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Iodine-Catalyzed Oxidative Aromatization: A Metal-Free Concise Approach to *meta*-Substituted Phenols from Cyclohex-2-enones

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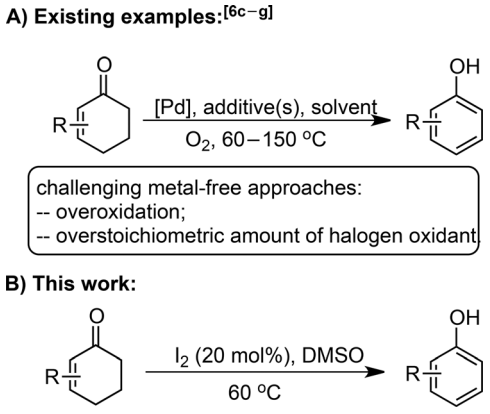
Abstract: A metal-free approach to *meta*-substituted phenols from cyclohex-2-enone *via* catalytic oxidative aromatization has been developed. The transformations are initiated with a catalytic amount of molecular iodine as the direct oxidant, while dimethyl sulfoxide is employed as the terminal oxidant. This practical approach is capable of avoiding the use of metal promoters and costly reagents, the lengthy synthesis, and overoxidation of products, and thus facilitates the efficient construction of *meta*-substituted phenol derivatives from inexpensive commercial chemicals under mild conditions. The synthetic utility of this approach is evident in the *de novo* syntheses of two bioactive molecules with good total yields, in which easily available chemicals were employed, protective groups were not utilized, and no unwanted carbon atoms were removed in each step.

Keywords: enones; iodine; oxidative aromatization; phenols; synthetic methods

Introduction

Phenols are ubiquitous in nature and have a variety of applications in synthetic organic chemistry as valuable precursors in the construction of natural products, bioactive compounds, fine chemicals, and functional materials.[1] Conventional strategies for the syntheses of substituted phenols relied on functionalizations and functional group transformations around the periphery of a preexisting aromatic ring such as selective hydroxylations of benzenes, nucleophilic and electrophilic aromatic substitutions, and metal-catalyzed cross-coupling reactions.[2] These strategies enriched straightforward routes to *ortho*- and *para*-substituted phenols. By contrast, the regiospecific synthesis of *meta*-substituted phenols through such strategies frequently suffered from tedious multistep synthesis or pre-installation of directing groups due to the fact that regioselectivities strongly depend on electronic effects in aromatic substitution chemistry.[3,4] Accordingly, oxidative aromatization of non-aromatic precursors provides an alternative choice.[5] Very recently, several research groups have made extensive progress in the metal-catalyzed oxidative aromatization of cyclohexenones to phenols (Scheme 1A).[6] However, the advances on related metal-free approaches have been frustrating, particularly in relation to the overoxidation of products, a competitive reaction with oxidative aromatization because of the susceptibility of phenols under the oxidative conditions. In order to bypass the problem, the existing examples employed indirect protocols by the installation of groups in advance at the susceptible positions of phenols to prevent overoxidation or by the use of preoxidized substrates through eliminative aromatization to keep the oxidants away from phenols.[7] Therefore, it would be of significant importance to develop a direct protocol



Scheme 1. Catalytic oxidative aromatization of substituted cyclohex-2-enones to phenols.

so that *meta*-substituted phenols can be regiospecifically and facilely achieved in the absence of metal promoters, but would not be overoxidized.

Molecular iodine has been a catalyst with substantial applications in various organic reactions.[8] It is widely available, relatively inexpensive, stable toward air and moisture, and of low toxicity. Nevertheless, there are no synthetic methodologies to substituted phenols involving iodine-catalyzed oxidative aromatization.[7j] Here we report an unprecedented approach to phenols catalyzed by molecular iodine (Scheme 1B). This finding provides a general access to *meta*-substituted phenols in which metal catalysts are unnecessary while the lengthy synthesis and overoxidation of products can be avoided.

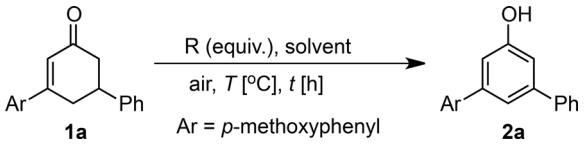
Results and Discussion

At the outset of the investigation, we chose 3,5-diarylcyclohex-2-enone **1a** as the substrate in the model reaction (Table 1) since it could be prepared readily from easily available starting materials (*p*-methoxyacetophenone, benzaldehyde, and acetone). It was disclosed in previous research that the dehydrogenative oxidation of alcohol was achieved with molecular iodine in the presence of potassium *tert*-butoxide at 10 °C.[9] However, **1a** could not be oxidized under similar conditions (Table 1, entry 1). The use of *tert*-butyl alcohol as solvent led to the consumption of **1a**, but no desired product was isolated (entries 4 and 5). Meanwhile, we noticed that molecular iodine itself was capable of oxidizing cyclohex-2-enones in an appropriate solvent (entries 8 and 9).[10] Therefore, dimethyl sulfoxide (DMSO) was tested as solvent at a moderate temperature, and the desired phenol was obtained in 96% yield by the use of a stoichiometric amount of iodine (entry 10). This promising result encouraged us to conduct the reaction with a catalytic amount of iodine. Fortunately, **2a** was obtained in excellent yield with extension of the reaction time by the use of 20 mol% of iodine (entries 11 and 12). Significantly, the transformation worked well at a wide range of temperature (60–100 °C). When the temperature was lower than 60 °C, the reaction was slow (entries 13–16). Thus, 60 °C was the optimal temperature for the transformation. The experiments on halogen source screening showed that NIS was slightly less efficient than molecular iodine, whereas NCS, NBS and KI failed to produce **2a** at 60 °C (entries 20–24).

To assess the scope of the present approach, various 3,5-disubstituted cyclohex-2-enones were prepared, and they were examined under the optimized reaction conditions (Table 2). An array of 3,5-disubstituted phenols **2a–r** was obtained in mostly excellent yields from readily available starting materials. No overoxidized products were observed in all the cases.[11] Generally, the substrates containing electron-donating substituted aryl groups at the 5-position were less active than those containing electron-withdrawing groups (entries 1–6 *vs.* 7 and 8). Nevertheless, the conversions of sluggish substrates, especially those containing an electron-rich aryl at 5-position, such as **1g** and **1h** (entries 7 and 8), could be realized in good yields through extension of the reaction time.

On the other hand, the aryls at the 3-position of cyclohex-2-enones had insignificant impacts on the reactivity. The substrates bearing either an electron-rich or electron-poor phenyl at the 3-position of the cyclohex-2-enone ring were smoothly transformed into the desired phenols under the standard conditions (entries 1–6 and 9–12).

Table 1. Optimization of the reaction conditions.[a]



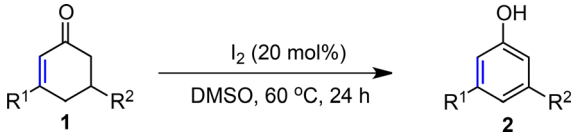
Entry	R (equiv.)	Solvent	*T* [°C]	*t* [h]	Yield [%]
1	I_2 (1)/*t*-BuOK (2)	DCM	10	12	N.R.
2	I_2 (2)	*t*-BuOH	85	8	N.R.
3	I_2 (1)/CuO (1)	*t*-BuOH	80	8	N.R.
4	I_2 (1)/*t*-BuOK (2)	*t*-BuOH	25	8	0[b]
5	I_2 (1)/*t*-BuOK (3)	*t*-BuOH/DCM	25	24	0[c]
6	I_2 (1)/*t*-BuOK (3)	Et_2O	25	24	0[c]
7	I_2 (1)/*t*-BuOK (3)	MeCN	25	24	0[c]
8	I_2 (4)	DME	85	4	0[b]
9	I_2 (0.2)	DME	60	12	0[c]
10	I_2 (1)	DMSO	60	8	96
11	I_2 (0.2)	DMSO	60	20	95
12	I_2 (0.2)	DMSO	60	24	96
13	I_2 (0.2)	DMSO	r.t.	12	trace
14	I_2 (0.2)	DMSO	50	12	78
15	I_2 (0.2)	DMSO	80	20	94
16	I_2 (0.2)	DMSO	100	20	92
17	I_2 (0.2)	CH_3CN	60	12	N.R.
18	I_2 (0.2)	toluene	60	12	N.R.
19	I_2 (0.2)	THF	60	12	N.R.
20	–	DMSO	60	12	N.R.
21	NIS (0.2)	DMSO	60	24	94
22	NCS (0.2)	DMSO	60	12	N.R.
23	NBS (0.2)	DMSO	60	12	N.R.
24	KI (0.2)	DMSO	60	12	N.R.

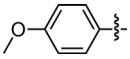
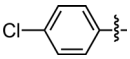
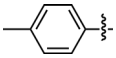
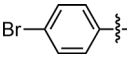
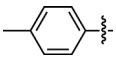
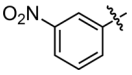
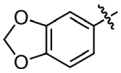
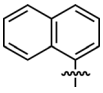
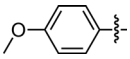
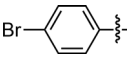
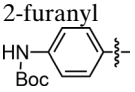
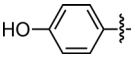
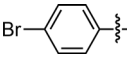
[a] *Reaction conditions*: **1a** (0.2 mmol), solvent (1 mL) under air. Yield of isolated product. NIS = *N*-iodosuccinimide, NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide, N.R. = no reaction.

[b] Thin-layer chromatography (TLC) indicated that **1a** was completely transformed into a complicated mixture, and no confirmed compound was identified.

[c] TLC indicated that **1a** was partially transformed into a complicated mixture, but no confirmed compound was identified.

Table 2. Substrate scope of the catalytic oxidative aromatization of 3,5-disubstitued cyclohex-2-enones.[a]



Entry	R^1	R^2	1/2	Yield
1		Ph	**1a/2a**	96%
2		Ph	**1b/2b**	94%
3		Ph	**1c/2c**	94%
4	Ph	Ph	**1d/2d**	92%
5		Ph	**1e/2e**	92%
6			**1f/2f**	96%
7	Ph		**1g/2g**	88%[b]
8	Ph		**1h/2h**	74%[c]
9			**1i/2i**	96%
10	2-furanyl	Ph	**1j/2j**	89%[d]
11		Ph	**1k/2k**	92%
12		Ph	**1l/2l**	91%
13	Ph	CO_2H	**1m/2m**	97%
14		CO_2H	**1n/2n**	96%
15	Ph	CO_2Et	**1o/2o**	97%[d]
16	Ph	CONHBn	**1p/2p**	82%[e]
17	Ph	CONHPh	**1q/2q**	95%[d,e]
18	Ph	R^3	**1r/2r**	97%[d,e]

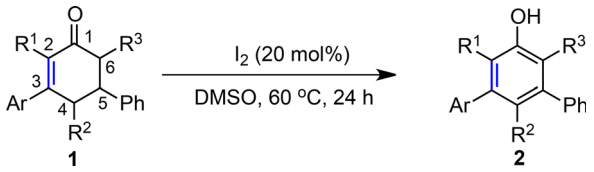
[a] *Reaction conditions:* **1** (0.2 mmol), I_2 (20 mol%), DMSO (1 mL), under air for 24 h unless otherwise stated. Isolated yields are given. R^3 = 4-methoxyanilinocarbonyl.
[b] The reaction time was 48 h.
[c] The reaction time was 72 h.
[d] The reaction time was 36 h.
[e] With 50 mol% of I_2.

Fascinatingly, several *meta*-hydroxybenzoic acid derivatives were prepared effectively (entries 13–18). Substituted *meta*-hydroxybenzoic acids are highly valuable building blocks for organic synthesis, but the existing methods are indirect or use harsh conditions, and normally give benzoates rather than the free acids.[4,5c] The present approach flexibly provides a direct and facile access to *meta*-substituted benzoic acid derivatives as well as the related carboxylic acid.

Remarkably, many susceptible functional groups could survive the reaction conditions, including some that are often incapable of tolerating the conditions of Pd- or Cu-mediated reactions at an elevated temperature, such as chloroaryl (entry 2) and bromoaryl (entries 5, 9, 14), some that are sensitive to strong acids, such as acetal (entry 7), furanyl (entry 10) and NHBoc (entry 11), and some that are intolerable to strong reducers or oxidizers, such as nitro (entry 6), furanyl (entry 10), and phenol (entry 12). They all delivered the products in excellent yields (88–96%). This broad functional group compatibility and mild conditions would provide an enormous potential to further functionalize the aromatization products.

To gain some insights into the reaction mechanism, several control experiments were performed (Table 3). The oxidative aromatization could be initiated by iodation of the C–H bond at the 2-, 4- or 6-position of the cyclohex-2-enone ring. The substrate having a substituent at the 2-position of the ring was transformed into phenol **2s** in 89% yield (Table 3, entry 1), whereas those containing a group at the 4- or 6-position resulted in only moderate to poor yields (entries 2–6). These results suggested that iodation of the cyclohex-2-enone ring at the 4- or 6-position was more reasonable than that at the 2-position. Meanwhile, the substrates free of a substituent at the 6-position were transformed faster than those free at the 4-position (entries 2–3 *vs.* 4–6), which was consistent with the fact that deprotonation of cyclohex-2-enone

Table 3. Control experiments.[a]



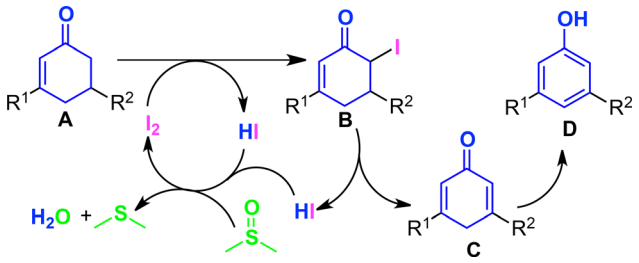
Entry	Ar	R^1	R^2	R^3	1/2	Yield
1	Ar^1	Me	H	H	**1s/2s**	89%
2	Ph	H	Me	H	**1t/2t**	58%
3	Ph	H	CO_2Et	H	**1u/2u**	21%
4	Ar^1	H	H	CO_2Et	**1v/2v**	10%
5	Ar^1	Me	H	Me	**1w/2w**	11%
6	Ar^1	Me	H	CO_2Me	**1x/2x**	trace
7	Ar^2	H	H	H	**1y/2y**	trace
8	Ar^3	H	H	H	**1k/2k**	92%
9	**1a** → **2a** (KI (20 mol%), DMSO, 60 °C, 24 h)					N.R.
10	**1a** → **2a** (I_2 (20 mol%), DMSO, r.t., dark, 7 days)					31%
11	**1a** → **2a** (I_2 (20 mol%), TEMPO (20 mol%), DMSO, r.t., dark, 7 days)					24%

[a] *Reaction conditions:* **1** (0.2 mmol), I_2 (20 mol%), DMSO (1 mL), under air for 24 h unless otherwise stated. Isolated yields are given. Ar^1 = 4-methoxyphenyl; Ar^2 = 4-aminopthenyl; Ar^3 = 4-*t*-butoxycarbonylaminophenyl; TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl.

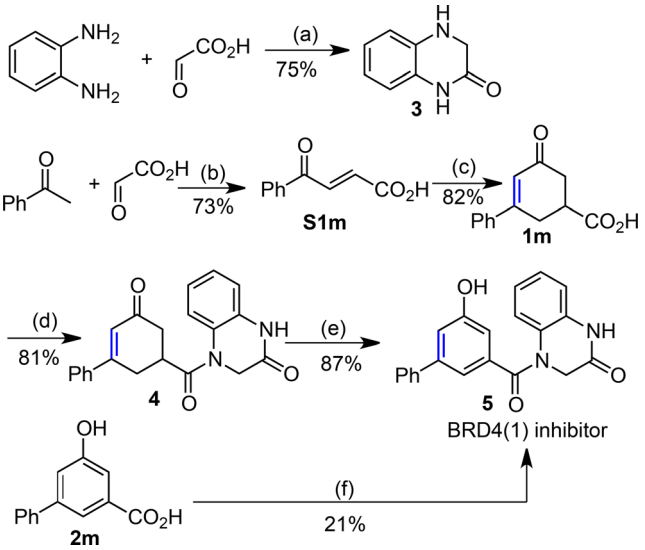
took place at the 6-position more easily than at the 4-position and subsequently afforded cyclohexa-1,5-dienolate rather than cyclohexa-1,3-dienolate.[12] We presume that the steric hindrance of the substituent obstructed the iodation of cyclohexa-1,5-dienolate when 6-substituted substrates were employed, and thereby retarded such substrates from the oxidative aromatization. Therefore, the oxidative aromatization was possibly initiated by iodation at the 6-position of the cyclohex-2-enone ring.

To elucidate the role of molecular iodine, control experiments of entries 7–11 were conducted. For the substrate containing an alkaline amino group, the transformation was difficult to proceed (entry 7). But for the amino-protected substrate, the reaction worked well (entry 8). In addition, KI failed to accomplish the reactions (entry 9), which supported that (i) it was not DMSO but molecular iodine that acted as the direct oxidizer under the standard conditions, and (ii) iodide ion was difficult to be oxidized into molecular iodine by DMSO in a neutral or alkaline environment.[11a,b] However, if the acidity of the reaction system was increased, the aromatic ring of the products could be further iodated.[11c] Thus, external acid or base was unnecessary for the catalytically oxidative aromatization since HI produced *in situ* was capable of transmitting the catalytic cycle fluently. When the reactions were performed in a dark environment, in the presence or absence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, a radical scavenger),[13] and at room temperature, the phenols were slowly produced (entries 10 and 11), which supported the process of catalytically oxidative aromatization combined with an ionic mechanism rather than a radical one.

On the basis of the above studies and reported literature,[11,14] a catalytic cycle of iodine-mediated oxidative aromatization is illustrated in Scheme 2. The iodation of cyclohex-2-enone **A** produces iodo ketone **B** and hydrogen iodide. The elimination of another molecule of hydrogen iodide from **B** generates cyclohexadienone **C**. The tautomerization of **C** furnishes the intended phenol **D**. The oxidation of hydrogen iodide by DMSO leads to the regeneration of molecular iodine that is needed in the next catalytic cycle.[11,14]

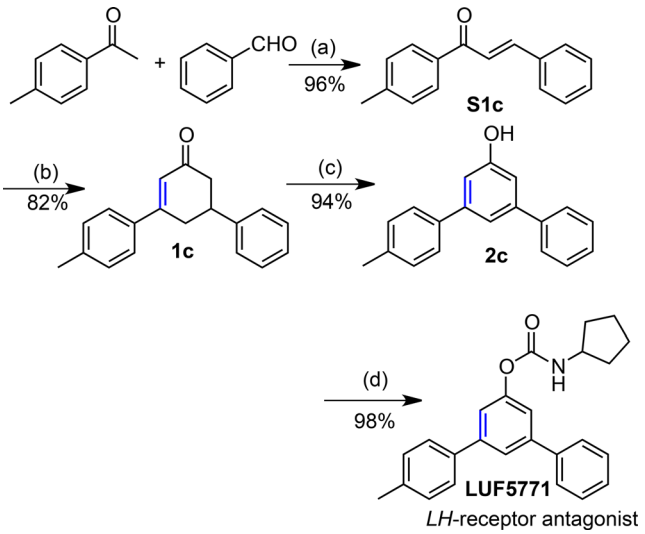


Scheme 2. Proposed mechanism.



Scheme 3. *De novo* synthesis of BRD4(1) inhibitor **5**. *Reaction conditions:* (a) (i) EtOH, room temperature 4 h, then 45 °C 4 h; (ii) $NaBH_4$, 0 °C, 4 h, then room temperature, 4 h. (b) HOAc, HCl (conc.), reflux, 18 h. (c) acetone, pyrrolidine (50 mol%), 40 °C, 24 h. (d) (i) oxalyl dichloride, CH_2Cl_2, DMF (cat.), 0 °C to room temperature, 2 h; (ii) **3**, THF, K_2CO_3, 0 °C to room temperature, 8 h. (e) I_2 (50 mol%), DMSO, 60 °C, 60 h. (f) (i) oxalyl dichloride, CH_2Cl_2, room temperature: (ii) **3**, THF, TEA, 0 °C to room temperature, see: ref.[15b]

The synthetic utility of our methodology is demonstrated by the preparation of the bioactive molecules shown in Scheme 3 and Scheme 4.



Scheme 4. *De novo* synthesis of bioactive **LUF5771**. *Reaction conditions:* (a) NaOH, EtOH, room temperature, 6 h. (b) acetone, NaOMe, 50 °C, 2 h. (c) I_2 (20 mol%), DMSO, 60 °C, 24 h. (d) isocyanatocyclopentane, TEA, CH_2Cl_2, room temperature, 12 h.

Dihyroquinoxalinone **5** was recently identified as a novel inhibitor of BRD4(1), one of the particularly important members of the bromodomains (BRDs) which have been thought to be possible drug targets for cancer, inflammation, diabetes and cardiovascular therapeutics.[15] By the use of oxidative aromatization strategy, the first *de novo* synthesis of **5** was achieved in 5 steps from inexpensive commercial chemicals with good yields in each step (Scheme 3). The fragment of quinoxalinone (**3**) was synthesized in a one-pot procedure from *o*-phenylenediamine and glyoxylic acid by sequential dehydration condensation, cyclization and *in situ* reduction, while the fragment of keto acid (**1m**) was prepared from acetophenone, glyoxylic acid, and acetone *via* sequential aldol condensation and Robinson annulation. The amidation of **1m** with **3** furnished amide **4**. The iodine-catalyzed oxidative aromatization of **4** afforded BRD4(1) inhibitor **5**. By the use of this route, metal reagents and protective groups were not utilized, no unwanted carbon atoms were removed in each step, and the coupling of phenolic acid **2m** and amine **3** was avoided. Comparatively, the direct coupling of **2m** and **3** resulted in poor yield.[15b,16]

The application of this approach was further exemplified in the efficient synthesis of **LUF5771**,[17] a *meta*-substituted phenol-derived antagonist of the human luteinizing hormone (LH) receptor (Scheme 4). We accomplished the *de novo* synthesis of this compound in 4 steps with more than 70% total yield from easily available starting materials (*p*-methylacetophenone, benzaldehyde, acetone, and isocyanatocyclopentane). The reported syntheses of **LUF5771** required the use of either fluorinating reagents or noble metal catalysts.[6c,7i,17] By contrast, the present synthesis totally avoided the requirements of rigorous reaction conditions and special or expensive reagents.

Conclusions

In conclusion, we have developed the first metal-free approach to substituted phenols from cyclohex-2-enone *via* catalytic oxidative aromatization, which integrates several advantages of an ideal methodology, such as the substrates could be facilely prepared, the reagents are of low cost, the optimized temperature range is wide, the operations are safe, convenient and easily controllable, and the transformations are highly atom-economic with broad functional group compatibility and excellent efficiency. The oxidative conditions are so mild that the overoxidation of products has not been observed. Our approach provided a general access to *meta*-substituted phenols, facilitated the *de novo* syntheses of *meta*-substituted phenol derivatives, and therefore efficiently afforded two examples of bioactive molecules. The applications of functionalized *meta*-substituted phenols are under investigation in our lab.

Experimental Section

General Methods

Unless otherwise noted, commercially available reagents were used as received. All solvents for chromatographic separations were distilled before use. Solvents for the water-free reactions were dried with standard procedures and stored in Schlenk flasks over molecular sieves. Column chromatography was carried out with 200–300 mesh silica gel. Thin-layer chromatography (TLC) was performed on glass-backed silica plates. UV light, I_2, and solutions of 2,4-dinitrophenylhydrazine and potassium permanganate were used to visualize products. Concentrating a solution under reduced pressure refers to distillation using a rotary evaporator attached to a vacuum pump (3–10 mmHg). Products obtained as solids or high boiling oils were dried under vacuum (1–3 mmHg). ^{1}H and ^{13}C NMR spectra were recorded on a 600 MHz spectrometer (Bruker) at 293 K and the chemical shifts (δ) were internally referenced by the residual solvent signals relative to tetramethylsilane ($CDCl_3$ at 7.26 ppm for ^{1}H, and at 77.00 ppm for ^{13}C; DMSO-d_6 at 2.50 ppm for ^{1}H, and at 39.50 ppm for ^{13}C). Data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. High-resolution mass spectrometry (HR-MS) for accurate mass measurements was performed on a Waters Synapt-G2 mass spectrometer unless otherwise noted. All the known products were confirmed by comparison with spectroscopic analysis of the authentic samples. The yields in the text refer to isolated yields of compounds (average of two runs).

General Procedure for the Iodine-Catalyzed Oxidative Aromatization

In a typical run, a 10-mL Schlenk tube was charged with a solution of **1** (0.2 mmol) and I_2 (10 mg, 0.04 mmol) in DMSO (1 mL), then covered with a rubber stopper under ambient atmosphere. The mixture was continually stirred at 60 °C until **1** had disappeared as monitored by TLC (typically, for 24 h). After being cooled to the ambient temperature, the reaction was quenched with 3 mL of saturated aqueous solution of $Na_2S_2O_3$ and then extracted 3 times with EtOAc. The combined organic extracts were sequentially washed with deionized water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by column chromatography (silica, petroleum ether/EtOAc mixture as eluent). The isolated products were confirmed by ^{1}H and ^{13}C NMR. The exact time for each reaction is shown in Table 2.

De novo Synthesis of BRD4(1) Inhibitor 5

Aldol condensation to form S1m: Acetophenone (360 mg, 3 mmol) and glyoxylic acid monohydrate (414 mg, 4.5 mmol) were added in sequence to a solution of concentrated HCl (0.5 mL) in AcOH (10 mL). The mixture was heated to reflux for 18 h. After the reaction was complete as

monitored by TLC, the mixture was cooled to the ambient temperature, and dried under vacuum. The crude product, (*E*)-4-oxo-4-phenylbut-2-enoic acid (**S1m**) was used directly for next step.

Robinson annulation to form 1m: To a mixed solvent of methanol (4 mL) and acetone (1.5 mL, 20 mmol) were sequentially added **S1m** (176 mg, 1 mmol) and pyrrolidine (42 μL, 0.5 mmol). The solution was heated to 40 °C for 24 h. After the reaction was complete, the solvent was removed under vacuumn, and then EtOAc (10 mL) and water (10 mL) were added. The product was extracted with EtOAc (3 times). The combined organic phase was dried over anhydrous Na_2SO_4. The crude product was purified by silica gel chromatography to provide 5-oxo-3-phenylcyclohex-3-enecarboxylic acid (**1m**) [18] as a white solid; yield: 177 mg (82%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.93 (s, 1H), 7.59–7.53 (m, 2H), 7.46–7.40 (m, 3H), 6.47 (s, 1H), 3.31–3.23 (m, 1H), 3.09 (t, J = 8.1 Hz, 2H), 2.82 (dd, J = 16.8, 4.6 Hz, 1H), 2.74 (dd, J = 16.8, 10.6 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 197.4, 178.4, 157.8, 137.9, 130.5, 128.9, 126.3, 125.2, 125.2, 39.7, 38.6, 30.1.

Sequential dehydration cyclization and reduction to form 3: Glyoxylic acid monohydrate (184 mg, 2 mmol) was added to a solution of *o*-phenylenediamine (218 mg, 2 mmol) in EtOH (10 mL). The mixture was stirred at room temperature for 4 h, then at 45 °C for 4 h. After the reaction was complete as monitored by TLC, the mixture was cooled in an ice-water bath, and sodium borohydride (530 mg, 14 mmol) was added with stirring in one portion. The solution was stirred in the cooling bath for 4 h, then at room temperature for 4 h, quenched with a saturated aqueous solution of NH_4Cl, and extracted with EtOAc (3 times). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4. The crude product was purified by silica gel chromatography to provide 3,4-dihydroquinoxalin-2(1*H*)-one (**3**) [19] as a white solid; yield: 222 mg (75%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.62 (br.s, 1H), 6.92–6.84 (m, 1H), 6.78–6.70 (m, 2H), 6.67 (d, J = 7.8 Hz, 1H), 3.99 (s, 2H), 3.86 (br.s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.0, 133.8, 125.5, 124.0, 119.6, 115.7, 114.1, 47.2.

Amidation of 1m to form cyclohex-2-enone 4: (a) *In situ* preparation of the acyl chloride of **1m** before use. To a solution of carboxylic acid **1m** (108 mg, 0.5 mmol) in dry CH_2Cl_2 (5 mL) were added oxalyl chloride (64 μL, 0.75 mmol) and DMF (one drop) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. Then the solvents were removed under vacuum, and the residue was diluted with dry dichloromethane (2 mL), and then concentrated under vacuum. The residue was dissolved in dry THF (2 mL) for immediate use. (b) Amidation with amine **3**. To a solution of amine **3** (75 mg, 0.5 mmol) in dry THF (3 mL) was added K_2CO_3 power (138 mg, 1 mmol). The suspension was cooled in an ice-water bath. The acyl chloride solution of **1m** prepared in the above step was added dropwise with stirring. After removal of the cooling bath, the reaction mixture was stirred at room temperature for 8 h, then quenched with a saturated aqueous solution of $NaHCO_3$, and extracted with dichloromethane (3 times). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4. The crude product was purified by silica gel chromatography to provide **4** as a white solid '; yield: 141 mg (81%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.53 (s, 1H), 7.47 (d, J = 6.1 Hz, 2H), 7.39 (dd, J = 10.4, 5.2 Hz, 4H), 7.24 (d, J = 7.7 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 6.41 (s, 1H), 4.64 (s, 1H), 4.43 (d, J = 16.4 Hz, 1H), 3.83 (s, 1H), 3.19 (ddd, J = 17.7, 10.7, 2.1 Hz, 1H), 2.81 (dd, J = 16.5, 13.1 Hz, 2H), 2.58 (d, J = 15.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 197.3, 172.9, 169.2, 157.6, 138.0, 131.7, 130.4, 128.9, 127.6, 126.5, 126.1, 124.6, 123.7, 123.5, 117.3, 46.6, 39.8, 37.9, 31.1; HR-MS (ESI-TOF): m/z = 369.1219, calcd. for $C_{21}H_{18}N_2NaO_3$ $[M+Na]^+$: 369.1210.

Catalytic oxidative aromatization of 4 to form 5: The reaction was performed according to the general procedure. A mixture of **4** (70 mg, 0.2 mmol) and I_2 (25 mg, 0.1 mmol) in DMSO (1 mL) was stirred at 60 °C for 60 h. After the reaction was completed, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and then extracted 3 times with EtOAc. The combined organic extracts were sequentially washed with deionized water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography to provide compound **5**[15b] as a yellow solid; yield: 60 mg (87%). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.80 (s, 1H), 9.86 (s, 1H), 7.48–7.39 (m, 4H), 7.35 (t, J = 7.1 Hz, 1H), 7.13–7.08 (m, 2H), 7.05 (d, J = 7.9 Hz, 1H), 6.98 (s, 1H), 6.82–7.78 (m, 3H), 4.41 (s, 2H); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 168.6, 167.4, 158.2, 142.0, 139.9, 136.8, 131.7, 129.4, 128.3, 127.5, 127.0, 126.3, 124.8, 122.2, 118.0, 116.7, 116.3, 114.6, 41.0.

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