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Photoinduced Temperature-Regulated Selective Carbene C−H Insertion for the Synthesis of Functionalized Spiro-β-lactones and -lactams

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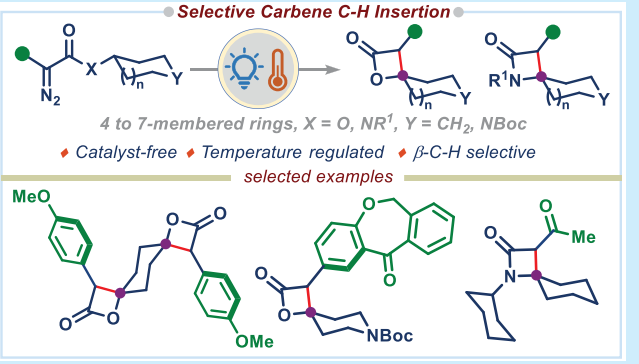
ABSTRACT: A temperature-regulated catalyst-free photoinduced selective carbene C−H insertion strategy was realized to efficiently synthesize spiro-β-lactones and -lactams, which hold considerable promise in drug discovery programs. The reaction shows broad applicability across a range of α-diazo esters and amides with various ring sizes and substituents and has been demonstrated to successfully achieve the late-stage spirocyclization of natural/bioactive compounds. The obtained products could be transformed into spiro-oxetanes, -azetidines, and -cyclopropanes, privileged scaffolds with broad utility in medicinal chemistry.



Spirocyclic scaffolds are becoming increasingly prominent structural motifs in drug discovery programs, allowing fine-tuning of a drug candidate's physicochemical and pharmacokinetic properties.[1] Because of the restricted conformation of their three-dimensional structure, a single spirocyclic unit can populate the third dimension without needing extra connecting modules, whereas the traditional drug design based on (hetero)aromatic cores requires linking several segments to address the third dimension fully.[1] Identifying such salient features has stimulated a recent surge in reports of spirocycle-based biologically active molecules.[2] Among spirocycles, spiro-β-lactones and -lactams are the most prevalent substructures, which are present in numerous drug candidates and bioactive molecules exhibiting a wide spectrum of activities such as androgen receptor, inhibition of cholesterol absorption, and $GABA_A$ antagonist (Scheme 1A).[3] Furthermore, due to the exceptional reactivity of the strained ring system, they can participate in various ring-fragmentation or ring-expansion reactions leading to highly valuable ring-opened products and heterocycles.[4] Additionally, they can be easily transformed into spiro-oxetanes and -azetidines, other privileged scaffolds with broad utility in medicinal chemistry.[5] Consequently, developing new, efficient, and sustainable methods for synthesizing these spirocyclic scaffolds is an important target in organic chemistry and would be valuable for discovering new bioactive compounds.

Direct C−H bond functionalization strategies are among the most powerful tools in organic chemistry due to not only the vast abundance of C−H bonds but also their ability to construct structurally unique skeletons efficiently and selectively.[6] A very promising C−H functionalization is the insertion of a metal-bound carbene into a C−H bond.[7] The groups of Davies, Doyle, Che, and Wang have developed highly useful synthetic methods via C−H functionalization with donor/acceptor-substituted metal carbenes, and this strategy has been used in the total synthesis of various natural products and pharmaceutical agents.[8] However, the application of this strategy for accessing spiro-β-lactones and -lactams has rarely been investigated, which could be due to the challenges associated with the regioselective activation of the β-C−H bond in the presence of the highly preferred γ-C−H bond. In 1990, Lee and co-workers first reported rhodium(II) acetate-catalyzed intramolecular C−H insertion strategy for the synthesis of spiro-β-lactones and found that the site selectivity depends on both the substrate and conformational bias of the metallocarbene (Scheme 1B).[9] In 2017, Moody and co-workers developed a selective C−H insertion protocol for the synthesis of spiro-β-lactones using rhodium-stabilized donor/acceptor carbenes.[10] While these strategies are effective, they require expensive rhodium or are effective only for the synthesis of spiro-β-lactones, which limits their broader applications in medicinal chemistry programs. In the spirit of

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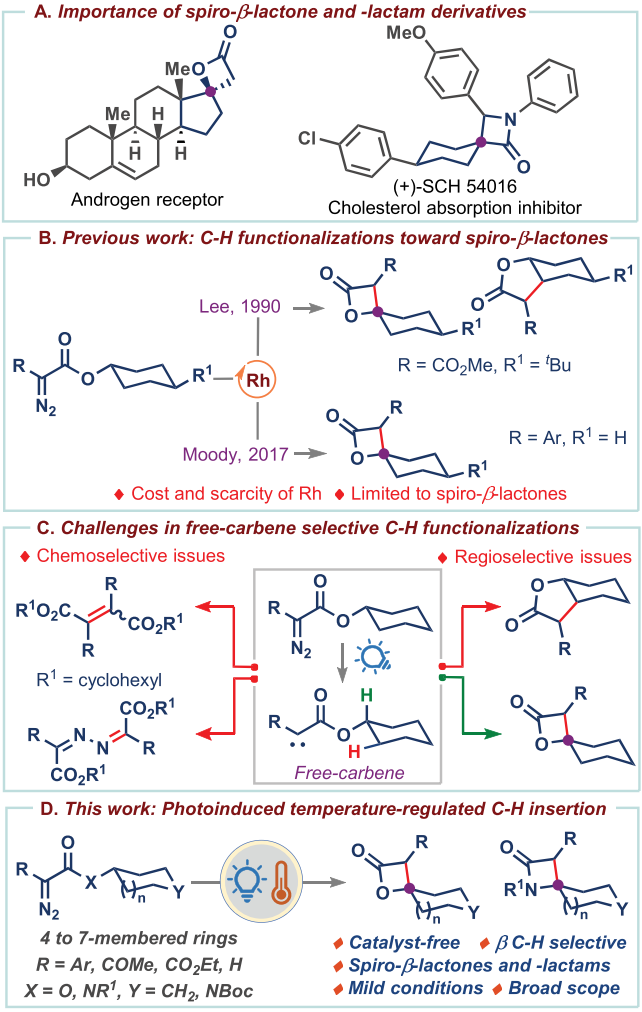
Scheme 1. Importance and Synthetic Approaches to Spiro-β-lactones and -lactams

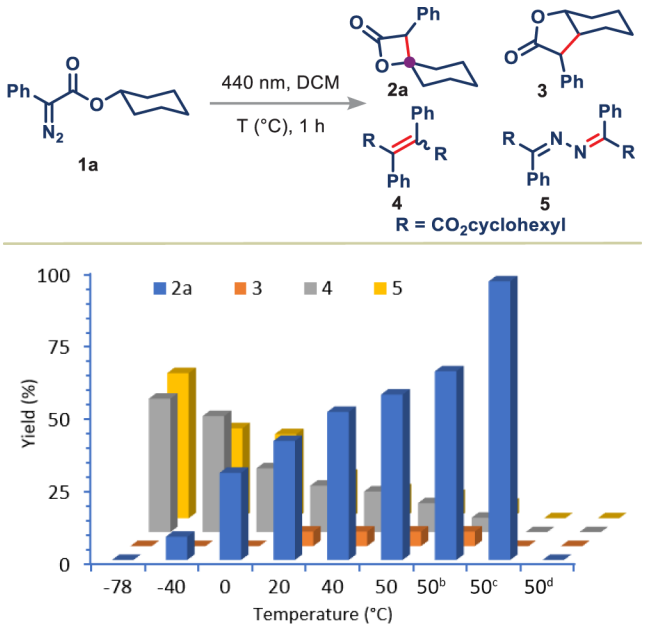


developing environmentally benign synthetic methods, catalyst-free and low-energy-consuming strategies for selective C−H functionalizations are of high importance.

Recently, the generation of carbenes from diazo compounds under visible-light irradiation emerged as an attractive approach toward sustainable carbene transfer reactions under mild and metal-free conditions.[11] This strategy has been successfully employed in efficient cyclopropanation, cyclopropenation, X−H insertions (X = C, O, and S), olefinations, and benzannulations by Davies, Koenigs, Gryko, and others.[12] Despite these advancements, controlling chemoselectivity and regioselectivity, especially for functionalization at specific C−H bonds in free-carbene transfer reactions are highly challenging (Scheme 1C), unlike in the transition-metal-catalyzed reactions, where the selectivities are better controlled via singlet metal carbene intermediates.[13] In this context, controlling the reactivity and selectivity of free carbenes using quickly and conveniently controlled physical variables would thus overcome a long-standing problem and represent a significant advancement in carbene chemistry. Herein we report our success in developing a temperature-regulated photoinduced catalyst-free selective carbene C−H insertion protocol, which leads to a wide range of functionalized spiro-β-lactones (Scheme 1D). We show that this process is general and can also be applied for the synthesis of spiro-β-lactams, which are finding increasing applications in pharmaceuticals. Furthermore, the obtained products can be easily transformed into other important scaffolds such as spiro-oxetanes, -azetidines, and -cyclopropanes.

We commenced our investigations by studying the reaction of cyclohexyl 2-diazo-2-phenylacetate (**1a**) under blue-light irradiation using DCM as the solvent at 20 °C. We found that the diazo compound **1a** was completely consumed within 1 h and gave a complex mixture of compounds (Scheme 2, column

Scheme 2. Optimization of the Reaction Conditions[a]



[a]Reaction conditions: **1a** (0.15 mmol), DCM (1.5 mL, 0.1 M), 440 nm, 1 h. Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b]0.05 M. [c]**1b** instead of **1a**. [d]No light.

4). Carefully analyzing the reaction mixture revealed that the desired spiro-β-lactone **2a** was formed in 41% yield along with fused compound **3** (5%), dimers **4** (16%), and azine **5** (15%). Sander and co-workers reported that temperature could influence the spin state of free diaryl carbenes and their singlet−triplet splitting,[14] thus allowing for spin-dependent selective reactions of free carbene intermediates, so the effect of temperature was examined here too. When the reaction was conducted at −78 °C under blue-light irradiation, we did not observe spiro-β-lactone **2a**. Instead, we obtained azine **5** in 50% yield alongside dimers **4** in 46% yield. With a gradual temperature increase (Scheme 2, columns 2−6), the amounts of spiro-β-lactone **2a** and fused compound **3** were increased, and we were delighted to find that the desired product **2a** was obtained in 57% yield at 50 °C. Lowering the concentration improved the yield to 64% (Scheme 2, column 7). Among the solvents tested, DCM was found to be optimal for the reaction (see the Supporting Information (SI) for complete optimization studies). Song and Sheridan investigated the effect of methoxy substitution on the spin states of phenyl(trifluoromethyl)carbene and found that *para* substitution leads to a switching of the spin state to singlet.[15] To our delight, when we subjected cyclohexyl 2-diazo-2-(4-methoxyphenyl) acetate (**1b**) to the standard reaction conditions, the

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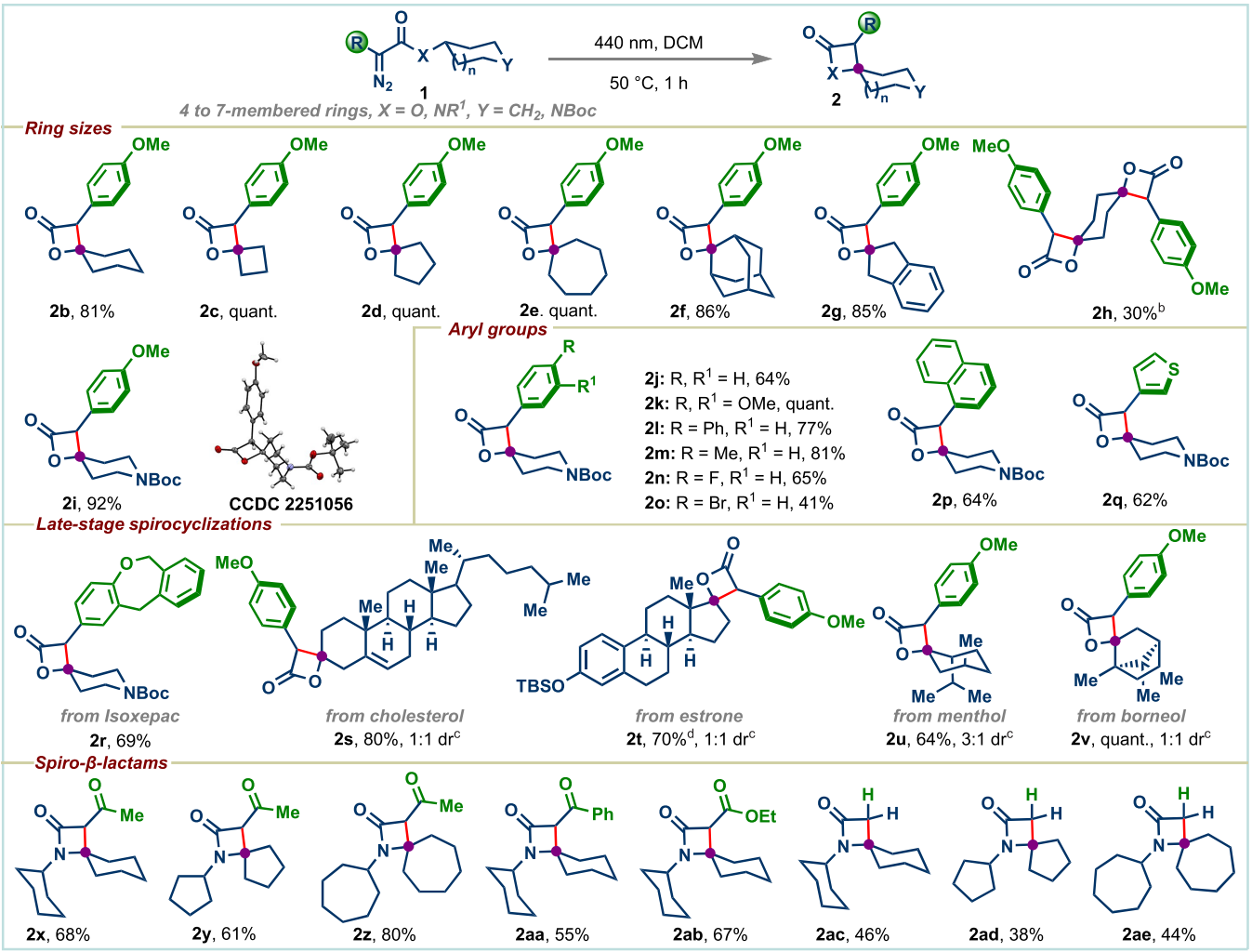
Scheme 3. Access to Spiro-β-lactones and -lactams[a]



[a]Reaction conditions: **1** (0.3 mmol) in DCM (6.0 mL), blue LED, 1 h. Yields of isolated products are reported. [b]0.07 mmol scale. [c]dr determined by ^{1}H NMR analysis. [d]0.125 mmol.

desired product **2b** was obtained in 96% yield (Scheme 2, column 8). To demonstrate that light is necessary, we performed the reaction in the dark at 50 °C; no decomposition of diazo **1a** was observed (Scheme 2, column 9).

Having established the optimal conditions, we investigated the robustness of this method by testing various cycloalkyl diazoacetates. The results are summarized in Scheme 3. The reaction worked efficiently with cyclobutyl, cyclopentyl, and cycloheptyl diazo esters, providing the corresponding four-, five-, and seven-membered-ring-containing spiro-β-lactones in quantitative yields (products **2c**−**2e**). The bulky 2-adamantyl-derived diazo ester could also be tolerated well, giving the desired spirocycle **2f** in 86% yield. Notably, spiro-fused lactone **2g**, a valuable structural motif in medicinal chemistry, was accessed in excellent yield. The C−H insertions of carbenes derived from bis(diazo) compounds are very rare. In 2021, Koenigs and co-workers reported gold-catalyzed multi-C−H functionalization of carbazole using bis(diazo ester).[16] Next, we subjected 1,4-cyclohexdiyl bis(diazo acetate) **1h** to the standard conditions. To our delight, we obtained the desired bis-spirocycle **2h** in 30% yield.[17] Piperidine-bearing spirocycles are considered as important building blocks in drug discovery programs.[2] Indeed, a few spirocyclic piperidine drugs have been authorized for market access. We were pleased to find that the piperidine-derived diazo ester underwent spirocyclization successfully, providing the desired product **2i** in 92% yield. The structure of **2i** was unambiguously determined by X-ray analysis (CCDC 2251056). We next explored the scope of the aryl groups using piperidine-derived diazo esters. A range of aryl groups with different electronic and steric properties worked well (products **2j**−**2p**). Notably, bromo-substituted spirocycle **2o**, bearing a useful handle for further transformations, could be isolated in 41% yield. Aryl diazo esters bearing electron-withdrawing substituents, such as nitro and trifluoromethyl groups, did not deliver the desired products (see the SI for more details). Pleasingly, thiophene-containing diazo ester also reacted well and gave desired product **2q** in 62% yield.

Introducing a spirocyclic motif into a drug molecule allows the improvement, alteration, or modulation of both physicochemical and pharmacokinetic properties.[1,18] Next, our method was applied to the late-stage spirocyclization of a diazo derivative of isoxepac, a nonsteroidal anti-inflammatory drug with analgesic and antipyretic activity, which could be smoothly converted to the corresponding spirocycle **2r** in 69% yield. Given the prevalence of alcohols in nature, we

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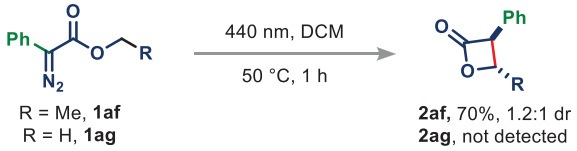
prepared spiro-β-lactones from a range of diverse natural products. We were delighted to find that diazo derivatives of steroids underwent the desired spirocyclization successfully to give the corresponding products **2s** and **2t** in 80% and 70% yield, respectively. The reaction was also successful with the terpenes menthol and borneol (products **2u** and **2v**). These late-stage spirocyclizations further highlight the chemo- and regioselectivity of the present method in the presence of other functional groups, which can react with free carbene intermediates.

Next, we investigated the potential of this method for the synthesis of functionalized spiro-β-lactams, which constitute the core frameworks of several bioactive compounds.[3,19] When *N*,*N*-dicyclohexyl-2-diazo-3-oxobutanamide (**1x**) was subjected to the standard conditions, the corresponding spiro-β-lactam **2x** was afforded in 68% yield. Diazo amides bearing five- and seven-membered rings also successfully participated in this reaction, giving the desired products **2y** and **2z** in good yields. The benzoyl group and ester substitution α to the amide diazo were well-tolerated (products **2aa** and **2ab**). Notably, simple acceptor diazo amides with different ring sizes were also viable substrates in this reaction, providing the products **2ac**−**2ae** in moderate to good yields.

The methodology was not limited to the carbene insertion into tertiary C−H bonds: diazo compound **1af** containing secondary C−H bonds also participated well in this reaction, giving the corresponding β-lactone in 70% yield with 1.2:1 dr (Scheme 4).[20] Primary C−H bonds did not provide the C−H insertion product, presumably because of their lower C−H bond nucleophilicity.

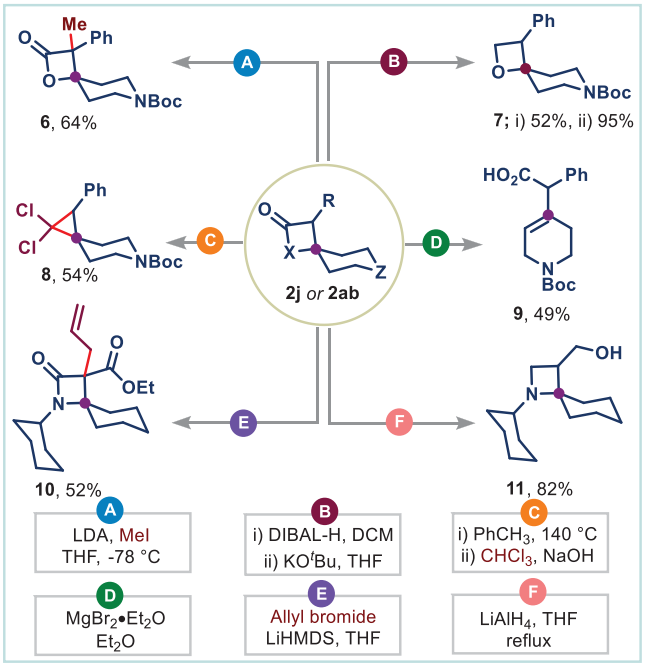
Scheme 4. Access to β-Lactones



To demonstrate the practicality of our method, we first scaled-up the reaction to 2 mmol using diazo compounds **1j** and **1ab**; the desired products **2j** and **2ab** were obtained in 62% and 76% yield, respectively. Subsequently, we showed the synthetic utility of the obtained products by carrying out several downstream transformations (Scheme 5). Methylation of **2j** gave fully substituted spiro-β-lactone **6**. Notably, it was also possible to convert spirolactone **2j** into spiro-oxetane **7**, an ideal scaffold for drug discovery, through the DIBAL-H reduction/cyclization sequence.[10] Decarboxylation followed by cyclopropanation gave cyclopropylspiropiperidine derivative **8** in 54% yield. When spiro-β-lactone **2j** was treated with magnesium bromide, tetrahydropiperidine acetic acid derivative **9** was obtained in 49% yield. Next, we explored the synthetic usefulness of spiro-β-lactam **2ab**. Treatment of **2ab** with allyl bromide and LiHMDS gave the highly substituted spiro-β-lactam derivative **10** in 52% yield. Finally, we were delighted to find that **2ab** could be efficiently converted into spiroazetidine **11**, a core motif present in several bioactive compounds.[21]

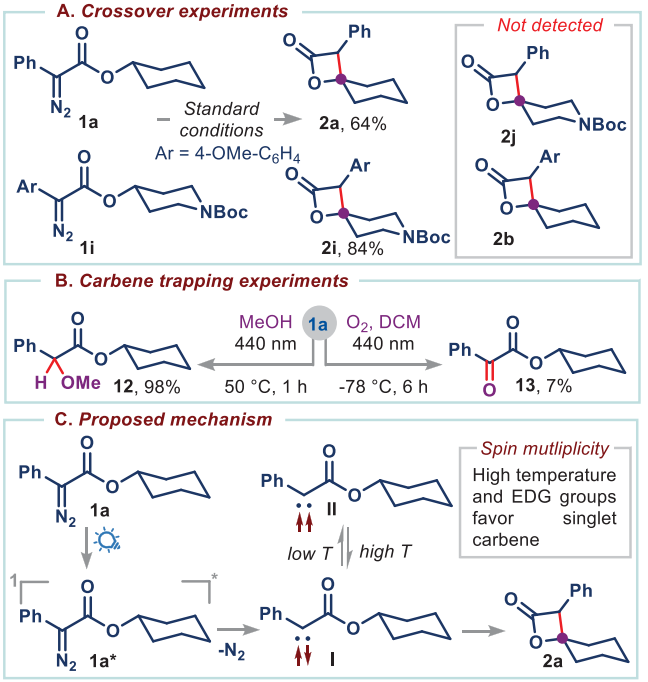
We next focused on the mechanism of the spirocyclization reaction. In 2022, Tantillo and co-workers proposed that the Rh-catalyzed C−H insertion strategy for β-lactone formation suffers from a post-transition-state bifurcation.[22] As a result, it

Scheme 5. Synthetic Utility



competes with the fragmentation reaction, leading to ketones and ketenes, which further react to give the β-lactone. In our photoreaction, if a similar stepwise fragmentation/cycloaddition sequence were operative, a crossover experiment with a mixture of diazo compounds would provide four different products. When we subjected a mixture of **1a** and **1i** to the standard reaction conditions, we did not observe crossover products **2b** and **2j**, which indicates that the intramolecular C−H insertion is operative (Scheme 6A). Tomioka and co-workers reported that the non-carbenic pathway is most likely involved in the intramolecular C−H

Scheme 6. Mechanistic Investigations



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insertion of diazo compounds under photolysis.[23] If this were the case in our reaction, one would expect that the addition of methanol, an efficient quencher for singlet carbene, would not affect the yield of **2a**. However, when **1a** was subjected to standard conditions using methanol as the solvent, no spirocyle product **2a** was observed; instead, the O−H insertion product **12** was obtained in 98% yield, which suggests that the carbenic pathway is operating in our reaction (Scheme 6B).[24] Furthermore, the photolysis of **1a** in DCM at −78 °C with molecular oxygen delivered keto ester **13** along with a mixture of dimers **4** and azine **5** (see SI). These results not only support the carbenic pathway but also suggest the existence of singlet and triplet carbenes **I** and **II** at low temperatures. With increasing temperature, the yield of dimers decreases and the yield of C−H insertion product increases, which indicates the change of spin multiplicity with temperature.[25] Furthermore, electronics also played an important role in switching the spin multiplicity.[15a,26] Based on the literature reports and our own observations, we propose a plausible mechanism in Scheme 6C. Photoirradiation of diazo compound **1a** generates a higher-energy singlet state **1a*** that undergoes extrusion of N_2 to give singlet carbene **I**. Subsequently, the singlet carbene undergoes selective β-C−H insertion to provide the desired spirocycle **2a**.

In summary, we have reported an efficient protocol for the synthesis of spiro-β-lactones and -lactams employing a temperature-regulated photoinduced carbene C−H insertion strategy. The reaction is operationally simple and high-yielding and proceeds under catalyst-free conditions, requiring only blue-light irradiation. A broad range of α-diazo esters and amides can be employed, and the reaction is amenable to the late-stage functionalization of complex bioactive compounds. Furthermore, we demonstrated the applicability of the obtained products as building blocks for the synthesis of medicinally relevant spirocyclic compounds. We believe that due to its simplicity, efficiency, and mild conditions, this spirocyclization strategy will find applications in medicinal chemistry.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01549.

General experimental procedures, optimization of the reaction, mechanistic experiments, X-ray structure of **2i**, characterization and crystal data, and NMR spectra of new compounds (PDF)

Accession Codes

CCDC 2251056 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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