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Letter

Cu(II)-Catalyzed 6π-Photocyclization of Non-6π Substrates

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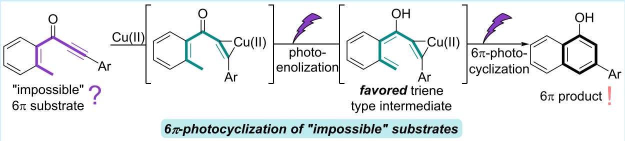
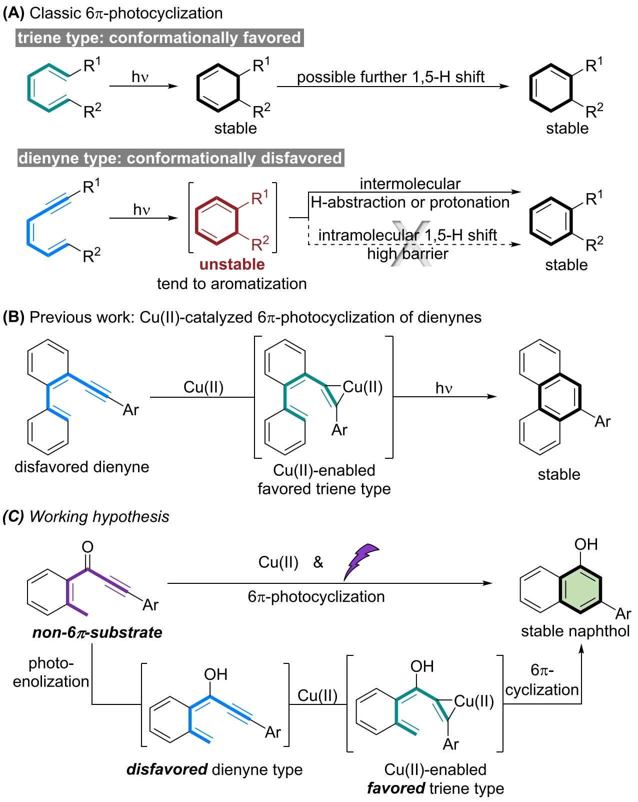
ABSTRACT: This research successfully achieved a Cu(II)-catalyzed 6π-photocyclization of non-6π substrates. The photoenolization converts *ortho*-alkylphenyl alkynl ketones into a triene-type intermediate which undergoes the subsequent 6π-photocyclization to give naphthol as the final product. Cu(II) catalyst facilitates both photoenolization and 6π-photocyclization. This research highlighted the tandem reaction strategy and the importance of metal catalysis in photochemistry.



6π-Photocyclization has become one of the well-established photocyclization reactions since its discovery in the 1980s.[1] It provides a convenient way to construct 1,3-cyclohexadiene and aromatic rings by further dehydrogenation or elimination. Thus, 6π-photocyclization is widely used in total synthesis,[2,3] medicine discovery,[4] and photoresponsive material design.[5] One of the typical 6π-photocyclization substrates is triene with an *s*-cis,*Z*,*s*-cis conformation (Scheme 1A, top).[6] The π system of *s*-cis,*Z*,*s*-cis triene has a similar conformation as the 6-membered transition state of 6π-photocyclization, and the termini of the π system are close enough to form a new σ bond.[7] For other conformers of triene, the isomerization of the triene system is inevitable before the 6π-photocyclization.[8] For the dienyne-type substrate, the 6π-photocyclization is much more difficult (Scheme 1A, bottom).[9,10] The termini of the dienyne π system are far away, leading to a higher kinetic barrier to form both a 6-membered transition state and the new σ bond. In addition, the corresponding primary 6π-photocyclization product is 6-membered cyclic allene, which is highly unstable.[9] The subsequent aromatization via 1,5-H shift, H abstraction, or protonation is necessary to achieve this transformation, affording aromatic rings as final products.[10] In most cases, O_2 and amines can facilitate the H abstraction,[10a] while protic solvent may provide proton for the protonation.[10d] Compared with those two pathways, the 1,5-H shift has dramatically higher kinetic barrier, which is normally the minor aromatization pathway.[10a,b] Overall, the 6π-photocyclization of dienyne is conformationally disfavored, and extra reagents are necessary for the transformation from the highly unstable primary product to the final aromatic product. Considering the broad application of 6π-photocyclizations, new methods for 6π-photocyclization of dienyne is highly desired yet challenging.

In 2016, we reported a Cu(II)-catalyzed 6π-photocyclization of dienynes (Scheme 1B).[11] The Cu(II) catalyst showed dual functions in this reaction: (1) The Cu(II)−alkyne complex has a twisted "alkene-like" conformation. Thus, the coordination of Cu(II) can transfer disfavored dienyne type substrate into

Scheme 1. Previous 6π-Photocyclizations and Working Hypothesis



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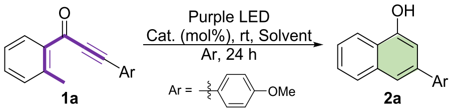
favored triene type intermediate. (2) The Cu(II)−alkyne complex has enhanced absorption toward the uncoordinated substrate. Thus, the quantum yield of the reaction is also improved. With such a Cu(II) catalysis strategy established, we further questioned whether we could use this method to achieve more challenging 6π-photocyclizations.

The photochemical property of *o*-alkyl aromatic ketone is very interesting. Upon proper photoirradiation, it can isomerize to photoenol via 1,5-H transfer and intersystem crossing (ISC).[12] The photoenol is a unique intermediate and shows dual reactivity as a diene and an enol.[13,14] Many interesting transformations were developed on the basis of this process. However, as a diene, the reactivity exploration of photoenol was limited to Diels−Alder reaction.[14] With our continued interest in 6π-photocyclization, we questioned whether the reactivity exploration could be expanded to 6π-photocyclization (Scheme 1C). If *o*-alkylaromatic alkynyl ketone is used as the starting reactant, the in situ generated photoenol may provide an additional π system to form a transient dienyne type 6π intermediate. On the basis of our previous results, the incorporation of proper Cu(II) catalyst may transfer this disfavored dienye-type intermediate into a favored triene-type species. Hence, we may achieve a new 6π-photocyclization using a non-6π substrate. Herein, we report our recent results on Cu(II)-catalyzed 6π-photocyclization of *o*-alkylphenyl alkynyl ketones.

The initial attempt was carried out using *o*-tolyl 4-methoxyphenylacetylenyl ketone (**1a**) as the model substrate. A series of Cu(II) salts were first screened (Table 1, entries 1−3). The results revealed that $Cu(OTf)_2$ showed remarkable catalytic activity compared to other Cu(II) salts. Other π acids, like AgOTf and PPh_3AuCl, were also tried, but only led to unidentified decompositions (Table 1, entries 4 and 5). Thus, $Cu(OTf)_2$ was chosen as catalyst for further studies. Solvent screening demonstrated that THF showed the highest yield among the tested solvents (Table 1, entries 6−11). Decreasing the loading of $Cu(OTf)_2$ to 1 mol % gave slightly higher yield of **2a** (Table 1, entries 12−14). Finally, control experiments were carried out (Table 1, entries 15 and 16). Light was proved to be necessary for this transformation, while the absence of $Cu(OTf)_2$ led to unidentified decomposition of all of the starting material. Thus, conditions A (**1** and 1 mol % of $Cu(OTf)_2$ in THF (0.02 M) irradiated by purple LED under argon atmosphere at rt for 24 h) were chosen as the optimized conditions for further studies.

With the optimized conditions in hand, we next examined the substrate scope of this reaction (Scheme 2). Functional groups at R were first studied (**2a**−**k**). Strong electron-donating groups (EDG), such as methoxy (**2a**) and acetoxy (**2b**), as well as weak EDG, such as *tert*-butyl (**2c**) and methyl (**2d**), were tolerant in the formation of **2**. Halogens (F, Cl, Br) were also tested and gave good results (**2f**-**h**). Substrates with strong electron-withdrawing groups (EWG), like methoxycar-

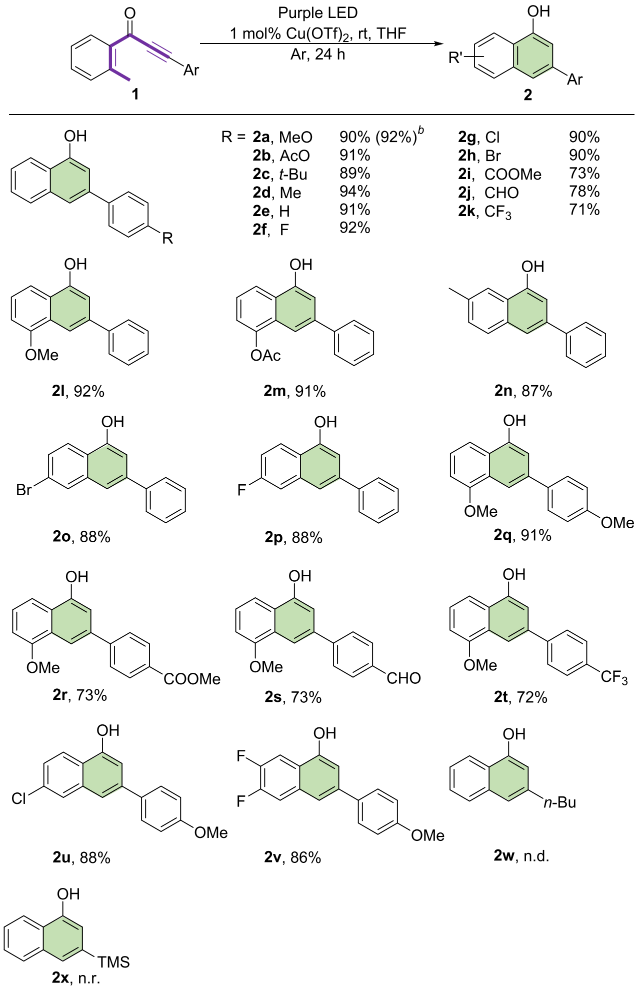
Table 1. Screening of the Conditions.[a]



entry	cat. (mol %)	solvent	**2a** (%)
1	$CuSO_4$ (10)	THF	14
2	$Cu(OAc)_2$ (10)	THF	10 (2)[b]
3	$Cu(OTf)_2$ (10)	THF	89
4	AgOTf (10)	THF	nd
5	PPh_3AuCl (10)	THF	nd
6	$Cu(OTf)_2$ (10)	EA	nd (26)[b]
7	$Cu(OTf)_2$ (10)	CH_3CN	nd (26)[b]
8	$Cu(OTf)_2$ (10)	CH_3OH	nd (65)[b]
9	$Cu(OTf)_2$ (10)	CH_2Cl_2	6 (20)[b]
10	$Cu(OTf)_2$ (10)	Toluene	26 (15)[b]
11	$Cu(OTf)_2$ (10)	Acetone	nd (43)[b]
12	$Cu(OTf)_2$ (5)	THF	88
13	$Cu(OTf)_2$ (3)	THF	90
14	$Cu(OTf)_2$ (1)	THF	91 (90)[c]
15	–	THF	nd
16[d]	$Cu(OTf)_2$ (1)	THF	nr (100)[b]

[a] A solution of **1a** (0.2 mmol) and catalyst in anhydrous solvent (10 mL) was irradiated by a purple LED light under argon atmosphere at rt. Yield and recovery was determined by ^1H NMR analysis (400 MHz) of the crude reaction mixture using CH_2Br_2 (0.2 mmol) as the internal standard; [b] Recovery of **1a**; [c] Isolated yield of **2a**; [d] The reaction was carried out without light. nd = not detected. nr = no reaction.

Scheme 2. Substrate Scope[a]

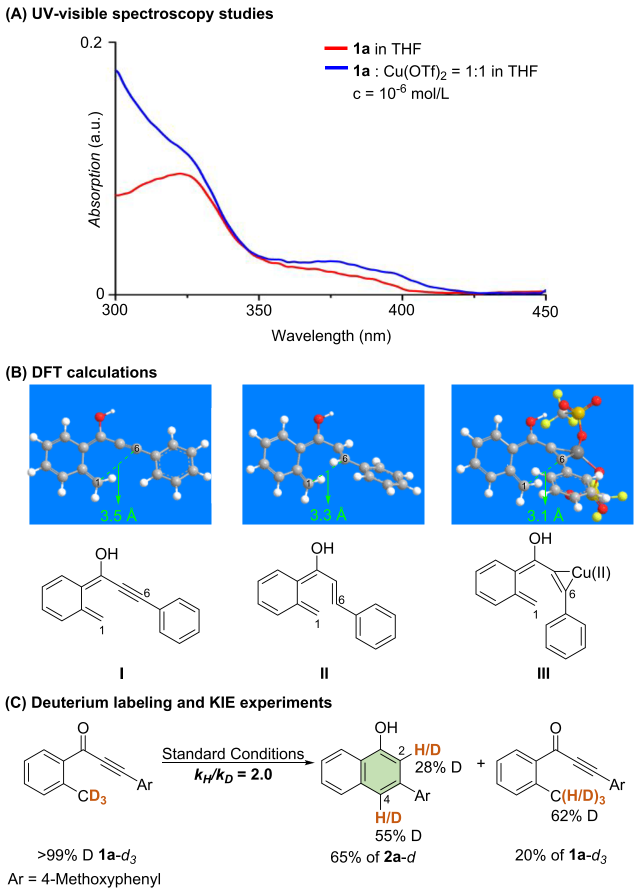


[a] Conditions: **1** (0.2 mmol) and 1 mol % of $Cu(OTf)_2$ in THF (10 mL) was irradiated by purple LED under argon atmosphere at rt for 24 h. Isolated yield was reported. [a] Isolated yield of gram-scale (4 mmol) reaction.

bonyl (**2i**), formyl (**2j**), and trifluormethyl (**2k**), also worked well. Next, substituents at the linking phenyl ring were examined. The tested substrates showed good reactivity (**2l–p**). Disubstituted substrates were synthesized and tried. Di-EDG (**2q**), EDG-EWG (**2r-t**), and EWG-EDG (**2u**) also gave good yield (**2v**). Substrates where Ar was replaced by *n*-Bu (**2w**) or TMS (**2x**) did not show good reactivity. Thus, this reaction showed good substrate scope and functional group tolerance.

After the substrate scope exploration, we next focused on mechanistic studies. First, UV–vis spectroscopy was conducted to identify what is excited during the reaction process. As shown in Scheme 3A, the addition of 1 equiv of $Cu(OTf)_2$ into the **1a** solution induced a new absorption peak at a low wavelength region. This observation suggested that a new ground-state complex was formed upon the complexation of $Cu(OTf)_2$ to **1a**. Furthermore, the Cu(II)–**1a** complex showed slightly enhanced absorption compared to pure **1a** at the purple LED emitting region (for the emission spectra of purple LED, see Figure S1). This result indicated that the Cu(II)–**1a** complex is easier to be excited than pure **1a** under purple LED irradiation.

Scheme 3. Mechanism Studies

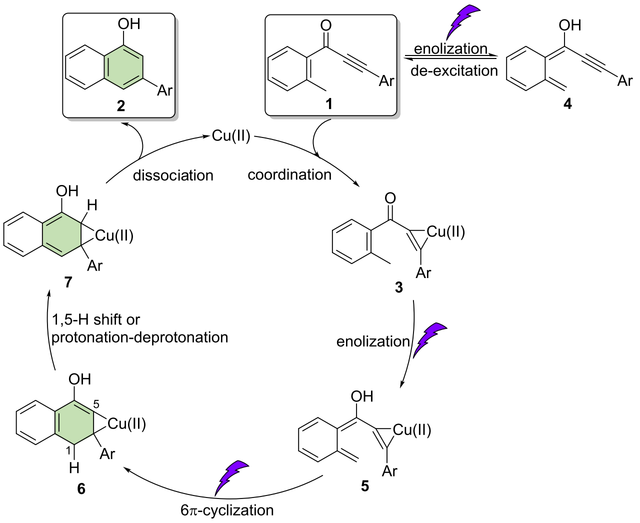


To gain a better understanding of the behavior of Cu(II) in this reaction, DFT calculations of the enolized intermediates (**I**, **II**, and **III**) were then carried out (Scheme 3B). Clearly, with the coordination of $Cu(OTf)_2$, the triple bond in **III** was twisted (bond angle was 151.5° and 156.6°). Further comparison of the C1–C6 distance revealed that the enolized intermediate **I** has the longest C1–C6 distance (3.490 Å) among the three simulated species. This observation is in consistent with the fact that 6*π*-photocyclization of dienyne is conformationally disfavored.[9] The longer distance caused a higher energy barrier in the new C1–C6 *σ* bond formation. To our surprise, the C1–C6 distance of the favored triene type intermediate **II** is even longer than that of **III**. The main reason might be the rigid bond angle (126.9° and 124.2°) of the alkene, which dramatically decreased the coplanner property of **II**. The dihedral angle between the two phenyl is 48.3°. On the contrary, the bond angles in **III** are 151.5° and 156.6°, and the dihedral angle is only 22.5°. With less tortuosity in **III**, the distance between C1–C6 is shorter than that in **II**. This observation suggested that this Cu(II)-enabled 6*π*-photocyclization of triene may have an even lower kinetic barrier than the typical triene-type reaction. Experimentally, only alkene isomerization occurred when a triene-type substrate was applied under the same conditions (for a detailed discussion, see Scheme S1).

Next, deuterium labeling and KIE experiments were carried out to gain insight to the H atom transfer in this reaction (Scheme 3C). Methyl-deuterated substrate **1a**-d_3 was synthesized and tried under standard conditions. Then 65% of **2a**-*d* was generated with both 2- and 4-positions deuterated; 20% of **1a**-d_3 was recovered with 62% deuterium content at methyl. The deuterium content loss of **1a** and **2a** was mainly due to the de-excitation pathways during formation of photoenol (for a detailed discussion, see Scheme S2).[12] The D atom transfer from the starting methyl to 2-position in **2a** could be a strong evidence for the 1,5-H shift during the cyclization process. The lower deuterium content at the 2-position than 4-position could be reasoned in other aromatization pathways, such as protonation.[9] The k_H/k_D was calculated to be 2.0, which indicated the C–H bond cleavage or formation is the rate-determining step (RDS). Since both photoenolization and 6*π*-photocyclization processes contained C–H bond cleavage and/or formation, it is hard to determine which step is the RDS with the evidence so far.

With the evidence above and literature precedent, a possible reaction mechanism was proposed in Scheme 4. With the coordination of a catalytic amount of Cu(II) to starting material **1**, there are two existing species in the reaction mixture: Cu(II)–alkyne complex **3** and uncoordinated **1**. Both

Scheme 4. Proposed Mechanism



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species can be excited by purple LED light, while **3** showed enhanced absorption than **1** (Scheme 3A). Upon excitation, **1** can be converted to photoenol **4** (for a detailed process, see Scheme S3). Intermediate **4** is a disfavored dienyne-type intermediate for 6π-photocyclization. The lifetime of **4** is around 50 μs,[15] which means it has little chance to coordinate with 1 mol % of Cu(II) to form a favored triene-type intermediate. Thus, the majority of **4** may de-excite and return to **1**. The excitation of Cu(II)−alkyne complex **3** leads to **5**, which is a favored triene-type intermediate. Then 6π-photocyclization of **5** occurs, and primary product **6** is generated. Subsequently, 1,5-H shift or protonation−deprotonation gives **7**. The dissociation of Cu(II) yields the naphthol **2** as the final product.

In conclusion, a Cu(II)-catalyzed 6π-photocyclization reaction of *o*-alkylphenyl alkynyl ketone was developed. This strategy successfully transferred the non-6π substrate into a favored triene type intermediate. This reaction showed broad substrate scope and function group tolarance. Mechanistic studies indicated that the Cu(II) catalyst facilitated both photoenolization and 6π-photocyclization processes. Further photophysical investigation and application of this strategy are ongoing in our group.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01854.

> Figure S1, Schemes S1−S3, experimental procedures, and characterization of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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