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Gold-Catalyzed Spirocyclization of Furan-ynones and Unexpected Skeleton Rearrangement of the Resulting Spirohydrofurans

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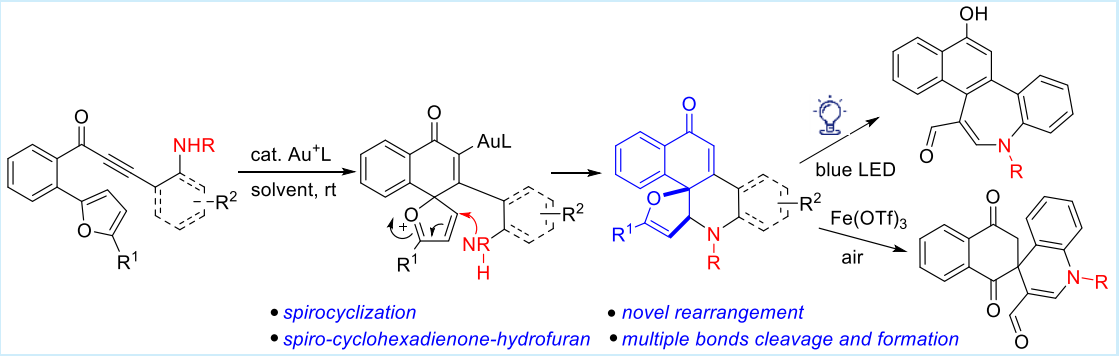

ABSTRACT: A gold-catalyzed cyclization of aniline-tethered furan-ynones has been developed. The reaction proceeds via trapping of the resulting stabilized cationic intermediate with an amide group leading to polycycles featured with a spiro-cyclohexadienone-hydrofuran framework with high efficiency. The resulting *N*-alkyl products undergo photorearrangements to afford the ring-enlarged benzo[*b*]azepine derivatives or iron-promoted novel rearrangement to diketone-containing spirocycles involving multiple C−X bond cleavages and formations.

In recent years, gold-catalyzed cascade reactions have attracted considerable attention since these processes provide a highly efficient, economically friendly route for the rapid access to complex molecules.[1] In this context, the gold-catalyzed cycloisomerization of furan-ynes represents a useful protocol for the construction of polysubstituted aromatic compounds or polycycles, as developed by Hashmi,[2] Echavarren,[3] us,[4] and other groups.[5] In most cases, terminal alkynes undergo *exo*-cyclization to produce the phenol derivatives.[2a−e,3a,c,d] For internal alkynes, *endo*-cyclization is preferred.[4a−d,6] The subsequent transformations proceed mainly through the formation of the gold-carbene intermediate **II** generated from the stabilized cationic intermediate **I** or cyclopropyl gold-carbenoid,[2e] leading to vinyl ketone derivatives (Scheme 1a, mode a). It is possible that the intermediate **I** could also be trapped by a nucleophile to furnish a product without ring-opening of the furan moiety (Scheme 1a, mode b). These reactions would be of special interest since they allow the straightforward assembly of spiro-heterocycles, which are found as key structural units in many bioactive substances and pharmaceutically useful compounds. The main challenge in developing this type of reaction is to avoid the opening of the furan ring and minimize the competitive addition of the additional nucleophile to the alkyne. The gold-catalyzed spirocyclization/nucleophilic attack cascade has been well investigated using indole, phenol, or naphthol-ynes as the substrates.[7] However, there are few reports with furan-ynes. To the best of our knowledge, there are only two examples involving the reaction pattern of mode b. In 2009, Hashmi et al. reported that cyclization of furan-ynes with an alkynylether moiety led to tetracyclic heterocycles (Scheme 1b).[2f] The use of ynamide instead of the alkynylether framework resulted in ring-opening of the dihydrofuran moiety of the product.[2g] However, these reactions limited to special alkynes. During our ongoing work on furan-ynes,[4] we envisioned that if an appropriate nucleophile, either located within the furan-yne or as an external nucleophile, was employed, the expected spirocyclization/nucleophilic attack might occur. If it works, it would offer a useful route for spirocyclization of furan-ynes without the need for an alkynylether or ynamide moiety while opening up new possibilities for the construction of spirocycles. As a result, we found that furan-ynones[8] **1** bearing an aniline moiety at the alkyne terminus could serve as effective substrates for this target. In this communication, we demonstrate that when furan-ynones **1** are utilized, the gold

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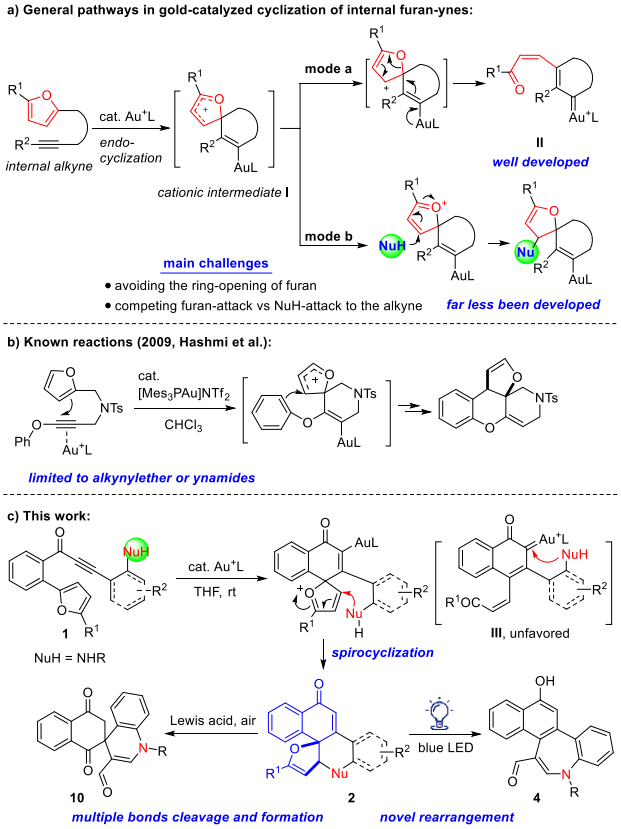
Scheme 1. Gold-Catalyzed Cyclization of the Internal Furan-ynes



carbene intermediate **III** is not formed; instead, the reactions proceed rapidly and efficiently via trapping of the cationic intermediate (Scheme 1c). Interestingly, the resulting spirodihydrofurans could be efficiently transformed to the ring-enlarged polycycles **4** or a new type of spirocycles **10** under visible light irradiation or in the presence of a Lewis acid, respectively. Typical examples of the biologically active natural products featured with a spiro-cyclohexadienone-hydrofuran core are shown in Figure 1.[9]

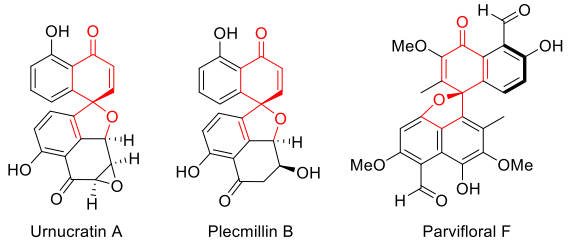
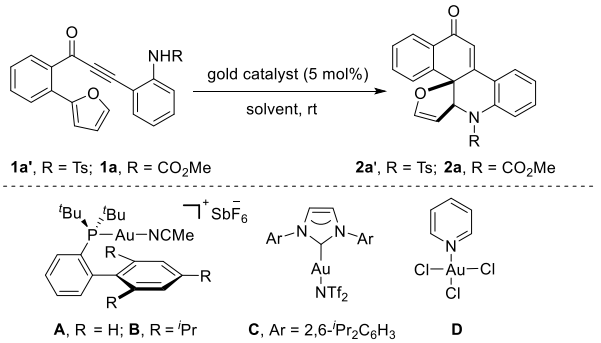


Figure 1. Natural products containing the spiro-cyclohexadienone-hydrofuran fragment.

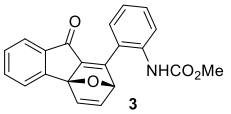
Our initial investigation was performed using furan-ynone **1a′** with a *N*-tosyl-protected aniline moiety as the substrate. After examination of the reaction conditions, we found that the desired product of pentacyclic spirocycle **2a′** could be formed in the presence of various gold catalysts. The best result was achieved using 5 mol % gold(I) complex bearing a sterically demanding ^{t}BuXphos ligand (catalyst **B**) as the catalyst (Table 1, entry 1). The results indicated that the ring-opening of the furan moiety did not occur during the reaction. However, it is

Table 1. Optimization of the Reaction Conditions



entry	catalyst (mol%)	solvent	time (h)	product	yield (%)[a]
1	**B** (5)	DCE	2	**2a'**	89[b,c]
2	$PPh_3AuCl/AgSbF_6$ (5)	DCE	2	**2a**	60
3	PPh_3AuNTf_2 (5)	DCE	1	**2a**	68
4	**A** (5)	DCE	1	**2a**	67
5	**B** (5)	DCE	1	**2a**	84
6	**C** (5)	DCE	24	**2a**	61
7	**D** (5)	DCE	23	**2a**	- (65)
8	$AuBr_3$ (5)	DCE	24	**2a**	- (67)[d]
9	**B** (5)	DCM	2	**2a**	82
10	**B (5)**	**THF**	**1**	**2a**	**90, 89**[b]
11	**B** (5)	MeCN	11	**2a**	85
12	**B** (5)	Toluene	2	**2a**	80
13	^{t}BuXPhosAuCl (5)	THF	24	**2a**	- (93)
14	$AgSbF_6$(10)	THF	22	**2a**	- (95)
15	$HNTf_2$ (10)	THF	22	**2a**	- (86)
16	none	THF	23	**3**	23[b,d]

[a]Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene or mesitylene as an internal standard. The NMR yields of unreacted **1a** are shown in parentheses. [b]Isolated yields. [c]The product contains a small amount of impurity. [d]80 °C.



hard to obtain the product with high purity through column chromatography. To our delight, the clean product **2a** could be obtained by switching the *N*-tosyl to an *N*-ester group. Thus, furan-yne **1a** bearing an *N*-CO_2Me protecting group was chosen as a model substrate to evaluate the cyclization reaction. Treatment of **1a** with 5 mol % of $PPh_3AuCl/AgSbF_6$ afforded **2a** in 60% yield in DCE at room temperature within a short reaction time (entry 2). The use of PPh_3AuNTf_2 gave **2a** in a slightly higher yield (entry 3). Gratifyingly, ^{t}BuXphosAu(MeCN)SbF_6 (catalyst **B**) displayed high catalytic activity, and the yield of **2a** was improved dramatically (entry 5, 84%). Using the N-heterocyclic carbene-gold(I) complex of $IPrAuNTf_2$ as the catalyst led to **2a** in a lower yield (entry 6). No desired **2a** was formed when pyridine-$AuCl_3$ or $AuBr_3$ was used as the catalyst (entries 7 and 8). Among the various solvents, THF gave the best result (entries 9−12). Control experiments run with ^{t}BuXphosAuCl or $AgSbF_6$ alone resulted in no formation of **2a** (entries 13 and 14). Brønsted acid such as $HNTf_2$ also failed to catalyze the reaction (entry 15). In the absence of a catalyst, the cyclized product **3**[10] was formed via intramolecular [4 + 2] cycloaddition of the furan with the alkyne moiety in 23% yield at 80 °C (entry 16).

With the optimized reaction conditions in hand (Table 1, entry 10), the substrate scope of various furan-yne derivatives were investigated (Scheme 2). We first examined the substituent effects on *N*-aryl rings. Substrates bearing electron-withdrawing groups such as 4-Cl or 4-F on the *N*-

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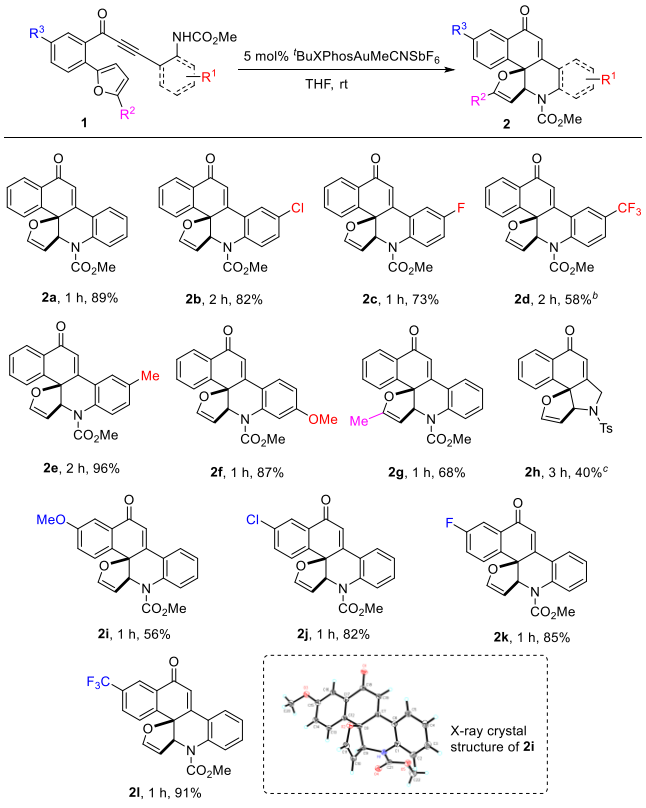
Scheme 2. Scope of Furan-yne Substrates[a]

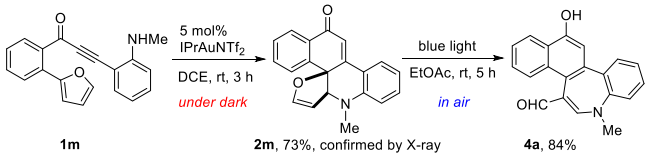


[a]Isolated yields. [b]80 °C. [c]In DCE.

aryl rings gave **2b** or **2c** in 73−82% yields. However, with a 4-CF_3-substituent, increasing the reaction temperature to 80 °C was required in order to completely consume the starting materials (**2d**). High yields were obtained with 4-Me- or 5-OMe-substituted aryl alkynes (**2e** and **2f**). The results showed that the less electron-deficient ynones gave the better yields, possibly due to the facile formation of the gold-alkyne complex using these substrates. Methyl-substituted furan was rapidly transformed to **2g**. The alkyl alkyne **1h** tethered with a −NHTs moiety was also compatible for this reaction (**2h**). Substrates bearing an −OMe, −Cl, −F, or $-CF_3$ functional group at the parent phenyl ring were smoothly converted into the corresponding **2i**−**2l** in 56−91% yields.[10]

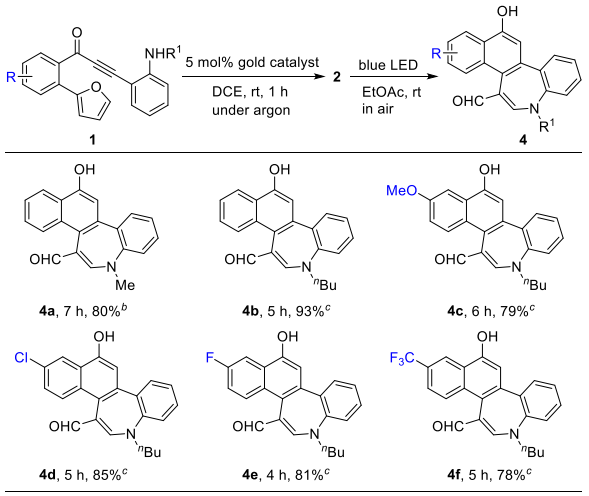
In order to understand the effect of *N*-substituent in substrate **1** on the reaction course, the *N*-methyl-substituted furan-yne **1m** was prepared. The ensuing gold-catalyzed cyclization of **1m** proceeded efficiently; however, except for the expected product **2m**, a small amount of byproducts was also observed, which could not be separated from **2m**. We suspected that the product **2m** might be photosensitive during the reaction and the isolation processes. To verify this hypothesis, the gold-catalyzed reaction of **1m**, and the subsequent workup including evaporation, filtration, column chromatography, and recrystallization were all performed under dark. To our delight, the desired product **2m** could be isolated cleanly in 73% yield using $IPrAuNTf_2$ as the catalyst (Scheme 3). Interestingly, pure **2m** could be readily converted to a ring-enlarged benzo[*b*]azepine derivative **4a** within 5 h in ethyl acetate under the irradiation of the blue light (Scheme 3).[11] Without irradiation, no **4a** was formed. The results indicated that **2m** is indeed unstable upon exposing to the

Scheme 3. Discovery of the Photoinduced Ring-Enlargement of 2m



light, which undergoes photoinduced ring-opening of the dihydrofuran moiety leading to the ring-enlarged product **4a**.[12] To avoid the tedious operation procedure for the formation of **4a**, a two-step process was established. That is, after the gold-catalyzed reaction, the mixture was filtered and the solvent was evaporated. The crude product thus obtained was irradiated by a 12 W blue LED belt (λ_{max} = 465 nm) in ethyl acetate at room temperature under air. The desired product **4a** could be obtained cleanly in high overall yield (Scheme 4). It is noted

Scheme 4. Substrate Scope for the Formation of 4[a]



[a]Isolated yields. [b]$IPrAuNTf_2$ was used. [c]JohnphosAu(MeCN)SbF_6 was used.

that there is no need to protect the reactions and the following operations from the light. The substrate scope for this two-step reaction was also investigated. For *N*-butyl-substituted substrates, JohnPhosAu(MeCN)SbF_6 showed better activity for the first step. Various functional groups such as −OMe, −Cl, −F, and $-CF_3$ were well tolerated, and the corresponding products **4c**−**4f** were formed in 78−85% yields.

It is well-known that the photoreactions of cyclohexa-2,5-dien-l-ones are among the most intriguing and exciting subjects in classical photochemical transformations because of their unique molecular rearrangements and their utility in the synthesis of medically relevant substances.[13] For example, the famous photorearrangement reaction of santonin has been found to produce various valuable derivatives such as lumisantonin, mazdasantonin, isophotosantonic lactone, etc.[14] and have been applied to natural product syntheses.[15] However, the photochemistry of spirocyclic cyclohexadienones are quite rare. We propose that the photoreaction of **2** to **4** occurs via a diradical mechanism. As shown in Scheme 5, after the excitation of **2**, a diradical species **5** is formed, which undergoes *β*-scission to give intermediate **6**. **6** rearranges to afford a fused cyclopropane intermediate **8**, which undergoes

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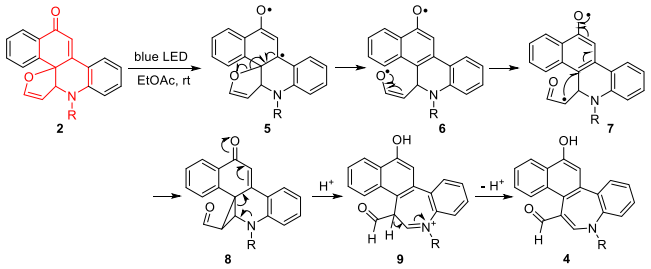
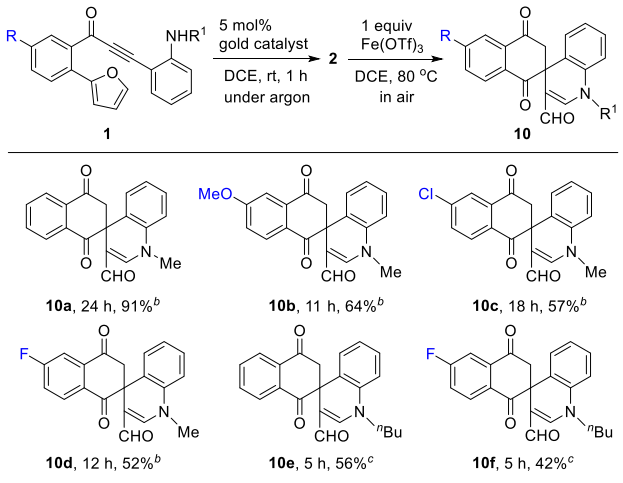
Scheme 5. Possible Mechanism for the Formation of 4



strain release by cleavage of the three-membered ring leading to the observed product **4**. It is noted that no catalyst and additives are required in these photoreactions.

Considering that the dihydrofuran moiety in products **2** might be prone to undergo ring-opening reactions under acid conditions, we also investigated the reactivity of **2** in the presence of various Lewis acids. To our pleasure, when the reaction of crude **2m** in DCE was treated with 1 equiv of $Fe(OTf)_3$ at 80 °C for 24 h in the air, a novel spirocycle **10a** with an additional oxygen functionality was formed cleanly in 91% overall yield (Scheme 6). Without $Fe(OTf)_3$, **10a** was not

Scheme 6. Lewis Acid-Promoted Formation of 10[a]

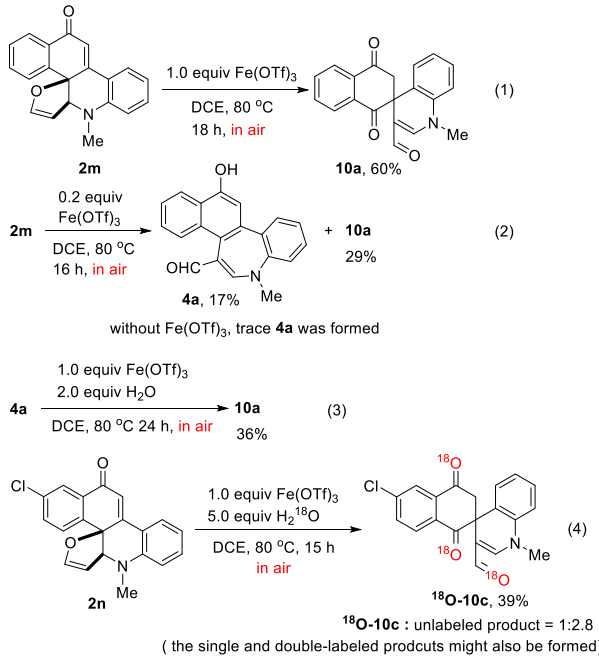


[a]Isolated yields. [b]$IPrAuNTf_2$ was used. [c]JohnphosAu(MeCN)SbF_6 was used.

formed. During this unprecedented cascade process, one C−O and C−C bonds of **2m** are broken, while C=O and C−C bonds are formed. Under the conditions noted, various furan-ynes transformed to the products **10** in moderate to good yields.

To understand the reaction pathway, various control experiments were carried out (Scheme 7). Treatment of pure **2m** with 1.0 equiv of $Fe(OTf)_3$ in DCE at 80 °C afforded **10a** in 60% yield (Scheme 7, eq 1). Decreasing the amount of $Fe(OTf)_3$ to 0.2 equiv afforded the ring-expanded product **4a** in 17% yield and **10a** in 29% yield (Scheme 7, eq 2). The reaction of **4a** with 1.0 equiv of $Fe(OTf)_3$ and 2.0 equiv of water gave **10a** in 36% yield, indicating that **4a** might be the intermediate for **10a**. ^{18}O-labeling experiment with **2n** as the substrate was performed by addition of 5 equiv of $H_2{}^{18}O$ to the reaction mixture. After stirring for 15 h, a triple-labeled ^{18}O product was observed. (The single and double-labeled products might also be formed, which cannot be identified

Scheme 7. Control Experiments



by HRMS due to the existence of the isotopic chlorine.)[16] Possibly, oxygen exchange between the oxygen moiety in the intermediates or the carbonyl groups in the products with $H_2{}^{18}O$ occurs during the reaction. Therefore, we could not make clear that if the additional ketone-oxygen come from water or not. The detailed mechanistic discussions still need to await further studies.[17]

In summary, we have developed a new and efficient strategy for the construction of polycyclic spiro-heterocycles via gold-catalysis. The overall process includes the nucleophilic attack of the furan moiety to the alkyne followed by trapping of the resulting cationic intermediate with an amino moiety. The resulting *N*-alkyl spirohydrofurans can engage in visible light-induced photorearrangement reactions and iron-promoted rearrangement involving C−C bond migration to diketone-containing spirocycles. Further extensions by exploring the reactivity of furan-ynes bearing additional nucleophilic groups are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04312.

Experimental details and spectroscopic characterization of all products and new substrates, crystal data and structural refinement for compounds **1i**, **2i**, **2m**, **3**, **4a**, and **10a** (PDF)

Accession Codes

CCDC 2019256−2019260 and 2019264 contain 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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Notes

The authors declare no competing financial interest.

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(11) Addition of radical scavenger TEMPO did not suppress the photoreaction of **2m**. However, the use of galvinoxyl significantly disturbed the reaction. In this case, the substrate **2m** was consumed completely, and a trace of **4a** was observed. The results suggest that the radical species might be involved in the reaction.

(12) *N*-Ester substrate **1a** shows no absorption in the range of visible light, *N*-alkyl substrate **1m** gives the absorption peaks around 417 nm (see the Supporting Information). Thus, **1m** undergoes the photoreaction easier than **1a** under visible light.

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(16) ^{18}O-labeling experiment with **2m** was also performed; a mixture of single, double, and triple-labeled ^{18}O products was formed with the abundance of 44%, 30%, and 7%, respectively.

(17) For more results of mechanistic studies and a proposed mechanism for the formation of **10**, see the Supporting Information..

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