

Copper-Catalyzed Dehydrogenative Diels–Alder Reaction

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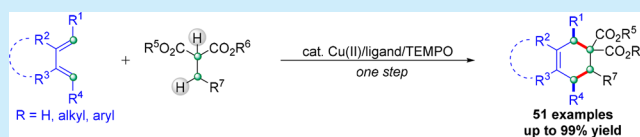
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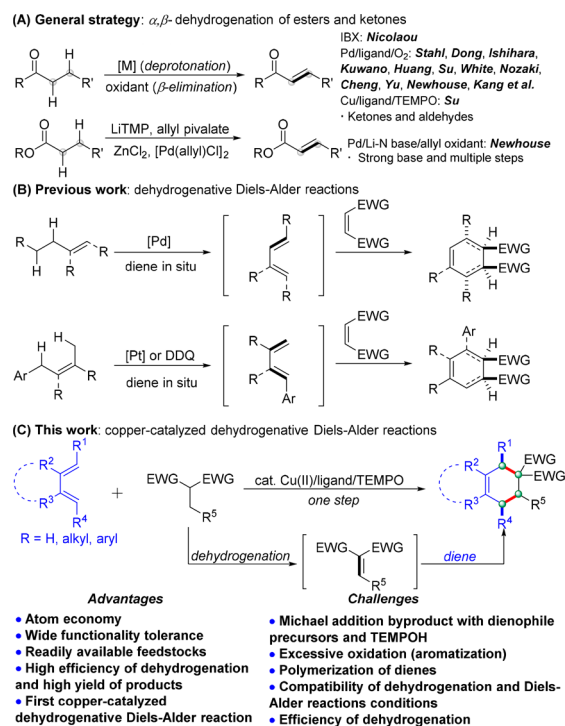
S Supporting Information

ABSTRACT: A practical and effective copper-catalyzed dehydrogenative Diels–Alder reaction of *gem*-diesters and ketone with dienes has been established. The active dienophiles were generated in situ via a radical-based dehydrogenation process, which reacted with a wide variety of dienes to afford various polysubstituted cyclohexene derivatives in good to excellent yields.



The Diels–Alder reaction is probably one of the most powerful reactions for the construction of six-membered rings.¹ Accordingly, it has been widely used for the synthesis of many natural products and pharmaceuticals.² Nevertheless, there are still limitations associated with this important reaction.³ For example, there is still the need to prepare the highly reactive and toxic dienophiles before the reaction. Therefore, methods that can generate the reactive dienophiles in situ from easily accessible and more stable compounds in the reaction will be highly desirable. We envisage that dienophiles generated in situ via dehydrogenation of alkanes will be useful. It is important to note that dehydrogenation processes to yield alkenes have been documented by the groups of Stahl,⁴ Dong,⁵ Nicolaou,⁶ Ishihara,^{7a} Kuwano,⁸ Huang,⁹ Su,¹⁰ White,¹¹ Nozaki,¹² Cheng,¹³ Yu,¹⁴ Newhouse,¹⁵ and Kang.¹⁶ On the other hand, Su and co-workers have elegantly utilized this process for the amine conjugate addition.^{10c} Moreover, a few examples on dehydrogenative Diels–Alder reactions have emerged as unique protocols for the one-step construction of unsaturated six-membered carbocycles. One such case is via Pd, Pt/C-catalyzed, or oxidative dehydrogenation to generate reactive diene intermediates (Scheme 1), which was reported by White,^{11a} Porco,^{17a} Ishihara,^{7b} Zhang,¹⁸ and others.¹⁹ Another example developed by Porco and co-workers is an Rh/C-catalyzed dehydrogenative reaction of cyclopentanone derivatives to form very reactive cyclopentadienone dienophiles.^{17b} Therefore, we envision that a highly efficient *gem*-diester or ketone dehydrogenation process in combination with a subsequent Diels–Alder reaction would provide an appealing, atom-economic alternative to the traditional way by eliminating the need for troublesome pre-preparation and isolation of α,β -unsaturated carbonyl compounds. To realize this design, the catalytic system must conform to the following requirements: (a) the catalytic system selectively dehydrogenates *gem*-diester or ketone over a cyclohexene product to avoid overoxidation;

Scheme 1. Oxidative Dehydrogenative Diels–Alder Reactions



(b) the catalytic system selectively takes place prior to a Michael conjugate addition to overcome the byproduct from the dienophile precursor and TEMPOH; (c) the oxidative

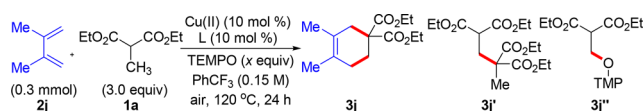
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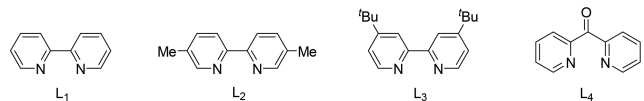
dehydrogenation conditions are compatible with a Diels–Alder cyclization donor (an accessible electron-rich diene); and (d) the catalytic system is capable of facilitating both dehydrogenation and Diels–Alder reactions. With our continued interest in a Diels–Alder reaction to construct six-membered ring-containing frameworks efficiently,^{3q,20,21} we hereby report a copper-catalyzed dehydrogenative Diels–Alder reaction that uses *gem*-diester or ketone as the direct dienophile through an acrylate or enone intermediate generated in situ.

First, we evaluated the model reaction with 2,3-dimethylbuta-1,3-diene and the dienophile precursor diethyl 2-methylmalonate, and the results are summarized in Table 1. Pleasingly, the

Table 1. Development of the Tandem Dehydrogenation/Diels–Alder Reaction^a



entry	catalyst	solvent	ligand	TEMPO (x equiv)	atmosphere	yield ^b of 3j (%)
1	Cu(OAc) ₂	PhCl	L ₁	1.0	Ar	65
2	Cu(OAc) ₂	ODCB	L ₁	1.0	Ar	67
3	Cu(OAc) ₂	toluene	L ₁	1.0	Ar	52
4	Cu(OAc) ₂	PhCF ₃	L ₁	1.0	Ar	71
5	Cu(OAc) ₂	PhCl	L ₁	1.2	Ar	75
6	Cu(OAc) ₂	PhCl	L ₁	1.6	Ar	82
7	Cu(OAc) ₂	PhCl	L ₁	1.8	Ar	82
8	Cu(OTf) ₂	PhCl	L ₁	1.6	Ar	48
9	CuCl ₂	PhCl	L ₁	1.6	Ar	63
10	CuBr ₂	PhCl	L ₁	1.6	Ar	69
11	Cu(OAc) ₂	PhCl	L ₂	1.6	Ar	82
12	Cu(OAc) ₂	PhCl	L ₃	1.6	Ar	83
13	Cu(OAc) ₂	PhCl	L ₄	1.6	Ar	85
14	Cu(OAc) ₂	PhCF ₃	L ₄	1.6	air	93
15 ^c	Cu(OAc) ₂	PhCF ₃	L ₄	1.6	air	92
16	–	PhCF ₃	L ₄	1.6	air	nr
17	Cu(OAc) ₂	PhCF ₃	L ₄	–	air	nr
18	Cu(OAc) ₂	PhCF ₃	–	1.6	air	52



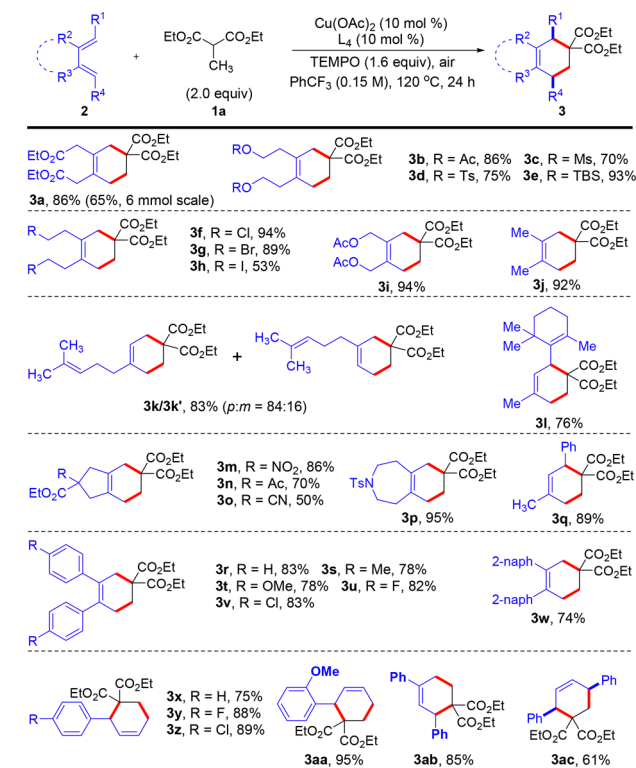
^aReaction conditions: 2,3-dimethylbuta-1,3-diene **2j** (0.3 mmol), diethyl 2-methylmalonate **1a** (0.9 mmol), Cu(OAc)₂ (0.03 mmol), L (0.03 mmol), TEMPO, solvent (2 mL), 24 h. ^bYield was determined by ¹H NMR spectroscopic analysis using mesitylene as an internal standard. ^cDiethyl 2-methylmalonate (2.0 equiv) was used. ODCB: 1,2-dichlorobenzene. ^d**3j'** and **3j''** could be detected in less than 1% yield by crude ¹H NMR spectroscopic analysis.

dehydrogenative Diels–Alder reaction product **3j** was obtained in a promising yield (65%) in the presence of 10 mol % of Cu(OAc)₂ as catalyst and TEMPO (1.0 equiv) as oxidant in chlorobenzene (PhCl) at 120 °C being stirred for 24 h under argon atmosphere (Table 1, entry 1). Therefore, a series of solvents, catalysts, and ligands were examined sequentially. It was found that the yield of the product could be improved up to 93% by employing the Cu(OAc)₂/di(pyridin-2-yl)methanone catalytic system upon increasing the loading of TEMPO (1.6 equiv) in (trifluoromethyl)benzene (PhCF₃) under air atmosphere (Table 1, entry 14). The dehydrogenation efficiency was not affected, even if we reduced the dienophile precursor to 2 equiv (Table 1, entry 15). Control experiments indicated that all components in this catalytic system were essential to afford the cyclohexene derivative **3j** in an excellent yield.

After determining the optimized reaction conditions, we further investigated the substrate scope and limitation of dienes

by employing diethyl 2-methylmalonate as dienophile precursor (Scheme 2). We found that a wide variety of readily available

Scheme 2. Substrate Scope of Dienes^a

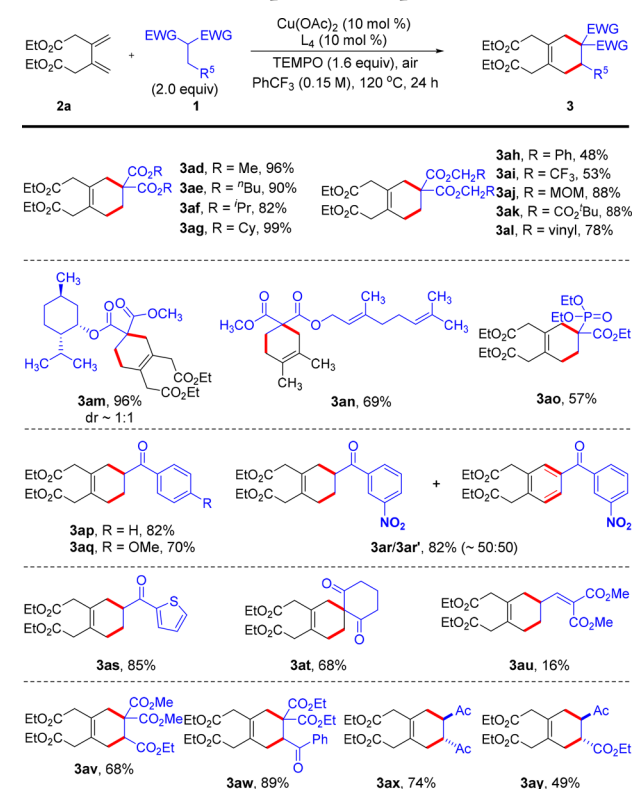


^aReaction conditions: **2** (0.3 mmol), diethyl 2-methylmalonate **1a** (0.6 mmol), Cu(OAc)₂ (0.03 mmol), L₄ (0.03 mmol), TEMPO (1.6 equiv), (trifluoromethyl)benzene (2 mL), air atmosphere, 24 h.

diene with alkyl substituents tethering various functionalities at the C-2 and/or C-3 positions could provide the corresponding cyclohexene derivatives in moderate to excellent yields (**3a–i**). The dienes with reactive halide substituents, in particular, the iodide group, could also be tolerated in the reaction to give the corresponding products in moderate to excellent yields, respectively. Moreover, the volatile 2,3-dimethylbuta-1,3-diene also smoothly underwent cyclization reaction to generate the desired product **3j** in 92% yield. We also observed that myrcene with an additional double bond could be well-tolerated, while a mixture product **3k/3k'** in total 83% yield and with moderate regioselectivity (*p/m* = 84:16) was obtained. On the other hand, when the diene derived from irisone reacted with diethyl 2-methylmalonate, an exclusive isomer product **3l** in 76% yield was isolated. Furthermore, other five-membered and seven-membered dienes bearing nitro, acetyl, cyano, or Ts-protected amine groups were subjected to this transformation. All of the desired bridged products were obtained in moderate to high yields (**3m–p**). Subsequently, we also evaluated the dienes with respect to different aryl substituents (**3q–ac**). A variety of substrates with electronically diverse functionalities on the phenyl ring were tolerated to afford the corresponding products in 61–95% yields. It is worth mentioning that the dienes with an aryl group at the C-1 position showed highly reactive efficiency and excellent regioselectivities (**3q,x–ac**). Finally, a gram-scale dehydrogenative Diels–Alder reaction for the synthesis of cyclized product **3a** was proven to be feasible in a slightly decreased yield.

To show the generality of this transformation, we next tested potential application of the current Cu(II)-catalyzed dehydrogenation Diels–Alder strategy to other *gem*-diesters and ketones (Scheme 3). We found that various readily available

Scheme 3. Substrate Scope of Dienophile Precursors



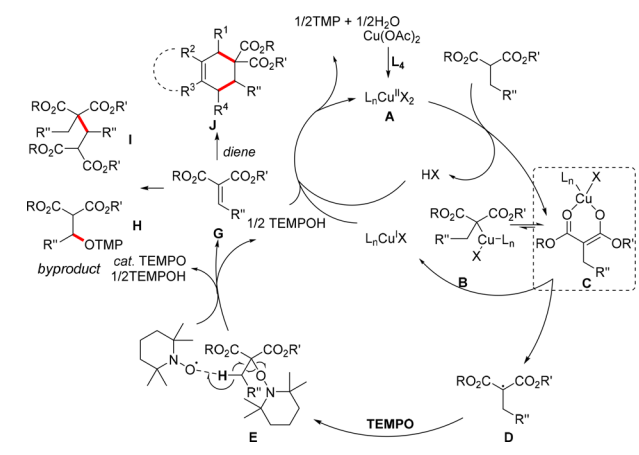
^aReaction conditions: diethyl 3,4-dimethylhexanedioate **2a** (0.3 mmol), **1** (0.6 mmol), $\text{Cu}(\text{OAc})_2$ (0.03 mmol), L_4 (0.03 mmol), TEMPO (1.6 equiv), (trifluoromethyl)benzene (2 mL), air atmosphere, 24 h.

gem-diesters bearing primary or secondary alkyl substituents on the oxygen atom all provided the corresponding cyclohexene derivatives successfully. Despite some functionalities existing in the *gem*-diesters that were prone to being oxidized, the established oxidative conditions enabled these *gem*-diesters to participate in this transformation smoothly and afford the desired products in moderate to high yields (**3ah–al**). To access the enantioselective cyclohexene products, the use of chiral auxiliaries is one of many powerful and efficient strategies to produce the desired stereoisomer.²² Herein, we attempted to introduce the chiral (–)-menthol to dienophile precursor in order to realize the stereoselective transformation. An excellent isolated yield of the desired products **3am** could be observed with poor diastereoselectivity, most probably due to the need for high temperature. When a geraniol-derived *gem*-diester was subjected to this reaction, the corresponding product **3an** with multiple double bonds was isolated in 69% yield. Additionally, the substrate bearing a phosphate group was also compatible and yielded the desired product **3ao**. Moreover, this catalytic protocol is not only limited to *gem*-diesters but also applicable to a variety of ketones. The cyclic adducts were also obtained in good yields under the optimal reaction conditions (**3ap–as**). We noted that when 1-(3-nitrophenyl)propan-1-one was used to react with diethyl 3,4-dimethylhexanedioate, a mixture of

aromatization product and normal adduct could be obtained in 82% yield (**3ar/3ar'**). In addition, *gem*-diketone was also effective in affording the spiro product **3at** in 68% yield. Subsequently, we used dimethyl 2-allylmalonate as the precursor via a dienolate intermediate, but unfortunately, only 16% yield of the desired product (**3au**) was obtained, possibly due to its low conversion of the starting materials under the optimized reaction conditions. Pleasingly, the corresponding tetrasubstituted cyclohexene derivatives were also formed in moderate to good yields when the ethane-1,1,2-tricarbonyl or 1,2-dicarbonyl compounds were applied to react with diethyl 3,4-dimethylhexanedioate (**3av–ay**).

On the basis of the previous reports,^{10c,d} a plausible mechanism was proposed as shown in Scheme 4. First,

Scheme 4. Proposed Possible Mechanism



$\text{Cu}(\text{OAc})_2$ reacts with *gem*-diester to form an organocopper species **B** or a chelate copper–enolate complex **C**. Thus, a radical intermediate **D** could be generated via a homolysis process, along with formation of a Cu(I) complex. Following this, the radical intermediate **D** would be captured by TEMPO to form α -TEMPO-substituted intermediate **E**, which then undergoes a fast TEMPOH elimination to furnish the dienophile **G** in the presence of another TEMPO (**F**). Finally, the α,β -unsaturated carbonyl compounds generated in situ will react with various dienes under the Cu(II)/ L_4 catalytic system to afford the cyclohexene derivatives **J** as well as a trace amount of undesired Michael addition byproducts **H** and **I**.

In conclusion, we have demonstrated a new strategy for a copper-catalyzed dehydrogenative Diels–Alder reaction of easily available *gem*-diesters and ketones with a wide variety of dienes. This strategy avoids the need of additional steps for the preparation of unstable α,β -unsaturated carbonyl compounds. This work also opens a new method of constructing the cyclohexene derivatives in a highly efficient fashion. This work also features high efficiency in dehydrogenation, atomic economy, and good functional compatibility. Further in-depth application studies of this oxidative radical dehydrogenation Diels–Alder reaction in organic synthesis are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01067.

Detailed experimental procedures and spectral data (PDF) for all new compounds (^1H NMR, ^{13}C NMR, ^{19}F NMR, ^1H – ^1H COSY NMR HR-MS) (PDF)

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Notes

The authors declare no competing financial interest.

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