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Research Article

Radical Redox Annulations: A General Light-Driven Method for the Synthesis of Saturated Heterocycles

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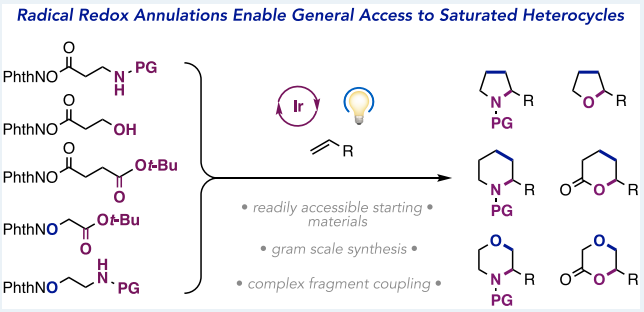
ABSTRACT: We introduce here a two-component annulation strategy that provides access to a diverse collection of five- and six-membered saturated heterocycles from aryl alkenes and a family of redox-active radical precursors bearing tethered nucleophiles. This transformation is mediated by a combination of an Ir(III) photocatalyst and a Brønsted acid under visible-light irradiation. A reductive proton-coupled electron transfer generates a reactive radical which undergoes addition to an alkene. Then, an oxidative radical-polar crossover step leading to carbocation formation is followed by ring closure through cyclization of the tethered nucleophile. A wide range of heterocycles are easily accessible, including pyrrolidines, piperidines, tetrahydrofurans, morpholines, δ-valerolactones, and dioxanones. We demonstrate the scope of this approach through broad structural variation of both reaction components. This method is amenable to gram-scale preparation and to complex fragment coupling.



KEYWORDS: *annulation, photocatalysis, PCET, heterocycles, carbocations*

Annulation reactions enabling the synthesis of saturated carbocyclic and heterocyclic ring systems are of central importance in organic synthesis. Indeed, ring formation is a key consideration in the retrosynthetic analysis of complex target molecules,[1−5] and general annulation methods are often indispensable synthetic technologies. In this regard, two-component annulation reactions are particularly valuable as they allow for the rapid construction of molecular complexity from simpler, often acyclic, starting materials. Many classical methods for two-component annulation still find frequent use, including pericyclic Diels−Alder [4 + 2] cycloadditions,[6,7] Paternò−Büchi [2 + 2] photocycloadditions,[8,9] and polar Robinson annulations (Figure 1A).[10−12] Moreover, annulation chemistry remains an active area of research, and many novel (photo)catalytic strategies have been developed in recent years to broaden the scope and impact of these approaches (Figure 1B).[13]

While being powerful, annulation methods generally place limitations on (i) the nature of the functional groups present in the two reaction partners, (ii) the nature of the atoms involved in the bond formation (carbon or heteroatom), and (iii) the ring size of the annulation product (by necessarily requiring correct spacing between two reactive sites). While being widely applied, most are specific to a narrow subset of (hetero)cyclic products, and each transformation requires different reaction conditions and/or catalysts to proceed. We envisioned a distinct annulation strategy that would enable access to a diverse set of saturated heterocycles in a predictable and modular manner from a common set of reagents under a common set of reaction conditions (Figure 1C). Key to this design was the integration of excited-state electron transfer processes, which allow the two bond-forming events in the annulation to proceed through distinct elementary steps *via* oxidative radical-polar crossover (ORPC), thus circumventing many of the limitations enumerated above. This report describes the successful realization of these aims and introduces a broadly applicable method for the synthesis of saturated heterocycles—including pyrrolidines, piperidines, tetrahydrofurans, morpholines, δ-valerolactones, and dioxanones—*via* visible light-driven [*n* + 2] annulation between redox-active *N*-hydroxyphthalimide (NHPI) ester or ether reagents and aryl alkene or diene coupling partners.

Our reaction design consists of a bifunctional reagent[14] carrying an NHPI ester and a tethered nucleophile, which we hypothesized would pair with an aryl alkene partner through the following sequence of elementary steps (Figure 1D). First, single-electron reduction of the NHPI ester by the excited state

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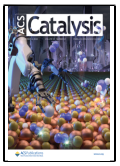

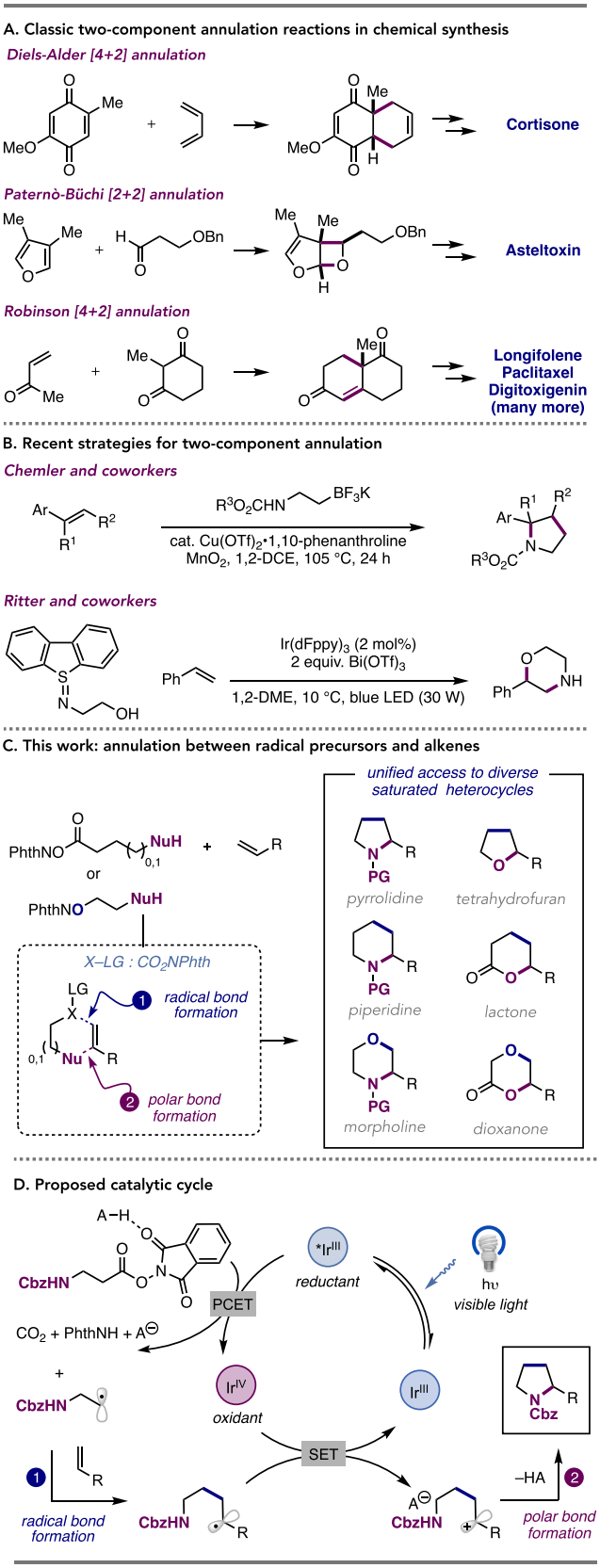

Figure 1. (A) Examples of classic annulation reactions in chemical synthesis. (B) Recent related catalytic methods for two-component annulation. (C) This work: a photocatalytic, two-component annulation of redox-active phthalimides and alkenes. (D) Proposed catalytic cycle.

of a photocatalyst, followed by fragmentation, would initiate the reaction *via* radical generation. Then, *anti*-Markovnikov addition of this nascent radical to the partner aryl alkene would forge a new bond and yield a linear intermediate bearing both a benzylic radical and the tethered nucleophile. Finally, an ORPC event would follow, wherein single-electron oxidation of the benzylic radical by the oxidized state of the photocatalyst furnishes a reactive carbocation.[15−30] Cyclization would then occur through addition of the tethered nucleophilic group to the electrophilic cation to yield the desired annulation product. Importantly, this reaction design should accommodate the use of both a variety of radical types and numerous nucleophilic functional groups with varying tether lengths. Thus, we anticipated that this redox-neutral, catalytic method would provide access to a diverse range of saturated heterocyclic scaffolds through a single experimental protocol.

Similar mechanistic scenarios have been successful in promoting a number of three-component alkene 1,2-difunctionalization reactions, including oxyalkylation,[31−33] fluoroalkylation,[34] bisalkylation,[35] hydroesterification,[36,37] oxyamination,[38] and diamination.[39,40] We specifically highlight the work of Chemler and Um, who demonstrated that carbamate-appended trifluoroborate salts serve as reagents for the net-oxidative synthesis of pyrrolidines from styrenes,[41] and recent work from Ritter and co-workers demonstrated a similar concept of nucleophile-tethered reductive *N*-centered radical precursors for the synthesis of morpholines and homomorpholines from styrenes (Figure 1B).[42]

With this framework in mind, our model system for reaction discovery consisted of an *N*-protected *β*-alanine NHPI ester and styrene, where the desired product of the reaction would be the corresponding *N*-protected *α*-phenyl pyrrolidine (**2**) *via* a [3 + 2] annulation (Table 1). In this planning stage, we reasoned that inclusion of a Brønsted acid additive would facilitate a proton-coupled electron transfer (PCET) mechanism for reduction of the NHPI ester substrate.[43−54] This would allow for a single photocatalyst to span a greater range of potentials between the excited-state Ir(III) photoreductant and the corresponding Ir(IV) ground-state oxidant, thus increasing the driving force available for the coupled ORPC step. A Cbz-protected *β*-alanine NHPI ester was readily synthesized *via* Steglich esterification on multigram scale through a chromatography-free protocol. With this reagent in hand, we set about optimization of the desired process through systematic variation of these highlighted reaction parameters.

We found that with NHPI ester **1** ($E_{p/2}$ = −1.52 V vs Fc^+/Fc in MeCN) and styrene as model substrates in a 1:2 ratio, pyrrolidine **2** was formed in 76% yield in the presence of 1 mol % Ir(*p*-CF_3-ppy)$_3$ ($E_{1/2}$ Ir(IV)/*Ir(III) = −2.03 V vs Fc^+/Fc in MeCN)[55] and 25 mol % diphenyl phosphoric acid in acetone under blue light irradiation (Table 1, entry **1**). The annulation could be performed with a range of other photoreductants; *for example*, Ir(*p*-F-ppy)$_3$ ($E_{1/2}$ Ir(IV)/*Ir(III) = −2.24 V vs Fc^+/Fc in MeCN)[55] and Ir(ppy)$_3$ ($E_{1/2}$ Ir(IV)/*Ir(III) = −2.26 V vs Fc^+/Fc in MeCN)[56] were also viable. These photocatalysts facilitated both the reduction of **1** and the oxidation of the resulting secondary benzylic radical (e.g., for the benzylic radical derived from ethylbenzene, $E_{1/2}$ = −0.01 V vs Fc^+/Fc in MeCN)[57] to deliver **2** in 75% and 52% yields, respectively (Table 1, entries **2**−**3**). Either decreasing the styrene loading to 1 equiv. or using NHPI ester **1** in excess led to formation of pyrrolidine **2** in moderate to good yields (entries **4**−**5**); this flexibility in

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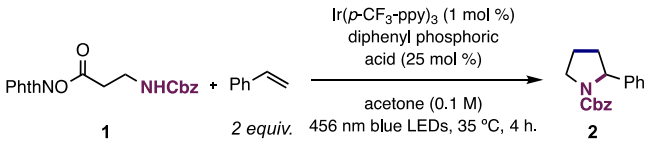
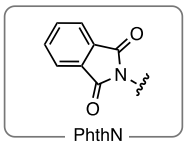
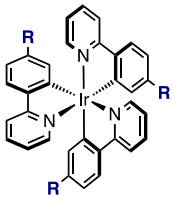
Table 1. Reaction Sensitivity Screen[a]



1 2

Entry	Deviation	% Yield
1	none	76
2	Ir(*p*-F-ppy)$_3$	75
3	Ir(ppy)$_3$	52
4	1 equiv. **1**, 1 equiv. styrene	44
5	2 equiv. **1**, 1 equiv. styrene	60
6	without diphenyl phosphoric acid	12
7	1 equiv. diphenyl phosphoric acid	61
8	2 equiv. diphenyl phosphoric acid	29
9	0.3 M	53
10	0.6 M	17
11	acetonitrile	59
12	dichloromethane	50
13	without photocatalyst	0
14	without light	0





R = H
Ir(IV)/*Ir(III) = –2.26 V
Ir(IV)/Ir(III) = +0.39 V

R = F
Ir(IV)/*Ir(III) = –2.24 V
Ir(IV)/Ir(III) = +0.59 V

R = CF_3
Ir(IV)/*Ir(III) = –2.03 V
Ir(IV)/Ir(III) = +0.67 V

[a]Reactions were run on a 0.1 mmol scale. Yields were determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. Redox potentials are reported in volts vs Fc^+/Fc in MeCN. See refs 55 and 56 for photocatalyst potentials.

stoichiometry can be useful for planning complex fragment couplings (*vide infra*). The annulation reaction proceeds with poor efficiency in the absence of diphenyl phosphoric acid; the reaction yield is the highest with 25 mol % acid as opposed to 1 or 2 equiv. (entries **6**–**8**). The dependence of the reaction yield on the exogenous acid concentration is consistent with a reductive PCET event initiating radical generation. This hypothesis is further supported by an observed increase in the luminescence quenching of *Ir(*p*-CF_3-ppy)$_3$ by **1** in the presence of diphenyl phosphoric acid (K_{sv} = 1146 M^{-1} with acid vs K_{sv} = 603 M^{-1} without acid) (see the Supporting Information for details). While reactions run in either acetonitrile or dichloromethane afforded pyrrolidine **2** in moderate yields (entries **11**–**12**), acetone proved to be the optimal solvent for the transformation. Finally, control experiments demonstrated that both light and photocatalyst are required for product formation (entries **13**–**14**). We provide additional details of further optimization experiments for other substrate classes in the Supporting Information.

With optimal conditions established, we first explored pyrrolidine synthesis with respect to the alkene coupling partner (Figure 2). An investigation of electronically varied 4-substituted styrenes showed that electron-neutral and electron-rich olefins undergo annulation in good yields (**2**–**5**). Additionally, 1,1-disubstituted and trisubstituted styrenes are effective annulation partners, providing pyrrolidines **6** and **9** bearing fully substituted α-centers, a challenging structural motif to access in a general fashion.[58−60]

Although simple, unactivated alkyl olefins were ineffective substrates under the standard conditions, we found that aryl-substituted α,β-unsaturated carbonyls and dienes proved amenable to annulation. Specifically, pyrrolidines **7** and **8** were generated in 42% and 60% yields from an α-phenyl acrylate ester and an α-phenyl acrylamide, respectively. The success of these alkenes is notable, given the difficulty of accessing α-carbonyl carbocations.[61] Additionally, simple dienes such as cyclopentadiene and 1,3-cyclohexadiene afforded fused bicycles **10** and **11** in 60% and 33% yields, respectively, with excellent diastereoselectivity. Alternative routes to related fused bicyclic pyrrolidines generally require multistep sequences *via* linear cyclization precursors.[62−64] Furthermore, an exocyclic diene, which is an intermediate in the synthesis of the insect antifeedant sesquiterpene polygodial,[65] underwent annulation to furnish **12** in 62% yield. A 3-vinylindole also undergoes [3 + 2] annulation to provide **13** in good yield.

Next, we found that a variety of commonly used amine protecting groups could be introduced onto the amine-tethered NHPI ester partner, providing *N*-Ts, *N*-Bz, and *N*-Boc pyrrolidines **14**, **15**, and **16** in good yield. No evidence of competing *O*-cyclization of the protecting group was observed, in contrast to some examples of carbocation cyclization reactions of carbamates and amides.[38,66,67] Due to the synthetic accessibility of β-amino acid derivatives,[68] a number of α- and β-functionalized NHPI esters could be readily prepared. These reagents then gave the corresponding pyrrolidines bearing C-4 and C-5 substituents in good yields and modest d.r. (**17**–**23**). The synthesis of an α-arylated proline derivative **22** from an L-aspartic acid-derived annulation reagent and a densely functionalized spirocyclic pyrrolidine **23** proceeded in 70% and 54% yields, respectively. Prior access to structures such as **22** required multistep synthetic routes,[69] typically deriving from pyroglutamic acid or *N*-protected prolines *via* Shono oxidation.[70−73]

We next sought to investigate the adaptability of the annulation strategy to access other heterocycle classes. Specifically, by changing the pendent nucleophile on the NHPI ester reagent to an alcohol, we anticipated access to tetrahydrofuran products. Using styrene as the annulation partner together with NHPI esters derived from β-hydroxy acids, the desired α-aryl- and α-carboxylate ester-substituted tetrahydrofurans **24** and **26** were formed in good yield under conditions similar to those used in the pyrrolidine-forming reactions. Using this method, a rare 2-trifluoromethyl-substituted tetrahydrofuran **25** was prepared. The introduction of spirocyclic scaffolds into lead structures is also of broad interest in medicinal chemistry; however, it is often accompanied by increased synthetic effort.[74,75] We found that the annulation protocol also offers a straightforward route to α-substituted spirocyclic tetrahydrofurans in serviceable yields (**27**–**29**). Here, we highlight pyrrolidine **23** and tetrahydrofuran **29** as examples of nitrogen- and oxygen-containing analogues of otherwise-identical spirocyclic scaffolds.

The annulation reaction also enables the synthesis of a variety of six-membered saturated heterocycles through the use of NHPI ester partners with an extended tether to the

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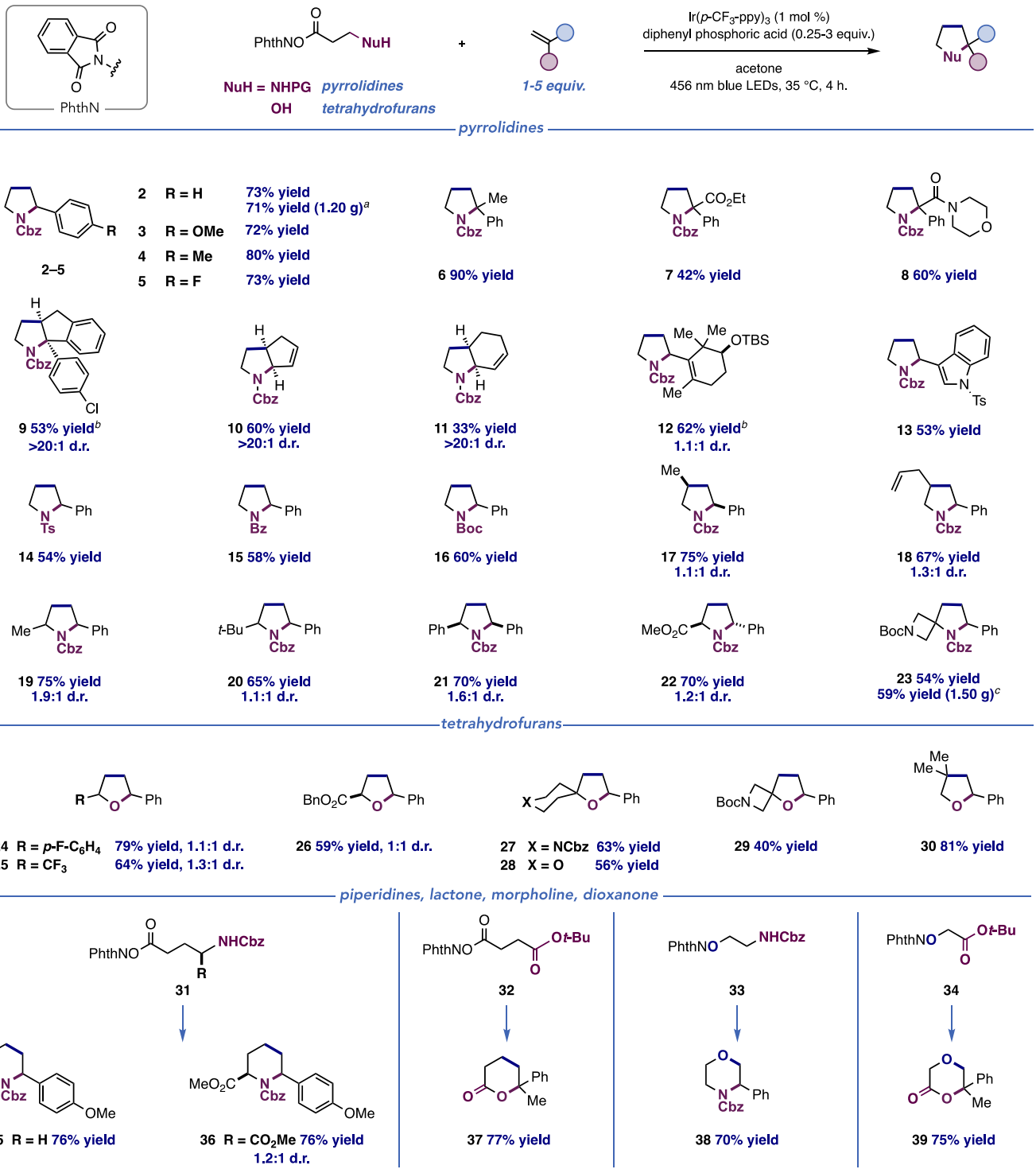

Figure 2. Substrate scope of [3 + 2] and [4 + 2] annulation reactions. Reactions run on 0.5 mmol scale unless otherwise noted. Yields are for isolated material and are the average of two runs. All products generated from achiral starting materials are racemic. [a]Gram-scale reaction performed using 0.2 mol % photocatalyst with 24 h. reaction time. [b]Reaction performed on 0.1 mmol scale. [c]Gram-scale reaction performed using 0.5 mol % photocatalyst. See the Supporting Information for details on relative stoichiometries of reagents.

nucleophile. To achieve efficient reactivity with these precursors, use of 1−3 equiv. of diphenyl phosphoric acid was necessary. With this modification, piperidines **35** and **36** were prepared in good yield, with **36** arising from annulation of a readily available derivative of L-glutamic acid. A tethered *t*-Bu ester can also serve as a pendent nucleophile in the synthesis of six-membered *δ*-valerolactone **37**. Further highlighting the modularity of this protocol, we found that use of NHPI ether reagents[76−80] in place of the esters, without otherwise altering reaction conditions, enabled the preparation of a distinct set of heterocycle classes bearing two heteroatoms. Here, the reaction proceeds *via* generation of an oxygen-centered radical that undergoes alkene addition, ORPC, and nucleophilic cyclization. *For example*, morpholine **38** and dioxanone **39**

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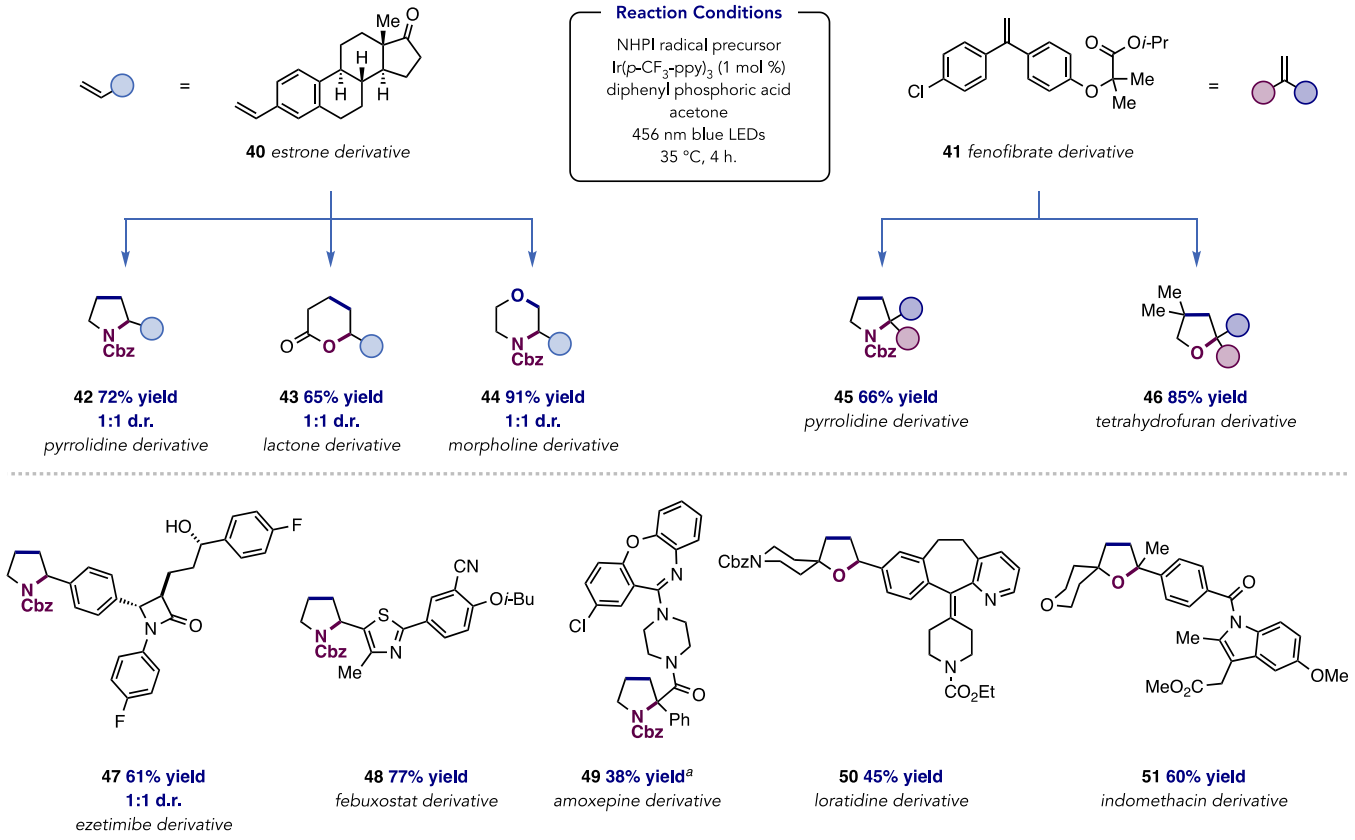

Figure 3. Substrate scope of [3 + 2] and [4 + 2] annulation reactions with complex alkenes. Reactions run on 0.1 mmol scale unless otherwise noted. Yields are for isolated material and are the average of two runs. [a]Reaction performed in acetonitrile. See the Supporting Information for details on relative stoichiometries of reagents.

were formed in 70% and 75% yields, respectively. Notably, this protocol provides the alternative regiochemical outcome in the cyclization compared to the recent report of morpholine synthesis from Ritter and co-workers.[42]

All of the NHPI ester and ether reagents studied above were prepared on >1.0 g scale, and the majority are accessible through chromatography-free protocols. All pyrrolidine, piperidine, morpholine, lactone, and dioxanone reagents above are bench-stable, and comparable yields of pyrrolidines **2** and **16** were realized when using a *ca.* 12 month old batch of NHPI ester reagent compared to a batch that was freshly prepared. We opted to store the tetrahydrofuran precursors at −20 °C, where they demonstrate stability and reaction viability without deterioration over *ca.* 6 months. This annulation methodology suffers from some limitations with respect to the electronic character of the alkene. *For example*, in reactions of more electron-deficient styrenes, products resulting from either carbocation hydration and/or elimination predominate. For cases where ORPC does not occur, linear radical reduction products are observed. Cyclization of piperidine substrates also appears limited to electron-rich styrenes. A list of modestly performing and unsuccessful substrates is included in the Supporting Information.

The modular nature of this annulation protocol enables the generation of a library of diverse heterocycles from a single alkene substrate (Figure 3). To highlight this ability, we selected two pharmaceutically relevant alkenes—deriving from estrone and fenofibrate—bearing styrenyl and 1,1-diarylethylene motifs, respectively, and exposed them to an array of coupling partners. Pyrrolidine (**42**), *δ*-valerolactone (**43**), and morpholine (**44**) fragments could all be appended to vinyl estrone in good-to-excellent yields. Fenofibrate was also readily derivatized to the corresponding pyrrolidine **45** and tetrahydrofuran **46** analogues.

Numerous complex alkenes were amenable to annulation, highlighting the functional group tolerance of the method toward *β*-lactams (**47**), unprotected benzylic alcohols, nitriles, amides, tertiary amidines, and esters. In the case of loratidine as an alkene partner, complete selectivity is observed for radical addition to the less substituted styrenyl fragment as opposed to an internal, tetrasubstituted alkene (**50**). Finally, this suite of complex alkenes contains an array of heterocyclic functionality that is tolerated under the annulation conditions, including thiazoles (**48**), piperazines and oxazepines (**49**), pyridines (**50**), and indoles (**51**).

We next examined the reactivity of pharmaceutical-derived NHPI esters for olefin annulation (Figure 4). These reagents are practical and convenient to prepare in two to four steps from the commercial drug substances in 68−90% overall yields (see the Supporting Information for details). A complex sulfonamide-tethered NHPI ester derived from COX-2 inhibitor celecoxib (**52**) was a competent partner in the annulation, delivering pyrrolidine **55** in 77% yield. Baclofen, an unnatural amino acid used as a muscle relaxant, could be easily derivatized to its corresponding NHPI ester **53** and subjected to annulation conditions with vinyl anisole to deliver piperidine **56** in 77% yield.

Additionally, an acetonide-protected NHPI ester derived from atorvastatin (**54**)—a drug used for prevention of cardiovascular disease—was synthesized and subjected to the

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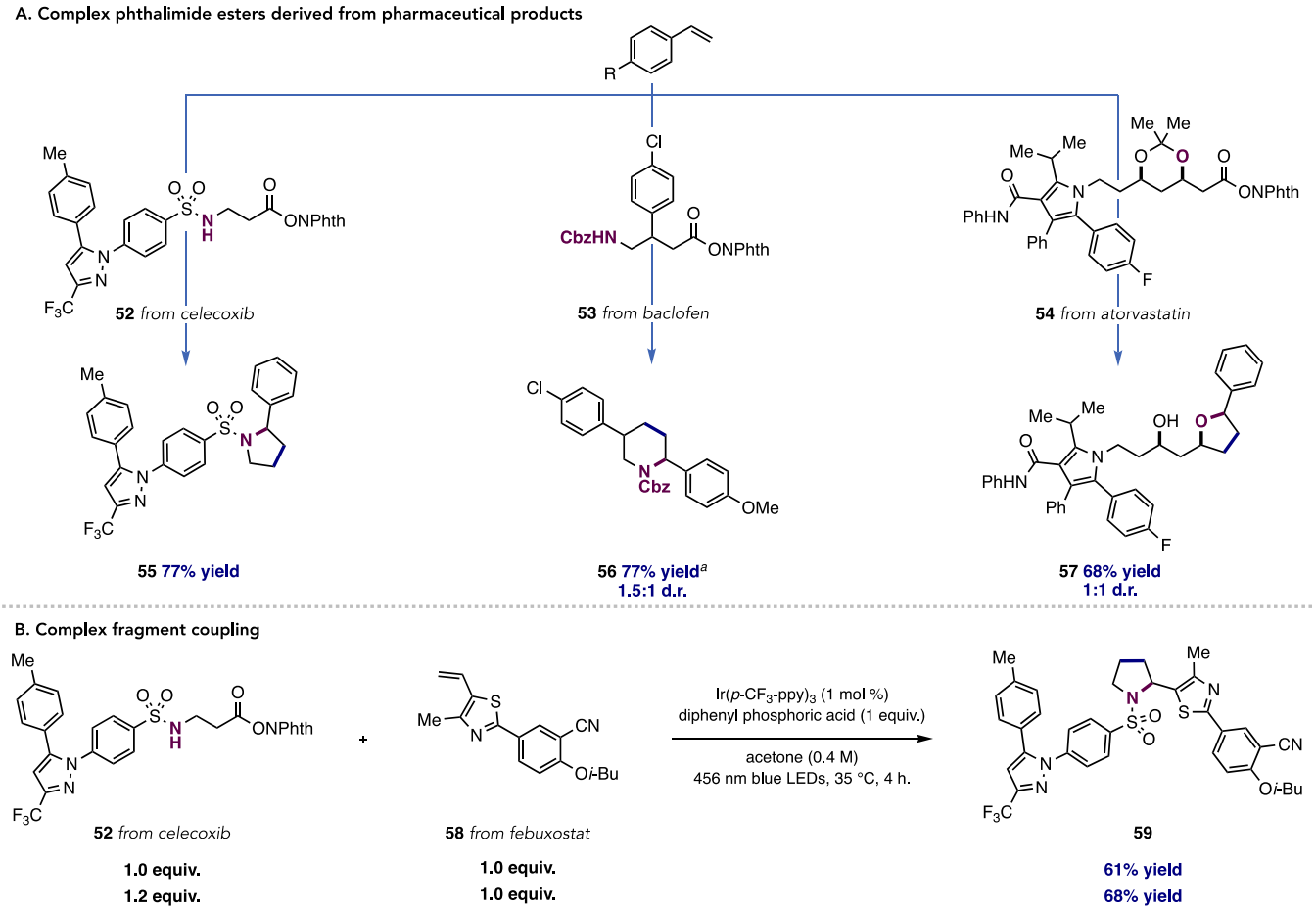

Figure 4. Annulation reactions with complex NHPI ester substrates. Reactions run on 0.1 mmol scale unless otherwise noted. Yields are for isolated material and are the average of two runs. (A) Examples of [3 + 2] and [4 + 2] annulation reactions from pharmaceutical-derived phthalimide esters. (B) Complex fragment coupling. See the Supporting Information for more details on relative stoichiometries of reagents. [a]Reaction performed on 0.5 mmol scale.

annulation conditions. Here, we observed that the acetonide was a competent nucleophile in pairing with the carbocation intermediate, delivering tetrahydrofuran **57** in 68% yield and 1:1 d.r.. Whereas these examples were conducted using excess styrene relative to the more valuable phthalimide ester, we found that complex fragment couplings can be accomplished efficiently using matched stoichiometries of both redox-active ester and alkene partners; *for example*, an annulation reaction between a febuxostat-derived alkene **58** and celecoxib-derived NHPI ester **52** proceeded in 61% yield with 1:1 relative stoichiometry. A slight increase in yield was noted with 1.2 equiv of **52** (68% yield). Finally, to highlight the utility of this protocol for preparative-scale synthesis, we carried out annulation reactions on a 6 mmol scale, delivering gram quantities of pyrrolidines **2** and **23** (Figure 2), with reduced photocatalyst loadings of 0.2 mol % and 0.5 mol %, respectively. Gratifyingly, these products were delivered in nearly identical yield compared to those performed on 0.5 mmol scale.

In summary, we introduce here a photocatalytic, two-component annulation strategy for the general synthesis of valuable five- and six-membered saturated heterocycles from alkenes and redox-active radical precursors bearing tethered nucleophiles. A number of distinct heterocycle classes were accessed using this approach, including pyrrolidines, piperidines, tetrahydrofurans, morpholines, δ-valerolactones, and dioxanones. We demonstrate the utility of this methodology for late-stage derivatization, heterocycle library synthesis, and gram-scale preparation. Furthermore, this annulation protocol readily accommodates complexity in both the redox-active radical precursor and alkene components, a feature particularly demonstrated through an example of complex fragment coupling between a celecoxib-derived NHPI ester and a febuxostat-derived alkene. We anticipate that other classes of heterocycles, other ring sizes, and more diverse bicyclic structures should all be accessible using the approach presented here. Efforts toward these ends are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c04316.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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