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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Article

Excited-State Copper-Catalyzed [4 + 1] Annulation Reaction Enables Modular Synthesis of α,β-Unsaturated-γ-Lactams

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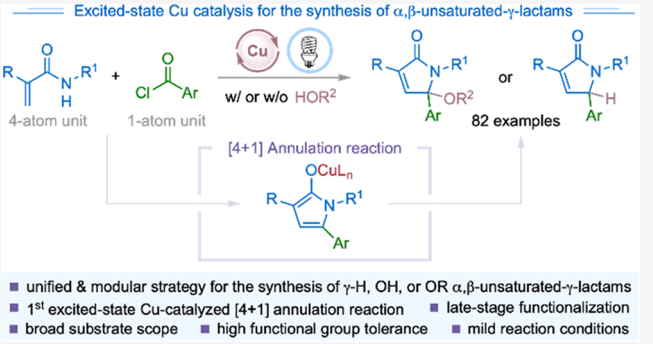
Cite This: J. Am. Chem. Soc. 2022, 144, 20884−20894

ABSTRACT: Synthesis of α,β-unsaturated-γ-lactams continue to attract attention due to the importance of this structural motif in organic chemistry. Herein, we report the development of a visible-light-induced excited-state copper-catalyzed [4 + 1] annulation reaction for the preparation of a wide range of γ-H, −OH, and −OR-substituted α,β-unsaturated-γ-lactams using acrylamides as the 4-atom unit and aroyl chlorides as the 1-atom unit. This modular synthetic protocol features mild reaction conditions, broad substrate scope, and high functional group tolerance. The reaction is amenable to late-stage diversification of complex molecular architectures, including derivatives of marketed drugs. The products of the reaction can serve as versatile building blocks for further derivatization. Preliminary mechanistic studies suggest an inner-sphere catalytic cycle involving photoexcitation of the Cu(BINAP) catalyst, single-electron transfer, and capture of radical intermediates by copper species, followed by reductive elimination or protonation to give the desired γ-functionalized α,β-unsaturated-γ-lactams.



INTRODUCTION

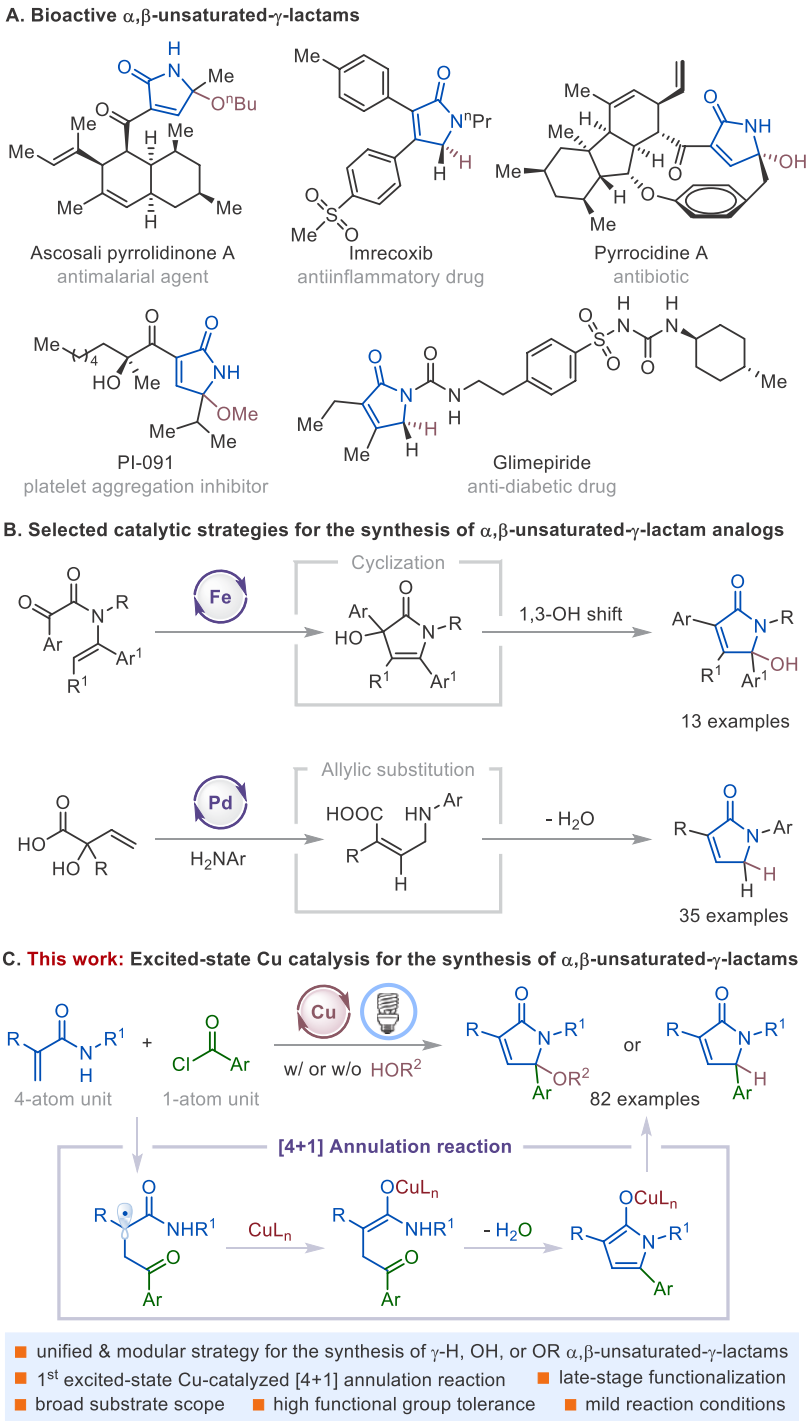
α,β-Unsaturated-γ-lactams are core structural elements in natural and synthetic organic compounds possessing a wide diversity of important biological activities.[1] For example, natural products, such as ascosali pyrrolidinone A, and marketed drugs, including imrecoxib and glimepiride, are used as antimalarial, anti-inflammatory, and anti-diabetic agents, respectively (Scheme 1A). The α,β-unsaturated-γ-lactam fragment also serves as a versatile synthetic building block and has been used in the preparation of functionalized γ-lactams[2] and pyrroles.[3] Consequently, considerable effort has been devoted to the synthesis of α,β-unsaturated-γ-lactam scaffolds, leading to the development of many attractive stoichiometric and catalytic synthetic strategies.[4,5] For example, Wang et al. reported the Fe-catalyzed intramolecular cyclization of tertiary enamides followed by an intriguing 1,3-OH shift to afford γ-hydroxy α,β-unsaturated-γ-lactam derivatives (Scheme 1B).[5d] More recently, Kleij and co-workers developed an elegant Pd-catalyzed domino synthesis of γ-hydrogen α,β-unsaturated-γ-lactams.[5i] Despite these advances, a catalytic protocol for the preparation of γ-alkoxyl α,β-unsaturated-γ-lactam derivatives is rare.[6] As such, the development of an operationally simple, modular, and unified method to access a diverse range of γ-alkoxyl, γ-hydroxy, and γ-hydrogen α,β-unsaturated-γ-lactams is highly desirable.

Visible-light-induced excited-state catalysis is becoming a versatile tool in organic synthesis because it allows access to an excited-state reaction landscape for the discovery of novel chemical transformations.[7] The use of ecologically benign and cost-effective copper complexes (Cu: US$0.512/mol)[8] replacing precious metal Ru^{II} polypyridine (Ru: US$2,015/mol) or cyclo-metallated Ir^{III} complexes (Ir: US$30,282/mol) as photocatalysts has recently attracted increasing attention.[9−11] In addition to the economic benefits of their use, copper photocatalysts have dual catalytic reactivity and can serve as both photocatalysts and coupling catalysts,[11] participating in inner-sphere catalysis through direct engagement with radical intermediates. We have a continuing interest in advancing fundamental knowledge in excited-state and radical chemistry,[12] expanding the reaction profile of Cu catalysis,[12g] and exploring synthetic applications of the umpolung reactivity of acyl radicals.[12b−d,g] Accordingly, we questioned if a copper catalyst could capture a radical intermediate generated from the addition of a nucleophilic acyl radical to acrylamide and

Received: August 26, 2022
Published: November 3, 2022

https://doi.org/10.1021/jacs.2c09006
J. Am. Chem. Soc. 2022, 144, 20884−20894

Scheme 1. Applications and Synthesis of *α,β*-Unsaturated-*γ*-Lactams



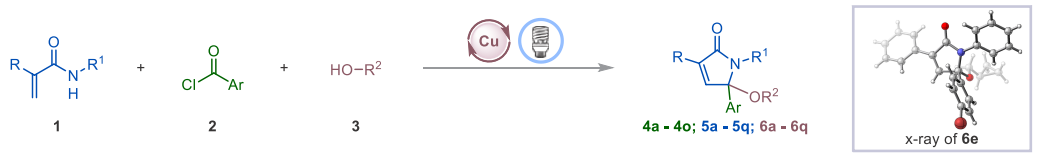
undertake a reaction pathway distinct from the Ir-photocatalyst-mediated reaction (Scheme 1C).[13] Herein, we report the realization of this goal, leading to the first excited-state Cu-catalyzed [4 + 1] annulation reaction for the construction of a broad array of valuable *γ*-functionalized *α,β*-unsaturated-*γ*-lactams.

RESULTS AND DISCUSSION

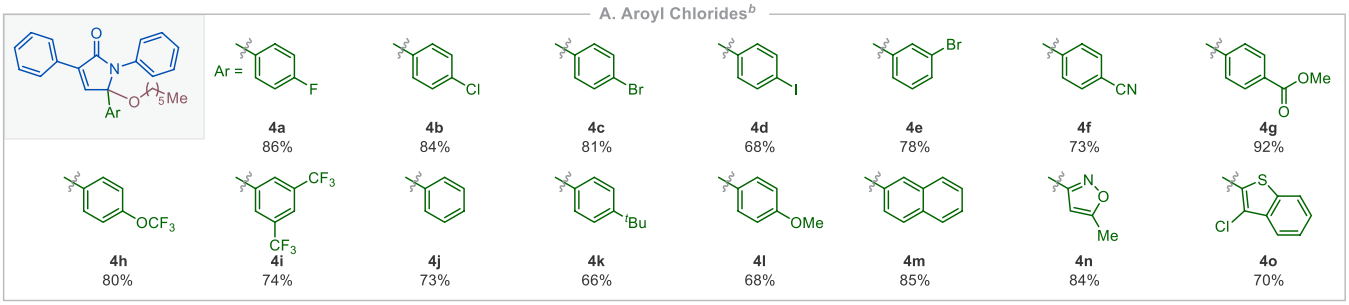
We began our investigation with the evaluation of a broad set of conditions, including different catalysts, ligands, and solvents (Tables S1−S3, Supporting Information). Upon exposing *N*-2-diphenylacrylamide (**1a**), 4-fluorobenzoyl chloride (**2a**), and *n*-hexanol (**3r**) to visible light from 100 W blue light-emitting diodes (LED) in the presence of Cu_2O (10.0 mol %) and *rac*-BINAP (20.0 mol %) in a 1:1 mixture of *p*-xylene/1,2-dichloroethane (DCE) (0.100 M) at room temperature, we obtained the desired *γ*-hexyloxy *α,β*-unsaturated-*γ*-lactam **4a** in a 98% NMR yield (Table S4, SI).[14] Control experiments showed that the copper catalyst, the *rac*-BINAP ligand, and light are essential for the reaction, and the absence of any one of these afforded no desired product. It is worth noting that conventional Ru- and Ir-based photocatalysts failed to generate the desired product (Table S1, SI), demonstrating the distinct reactivity of the copper photocatalyst.

https://doi.org/10.1021/jacs.2c09006
J. Am. Chem. Soc. 2022, 144, 20884−20894

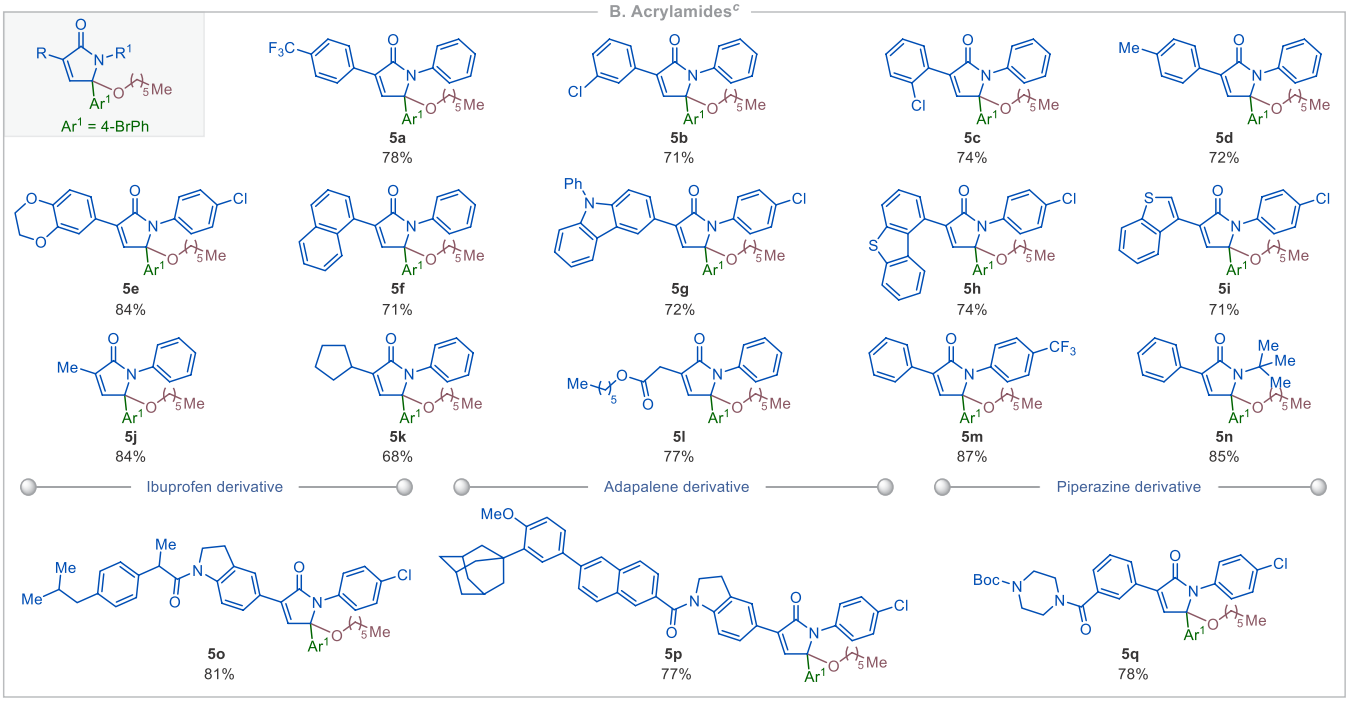
Table 1. Scope of Aroyl Chlorides, Acrylamides, and Alcohols for the Synthesis of γ-Alkoxy, γ-Hydroxy α,β-Unsaturated-γ-Lactams[a]



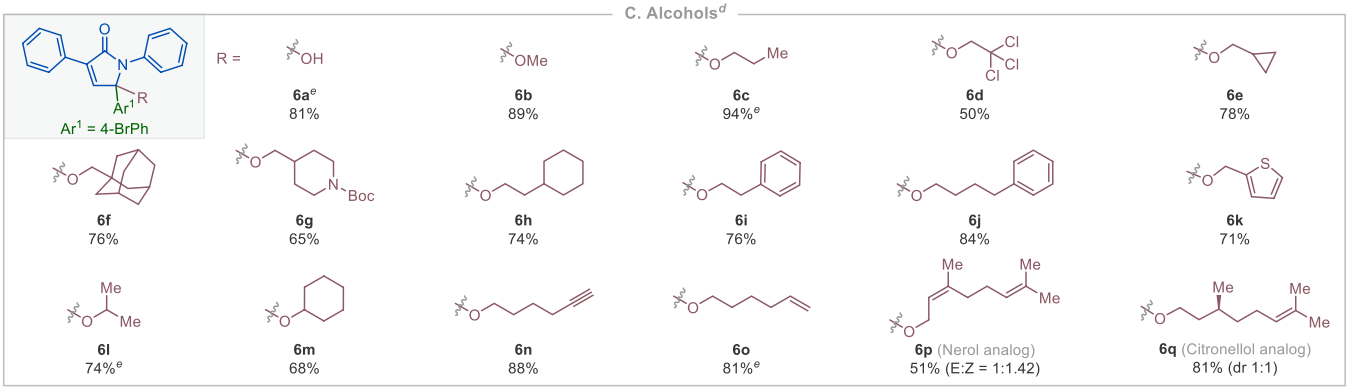
A. Aroyl Chlorides[b]



B. Acrylamides[c]



C. Alcohols[d]



[a]See the Supporting Information for experimental details. Standard conditions A: **1** (1.00 equiv), **2** (2.00 equiv), **3** (5.00 equiv), Cu_2O (10.0 mol %), *rac*-BINAP (20.0 mol %), *p*-xylene/DCE (1:1, 0.100 M), 100 W blue LED, room temperature (rt), 22 h. Cited yields are of isolated material following chromatography. [b]*N*-2-Diphenylacrylamide (**1a**) was used as a coupling partner in the presence of hexanol (**3r**). [c]4-Br-Benzoyl chloride (**2c**) was used as a coupling partner in the presence of **3r**. [d]**1a** and **2c** were used as the standard reactants. [e]Benzoyl chloride (**2j**) was used as a coupling partner.

https://doi.org/10.1021/jacs.2c09006
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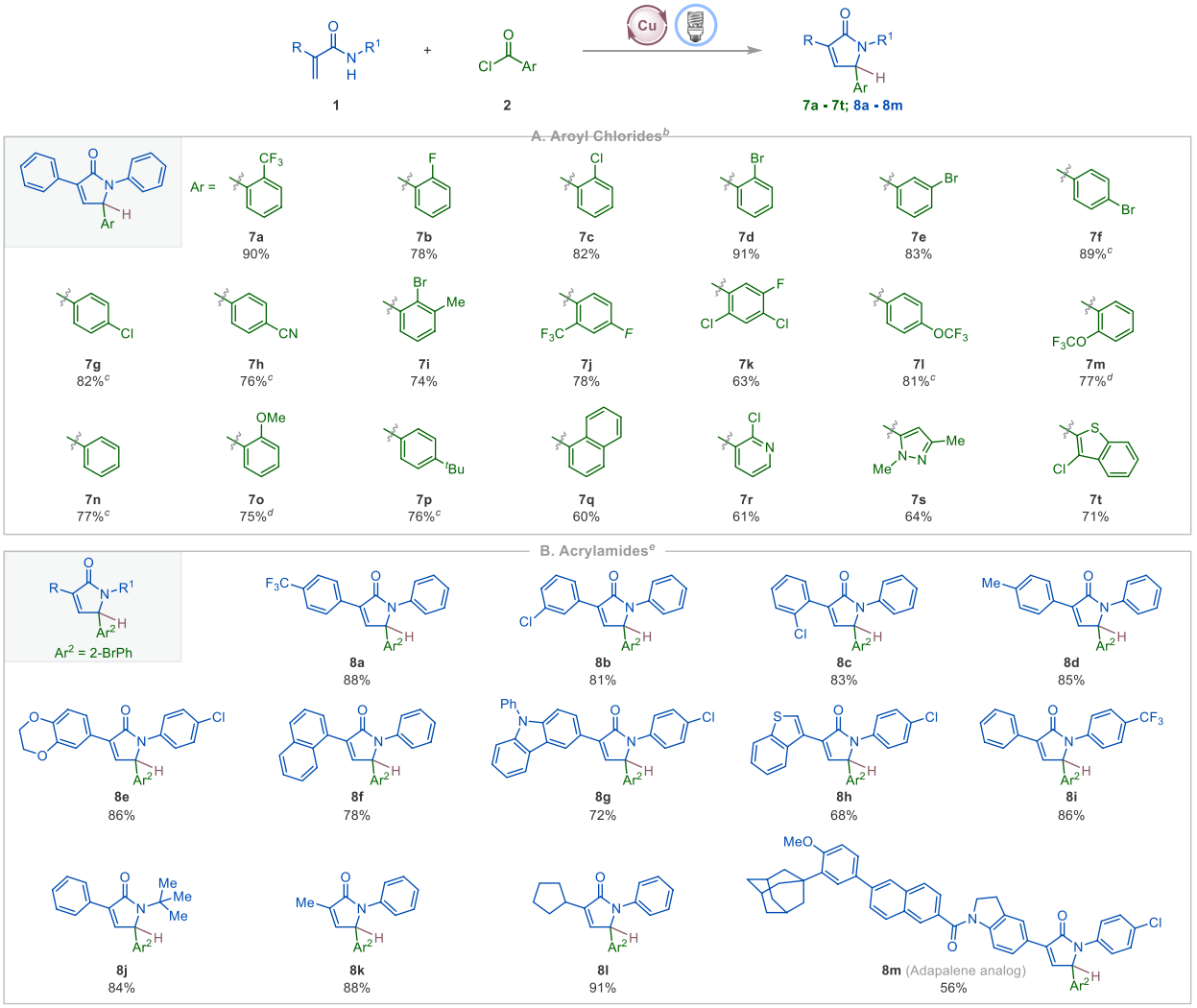
Table 2. Scope of Aroyl Chlorides and Acrylamides for the Synthesis of γ-Hydrogen α,β-Unsaturated-γ-Lactams[a]



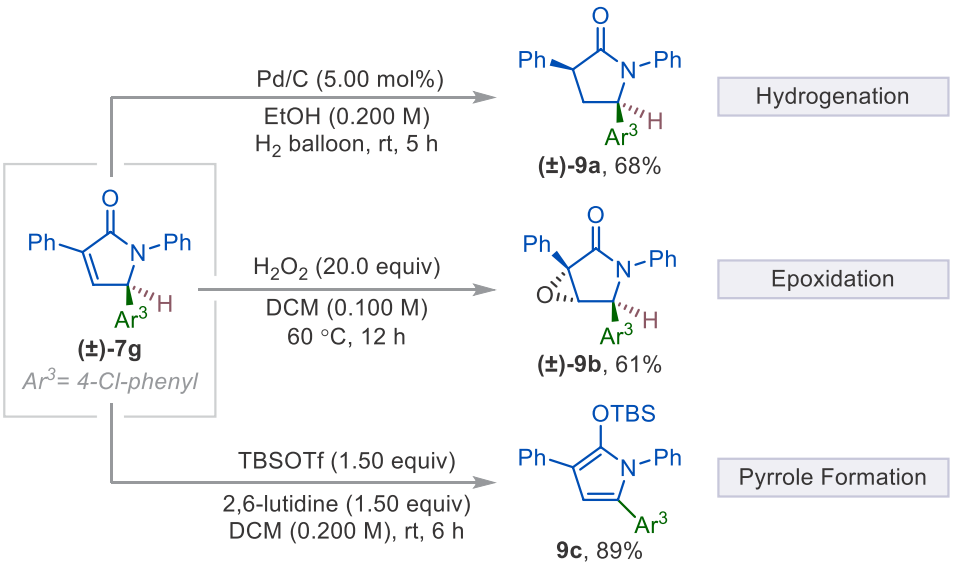
[a]See the Supporting Information for experimental details. Standard conditions B: **1** (1.00 equiv), **2** (2.00 equiv), CuI (10.0 mol %), *rac*-BINAP (20.0 mol %), *p*-xylene (0.100 M), 100 W blue LED, rt, 22 h. Cited yields are of isolated material following chromatography. [b]*N*-2-Diphenylacrylamide (**1a**) was used as a coupling partner. [c]0.50 equiv of $PhSiH_3$ was added, 36 h. [d]The reaction time was extended to 36 h. [e]2-Br-Benzoyl chloride (**2d**) was used as a coupling partner.

With the optimized reaction conditions established, we explored the scope of the reaction by examining a variety of (hetero)aroyl chlorides, enamides, and alcohols (Table 1). The reaction tolerated a range of (hetero)aroyl chlorides with different electronic properties and functional groups (Table 1A). For example, electron-deficient aroyl chlorides substituted with halogen, nitrile, ester, trifluoromethoxyl, and trifluoromethyl groups reacted smoothly, furnishing the desired products (**4a**–**4i**) in 68–92% yield. Electron-neutral (**4j**) and electron-rich aroyl chlorides (**4k**–**4l**) are viable substrates. Although alkyl acyl chlorides failed, aroyl chlorides with extended π-conjugation such as a β-napthyl ring (**4m**) and heteroaroyl chlorides, including isoxazolyl (**4n**) and benzothiophenyl rings (**4o**), tolerate the reaction conditions and afford the corresponding γ-hexyloxy α,β-unsaturated-γ-lactams in 70–85% yield.

The reaction proceeded well with a broad array of acrylamide derivatives with simple or complex molecular skeletons (Table 1B). Acrylamides bearing α-aromatic substituents with different electronic properties and substitution patterns reacted under the standard reaction conditions, affording the desired products **5a**–**5f** in 71–84% yield. Investigations into medicinally relevant heterocyclic scaffolds demonstrated that carbazole, dibenzothiophene, and benzothiophene-derived acrylamides could be employed to generate the corresponding products (**5g**–**5i**) in good yields. α-Alkyl-substituted acrylamides (**5j**–**5l**) are also viable substrates under this protocol. Both *N*-aryl- and *N*-alkyl-protected acrylamides reacted smoothly, furnishing the corresponding products (**5m**, **5n**) in 87% and 85% yield, respectively. Late-stage modifications of biologically active molecules are often a key to the identification of medicinal agents.[15] To demonstrate the applicability of this excited-state copper-catalyzed [4 + 1] annulation reaction in late-stage diversification, derivatives of bio-relevant molecules, such as ibuprofen, adapalene, and piperazine, were subjected to the standard reaction conditions, and they delivered the desired products (**5o**–**5q**) in good yields. Thus, our strategy can increase structural diversity and synthetic efficiency and is compatible with biologically active pharmaceutical scaffolds.

https://doi.org/10.1021/jacs.2c09006
J. Am. Chem. Soc. 2022, 144, 20884–20894

Scheme 2. Post-Functionalization of α,β-Unsaturated-γ-Lactam 7g



We next sought to examine the generality of this transformation by exploring the scope of the alcohol coupling partner. As outlined in Table 1C, a wide variety of hydroxy compounds reacted efficiently in this excited-state copper-catalyzed cross-coupling protocol. Water can be used as a coupling partner to furnish the γ-hydroxy α,β-unsaturated-γ-lactam (**6a**). A series of primary and secondary alcohols bearing trichloromethane, cyclopropane, adamantane, *N*-boc-piperidine, cyclohexane, a phenyl ring, and thiophene are compatible under the standard conditions, affording the desired products (**6b**−**6m**) with up to 94% yield. It is noteworthy that alkyne and alkene functionalities survive the reaction intact (**6n**−**6o**), providing useful handles for further synthetic elaboration. Naturally occurring alcohols, such as nerol and (−)-citronellol, can be used directly to furnish the corresponding products **6p** and **6q** in 51% and 81% yield, respectively, further demonstrating the synthetic utility of the transformation. The structure of the coupling products was unambiguously confirmed by single-crystal X-ray analysis of compound **6e** (Table 1).

During the exploration of the substrate scope, 2-trifluoromethyl benzoyl chloride afforded the desired γ-hexyloxy α,β-unsaturated-γ-lactam in only 11% yield. Interestingly, careful examination of the reaction mixture led to the identification of γ-hydrogen α,β-unsaturated-γ-lactam **7a** (Table 2). Fine-tuning the reaction conditions by modifying the catalysts and solvents and removal of alcohol additives furnished the desired product **7a** in 91% yield (Tables S5−S8, SI). The reaction proved to be general and tolerated (hetero)aroyl chlorides with diverse electronic and substitution patterns (Table 2A). Both electron-rich and electron-poor aroyl chlorides were converted into the corresponding α,β-unsaturated-γ-lactams (**7a**−**7q**) in good-to-excellent yields. Ortho-, meta-, and para-substituents on the ring are tolerated (**7d**−**7f**), although the reaction of the para-substituted substrate required the addition of 0.50 equiv of $PhSiH_3$ to give the desired product in high yield. Our protocol was also efficient toward substrates with the pharmaceutically relevant heteroarenes (**7r**−**7t**), trifluoromethyl (**7a**, **7j**), fluoro (**7b**, **7j**, **7k**), and trifluoromethoxyl (**7l**, **7m**) groups. Functional groups such as nitrile (**7h**), chloride (**7c**, **7g**, **7k**, **7r**, and **7t**), or bromide (**7d**−**7f**, **7i**) that are frequently reactive in typical late transition-metal catalysis are also compatible. These groups are very valuable for further orthogonal manipulations and buildup of molecular complexity.

The scope with respect to the acrylamides was also investigated (Table 2B). In general, acrylamides with (i) α-aryl (**8a**−**8f**, **8i**, **8j**), α-heteroaryl (**8g**, **8h**, **8m**), and α-alkyl (**8k**, **8l**) substituents, (ii) aryl (**8a**−**8i**, **8k**−**8m**) or alkyl (**8j**) *N*-protecting groups, and (iii) derivatives of bioactive molecules (**8m**) were competent under the optimized reaction conditions, affording the desired products with up to 91% yield. It is of note that 80 of the 82 compounds reported here have not been prepared previously, demonstrating that our protocol allows access to unexplored chemical space, thus aiding the discovery of new pharmaceuticals, agrochemicals, and functional materials.

To demonstrate the synthetic utility of the α,β-unsaturated-γ-lactam products toward useful molecular scaffolds, a series of transformations were carried out (Scheme 2). Treatment of the α,β-unsaturated-γ-lactam product **7g** with Pd/C in the presence of H_2 (1 atm) gave the corresponding γ-lactam **9a** in 68% yield with >20:1 diastereoselectivity. Epoxidation of **7g** using hydrogen peroxide at 60 °C formed a compound **9b** with an oxa-azabicyclohexan-2-one ring in 61% yield. Product **7g** could be converted to a *tert*-butyldimethylsilyl (TBS)-protected pyrrole **9c** in 89% yield using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) at room temperature.

A series of mechanistic studies were conducted to gain a better understanding of the reaction mechanism. The addition of a radical scavenger, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), to the standard three-component reaction was found to inhibit the formation of the desired product **4a** (Scheme 3A). Although we could not isolate the TEMPO-trapped adduct, we were able to obtain adduct **10a** in 54% yield when 1,1-diphenylethylene was used as a radical trap (Scheme 3A). These experiments imply that the reaction is likely a radical process involving an aroyl radical intermediate. To determine whether the γ-alkoxylated product is formed through an *N*-acyliminium ion intermediate generated from the corresponding γ-hydroxy adduct such as **6a**,[6e] we carried

https://doi.org/10.1021/jacs.2c09006
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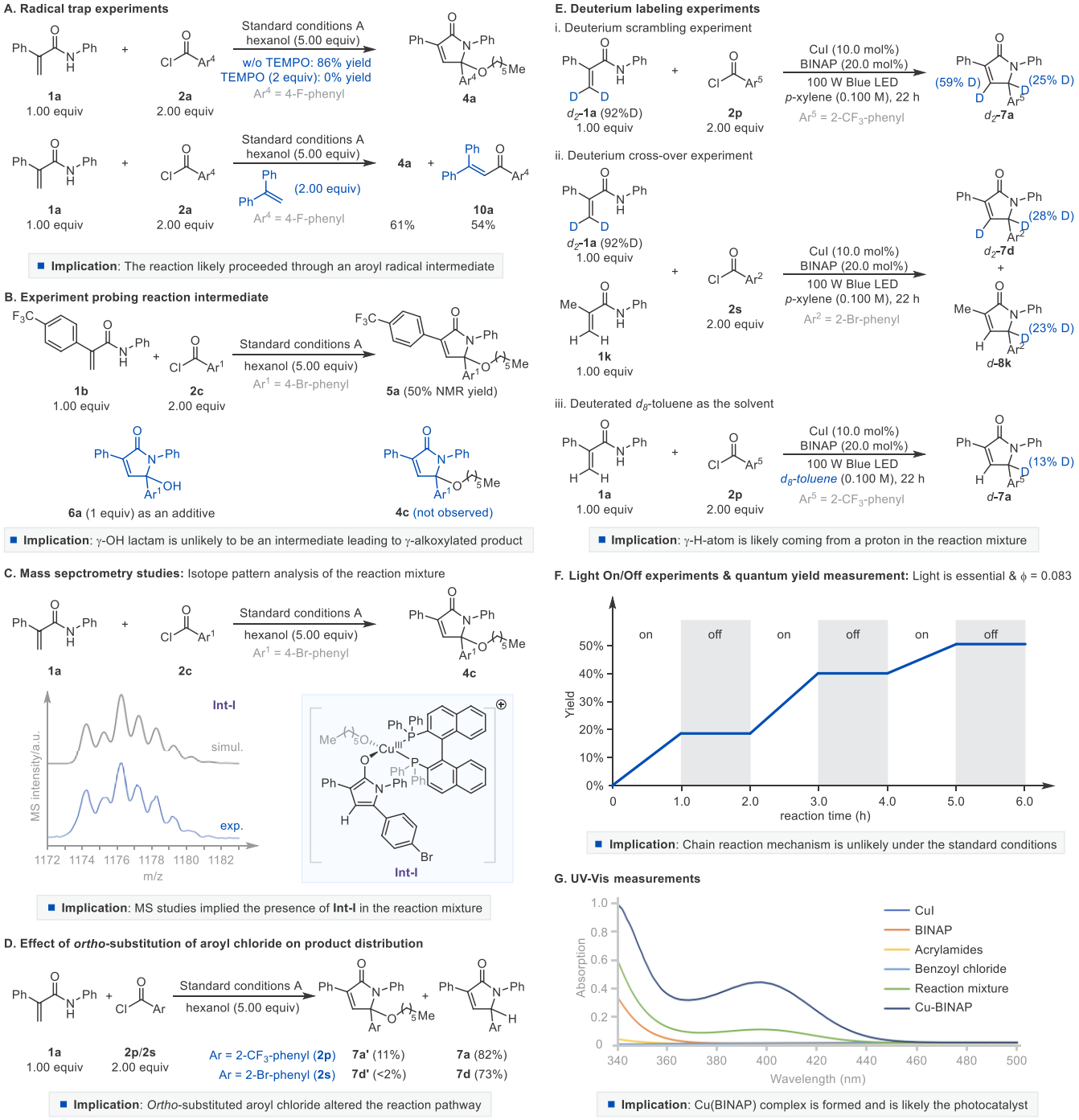
Scheme 3. Mechanistic Studies[a]



[a]See the Supporting Information for experimental details.

out a standard reaction using **1b** and **2c** as substrates, with **6a** as an additive (Scheme 3B). This reaction afforded product **5a** only and none of the product **4c** derived from **6a**, indicating that γ-hydroxy adduct is unlikely to be an intermediate leading to the γ-alkoxylated product. To identify potential reaction intermediates, we also conducted a time-dependent mass spectrometry analysis of the three-component reaction using **1a** and **2c** as starting materials (Scheme 3C). Analysis of isotope patterns and collision-induced fragmentation of the reaction mixture implied the formation of copper complex **Int-I** (Scheme 3C and Figure S5, SI). We envisioned that the copper(III) catalyst in **Int-I** migrates to the γ-position, and subsequent reductive elimination liberates the desired product **4c**, regenerating the Cu(I)BINAP catalyst.[11,16] However, when an ortho-substituted aroyl chloride is used as the substrate, this reaction pathway is disfavored by a steric interaction between the phosphine ligand and the γ-aryl ring of **Int-I**. In this case, **Int-I** is more likely to be protonated and then tautomerized, forming γ-hydrogenated products such as **7a** and **7d** (Scheme 3D).

The formation of the γ-hydrogenated product is very intriguing, and we performed a series of deuterium labeling

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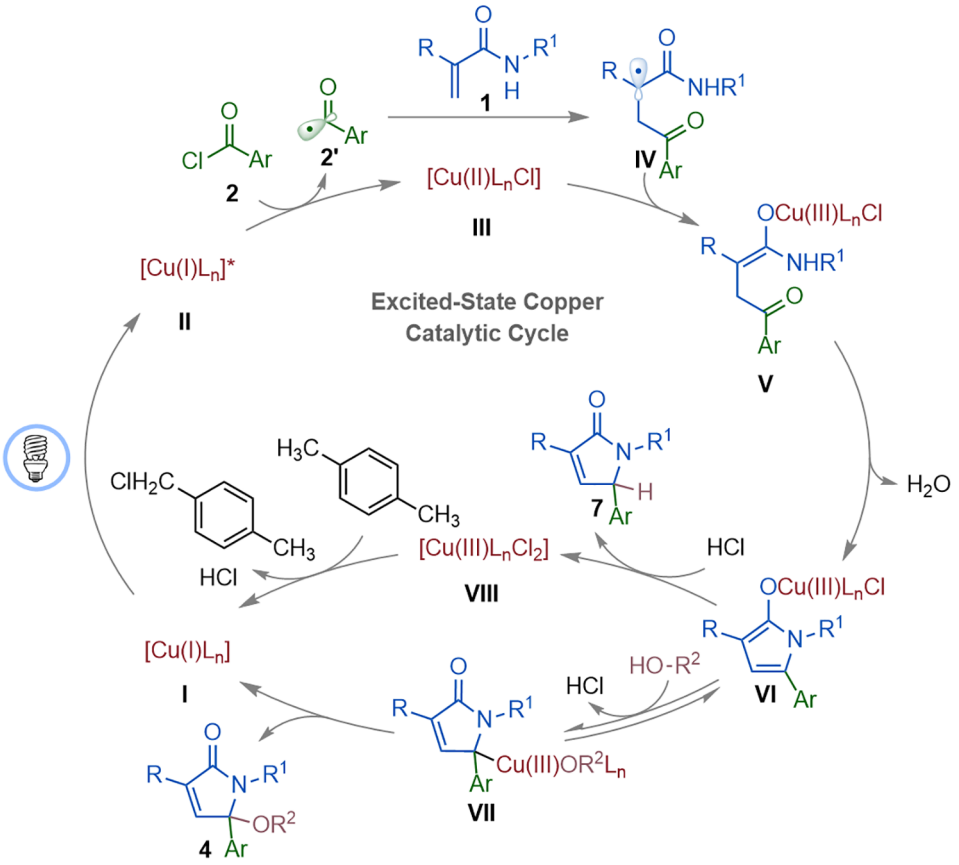
Scheme 4. Proposed Reaction Mechanisms



experiments to investigate the origin of the γ-hydrogen atom in the product (Scheme 3E). Deuterated compound d_2-**1a** was used as a starting material, and in this case, we obtained the desired product d_2-**7a** with 25% deuterium incorporation at the γ-position. Also, a cross-over experiment using d_2-**1a** and **1k** as starting materials afforded the products d_2-**7a** and *d*-**8k** with 28 and 23% γ-deuterium incorporation, respectively. Gas chromatography−mass spectrometry (GC−MS) analysis of the reaction mixture revealed the formation of chlorinated *p*-xylene (Figure S6, SI).[17] Using d_8-toluene as the solvent, we obtained a product *d*-**7a** with 13% γ-deuteration. Collectively, these results suggest that the γ-hydrogen atom originates from both acrylamide and the solvent.

Light On/Off experiments showed that the reaction stops in the absence of light (Scheme 3F). The quantum yield of the standard reaction forming the γ-hydrogenated product is 0.083 (Figure S8, SI), implying that an extended radical chain process is unlikely. The ultraviolet−visible (UV−Vis) absorption spectra of the CuI−BINAP complex show a peak at 397 nm, with a tail into the visible region, which resembles the UV−Vis absorption spectra of the standard reaction mixture (Scheme 3G). This indicates the involvement of the CuI−BINAP photoactive complex in the reaction medium. A preformed CuI−BINAP complex was catalytically competent and afforded the desired product in 91% yield (Figure S10, SI). Finally, 4-fluorobenzoyl chloride (**2a**) was shown to quench the luminescence of the CuI−BINAP complex. (Figure S11, SI).

Based on these mechanistic insights, a plausible reaction mechanism was proposed and is depicted in Scheme 4. Blue light photoexcitation of Cu^{I}−BINAP complex **I** generates excited *[Cu^{I}−BINAP] complex **II**, which reduces the aroyl chloride **2** (E_p of benzoyl chloride = −1.02 V vs saturated calomel electrode (SCE))[13c] to form copper complex **III**, liberating aroyl radical **2′**. The addition of **2′** to the alkene of acrylamide **1** affords tertiary alkyl radical **IV**, which is captured by **III** to form intermediate **V**. Intramolecular condensation of **V** furnishes intermediate **VI**. In the presence of alcohol, **VI** undergoes ligand exchange and migration of the copper center to the γ-position followed by reductive elimination, liberating the desired γ-alkoxylated product **4** and regenerating copper catalyst **I**. In the absence of alcohols or if an ortho-substituted aroyl chloride is used, complex **VI** will proceed through protonation and tautomerization to form γ-hydrogenated product **7** and copper species **VIII**. Reduction of **VIII** by *p*-xylene affords copper catalyst **I**,[17] closing the catalytic cycle.

SUMMARY

In summary, we report the development of an excited-state copper-catalyzed [4 + 1] annulation reaction. This provides a unified and modular strategy for the preparation of a wide array of γ-hydrogen, -hydroxy, and -alkoxy α,β-unsaturated-γ-lactams. The reaction features mild reaction conditions, has broad substrate scope, and tolerates complex molecular architecture, including derivatives of marketed drugs. The α,β-unsaturated-γ-lactam products can serve as versatile building blocks for the synthesis of useful heterocycles. Preliminary mechanistic studies suggest an inner-sphere catalytic cycle that involves photoexcitation of the Cu(BINAP) catalyst, single-electron transfer, and trapping of radical

https://doi.org/10.1021/jacs.2c09006
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intermediates by copper species, followed by reductive elimination or protonation to give the desired coupling products. Further studies of the reaction mechanism and expansion of the substrate scope as well as the asymmetric process are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c09006.

Experimental details and characterization data for all new compounds (PDF)

Accession Codes

CCDC 2202589 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, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research reported in this publication was partially supported by the National Institutes of General Medical Sciences (R35-GM119652 to M.-Y.N.), the National Science Foundation [CHE-1905172 to C.J.J.]. The Shimadzu UPLC/MS used for portions of this work were purchased with funds from NIGMS equipment administrative supplement (R35-GM119652-04S1), Shimadzu Scientific Instruments Grant, and Office of the Vice President for Research at Stony Brook University. The authors thank Dr. Vincent M. Lynch (University of Texas, Austin) for the X-ray data of **6e**. The authors also expresss sincere gratitude to anonymous reviewer 2 for careful reading of the manuscript and for the comprehensive comments and suggestions.

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J. Am. Chem. Soc. 2022, 144, 20884−20894

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(17) The exact mechanism of how the chlorinated *p*-xylene was formed is unclearly and is the subject of future studies. A possible mechanism involves comproportionation of Cu(I) and Cu(III) to form Cu(II), which undergoes LMCT under photo-irradiation to liberate Cu(I) species and Cl radical. The Cl radical abstracts benzylic hydrogen to generate benzylic radical that is captured by Cu(II)Cl followed by reductive elimination, affording benzyl chloride and the Cu(I) catalyst. For examples of LMCT process of copper catalysts, see refs 11z 11aa 11ab, and 11ac.

https://doi.org/10.1021/jacs.2c09006
J. Am. Chem. Soc. 2022, 144, 20884−20894