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Conversion of Simple Cyclohexanones into Catechols

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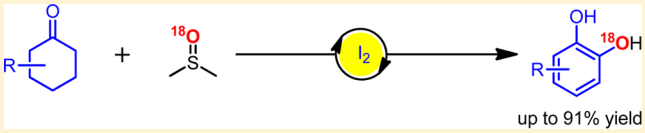
Supporting Information

ABSTRACT: A novel I_2-catalyzed direct conversion of cyclohexanones to substituted catechols under mild and simple conditions has been described. This novel transformation is remarkable with the multiple oxygenation and dehydrogenative aromatization processes enabled just by using DMSO as the solvent, oxidant, and oxygen source. This metal-free and simple system demonstrates a versatile protocol for the synthesis of highly valuable substituted catechols and therefore streamlines the synthesis and modification of biologically important molecules for drug discovery.



INTRODUCTION

Catechols are ubiquitous structural motifs of various natural products, bioactive molecules, and drugs (Figure 1).[1] There are more than 300 000 compounds containing a catechol component that bear useful pharmacological activity. Moreover, catechols are also used extensively in the chemical industries, and more than 3.0×10^7 kg/year are produced.[2] Hence, the development of a simple and efficient approach to substituted catechols is of considerable interest. The traditional synthetic methodologies generally involve an *ortho*-formylation of phenols followed by a subsequent Dakin oxidation or oxidation of phenols into *ortho*-quinones with subsequent reduction (Scheme 1a).[3] However, these approaches always provide lower regioselectivity and afford a mixture of *ortho*-, *meta*-, and *para*-isomers. Recently, transition-metal-catalyzed directing group assisted C−H bond hydroxylation[4,5] of phenol derivatives has been significantly developed, which features high site selectivity and a broad functional group tolerance (Scheme 1b).[6] However, multistep procedures with charging and removing the directing groups of aromatic substrates and the requirement of transition-metal catalysis with strong oxidants limit their application.

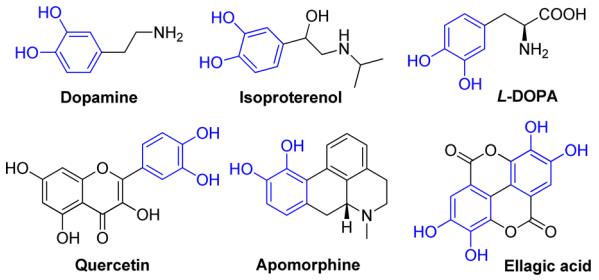
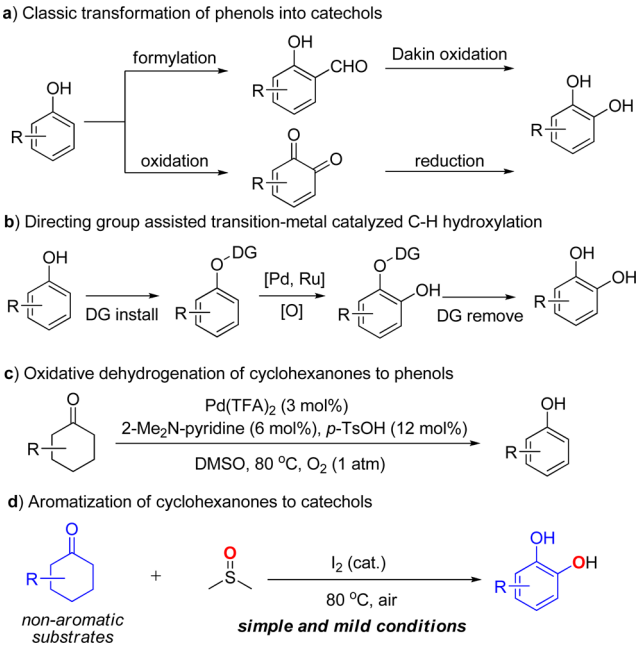


Figure 1. Natural products and drugs with catechol substructure.

Scheme 1. Strategies for the Synthesis of Catechols or Phenols



Cyclohexanones are cheap, stable, and readily available bulk chemicals.[7] Therefore, the selective dehydrogenative aromatization of cyclohexanones has been widely used as a complementary and attractive approach to substituted phenols, even with required stoichiometric oxidants such as DDQ or harsh conditions (≥200 °C).[8] Especially, the Stahl group recently developed an elegant Pd-catalyzed aerobic dehydro-

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genation of cyclohexanones for the synthesis of phenols (Scheme 1c),[9] which significantly improved the wide application of cyclohexanones for the synthesis of aromatic molecules. In contrast, to the best of our knowledge, the direct transformation of this cheap bulk chemical cyclohexanone to catechols is still unknown because there are two challenging issues: (1) One oxygen atom lacks from cyclohexanones to catechols which requires an additional O source. Generally, the O-incorporation process is very complicated as reported in the reported methods (Scheme 1a-b). (2) The transformation from cyclohexanones to catechols requires multiple processes including oxygenation, oxidation, and aromatization, which should be efficient, compatible, and orderly in good relay.

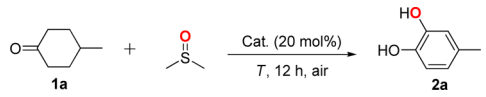
Herein, we describe a novel I_2-catalyzed aromatization of cyclohexanones for the synthesis of substituted catechols with simple DMSO as the solvent, hydrogen acceptor, and oxygen source (Scheme 1d). The advantages of the current protocol can be summarized as follows: (1) This is a novel and efficient metal-free approach to catechols. The simple and readily available I_2 has emerged as an efficient catalyst instead of a transition metal catalyst which is often expensive and required to be completely removed from products especially in the synthesis of pharmaceutical compounds.[10] (2) DMSO, a cheap and common solvent which has been widely used as a nontoxic solvent with no risk to human health by the U.S. Environmental Protection Agency (EPA),[11] was employed as a mild oxidant and oxygen source. Therefore, the I_2–DMSO system is simple, mild, practical, and easily handled and shows great potential for industrial applications. (3) A diverse range of readily available cyclohexanones could be used for the synthesis of high-value substituted catechols. The modification of bioactive compound could also be applied by this protocol.

RESULTS AND DISCUSSION

Inspired by recently developed DMSO oxidative reactions,[12,13] we envisioned that halide-containing reagent could be used as the catalyst for the oxygenation of the C–H bond. At the outset of our study, we examined the reaction of 4-methylcyclohexanone **1a** with DMSO as solvent and oxidant (Table 1). Disappointingly, no reaction was observed when KI was employed as catalyst (entry 1). To our surprise, the hydroxylation and aromatization product, 4-methylcatechol **2a**, was obtained as the unexpected product in 51% yield when NIS was used as the catalyst (entry 2). Subsequently, various iodide-containing reagents were investigated. Among them, HI was also an efficient catalyst for this transformation (entry 3), whereas ZnI_2, NH_4I, and TBAI failed to give the product (entries 4–6). To our delight, the yield of 4-methylcatechol could be improved to 62% when I_2 was employed as the catalyst (entry 7). The yield decreased significantly when the reaction was conducted at lower (60 °C) or higher temperature (100 °C) (entries 8 and 9). Only a trace amount of product was observed when the reaction was carried out in other solvents such as DCE, CH_3CN, dioxane, or CH_3NO_2 (entries 10–13). The reaction failed to give product in the absence of I_2 catalyst (entry 14). It is noteworthy that this transformation worked well under Ar atmosphere, which indicates that the terminal oxidant was DMSO (entry 15).

Subsequently, the scope of this oxidative aromatization of various cyclohexanones for the synthesis of monosubstituted catechols was investigated (Table 2). Cyclohexanones bearing an alkyl substituent at the *para* position were smoothly converted to the corresponding products **2a–2f** in good yields.

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	solvent	temp (°C)	yield[b] (%)
1	KI	DMSO	80	0
2	NIS	DMSO	80	51
3	HI	DMSO	80	43
4	ZnI_2	DMSO	80	0
5	NH_4I	DMSO	80	trace
6	TBAI	DMSO	80	0
7	**I_2**	**DMSO**	**80**	**62**
8	I_2	DMSO	60	21
9	I_2	DMSO	100	26
10[c]	I_2	DCE	80	trace
11[c]	I_2	CH_3CN	80	trace
12[c]	I_2	dioxane	80	trace
13[c]		CH_3NO_2	80	trace
14	–	DMSO	80	0
15[d]	I_2	DMSO	80	58

[a]Reaction conditions: **1a** (0.5 mmol), cat. (20 mol %), solvent (1 mL), under air for 12 h. [b]Isolated yields. [c]With 3.0 equiv of DMSO. [d]Under argon atmosphere.

Aryl-substituted cyclohexanones such as 4-phenylcyclohexanone **1g** and 4-(4-hydroxyphenyl)-cyclohexanone **1h** also participated well in this process, converting to the corresponding products **2g** and **2h** efficiently. To our delight, functional groups, such as cyano, aldehyde, ester, carboxyl, and amide groups, were all well tolerated in this transformation to afford the corresponding products **2i–2m** in excellent yields. When 4-hydroxycyclohexanone was used as the substrate, catechol **2n** could be obtained under the standard conditions. Moreover, interesting results were also observed for 4-methoxy or pivalate-substituted cyclohexanone that catechol **2n** was formed via 4-oxygen-substitutent elimination, which indicates that a reverse Michael addition reaction may occur in these reactions.

Interestingly, the reaction of 3-ester and carboxyl-substituted cyclohexanones **1q** and **1r** selectively generated **2k** and **2l** as the product, respectively, which is consistent with the reaction of the corresponding 4-substituted cyclohexanones **1k** and **1r**, which indicates that the oxygenation step highly regioselectively occurred at the less hindered position of the ketone group. This reaction is sensitive to 2-substituents, affording 3-substituted catechols **2s–2u** in relatively low yields. When 2-ester-substituted cyclohexanone was tested, the catechol **2v** and pyrogallol **2v′** products were obtained in a combined yield of 79%. Moreover, the reaction of **1g** could be easily performed in gram scale affording **2g** in 72% yield.

3,3′,4,4′-Tetrahydroxybiphenyl **3** could inhibit the aggregation of Alzheimer's amyloid-β peptide (Aβ).[14] Furthermore, it has been widely used as a ligand for transition metals in coordination chemistry.[15] This valuable molecule was synthesized by the traditional Pd-catalyzed Suzuki coupling of 3,4-dimethoxyphenylboronic acid **4** with 3,4-dimethoxybromobenzene **5** followed by the cleavage of the methyl ethers with boron tribromide.[14] However, the harsh reaction conditions result in low yields of the biaryl intermediate and the desired 3,3′,4,4′-tetrahydroxybiphenyl (48% and 43% yields, respectively). In contrast, it can be easily prepared from 4,4′-bicyclohexanone **6**, a simple and readily commercially available substrate which could be simply prepared from 1,4-cyclohexadione,[16] in 51%

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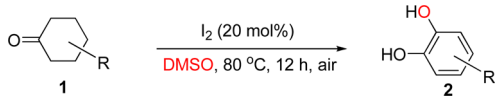
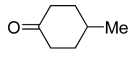
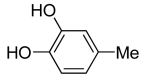
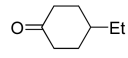
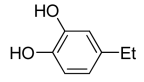
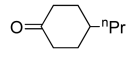
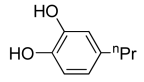
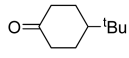
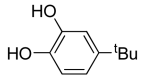
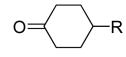
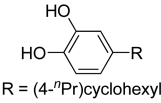
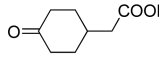
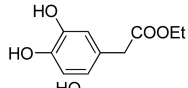
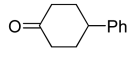
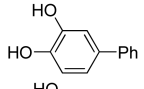
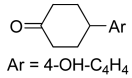
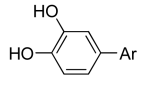
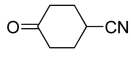
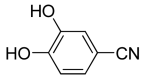
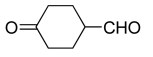
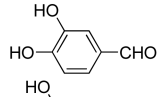
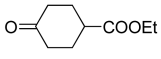
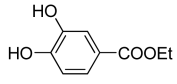
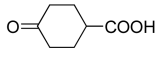
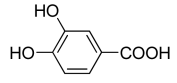
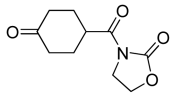
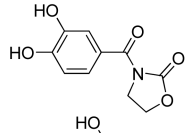
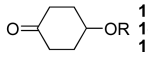
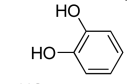
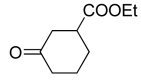
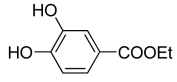
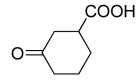
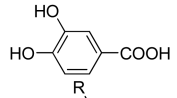
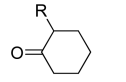
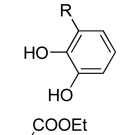
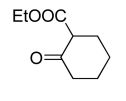
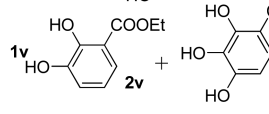
Table 2. Conversion of Cyclohexanones to Catechols[a]

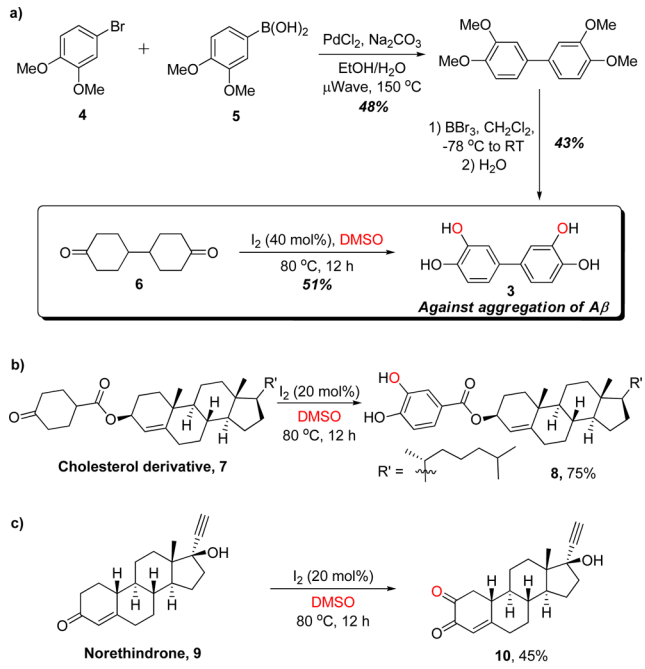


entry	substrate		product	yield[b]
1		**1a**		**2a**, 62%
2		**1b**		**2b**, 65%
3		**1c**		**2c**, 60%
4		**1d**		**2d**, 58%
5		**1e**	 R = (4-^{n}Pr)cyclohexyl	**2e**, 43%
6		**1f**		**2f**, 41%
7		**1g**		**2g**, 74% 72%[c]
8	 Ar = 4-OH-C$_4$H$_4$	**1h**		**2h**, 73%
9		**1i**		**2i**, 86%
10		**1j**		**2j**, 81%
11		**1k**		**2k**, 84%
12		**1l**		**2l**, 84%
13		**1m**		**2m**, 71%
14 15 16		**1n**, R = H **1o**, R = Me **1p**, R = Piv		R = H, 63% **2n**, R = Me, 63% R = Piv, 91%
17		**1q**		**2k**, 53%
18		**1r**		**2l**, 63%
19 20 21		**1s** **1t** **1u**		**2s**, R = CH$_3$, 16% **2t**, R = Bn, 21% **2u**, R = Ph, 23%
22		**1v**	 **2v** + **2v'**	**2v+2v'**, 79%[d]

[a]Reaction conditions: monosubstituted cyclohexanones **1** (0.5 mmol), I_2 (20 mol %), and DMSO (1 mL), under air, at 80 °C for 12 h. [b]Isolated yields. [c]Gram scale. [d]**2v** (23%), **2v′** (56%).

yield by this present approach (Scheme 2a). It also should be mentioned that the complete removal of Pd catalyst from products is avoided by the present protocol.

Scheme 2. Synthetic Utilities of this Protocol



Within the broad substrate scope and the mild reaction conditions, we applied the present method to the diversification of bioactive molecules. Remarkably, the derivative of cholesterol **7** could be converted to catechol product **8** in good yield under the standard conditions without affecting the complex steroid structure (Scheme 2b). Interestingly, norethindrone **9** delivered the α-carbonylation product **10** instead of the aromatization product in moderate yield (Scheme 2c), providing valuable information for the reaction mechanism.

When the reaction of **1g** was performed with ^{18}O-labeled DMSO, the ^{18}O-labeled product ^{18}O-**2g** was detected, along with the O-isotope exchange product **2g** and $^{18}O_2$-**2g**, with the ratio of 1:0.28:1.03 based on HRMS analysis (Scheme 3a). When 3.0 equiv of $H_2{}^{18}O$ was added into the control reaction of **2g** under the standard conditions, the three products could also be obtained with the ratio 1:0.52:0.52 (Scheme 3b). Interestingly, the I_2 catalyst is essential for the O-isotope exchange, and DMSO is not required (Scheme 3b). The above ^{18}O-labeling experiments suggest that the additional oxygen atom in the catechol product is original form DMSO, and the O-isotope exchange products are probably generated from exchange with $H_2{}^{18}O$, which was the byproduct in the ^{18}O–DMSO oxidative regeneration of iodine catalyst (for a proposed mechanism for O-exchange, see SI). In contrast to the reaction of **1g**, the corresponding cyclohexenone **11** reacted under the standard conditions to afford the phenol product **12** instead of the catechol product **2g**, which excludes the possibility of the cyclohexenone intermediate for the formation of catechol product (Scheme 3c). Although the α-iodo cyclohexanone was not detected by GC-MS and NMR analysis during the reaction, when 2-iodo-4-phenylcyclohexanone **13** was employed as the starting material under the standard conditions, **2g** was selectively obtained in 77% yield (Scheme

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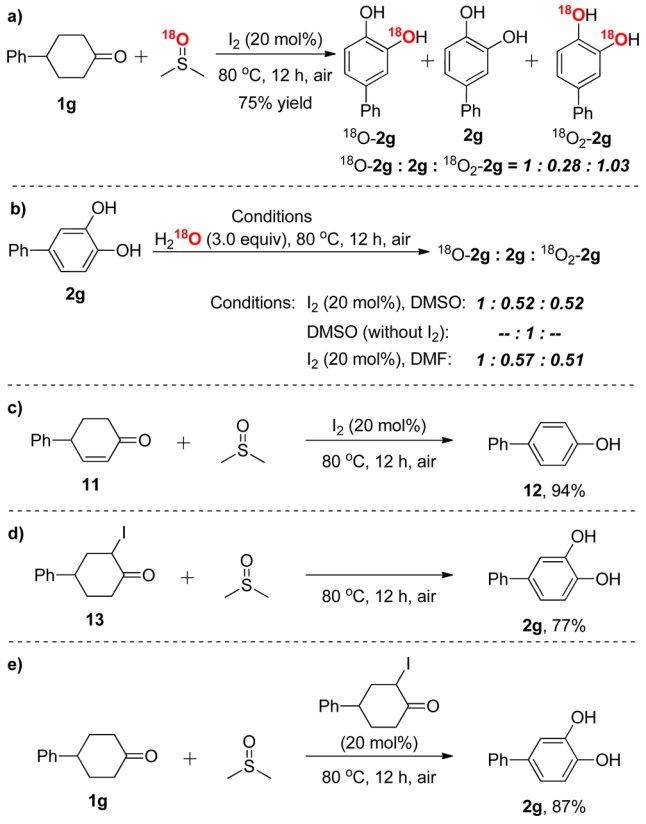
Scheme 3. Mechanistic Studies

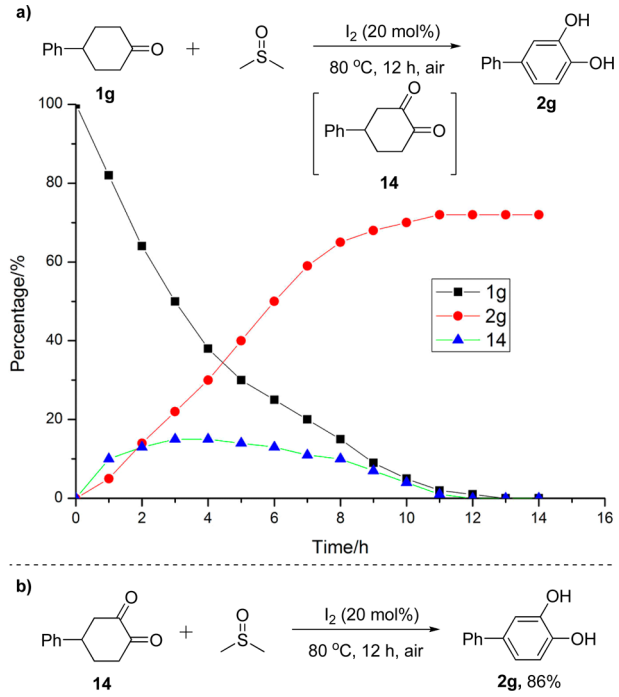


3d). Moreover, the reaction of **1g** with DMSO could also proceed efficiently when **13** was used as catalyst (Scheme 3e), which indicates that α-iodo cyclohexanone is a possible intermediate for this reaction.

The reaction result of norethindrone **9** (Scheme 2c) suggested that the cyclohexane-1,2-dione may also be the reaction intermediate in the transformation. To explore whether this reaction went through the cyclohexane-1,2-dione intermediate specifically, we monitored the reaction kinetics. The kinetic time course revealed the formation and disappearance of the 1,2-cyclohexanedione intermediate (Scheme 4a). In addition, when 4-phenylcyclohexane-1,2-dione **14** was tested as the substrate, **2g** was isolated in 86% yield (Scheme 4b). These results demonstrate that the corresponding cyclohexane-1,2-dione is another key intermediate of this novel transformation.

To further understand the mechanism of this transformation and the chemoselectivity between catechol and phenol, we conducted a density functional theory (DFT) calculation investigation into the aromatization reaction of 4-phenylcyclohexanone **1g** and 4-phenylcyclohexenone **11** as model reactions (Figure 2a).[17] After iodination of **1g**, the formed iodocyclohexanone could undergo the key step of S_N2 or E2 reactions with DMSO to provide catechol or phenol, respectively. The S_N2 reaction of iodocyclohexanone with DMSO undergoing Kornblum reaction[18] using DMSO as the O-source[19] via transition states **TSa-S$_N$2-1g** and **TSe-S$_N$2-1g** requires an activation free energy of 27.6 and 20.1 kcal/mol to afford catechol. The iodocyclohexanone undergoes an alternative pathway corresponding to the E2 process with DMSO with an activation free energy of 27.9 and 23.3 kcal/mol to form phenol. **TSe-S$_N$2-1g** is 3.2 kcal/mol lower in energy than

Scheme 4. Kinetic Profile and Conformed Reaction



TSa-E2-1g, and this difference is qualitatively consistent with the experimentally observed good chemoselectivity for the catechol **2g** formation under the standard conditions. When **11** was used as the starting material, the S_N2 reaction via transition states **TSa-S$_N$2-11** and **TSe-S$_N$2-11** requires an activation free energy of 31.3 and 27.5 kcal/mol to afford catechol. An alternative pathway corresponds to the E2 process with DMSO with an activation free energy of 22.1 and 27.2 kcal/mol to form the phenol product. As a result, **TSa-E2-11** is favored over **TSe-S$_N$2-11** by 5.4 kcal/mol, once again in complete accord with the experimental good chemoselectivity for the phenol **12** formation. The low energy for **TSa-E2-11** may be attributed to the formation of π-conjugated system and large dipole moment in the transition state. In the case of **1g**, the E2 process with DMSO is no more stabilized by the π-conjugated system, making the S_N2 reaction kinetically favorable. Our calculation further confirms that the chemoselectivity for the catechol and phenol formation also has universality, in which monosubstituted cyclohexanone tends to give catechol product, while cyclohexenone is favored to deliver phenol product.

Moreover, for the multisubstituted cyclohexanones, the calculation of 3,5-dimethylcyclohexanone **I** as a model substrate indicates that the **TS-S$_N$2-I** is less stable over 4.3 kcal/mol than **TS-E2-I** (Figure 3), which suggests that phenols would be predicted to be formed instead of catechols. In order to further understand the DFT calculation, the transformation of multisubstituted cyclohexanones under the present conditions was investigated (Table 3). In accordance with the DFT calculation, the corresponding phenols were formed as the product in most cases with multisubstituted cyclohexanones (Table 3). It should be noted that although the transition-metal-catalyzed oxidative dehydrogenation[20] of cyclohexanones for the synthesis of phenols is known,[9,21] to the best of our knowledge, this is the first example of metal-free oxidative transformation of cyclohexanones to phenols.

Although the mechanism is not completely clear yet, a possible reaction pathway for the formation of catechols is

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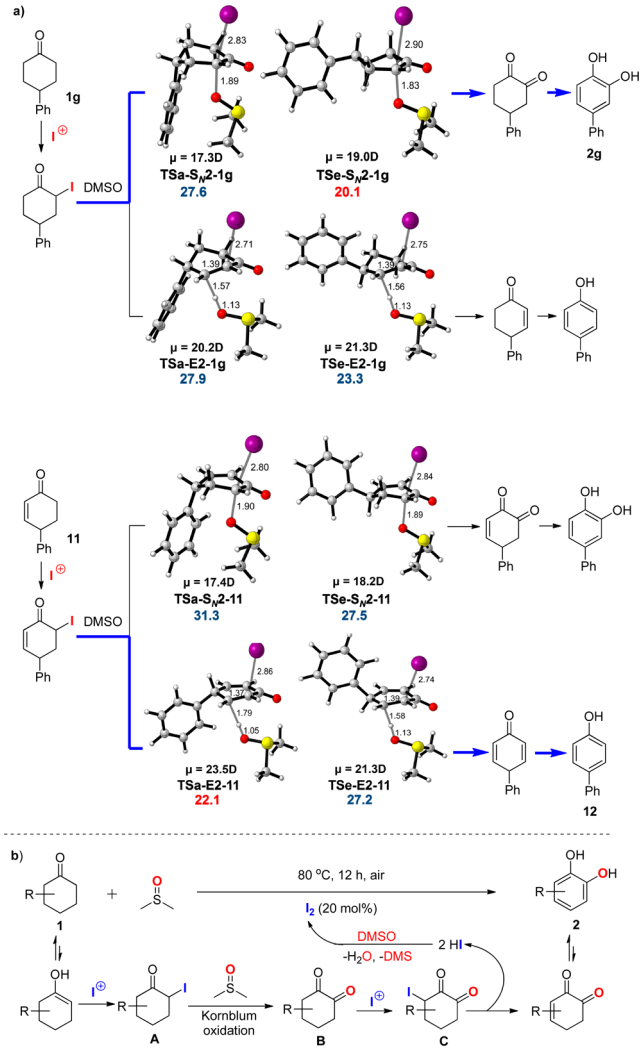


Figure 2. DFT calculation and the proposed mechanism.

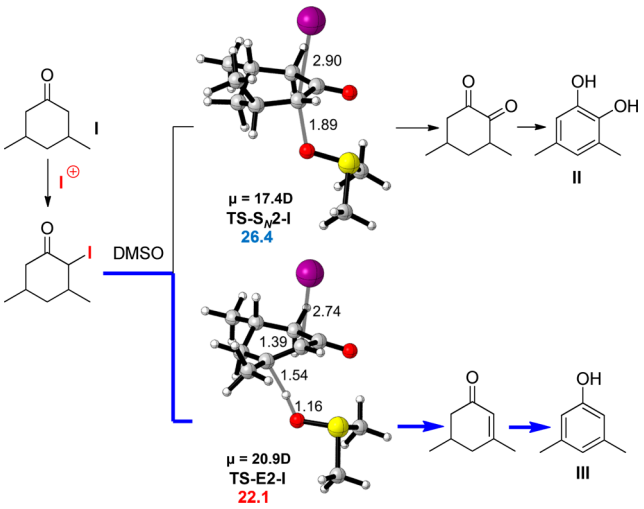
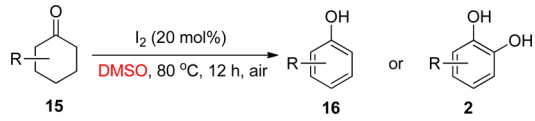
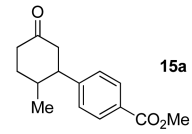
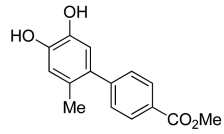
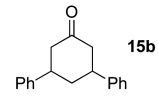
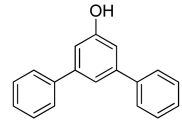
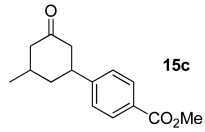
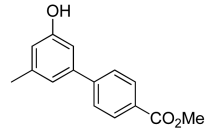
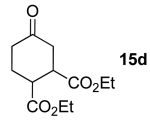
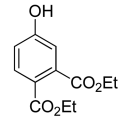
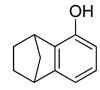
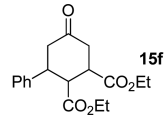
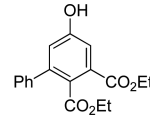


Figure 3. DFT calculation for multisubstituted cyclohexanones.

proposed (Figure 2b). Initially, electrophilic iodization of cyclohexanones by the iodine catalyst occurs to afford α-iodo cyclohexanones **A**, and then Kornblum oxidation[18] occurs to generate 1,2-cyclohexanediones **B**, followed by further α-iodization to give intermediates **C**. Subsequently the intermediates **C** undergo HI elimination and then tautomerize to afford catechol products. The oxidation of HI in the presence of DMSO would generate $(CH_3)_2S$ and H_2O and regenerate iodine catalyst for the next catalytic cycle.[22] In addition, dimethyl sulfide was detected by GC-MS analysis of reaction products. The whole energy profiles were calculated to better understand the mechanism (see Figure S1 in SI for detail).

Table 3. Oxidation of Multisubstituted Cyclohexanones[a]



entry	substrate	product	yield[b]
1	 **15a**		**2w**, 33%
2	 **15b**		**16b**, 85%
3	 **15c**		**16c**, 40%
4	 **15d**		**16d**, 61%
5	 **15e**		**16e**, 25%
6	 **15f**		**16f**, 59%

[a]Reaction conditions: multisubstituted cyclohexanones **15** (0.5 mmol), I_2 (20 mol %), DMSO (1 mL), under air, at 80 °C for 12 h. [b]Isolated yields.

CONCLUSION

In summary, we have developed a unique I_2-catalyzed aromatization of easily accessible cyclohexanones for the synthesis of substituted catechols via selective oxygenation and dehydrogenation processes. The usage of inexpensive DMSO as the oxidant, oxygen source, and solvent with easy operation makes this protocol very green and practical. The current method also provides an efficient and concise synthetic methodology to valuable aromatic compounds. The modification of bioactive compounds could also be applied by this protocol. Further studies to elucidate the detailed reaction mechanism and synthetic applications are in progress in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07269.

Experimental procedures, analytical data for products, and NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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