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Letter

# Copper(I)/DDQ-Mediated Double-Dehydrogenative Diels–Alder Reaction of Aryl Butenes with 1,4-Diketones and Indolones

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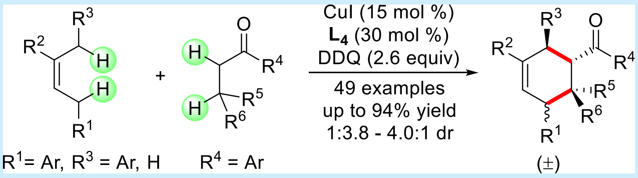
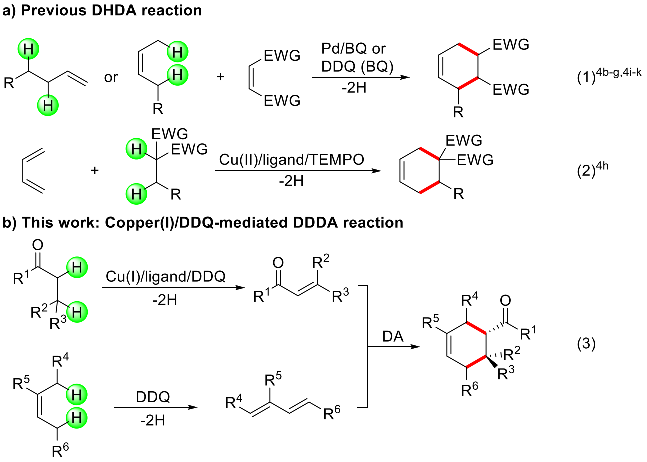
**ABSTRACT:** A copper(I)/DDQ-mediated double-dehydrogenative Diels–Alder (DDDA) reaction of simple butenes with 1,4-diketones and indolones has been established for the first time. This strategy is based on a tandem double-dehydrogenation/Diels–Alder reaction from nonprefunctionalized starting materials, in which both a diene and dienophile were in situ generated via activation of fourfold inert $C(sp^3)$–H bonds in one catalytic system.



Cross-dehyrogenative coupling (CDC) reactions allow molecular complexity and diversity to be created by the functionalization of $C(sp^3)$–H, representing efficient methodologies for constructing C–C and C–heteroatom bonds in a single operation.[1] The Diels–Alder (DA) reaction remains arguably one of the most atom-economic strategy for the construction of cyclohexene derivatives,[2] which has extensive applications in natural product synthesis, clinical drug discovery, and functional molecule design.[3] However, prefunctionalization of a diene and dienophile component is extraordinarily tedious before the reaction, which contains great opportunities for simplifying the DA process. Consequently, diverse dehydrogenative Diels–Alder (DHDA) reactions have been emerged,[4] including oxidative generation of dienes by White,[4b] Porco,[4c] Zhou,[4d,j,k] Zhang,[4e] Yao,[4f] Antonchick,[4g] and Li[4i] (Scheme 1, eq 1), and a Cu(II)-catalyzed oxidative generation of a dienophile approach by Xu and Loh[4h] (Scheme 1, eq 2). Despite the progress in these DHDA reactions, either the dienophile or diene still needs to be preprepared. A question raised is whether both diene and dienophile can be generated in one process, and then react with each other to complete the DA reaction. It would be appealing if these two oxidation processes could be performed in one pot. Thus, a double-dehydrogenation/Diels–Alder (DDDA) reaction in a single operation would provide a step-economic, eco-friendly alternative to the traditional method by eliminating the need for tedious preparation of the diene and dienophile (Scheme 1, eq 3). To the best of our knowledge, the DDDA reaction from readily available starting materials via activation of fourfold inert $C(sp^3)$–H bonds has not been reported to date. This is because there are great challenges still imbedded in this unparalleled DDDA reaction, including the following: (1) discovery of compatible reaction partners to match LUMO with HOMO; (2) establishment of a new catalytic system to abstract hydrogen from both electron-rich C–H bonds and electron-deficient ones; (3) the compatibility of the oxidative double-dehydrogenative reaction and the Diels–Alder reaction.

**Scheme 1. DHDA and DDDA Reactions**



Recently, we have reported several DDQ-mediated DHDA reactions from prenyl derivatives via in situ generated diene intermediates.[4d,j,k] With our continued interest in exploring efficient cycloaddition reactions and oxidative dehydrogenations,[5] we envisioned that the DDDA reaction would be realized by combination of our previously reported DHDA strategy with a metal-catalyzed dehydrogenative generation of dienophile. Among the metal-catalyzed dehydrogenative strategies, copper-catalyzed dehydrogenations have exhibited

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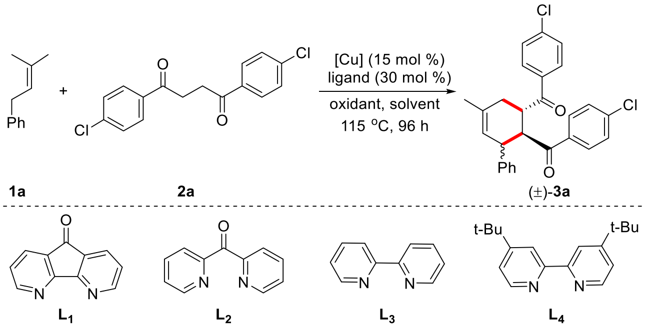
their powerful ability to convert alkanes to alkenes.[6] From the mechanistic point of view, copper(II) species should coordinate to a carbonyl substrate during the desaturation of the dienophile precursor.[6e,i] However, electron-rich dienes generally used in the DA reaction usually do not contain a carbonyl group. As a result, a catalytic oxidant system, which has been developed in those dehydrogenative approaches, may be not applicable to the DDDA reaction. Thus, to realize our hypothesis, a new catalytic system for double-dehydrogenation of dienophile and diene precursors should be established. Herein, we describe a copper(I)/DDQ-mediated DDDA reaction of butenes with 1,4-diketones and indolones via activation of fourfold inert C($sp^3$)−H bonds (Scheme 1, eq 3).

We initially investigated the DDDA reaction of prenyl benzene **1a** wth 1,4-bis(4-chlorophenyl)butane-1,4-dione **2a** in the presence of CuI as a catalyst, DDQ as an oxidant, and several common *N*-containing bidentate ligands (Table 1, entries 1−4). The target product **3a** was obtained in the presence of CuI (15 mol %), $\mathbf{L}_1$ ligand (30 mol %), and DDQ (2.6 equiv) in chlorobenzene at 115 °C for 96 h, which is constant with our hypothesis. Of the ligands examined (entries 1−4), 4,4′-di-*tert*-butyl-2,2′-bipyridine ($\mathbf{L}_4$) gave the best result (entry 4) for the copper-catalyzed DDDA reaction. Di-*tert*-butyl peroxide, generally used in many reported metal-catalyzed oxidative dehydrogenation reactions, returned only a trace amount of the desired product (entry 6). Subsequently, a variety of copper catalysts and solvents were evaluated sequentially (entries 7−15). When the DDDA reaction was performed by employing DDQ as the oxidant, CuI as the catalyst, and 4,4′-di-*tert*-butyl-2,2′-bipyridine ($\mathbf{L}_4$) as the ligand in trifluoromethylbenzene, the expected product **3a** could be isolated in 91% yield (entry 15). Reducing the loading of catalyst and ligand to 10 mol % and 20 mol % led to a lower yield (entry 16). Surprisingly, in the absence of a copper catalyst, product **3a** was obtained in 19% yield (entry 17), while no desired product was detected when the reaction was conducted in the absence of $\mathbf{L}_4$ (entry 18). These results suggest that the ligand plays a critical role in the oxidation of 1,4-diketone **2a** to a 1,4-enedione intermediate. As expected, in the absence of oxidant no reaction resulted (entry 19). These control experiments revealed that all reaction components in the DDDA reaction were indispensable. Notably, although poor diastereoselectivities of **3a** were observed, both of them are *endo*-selectivity, resulting from the stereospecificity of the DA reaction.

**Table 1. Optimization of the Reaction Conditions**[a]



| entry | catalyst | solvent | ligand | oxidant | yield (%)[b] | dr[c] |
|---|---|---|---|---|---|---|
| 1 | CuI | PhCl | $\mathbf{L}_1$ | DDQ | 26 | 1:1.2 |
| 2 | CuI | PhCl | $\mathbf{L}_2$ | DDQ | 73 | 1:1.1 |
| 3 | CuI | PhCl | $\mathbf{L}_3$ | DDQ | 37 | 1:1.2 |
| 4 | CuI | PhCl | $\mathbf{L}_4$ | DDQ | 89 | 1:1.3 |
| 5 | CuI | PhCl | $\mathbf{L}_4$ | BQ[d] | n.d. | – |
| 6 | CuI | PhCl | $\mathbf{L}_4$ | DTBP[e] | trace | – |
| 7 | CuBr | PhCl | $\mathbf{L}_4$ | DDQ | 77 | 1:1.3 |
| 8 | CuCl | PhCl | $\mathbf{L}_4$ | DDQ | 80 | 1:1.3 |
| 9 | $CuCl_2$ | PhCl | $\mathbf{L}_4$ | DDQ | 24 | 1:1.2 |
| 10 | $CuBr_2$ | PhCl | $\mathbf{L}_4$ | DDQ | 21 | 1:1.1 |
| 11 | $CuSO_4$ | PhCl | $\mathbf{L}_4$ | DDQ | trace | – |
| 12 | $Cu(OAc)_2$ | PhCl | $\mathbf{L}_4$ | DDQ | trace | – |
| 13 | CuI | PhBr | $\mathbf{L}_4$ | DDQ | 75 | 1:1.2 |
| 14 | CuI | $PhCH_3$ | $\mathbf{L}_4$ | DDQ | 72 | 1:1.3 |
| **15** | **CuI** | **$PhCF_3$** | $\mathbf{L}_4$ | **DDQ** | **91** | **1:1.3** |
| 16[f] | CuI | $PhCF_3$ | $\mathbf{L}_4$ | DDQ | 78 | 1:1.2 |
| 17 | – | $PhCF_3$ | $\mathbf{L}_4$ | DDQ | 19 | 1:1.1 |
| 18 | CuI | $PhCF_3$ | – | DDQ | n.d. | – |
| 19 | CuI | $PhCF_3$ | $\mathbf{L}_4$ | – | n.d. | – |

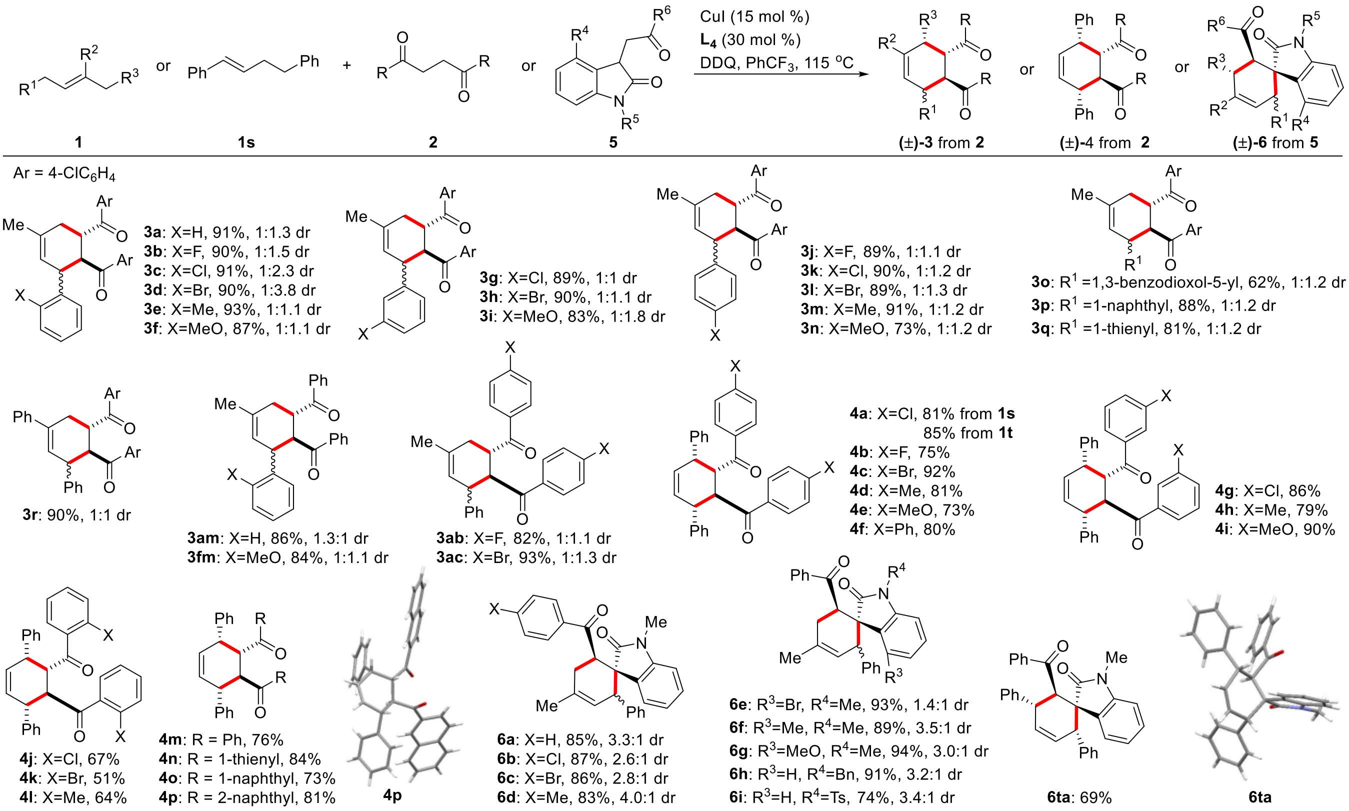
[a] Reactions were carried out with **1a** (0.20 mmol), **2a** (0.10 mmol), DDQ (0.26 mmol), CuI (15 mol %), **L** (30 mol %) at 115 °C in solvent (2.0 mL) under $N_2$ for 96 h. [b] Isolated yield. [c] The dr value was determined by $^1H$ NMR. [d] BQ = *p*-benzoquinone. [e] DTBP = di-*tert*-butyl peroxide. [f] CuI (10 mol %) and $\mathbf{L}_4$ (20 mol %) were used.

With the optimal catalytic conditions determined, we then evaluated the substrate scope in terms of substituted but-2-enes by employing 1,4-bis(4-chlorophenyl)butane-1,4-dione **2a** as the dienophile precursor. As shown in Scheme 2, the reaction could be amenable to a wide range of butene **1** with diverse substituents, furnishing cyclohexene derivatives **3** in good to excellent yields and excellent endo selectivities. Prenyl benzene substrates bearing varieties of functional groups such as halogens, alkoxy, and alkyl at the ortho-, meta-, and para-position of the phenyl ring were subjected to this new DDDA reaction, and the corresponding products, in most cases, were obtained in excellent yields (**3a−m**, 83−91%; **3n−o**, 73% and 62%). Excellent yields were also gained with either thienyl- or naphthalenyl-substituted prenyl substrates (**3p−q**, 88% and 81%). Moreover, diphenyl substituted but-2-ene **1r** returned the expected product **3r** in 90% yield. In addition, several 1,4-diketones were further explored, and the reactions proceeded smoothly to generate the desired products in excellent yields (**3am−ac**, 82−93%).

Subsequently, the substrate scope with respect to diaryl-substituted 1,4-diketones was investigated with the use of diphenyl substituted butenes. Notably, but-1-ene-1,4-diyldibenzene (**1s**) and but-2-ene-1,4-diyldibenzene (**1t**) were all compatible and afforded the same desired product **4a** in 81% and 85% yields, respectively. As summarized in Scheme 2, a series of diaryl-substituted 1,4-diketones bearing electronically diverse functionalities at any position on the phenyl ring smoothly underwent the DDDA reaction with also exclusive endo selectivity (**4b−m**, 51−92%, from **1t**). Nevertheless, 1,4-diketones with different substituents at the ortho-positon of the phenyl ring exhibited lower reactivity probably due to steric hindrance, and only moderate yields were furnished (**4j−l**, 51−67%). Additionally, thienyl- and naphthyl-substituted 1,4-diketones were well-tolerated, and high yields were observed (**4n−p**, 73−84%, from **1t**). The structure of product **4p** was further assigned by X-ray analysis (CCDC 1961346).

To further enlarge the generality of the DDDA reaction, we performed this protocol with benzoylmethyl indolones. As shown in Scheme 2, an array of indolones derived from *N*-methyl isatins reacted effectively with prenyl benzene **1a** under the optimal catalytic conditions, leading to the desired

**Scheme 2. Scope of the DDDA Reaction**[a]

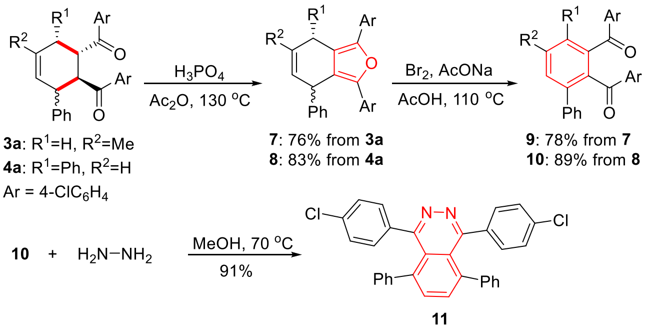


[a] Reactions were carried out with **1** (0.20 mmol), **2** (0.10 mmol), DDQ (0.26 mmol; 0.29 mmol for product **4**), CuI (15 mol %), $\mathbf{L_4}$ (30 mol %) at 115 °C in $PhCF_3$ (2.0 mL) under $N_2$ for 96 h (120 h for product **4**). Isolated yield. The dr value was determined by $^1H$ NMR.

spirocyclic oxindoles in good to excellent yields (**6a–g**, 83–94%). Furthermore, Ts- and Bn-protected indolones also proved to be compatible substrates and returned the corresponding products **6h** and **6i** in excellent yields. Interestingly, butene **1t** was also compatible, and a fair yield (69%) of the desired product **6ta** could be observed with exclusive diastereoselectivity. The structure of pruduct **6ta** was also confirmed by X-ray crystallography (CCDC 1961351).

To validate the synthetic practicability of the reaction, the selective manipulations of these products were further instantiated (Scheme 3). Compounds **3a** and **4a** can be further converted to dihydroisobenzofuran **7** and **8**.[7] Further aromatization of **7** and **8** gave the corresponding 1,2-phenylenebis(phenylmethanone) **9** and **10** in high yields, which are key intermediates in material chemistry.[8] For example, **10** is an important precursor of 1,4-diphenylphthalazine **11**, which is a promising ligand in near-infrared-(NIR-) emitting materials.[9]

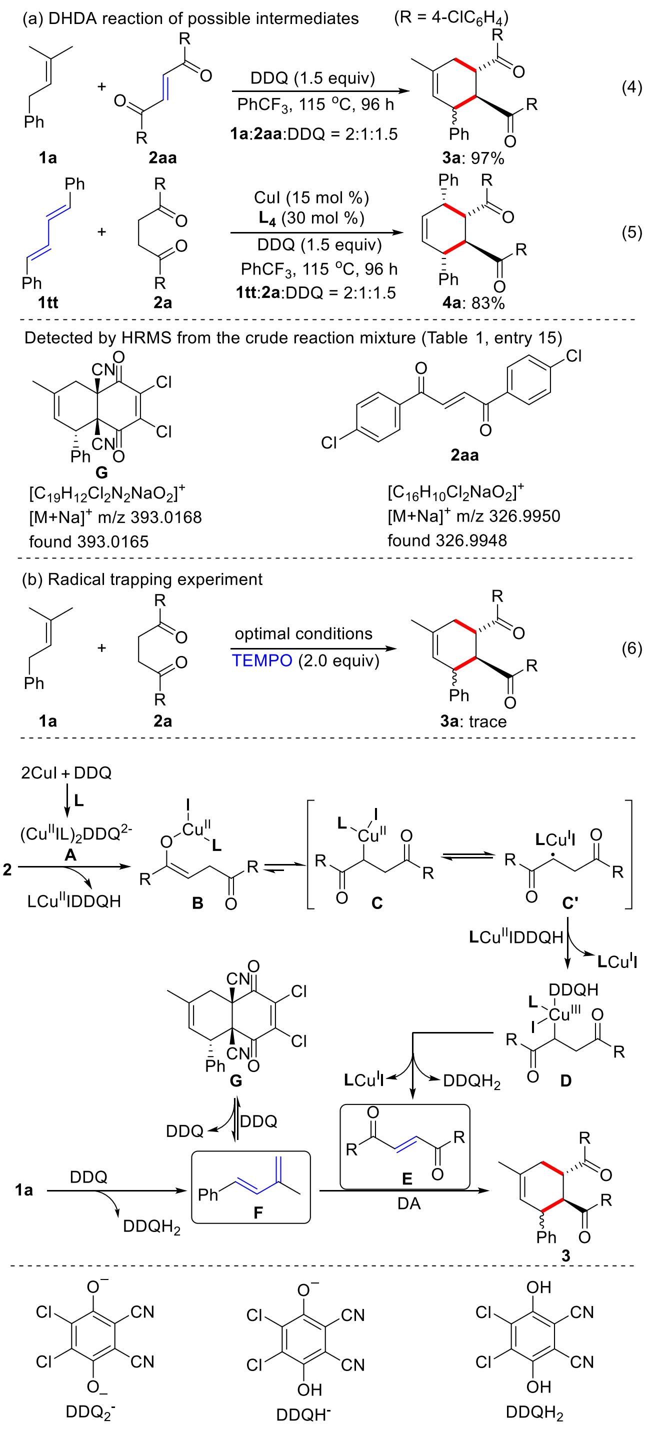
**Scheme 3. Synthesis of Compounds 9−11**



To gain insight into the DDDA reaction mechanism, a series of control experiments were performed. As outlined in Scheme 4, to test our double-dehydrogenative hypothesis, we carried out two parallel DHDA reactions by employing 1,4-enedione **2aa** and 1,3-butadiene **1tt** as possible intermediates, respectively. In the first case, prenyl benzene **1a** was treated with the intermediate **2aa** in the absence of CuI and ligand, and the product **3a** was generated in extremely excellent yield (Scheme 4, eq 4). In the second case, when the amount of DDQ was reduced from 2.6 equiv in the standard reaction conditions to 1.5 equiv, the DHDA reaction of **2a** with intermediate **1tt** also proceeded smoothly to afford the product **4a** in 83% yield (Scheme 4, eq 5). In addition, HRMS analysis of the crude model reaction captured the masses of key intermediates **G** and **2aa**. These outcomes indicated that the DDDA reaction includes the following reaction sequence: first, double-dehydrogenation of butenes and 1,4-diketones to give 1,3-butadienes and 1,4-enediones; then, Diels–Alder reaction of 1,3-butadienes and 1,4-enediones to yield the final product. Moreover, a radical trapping experiment was also conducted in the presence of TEMPO as a radical scavenger, and even no desired product was generated in the DDDA reaction of **1a** and **2a** (Scheme 4, eq 6). To a certain degree, these results suggest that this strategy involved a radical process.

Based on the mechanistic studies mentioned above and previous literature, a plausible mechanism was proposed for the unprecedented reaction (Scheme 4).[4j,6i,10] First, CuI is oxidized to the copper(II) species **A** by DDQ,[11] which

Scheme 4. Control Experiments and Proposed Mechanism



coordinates with **2** to generate a LCu(II)-enolate species **B** or an organocopper complex **C** (**C′**).[6e] Then, based on the radical property, organocopper complex **C** (**C′**) gives rise to the Cu(III) intermediate **D** and a Cu(I) species in the presence of the Cu(II) species.[6f,11] Subsequently, the generated **D** undergoes oxidative elimination to generate intermediate dienophiles **E** and another Cu(I) species.[12] Then the resulting Cu(I) species is oxidized to the Cu(II) species by DDQ and the process repeats. Moreover, prenyl benzene **1a** was synchronously oxidized by DDQ to generate intermediate diene **F**, where a thermal reversible DA process was involved.[4j] Finally, the Diels–Alder reaction takes place to afford the corresponding product **3**.

In summary, we have established a novel copper-catalyzed DDDA reaction from simple nonprefunctionalized alkene and saturated ketones via direct functionalization of four C–H bonds in one reaction. This protocol avoids the need for extra steps for preparation of dienes and dienophiles and, therefore, represents a straightforward and step-economical concept. This unprecedented reaction shows broad substrate scope and excellent functional group tolerance. Mechanistic studies disclosed that the Cu(I)/DDQ-mediated tandem double-dehydrogenation/Diels–Alder reaction represented an unparalleled radical-based process. This work will not only contribute to the field of copper-based catalyst system and Diels–Alder reaction but also serve as a powerful approach in the synthesis of cyclohexene-derived diketones and spirocyclic oxindoles.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02486.

Experimental detail, X-ray crystal structures of **4p** and **6ta**, spectroscopic and analytical data for new compounds (PDF)

### Accession Codes

CCDC 1961346 and 1961351 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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