

Rapid Access to Free Phenols by Photocatalytic Acceptorless Dehydrogenation of Cyclohexanones at Room Temperature

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Abstract

Phenols are ubiquitous substructures in natural products and bioactive compounds. However, practical methods for the direct construction of phenols under mild conditions remains challenging. Herein, a photocatalytic acceptorless dehydrogenative aro-matization of cyclohexanones or cyclohexenones at room temperature has been developed. The reaction features the visible-light and cobalt co-catalyzed sequential dehydrogenation of in-situ formed enol silyl ethers, which are regarded as a challenging process. This operationally simple method enables the synthesis of a series of phenols with diverse substitution patterns from cyclohexanones or cyclohexenones. Moreover, diverse substituted 1,2-, 1,3-, and 1,4-benzenediols were obtained from cyclo-hexanediones, providing a general and straightforward method for the synthesis of phenols from simple starting materials un-der mild conditions

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Abstract: Phenols are ubiquitous substructures in natural products and bioactive compounds. However, practical methods for the direct construction of phenols under mild conditions remains challenging. Herein, a photocatalytic acceptorless dehydrogenative aromatization of cyclohexanones or cyclohexenones at room temperature has been developed. The reaction features the visible-light and cobalt co-catalyzed sequential dehydrogenation of *in-situ* formed enol silyl ethers, which are regarded as a challenging process. This operationally simple method enables the synthesis of a series of phenols with diverse substitution patterns from cyclohexanones or cyclohexenones. Moreover, diverse substituted 1,2-, 1,3-, and 1,4-benzenediols were obtained from cyclohexanediones, providing a general and straightforward method for the synthesis of phenols from simple starting materials under mild conditions.

Phenol and its derivatives widely exist in drug molecules,^[1] pesticide molecules,^[2] dyes,^[3] flavor components (Fig. 1).^[4] Moreover, phenols serve as important precursors for the synthesis of a range of value-added targets.^[5] Thus, the synthesis of phenols from diverse precursors has attracted great attention from the community.^[6] Industrial production of simple phenol is through Hock (cumene oxidation) process,^[7] accounting for annual production of more than 10⁶ tons. On the other hand, synthesis of phenols in laboratory heavily rely on nucleophilic substitution of arenes^[8] and transition metal-catalyzed coupling with oxygen-nucleophile reagent.^[9] Despite the massive progress, these methods typically require the use of strong bases^[10] and high temperatures.^[11] Moreover, phenols can also be prepared by oxidation the C-H bond of arenes^[12] or

arylboron compounds.^[13] However, these methods require the use of preformed aromatic compounds as precursors. Thus, developing the synthesis of phenol from non-aromatic compound precursors is attractive.

Figure 1 . Selected natural products and drug molecules containing phenols.

Scheme 1. Dehydrogenative strategies for cyclohexanone.

In 2011, Stahl reported the seminal work on the synthesis of phenols from cyclohexanones via a palladium-catalyzed oxidative aromatization strategy under 1 atm O₂ in DMSO at 80 °C.^[14] Cyclohexanones undergo α -C-H activation to form Pd(II) species, followed by C-H activation and β -H elimination to form cyclohexenones. Subsequently, cyclohexenone undergoes an iterative process to give the phenol product. Recently, Leonori reported the preparation of aniline from cyclohexanone under the dual catalytic conditions of photocatalyst and cobalt catalyst.^[15] Mechanistic studies reveal that in situ generated enamine undergoes two SET oxidations, deprotonation, and release of hydrogen. This method has achieved great success in the preparation of various substituted aniline compounds. However, the photocatalytic preparation of phenol from the simple cyclohexanones remains underdeveloped, partially due to the high oxidation of silyl enol ethers and their unproductive competing nucleophilicity. Herein, we reported a photocatalytic acceptorless synthesis of phenols from cyclohexanones at room temperature.^[16] The mild conditions allow for the direct dehydrogenative aromatization of cyclohexanones or cyclohexenones under the dual catalysis of light and cobalt, affording a wide range of phenols with diverse substitution patterns.

We started to investigate the feasibility of this proposal using 4-methylcyclohexanone (**1a**) as the prototype substrate (Table 1). After extensive evaluation, we define the use of 1 mol% of Ir(dF(CF₃)ppy)₂(4,4'-dCF₃bpy)(E^{*}_{red} = +1.65 V)^[17] and 5 mol% of Co(dmgH)₂(DMAP)Cl as catalyst, TIPSOTf (1.4 eq) as activating

Table 1 . Condition evaluation for the photocatalytic dehydrogenative phenol synthesis from cyclohexanones.^[a]

Entry	variation from "standard conditions"	yield of 2 ^[b]
1	none	89% (85%) ^[c]
2	[Ir(dF(CF ₃)-ppy) ₂ (5,5'-dCF ₃ -bpy)]PF ₆	81%
3	[Ir(dF(CF ₃)-ppy) ₂ (5,5'-dF-bpy)]PF ₆	71%
4	[Ir(dF(CF ₃)-ppy) ₂ (dtbbpy)]PF ₆	34%
5	Co(dmgH) ₂ PyCl	88%
6	Co(dmgH) ₂ Cl ₂	44%
7	Co(dmgBF ₂) ₂ ·H ₂ O	18%
8	TBSOTf	82%
9	TESOTf	6%
10	TMSOTf	5%
11	2,6-di-Me-Pyr	81%
12	DABCO	n.d.
13	DIPEA	n.d.
14	KOAc	n.d.
15	DCE	77%
16	DCM	61%
17	CH ₃ CN	45%
18	No light	n.d.
19	No PC or Co	n.d.

[a] Reaction was conducted using **1a** (0.2 mmol), TIPSOTf (0.28 mmol), [Ir(dF(CF₃)-ppy)₂(4,4'-dCF₃-bpy)]PF₆ (1 mol%), Co(dmgH)₂(DMAP)Cl (5 mol%), 2,4,6-tri-Me-Pyr (0.52 mmol) for 10 h in DCE/DCM = 3:2 (0.4 M) under two 30 W blue LEDs at rt unless otherwise stated. n.d. = not detected. [b] ¹H NMR

yield of crude mixture of reaction using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield.

reagent, 2,4,6-collidine (2.6 eq) as base in DCE:DCM = 3:2 (0.4 M) under blue LED irradiation at room temperature as the optimal reaction conditions, affording the desired phenol product **2** in 85% isolated yield (Table 1, entry 1). Replacing Ir(dF(CF₃)ppy)₂(4,4'-dCF₃bpy) with other Ir^{III} based photocatalysts could mediate the reaction, albeit leading to inferior results (Table 1, entries 2-4). Next, a survey of cobalt catalysts revealed that the cobalt catalyst with a pyridine coordination significantly enhanced the reaction. Other cobalt catalysts, such as Co(dmgH)₂Cl₂ and Co(dmgBF₂)₂·H₂O, could also catalyze the reaction, albeit with lower efficiency (Table 1, entries 5-7). Interestingly, evaluation of the activating reagent R₃SiOTf disclosed that the steric hindrance of the R group has a great influence on the reaction. Bulkier TBSOTf as the activating reagent delivered **2** in 82% yield (Table 1, entry 8). Using less hindered triethylsilyltriflate or trimethylsilyltriflate as activating reagents resulted in poor yields of **2** (Table 1, entries 9-10). This may be due to the stability of the corresponding enol silyl ether. The base was of critical importance for the reaction. Using 2,6-lutidine as base delivered **2** in 81% yield, yet the use of other organic or inorganic bases, such as DABCO, DIPEA and KOAc were totally ineffective (Table 1, entries 11 to 14). Solvent effect evaluation revealed that both 1,2-dichloroethane (DCE) and dichloromethane (DCM) are good solvents for this reaction, allowing the formation of **2** in 77% and 61% yields (Table 1, entries 15-17). Control experiments showed that light, photocatalyst and Co-catalyst are essential to this phenol synthesis (Table 1, entries 18 and 19).

With the optimized reaction conditions in hand, we set out to explore the scope of this transformation. First, the scope of cyclohexanone (**1**) was examined (Scheme 2). *para*-Substituted phenols, including alkyl- and aryl-substituted phenol derivatives (**2** - **5**), were accessed via the photocatalyzed dehydrogenative aromatization of the corresponding cyclohexanone derivatives. Cyclohexanones with an ester group at *para*-position were readily converted to the corresponding phenol products in 71%-91% yield (**6** - **13**). To our delight, alkenyl (**7**) and alkynyl groups (**8**) remain intact in this transformation, leaving chemical space for further elaboration. Notably, alkyl-Cl (**9**), aryl-Cl (**10**), and aryl-Br (**11**) were well-tolerated, providing further functionalized handles for cross-coupling reaction. Notably, 2-substituted cyclohexanones were successfully transformed corresponding *ortho*-substituted phenols (**14** - **16**) in 40%-67% yields. Next, aryl fused cyclohexanones were tested. Electron-withdrawing and electron-donating groups on aromatic rings can be tolerated, affording corresponding 1- and 2-naphthol products (**17** - **24**) in 50%-92% yields. Moreover, heterocycles including thiophenes (**12** and **25**), furans (**13**) and pyrroles (**26**), were also compatible in the reaction. Interestingly, 1,2-, 1,3-, and 1,4-cyclohexanediones could be applied to this reaction, furnishing the corresponding diphenol products (**27** - **30**) in synthetic useful yields. Finally, complex molecule-derived cyclohexanones were also successfully applied to the reaction. Cyclohexanones containing *L*-menthol, (+)-fenchol, diacetonefructose, cholesterol and diosgenin, were smoothly converted to the corresponding phenol products (**31** - **35**) in 69-81% yields.

Next, further extension of this phenol synthesis protocol to cyclohexenones was examined (Scheme 3). 2-Aryl substituted cyclohexenones, with different substituent groups on the benzene ring were good substrates for this photocatalytic dehydrogenative reaction, affording corresponding 2-arylphenol products (**16**, **36** - **39**) in 63-71% yields. Diverse 3-aryl substituted phenols (**40** - **45**) were also obtained in moderate yields via the dehydrogenation of corresponding 3-aryl cyclohexenones. Additionally, 3,5-disubstituted phenols (**46** - **56**) could be obtained from cyclohexenones in synthetic useful yields. It is noteworthy that 3,5-disubstituted phenol derivatives are ubiquitous core structures for many bioactive molecules,^[18] yet are inaccessible

Scheme 2. Scope for the synthesis of phenols from cyclohexanones. For the details of "standard conditions", see Table 1, entry 1. [a] 2,6-di-Me-Pyr as base. [b] 24 h. [c] TIPSOTf (1.6 eq), 2,4,6-tri-Me-Pyr (2.8 eq), CH₃CN (0.4 M). [d] TIPSOTf (2.6 eq), 2,4,6-tri-Me-Pyr (3.8 eq). [e] 2,6-di-Me-Pyr as base, 14 h.

by electrophilic aromatic substitution of phenols.^[19] The structure of **51** was ambiguously confirmed by X-ray diffraction analysis. To further demonstrate practicality of the protocol for the synthesis of phenols, the reaction was scaled up to 2.0 mmol scale using 4-acetoxycyclohexanone **1e**, delivering corresponding phenol **6**

in 78% yield (Scheme 4a). Next, the reaction of 3,5-diaryl-substituted phenol product **47** with cyclopentyl isocyanate afforded biologically active compound LUF5771 in 76% yield (Scheme 4b).^[20]

To shed light on the reaction mechanism, a series of controlled experiments were conducted. First, the reaction was carried out in the presence of TEMPO as a radical scavenger under otherwise identical to standard conditions, the desired transformation was completely inhibited (Scheme 5a). Second, 4-methylcyclohexanone **1a** delivered silyl enol ether **1bf** in 97% yield in dark under otherwise identical to standard conditions (Scheme 5b). Interestingly, **1bf** was successfully converted to phenol **2** in 78%% yield in the presence of 20 mol% trifluoromethanesulfonic acid under otherwise identical to standard conditions (Scheme 5b). These experiments suggest that the silyl enol ether may serve as key intermediate in the reaction. Moreover, the reaction of silyl enol ether **1be** under standard conditions in the presence of benzalmalononitrile **1bg** delivered **57** in 85% yield (dr = 2:1). Alternatively, the reaction of silyl enol ether **1be** under standard conditions in the presence of α,β -unsaturated sulfones **1bh** afforded β -substituted cyclohexanone **58** in 69% yield (Scheme 5c). The results indicate the reaction is likely to undergo an allylic radical intermediate. In

Scheme 3. Scope for the synthesis of phenols from cyclohexenones. See Table 1, entry 1 for detailed conditions. [a] 24 h. [b] TIPSOTf (1.6 eq), 2,4,6-tri-Me-Pyr (2.8 eq), CH₃CN (0.4 M).

addition, Stern–Volmer luminescence quenching experiments were performed. Both 4-methylcyclohexanone and 2,4,6-collidine did not show significant quench of the excited state of photocatalyst [Ir(III)]^{*}. Silyl enol ether showed a relatively strong quenching effect to the excited photocatalyst (Scheme 5d). These observations confirmed that the reaction was initiated by the single-electron oxidation of silyl enol ether by photocatalyst.

Based on literature reports and the above mechanistic investigations, a plausible mechanism is proposed and depicted in Scheme 6.^[21] First, reaction of 4-methylcyclohexanone **1** and TIPSOTf led to the in situ generation of silyl enol ether **A**, which was oxidized by the excited-state photosensitizer [Ir(III)]^{*} to give radical cation species **B** and [Ir(II)]. Next, **B** was deprotonated at the acidic β -methylene position in the presence of a base to give the allylic radical **C**, which was then trapped by Co(II), followed by β -H elimination to deliver the silyl dienol ether intermediate **D** and cobalt(III) hydride species. Subsequently, Co((III)-H species was protonated to release H₂ and regenerate Co^{III}(dmgH)₂(DMAP)Cl. Single electron transfer between Ir(II) and Co^{III}(dmgH)₂(DMAP)Cl generated Ir(III) and Co(II) to close the photoredox catalysis cycle. Silyl dienol ether **D** repeated first catalytic cycle to give the silyl ether of phenol **F**, which was deprotected by tetrabutylammonium fluoride to give the target phenol product **2**.

In summary, a general photocatalytic dehydrogenative aromatization of cyclohexanones or cyclohexenones phenols has been developed. The mechanistic investigations indicate that the reaction undergoes a dual catalyzed free radical cation process of the enol silyl ether. The reaction features the synthesis of phenols from cyclohexanones and cyclohexenones with diverse

Scheme 4. Scale-up and application experiments.

substitution patterns, which are difficult to access otherwise. This one-pot procedure circumvents the preformation of silyl enol ethers from cyclohexanones, providing a direct and straightforward access to phenols.

Scheme 5. Mechanistic investigations.

Scheme 6 . Proposed mechanism for the reaction.

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Keywords: Phenols * Photocatalysis * Dehydrogenation * Cyclohexanone * Cobalt catalyst

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