

Titania-Promoted Carboxylic Acid Alkylations of Alkenes and Cascade Addition–Cyclizations

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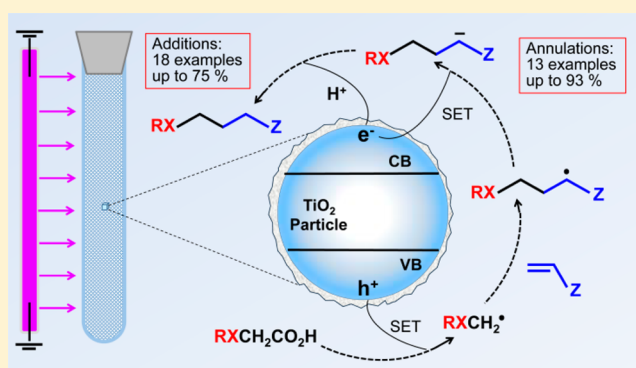
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Supporting Information

ABSTRACT: Photochemical reactions employing TiO₂ and carboxylic acids under dry anaerobic conditions led to several types of C–C bond-forming processes with electron-deficient alkenes. The efficiency of alkylation varied appreciably with substituents in the carboxylic acids. The reactions of aryloxyacetic acids with maleimides resulted in a cascade process in which a pyrrolochromene derivative accompanied the alkylated succinimide. The selectivity for one or other of these products could be tuned to some extent by employing the photoredox catalyst under different conditions. Aryloxyacetic acids adapted for intramolecular ring closures by inclusion of 2-alkenyl, 2-aryl, or 2-oximinyl functionality reacted rather poorly. Profiles of reactant consumption and product formation for these systems were obtained by an in situ NMR monitoring technique. An array of different catalyst forms were tested for efficiency and ease of use. The proposed mechanism, involving hole capture at the TiO₂ surface by the carboxylates followed by CO₂ loss, was supported by EPR spectroscopic evidence of the intermediates. Deuterium labeling indicated that the titania likely donates protons from surface hydroxyl groups as well as supplying electrons and holes, thus acting as both a catalyst and a reaction partner.



INTRODUCTION

Carboxylic acids are pervasive in nature and are produced industrially on a large scale. Therefore, methods of employing them in organic preparations have received a lot of attention. Hard UV ($\lambda \leq 250$ nm) irradiations generate carbon-centered radicals but also induce much degradation.^{1,2} Conventionally, decarboxylative alkylations have relied on preparations of unappealing precursors such as peroxides,³ Barton esters,⁴ or Hunsdieker salts.⁵ Recently attention shifted toward discovering catalytic systems capable of utilizing them in target-oriented syntheses. Decarboxylative copper-catalyzed reactions of carboxylic acids with carbonyls⁶ and with aldimines,⁷ and of amino acids with alkynes⁸ have been reported. Photoredox methods have also been used for this purpose⁹ but can suffer from difficulties in removing the catalyst. Interest in heterogeneous photoredox methods for carboxylates dates back to the 1970s and the photo-Kolbé reaction.¹⁰

Semiconductor photoredox catalysis (SCPC) offers tangible advantages for organic preparations. The chosen semiconductor can be nontoxic and can easily be removed by filtration, and when visible or soft UVA light is used, the procedure can be convenient and benign. Most applications of TiO₂ SCPC have utilized aerobic conditions, resulting in selective oxidations of

organic substrates¹¹ or more complete substrate mineralizations.¹² Under anhydrous, anaerobic conditions and with certain substrates, TiO₂ SCPC can lead to the generation of specific radicals adapted for molecular assembly applications. To date, however, only a modest number of such processes have been identified and developed.¹³ Notably, SCPC additions of enol ethers to various acceptors have been investigated,¹⁴ and successful additions of tertiary amines to electron-deficient alkenes, some bearing chiral auxiliaries, have been described.¹⁵ We recently discovered that under dry, anaerobic conditions, TiO₂ mediation with carboxylic acid precursors could result in carbon–carbon bond-forming processes. Alkylations and annulations were achieved when photolyses of certain acid precursors were carried out in the presence of suitable electron-deficient alkenes.¹⁶ This paper reports advances in crucial aspects of this process in the following areas: (1) structural features in the carboxylic acids that are necessary and sufficient; (2) the range of functionality in the alkene acceptors that can be tolerated; (3) how the reactions respond to modifications to

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the catalyst form and the catalyst support; and (4) the mechanism followed by the reaction.

RESULTS AND DISCUSSION

In our preliminary study,¹⁶ we discovered an experimental protocol with reasonably wide applicability utilizing Degussa (Evonik) P25 as a 1–5 mg mL⁻¹ dispersion in dried acetonitrile. This dispersion, with added carboxylic acid and substrate, in an oven-dried Pyrex tube was purged with argon and then irradiated by two face-to-face sunlamp arrays (UVA) at ambient temperature. After photolysis, the catalyst was removed by filtration and the products were isolated by conventional organic techniques.

1. Alkylations of Maleimide with Aliphatic Carboxylic Acids. During initial investigations, *N*-phenylmaleimide (**2**) was found to be an ideal radical acceptor in this system, as it is symmetrical and photostable, its photodimerization is negligible (under our experimental conditions), and its electron-withdrawing character favors addition by weakly nucleophilic radicals. This alkene was therefore chosen to test the applicability of our process with simple aliphatic carboxylic acids **1**. Standard unoptimized conditions were adopted so a clear comparison of behavior from acid to acid could be obtained (Table 1). In all instances, 0.1 mmol of **1** and 0.2

Table 1. TiO₂-Promoted Reactions of *N*-Phenylmaleimide with Aliphatic Carboxylic Acids

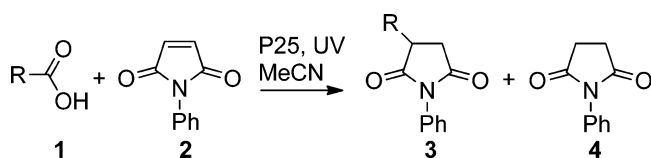
entry	R in 1	yield (%) ^a	
		adduct 3	4
1	Me	23	41
2	Me(CH ₂) ₄	4	2
3	<i>t</i> -BuCH ₂	18	40
4	<i>i</i> -Pr	25	25
5	<i>t</i> -Bu	38	31
6	CF ₃	~1	trace

^aNMR yields.

mmol of **2** were photolyzed in a suspension of the P25 catalyst (12 mg, 0.15 mmol) in CH₃CN (12 mL) for 18 h. The reactions did indeed lead to the formation of adducts **3** incorporating the R moiety of the carboxylic acid and an additional H atom, together with significant amounts of succinimide **4** (Scheme 1).

For acids that decarboxylated to give methyl (entry 1) or primary radicals (entries 2 and 3), the yields were low; however, increased yields were obtained with secondary and tertiary radicals (entries 4 and 5). Negligible adduct was detected for the destabilized, σ -type CF₃ radical (entry 6).

Scheme 1. P25-Promoted Alkylations of *N*-Phenylmaleimide with Simple Carboxylic Acids

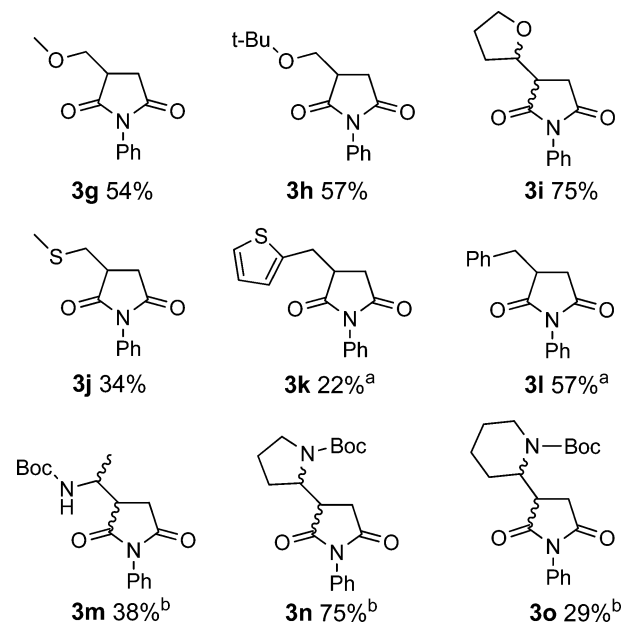


- a;** R=Me **b;** R=*n*-C₅H₁₁
c; R=*t*-BuCH₂ **d;** R=*i*-Pr
e; R=*t*-Bu **f;** R= CF₃

The efficiency of the process evidently increased as the stabilization energy of the released radical increased (see the Supporting Information for a plot of radical stabilization energy vs yield). The observation of a significant amount of **4** in each case suggested that alkene **2** plays the role of an electron sink, consuming electrons in two sequential reduction–protonations.

2. Additions of Stabilized Radicals to *N*-Phenylmaleimide. We next examined a set of addition reactions with *N*-phenylmaleimide involving more diverse carboxylic acids (Scheme 2). Primary alkyl radicals stabilized by α -alkoxy

Scheme 2. P25-Promoted Alkylations of *N*-Phenylmaleimide with Diverse Carboxylic Acids



^aAccompanied by dimers (see the text). ^bObtained as a 1:1 mixture of two diastereoisomers.

groups proved to be a good deal more reactive than the simple alkyl radicals. Methoxy- and *tert*-butoxyacetic acids gave the corresponding adducts (**3g** and **3h**) in reasonable yields of 54% and 57%, respectively, while 2-tetrahydrofuroic acid furnished a 1:1 mixture of the two diastereomers of **3i** in a very pleasing yield of 75%. However, methylthioacetic acid returned only a disappointing 34% yield of the desired product **3j**. Moderate and poor yields were obtained with benzyl (57%) and 2-thienylmethyl acids (22%), but these adducts (**3k** and **3l**) were accompanied by the dimers bibenzyl (18%) and 1,2-bis-(thiophen-2-yl)ethane (27%), respectively.

Decarboxylative additions also worked with Boc-protected α -amino acids, and the bottom row in Scheme 2 displays the adducts and the useful yields obtained. While Boc-proline was transformed into adduct **3n** in a fine yield of 75%, Boc-alanine and the unnatural α -amino acid Boc-piperidinecarboxylic acid gave much more modest yields of 38% and 29%, respectively. As expected, these adducts were 1:1 mixtures of stereoisomers. No retention of chirality was observed when optically pure amino acids were employed because the released radicals have planar, or close to planar, configurations at their reactive centers. Surprisingly, vinylacetic, ethynylacetic, and cyanoacetic acids failed to react, even though the released radicals would be strongly stabilized.

3. Comparison of Catalyst Efficiencies. To compare the efficiencies of different forms of the titania catalyst, the reaction of phenoxyacetic acid with acrylamide, which was clean and efficient (82% adduct isolated)¹⁶ was chosen. For each photolysis, suboptimum conditions of phenoxyacetic acid (0.1 mmol) and acrylamide (0.2 mmol) with irradiation for 17 h in anhydrous CH₃CN (12 mL) were employed. Where applicable, TiO₂ (12 mg) was employed in a 1 mg mL⁻¹ dispersion (see the Supporting Information for full details). With P25 itself (Table 2, entry 1), a 47% yield of the 4-phenoxybutanamide

Table 2. Comparison of TiO₂ Catalysts for the Reaction of Phenoxyacetic Acid with Acrylamide

entry	catalyst	yield of adduct (%) ^a
1	P25	47 (82 ^b)
2	PC500 ^c	39
3	sol-gel tube ^d	73 (68 ^e)
4	Photospheres ^f	9

^aNMR yields. ^bIsolated yield from 5:1 acid/acrylamide irradiated for 62 h. ^cMillenium PC500 (anatase, surface area ~300 m² g⁻¹, particle size 5–10 nm). ^dSchlenk tubes coated internally with P25 by a sol-gel process. ^eYield of the isolated product. ^fHollow glass spheres (mean diameter 45 μm, density 0.22 g/mL) coated with TiO₂, from Microsphere Technology.

adduct was recorded. With Millenium PC500 titania, having about 6 times the surface area,¹⁷ the yield dropped slightly (entry 2). Reactions were also carried out in Schlenk tubes coated with a fine internal layer of TiO₂ by a sol-gel process (see the Supporting Information for details). These proved to be very efficient and led to the best yield (entry 3). TiO₂ Photospheres consisting of hollow Pyrex beads coated externally with rutile titania¹⁸ delivered lower conversion and adduct yields (entry 4). This was attributed to difficulties in dispersing the Photospheres satisfactorily throughout the reaction flask. Because of their buoyancy, they tended to accumulate at the top, and this was compounded by the fact that the high rate of magnetic stirring used in attempts to overcome this tended to result in their becoming damaged. An isolated yield of 68% was achieved upon scale-up of the reaction in the coated tube (entry 3). Incorporation of 4-*tert*-butyl and 4-trifluoromethyl substituents in the aryl ring of the acid component furnished the corresponding adducts in similarly pleasing yields of 68% and 66%, respectively. Although the sol-gel-coated tubes gave the best yields and conversions, the coatings tended to detach, so they could only be used about three times. We therefore concluded that for ease of handling with conventional organic techniques, scale-up, and efficient product formation, the orthodox P25 catalyst was the best compromise.

4. Addition–Cyclizations with Aryloxyacetic Acids.

The reaction of aryloxyacetic acids (**5**) with *N*-substituted maleimides (**2**) led to *N*-substituted-3,4-dihydrochromeno[3,4]pyrrole-1,3-dione derivatives **6**, each accompanied by a significant amount of the expected adduct **7** (Scheme 3). Tricyclics **6** presumably resulted from cyclization of the initial adduct radical onto the aryl ring followed by rearomatization. Good to excellent overall yields were obtained under all conditions (Table 3). A moderate amount of succinimide (11–43% yield) was also formed in each case.

Table 3 shows that the process worked well with both electron-releasing and electron-withdrawing substituents in the

Scheme 3. Titania-Promoted Reactions of Aryloxyacetic Acids with *N*-Substituted Maleimides

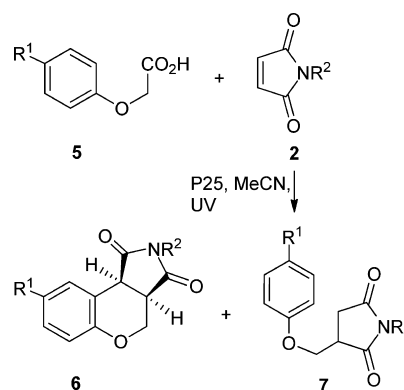


Table 3. Titania-Promoted Reactions of Aryloxyacetic Acids with Maleimides

entry	R ¹ R ² (a–f)	conditions ^a	yield (%) ^b	6:7 ratio
1	H Me (a)	P25, 20 h	75	2.38:1.0
2	H Me (a)	P25 dd, 45 h	75 ^c	10:1
3	H Me (a)	coated tube, 22 h	75 ^c	0.25:1.0
4	H Ph (b)	P25, 11 h	79	1.0:1.0
5	H Ph (b)	coated tube, 22 h	85 ^c	0.18:1.0
6	<i>t</i> -Bu Me (c)	P25, 22 h	57 ^d	4.20:1.0
7	<i>t</i> -Bu Me (c)	P25 dd, 42 h	56 ^e	>10:1.0 ^e
8	<i>t</i> -Bu Ph (d)	P25, 18 h	74	1.64:1.0
9	<i>t</i> -Bu Ph (d)	coated tube, 19 h	51 ^c	0.82:1.0
10	CF ₃ Me (e)	P25, 16 h	61	1.10:1.0
11	CF ₃ Me (e)	P25 dd, 42 h	62 ^c	1.70:1.0
12	CF ₃ Ph (f)	P25, 16 h	63	0.57:1.0
13	CF ₃ Ph (f)	coated tube, 17 h	93 ^c	0.38:1.0

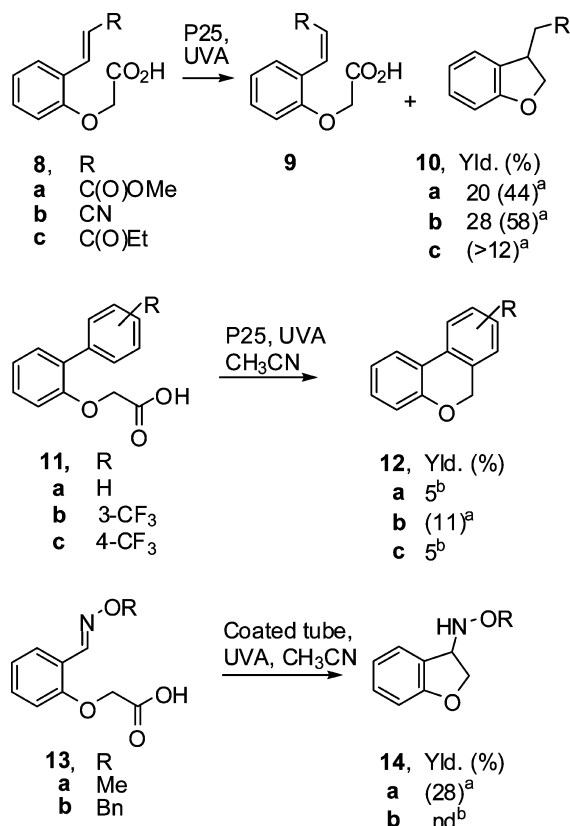
^aDispersion of 1 mg mL⁻¹ except for dd = dense dispersion of 5 mg mL⁻¹. ^bmol % isolated products, except as noted. ^cNMR yield. ^d15% **6** was obtained in the absence of P25. ^eOnly **6** was observed.

aromatic ring and for methyl- and phenyl-substituted maleimides. The reactions with just P25 generally gave a slight excess of the chromenopyrrole **6** (entries 1, 4, 6, 8, and 10), except in the case of the CF₃ substituent (entry 12), for which an excess of adduct **7** was observed. The selectivity for chromenopyrroles **6** was improved by using a more dense dispersion of P25 (entries 2, 7, and 11). On the other hand, photolyses in the sol-gel TiO₂-coated tubes (entries 3, 5, 9, and 13) led to a reversal in selectivity with predominant formation of adduct **7**. The possibility to tune the selectivity of reactions in this manner is an advantage of the technique. The ¹H NMR spectra of all **6** had ³J_{H–H} coupling constants between the two protons at the junction of the pyran and dihydropyrrole rings within the range of 9.2–9.3 Hz. This indicated a *cis* arrangement,¹⁹ in agreement with the conclusion that the reaction selectively formed the *cis* isomer in every case. Very few syntheses of dihydrochromeno[3,4]pyrrole-1,3-diones **6** have been reported,²⁰ but compounds with the corresponding reduced ring system, chromenopyrrolidines, are well-known biologically active species.²¹

5. Intramolecular Ring Closures with Acceptor-Functionalized Aryloxyacetic Acids. Three types of acid framework with different acceptor groups were prepared to test the applicability of P25-mediated ring closures. 2-(2-Vinylphenoxy)acetic acids having alkene acceptors with ester

(8a), nitrile (8b), and ketone (8c) substituents (Scheme 4) were obtained by treatment of 2-formylphenoxyacetic acid with

Scheme 4. Substrates and Products for Intramolecular Reactions



^aYields in brackets are maximum yields from NMR monitoring of sol-gel tube reactions. ^bYield estimated by ¹H NMR analysis (nd = not determined).

the appropriate phosphorane (see the Experimental Section). 2-(Biphenyl-2-yloxy)acetic acids **11a–c** having aromatic acceptors were prepared by coupling of the appropriate 1,1'-biphenyl-2-ol with methyl bromoacetate and subsequent hydrolysis of the ester with LiOH in MeOH/H₂O. Acids **13a** and **13b** having oxime ether acceptor groups were prepared by condensation of 2-formylphenoxyacetic acid with the appropriate alkoxyamine hydrochloride. Reactions with these acids were carried out in two ways. The first used P25 under standard conditions as described above. The second used 1 mL aliquots of acid solutions (10 mM) in CD₃CN (5 mL) in sol-gel-coated NMR tubes. The tubes were purged with argon and then placed in an overhead stirrer (turned on its side), which was then spun at 250 rpm. The tube was held at a slight angle with respect to horizontal in the “chuck” of the overhead stirrer so that, when rotated, it described a small (ca. 2 cm) circle at its non-chuck-held end so as to agitate the reaction solution. Irradiation was performed using a photoreactor with twelve 8 W black light blue (BLB) UV lamps ($\lambda_{\text{max}} = 365$ nm) (see the Supporting Information for a graphic). Periodically the tube was removed for NMR analysis. This was repeated until all of the starting material had been consumed or the product concentration plateaued. For acids **8a–c** with alkene acceptors, control photolyses in the absence of TiO₂ showed that *E/Z* isomerization was significant (52–79%). In conventional P25-

mediated reactions, **8a–c** all gave rather complex product mixtures containing unreacted alkene as a mixture of *E* and *Z* isomers (**8/9**) as well as the 5-*exo* ring-closed dihydrobenzofurans **10**. None of the 4-substituted chroman derivatives from 6-*endo* cyclizations were detected. Disappointing yields of **10a** and **10b** were isolated. The acids with aromatic acceptors **11a–c** all reacted very poorly under both sets of conditions. NMR and GC-MS analyses showed complex product mixtures containing possible trace amounts of the cyclized 6*H*-benzo[*c*]chromenes **12a–c**. The 2,3-dihydrobenzofuran core of **10** is found in many natural products and pharmaceutically relevant molecules and has generated much interest.²²

The reaction profile from irradiation of acid **8a** in a sol-gel-coated tube obtained by NMR monitoring (Figure 1) shows

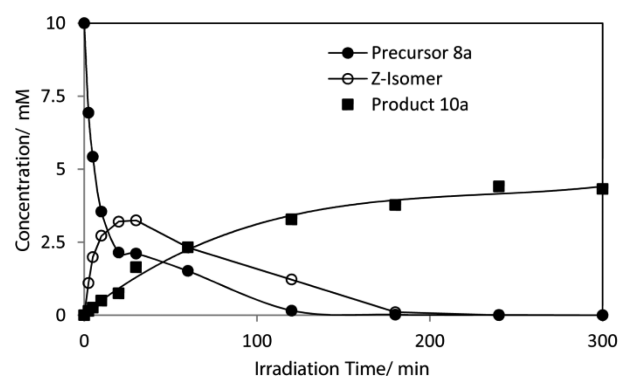


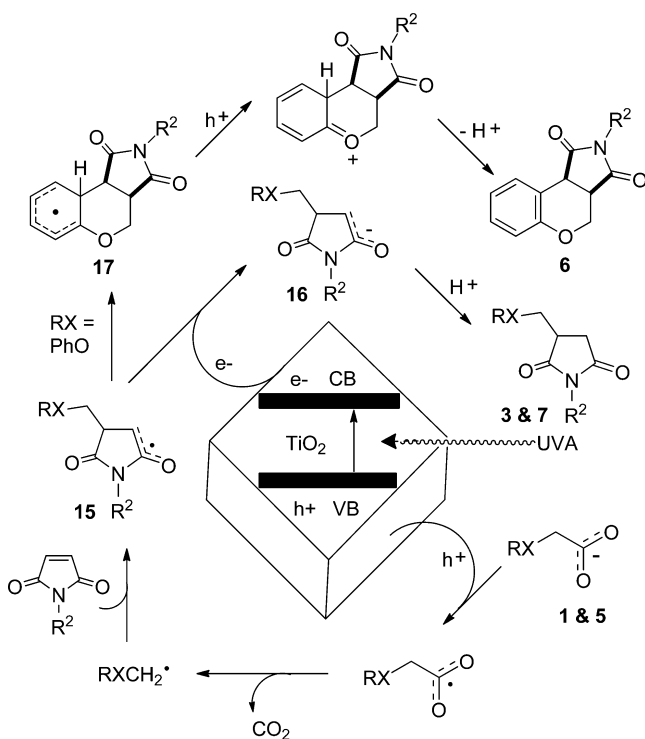
Figure 1. Reaction profile for acid **8a** obtained by NMR monitoring.

the sharp decrease in **8a** (the *E* isomer), which was all consumed in <150 min. The *Z* isomer **9a** initially increased, passed through a maximum at about 25 min, and then steadily decreased as it too was converted to cyclic product **10a**. The latter steadily increased, reaching a plateau by about 200 min. Analogous reaction profiles were obtained for the sol-gel tube reactions of **8a–c**, **11b**, and **13a**. No cyclized product was identified in the sol-gel tube reactions of **11a** and **11b**. A significant yield (28%) of the cyclized product *N*-(2,3-dihydrobenzofuranyl)-*O*-methylhydroxylamine (**14a**) was found in the sol-gel tube reaction of oxime ether-functionalized acid **13a** (Scheme 4). However, attempts to isolate and fully characterize this alkoxyamine were not successful.

6. Mechanism of the Reaction. Hole capture at the TiO₂ surface by a carboxylate creates the corresponding acyloxyl radical. Decarboxylation of this species furnishes the corresponding alkyl radical. Radicals of this type were directly observed by CW X-band EPR spectroscopy of frozen suspensions of P25 and *t*-BuCO₂H in CH₃CN.¹⁶ Transient *t*-Bu• radicals and PhOCH₂• radicals were observed during UV irradiation of the acids *t*-BuCO₂H and PhOCH₂CO₂H, respectively, with PC-500²³ in fluid PhH at 300 K.¹⁶ In similar EPR experiments with vinylacetic acid and 2,2,2-triphenylacetic acid, we were also able to detect and characterize allyl and triphenylmethyl radicals, respectively (see the Supporting Information). The isotropic character of the solution EPR spectra of all the RXCH₂• radicals established that in the main they were freely tumbling and not attached to the TiO₂ surface (Scheme 5).

Literature precedents imply that weakly nucleophilic RXCH₂• radicals should add rapidly to the electron-deficient double bonds of maleimides (and similar acceptors).²⁴ Most likely the resulting adduct radicals **15** will be converted to

Scheme 5. Proposed Mechanism for TiO₂-Promoted Reactions of Carboxylic Acids and Maleimides

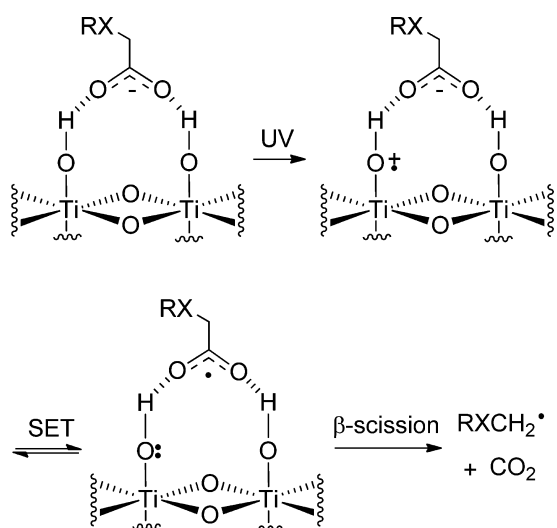


enolates **16** by electron transfer from the TiO₂ particles. Ready protonation²⁵ will afford adducts **3**, **7**, etc. (Scheme 5). For ArOCH₂• radicals containing aromatic rings, addition produces electrophilic imidoalkyl radicals **15**, for which a competition exists between reduction to adducts **7** or homolytic closure (6-*endo-trig*) onto the aryl ring. As radicals **15** are weakly electrophilic in character, this annulation should be favored by increasing the electron density in the ring and, conversely, disfavored by decreasing it.²⁶ In agreement with this, the proportion of **6** increased when an electron-releasing *tert*-butyl group was introduced to the ring, whereas it decreased when an electron-withdrawing trifluoromethyl group was introduced. The resonance-stabilized cyclohexadienyl-type radicals **17** will rearomatize to yield the functionalized chromenes **6**. This aromatization could result from hole capture from TiO₂ by the radicals **17** and subsequent proton loss as shown. Alternatively, electron transfer to maleimide might take place, as suggested in related work by Hoffmann.^{15b,c} Protonation of the resulting maleimide radical anions, followed by further electron capture and protonation steps, would explain the significant yields of succinimides obtained in our reactions. However, as greater amounts of succinimides than cyclized products **6** were generally formed, it is thought that direct reduction of the maleimide acceptor by the conduction band of the P25 also initiates this process.

From the results described in Schemes 1 and 2 and Table 1, it can be deduced that the stability of the initial radicals is an important factor in this system. Carboxylic acids dissociate on the TiO₂ surface to give the corresponding surface-bound carboxylate and a proton.²⁷ Photolysis with UVA and resultant photoexcitation generates an electron–hole pair, which can migrate through the bulk of the semiconductor to the surface. The TiO₂ surface is extensively hydroxylated,²⁸ and it is thought that these species act as surface trapping sites for the

valence-band holes.²⁹ Electron transfer from the π system of the carboxylate to a hole trap site furnishes the surface-bound RXCH₂–CO₂• radical. We propose that a competition exists between β -scission of this surface-bound species to yield the desired free RXCH₂• radical and back transfer of the electron, either from the trap site or from trapped conduction-band electrons, to the carboxylate. For acid precursors that generate stabilized RXCH₂• radicals, such as those depicted in Scheme 2, the decarboxylation step is more favorable, thus explaining the improved yields and conversions recorded. Conversely, for the simple aliphatic acids of Table 1, the radical stabilization energy from the RX groups is minimal, so back transfer of an electron to the TiO₂ will take precedence over the loss of CO₂. This is illustrated in Scheme 6.

Scheme 6. SET Photooxidation Events Taking Place between Carboxylic Acids RXCH₂CO₂H and the TiO₂ Surface

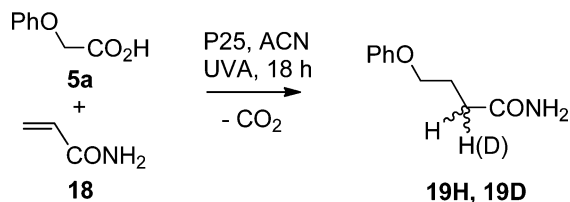


It should be noted that while we believe radical stability to be a key aspect in this system, it is clear that there are other factors at play as well and that these take precedence in deciding the reaction outcome in a few instances. For example, vinylacetic acid would be expected to generate the allyl radical very readily in the presence of photoexcited TiO₂. While we did observe the allyl radical in our EPR experiments, no products at all were observed in the preparative photolysis involving vinylacetic acid and **2**. In this case, other as yet unknown factors at the TiO₂ surface must come into play.

A crucial feature of the process is that in the formation of adducts **3** and **7** a hydrogen atom is gained from some source within the dispersion. This is *not the proton lost from the aromatic ring* because reduced adducts were formed equally well from acids lacking aromatic rings. Several deuterium labeling experiments were carried out to try to identify the source. The reaction of phenoxyacetic acid with acrylamide was again chosen as a test-bed process (Scheme 7) because it was clean and practically quantitative.

When this reaction was carried out in *d*₃-CH₃CN solvent, the isolated adduct was screened for D incorporation by ¹H and ²H NMR spectroscopy and GC–MS. However, no deuterium could be detected in the 4-phenoxybutanamide (**19H**). Reaction with *d*₁-phenoxyacetic acid also yielded adduct with no detectable D incorporation. Thus, unless the acidic D atom of **5a** rapidly and completely exchanges, the source of the

Scheme 7. Deuterium Labeling Test Reactions



additional H atom is neither the acid nor the solvent. The most likely source therefore is the P25 semiconductor. Obviously it is counterintuitive that a metal oxide would supply protons. However, it is well-established that H₂O molecules and HO groups are attached to the surface of the TiO₂ particles.^{28a} Drying P25 in a vacuum at 150 °C removes a significant amount of the surface H₂O while leaving the chemically attached HO groups. When P25 dried in this way was used, the yield of **18** was scarcely reduced, suggesting that the OH groups were likely the proton donors. Attempts were made to deuterate the H₂O and OH groups on the P25 surface by refluxing in degassed D₂O in a glovebox. However, it was found that back exchange occurred immediately upon exposure to air and rapidly with any moisture traces in solvents or on surfaces. Only partly deuterated P25 (ca. 80% as judged by IR) could be obtained. Definitive experiments were difficult to achieve because of this. When the partly deuterated P25D was photolyzed with the undeuterated acid, the phenoxybutanamide product contained no deuterium. It seemed possible, however, that P25 surface OD groups could have rapidly exchanged with protons from the COOH groups of **5a**. Experiments with partly deuterated P25D and **5a**-COOD were also carried out, but deuterated **19D** was again not found. In view of the partially deuterated nature of the P25D and the ease with which it reverts to the protiated form, making handling difficult, our tentative conclusion is still that the P25 is the source of the H atoms.

CONCLUSIONS

We have found that photochemical reactions employing P25 and carboxylic acids under dry anaerobic conditions generate C-centered radicals that can be deployed in several types of C–C bond-forming processes. Simple aliphatic carboxylic acids alkylated *N*-phenylmaleimide, albeit rather inefficiently. Acids that yielded alkoxyalkyl, alkylthioalkyl, and benzyl radicals alkylated electron-deficient alkenes in moderate to good yields. Boc-protected amino acids furnished aminoalkyl radicals that alkylated *N*-phenylmaleimide in useful yields. The reactions of aryloxyacetic acids with maleimides resulted in a cascade process in which a pyrrolochromene derivative accompanied the alkylated succinimide. Selectivity for one or other of these products could be tuned to some extent by employing the TiO₂ catalyst under different conditions. Aryloxyacetic acids adapted for intramolecular ring closures by the inclusion of 2-alkenyl, 2-aryl, or 2-oximinyl functionality reacted rather poorly, especially the 2-aryl acceptor types.

The mechanism (Scheme 5) is supported by EPR spectroscopic evidence of the intermediates. An intriguing aspect of the process is the identity of the proton donor. Experiments with deuterium-labeled solvent and reactants implied that this was the hydroxyl groups on the surface of the P25. It appears that the titania supplies electrons and holes upon photostimulation but also donates protons from surface

hydroxyl groups, thus acting as both a catalyst and a reaction partner.

These photoredox reactions are cleanly, safely, and cheaply carried out in the laboratory, and the heterogeneous catalyst is simply filtered off during workup. Thus, with the exception mentioned above, they constitute a useful synthetic protocol.

EXPERIMENTAL SECTION

General Procedure for TiO₂ Photoredox Experiments. To a suspension of semiconductor (1–5 mg mL⁻¹) in MeCN (freshly distilled over CaH₂) in an oven-dried Pyrex tube were added known amounts of the desired carboxylic acid and alkene. The resulting suspension was degassed by bubbling with argon for 20 min. The mixture was then irradiated with eight 29 cm 15 W Philips Cleo tubes ($\lambda = 350$ nm) for the desired reaction time at ambient temperature. Following irradiation, the semiconductor powder was removed by filtration through a Celite pad. The solvent was removed under reduced pressure, and the reaction mixture was purified by chromatography. Yields were determined from the amounts of isolated products and/or from the ¹H NMR spectra by reference to CH₂Br₂ as an internal standard. Additional general procedures are described in the Supporting Information.

NMR Tube Irradiations. Irradiations were carried out using titania sol–gel-coated NMR tubes. A photoreactor consisting of two lots of six 8 W BLB UV lamps (emission $\lambda_{\text{max}} = 365$ nm), each arranged in a semicylinder with an aluminum reflector, was used to irradiate the contents of the NMR tube. The two photoreactor semicylinders were brought together to surround the NMR tube (see the Supporting Information for a graphic). For a typical reaction, a stock solution comprising acid (10 mM) in *d*₃-CH₃CN was prepared. This solution was purged with argon for 5 min, and then 1 mL was pipetted into an argon-flushed sol–gel-coated NMR tube. The cap was quickly replaced on the tube and sealed with Parafilm. The loaded NMR tube was placed in an overhead stirrer (turned on its side), which was spun at 250 rpm. The tube was held at a slight angle with respect to horizontal in the chuck of the overhead stirrer so that, when rotated, it described a small (ca. 2 cm) circle at its non-chuck-held end so as to agitate the reaction solution. Once the NMR tube was in place, the irradiation was started, and the tube was periodically removed and analyzed by NMR.

Deuterium Labeling Experiments. These experiments were carried out in a similar fashion to the photoredox experiments outlined above. Following photolysis, the reaction mixtures were scrutinized for deuterium incorporation by ¹H and ²H NMR spectroscopy and GC–MS. Further details of these experiments are provided in the Supporting Information.

3-Methyl-1-phenylpyrrolidine-2,5-dione (3a). Acetic acid (6 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol), and TiO₂ (12 mg, 0.15 mmol) were reacted in accordance with the general procedure to yield **3a** (24% by NMR) as a white solid. Mp: 94–96 °C. ¹H NMR (400 MHz, CDCl₃, 296 K): δ 1.44 (d, *J* = 7.2 Hz, 3H), 2.47–2.54 (m, 1H), 2.97–3.14 (m, 2H), 7.27–7.30 (m, 2H), 7.36–7.42 (m, 1H), 7.44–7.50 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, 297 K): δ 16.9, 34.9, 36.7, 126.4, 128.6, 129.2, 132.0, 175.5, 179.6. LR-ESIMS: *m/z* 190 [M + H]⁺. HR-ESIMS: *m/z* 190.0861 (calcd for C₁₁H₁₂NO₂, 190.0863). Also observed was *N*-phenylsuccinimide (41% by NMR).

3-Pentyl-1-phenylpyrrolidine-2,5-dione (3b). *n*-Hexanoic acid (11.6 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol), and TiO₂ (12 mg, 0.15 mmol) were reacted in accordance with the general procedure. Following irradiation, a yield of 4% (0.04 mmol) was determined for **3b**. Yields were determined by assigning peaks “a” and “b” by analogy with the previously characterized 3-ethyl adduct.³⁰ ¹H NMR (500 MHz, CDCl₃, 295 K): δ 2.60 (dd, *J* = 3.3, 17.0 Hz, 1H), 2.97–3.07 (m, 1H). Also observed were *N*-phenylsuccinimide (4% by NMR) and unreacted *n*-hexanoic acid (65% conversion by NMR).

3-Neopentyl-1-phenylpyrrolidine-2,5-dione (3c). *tert*-Butylacetic acid (11.6 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol), and TiO₂ (12 mg, 0.15 mmol) were reacted in accordance

with the general procedure to yield **3c** (18% by NMR) as a white solid. Mp: sample decomposed at >250 °C. ¹H NMR (400 MHz, CDCl₃, 296 K): δ 0.94 (s, 9H), 1.36 (dd, *J* = 10.7, 14.0 Hz, 1H), 2.12 (dd, *J* = 2.0, 13.9 Hz, 1H), 2.54 (dd, *J* = 5.3, 18.1 Hz, 1H), 3.03 (dd, *J* = 9.1, 18.1 Hz, 1H), 2.84–2.92 (m, 1H), 7.19–7.22 (m, 2H), 7.29–7.34 (m, 1H), 7.37–7.42 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, 297 K): δ 29.6, 29.7, 31.0, 37.6, 45.9, 126.4, 128.6, 129.2, 132.1, 175.8, 179.8. LR-ESIMS: *m/z* 246 [M + H]⁺. HR-ESIMS: *m/z* 246.1486 (calcd for C₁₅H₂₀NO₂, 246.1489). Also observed was *N*-phenylsuccinimide (40% by NMR).

3-Isopropyl-1-phenylpyrrolidine-2,5-dione (3d). Isobutyric acid (8.1 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol), and TiO₂ (12 mg, 0.15 mmol) were reacted in accordance with the general procedure to yield **3d** (25% by NMR) as a white solid. Mp: 90–92 °C. ¹H NMR (400 MHz, CDCl₃, 297 K): δ 0.99 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 2.32–2.40 (m, 1H), 2.56 (dd, *J* = 4.4, 18.3 Hz, 1H), 2.79 (dd, *J* = 9.4, 18.3 Hz, 1H), 2.87–2.92 (m, 1H), 7.18–7.21 (m, 2H), 7.29–7.34 (m, 1H), 7.37–7.43 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, 300 K): δ 17.3, 20.0, 29.2, 30.6, 45.8, 126.5, 128.6, 129.2, 131.9, 175.9, 178.4. LR-ESIMS: *m/z* 218 [M + H]⁺. HR-ESIMS: *m/z* 218.1178 (calcd for C₁₃H₁₆NO₂, 218.1176). Also observed was *N*-phenylsuccinimide (25% by NMR).

3-tert-Butyl-1-phenylpyrrolidine-2,5-dione (3e). Pivalic acid (10.2 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol), and TiO₂ (12 mg, 0.15 mmol) were reacted in accordance with the general procedure to yield **3e** (38% by NMR) as a white solid. Mp: 101–103 °C. ¹H NMR (400 MHz, CDCl₃, 300 K): δ 1.12 (s, 9H), 2.67–2.80 (m, 2H), 2.89 (dd, *J* = 8.8, 17.6 Hz, 1H), 7.24–7.26 (m, 2H), 7.36–7.41 (m, 1H), 7.45–7.49 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, 300 K): δ 27.2, 32.0, 33.8, 49.9, 126.6, 128.6, 129.2, 132.0, 175.6, 177.4. LR-ESIMS: *m/z* 232 [M + H]⁺. HR-ESIMS: *m/z* 232.1326 (calcd for C₁₄H₁₈NO₂, 232.1332). Also observed was *N*-phenylsuccinimide (31% by NMR).

3-(Trifluoromethyl)-1-phenylpyrrolidine-2,5-dione (3f). Trifluoroacetic acid (11.4 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol), and TiO₂ (12 mg, 0.15 mmol) were reacted in accordance with the general procedure to yield **3f** (~1% by NMR). ¹H NMR (400 MHz, CDCl₃, 295 K): δ 2.86 (dd, *J* = 5.5, 18.6 Hz, 1H), 2.99 (dd, *J* = 9.5, 18.6 Hz, 1H), 3.61 (m, 1H), 7.10 (m, 2H), 7.39 (m, 3H). ¹⁹F NMR (375 MHz, CDCl₃, 296 K): δ –69.3 (s, 3F). Data are consistent with literature values.³¹ Also observed was *N*-phenylsuccinimide (trace).

3-(Methoxymethyl)-1-phenylpyrrolidine-2,5-dione (3g). Methoxyacetic acid (54.4 mg, 0.63 mmol), *N*-phenylmaleimide (433.6 mg, 2.50 mmol), and TiO₂ (75 mg, 0.94 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 h, the reaction mixture was purified by column chromatography on silica gel (eluent: 30% EtOAc in petroleum ether 40–60) to yield **3g** as a white powder (74.4 mg, 54%). Mp: 109–111 °C. ¹H NMR (400 MHz, CDCl₃, 299 K): δ 2.86–2.99 (m, 2H), 3.08–3.15 (m, 1H), 3.38 (s, 3H), 3.36 (dd, *J* = 3.3, 9.1 Hz, 1H), 3.91 (dd, *J* = 3.9, 9.1 Hz, 1H), 7.26–7.30 (m, 2H), 7.36–7.41 (m, 1H), 7.44–7.49 (m, 2H). ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 31.9, 41.2, 59.3, 70.8, 126.6, 128.6, 129.1, 132.1, 175.8, 177.3. Data are consistent with literature values.¹⁶

3-(tert-Butoxymethyl)-1-phenylpyrrolidine-2,5-dione (3h). *tert*-Butoxyacetic acid (87.3 mg, 0.66 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol), and TiO₂ (80 mg, 1.0 mmol) were reacted in accordance with the general procedure. Following irradiation for 17 h, ¹H NMR analysis revealed that *N*-phenylmaleimide had been consumed entirely while a significant quantity of *tert*-butoxyacetic acid remained. A further 462.3 mg of *N*-phenylmaleimide was hence added, and the reaction was photolyzed for another 18 h. The reaction mixture was then purified by column chromatography on silica gel (eluent: 25% EtOAc in pentanes) to yield **3h** as a yellow oil (97.8 mg, 57%). ¹H NMR (500 MHz, CDCl₃, 295 K): δ 1.18 (s, 9H), 2.85–2.89 (m, 2H), 3.07–3.11 (m, 1H), 3.59 (dd, *J* = 2.9, 8.5 Hz, 1H), 3.91 (dd, *J* = 3.5, 8.5 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 27.4, 32.3, 41.3, 60.7, 73.3, 126.6, 128.6, 129.2, 134.2, 176.3, 178.0. LR-

ESIMS: *m/z* 262 [M + H]⁺. HR-ESIMS: *m/z* 262.1440 (calcd for C₁₅H₂₀NO₃, 262.1438).

1-Phenyl-3-(tetrahydrofuran-2-yl)-pyrrolidine-2,5-dione (3i). 2-Tetrahydrofuroic acid (76.6 mg, 0.66 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol), and TiO₂ (80 mg, 1.00 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 h, the reaction mixture was purified by column chromatography on silica gel (eluent: Et₂O) to yield a 1:1 mixture of the two diastereoisomers of **3i** as a yellow oil (121.8 mg, 75%). *Diastereomer 1*: ¹H NMR (400 MHz, CDCl₃, 295 K): δ 1.92–2.02 (m, 2H), 2.02–2.12 (m, 2H), 2.79–2.84 (m, 1H), 2.99 (dd, *J* = 9.3, 18.3 Hz, 1H), 3.26–3.30 (m, 1H), 3.76–3.84 (m, 2H), 4.23–4.27 (m, 1H), 7.26–7.32 (m, 2H), 7.37–7.42 (m, 1H), 7.45–7.51 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, 297 K): δ 25.9, 27.9, 32.7, 43.4, 68.8, 79.1, 126.6, 128.6, 129.1, 132.0, 175.7, 175.9. *Diastereomer 2*: ¹H NMR (500 MHz, CDCl₃, 295 K): δ 1.63–1.71 (m, 1H), 1.92–2.02 (m, 2H), 2.10–2.19 (m, 1H), 2.79–2.84 (m, 2H), 3.08–3.12 (m, 1H), 3.86–3.94 (m, 2H), 4.39–4.44 (m, 1H), 7.26–7.32 (m, 2H), 7.37–7.42 (m, 1H), 7.45–7.51 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, 297 K): δ 25.9, 29.7, 29.8, 44.4, 68.8, 77.3, 126.6, 128.6, 129.1, 132.0, 176.5, 177.4. GC-MS: for *t*_R = 15.75 min, *m/z* (%) 245 (38), 217 (10), 202 (58), 175 (100), 147 (10), 119 (28), 111 (11), 71 (98); for *t*_R = 16.20 min, *m/z* (%) 245 (51), 217 (11), 202 (33), 175 (81), 147 (6), 119 (22), 111 (12), 71 (100). LR-ESIMS: *m/z* 246 [M + H]⁺. HR-ESIMS: *m/z* 246.1127 (calcd for C₁₄H₁₆NO₃, 246.1125).

3-(Methylthiomethyl)-1-phenylpyrrolidine-2,5-dione (3j). Methylthioacetic acid (70.8 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol), and TiO₂ (80 mg, 1.00 mmol) were reacted in accordance with the general procedure. Following irradiation for 42 h, the reaction mixture was purified by column chromatography on silica gel (eluent: gradient of 20–40% EtOAc in petroleum ether 40–60) to yield **3j** as a white powder (53.6 mg, 34%). Mp: 90–94 °C. ¹H NMR (500 MHz, CDCl₃, 299 K): δ 2.14 (s, 3H), 2.84 (dd, 1H, *J* = 5.0, 18.4 Hz), 2.92 (dd, 1H, *J* = 7.4, 13.5 Hz), 3.01 (dd, 1H, *J* = 9.2, 18.4 Hz), 3.04 (dd, 1H, *J* = 4.1, 13.5 Hz), 3.21–3.28 (m, 1H), 7.22–7.27 (m, 2H), 7.35–7.39 (m, 1H), 7.42–7.47 (m, 2H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 16.5, 33.7, 35.5, 40.1, 126.5, 128.7, 129.2, 131.9, 175.2, 177.5. LR-ESIMS: *m/z* 236 [M + H]⁺. HR-ESIMS: *m/z* 236.0741 (calcd for C₁₂H₁₄NO₂S, 236.0740).

1-Phenyl-3-(thiophen-2-ylmethyl)pyrrolidine-2,5-dione (3k). 2-Thiopheneacetic acid (93.9 mg, 0.66 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol), and TiO₂ (80 mg, 1.00 mmol) were reacted in accordance with the general procedure. Following irradiation for 17 h, the reaction mixture was purified by column chromatography on silica gel (eluent: 20% EtOAc in pentanes) to yield **3k** as a yellow oil (45.9 mg, 26%). ¹H NMR (500 MHz, CDCl₃, 295 K): δ 2.72 (dd, *J* = 4.8, 18.4 Hz, 1H), 2.98 (dd, *J* = 9.2, 18.4 Hz, 1H), 3.30–3.35 (m, 1H), 3.37–3.45 (m, 2H), 6.89 (m, 1H), 6.98 (m, 1H), 7.20 (m, 2H), 7.39 (m, 1H), 7.46 (m, 2H). ¹³C NMR (75 MHz, CDCl₃, 297 K) 30.7, 33.4, 41.3, 125.0, 126.5, 127.0, 127.3, 128.7, 129.2, 131.8, 138.2, 175.2, 177.8, 177.5. LR-ESIMS: *m/z* 272 [M + H]⁺. HR-ESIMS: *m/z* 272.0743 (calcd for C₁₅H₁₄NO₂S, 272.0740). 1,2-Bis(thiophen-2-yl)ethane was also isolated as a clear oil (14.1 mg, 22%). ¹H NMR (500 MHz, CDCl₃, 295 K): δ 3.20 (s, 4H), 6.80 (d, *J* = 3.4 Hz, 2H), 6.91–6.94 (m, 2H), 7.14 (d, *J* = 5.2 Hz, 2H). Data are consistent with literature values.³²

3-Benzyl-1-phenylpyrrolidine-2,5-dione (3l). Phenylacetic acid (89.9 mg, 0.66 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol), and TiO₂ (80 mg, 1.00 mmol) were reacted in accordance with the general procedure. Following irradiation for 22 h, the reaction mixture was purified by dry flash chromatography on silica gel (eluent: gradient of 10–20% EtOAc in CH₂Cl₂) to yield **3l** as a white powder (99.3 mg, 57%). ¹H NMR (500 MHz, CDCl₃, 295 K): δ 2.65 (dd, *J* = 4.7, 18.5 Hz, 1H), 2.88 (dd, *J* = 9.2, 18.5 Hz, 1H), 3.08 (dd, *J* = 8.0, 13.8 Hz, 1H), 3.25 (dd, *J* = 4.4, 13.8 Hz, 1H), 3.30–3.35 (m, 1H), 7.17 (m, 2H), 7.22 (m, 2H), 7.29 (m, 1H), 7.34 (m, 2H), 7.39 (m, 1H), 7.46 (m, 2H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 33.5, 36.7, 41.4, 77.2, 126.6, 127.4, 128.8, 129.0, 129.3, 129.4, 132.0, 136.8, 175.4, 178.4. Data are consistent with literature values.³³ Bibenzyl (10.9 mg, 18%) was observed by NMR prior to purification of the reaction mixture. ¹H

NMR (500 MHz, CDCl₃, 298 K): δ 2.95 (s, 4H), 7.21–7.24 (m, 6H), 7.30–7.33 (m, 4H). Data are consistent with literature values.³⁴

tert-Butyl (1-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)ethyl)-carbamate (3m). *N*-Boc-L-alanine (126.2 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol), and TiO₂ (80 mg, 1.00 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 h, the mixture was purified by column chromatography on silica gel (eluent: gradient of 20–40% EtOAc in petroleum ether 40–60) to yield two diastereomers of **3m**. *Diastereomer 1* was isolated as a white powder (36.7 mg, 18%). Mp: 155–157 °C. ¹H NMR (400 MHz, CDCl₃, 296 K): δ 1.29 (d, *J* = 6.9 Hz, 3H), 1.38 (s, 9H), 2.78 (dd, *J* = 4.8, 18.6 Hz, 1H), 2.89 (dd, *J* = 9.1, 18.5 Hz, 1H), 3.15–3.20 (m, 1H), 4.08–4.18 (m, 1H), 4.53 (bs, 1H), 7.18–7.22 (m, 2H), 7.30–7.35 (m, 1H), 7.38–7.43 (m, 2H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 18.7, 28.3, 32.2, 45.3, 47.7, 80.2, 126.5, 128.7, 129.2, 131.8, 155.5, 175.3, 176.6. LR-ESIMS: *m/z* 341 [M + Na]⁺. HR-ESIMS: *m/z* 341.1467 (calcd for C₁₇H₂₂O₄N₂Na, 341.1472). *Diastereomer 2* (20% wrt CH₂Br₂ standard) was obtained as a 1:1 mixture with *N*-phenylsuccinimide. ¹H NMR (500 MHz, CDCl₃, 297 K): δ 1.25 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H), 2.63 (dd, *J* = 4.5, 18.6 Hz, 1H), 3.00 (dd, *J* = 9.6, 18.5 Hz, 1H), 3.17–3.23 (m, 1H), 4.13–4.17 (m, 1H), 5.20 (bs, 1H), 7.27–7.30 (m, 2H), 7.39–7.42 (m, 1H), 7.46–7.50 (m, 2H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 17.1, 28.5, 31.9, 45.1, 47.1, 80.0, 126.6, 128.8, 129.3, 131.8, 155.2, 175.2, 177.5. LR-ESIMS: *m/z* 341 [M + Na]⁺. HR-ESIMS: *m/z* 341.1475 (calcd for C₁₇H₂₂O₄N₂Na, 341.1472).

tert-Butyl 2',5'-Dioxo-1'-phenyl-[2,3'-bipyrrrolidine]-1-carboxylate (3n). *N*-Boc-L-proline (144.3 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol), and TiO₂ (80 mg, 1.00 mmol) were reacted in accordance with the general procedure. Following irradiation for 17 h, the crude mixture was purified by dry flash chromatography on silica gel (eluent: gradient of 20–60% EtOAc in petroleum ether 40–60) to yield an inseparable mixture of two diastereomers of **3n** (171 mg, 75%, 1:1 ratio) that also contained 7% *N*-phenylsuccinimide. ¹H NMR (500 MHz, CDCl₃, 326 K): *diastereomer 1* δ 1.44 (s, 9H), 1.94–1.99 (m, 2H), 2.18–2.24 (m, 2H), 2.73–2.75 (m, 1H), 2.83 (dd, *J* = 3.8, 9.4 Hz, 1H), 3.53 (dd, *J* = 7.3, 11.1 Hz, 1H), 3.79–3.85 (m, 2H), 4.34–4.39 (m, 2H), 7.27–7.47 (m, 5H); *diastereomer 2* δ 1.49 (s, 9H), 2.14–2.17 (m, 2H), 1.66–1.71 (m, 2H), 2.69–2.71 (m, 1H), 2.86 (dd, *J* = 4.3, 9.7 Hz, 1H), 3.30 (dd, *J* = 3.4, 7.8 Hz, 1H), 3.95–3.99 (m, 2H), 4.31–4.35 (m, 2H), 7.27–7.47 (m, 5H). ¹³C NMR (75 MHz, CDCl₃, 300 K): δ 23.3–24.0, 27.9, 28.4, 28.5, 29.7–30.1, 31.8, 43.7–44.1, 47.2–47.8, 57.1–57.8, 79.9–80.5, 126.5–126.8, 128.4–129.2, 131.2–132.0, 155.0–156.0, 174.1–177.3. GC–MS: for *t*_R = 19.81 min, *m/z* (%) 344 (2), 288 (19), 271 (17), 243 (48), 175 (16), 114 (50), 70 (100) 57 (41); for *t*_R = 20.09 min, *m/z* (%) 344 (2), 288 (19), 271 (17), 243 (48), 175 (16), 114 (50), 70 (100) 57 (41). LR-ESIMS: *m/z* 367 [M + Na]⁺. HR-ESIMS: *m/z* 367.1632 (calcd for C₁₉H₂₄N₂O₄Na, 367.1628).

tert-Butyl 2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)piperidine-1-carboxylate (3o). *N*-Boc-D/L-2-piperidinecarboxylic acid (151.4 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol), and TiO₂ (80 mg, 1.00 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 h, the crude mixture was purified by column chromatography on silica gel (eluent: 30% EtOAc in pentanes) to yield two diastereomers of **3o**. *Diastereomer 1* was isolated as an off-white solid (32.7 mg, 14%). Mp: 107–110 °C. ¹H NMR (500 MHz, CDCl₃, 295 K): δ 1.39 (s, 9H), 1.46–1.59 (bm, 2H), 1.67–1.79 (bm, 4H), 2.52 (dd, *J* = 3.0, 18.2 Hz, 1H), 2.98 (dd, *J* = 8.9, 18.2 Hz, 1H), 3.04 (t, *J* = 13.2 Hz, 1H), 3.26–3.30 (m, 1H), 4.06 (d, *J* = 13.2 Hz, 1H), 4.34–4.37 (m, 1H), 7.32–7.36 (m, 3H), 7.41–7.45 (m, 2H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 18.9, 24.8, 27.0, 28.4, 34.2, 38.1, 40.2, 53.3, 79.9, 126.7, 128.4, 128.9, 132.1, 155.5, 174.9, 176.1. LR-ESIMS: *m/z* 381 [M + Na]⁺. HR-ESIMS: *m/z* 381.1787 (calcd for C₂₀H₂₆N₂O₄Na, 381.1785). *Diastereomer 2* (15% wrt CH₂Br₂ standard) was obtained as a 1:2 mixture with *N*-phenylsuccinimide. ¹H NMR (500 MHz, CDCl₃, 295 K): δ 1.42 (s, 9H), 1.53 (m, 1H), 1.68–1.72 (m, 1H), 1.90–1.96 (m, 1H), 2.21–2.23 (m, 1H), 2.40–2.45 (m, 1H), 2.54–2.58 (m, 1H), 2.95 (dd, *J* = 4.4, 19.0 Hz, 1H), 3.05 (dd, *J* = 9.6, 17.6 Hz, 1H), 3.26 (dd, *J* = 9.1,

19.0 Hz, 1H), 3.35 (dd, *J* = 6.3, 17.6 Hz, 1H), 3.37–3.42 (m, 1H), 3.94–3.98 (m, 1H), 7.38–7.42 (m, 3H), 7.44–7.49 (m, 2H). ¹³C NMR (125 MHz, CDCl₃, 295 K): δ 19.6, 24.4, 24.6, 28.3, 33.4, 37.8, 39.5, 46.1, 82.5, 126.4, 128.5, 129.1, 131.4, 152.6, 175.2, 175.5. LR-ESIMS: *m/z* 381 [M + Na]⁺. HR-ESIMS: *m/z* 381.1787 (calcd for C₂₀H₂₆N₂O₄Na, 381.1785).

Attempted Preparation of 2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)acetoneitrile. Cyanoacetic acid (56.2 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol), and TiO₂ (80 mg, 1.00 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 h, the reaction mixture was scrutinized by ¹H NMR and GC–MS, but none of the desired product was obtained.

***N*-Methyl-3-(phenoxy)methylpyrrolidine-2,5-dione (7a) and *N*-Methyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione (6a).** Phenoxyacetic acid (100 mg, 0.65 mmol), *N*-methylmaleimide (145 mg, 1.3 mmol), and TiO₂ (75 mg, 0.98 mmol) were reacted in accordance with the general procedure. Following irradiation for 20 h, the crude mixture was purified by column chromatography on silica gel (eluent: 20% EtOAc in petroleum ether 40–60) to yield **7a** as a colorless oil (32.6 mg, 23%). ¹H NMR (400 MHz, CDCl₃, 297 K): δ 2.88–2.90 (m, 2H), 3.04 (s, 3H), 3.17–3.23 (m, 1H), 4.17 (dd, *J* = 3.4, 9.2 Hz, 1H), 4.40 (dd, *J* = 4.4, 9.2 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 25.4, 32.1, 41.1, 66.4, 115.1, 122.0, 130.0, 158.5, 177.0 178.0. **6a** was also obtained as a white powder (77.8 mg, 55%). ¹H NMR (400 MHz, CDCl₃, 296 K): δ 3.00 (s, 3H), 3.36–3.40 (m, 1H), 4.01 (dd, *J* = 4.2, 11.4 Hz, 1H), 4.07 (d, *J* = 9.2 Hz, 1H), 4.62 (dd, *J* = 2.9, 11.4 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 27.8, 40.1, 42.7, 64.3, 118.1, 118.3, 123.2, 129.4, 130.5, 155.7, 176.6, 177.2. Data are consistent with literature values.¹⁶

3-(Phenoxy)methyl-1-phenylpyrrolidine-2,5-dione (7b) and *N*-Phenyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione (6b). Phenoxyacetic acid (100 mg, 0.65 mmol), *N*-phenylmaleimide (230 mg, 1.3 mmol), and TiO₂ (75 mg, 0.98 mmol) were reacted in accordance with the general procedure. Following irradiation for 11 h, the crude mixture was purified by column chromatography on silica gel (eluent: 20% EtOAc in petroleum ether 40–60) to yield **7b** as a yellow oil (71.5 mg, 39%). ¹H NMR (400 MHz, CDCl₃, 297 K): δ 3.01–3.07 (m, 2H), 3.33–3.39 (m, 1H), 4.28 (dd, *J* = 3.2, 9.0 Hz, 1H), 4.55 (dd, *J* = 4.1, 9.1 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.00 (t, *J* = 7.3 Hz, 1H), 7.28–7.33 (m, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 7.2, 2H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 32.4, 41.1, 66.9, 115.1, 122.1, 127.0, 129.2, 129.7, 130.0, 132.4, 158.5, 175.9, 177.1. **6b** was also obtained as a white powder (72.8 mg, 40%). ¹H NMR (400 MHz, CDCl₃, 297 K): δ 3.54–3.58 (m, 1H), 4.11, (dd, *J* = 4.4, 11.4 Hz, 1H), 4.23 (d, *J* = 9.3 Hz, 1H), 4.7 (dd, *J* = 3.3, 11.4 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.22–7.27 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.1 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 40.2, 42.6, 64.4, 77.1, 77.5, 77.9, 117.7, 118.3, 123.3, 126.7, 129.2, 129.5, 129.6, 130.7, 132.1 155.7 175.5, 176.1. Data are consistent with literature values.¹⁶

3-((4-(*tert*-Butyl)phenoxy)methyl)-1-methylpyrrolidine-2,5-dione (7c) and 8-(*tert*-Butyl)-2-methyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione (6c). 4-(*tert*-Butyl)phenoxyacetic acid (130.3 mg, 0.62 mmol), *N*-methylmaleimide (275.6 mg, 2.48 mmol), and TiO₂ (75 mg, 0.98 mmol) were reacted in accordance with the general procedure. Following irradiation for 22 h, the reaction mixture was purified by column chromatography on silica gel (eluent: 20% EtOAc in petroleum ether 40–60) to yield **7c** as a clear oil (18.4 mg, 11%). ¹H NMR (400 MHz, CDCl₃, 296 K): δ 1.29 (s, 9H), 2.84–2.89 (m, 2H), 3.03 (s, 3H), 3.21–3.16 (m, 1H), 4.16 (dd, *J* = 3.4, 9.2 Hz, 1H), 4.39 (dd, *J* = 4.4, 9.2 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃, 296 K): δ 25.0, 29.7, 31.5, 34.1, 40.7, 66.1, 114.2, 126.4, 144.4, 155.8, 176.6, 177.6. LR-ESIMS: *m/z* 276 [M + H]⁺. HR-ESIMS: *m/z* 276.1599 (calcd for C₁₆H₂₂NO₃, 276.1594). **6c** was also obtained as a white powder (77.2 mg, 46%). Mp: 134–137 °C. ¹H NMR (400 MHz, CDCl₃, 296 K): δ

1.32 (s, 9H), 2.98 (s, 3H), 3.33–3.37 (m, 1H), 3.98 (dd, $J = 4.1, 11.3$ Hz, 1H), 4.05 (d, $J = 9.2$ Hz, 1H), 4.59 (dd, $J = 3.0, 11.3$ Hz, 1H), 6.82 (d, $J = 8.6$ Hz, 1H), 7.23 (dd, $J = 2.4, 8.6$ Hz, 1H), 7.58 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3 , 296 K): δ 25.8, 31.9, 34.8, 40.3, 42.7, 64.3, 117.1, 117.6, 126.5, 127.3, 146.0, 153.3, 176.7, 177.3. LR-ESIMS: m/z 274 $[\text{M} + \text{H}]^+$. HR-ESIMS: m/z 274.1442 (calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_3$, 274.1438).

3-((4-(tert-Butyl)phenoxy)methyl)-1-phenylpyrrolidine-2,5-dione (7d) and 8-(tert-Butyl)-2-phenyl-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione (6d). 4-(tert-Butyl)phenoxyacetic acid (70 mg, 0.33 mmol), *N*-phenylmaleimide (117 mg, 0.66 mmol), and TiO_2 (40 mg, 0.5 mmol) were reacted in accordance with the general procedure. Following irradiation for 19 h, the crude mixture was purified by column chromatography on silica gel (eluent: 20% EtOAc in petroleum ether 40–60) to yield **7d** as a clear oil (31.2 mg, 28%). ^1H NMR (300 MHz, CDCl_3 , 295 K): δ 1.30 (s, 9H), 2.98–3.13 (m, 2H), 3.30–3.37 (m, 1H), 4.23 (dd, $J = 3.2, 9.1$ Hz, 1H), 4.53 (dd, $J = 3.9, 9.1$ Hz, 1H), 6.85 (d, $J = 8.9$ Hz, 2H), 7.27–7.33 (m, 3H), 7.40–7.51 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3 , 297 K): δ 29.7, 31.5, 34.2, 40.8, 66.6, 114.2, 126.4, 126.6, 128.7, 129.2, 132.0, 144.6, 155.8, 175.6, 176.8. LR-ESIMS: m/z 338 $[\text{M} + \text{H}]^+$. HR-ESIMS: m/z 338.1755 (calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_3$, 338.1751). **6d** was also obtained as a clear oil (50.3 mg, 46%). ^1H NMR (300 MHz, CDCl_3 , 296 K): δ 1.32 (s, 9H), 3.51–3.56 (m, 1H), 4.10 (dd, $J = 4.3, 11.4$ Hz, 1H), 4.23 (d, $J = 7.3$ Hz, 1H), 4.66 (dd, $J = 3.3, 11.5$ Hz, 1H), 6.87 (d, $J = 8.1$ Hz, 1H), 7.24–7.29 (m, 2H), 7.33–7.48 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3 , 297 K): δ 31.5, 34.4, 40.0, 42.3, 64.1, 116.4, 117.3, 126.3, 127.0, 128.7, 129.1, 131.8, 134.2, 145.7, 153.0, 175.2, 175.7. LR-ESIMS: m/z 336 $[\text{M} + \text{H}]^+$. HR-ESIMS: m/z 336.1598 (calcd for $\text{C}_{21}\text{H}_{22}\text{NO}_3$, 336.1600).

1-Methyl-3-((4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-2,5-dione (7e) and 2-Methyl-8-(trifluoromethyl)-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione (6e). 4-(Trifluoromethyl)phenoxyacetic acid (143 mg, 0.65 mmol), *N*-methylmaleimide (145 mg, 1.3 mmol), and TiO_2 (75 mg, 0.98 mmol) were reacted in accordance with the general procedure. Following irradiation for 16 h, the reaction mixture was purified by two rounds of column chromatography on silica gel (eluent: 20% EtOAc in petroleum ether 40–60 and subsequently 10% EtOAc in CH_2Cl_2) to yield **7e** as a clear oil (54.7 mg, 29%). ^1H NMR (400 MHz, CDCl_3 , 300 K): δ 2.82–2.96 (m, 2H), 3.05 (s, 3H), 3.20–3.26 (m, 1H), 4.22 (dd, $J = 3.4, 9.2$ Hz, 1H), 4.46 (dd, $J = 4.3, 9.2$ Hz, 1H), 6.94 (d, $J = 8.5$ Hz, 2H), 7.54 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3 , 300 K): δ 25.1, 31.6, 40.5, 66.1, 114.6, 123.9 (q, $^2J_{\text{C-F}} = 32.9$ Hz, 1C), 124.4 (q, $^3J_{\text{C-F}} = 271.2$ Hz, 2C), 127.0 (q, $^1J_{\text{C-F}} = 3.7$ Hz, 1C), 160.4, 176.2, 177.1. ^{19}F NMR (376 MHz, CDCl_3 , 300 K): δ –62.1. LR-ESIMS: m/z 288 $[\text{M} + \text{H}]^+$. HR-ESIMS: m/z 288.0838 (calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_3\text{F}_3$, 288.0842). **6e** was also obtained as a clear oil (60.1 mg, 32%). ^1H NMR (400 MHz, CDCl_3 , 298 K): δ 3.01 (s, 3H), 3.40–3.44 (m, 1H), 4.04–4.10 (m, 2H), 4.64 (dd, $J = 3.2, 11.5$ Hz, 1H), 6.98 (d, $J = 8.6$ Hz, 1H), 7.46 (d, $J = 8.5$ Hz, 1H), 7.87 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 25.5, 39.4, 41.8, 64.0, 117.9, 118.4, 123.9 (q, $^1J_{\text{C-F}} = 271.7$ Hz, 1C), 125.1 (q, $^2J_{\text{C-F}} = 33.1$ Hz, 1C), 127.2 (q, $^3J_{\text{C-F}} = 3.5$ Hz, 1C), 127.6 (q, $^3J_{\text{C-F}} = 3.8$ Hz, 1C), 157.7, 175.3, 176.1. ^{19}F NMR (376 MHz, CDCl_3 , 298 K): δ –62.3. LR-ESIMS: m/z 286 $[\text{M} + \text{H}]^+$. HR-ESIMS: m/z 286.0687 (calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_3\text{F}_3$, 286.0686).

1-Phenyl-3-((4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-2,5-dione (7f) and 8-(Trifluoromethyl)-2-phenyl-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione (6f). 4-(Trifluoromethyl)phenoxyacetic acid (143 mg, 0.65 mmol), *N*-phenylmaleimide (230 mg, 1.3 mmol), and TiO_2 (75 mg, 0.98 mmol) were reacted in accordance with the general procedure. Following irradiation for 16 h, the reaction mixture was purified by column chromatography on silica gel (eluent: 25% EtOAc in petroleum ether 40–60) to yield **7f** as a colorless solid (52.9 mg, 40%). Mp: 121–124 °C. ^1H NMR (400 MHz, CDCl_3 , 297 K): δ 2.98–3.13 (m, 2H), 3.35–3.40 (m, 1H), 4.28 (dd, $J = 3.1, 9.1$ Hz, 1H), 4.57 (dd, $J = 4.0, 9.1$ Hz, 1H), 6.97 (d, $J = 8.5$ Hz, 2H), 7.29 (d, $J = 7.2$ Hz, 2H), 7.41 (t, $J = 7.3$ Hz, 1H), 7.49 (t, $J = 7.2$ Hz, 2H), 7.56 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3 , 297 K): δ 31.9, 40.6,

66.6, 114.7, 124.0 (q, $^2J_{\text{C-F}} = 32.8$ Hz, 1C), 124.3 (q, $^1J_{\text{C-F}} = 271.1$ Hz, 1C), 126.5, 127.1 (q, $^3J_{\text{C-F}} = 3.7$ Hz, 2C), 128.8, 129.3, 131.9, 160.4, 175.2, 176.3. ^{19}F NMR (376 MHz, CDCl_3 , 297 K): δ –62.1. LR-ESIMS: m/z 367 $[\text{M} + \text{NH}_4]^+$. HR-ESIMS: m/z 367.1269 (calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3\text{F}_3$, 367.1275). **6f** was also obtained as a yellow oil (90 mg, 23%). ^1H NMR (400 MHz, CDCl_3 , 297 K): δ 3.57–3.61 (m, 1H), 4.15 (dd, $J = 4.2, 11.4$ Hz, 1H), 4.25 (d, $J = 9.3$ Hz, 1H), 4.71 (dd, $J = 3.4, 11.4$ Hz, 1H), 7.04 (d, $J = 8.5$ Hz, 1H), 7.24–7.27 (m, 2H), 7.36–7.51 (m, 4H), 7.93 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3 , 297 K): δ 39.5, 41.7, 64.1, 117.7, 118.5, 123.9 (q, $^1J_{\text{C-F}} = 271.8$ Hz, 1C), 125.2 (q, $^2J_{\text{C-F}} = 33.0$ Hz, 1C), 126.2, 126.4 (q, $^3J_{\text{C-F}} = 3.5$ Hz, 1C), 127.7 (q, $^3J_{\text{C-F}} = 3.7$ Hz, 1C), 128.9, 129.2, 131.5, 157.8, 174.3, 175.0. ^{19}F NMR (376 MHz, CDCl_3 , 297 K): δ –62.3. LR-ESIMS: m/z 365 $[\text{M} + \text{NH}_4]^+$. HR-ESIMS: m/z 365.1114 (calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3\text{F}_3$, 365.1108).

(E)-2-(2-(3-Methoxy-3-oxoprop-1-en-1-yl)phenoxy)acetic Acid (8a). A THF (60 mL) solution of methyl bromoacetate (0.62 mL, 6.54 mmol, 1.0 equiv) and triphenylphosphine (1.715 g, 6.54 mmol, 1.0 equiv) was heated at reflux for 4 h until a white precipitate formed. The suspension was allowed to cool to room temperature before filtration; the precipitate was washed with Et_2O (3 × 50 mL), and the precipitate was then redissolved in CH_2Cl_2 (30 mL) and H_2O (20 mL). Then 2 M NaOH (10 mL) was added, and the biphasic mixture was stirred overnight. The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with brine, dried (MgSO_4), and concentrated under reduced pressure to yield the phosphorane as a colorless powder (1.923 g, 88%). ^1H NMR (400 MHz, CDCl_3 , 295 K): δ 2.90 and 3.51 (br, 3H), 7.43–7.48 (m, 6H), 7.52–7.57 (m, 3H), 7.62–7.70 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3 , 298 K): δ 49.9, 128.5 (d, $J = 12.0$ Hz), 128.8 (d, $J = 12.2$ Hz), 131.9 (d, $J = 2.7$ Hz), 132.1 (d, $J = 9.8$ Hz), 132.9, 133.0 (d, $J = 10.2$ Hz). ^{31}P NMR (161 MHz, CDCl_3 , 295 K): δ 17.73. LR-ESIMS: m/z 335 $[\text{M} + \text{H}]^+$. HR-ESIMS: m/z 335.1200 (calcd for $\text{C}_{21}\text{H}_{20}\text{O}_2\text{P}$, 335.1195). A CHCl_3 (200 mL) solution of phosphorane (1.893 g, 5.66 mmol, 1.1 equiv) and 2-formylphenoxyacetic acid (0.927 g, 5.15 mmol, 1.0 equiv) was heated at reflux for 18 h. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography (eluent: gradient of petroleum ether to 1:1 EtOAc/petroleum ether) to yield **8a** as a colorless powder (1.037 g, 85%). Mp: 96 °C. ^1H NMR (300 MHz, CDCl_3 , 295 K): δ 3.80 (s, 3H), 4.77 (s, 2H), 6.61 (d, $J = 16.2$ Hz, 1H), 6.81 (d, $J = 8.3$ Hz, 1H), 7.03 (t, $J = 7.6$ Hz, 1H), 7.33 (td, $J = 1.7, 7.5$ Hz, 1H), 7.54 (dd, $J = 1.6, 7.7$ Hz, 1H), 8.04 (d, $J = 16.2$ Hz, 1H), 8.89–9.30 (br, 1H). ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 52.2, 65.4, 112.5, 119.5, 122.5, 124.4, 129.8, 131.8, 140.4, 156.7, 168.6, 173.8. LR-ESIMS: m/z 235 $[\text{M} - \text{H}]^-$. HR-ESIMS: m/z 235.0610 (calcd for $\text{C}_{12}\text{H}_{11}\text{O}_5$, 235.0612).

(E)-2-(2-(2-Cyanovinyl)phenoxy)acetic Acid (8b). Prepared in the same manner as **8a**. Bromoacetonitrile (0.88 mL, 12.5 mmol) and PPh_3 (3.28 g, 12.5 mL) were reacted to give the salt (4.580 g, 96%). The phosphorane was prepared as before to give a colorless powder (3.422 g, 91%). ^1H NMR (300 MHz, CDCl_3 , 297 K): δ 7.45–7.70 (m, 15H). ^{13}C NMR (121 MHz, CDCl_3 , 297 K): δ 128.9 (d, $J = 12.1$ Hz), 129.5 (d, $J = 12.4$ Hz), 132.3 (d, $J = 2.6$ Hz), 132.5 (d, $J = 9.9$ Hz), 133.0 (d, $J = 2.1$ Hz), 133.2 (d, $J = 10.1$ Hz). ^{31}P NMR (121 MHz, CDCl_3 , 295 K): δ 23.3. **8b** was prepared from the phosphorane (3.346 g, 11.11 mmol) and 2-formylphenoxyacetic acid (1.819 g, 10.10 mmol) to give a colorless powder (1.477 g, 72%). Mp: 118 °C. ^1H NMR (400 MHz, CDCl_3 , 297 K): δ 4.67 (s, 3H), 6.31 (d, $J = 16.8$ Hz, 1H), 6.83 (d, $J = 1.1$ Hz, 1H), 7.01 (t, $J = 7.6$ Hz, 1H), 7.33–7.39 (m, 2H), 7.62 (d, $J = 16.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3 , 297 K): δ 65.1, 98.0, 112.2, 119.1, 121.9, 123.0, 129.8, 132.2, 146.5, 156.5, 170.5. LR-ESIMS: m/z 202 $[\text{M} - \text{H}]^-$. HR-ESIMS: m/z 202.0511 (calcd for $\text{C}_{11}\text{H}_8\text{O}_3\text{N}$, 202.0510).

(E)-2-(2-(3-Oxopent-1-en-1-yl)phenoxy)acetic Acid (8c). Prepared in the same manner as **8a**. 1-Bromo-2-butanone (1.0 g, 6.62 mmol) and PPh_3 (1.737 g, 6.62 mmol) were reacted to give the salt (2.613 g, 96%). The phosphorane was prepared as before (2.051 g, 93%). ^1H NMR (500 MHz, CDCl_3 , 295 K): δ 1.18 (t, $J = 7.6$ Hz, 3H), 2.33 (qd, $J = 1.3, 7.6$ Hz, 2H), 7.43–7.47 (m, 6H), 7.52–7.56 (m, 3H), 7.62–7.67 (m, 6H). **8c** was prepared from the phosphorane

(1.712 g, 5.15 mmol) and 2-formylphenoxyacetic acid (0.843 g, 4.70 mmol) to give a colorless powder (0.829 g, 75%). Mp: 125 °C. ^1H NMR (400 MHz, CDCl_3 , 295 K): δ 1.17 (t, $J = 7.3$ Hz, 3H), 2.73 (q, $J = 7.3$ Hz, 2H), 4.78 (s, 2H), 6.82 (d, $J = 6.82$ Hz, 1H), 6.90 (d, $J = 16.4$ Hz, 1H), 7.04 (t, $J = 7.1$ Hz, 1H), 7.35 (td, $J = 1.7, 7.4$ Hz, 1H), 7.58 (dd, $J = 1.7, 7.7$ Hz, 1H), 7.96 (d, $J = 16.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3 , 298 K): δ 8.3, 33.5, 65.4, 112.2, 121.8, 124.0, 127.2, 128.9, 131.5, 137.8, 156.7, 170.6, 202.5. LR-ESIMS: m/z 233 $[\text{M} - \text{H}]^-$. HR-ESIMS: m/z 233.0820 (calcd for $\text{C}_{13}\text{H}_{13}\text{O}_4$, 233.0819).

2-([1,1'-Biphenyl]-2-yloxy)acetic Acid (11a). 2-Bromophenol (6.4 mL, 60.5 mmol), *tert*-butyldimethylsilyl chloride (10.0 g, 66.5 mmol), and imidazole (8.23 g, 121.0 mmol) were dissolved in the minimum volume of DMF, and the mixture was allowed to stir at room temperature overnight. The DMF was removed under reduced pressure, and the resultant residue was taken up in EtOAc and washed with 1 M HCl, sat. NaHCO_3 , and sat. LiCl before being dried over MgSO_4 . The solvent was then removed under reduced pressure to yield 2-bromophenoxy(*tert*-butyl)dimethylsilane (17.29 g, 99%). ^1H NMR (400 MHz, CDCl_3 , 296 K): δ 0.25 (s, 6H), 1.05 (s, 9H), 6.80–6.84 (m, 1H), 6.87 (dd, $J = 1.5, 8.1$ Hz, 1H), 7.14–7.19 (m, 1H), 7.51 (dd, $J = 1.7, 7.9$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3 , 297 K): δ -4.2, 18.4, 25.8, 115.4, 120.3, 122.4, 128.2, 133.4, 152.6. LR-ESIMS: m/z 287 $[\text{M} + \text{H}]^+$. HR-ESIMS: m/z 287.0461 (calcd for $\text{C}_{12}\text{H}_{20}\text{OSi}$, 287.0461). The aforementioned silane (0.54 g, 1.9 mmol) was coupled with phenylboronic acid (0.27 g, 2.2 mmol) by refluxing overnight in toluene (20 mL) and ethanol (5 mL) with $\text{Pd}[\text{P}(\text{Ph})_3]_4$ (0.2 g, 0.2 mmol) and K_2CO_3 (0.9 g, 6.5 mmol). The solvent was then removed under reduced pressure, and the reaction mixture was taken up in H_2O before being extracted with EtOAc. The combined extracts were dried over MgSO_4 before being concentrated under reduced pressure. The resultant mixture was subjected to column chromatography on silica gel (eluent: 25% CH_2Cl_2 in petroleum ether 40–60) to yield [1,1'-biphenyl]-2-yloxy(*tert*-butyl)dimethylsilane (0.39 g, 73%). ^1H NMR (400 MHz, CDCl_3 , 296 K): δ -0.05 (s, 6H), 0.83 (s, 9H), 6.92 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.04 (td, $J = 1.2, 7.5$ Hz, 1H), 7.21–7.24 (m, 1H), 7.30–7.33 (m, 2H), 7.36–7.40 (m, 2H), 7.50 (dd, $J = 1.5, 8.5$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3 , 297 K): δ -4.6, 18.1, 25.6, 120.4, 121.6, 126.7, 127.8, 128.3, 129.8, 130.9, 133.6, 139.2, 152.6. The aforementioned biphenylsilane (0.36 g, 1.3 mmol) was treated overnight with acetyl chloride (0.3 mL, 0.4 mmol) in methanol (15 mL). Following removal of the solvent under reduced pressure, the reaction mixture was subjected to column chromatography on silica gel (eluent: CH_2Cl_2) to yield [1,1'-biphenyl]-2-ol (0.19 g, 86%). ^1H NMR (400 MHz, CDCl_3 , 296 K): δ 5.13 (bs, 1H), 6.88–6.92 (m, 2H), 7.14–7.19 (m, 2H), 7.28–7.32 (m, 1H), 7.36–7.42 (m, 4H). The aforementioned biphenyl alcohol (0.19 g, 1.11 mmol), methyl bromoacetate (0.16 mL, 0.26 mmol), and K_2CO_3 (0.76 g, 5.5 mmol) were refluxed overnight in THF (20 mL). The solvent was then removed under reduced pressure, and the resultant residue was taken up in CH_2Cl_2 before being washed with H_2O and dried over MgSO_4 . The solvent was removed under reduced pressure, and the resultant mixture was subjected to column chromatography on silica gel (eluent: 25% CH_2Cl_2 in petroleum ether 40–60) to afford methyl 2-([1,1'-biphenyl]-2-yloxy)acetate (0.25 g, 94%). ^1H NMR (300 MHz, CDCl_3 , 294 K): δ 3.82 (s, 3H), 4.66 (s, 2H), 6.94 (d, $J = 8.3$ Hz, 1H), 7.15 (td, $J = 1.0, 7.5$ Hz, 1H), 7.33–7.51 (m, 5H), 7.69 (dd, $J = 1.4, 8.4$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3 , 295 K): δ 52.2, 65.8, 112.8, 122.2, 127.1, 128.1, 128.6, 129.7, 131.3, 131.4, 138.1, 154.8, 169.6. LR-ESIMS: m/z 243 $[\text{M} + \text{H}]^+$. HR-ESIMS: m/z 243.1020 (calcd for $\text{C}_{15}\text{H}_{15}\text{O}_3$, 243.1016). The aforementioned ester (0.19 g, 0.8 mmol) was hydrolyzed with LiOH (0.13 g, 3.2 mmol) in a 3:1 mixture of MeOH and H_2O . Following overnight stirring at room temperature, the reaction mixture was concentrated to ca. 10% of its original volume, diluted with sat. $(\text{NH}_3)_2\text{SO}_4$ (30 mL), adjusted to pH 3 with conc. H_2SO_4 , and extracted with EtOAc (3 \times 30 mL). The combined extracts were dried over MgSO_4 and concentrated under reduced pressure, and the resultant residue was chromatographed on silica gel (eluent: CH_2Cl_2) to yield **11a** (0.13 g, 73%). Mp: 84 °C. ^1H NMR (300 MHz, CDCl_3 ,

294 K): δ 4.63 (s, 2H), 6.92 (dd, $J = 1.1, 8.2$ Hz, 1H), 7.13 (td, $J = 1.1, 7.5$ Hz, 1H), 7.29–7.46 (m, 5H), 7.57 (dd, $J = 1.5, 8.4$ Hz, 2H), 8.80–10.10 (br, 1H). ^{13}C NMR (75 MHz, CDCl_3 , 295 K): δ 65.9, 113.4, 123.1, 127.7, 128.7, 129.1, 129.9, 131.8, 131.9, 138.3, 154.6, 173.7. LR-ESIMS: m/z 227 $[\text{M} - \text{H}]^-$. HR-ESIMS: m/z 227.0707 (calcd for $\text{C}_{14}\text{H}_{11}\text{O}_3$, 227.0714).

2-((3'-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)oxy)acetic Acid (11b). Prepared in the same manner as **11a**. (2-Bromophenoxy)-(*tert*-butyl)dimethylsilane (0.95 g, 3.3 mmol), 4-(trifluoromethyl)phenylboronic acid (0.75 g, 4.0 mmol), $\text{Pd}[\text{P}(\text{Ph})_3]_4$ (0.38 g, 0.33 mmol), and K_2CO_3 (1.2 g, 9.9 mmol) were reacted and then columned on silica gel (eluent: 25% CH_2Cl_2 in petroleum ether 40–60) to afford 3'-(trifluoromethyl)-[1,1'-biphenyl]-2-ol (0.13 g, 14%). ^1H NMR (400 MHz, CDCl_3 , 296 K): δ 4.98–5.10 (br, 1H), 6.96 (d, $J = 8.5$ Hz, 1H), 7.03 (td, $J = 1.1, 7.5$ Hz, 1H), 7.26–7.31 (m, 2H), 7.57–7.65 (m, 2H), 7.71 (d, $J = 7.5$ Hz, 1H), 7.78 (s, 1H). ^{19}F NMR (376 MHz, CDCl_3 , 296 K): δ -63.0. ^{13}C NMR (100 MHz, CDCl_3 , 297 K): δ 116.2, 121.3, 126.9, 129.3, 129.7, 130.5, 132.5, 138.3, 152.4. LR-ESIMS: m/z 237 $[\text{M} - \text{H}]^-$. HR-ESIMS: m/z 237.0526 (calcd for $\text{C}_{13}\text{H}_8\text{OF}_3$, 237.0533). The aforementioned biphenyl alcohol (0.13 g, 0.55 mmol) was alkylated as before with methyl bromoacetate (0.1 mL, 1.1 mmol) and K_2CO_3 (0.38 g, 2.7 mmol) and columned on silica gel (eluent: 50% CH_2Cl_2 in petroleum ether 40–60) to afford methyl 2-((3'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)oxy)acetate (0.14 g, 84%). ^1H NMR (400 MHz, CDCl_3 , 296 K): δ 3.79 (s, 3H), 4.65 (s, 2H), 6.89 (d, $J = 7.7$ Hz, 1H), 7.12 (td, $J = 1.0, 7.5$ Hz), 7.32–7.39 (m, 2H), 7.54 (t, $J = 7.7$ Hz, 1H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.81 (d, $J = 7.6$ Hz, 1H), 7.92 (s, 1H). ^{19}F NMR (376 MHz, CDCl_3 , 296 K): δ -62.9. ^{13}C NMR (100 MHz, CDCl_3 , 297 K): δ 52.3, 65.5, 112.3, 122.3, 123.8 (q, $^3J_{\text{CF}} = 3.7$ Hz), 124.4 (q, $^1J_{\text{CF}} = 272.2$ Hz), 126.5 (q, $^3J_{\text{CF}} = 3.7$ Hz), 128.5, 129.4, 129.7, 130.4 (q, $^2J_{\text{CF}} = 32.1$ Hz), 131.2, 133.0, 138.8, 154.6, 169.2. LR-ESIMS: m/z 328 $[\text{M} + \text{NH}_4]^+$. HR-ESIMS: m/z 328.1162 (calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3\text{F}_3$, 328.1155). The aforementioned ester (0.14 g, 0.5 mmol) was hydrolyzed with LiOH (0.08 g, 1.8 mmol) to afford **11b** (0.13 g, 95%). ^1H NMR (400 MHz, CDCl_3 , 296 K): δ 4.68 (s, 2H), 6.91 (d, $J = 8.2$ Hz, 1H), 7.14 (td, $J = 1.0, 7.5$ Hz, 1H), 7.34–7.39 (m, 2H), 7.54 (t, $J = 7.7$ Hz, 1H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.76 (d, $J = 7.6$ Hz, 1H), 7.87 (s, 1H). ^{19}F NMR (376 MHz, CDCl_3 , 296 K): δ -63.0. ^{13}C NMR (100 MHz, CDCl_3 , 297 K): δ 65.0, 112.4, 122.6, 123.9 (q, $^3J_{\text{CF}} = 3.3$ Hz), 124.2 (q, $^1J_{\text{CF}} = 272.4$ Hz), 126.4 (q, $^3J_{\text{CF}} = 3.6$ Hz), 128.5, 129.4, 129.7, 130.6 (q, $^2J_{\text{CF}} = 32.5$ Hz), 131.2, 132.8, 138.6, 154.1, 173.0. LR-ESIMS: m/z 314 $[\text{M} + \text{NH}_4]^+$. HR-ESIMS: m/z 314.1001 (calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_3\text{F}_3$, 314.0999).

2-((4'-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)oxy)acetic Acid (11c). Prepared in the same manner as **11a**. (2-Bromophenoxy)-(*tert*-butyl)dimethylsilane (0.63 g, 2.2 mmol), 4-(trifluoromethyl)phenylboronic acid (0.5 g, 2.6 mmol), $\text{Pd}[\text{P}(\text{Ph})_3]_4$ (0.22 g, 0.22 mmol), and K_2CO_3 (0.9 g, 6.5 mmol) were reacted and then columned on silica gel (eluent: 25% CH_2Cl_2 in petroleum ether 40–60) to afford 4'-(trifluoromethyl)-[1,1'-biphenyl]-2-ol (0.43 g, 82%). Mp: 99 °C. ^1H NMR (400 MHz, CDCl_3 , 296 K): δ 4.99 (s, 1H), 6.97 (dd, $J = 0.5, 8.1$ Hz, 1H), 7.04 (td, $J = 1.1, 7.5$ Hz, 1H), 7.26–7.32 (m, 2H), 7.64 (d, $J = 8.6$ Hz, 2H), 7.74 (d, $J = 8.6$ Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3 , 296 K): δ -63.05. ^{13}C NMR (100 MHz, CDCl_3 , 297 K): δ 116.2, 121.3, 124.1 (q, $^1J_{\text{CF}} = 272.0$ Hz), 125.9 (q, $^3J_{\text{CF}} = 3.7$ Hz), 126.9, 129.4 (q, $^2J_{\text{CF}} = 32.4$ Hz), 129.6, 129.8, 130.4, 141.1, 152.3. LR-ESIMS: m/z 237 $[\text{M} - \text{H}]^-$. HR-ESIMS: m/z 237.0539 (calcd for $\text{C}_{13}\text{H}_8\text{OF}_3$, 237.0533). The aforementioned biphenyl alcohol (0.4 g, 1.66 mmol) was alkylated as before with methyl bromoacetate (0.24 mL, 2.5 mmol) and K_2CO_3 (1.15 g, 8.3 mmol) and columned on silica gel (eluent: 25% CH_2Cl_2 in petroleum ether 40–60) to afford methyl 2-((4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)oxy)acetate (0.529 g, 99%). ^1H NMR (400 MHz, CDCl_3 , 296 K): δ 3.78 (s, 3H), 4.64 (s, 2H), 6.88 (d, $J = 8.2$ Hz, 1H), 7.10 (td, $J = 1.0, 7.5$ Hz, 1H), 7.32–7.36 (m, 2H), 7.67 (d, $J = 8.1$ Hz, 2H), 7.73 (d, $J = 8.1$ Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3 , 296 K): δ -62.9. ^{13}C NMR (100 MHz, CDCl_3 , 297 K): δ 52.2, 65.5, 112.3, 122.2, 124.4 (q, $^1J_{\text{CF}} = 271.6$ Hz), 124.9 (q, $^3J_{\text{CF}} = 3.7$ Hz), 129.1 (q, $^2J_{\text{CF}} = 32.4$ Hz), 129.4, 129.8, 129.9, 131.2, 141.7, 154.6, 169.2. LR-ESIMS: m/z 328 $[\text{M} + \text{NH}_4]^+$. HR-ESIMS: m/z 328.1158 (calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3\text{F}_3$, 328.1155). The aforementioned

ester (0.49 g, 1.6 mmol) was hydrolyzed with LiOH (0.26 g, 6.3 mmol) to afford **11c** (0.44g, 95%). Mp: 126 °C. ¹H NMR (400 MHz, CDCl₃, 296 K): δ 4.68 (s, 2H), 6.91 (dd, *J* = 1.1, 8.9 Hz, 1H), 7.13 (td, *J* = 1.0, 7.6 Hz, 1H), 7.33–7.39 (m, 2H), 7.66–7.72 (m, 4H). ¹⁹F NMR (376 MHz, CDCl₃, 296 K): δ -62.9. ¹³C NMR (100 MHz, CDCl₃, 297 K): δ 65.5, 112.9, 123.0, 125.0 (q, ¹*J*_{CF} = 273.5 Hz), 125.4 (q, ³*J*_{CF} = 3.9 Hz), 129.7 (q, ²*J*_{CF} = 31.2 Hz), 129.9, 130.3 (×2), 131.7, 142.0, 154.6, 173.2. LR-ESIMS: *m/z* 295 [M - H]⁻. HR-ESIMS: *m/z* 295.0592 (calcd for C₁₅H₁₀O₃F₃, 295.0588).

2-(2-((Methoxyimino)methyl)phenoxy)acetic Acid (13a). A suspension of 2-formylphenoxyacetic acid (0.515 g, 2.86 mmol, 1.0 equiv), methoxylamine hydrochloride (0.478 g, 5.72 mmol, 2.0 equiv), and sodium acetate (0.469 g, 5.72 mmol, 2.0 equiv) in ethanol (30 mL) was heated at reflux for 18 h. The solvent was removed under reduced pressure, and the crude residue was redissolved in H₂O (100 mL) and extracted into CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried (MgSO₄), concentrated under reduced pressure, and purified by column chromatography (5% EtOAc/CH₂Cl₂) to yield **13a** as a colorless solid (0.390 g, 65%). ¹H NMR (300 MHz, CDCl₃, 294 K): δ 4.01 (s, 3H), 4.72 (s, 2H), 6.91 (d, *J* = 8.2 Hz, 1H), 7.12 (m, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.40 (m, 1H), 8.15 (s, 1H). ¹³C NMR (75 MHz, CDCl₃, 295 K): δ 61.9, 66.6, 114.2, 120.6, 123.0, 131.7, 132.4, 148.8, 155.4, 169.5. LR-ESIMS: *m/z* 208 [M - H]⁻. HR-ESIMS: *m/z* 208.0614 (calcd for C₁₀H₁₀NO₄, 208.0615).

2-(2-((Benzyloxy)imino)methyl)phenoxy)acetic Acid (13b). A suspension of 2-formylphenoxyacetic acid (1.00 g, 5.55 mmol, 1.0 equiv), benzyloxylamine hydrochloride (1.773 g, 11.11 mmol, 2.0 equiv), and sodium acetate (0.911 g, 11.11 mmol, 2.0 equiv) in ethanol (60 mL) was heated at reflux for 18 h. The solvent was removed under reduced pressure, and the crude residue was redissolved in H₂O (100 mL) and extracted into CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried (MgSO₄), concentrated under reduced pressure, and purified by column chromatography (5% EtOAc/CH₂Cl₂) to yield **13b** as a colorless solid (0.422 g, 26%). ¹H NMR (300 MHz, CDCl₃, 294 K): δ 4.70 (s, 2H), 5.25 (s, 2H), 6.90 (d, *J* = 8.2 Hz, 1H), 7.11 (t, *J* = 6.6 Hz, 1H), 7.32–7.44 (m, 7H), 8.26 (s, 1H). ¹³C NMR (75 MHz, CDCl₃, 295 K): δ 66.5, 76.2, 114.0, 120.6, 122.9, 128.2, 128.5, 128.5, 131.7, 132.2, 136.6, 149.3, 155.3, 169.5. LR-ESIMS: *m/z* 284 [M - H]⁻. HR-ESIMS: *m/z* 284.0923 (calcd for C₁₆H₁₄NO₄, 284.0928).

d₁-Phenoxyacetic Acid (5aD). Phenoxyacetic acid (304 mg, 2.0 mmol) and SOCl₂ (0.74 mL, 10.0 mmol) were refluxed in CHCl₃ for 72 h. The volatiles were removed under reduced pressure to yield phenoxyacetyl chloride. ¹H NMR (400 MHz, CDCl₃, 296 K): δ 4.95 (s, 2H), 6.93 (m, 2H), 7.09 (m, 1H), 7.35 (m, 2H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 64.9, 77.2, 114.8, 122.3, 129.9, 157.5, 174.2. This compound was immediately treated with D₂O (0.9 mL, 5.0 mmol) in anhydrous CH₃CN (10 mL), and the mixture was allowed to stir overnight under an argon atmosphere. The solvent was removed under reduced pressure, and the resultant residue was recrystallized from anhydrous Et₂O to yield **5aD** as a white crystalline solid (141 mg, 46%). ¹H NMR (500 MHz, CDCl₃, 295 K): δ 4.70 (s, 2H), 6.93 (m, 2H), 7.03 (m, 1H), 7.32 (m, 2H). ²H NMR (76 MHz, CHCl₃, 315 K): δ 10.13 (bs, 1D). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 64.9, 114.8, 122.4, 129.9, 157.4, 172.8. LR-ESIMS: *m/z* 153 [M]⁺. HR-ESIMS: *m/z* 153.0543 (calcd for C₈H₈O₃D, 153.0513).

4-Phenoxybutanamide (19H). Phenoxyacetic acid (100 mg, 0.66 mmol) and acrylamide (93.9 mg, 1.32 mmol) in MeCN (45 mL) were reacted in accordance with the general procedure in a TiO₂ sol-gel-coated tube. Following irradiation for 24 h, the reaction mixture was purified by dry flash chromatography on silica gel (eluent: gradient of 2–10% MeOH in CH₂Cl₂) to yield **19H** as an off-white solid (79.8 mg, 68%). ¹H NMR (300 MHz, CDCl₃, 294 K): δ 2.13 (m, 2H), 2.45 (t, *J* = 7.2 Hz, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 5.63 (bs, 1H), 5.82 (bs, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 295 K): δ 25.4, 32.6, 67.1, 114.9, 121.2, 129.9, 159.2, 175.4. Data are consistent with literature values.¹⁶

4-(tert-Butyl)phenoxybutanamide. 4-(tert-Butyl)phenoxyacetic acid (137.5 mg, 0.66 mmol) and acrylamide (93.9 mg, 1.32 mmol) in MeCN (45 mL) were reacted in accordance with the general

procedure in a TiO₂ sol-gel-coated tube. Following irradiation for 30 h, the reaction mixture was purified by dry flash chromatography on silica gel (eluent: gradient of 2–7.5% MeOH in CH₂Cl₂) to yield the title compound as an off-white solid (105.4 mg, 68%) containing ~5% 4-(tert-butyl)phenol. Mp: 85–88 °C. ¹H NMR (400 MHz, CD₃OD, 297 K): δ 1.30 (s, 9H), 2.04–2.11 (m, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 7.30 (dd, *J* = 3.2, 11.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃, 297 K): δ 27.0, 32.4, 33.4, 35.3, 68.5, 115.5, 127.6, 144.8, 158.5, 179.0. LR-ESIMS: *m/z* 236 [M + H]⁺. HR-ESIMS: *m/z* 236.1647 (calcd for C₁₄H₂₂NO₂, 236.1645).

4-(Trifluoromethyl)phenoxybutanamide. 4-(Trifluoromethyl)phenoxyacetic acid (145.3 mg, 0.66 mmol) and acrylamide (93.9 mg, 1.32 mmol) in MeCN (45 mL) were reacted in accordance with the general procedure in a TiO₂ sol-gel-coated tube. Following irradiation for 24 h, the reaction mixture was purified by dry flash chromatography on silica gel (eluent: 5% MeOH in CH₂Cl₂) to yield the title compound as an off-white solid (108.4 mg, 66%). Mp: 93–94 °C. ¹H NMR (500 MHz, *d*₆-acetone, 295 K): δ 2.06–2.11 (m, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 4.14 (t, *J* = 5.9 Hz, 2H), 6.30 (bs, 1H), 6.86 (bs, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H). ¹³C NMR (75 MHz, *d*₆-acetone, 297 K): δ 29.9, 36.3, 72.7, 120.0, 127.2 (q, ²*J*_{C-F} = 33.1 Hz, 1C), 130.0 (q, ¹*J*_{C-F} = 271.1 Hz, 1C), 132.0 (q, ³*J*_{C-F} = 3.6 Hz, 2C), 167.2, 178.9. ¹⁹F NMR (470 MHz, *d*₆-acetone, 295 K): δ -61.8. LR-ESIMS: *m/z* 248 [M + H]⁺. HR-ESIMS: *m/z* 248.0896 (calcd for C₁₁H₁₃NO₂F₃, 248.0896).

Photocatalyzed Reaction of (E)-2-(2-(3-oxopent-1-en-1-yl)phenoxy)acetic Acid (8c). A suspension of **8c** (0.050 g, 0.21 mmol, 1.0 equiv) and TiO₂ (P25, 0.025 g, 0.32 mmol, 1.5 equiv) in MeCN (20 mL) was reacted in accordance with the general procedure for 9 h. Following removal of the solvent under reduced pressure, the mixture was subjected to analysis by ¹H NMR and GC-MS. The ¹H NMR spectrum showed a complex array of components. GC-MS indicated four major components, and one of these (*t*_R = 10.7 min) had the correct mass and fragmentation pattern for the cyclized product **10c**: *m/z* (%): 190 (40), 161 (36), 146 (18), 133 (23), 119 (38), 118 (100), 91 (41). ¹H NMR (400 MHz, CD₃CN, 298 K): δ 0.98 (t, *J* = 7.3 Hz, 3H), 2.47 (q, *J* = 7.3 Hz, 2H), 3.26–3.29 (m, 1H), 4.37 (dd, *J* = 2.3, 8.4 Hz, 1H), 4.94 (dd, *J* = 5.2, 9.4 Hz, 1H), 7.03–7.17 (m, 2H), 7.50–7.54 (m, 2H). Attempts to isolate and thoroughly characterize **10c** were not successful. Photoisomerization of **8c** to its *Z* isomer was observed during the course of this experiment. ¹H NMR (400 MHz, CD₃CN, 298 K): δ 7.38 (d, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 12.0 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.28 (d, *J* = 12.5 Hz, 1H), 4.69 (s, 2H), 2.47 (q, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

Photocatalyzed Reaction of 2-([1,1'-Biphenyl]-2-yloxy)acetic Acid (11a). A suspension of **11a** (0.052 g, 0.23 mmol, 1.0 equiv) and TiO₂ (P25, 0.027 g, 0.34 mmol, 1.5 equiv) in MeCN (20 mL) was reacted in accordance with the general procedure for 18 h. Following removal of the solvent under reduced pressure, ¹H NMR analysis of the reaction mixture showed mainly unreacted **11a** together with a small amount of the cyclized product **12a** (0.01 mmol, 5% wrt CH₂Br₂). ¹H NMR (400 MHz, CDCl₃, 296 K): δ 5.05 (s, 2H), 6.90–6.95 (m, 2H), 7.00–7.10 (m, obscured by SM), 7.60–7.70 (m, 3H). Attempts to isolate and thoroughly characterize **12a** were unsuccessful.

Methyl 2-(2,3-Dihydrobenzofuran-3-yl)acetate (10a). A suspension of **8a** (0.050 g, 0.21 mmol, 1.0 equiv) and TiO₂ (P25, 0.025 g, 0.32 mmol, 1.5 equiv) in MeCN (20 mL) was reacted according to the general procedure for 9 h to yield **10a** as a colorless powder (20% by NMR). ¹H NMR (400 MHz, CDCl₃, 294 K): δ 2.52 (dd, *J* = 9.5, 16.5 Hz, 1H), 2.73 (dd, *J* = 5.3, 16.5 Hz, 1H), 3.72 (s, 3H), 3.84–3.91 (m, 1H), 4.18 (dd, *J* = 6.3, 9.2 Hz, 1H), 4.68 (t, *J* = 9.0 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.86 (t, *J* = 8.3 Hz, 1H), 7.08–7.17 (m, 2H). ¹³C NMR (75 MHz, CDCl₃, 295 K): δ 38.7, 39.7, 52.3, 110.2, 114.1, 121.0, 124.6, 129.1, 129.5, 160.2, 172.7. LR-ESIMS: *m/z* 215 [M + Na]⁺. HR-ESIMS: *m/z* 215.0674 (calcd for C₁₁H₁₂O₃Na, 215.0679). Photoisomerization of **8a** to its *Z* isomer was observed during the course of this experiment. ¹H NMR (400 MHz, CD₃CN, 298 K): δ 7.48 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* =

12.5 Hz, 1H), 6.97 (t, $J = 7.6$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.01 (d, $J = 12.3$ Hz, 1H), 4.69 (s, 2H), 3.63 (s, 3H).

2-(2,3-Dihydrobenzofuran-3-yl)acetonitrile (10b). A solution of **8b** (0.050 g, 0.246 mmol) in MeCN (15 mL) in a TiO₂ sol–gel-coated tube was reacted according to the general procedure. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography (CH₂Cl₂) to yield **10b** as a colorless powder (0.007 g, 28%). ¹H NMR (400 MHz, CDCl₃, 296 K): δ 2.58–2.71 (m, 2H), 3.74–3.82 (m, 1H), 4.34 (dd, $J = 4.8, 9.6$ Hz, 1H), 4.69 (dd, $J = 8.7, 9.6$ Hz, 1H), 6.84 (d, $J = 8.1$ Hz, 1H), 6.93 (td, $J = 1.0, 7.5$ Hz, 1H), 7.22 (m, 1H), 7.32 (d, $J = 7.5$ Hz, 1H). ¹³C NMR (75 MHz, CDCl₃, 295 K): δ 22.8, 38.8, 75.4, 110.3, 117.7, 121.2, 124.4, 127.1, 129.7, 159.7. LR-ESIMS: m/z 159 [M]⁺. HR-ESIMS: m/z 159.0676 (calcd for C₁₀H₉NO, 159.0679). Photoisomerization of **8b** to its Z isomer was observed during the course of this experiment. ¹H NMR (400 MHz, CD₃CN, 298 K): δ 8.01 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.66 (d, $J = 12.5$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.11 (t, $J = 7.5$ Hz, 1H), 6.97 (d, $J = 8.3$ Hz, 1H), 5.64 (d, $J = 12.3$ Hz, 1H), 4.74 (s, 2H).

Photocatalyzed Reaction of 2-((4'-(Trifluoromethyl)-1,1'-biphenyl)-2-yl)oxy)acetic Acid (11c). A suspension of **11c** (59 mg, 0.20 mmol, 1.0 equiv) and TiO₂ (P25, 0.024 g, 0.30 mmol, 1.5 equiv) in MeCN (20 mL) was reacted in accordance with the general procedure for 18 h. Following removal of the solvent under reduced pressure, ¹H NMR analysis of the reaction mixture showed mainly unreacted acid (79%) together with a small amount of the cyclized product **12c** (0.01 mmol, 5% wrt CH₂Br₂). ¹H NMR (400 MHz, CDCl₃, 296 K): δ 5.07 (s, 2H), 6.93–6.96 (m, 2H), 6.98–7.04 (m; obscured by SM), 7.72–7.65 (m, 3H). GC–MS analysis of the reaction mixture showed **12c** as the main product: $t_R = 11.76$ min; m/z (%) 250 (58), 249 (100), 231 (6), 201 (10), 181 (10), 152 (16). Also observed was a trace of what was probably the direct reduction product 2-methoxy-4'-(trifluoromethyl)-1,1'-biphenyl: $t_R = 11.84$ min; m/z (%) 252 (82), 251 (48), 250 (61), 249 (100), 237 (20), 201 (16), 183 (26), 152 (32). Attempts to isolate and thoroughly characterize **12c** were unsuccessful.

Photocatalyzed Reaction of 2-(2-((Methoxyimino)methyl)phenoxy)acetic Acid (13a). A suspension of **13a** (51 mg, 0.24 mmol, 1.0 equiv) and TiO₂ (P25, 0.029 g, 0.36 mmol, 1.5 equiv) in MeCN (29 mL) was reacted in accordance with the general procedure for 24 h. Following removal of the solvent under reduced pressure, ¹H NMR analysis of the reaction mixture showed that **13a** had been entirely consumed and that a complex mixture of products had been formed. GC–MS analysis of the mixture revealed that **14a** had been formed: $t_R = 8.15$ min; m/z (%) 165 (29), 133 (12), 119 (100), 91 (77), 77 (26). Also observed were benzofuran-3(2H)-one O-methyl oxime [$t_R = 7.93$ min; m/z (%) 163 (100), 118 (91), 91 (52)], 2,3-dihydrobenzofuran [$t_R = 7.87$ min; m/z (%) 120 (27), 119 (100), 91 (57)], 2,3-dihydrobenzofuran-3-amine [$t_R = 5.06$ min; m/z (%) 135 (7), 134 (74), 119 (100), 117 (11)], and benzofuran [$t_R = 3.43$ min; m/z (%) 118 (100), 90 (22), 84 (30)]. Attempts to isolate and thoroughly characterize **14a**, or any other products, were unsuccessful.

Photocatalyzed Reaction of 2-(2-(((Benzoyloxy)imino)methyl)phenoxy)acetic Acid (13b). A suspension of **13b** (62 mg, 0.22 mmol, 1.0 equiv) and TiO₂ (P25, 0.026 g, 0.33 mmol, 1.5 equiv) in MeCN (26 mL) was reacted in accordance with the general procedure for 24 h. Following removal of solvent under reduced pressure, ¹H NMR analysis of the reaction mixture showed that **13b** had been entirely consumed and that a complex mixture of products had been formed. GC–MS analysis of the mixture revealed that **14b** had been formed: $t_R = 15.53$ min; m/z (%) 241 (9), 210 (9), 133 (6), 91 (100), 77 (14). Also observed were benzofuran-3(2H)-one O-benzyl oxime [$t_R = 15.37$ min; m/z (%) 239 (37), 222 (4), 148 (3), 119 (7), 91 (100), 77 (12)], 2,3-dihydrobenzofuran-3-amine [$t_R = 5.04$ min; m/z (%) 135 (7), 134 (74), 119 (100), 117 (11)], benzyl alcohol [$t_R = 3.77$ min; m/z (%) 108 (100), 107 (73), 79 (76)], benzofuran [$t_R = 3.41$ min; m/z (%) 118 (100), 90 (22), 84 (30)], and benzaldehyde [$t_R = 2.90$ min; m/z (%) 106 (87), 105 (100), 77 (66)]. Attempts to isolate and thoroughly characterize **14b** or any other product were unsuccessful.

SCPC Reaction of Phenoxyacetic Acid with Acrylamide and P25 Vacuum-Dried at 150 °C. TiO₂ (12 mg, 0.15 mmol) was dried overnight at 150 °C under a continuous vacuum in an oven-dried Schlenk tube. Phenoxyacetic acid (15.2 mg, 0.1 mmol) and acrylamide (14.2 mg, 0.2 mmol) in MeCN (12 mL) were added via syringe, and the resultant mixture was irradiated for 18 h. ¹H NMR analysis of the resultant mixture revealed **19H** (39% by NMR).

SCPC Reaction in Deuterated Acetonitrile (d₃-MeCN). Phenoxyacetic acid (15.2 mg, 0.1 mmol), acrylamide (14.2 mg, 0.2 mmol), and TiO₂ (12 mg, 0.15 mmol) in d₃-MeCN (12 mL) were irradiated for 18 h. ¹H NMR analysis of the resultant mixture revealed **19H** (55% by NMR). Any deuterium incorporation was below the NMR and MS detection limits.

SCPC Reaction with Deuterated Phenoxyacetic Acid. d₁-Phenoxyacetic acid (15.3 mg, 0.1 mmol), acrylamide (14.2 mg, 0.2 mmol), and TiO₂ (12 mg, 0.15 mmol) in MeCN (12 mL) were irradiated for 19 h. ¹H NMR analysis (wrt CH₂Br₂ standard) of the resultant mixture revealed **19H** (49% by NMR). Any deuterium incorporation was below the NMR and MS detection limits.

SCPC Reaction with Deuterated P25. An oven-dried Schlenk tube, complete with magnetic stirrer, was connected to a vacuum line, evacuated, and then back-filled with argon while still hot from the oven. In a glovebox, TiO₂ (P25, 0.15 mmol, 12 mg) was added, and the tube was then heated at 150 °C for 3 h under vacuum. In a separate oven-dried vessel, 10 mL of D₂O (freshly opened) was degassed by three freeze–pump–thaw cycles before being transferred by cannula to the tube containing the TiO₂ once it had cooled to ambient temperature. The resultant mixture was allowed to stir overnight before the D₂O was removed under reduced pressure. At this point the TiO₂ was again dried for 3 h at 150 °C under vacuum. In a separate oven-dried vessel, phenoxyacetic acid (0.1 mmol, 15.2 mg) and acrylamide (0.2 mmol, 14.2 mg) were dissolved in MeCN (12 mL) that had been freshly collected after distillation over calcium hydride. The resultant mixture was degassed for 15 min by bubbling with argon and then transferred via cannula to the tube containing the TiO₂ once it had cooled to ambient temperature. The resultant mixture was then irradiated in accordance with the general procedure for 19 h. ¹H NMR analysis of the resultant mixture revealed **19H** (58% by NMR). Any deuterium incorporation was below the NMR and MS detection limits.

SCPC Reaction with Deuterated Phenoxyacetic Acid and Deuterated P25. This reaction was performed as above using d₁-phenoxyacetic acid (15.3 mg, 0.1 mmol) for 19 h. ¹H NMR analysis of the resultant mixture revealed no clear signals indicating the formation of **19H** or **19D**.

■ ASSOCIATED CONTENT

📄 Supporting Information

General procedures, EPR spectra, NMR monitoring of coated tube reactions, and ¹H and ¹³C 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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