Chromium–Salen Complex / Nitroxyl Radical Cooperative Catalysis: A New Combination for Aerobic Intramolecular Dearomative Coupling of Phenols

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ABSTRACT: Herein we describe an aerobic intramolecular dearomative coupling reaction of phenols using a catalytic system with the combination of a chromium–salen (Cr–salen) complex and a nitroxyl radical. This novel catalytic system enables the construction of a spirocyclic dienone product, which is a potentially useful intermediate for the synthesis of various natural products such as alkaloids and phenylpropanoids from bisphenol in good yield under mild reaction conditions (under O_2 and ambient temperature). A preliminary mechanistic study suggests that this reaction system is promoted by a cooperative electron transfer between the Cr(III)–salen complex, nitroxyl radical and bisphenol substrate.

Intramolecular dearomative phenol coupling is regarded as a crucial process for the biosynthesis of natural products to expand molecular complexity and diversity.[1] It has been proposed that this process involves a unique dearomative aryl–aryl coupling catalyzed by an oxidase such as cytochrome P450 and the subsequent tautomerization. Interesting structural motifs such as spirocycles and complex bridged or fused ring systems are constructed via this transformation as the key step. Not only the structures, but also some of the natural products such as morphine and galantamine exhibit salient pharmacological activities (Fig. 1). For example, morphine is one of the strongest analgesics for treatment of severe pain.[2a–c] Galantamine inhibits acetylcholine esterase (AChE) and is used for the treatment of Alzheimer's disease.[2d] The fascinating features of these compounds have motivated chemists to reproduce the same reaction in a flask.

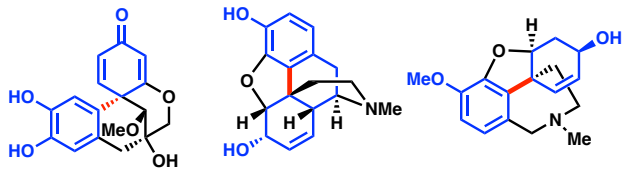
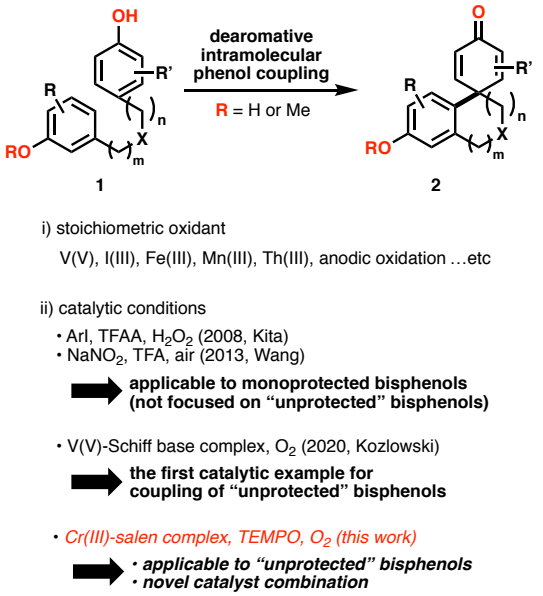


Figure 1. Natural products derived from intramolecular dearomative phenol coupling

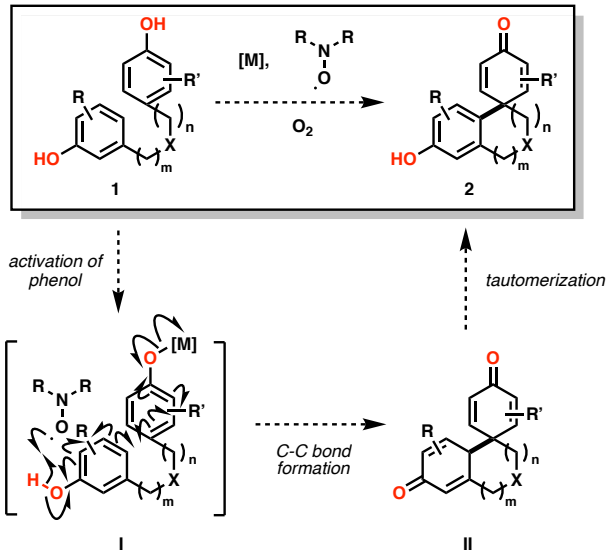
There are limited examples of precedents that enable successful *intra*molecular dearomative phenol coupling, although many schemes for *inter*molecular phenol (arenol) coupling reaction[3,4] have been reported (Scheme 1). Most of the schemes require a stoichiometric or excess amount of oxidant such as vanadium oxychloride ($VOCl_3$) or a hypervalent iodine reagent.[5] Therefore, a catalytic transformation is attractive to avoid such a wasteful and sometimes harsh conditions. To date, however, a few catalytic systems have been developed: one is iodine (III)-catalyzed conditions reported by Kita and co-workers in 2008[6] and another is nitrogen oxide-catalyzed conditions reported by Wang and co-workers in 2013.[7] Both systems require electron-donating substituents on the aromatic ring so that the intended reaction can proceed efficiently. Unfortunately, their substrate scopes are not focused on the "unprotected" bisphenol substrates, which are employed in biosynthesis. Very recently, Gilmartin and Kozlowski have reported the first example generating dearomatized coupled products under aerobic conditions using unprotected bisphenol as a substrate with vanadium(V)–oxo–Schiff base catalyst.[8] Herein we report an aerobic intramolecular dearomative coupling reaction of bisphenols utilizing an unprecedented catalyst combination, a chromium–salen (Cr–salen) complex and a nitroxyl radical. This novel catalytic system provides various dienone compounds from unprotected bisphenol substrates in good yield under mild reaction conditions.

Scheme 1. Overview of dearomative intramolecular phenol coupling



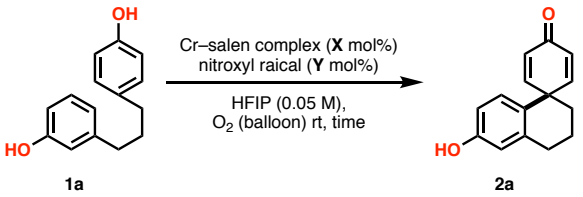
On the basis of our experience in the development of an aerobic alcohol oxidation system using copper(I)–nitroxyl radical catalysis,[9, 10] we envisioned that the combination of a transition metal that is known to activate phenols appropriately[3,4] and a radical mediator such as a nitroxyl radical would promote the desired coupling reaction. Our initial design is shown in Scheme 2, in which individual but precise simultaneous activation of one phenol by a transition metal and the other phenolic hydroxy group by a nitroxyl radical via the hydrogen atom transfer (HAT) pathway is crucial to escape from non-selective intermolecular coupling and to obtain thereby the intended coupled product efficiently.

Scheme 2. Working hypothesis



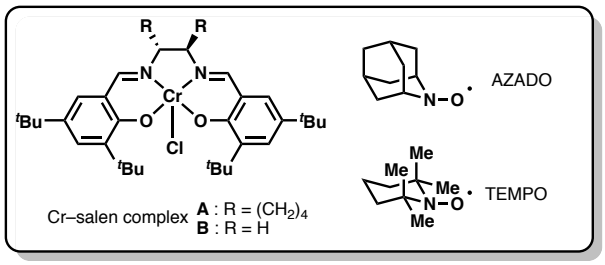
We commenced our investigation with bisphenol **1a** as the substrate and AZADO (2-azaadamantae *N*-oxyl)[11] as the radical mediator (Table 1). After extensive screening of transition metals that are reported to activate phenols, we found that a Cr–salen complex reported by Kozlowski promoted the desired transformation,[12] but the yield was very low in 1,2-dichloroethane (1,2-DCE) used as the solvent (entry 1). Other metal–salen complexes or chromium salts did not give the desired compound. Following the precedents about intermolecular phenol coupling reaction in the literature,[4g, 4i, 4n, 4o, 4p, 4r, 8] we found that using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a solvent is crucial for the reaction to proceed in a catalytic manner (entry 2). The presence of a nitroxyl radical is also essential for the reaction (entry 3). Moreover, we found that TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl), which is a more sterically hindered nitroxyl radical than AZADO (2-azaadamantae *N*-oxyl) showed higher yields (entries 4 and 5). The use of 1 equivalent of TEMPO improved the yield of **2a** (entry 6). We found that changing the salen ligand affected the yield of desired product **2a** and determined that Cr–salen complex **B** is the most suitable complex after screening of various salen ligands (entry 7). Next, we explored the appropriate ratio of the Cr–salen complex to TEMPO and found that the 1:2 ratio of Cr–salen to TEMPO provided almost the same yield as the 1 equivalent of TEMPO, although a longer reaction time was required (entry 8). A 1:1 ratio of Cr–salen to TEMPO resulted in a decrease in the yield of **2a** and the incomplete consumption of starting bisphenol **1a** (entry 9). To reduce the amount of the catalyst and solvent, we continued further optimization studies. We found that simply reducing the amount of the catalyst gave a similar yield of the product to entry 8 with the starting material remaining (entry 10). Finally, a mixed solvent system with HFIP and PhCl (9:1) enabled complete consumption of **1a** and gave **2a** in good yield. (entry 11).[13]

Table 1. Optimization of reaction conditions



1a 2a

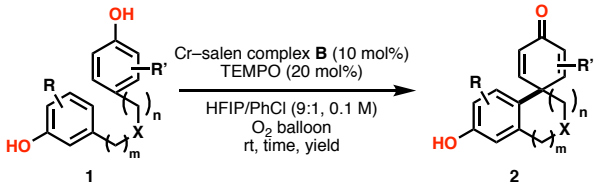
entry	Cr-salen complex	X (mol%)	nitroxyl radical	Y (mol%)	time (h)	yield (%)[a]
1[b]	A	15	AZADO	15	48	11
2	A	15	AZADO	15	18	47
3	A	15	none	0	48	8
4	A	15	AZADO	15	12	38(46)
5	A	15	TEMPO	15	12	34(56)
6	A	15	TEMPO	100	24	55(60)
7	B	15	TEMPO	100	24	64
8	B	15	TEMPO	30	30	65
9	B	15	TEMPO	15	30	50
10[c]	B	10	TEMPO	20	24	61
11[d]	**B**	**10**	**TEMPO**	**20**	**36**	**70**



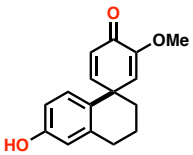
[a] Isolated yield (yields based on recovered starting material are shown in parentheses) [b] The reaction was conducted at 80 °C in 1,2-dichloroethane solvent. [c] 0.1 M HFIP was used as the solvent. [d] 0.1 M HFIP–PhCl (9:1) was used as the solvent.

With the optimized conditions determined, the substrate scope was explored. We found that this reaction converts various bisphenol substrates (**1**) into dearomatized dienone compounds (**2**). In particular, substrates having a "strong" electron-donating group (i.e., methoxy substituent) on only "dearomatized" phenols tend to be converted efficiently (for example, **2b** and **2c**). In contrast, substrates having a "weak" electron-donating group (giving product **2e** and **2f**) and an electron-donating group on only an "un-dearomatized" phenol (product **2g**) showed moderate yields of the desired products. These results indicate that this reaction is strongly affected by the electronic characteristics of substrates. This reaction can be conducted in air instead of O_2, although the reaction time is prolonged (**2b**–**2d**). We also examined other substituents on aromatic rings or alkyl tethers. Fluorine (**2h**) and chlorine (**2i**) substituents were tolerated to give the coupled product. The introduction of an ethyl ester group on an alkyl tetherto facilitate bond formation via the Thorpe–Ingold effect did not work well (**2j**). We consider that this might be due to the inductive effect of this substituent. Next, we tried substrates having heteroatom-containing tethers to evaluate the applicability of this reaction to the synthesis of various natural products shown in Figure 1 or novel spirocyclic dienone compounds. Although the yields are typically low or moderate and the reaction time was long, heteroatom-containing substrates were converted into desired spirocyclic dienones (**2k–2m**). A sulfur-containing dienone (**2m**) was obtained in good yield without oxidation of the sulfur atom. Furthermore, nitrogen-containing 7-membered spirocyclic dienones (**2n** and **2o**), which are key intermediates for the biosynthesis of various tyrosine alkaloids, were obtained. Unfortunately, this reaction system gave only a trace amount of the 5-membered spirocyclic dienone **2p**.

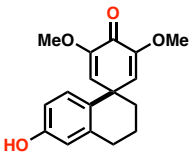
Scheme 3. Substrate scope of aerobic intramolecular dearomative coupling of phenols with Cr-salen / TEMPO catalytic system[a]



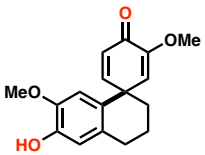
1 2



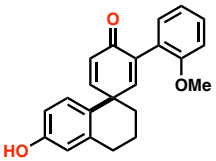
2b
88% / 2 h
90% / 24 h[b]



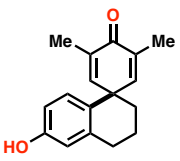
2c
96% / 1.5 h
93% / 10 h[b]



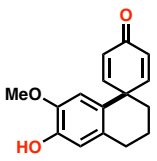
2d
67% / 2 h
54% / 10 h[b]



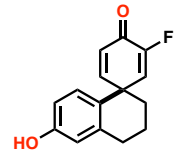
2e
48% / 60 h



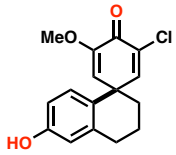
2f
31% / 4 h



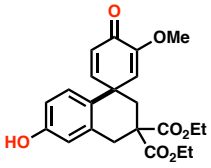
2g
35% / 6 h



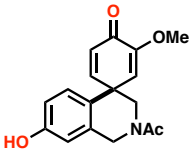
2h
18% (70% brsm) / 120 h



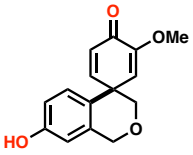
2i
70% / 1.5 h



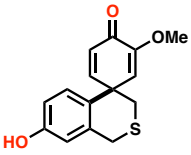
2j
27% (67% brsm) / 100 h



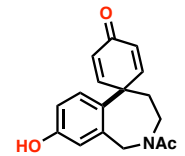
2k
37% / 168 h



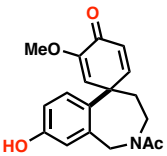
2l
27% (47% brsm) / 120 h



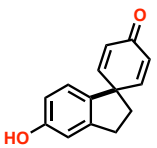
2m
74% / 10 h



2n
28% (51% brsm) / 120 h[c]



2o
23% / 120 h[c]

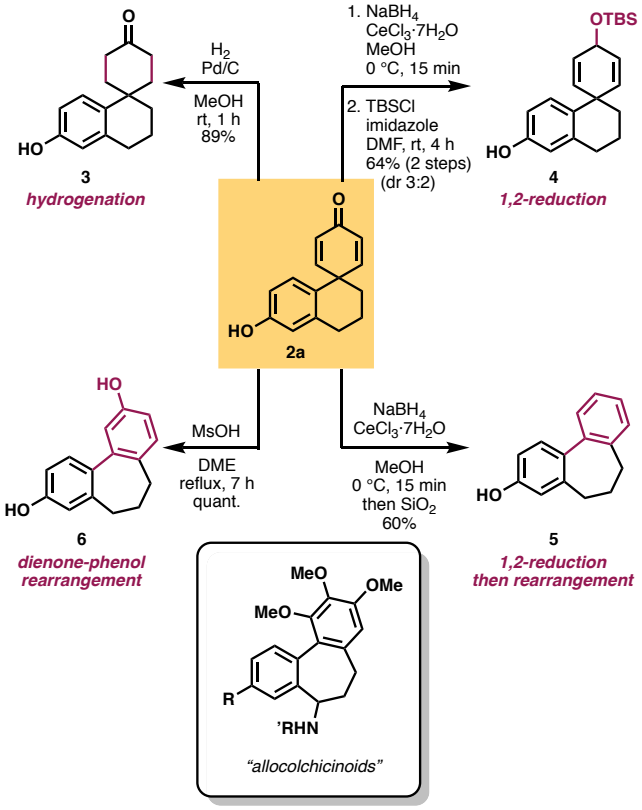


2p
trace / 48 h

[a] Isolated yield. [b] Air balloon was used instead of O_2 balloon. [c] At 50 °C

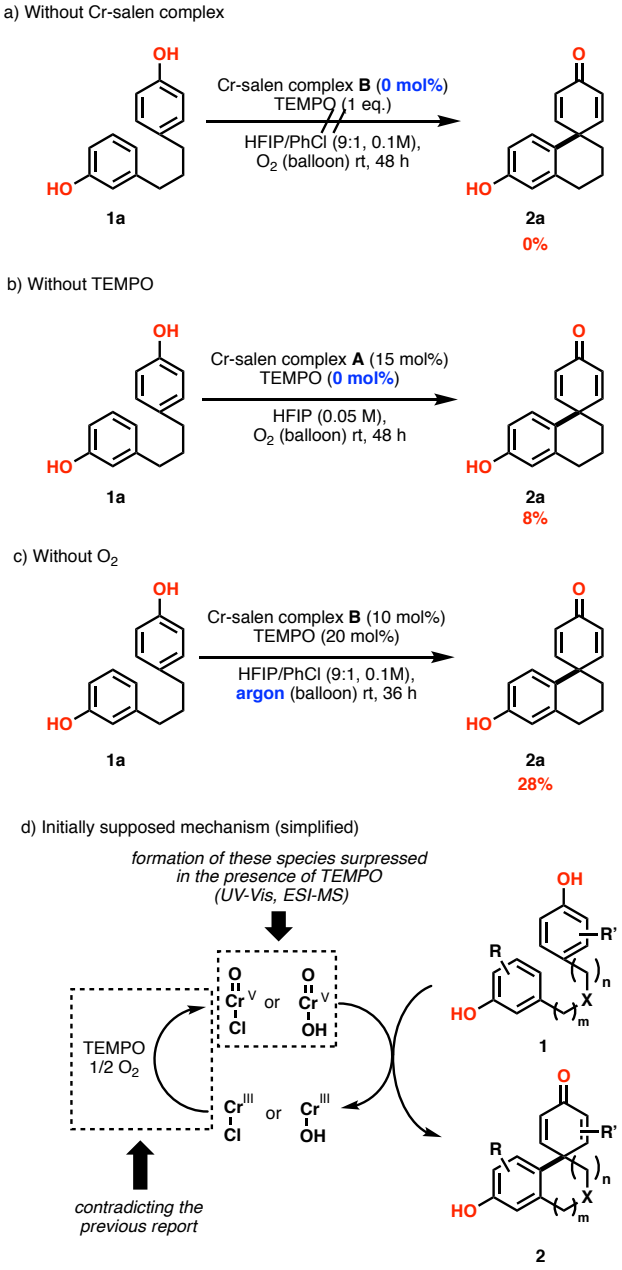
The versatile use of the dienone products is demonstrated in Scheme 4. Hydrogenation using Pd/C under hydrogen atmosphere gave spirocyclohexanone **3**. Luche reduction followed by protection gave spirocyclic 1,4-cyclohexadiene-3-ol **4**. These transformations provide novel spirocyclic compounds. Furthermore, **2a** can be transformed into 6-7-6 tricyclic mono- or bisphenols **5** and **6** by acid-mediated rearrangement.[14] These transformations would be applicable to the synthesis of various "allocolchicinoids" and their analogs.[15]

Scheme 4. Further derivatization of dienone 2a



To gain insight into the reaction mechanism, we conducted preliminary studies (**Scheme 5**). No conversion was observed when the reaction was conducted without a Cr–salen complex (**Scheme 5**, a). On the other hand, slight progress of the reaction was observed under conditions without TEMPO or O_2 (**Scheme 5**, b and c). These results lead to speculations that a Cr(V)–oxo–salen complex, which was generated by aerobic oxidation of the starting Cr(III)–salen complex, promotes the coupling reaction, and that TEMPO and O_2 regenerate an active Cr(V)–oxo species (**Scheme 5**, d). However, this scenario contradicts the observation of Kozlowski that TEMPO suppresses the oxidation of Cr(III) into Cr(V)–oxo species.[12] UV-Vis spectroscopy and ESI-MS spectra showed that a formation of Cr(V)–oxo species seems to be suppressed in the presence of TEMPO.[16, 17]

Scheme 5. Initial mechanistic proposal and its contradiction



On the basis of the experimental result shown in **Scheme 5** c, we surmise that TEMPO might generate a Cr complex other than the Cr(V)–oxo species and the species would involve the desired transformation because a Cr(V)–oxo species should not be generated under O_2-free conditions. Therefore, we conducted further ESI-MS studies to identify the active species generated in the reaction. As a result, we found a Cr(III)–TEMPO adduct in the reaction mixture (found *m/z*=699.4417 as [Cr(III)-salen **B**-TEMPO+H]$^+$: calcd. 699.4431 and *m/z*=781.4949 as [Cr(III)-salen **B**-TEMPO+2MeCN+H]$^+$: calcd 781.4962) (Figure 2). Interestingly, these molecular ion peaks were not detected when the Cr(III)–salen **B** complex and TEMPO were mixed in HFIP *without* bisphenol **1** and when bisphenol **1** was fully consumed. This result suggests that

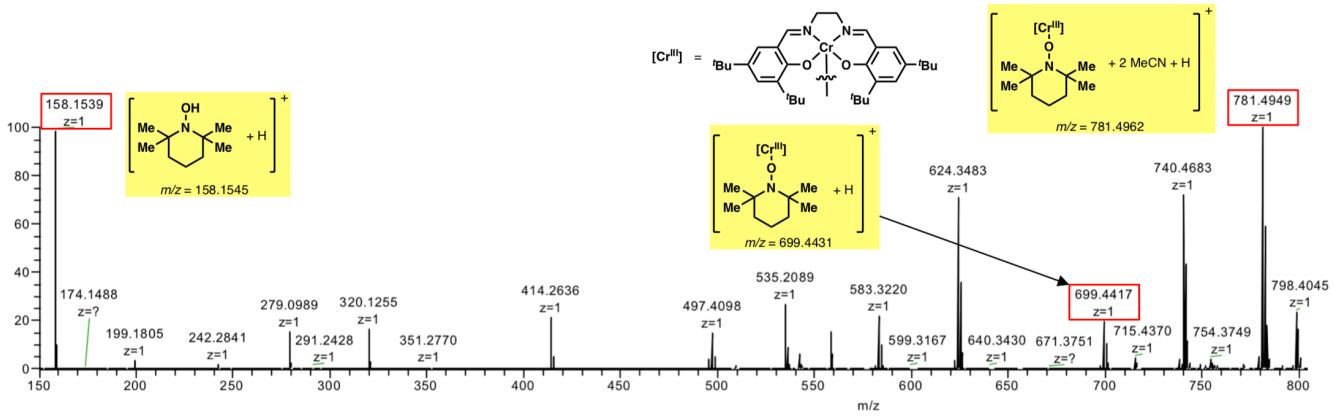


Figure 2. Positive ESI-MS spectra of the reaction mixture (**1b** was used as a substrate)

the Cr(III)–salen complex, TEMPO and the bisphenol substrate might work cooperatively in order that the desired reaction proceeds catalytically.

Although we cannot rule out other possibilities[18], a plausible mechanism that can explain all the observations is shown in Figure 3a. In the reaction mixture, we observed TEMPOH (hydroxylamine of TEMPO, m/z=158.1539 as $[TEMPOH+H]^+$) by ESI-MS (Figure 2).[19] Furthermore, monoprotected bisphenol substrates were not converted into the corresponding dienone compounds (see Supporting Information for details). On the basis of these observations, we considered that the nitroxyl radical plays two roles: one is hydrogen atom abstraction from free phenol and the other is electron transfer from Cr(III)-phenoxide complex **I**. We also suggest that the formation of bis Cr(III)-phenoxide complex **I'** followed by electron transfer might proceed via another path. After the C–C bond formation event to give **II**, the following tautomerization leads to dienone compound **2**. The Cr(III)–salen–TEMPO adduct and TEMPOH are converted into the original Cr(III)–salen species and nitroxyl radical by molecular oxygen. Other experiments (shown in Scheme 4b) suggest that the Cr(V)–oxo salen complex might also be involve in this reaction but not catalytically. We surmise that the resulting Cr(III)–OH or Cr(V)–oxo–OH might be inactive for the desired transformation. Therefore, a Cr(V)–oxo salen complex would be a "dead end" (Figure 3b). Further mechanistic studies are required to reveal the mechanistic details.

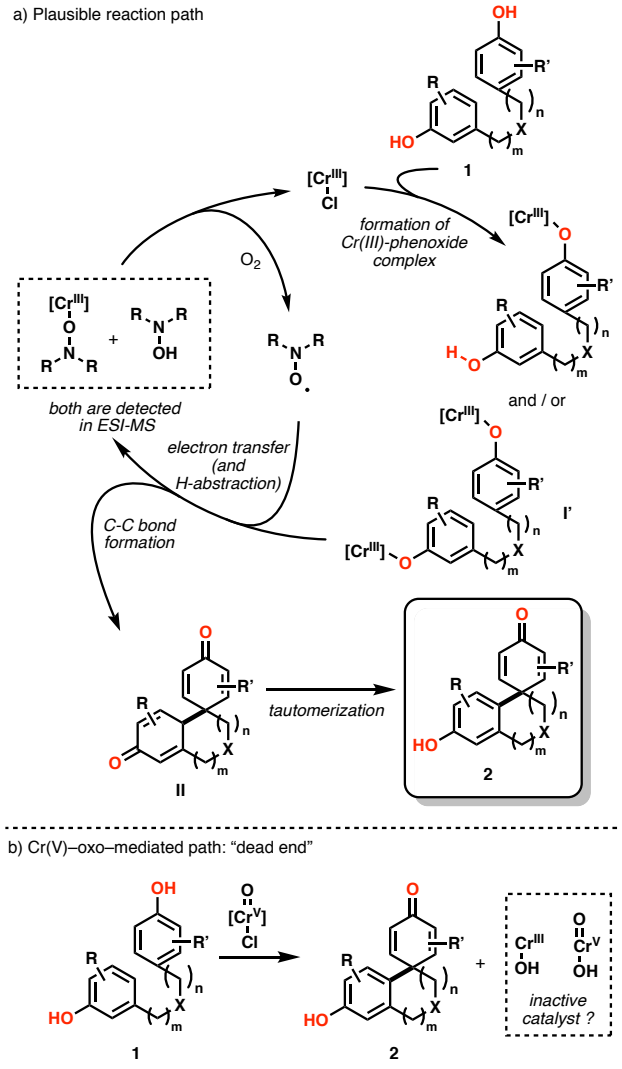


Figure 3. Plausible reaction mechanism

In summary, we have reported an aerobic intramolecular dearomative coupling of phenols with a Cr–salen/nitroxyl radical catalytic system. This system converts various bisphenol substrates into dienone compounds, which are important intermediate for biogenesis of tyrosine alkaloids and phenylpropanoids. To the best of

our knowledge, this is the first example of not only the use of chromium as a partner of a nitroxyl radical but also the oxidative transformation of phenols achieved using a transition metal/nitroxyl radical system. Further studies to expand the substrate scope and clarify the reaction mechanism are underway in our group.

ASSOCIATED CONTENT

Supporting Information

Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, compound characterization data, NMR spectra and ESI-MS spectra (PDF).

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Notes

The authors declare no competing financial interests.

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(16) See Supporting Information for actual data.

(17) We also confirmed that the oxoammonium species, which is a common active species of nitroxyl radical-mediated oxidative molecular transformation, did not promote the desired reaction. See Supporting Information for details.

(18) We also observed Cr(V)–oxo species derived molecular ion peaks, such as a Cr(V)–oxo–TEMPO adduct. Therefore, we cannot completely rule out a reaction pathway mediated by Cr(V)–oxo species.

(19) No $[TEMPOH+H]^+$ peak was observed when the Cr(III)–salen **B** complex and TEMPO were mixed in HFIP without bisphenol **1b**. $[TEMPO+H]^+$ (found *m/z*=157.1458, calcd 157.1467) was observed instead.

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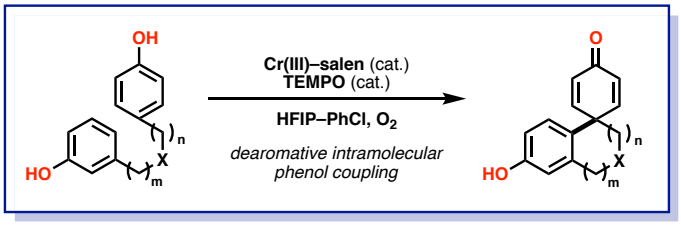

- ***mild conditions (room temperature, O_2 atmosphere)***
- ***applicable to "unprotected" bisphenol***
- ***novel catalyst combination (Cr(III) / nitroxyl radical)***