocatalytic dehydrogenative Pictet–Spengler cyclization. Variations from the model substrate (**1**) are highlighted in red. [a] Using *n*-PrOH in the place of CH_3OH. [b] Using CD_3OD in the place of CH_3OH.

used as a solvent in these reactions, unprotected alcohols incorporated into the substrate (**11**) do not suffer from competing oxidation under the photocatalytic conditions. CD_3OD provided a commercially available source of D_2CO equivalents that afford access to deuterium labeled products (**18**) in high yield. Finally, the use of other aliphatic alcohols, such as *n*-PrOH, provided good yields of the cyclized product (**13**).

The photocatalytic dehydrogenation was extended to other transformations involving imine intermediates (Figure 4). For example, the intermolecular aminomethylation of unprotected indole proceeds with the expected C3-selectivity to form **19** in 68% yield. This reaction also tolerates the use of tetrahydroisoquinoline, which is susceptible to dehydrogenation under a closely related set of photocatalytic conditions.[10c] Strecker reactions can be carried out using TMSCN as a cyanide source. Three-component Mannich reactions employing an excess of acetone yield the *β*-aminoketone product **23** in 57% yield. Finally, the combination of a secondary amine and an isonitrile generates an interrupted Ugi-type product (**24**) in 82% yield.[16] Notably, when unprotected proline was used as a coupling partner, the reaction was accompanied by methyl ester formation (**25**). A proposed mechanism is described in the Supporting Information and involves capture of the putative nitrilium intermediate by the pendant carboxylic acid.

In summary, metal/TiO_2 catalysts under visible/near-UV light irradiation promote the mild dehydrogenation of simple aliphatic alcohols. This process is compatible with a broad range of organic functional groups such that the aldehyde equivalents being generated can be productively utilized in multicomponent reactions involving imine intermediates. Collectively, these studies demonstrate the utility of oxophilic semiconducting materials in promoting photoredox reactions that are not strictly governed by outersphere electron transfer processes.

EXPERIMENTAL SECTION

General Information. All reactions were carried out using standard Schlenk techniques under an atmosphere of N_2. Reagents and solvents were purchased from commercial sources and used without further purification unless otherwise noted. TiO_2 (P-25, Aeroxide) was obtained from Sigma-Aldrich, and H_2PtCl_6 was obtained from Strem Chemical. ^1H and $^{13}C\{^1H\}$ NMR spectra are reported in parts per million relative to tetramethylsilane using the residual solvent resonances as an internal standard. High-resolution mass data were obtained using an Agilent 6320 Ion Trap MS system. ICP-MS data were obtained using a ThermoFinnigan Element2 instrument. XRD patterns were measured on a Panalytical Empyrean Powder X-ray diffractometer.

Residual Gas Analyzer. Gas evolution was analyzed using a residual gas analysis (RGA) mass spectrometer designed and built by the Amy Facility for Chemical Instrumentation at Purdue University. The headspace of the reaction mixture was collected with a gastight syringe and injected into the custom-made glass RGA cell. Argon was used as a carrier gas, and the gas mixture was drawn by a Varian model SH 100 vacuum pump into a Stanford Research Systems RGA 100 mass spectrometer equipped with an Alcatel ATH31 Series turbopump.

Preparation of Pt/TiO_2 (0.5 wt % Pt) Photocatalyst. A 20 mL microwave vial was charged with a magnetic stir bar, TiO_2 (P25, Aldrich, 1.0 g), *i*-PrOH (9.0 mL), and distilled water (7.0 mL). H_2PtCl_6 (0.5 wt % Pt relative to TiO_2, 13.3 mg) was added as a solution in distilled water (2.0 mL). The vial was sealed with a 14/20 rubber septum, and the mixture was sonicated for 30 min and then sparged with N_2 for 45 min. The reaction vessel was placed into a reflective dewar containing water at ambient temperature. The mixture was stirred under irradiation with a 100-W Hg lamp (UVP-Blak-Ray B-100YP). After 30 min, the reaction mixture was transferred to a centrifuge tube and spun down to a solid pellet. The liquid phase was decanted, and the solid was resuspended in distilled water before being spun down again. After the rinse was repeated twice, the gray solid was isolated and allowed to dry in a 125 °C oven overnight. ICP-MS analysis determined the amount of deposited platinum to be approximately 0.489%.

Preparation of Pd/TiO_2 (0.5 wt % Pd) Photocatalyst. A 20 mL microwave vial was charged with a magnetic stir bar, TiO_2 (P25, Aldrich, 1.0 g), *i*-PrOH (9.0 mL), and distilled water (7.0 mL).

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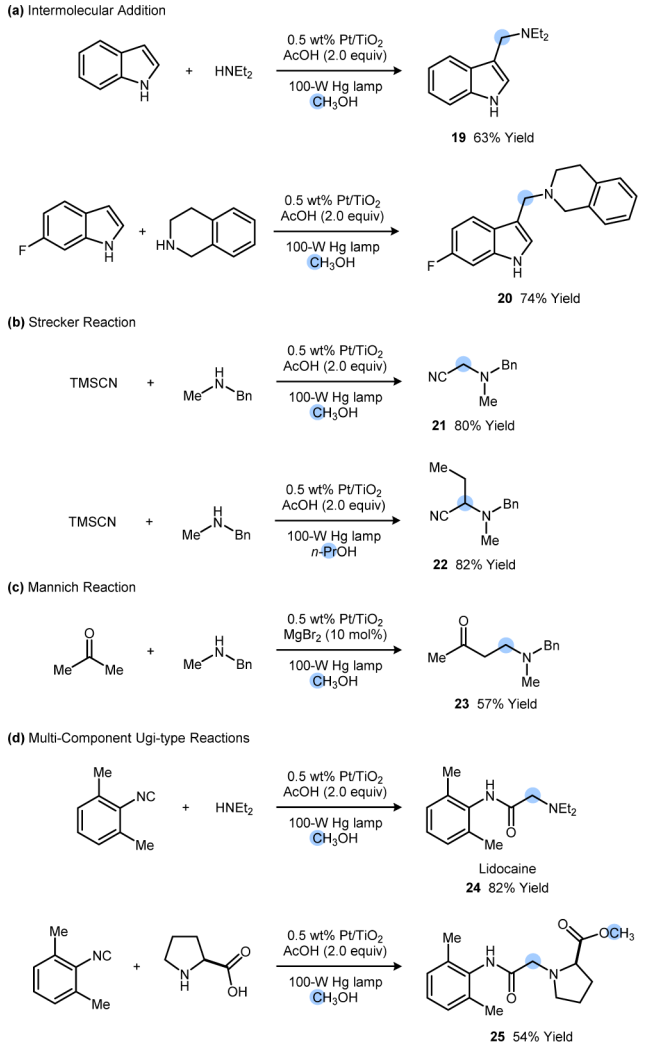

Figure 4. Multicomponent imine transformations enabled by the photocatalytic dehydrogenation of MeOH.

$Pd(NO_3)_2$ (0.5 wt % Pd relative to TiO_2, 26.0 mg) was added as a solution in distilled water (2.0 mL). The vial was sealed with a 14/20 rubber septum, and the mixture was sonicated for 30 min and then sparged with N_2 for 45 min. The reaction vessel was placed into a reflective dewar containing water at ambient temperature. The mixture was stirred under irradiation with a 100-W Hg lamp (UVP-Blak-Ray B-100YP). After 30 min, the reaction mixture was transferred to a centrifuge tube and spun down to a solid pellet. The liquid phase was decanted, and the solid was resuspended in distilled water before being spun down again. After the rinse was repeated twice, the gray solid was isolated and allowed to dry in a 125 °C oven overnight.

Preparation of Au/TiO_2 (0.5 wt % Au) Photocatalyst. A 20 mL microwave vial was charged with a magnetic stir bar, TiO_2 (P25, Aldrich, 1.0 g), *i*-PrOH (9.0 mL), and distilled water (7.0 mL). $HAuCl_4 \cdot H_2O$ (0.5 wt % Au relative to TiO_2, 9.0 mg) was added as a solution in distilled water (2.0 mL). The vial was sealed with a 14/20 rubber septum, and the mixture was sonicated for 30 min and then sparged with N_2 for 45 min. The reaction vessel was placed into a reflective dewar containing water at ambient temperature. The mixture was stirred under irradiation with a 100-W Hg lamp (UVP-Blak-Ray B-100YP). After 30 min, the reaction mixture was transferred to a centrifuge tube and spun down to a solid pellet. The liquid phase was decanted, and the solid was resuspended in distilled water before being spun down again. After the rinse was repeated twice, the purple solid was isolated and allowed to dry in a 125 °C oven overnight.

Preparation of Ag/TiO_2 (0.5 wt % Ag) Photocatalyst. A 20 mL microwave vial was charged with a magnetic stir bar, TiO_2 (P25, Aldrich, 1.0 g), *i*-PrOH (9.0 mL), and distilled water (7.0 mL). $AgNO_3$ (0.5 wt % Ag relative to TiO_2, 8.0 mg) was added as a solution in distilled water (2.0 mL). The vial was sealed with a 14/20 rubber septum, and the mixture was sonicated for 30 min and then sparged with N_2 for 45 min. The reaction vessel was placed into a reflective dewar containing water at ambient temperature. The mixture was stirred under irradiation with a 100-W Hg lamp (UVP-Blak-Ray B-100YP). After 30 min, the reaction mixture was transferred to a centrifuge tube and spun down to a solid pellet. The liquid phase was decanted, and the solid was resuspended in distilled water before being spun down again. After the rinse was repeated twice, the red solid was isolated and allowed to dry in a 125 °C oven overnight.

General Procedure for Tetrahydro-*β*-carboline Synthesis. A 50 mL Schlenk tube was charged with a magnetic stir bar, the tryptamine substrate (0.2 mmol), the Pt/TiO_2 catalyst (5 mg/0.2 mmol of substrate), AcOH (0.4 mmol), and MeOH (3.0 mL). The reaction vessel was sealed and degassed by the freeze−pump−thaw procedure. Reactions were stirred under irradiation by a 100-W Hg lamp (UVP-Blak-Ray B-100YP). After 15 h, the reaction mixture was quenched with aqueous sodium hydroxide (1.0 M, 10 mL), and the product was extracted using CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. Products were isolated following purification by column chromatography. All reactions were run in duplicate.

2-Benzyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2).[17] Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 43 mg, 83% Run 2: 51 mg, 97%. ^{1}H NMR (300 MHz, CDCl3) δ 7.66 (s, 1H), 7.51−7.32 (m, 6H), 7.27−7.24 (m, 1H), 7.17−7.08 (m, 2H), 3.78 (s, 2H), 3.59 (s, 2H), 2.95−2.91 (m, 2H), 2.86−2.82 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, CDCl3) δ 138.5, 136.1, 131.9, 129.2, 128.5, 127.3, 121.3, 119.4, 118.1, 110.8, 108.4, 62.1, 51.0, 50.2, 21.3.

2-(4-Fluorobenzyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4). Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 45 mg, 80% Run 2: 49 mg, 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.49 (d, J = 6.9 Hz, 1H), 7.40−7.35 (m, 2H), 7.29−7.26 (m, 1H), 7.17−7.10 (m, 2H), 7.05 (t, J = 8.7 Hz, 2H), 3.73 (s, 2H), 3.60 (s, 2H), 2.93−2.89 (m, 2H), 2.84 (d, J = 5.3 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.2 (d, $^1J_{C-F}$ = 245.2 Hz), 136.1, 134.2, 131.8, 130.7 (d, $^2J_{C-F}$ = 7.8 Hz), 127.3, 121.5, 119.5, 118.1, 115.3 (d, $^3J_{C-F}$ = 21.1 Hz), 110.8, 108.5, 61.3, 50.9, 50.2, 21.3. HRMS (ESI, m/z): [M + H]$^+$ calcd for $C_{18}H_{18}FN_2$, 281.1454; found, 281.1447.

2-(4-Methoxybenzyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (5). Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 46 mg, 78% Run 2: 49 mg, 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.47 (d, J = 6.7 Hz, 1H), 7.33−7.27 (m, 3H), 7.11 (qd, J = 7.1 Hz, 1.5 Hz, 2H), 6.91−6.87 (m, 2H), 3.82 (s, 3H), 3.73 (s, 2H), 3.65 (s, 2H), 2.93−2.90 (m, 2H), 2.84−2.80 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.0, 136.1, 131.9, 130.5, 127.4, 121.4, 119.5, 118.1, 113.8, 110.8, 108.5, 61.4, 55.4, 50.8, 50.1, 21.2. HRMS (ESI, m/z): [M + H]$^+$ calcd for $C_{19}H_{21}N_2O$, 293.1654; found, 293.1645.

2-(Naphthalen-1-ylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole (6). Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 49 mg, 79% Run 2: 52 mg, 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38−8.35 (m, 1H), 7.88−7.85 (m, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.61 (s, 1H), 7.55−7.44 (m, 5H), 7.29−7.28 (m, 1H), 7.15−7.06 (m, 2H), 4.20 (s, 2H), 3.71 (s, 2H), 3.03 (t, J = 5.9 Hz, 2H), 2.85 (t, J = 5.5 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.1, 134.0, 132.7, 128.6, 128.3, 127.6, 127.4, 126.1, 125.9, 125.3, 124.8, 121.5, 119.5, 118.1, 110.8, 108.6, 60.0, 51.3, 50.3, 21.3. HRMS (ESI, m/z): [M + H]$^+$ calcd for $C_{22}H_{21}N_2$, 313.1705; found, 312.1696.

2-(Pyridin-3-ylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (7). Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 43

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mg, 82% Run 2: 47 mg, 90%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.67 (s, 1H), 8.57 (d, J = 1.5 Hz, 1H), 8.49 (dd, J = 1.7 Hz, 4.8 Hz, 1H), 7.78 (dt, J = 1.8 Hz, 7.8 Hz, 1H), 7.39−7.33 (m, 2H), 7.26 (d, J = 7.9 Hz, 1H), 7.02−6.90 (m, 2H), 3.75 (s, 2H), 3.57 (s, 2H), 2.78 (d, J = 5.0 Hz, 1H), 2.69 (d, J = 5.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 150.0, 148.4, 136.5, 135.8, 134.1, 132.6, 126.7, 123.5, 120.3, 118.3, 117.4, 110.9, 106.3, 58.4, 50.5, 49.8, 21.1. HRMS (ESI, m/z): [M + H]+ calcd for $C_{12}H_{18}N_3$, 264.1501; found, 264.1505.

2-(Thiophen-2-ylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (8). Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 51 mg, 95% Run 2: 47 mg, 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.31−7.28 (m, 2H), 7.11 (qd, J = 1.6 Hz, 7.1 Hz, 2H), 7.00−6.97 (m, 2H), 4.01 (s, 2H), 3.76 (s, 2H), 2.98 (t, J = 6.2 Hz, 2H), 2.84 (t, J = 5.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 141.9, 136.2, 131.6, 127.4, 126.7, 126.3, 125.4, 121.5, 119.5, 118.1, 110.8, 108.5, 56.0, 50.6, 49.9, 21.1. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{16}H_{17}N_2S$, 269.1113; found, 269.1106.

2-((Perfluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole (9). The reaction was run with the following modifications from the general procedure: 10 mg of Pt/TiO_2, 10 equiv of AcOH, and a 24-h reaction time. Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 54 mg, 76% Run 2: 55 mg, 78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.29 (d, J = 7.3 Hz, 1H), 7.15−7.05 (m, 2H), 3.97 (s, 2H), 3.74 (s, 2H), 2.96 (t, J = 5.7 Hz, 2H), 2.84 (t, J = 5.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.2, 131.1, 127.3, 121.7, 119.6, 118.1, 110.9, 108.3, 50.6, 49.5, 48.0, 21.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ −143.0, −156.1, −163.5. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{18}H_{14}F_5N_2$, 353.1077; found, 353.1070.

2-Allyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (10).[17] Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 33 mg, 77% Run 2: 35 mg, 83%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.11 (qd, J = 1.5, 7.2 Hz, 2H), 6.04−5.92 (m, 1H), 5.30−5.20 (m, 2H), 3.71 (s, 2H), 3.29 (d, J = 6.5 Hz, 2H), 2.93−2.81 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.2, 135.2, 131.8, 127.3, 121.4, 119.4, 118.4, 118.1, 110.9, 108.4, 60.8, 50.8, 50.2, 21.3.

5-(1,3,4,9-Tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)pentan-1-ol (11). The reaction was run with the following modifications from the general procedure: 10 mg of Pt/TiO_2, 10 equiv of AcOH, and a 24-h reaction time. Isolated yields were determined following purification by column chromatography on (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 21 mg, 40% Run 2: 32 mg, 62%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.43 (d, J = 7.1 Hz, 1H), 7.28 (d, J = 7.3 Hz, 1H), 7.09 (qd, J = 1.2 Hz, 7.8 Hz, 2H), 3.68 (s, 2H), 3.60 (t, J = 6.3 Hz, 2H), 3.32 (s, 1H), 2.89−2.83 (m, 4H), 2.59 (t, J = 7.4 Hz, 2H), 1.66−1.51 (m, 4H), 1.39 (q, J = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.4, 130.3, 127.0, 121.7, 119.5, 118.1, 111.1, 107.7, 62.5, 57.1, 51.0, 50.1, 32.3, 26.3, 23.5, 20.6. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{16}H_{23}N_2O$, 259.1811; found, 259.1808.

2-(4-Chlorobenzyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole (12). Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 52 mg, 83% Run 2: 50 mg, 81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 7.7 Hz, 1H), 7.40−7.33 (m, 4H), 7.29−7.27 (m, 1H), 7.20 (td, J = 6.9 Hz, 1.2 Hz, 1H), 7.11 (td, J = 7.8 Hz, 1.2 Hz, 1H), 3.79 (s, 2H), 3.69 (s, 2H), 3.56 (s, 3H), 2.92−2.84 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.2, 137.1, 133.3, 133.0, 130.4, 128.7, 126.8, 121.0, 119.0, 118.1, 108.8, 107.3, 61.5, 50.9, 49.5, 29.3, 21.5. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{19}H_{20}ClN_2$, 311.1315; found, 311.1307.

1-Ethyl-2-(4-trifluoromethylbenzyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (13). The reaction was run with the following modifications from the general procedure: 10 mg of Pt/TiO_2, 10 equiv of AcOH, *n*-PrOH solvent, and a 24-h reaction time. Isolated yields were determined following purification by column chromatography (SiO_2, 1:10 acetone/petroleum ether). Run 1: 48 mg, 67% Run 2: 48 mg, 67%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 6.7 Hz, 3H), 7.34 (d, J = 7.2 Hz, 1H), 7.21−7.11 (m, 2H), 3.83 (q, J = 14.0 Hz, 2H), 3.55 (t, J = 6.4 Hz, 1H), 3.29−3.20 (m, 1H), 2.96−2.84 (m, 2H), 2.67−2.59 (m, 1H), 1.84 (q, J = 7.6 Hz, 2H), 1.01 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.4, 136.0, 135.2, 129.4 (q, $^2J_{C-F}$ = 32.2 Hz) 129.1, 127.4, 126.5 (q, $^1J_{C-F}$ = 233.9 Hz) 125.3 (d, $^3J_{C-F}$ = 3.5 Hz) 121.7, 119.5, 118.2, 110.8, 108.2, 58.5, 57.1, 45.2, 27.5, 18.3, 10.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.8. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{21}H_{22}F_3N_2$, 359.1735; found, 359.1732.

2-Benzyl-6-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]-indole (14). Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 43 mg, 74% Run 2: 40 mg, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.43−7.30 (m, 5H), 7.15 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 6.78 (dd, J = 2.5 Hz, 8.7, 1H), 3.86 (s, 3H), 3.77 (s, 2H), 3.60 (s, 2H), 2.91 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 5.3 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.1, 138.4, 132.8, 131.2, 129.3, 128.5, 127.8, 127.4, 111.5, 111.0, 108.3, 100.4, 62.1, 56.0, 51.0, 50.4, 21.3. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{19}H_{21}N_2O$, 293.1654; found, 293.1647.

2-Benzyl-7-fluoro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (15). Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 48 mg, 85% Run 2: 34 mg, 60%. ^{1}H NMR (300 MHz, CD_3OD) δ 7.42−7.29 (m, 7H), 6.95 (dd, J = 2.3 Hz, 10 Hz, 1H), 6.77−6.71 (m, 1H), 3.77 (s, 3H), 3.63 (s, 3H), 2.90−2.86 (m, 2H), 2.80−2.76 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD) δ 151.4 (d, $^1J_{C-F}$ = 234.2 Hz), 129.0, 128.4 (d, $^3J_{C-F}$ = 12.6 Hz), 121.3, 120.6, 120.0, 119.7, 119.1, 109.7 (d, $^3J_{C-F}$ = 10.1 Hz), 98.6, 98.3 (d, $^2J_{C-F}$ = 24.6 Hz), 88.5 (d, $^2J_{C-F}$ = 26.1 Hz), 53.7, 42.4, 41.7, 12.5. ^{19}F NMR (282 MHz, CD_3OD) δ −123.6. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{18}H_{18}FN_2$, 281.1454; found, 281.1451.

2-(1-Phenylethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (16). Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 43 mg, 78% Run 2: 49 mg, 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.42−7.28 (m, 6H), 7.10 (qd, J = 7.0 Hz, 1.4 Hz, 2H), 3.80−3.61 (m, 3H), 3.00−2.92 (m, 1H), 2.87−2.75 (m, 3H), 1.50 (d, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.5, 136.1, 132.3, 128.6, 127.7, 127.4, 127.2, 121.4, 119.4, 118.1, 110.8, 108.7, 63.9, 48.4, 48.2, 21.5, 20.6. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{19}H_{21}N_2$, 277.1705; found, 277.1701.

Methyl 2-Benzyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (17).[18] Isolated yields were determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 53 mg, 83% Run 2: 49 mg, 76%. ^{1}H NMR (300 MHz, CD_3OD) δ 7.41−7.23 (m, 8H), 7.06−6.94 (m, 2H), 4.14 (d, J = 15.2 Hz, 1H), 3.99 (s, 2H), 3.80−3.97 (m, 1H), 3.82 (d, J = 15.0 Hz, 1H), 3.65 (s, 3H), 3.19−3.03 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD) δ 165.2, 130.1, 128.5, 123.3, 120.8, 120.0, 119.0, 118.8, 112.4, 110.2, 108.8, 102.3, 96.5, 51.0, 50.2, 42.5, 37.8, 15.6.

2-Benzyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1,1-d_2 (18). Isolated yield was determined following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2) (40 mg, 76% Yield). ^{1}H NMR (300 MHz, CD_3OD) δ 7.72 (s, 1H), 7.50−7.23 (m, 7H), 7.11−7.07 (m, 2H), 3.77 (s, 2H), 2.96−2.82 (m, 4H).

Intermolecular Addition: *N*-((1*H*-Indol-3-yl)methyl)-*N*-ethylethanamine (19).[19] A 50 mL Schlenk tube was charged with a magnetic stir bar, the Pt/TiO_2 catalyst (5.0 mg), indole (23.4 mg, 0.2 mmol, 1.0 equiv), Et_2NH (41.3 μL, 0.4 mmol, 2.0 equiv), AcOH (22.9 μL, 0.4 mmol, 2.0 equiv), and MeOH (2.0 mL). The reaction vessel was sealed and degassed by the freeze−pump−thaw procedure. Reactions were stirred under irradiation by a 100-W Hg lamp. After 15 h, the reaction mixture was quenched with aqueous sodium hydroxide (1.0 M, 10 mL), and the product was extracted using CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. Products were isolated following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 23 mg, 58% Run 2: 27 mg, 68%. ^{1}H

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NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.15 (ds, J = 1.1 Hz, 7.0 Hz, 3H), 3.82 (s, 2H), 2.59 (q, J = 7.2 Hz, 4H), 1.11 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 136.3, 128.2, 123.7, 122.1, 119.58, 111.1, 48.0, 46.7, 12.0.

Intermolecular Addition: 2-((6-Fluoro-1*H*-indol-3-yl)methyl)-1,2,3,4-tetrahydroisoquinoline (20). The reaction was run according to the general procedure described for compound **19**. Isolated yields were determined following purification by column chromatography (SiO_2, 0−2% MeOH in CH_2Cl_2). Run 1: 38 mg, 82% Run 2: 30 mg, 65%. ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.69 (dd, J = 8.7, 5.4 Hz, 1H), 7.19−6.93 (m, 6H), 6.88 (td, 1H), 3.88 (s, 2H), 3.72 (s, 2H), 2.95−2.76 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.1 (d, $^1J_{C-F}$ = 237.2 Hz), 136.4, 135.1, 134.6, 128.8, 126.8, 126.2, 125.7, 124.6, 123.9 (d, $^3J_{C-F}$ = 3.6 Hz), (d, $^3J_{C-F}$ = 10.1 Hz), 113.0, 108.4 (d, $^2J_{C-F}$ = 24.3 Hz), 97.4 (d, $^2J_{C-F}$ = 26.1 Hz), 56.2, 53.5, 50.6, 29.9, 29.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ −122.84. HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{18}H_{17}FN_2$, 281.1454; found, 281.1447.

Strecker Reaction: 2-(Benzyl(methyl)amino)acetonitrile (21).[20] A 50 mL Schlenk tube was charged with a magnetic stir bar, the Pt/TiO_2 catalyst (5.0 mg), *N*-benzylmethylamine (24.2 mg, 0.2 mmol, 1.0 equiv), TMSCN (27.5 μL, 0.22 mmol, 1.1 equiv), AcOH (22.9 μL, 0.4 mmol, 2.0 equiv), and MeOH (2.0 mL). The reaction vessel was sealed and degassed by the freeze−pump−thaw procedure. Reactions were stirred under irradiation by a 100-W Hg lamp. After 24 h, the reaction mixture was quenched with aqueous sodium hydroxide (1.0 M, 10 mL), and the product was extracted using CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over MgSO4, filtered, and concentrated to dryness under reduced pressure. Run 1: 28 mg, 86% Run 2: 23 mg, 73%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.31 (m, 5H), 3.61 (s, 2H), 3.45 (s, 2H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 137.0, 129.0, 128.6, 127.8, 114.5, 60.1, 44.1, 42.3.

Strecker Reaction: 2-(Benzyl(methyl)amino)butanenitrile (22).[21] A 50 mL Schlenk tube was charged with a magnetic stir bar, the Pt/TiO_2 catalyst (5.0 mg), *N*-benzylmethylamine (24.2 mg, 0.2 mmol, 1.0 equiv), TMSCN (27.5 μL, 0.22 mmol, 1.1 equiv), AcOH (22.9 μL, 0.4 mmol, 2.0 equiv), and PrOH (3.0 mL). The reaction vessel was sealed and degassed by the freeze−pump−thaw procedure. Reactions were stirred under irradiation by a 100-W Hg lamp. After 24 h, the reaction mixture was quenched with aqueous sodium hydroxide (1.0 M, 10 mL), and the product was extracted using CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. Run 1: 32 mg, 84% Run 2: 30 mg, 80%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.28 (m, 5H), 3.77 (d, J = 13.3 Hz, 1H), 3.49−3.42 (m, 2H), 2.30 (s, 3H), 1.84−1.78 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 137.6, 128.8, 128.5, 127.6, 117.1, 59.8, 57.8, 38.0, 24.9, 10.6.

Mannich Reaction: 4-(Benzyl(methyl)amino)butan-2-one (23).[22] A 50 mL Schlenk tube was charged with a magnetic stir bar, the Pt/TiO_2 catalyst (10.0 mg), *N*-benzylmethylamine (24.2 mg, 0.2 mmol, 1.0 equiv), $MgBr_2$ (3.68 mg, 10 mol %), acetone (0.1 mL, 1.4 mmol, 7 equiv), and MeOH (2.0 mL). The reaction vessel was sealed and degassed by the freeze−pump−thaw procedure. Reactions were stirred under irradiation by a 100-W Hg lamp. After 24 h, the reaction mixture was quenched with aqueous sodium hydroxide (1.0 M, 10 mL), and the product was extracted using CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. Products were isolated following purification by column chromatography (SiO_2, 0−5% MeOH in CH_2Cl_2). Run 1: 21 mg, 55% Run 2: 23 mg, 59%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.23 (m, 5H), 3.50 (s, 2H), 2.73−2.70 (m, 2H), 2.65−2.62 (m, 2H), 2.19 (s, 3H), 2.14 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 208.3, 138.7, 129.2, 128.4, 127.3, 62.5, 52.1, 42.1, 30.1.

Ugi-Type Reaction: Lidocaine (24).[23] A 50 mL Schlenk tube was charged with a magnetic stir bar, the Pt/TiO_2 catalyst (5.0 mg), Et_2NH (20.7 μL, 0.2 mmol, 2.0 equiv), 2,6-dimethylphenylisonitrile (13.1 mg, 0.1 mmol, 1.0 equiv), AcOH (11.5 μL, 0.2 mmol, 2.0 equiv), and MeOH (2.0 mL). The reaction vessel was sealed and degassed by the freeze−pump−thaw procedure. Reactions were stirred under irradiation by a 100-W Hg lamp. After 24 h, the reaction mixture was quenched with aqueous sodium hydroxide (1.0 M, 10 mL), and the product was extracted using CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. Products were isolated following purification by column chromatography (SiO_2, 1:1 EtOAc/hexane). Run 1: 37 mg, 79% Run 2: 40 mg, 85%. ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.09 (s, 3H), 3.22 (s, 2H), 2.69 (q, J = 7.1 Hz, 4H), 2.24 (s, 6H), 1.14 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.4, 135.2, 134.1, 128.4, 127.2, 57.7, 49.1, 18.7, 12.8.

Ugi-Type Reaction: Methyl (2-((2,6-Dimethylphenyl)amino)-2-oxoethyl)prolinate (25).[24] A 50 mL Schlenk tube was charged with a magnetic stir bar, the Pt/TiO_2 catalyst (5.0 mg), L-proline (23.0 mg, 0.2 mmol, 2.0 equiv), 2,6-dimethylphenylisonitrile (13.1 mg, 0.1 mmol, 1.0 equiv), AcOH (11.5 μL, 0.2 mmol, 2.0 equiv), and MeOH (2.0 mL). The reaction vessel was sealed and degassed by the freeze−pump−thaw procedure. Reactions were stirred under irradiation by a 100-W Hg lamp. After 24 h, the reaction mixture was quenched with aqueous sodium hydroxide (1.0 M, 10 mL), and the product was extracted using CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. Products were isolated following purification by column chromatography (SiO_2, 1:1 EtOAc/hexane). Run 1: 28 mg, 48% Run 2: 35 mg, 60%. ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.09 (s, 3H), 3.74 (s, 3H), 3.65−3.53 (m, 2H), 3.39−3.30 (m, 2H), 2.66 (q, J = 7.8 Hz, 1H), 2.25 (s, 6H), 2.09−1.89 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 174.8, 169.6, 135.4, 134.1, 128.3, 127.2, 66.0, 58.8, 55.1, 52.2, 30.0, 24.5, 18.6.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00617.

Additional experimental details, cyclic voltammetry data, NMR spectra, and IR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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