ABSTRACT: We report a general visible-light-mediated strategy that enables the construction of complex C(sp^3)-rich N-heterospirocycles from feedstock aliphatic ketones and aldehydes with a broad selection of alkene-containing secondary amines. Key to the success of this approach was the utilization of a highly reducing Ir-photocatalyst and orchestration of the intrinsic reactivities of 1,4-cyclohexadiene and Hantzsch ester. This methodology provides streamlined access to complex C(sp^3)-rich N-heterospirocycles displaying structural and functional features relevant to fragment-based lead identification programs.

Growing evidence suggests that an increasing number of aromatic rings in lead compounds can result in greater attrition rates among pharmaceutical candidates due to poor solubility, bioavailability, and pharmacokinetics.¹ However, libraries of lead-like structures often comprise compounds with predominantly C(sp^2)-rich scaffolds. Consequently, the assessment of structurally distinct libraries of C(sp^3)-rich small molecules displaying diverse polar functionality could help to identify new lead candidates in fragment-based screening approaches that may exhibit enhanced physical and biological properties.² In considering the design of novel C(sp^3)-rich small molecules for fragment-based approaches,³ it is noticeable that conformationally restricted scaffolds show highly reproducible results in in silico screening programs; the well-defined spatial orientation of molecular features in a candidate compound often leads to increased binding affinities. One approach toward limiting structural flexibility within C(sp^3)-rich small molecules is through the introduction of a spirocycle.⁴ In comparison to aromatic scaffolds, fine-tuning the structural and functional features in these frameworks offers an alternative means through which to probe interactions with target binding sites by varying ring size, adjusting electronic properties, and manipulating substituent effects.⁵ As a result, spirocyclic motifs displaying polar functionality are emerging in pharmaceutical agents and lead compounds (Figure 1a).⁴

Despite the attractive properties offered by rigid saturated polar spirocyclic scaffolds, access to diversely functionalized variants mainly relies on multistep alkyl- and acylative methods.⁵ Notable advances on these approaches include dearomatization-based strategies, using Pd, Ir, or Fe catalysts,⁶⁻⁷ which harness the intrinsic reactivity of tethered (hetero)arene building blocks for the generation of a selection of spirocyclic N-heterocycles with different ring sizes. Bode and co-workers produced a range of spirocyclic N-heterocycles using their SnAP technology;⁶⁻⁷
iminium ion formation between amino-stannane reagents and cyclic ketones enables a stoichiometric copper(II) cyclization to access free-(NH)-secondary amino-spircyclic products. To complement these approaches, we reasoned that a photocatalytic strategy based on an intuitive retrosynthetic disconnection of tertiary amine-based N-heterospirocycles directly to feedstock ketones and readily available alkenyl-derived secondary amines could be realized through the intermediacy of an α-amino radical (Figure 1b)\textsuperscript{8} The structurally distinct C(sp\textsuperscript{3})-rich polar N-heterospirocycles generated by such a catalytic transformation could be of interest to synthetic and medicinal chemists.

We envisioned that visible-light-mediated photocatalytic single-electron reduction of an alkyl-iminium ion (int-I, Figure 1c), formed from the condensation of a saturated cyclic ketone with a secondary alkylamine, would form a cyclic-tertiary α-amino radical (int-II). Addition of this α-amino radical to an appended alkene on the amine component would give rise to a substituted pyrrolidine-based spirocyclic scaffold. Recent work from our group established a photocatalytic platform for the addition of nucleophilic α-amino radicals (formed from the corresponding iminium ions) to electron-deficient olefins.\textsuperscript{9} Critically, however, a catalytic manifold for the addition of all-alkyl-substituted α-amino radicals to unactivated alkenes remains an unsolved problem, principally due to the mismatched electronics and low thermodynamic driving force for such a reaction. The lone pair on the nitrogen atom stabilizes the α-amino radical but also renders it nucleophilic. Therefore, its addition to an unactivated alkene is polarity-mismatched and hinder the wider application of this type of process.

While mimetics for GPCR protein binding, where the orthogonality of the two nitrogen substituents is key to achieve the desired turn-characteristics.\textsuperscript{14} While the Ir(dMeppy)\textsubscript{3} photocatalyst had proven optimal for reactions using electron-rich ketones (to form 3a=3e, 3i, 3l), higher yields were observed for electron-deficient ketones (to form 3f=3h, 3j, 3k, and 3m=3t) using the less-reducing [Ir(dMeppy)]\textsubscript{2}(dtbbpy)\textsubscript{2}PF\textsubscript{6} photocatalyst.

We next assessed N-substituted alkenylamines 3u=3an, where useful functional groups such as sulfonamide, N-Boc-piperidine, heteroaryl motifs (3u=3ab), and a less nucleophilic aniline (3ac) could be built into the spirocycle products. Substitution on the alkene was tolerated (3ad=3ah), introducing valuable functionalities such as the ester and gem-difluoro in useful yields. While no cyclized product was observed from attempts at reacting N-benzyl allylamine (to afford azetidine-based spirocycles), a piperidine scaffold 3ai could be assembled via a 6-exo cyclization, further expanding scope of the process. Homocyclic amines containing Θ-substituents were effective in the

### Table 1. Selected Optimization Data\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>Hantzsch ester (equiv)</th>
<th>1,4-CHD (equiv)</th>
<th>yield (%)</th>
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<tr>
<td>1</td>
<td>Ir(ppy)\textsubscript{3}</td>
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<tr>
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<tr>
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<td>Ir(dMeppy)\textsubscript{3}</td>
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<td>–</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Ir(dMeppy)\textsubscript{3}</td>
<td>–</td>
<td>7.5</td>
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<tr>
<td>6</td>
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<td>2.0</td>
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</tr>
<tr>
<td>7</td>
<td>Ir(dMeppy)\textsubscript{3}</td>
<td>–</td>
<td>–</td>
<td>trace</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reactions employed a 40 W Blue Kessil lamp, and yields were calculated by GC assay with dodecane as internal standard.
<table>
<thead>
<tr>
<th>Reaction using</th>
<th>Reaction using</th>
<th>Reaction using</th>
<th>Reaction using</th>
</tr>
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<tbody>
<tr>
<td>Ir(dMeppy)$_3$</td>
<td>[Ir(dMeppy)$_2$(dtbpy)]PF$_6$</td>
<td>0.5 mol% [Ir]</td>
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**Table 2. Scope of Photocatalytic Synthesis of N-Heterospirocycles**

<table>
<thead>
<tr>
<th>Carbonyl Scope</th>
<th>Scope</th>
<th>Scope</th>
<th>Scope</th>
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</thead>
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<tr>
<td><img src="image1" alt="Carbonyl 1" /></td>
<td><img src="image2" alt="Scope 1" /></td>
<td><img src="image3" alt="Scope 2" /></td>
<td><img src="image4" alt="Scope 3" /></td>
</tr>
</tbody>
</table>

*Reaction using Ir(dMeppy)$_3$. *Reaction using [Ir(dMeppy)$_2$(dtbpy)]PF$_6$. 0.5 mol% [Ir].
cyclization process with both aldehydes and functionalized alicyclic ketones, in some cases with surprisingly high diastereoselectivities 3aj−3an. We found that the exceptionally hindered spirocycles 3ao and 3ap could be accessed in 49% and 47% yield respectively, affording access to a class of compounds that are challenging to synthesize using classical C=N bond-forming methods. be,15,16

Next, we questioned whether we could apply the α-amino radical to a cyclization process with simple alkynes, affording N-heterospirocycles carrying a useful alkenyl handle for further functionalization. N-Benzyl-4-aminobutyne derivatives smoothly reacted with a range of cyclic ketones, furnishing the desired spirocycles 4a−4g in 53−73% yield (Figure 2a). Finally, the alkenyl handle of 4d could be derivatized through a difluorocyclopropanation to afford 6 in 72% yield, whose structure comprises three different-sized ring systems and two adjacent spirocyclic centers, as well as different oxidative transformations (5 and 7, Figure 2b).17

We found that the addition of TEMPO, as a radical trap, significantly inhibited the reaction (Figure 3a). A reaction with cyclopropyl-substituted alkenylamine 1r led to the ring-opened product, supporting the existence of a cyclized radical intermediate (cf. Int-III). Stern–Volmer studies on a representative iminium ion (8) showed effective quenching of the excited state of the Ir(dMeppy)3 photocatalyst in comparison to Hantzsch ester (Figure 3c). On the basis of these studies and those outlined in our optimization (Table 1), we propose a tentative mechanism for the reaction which begins with visible-light excitation of Ir(dMeppy)3 to Ir(dMeppy)3* (Figure 3c). Single-electron reduction of the iminium ion (Int-I) by Ir(dMeppy)3* forms the α-amino radical (Int-II), which engages the pendant alkene in a 5-exo-trig cyclization to form an alkyl radical (Int-III). HAT from 1,4-CHD to the alkyl radical then forms N-heterospirocycle 3. The oxidized Ir(IV)(dMeppy)3 species is reduced to the active catalyst by single-electron transfer from the Hantzsch ester, closing the catalytic cycle.

In summary, we have developed a visible-light-mediated process to enable the facile synthesis of heterospirocyclic compounds from readily available starting materials. The photoredox strategy offers an intuitive retrosynthetic discon-
connection for difficult-to-access C(sp³)-rich N-hetero- spirocyclic scaffold olds that may be of interest to practitioners of both synthetic and medicinal chemistry.

**ASSOCIATED CONTENT**

* Supporting Information

Experimental procedures and spectral data (PDF)

X-ray crystallographic data for 6 (CIF)

X-ray crystallographic data for 4a (CIF)

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Notes

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

We are grateful to the Gates Cambridge Trust (N.J.F.) and Herchel Smith Scholarship Scheme (A.T.) for studentships, the EPSRC (EP/S020292/1 and EP/N031792/1), Ambitious Leader’s Program, Hokkaido University, Japan (Y.K.), and the Royal Society for a Wolfson Merit Award (M.J.G.). S.M.W. is a Fellow of the AstraZeneca Postdoctoral program. We are grateful to the EPSRC UK National Mass Spectrometry Facility at Swansea University for HRMS analysis.

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