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Visible Light Induced One-pot Synthesis of Spirocyclopropyl Oxindoles from Isatin Derivatives and Glycine Ester Hydrochloride

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Abstract: An integrated one pot protocol for the *in situ* generation of hazardous alkyl diazoacetates (from glycine ester hydrochloride) and their subsequent reaction with 3-alkenyl oxoindoles (generated *via* the *in situ* Wittig reaction from isatin derivatives) to afford diastereomeric mixtures of spirocyclopropyl oxoindoles in toluene at room temperature is presented. Spirocyclopropyl oxoindoles are interesting building blocks prevalent in many active pharmaceutical ingredients and in natural products. This protocol is devoid of any metal catalysts or bases.

Keywords: Alkyl diazo ester · Alkylidene oxindole · Blue LED · Spirocyclic oxindole

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1. Introduction

One-pot synthetic strategies encompass a broad class of methodologies wherein multiple reactions or sequential transformations are executed in a single reaction vessel without the need for intermediate isolation or work-up steps.[1] Such protocols offer significant advantages, including minimized solvent consumption, reduced chemical waste, time savings, and lower operational costs—parameters crucial for both sustainability and practical feasibility.

Pioneering contributions to this field include the biomimetic synthesis of progesterone by Johnson and coworkers, the total synthesis of endiandric acid by Nicolaou *et al.,* and the synthesis of proto-daphniphylline by Heathcock and Piettre.[2a–c] More recently, one-pot methodologies have been extended to organocatalysis, as exemplified by Enders' elegant diphenylprolinol silyl ether-catalyzed synthesis of optically active cyclohexenecarbaldehydes *via* a key enantioselective Michael addition.[2d]

A particularly valuable development in one-pot chemistry is the efficient and controlled *in situ* generation of reactive, unstable, or hazardous intermediates such as diazo compounds followed by their immediate transformation into synthetically valuable products.[3] Among these, alkyl diazoacetates have emerged as versatile carbene precursors, enabling access to a wide range of heterocyclic scaffolds of relevance to medicinal and synthetic chemistry.[4] Despite their utility, their intrinsic thermal instability, high reactivity, and explosive nature pose significant challenges in storage, transport, and handling.[5] As such, methods enabling

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their *in situ* generation and subsequent transformation into stable products within a single synthetic operation are highly attractive.

In this context, spirocyclopropyl oxoindoles hybrids of two pharmacophores, namely cyclopropane and 2-oxoindole are gaining prominence due to their broad biological and synthetic applications.[6,7] For instance, CFI-400945 (compound **A**), a spirocyclopropyl oxoindole, is a potent PLK4 inhibitor currently undergoing Phase I clinical trials for breast cancer (Fig. 1).[8] Compound **B** has demonstrated potent antiviral activity against HIV at nanomolar concentrations,[9] while compound **C** inhibits proliferation of DU-145 prostate cancer cells with low micromolar IC_{50} values.[10]

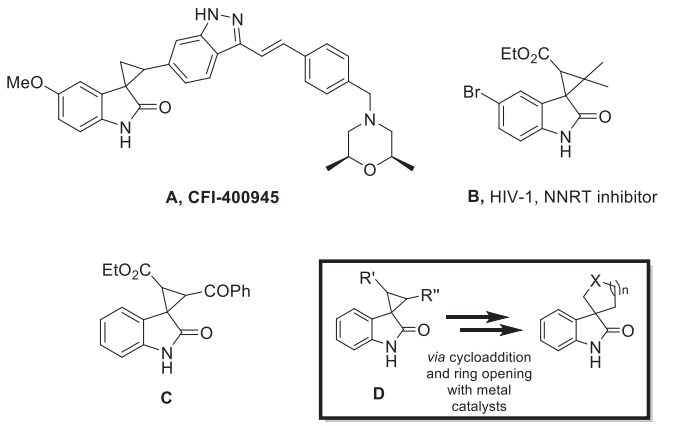


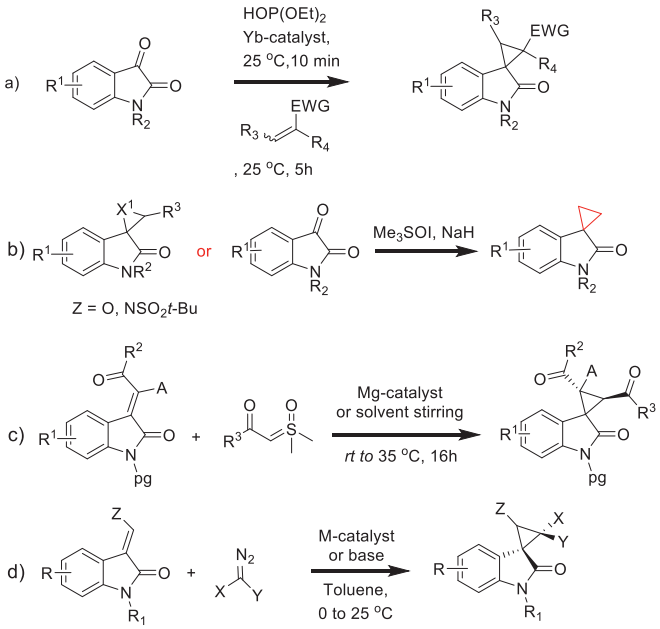
Fig. 1. Spirocyclopropyl oxoindoles as natural products and building blocks.

From a synthetic perspective, spirocyclopropyl oxoindoles serve as privileged intermediates in donor–acceptor cyclopropane chemistry, participating in reactions with dipolarophiles and nucleophiles to afford complex 2-oxoindole derivatives bearing quaternary stereocenters (Fig. 1).[11,12] Additionally, they have been proven as valuable substrates in various ring-opening and ring-expansion strategies, further expanding their synthetic utility.[11,12]

The synthetic and medicinal value of spirocyclopropyl oxoindoles has inspired the development of diverse strategies for their construction. A variety of precursor classes have been explored to access this structural motif.[13] For instance, Eberle *et al.* reported the synthesis of spirocyclopropyl oxoindoles *via* refluxing isatin with a phosphorus ylide, offering a straightforward approach (Scheme 1a).[13a] Peng *et al.* introduced a more elaborate four-step sequence involving a Pudovik reaction, Brooks rearrangement, Michael addition, and intramolecular nucleophilic substitution to generate the target scaffold from isatin, dialkyl phosphites, and activated alkenes under lanthanide amide catalysis.[13b] In a notable contribution, Hajra and colleagues employed a Corey–Chaykovsky-type domino protocol using Me_3SOI and sodium hydride in DMSO at room temperature to construct these frameworks directly from isatins (Scheme 1b).[13c]

Additionally, 3-alkenyl oxoindoles have emerged as versatile precursors for spirocyclopropanation.[14a] These substrates undergo cycloaddition reactions with a variety of dinucleophilic species, including sulfur ylides[14b,c] (Scheme 1c), Morita–Baylis–Hillman (MBH) carbonates,[14d] metal catalyzed reagents,[14e] diazo compounds,[14f] and carbenoids, furnishing spirocyclopropyl derivatives in good yields (Scheme 1d).[14a] Similarly, diazo-functionalized oxoindoles have been shown to participate in cyclopropanation reactions with alkenes in the presence of Lewis acids or transition metal catalysts such as $Hg(OTf)_2$, AuOTf, and Ru(II)-Pheox complexes.[15]

The nucleophilic C3-position of the oxoindole ring system renders it highly reactive towards dielectrophilic C2 synthons. Reagents such as dibromoethane, halogenated nitro olefins, vinyl selenones, vinyl diphenyl sulfonium triflates, and bromoethyl sulfonium salts have been employed to achieve spirocyclopropanation through electrophile-induced annulation.[16] Furthermore, 3-halooxoindoles have proven valuable intermediates owing to their ambiphilic nature, enabling cascade transformations that introduce diverse functionalities—including *para*-quinone, oxetane, thiazolone and spiro-2-oxoindole ring systems *via* tandem Michael addition and intramolecular nucleophilic displacement.[17] An alternative and innovative strategy by Charette and coworkers involved the intramolecular arylation of cyclopropyl-substituted 2-bromoanilides in the presence of silver(I) salts and palladium catalysts to deliver spirocyclic products.[18]



Scheme 1. Reported synthesis of spirocyclopropyl oxindoles.

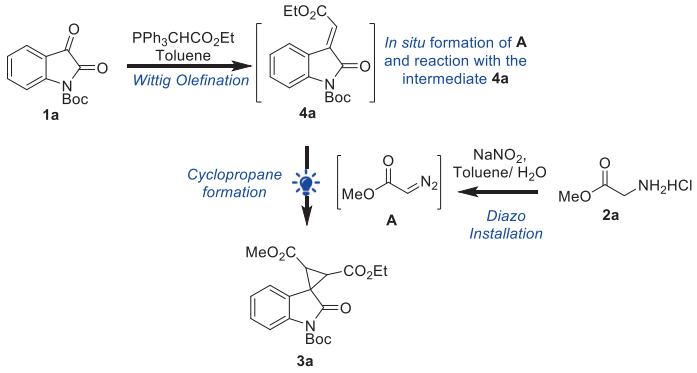
Despite the rich landscape of synthetic approaches, a sustainable and operationally simple one-pot method for the synthesis of spirocyclopropyl oxoindoles remains underexplored. This realization prompted us to develop an ecologically benign strategy that enables the formation of spirocyclopropyl oxoindoles from 3-alkenyl oxoindoles *via* a catalyst- and reagent-free visible-light-mediated protocol. Our integrated approach involves the *in situ* generation of alkyl diazoesters from glycine alkyl ester hydrochlorides, their photolysis under blue LED irradiation to generate carbenes, and subsequent spirocyclopropanation with 3-alkenyl oxoindoles. Notably, these 3-alkenyl oxoindoles are simultaneously formed in the same reaction medium from isatin and an appropriate phosphonium ylide thereby achieving full convergence in a single vessel.

The utility of visible-light-induced transformations of diazoesters has gained considerable momentum in recent years.[19] In particular, blue LED activation of both aryl and alkyl diazoesters has enabled a wide range of carbene-mediated transformations including addition, insertion, cycloaddition, and cyclopropanation reactions with various olefins and heterocycles.[19] This growing body of work underscores the potential of photoactive diazo chemistry in sustainable synthetic methodology.

2. Results and Discussion

The proposed sustainable synthetic route to spirocyclopropyl oxoindoles was successfully realized through a telescoped, one-pot, three-step reaction sequence (Scheme 2). The process commenced with the Wittig olefination of isatin **1a** using ethyl (triphenylphosphoranylidene)acetate (PPh_3CHCO_2Et) in toluene at ambient temperature. Upon confirmation of complete conversion to the corresponding 3-alkenyl oxoindole **4a**, as monitored by thin-layer chromatography (TLC), the second phase of the transforma-

tion was initiated. A premixed aqueous solution of glycine methyl ester hydrochloride (**2a**) and sodium nitrite ($NaNO_2$) in a water: toluene biphasic system (1:4 *v/v*) was added directly to the reaction mixture at room temperature under visible light irradiation.



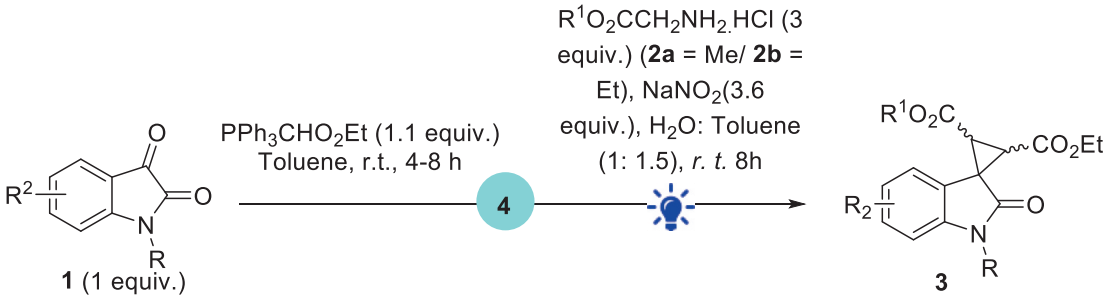
Scheme 2. One-pot synthesis of spirocyclopropyl oxoindole from isatin.

The photochemical component of the reaction was conducted using a commercial blue LED photoreactor (Aldrich® Penn PhD Photoreactor M2), equipped with IP68-rated, double-density 12V DC waterproof blue LED strips (λ_{max} = 450 nm, powered by 100–240 V AC, 50/60 Hz). Under these optimized conditions, the desired spirocyclopropyl oxoindole **3a** was isolated in an excellent 82% yield. The overall transformation encompasses a seamless one-pot progression: (i) base-free Wittig olefination to form **4a**, (ii) *in situ* generation of the alkyl diazoester intermediate **A** *via* diazotization of **2a**, and (iii) visible-light-induced carbene generation and subsequent cyclopropanation with **4a** (Scheme 2).

To probe the temporal role of visible light irradiation, a control experiment was performed wherein the blue LED was switched 'on' only after the completion of diazoester **A** formation which took nearly an hour. Interestingly, this modified protocol resulted in a reduced yield of 71%, indicating that continuous irradiation from the onset of diazoester generation is critical. It is likely that immediate photolysis of the freshly formed diazoester enabled timely carbene formation, which then efficiently engaged with the preformed olefin **4a** to furnish **3a**. The reaction after the formation of the diazo ester took nearly 5 to 6 hours to complete. This operational design not only avoids the isolation or accumulation of diazo compounds but also minimizes decomposition or side reactions commonly associated with free diazo species.

Overall, the protocol is operationally straightforward, performed under ambient conditions and open to air, underscoring its practical utility and ecological advantages. The success of this one-pot strategy highlights the synthetic potential of integrating classical reactivity with photochemical activation for the construction of complex spirocyclic frameworks in a sustainable fashion.

The generic reactions stipulated that the scope of isatin derivatives **1a**-**1q** were broad, providing diversly substituted spirocyclopropyl oxoindole **3a**-**3ah** in moderate to excellent yield with **2a** and **b** (Scheme 3). NH-free and NH-substituted (Boc- and acetyl-) products with a variety of halides (chloride, fluoride, and bromide) at C5 and C7 were well tolerated under the optimized reaction conditions. 5-Methyl and 5-methoxy-isatin derivatives were equally amenable under the optimized reaction conditions



Compound #	R	R^1	R^2	Yield	d.r.
3a	Boc	Me	H	82%	1:1
3b	H	Me	H	86%	1:1
3c	Ac	Me	H	69%	1:1
3d	H	Et	H	79%	1:1
3e	H	Me	7-Cl	89%	1:1
3f	Boc	Et	H	85%	1:1
3g	Ac	Et	H	71%	1:1
3h	H	Me	5- F	90%	1:1
3i	H	Et	7- Cl	89%	1:1
3j	H	H	5- F	91%	1:1
3k	Boc	Me	5- F	87%	1:1
3l	Boc	Et	5- F	86%	1:1
3m	H	Me	5-Br	91%	1:1
3n	Ac	Me	5- F	60%	1:1
3o	Boc	Me	7- Cl	78%	1:1
3p	Boc	Et	7-Cl	81%	1:1
3q	Ac	Et	5-F	61%	1:1

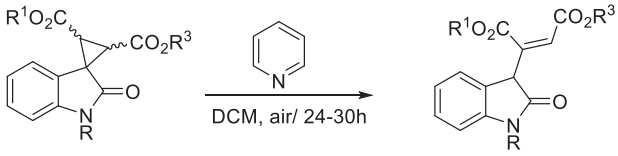
Compound #	R	R^1	R^2	Yield	d.r.
3r	H	Et	5-Br	80%	1:1
3s	Boc	Me	5-Br	91%	1:1
3t	Boc	Et	5-Br	93%	1:1
3u	Ac	Et	5-Br	69%	1:1
3v	Ac	Me	5-Br	71%	1:1
3w	H	Et	5- Me	79%	1:1
3x	H	Me	5-Me	71%	1:1
3y	H	Et	5-OMe	79%	1:1
3z	H	Me	5-OMe	83%	1:1
3aa	Boc	Me	5-Me	70%	1:1
3ab	Boc	Et	5-Me	80%	1:1
3ac	Boc	Me	5-OMe	75%	1:1
3ad	Boc	Et	5-OMe	78%	1:1
3ae	Ac	Me	5-OMe	65%	1:1
3af	Ac	Et	5-OMe	68%	1:1
3ag	Ac	Me	5-Me	70%	1:1
3ah	Ac	Et	5-Me	71%	1:1

Scheme 3. Library of spirocyclopropyl oxindoles.

(Scheme 3). In general, the NH-free **3d**, **3e**, **3h**, **3i**, **3m**, **3r** and **3w** - **3z** along with the *N*-Boc-derived products **3a**, **3f**, **3k**, **3l**, **3o**, **3p**, **3s**, **3t** and **3aa** - **3ad** (Scheme 3) had higher yields in comparison to the *N*-Acetyl analogues **3c**, **3g**, **3n**, **3q**, **3u**, **3v** and **3ae** - **3ah** (Scheme 3). The average time for the completion of the reaction sequence was 16–20 h. It is noteworthy that the time for the initial Wittig olefination varied with individual substrates. For electron poor substrates **1b**, **1d**, **1h**, **1j** and **1n** the reaction time was around 4 to 5 h whereas for the electron rich isatins like **1c**, **1e**, **1f**, **1i**, **1k**, **1l**, **1o**, **1p** and **1q** the reaction time was prolonged to around 8 to 10 h. It was also interesting to note that as a proof of concept the reaction was performed in such a way that the Wittig olefination and the diazo installation occurred at the same time; by adding **1a**, **2a** and the relevant reagents *i.e.* triphenyl phosphonium ethyl acetate, glycine methyl ester and sodium nitrite. This generated the desired product **3a**, all be it in a poor yield of 33%. The efficiency of a protocol is demonstrated by the ease with which it can be scaled up. Accordingly, under the optimized conditions compound **3c** was fluently synthesized from 1 gram of the isatin derivative **1m** to afford the desired product in 76% yield (Scheme 3). In the absence of a chiral catalyst the desired products were obtained as 1:1 mixtures of diastereomers.

Despite the substantial robustness of our protocol towards the synthesis of spirocyclopropyl oxoindoles there are a few limitations with this strategy. The reaction with aryl diazo acetate and dimethyl diazoacetate failed to provide the desired spirocyclopropyl oxindoles. With the phenyl diazoacetate negligible product formation was detected through HRMS, whereas the dimethyl diazo acetate remained completely unreacted.

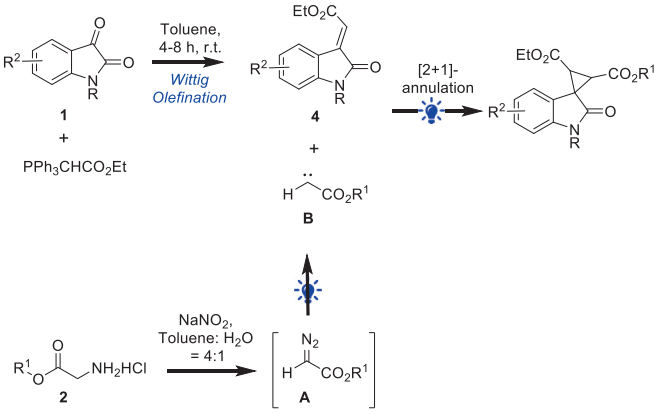
It is noteworthy that the spirocyclopropyl oxoindole derivatives **3** could be converted to their ring opened analogues under air to generate electron deficient olefins (EDOs) (Scheme 4). Electron-deficient olefins (EDOs) are highly reactive Michael acceptors widely used in organic synthesis, making them ideal partners for nucleophilic and radical additions, cycloadditions (*e.g.* [3+2], [4+2]), and hydrofunctionalization reactions. To demonstrate this, compounds **3a** and **3f** were treated with pyridine in DCM and they underwent ring opening reactions to provide 3-olefinic oxo-indoles **3a'** and **3f'** (Scheme 4) respectively in quantitative yields.



3a': R^1 = Et; R^3 = Me, R = Boc
3f': R^1 = R^3 = Et, R = Boc

Scheme 4. Ring opening reactions of spirocyclopropyl oxoindole **3a** and **3f** to afford **3a'** and **3f'**.

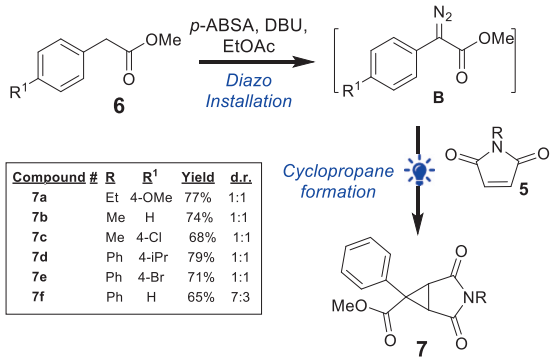
The proposed mechanism for the transformation initiates with the condensation of isatin derivatives and triphenylphosphonium ethyl acetate in toluene at ambient temperature, furnishing 3-alkenyl-3-oxoindoles **4** *via* a Wittig olefination. In parallel, glycine methyl esters **2** undergo diazotization in the presence of the freshly generated alkenyl-3-oxoindoles **4** and sodium nitrite ($NaNO_2$), thereby producing the diazoester intermediate **A** (Scheme 5). This species promptly extrudes molecular nitrogen under the reaction conditions, giving rise to a singlet carbene species **B**, in line with the observations reported by Platz and coworkers.[10] The transient carbene **B** then engages the electron-rich olefinic double bond of the 3-alkenyl-3-oxoindole **1** in a highly regioselective cyclopropanation, culminating in the formation of the spirocyclic cyclopropyl oxoindole scaffold **3** (Scheme 5).



Scheme 5. Reaction mechanism for the synthesis of spirocyclopropyl oxindoles.

Furthermore, we extended the utility of our photochemical carbene transfer methodology to *N*-substituted maleimides through a one-pot diazo transfer and cyclopropanation strategy. Herein, *in situ* diazo installation on appropriate aryl alkyl acetates (**6a**-**6e**) by using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA), blue LED irradiation for carbene formation and subsequent cyclopropanation with various *N*-substituted maleimides **5a**-**c** (methyl, ethyl, and phenyl-substituted), furnished the corresponding fused cyclopropanated maleimides **7a**-**7f** in moderate to good yields (Scheme 6). This demonstrates the utility of our protocol in engaging electron-deficient dipolarophiles such as maleimides for photochemical cyclopropanation (Scheme 6).

Interestingly, under the same conditions the more stable dimethyl 2-diazomalonate as a diazo precursor failed to generate the desired cyclopropanated products. This further underscores the limitation of this approach with stabilized diazo species, which may be less reactive or could undergo an alternative decomposition pathway under the given conditions.



Compound #	R	R^1	Yield	d.r.
7a	Et	4-OMe	77%	1:1
7b	Me	H	74%	1:1
7c	Me	4-Cl	68%	1:1
7d	Ph	4-iPr	79%	1:1
7e	Ph	4-Br	71%	1:1
7f	Ph	H	65%	7:3

Scheme 6. Reaction of *N*- alkyl/aryl maleimides with methyl 2-arylacetate.

3. Conclusions

In conclusion, we have developed a user-friendly and operationally simple one-pot protocol for the synthesis of spirocyclopropyl oxoindoles **3** from readily available isatin derivatives **1** and glycine ester hydrochlorides **2** under visible-light irradiation. The transformation proceeds in toluene at ambient temperature under blue LED light, affording the desired spirocyclopropane-fused oxoindole scaffolds in moderate to excellent yields across a range of substrates.

Mechanistically, the sequence involves the *in situ* formation of the 3-alkenyl oxoindole **4** *via* Wittig olefination of **1**, followed by the generation of alkyl diazo ester intermediate **A** from the diazotization of **2** with sodium nitrite in a biphasic aqueous-organic

system. Under blue light irradiation (λ ≈ 450 nm), **A** undergoes photolytic decomposition to furnish the corresponding carbene intermediate **B**, which then engages in a [2+1] cycloaddition with the unpurified 3-alkenyl oxoindole **4** to deliver the spirocyclopropyl oxoindole product **3**.

This telescoped, multistep protocol obviates the need for isolation or purification of reactive intermediates such as diazo esters, which are often associated with safety and storage concerns. By avoiding the direct handling of hazardous diazo compounds and operating under mild, metal-free, and photochemical conditions, this method offers a safer, greener, and more sustainable alternative to previously reported approaches for accessing this valuable class of molecules.

The spirocyclopropyl oxoindole framework is a privileged structural motif in medicinal chemistry and synthetic organic chemistry due to its unique three-dimensional architecture and potential biological relevance. Moreover, the scalability of this one-pot protocol has been demonstrated, further highlighting its practical utility for larger-scale applications. This work provides a blueprint for the integration of classical reactivity, photochemical activation, and green chemistry principles in the efficient construction of niche spiro- and fused cyclic scaffolds.

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Author Contributions

T. P., S. B., and K. V. performed the reaction. S. B. assisted S. S. to write the manuscript. S. S. wrote the manuscript and garnered funds for the project.

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