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Traceless piperidine-assisted one-pot tandem dearomative spiroannulation of phenolic compounds with nitrile oxides *via ortho*-quinone methide intermediates

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Dedicated to Prof. Graham Hutchings on his 70th birthday

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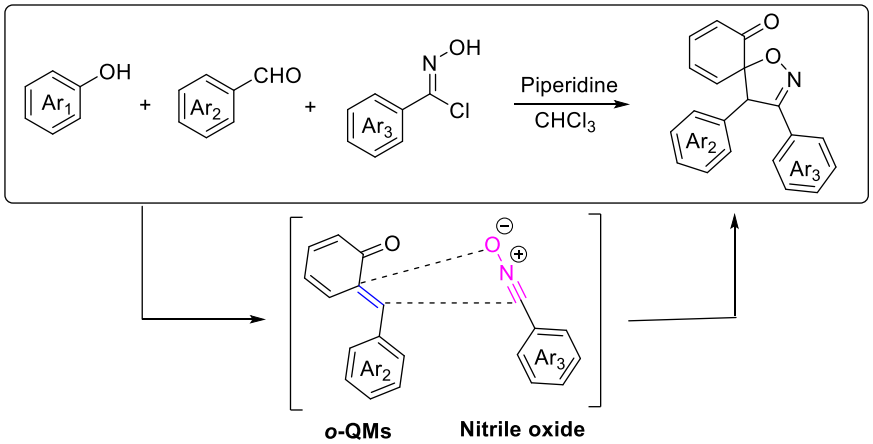
Abstract

Ortho-quinone methides (*o*-QMs), as useful synthetic intermediates, have been employed in numerous 1,4-additions and cycloannulations, the overall process driven by rearomatization. In this work, we discovered a dearomative [3+2] spiroannulation of *in situ* generated *o*-QMs and nitrile oxides. Based on this discovery, we developed a one-pot, three-component tandem reaction using phenol, aldehydes and chlorobenzaldehyde oxime, with piperidine as a traceless additive. This catalyst-free reaction system provides a new strategy for the synthesis of various spiro decene-6-ones with moderate yields and excellent diastereoselectivities.



Keywords: *Ortho*-quinone methides (*o*-QMs), nitrile oxides, dearomatization, [3+2] spiroannulation, spiro decene-6-ones.

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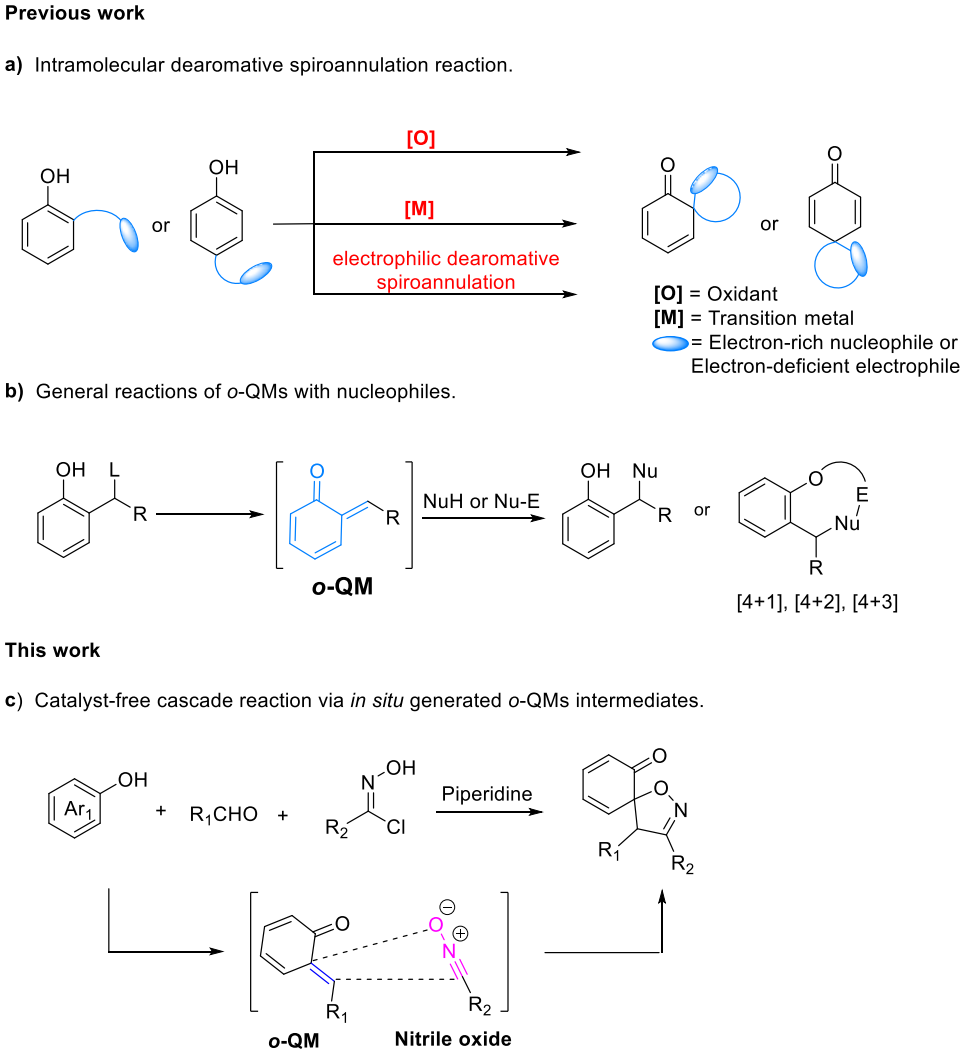
Introduction

Developing efficient and practical synthetic strategies for constructing complex molecular architectures has long been a crucial objective in synthetic chemistry. Among the available methodologies, dearomatization reactions have emerged as powerful and versatile tools for transforming planar aromatic compounds into stereochemically distinct molecules.[1-6] Although dearomatization reactions of various nitrogen-containing aromatic compounds, such as indoles, pyrroles and pyridines, have been well-developed, the dearomatization reactions of phenols remain underexplored.[7-17] In recent years, remarkable progress has been made in dearomative spiroannulation reactions of phenolic derivatives, mainly including: (a) oxidative dearomatization of phenol derivatives;[18-26] (b) transition metal-catalyzed dearomative spiroannulation of phenol derivatives;[27-37] and, (c) aromatic electrophilic dearomative spiroannulation[38-42] (Scheme 1a). However, most of these advances were limited to intramolecular reactions, requiring tedious synthetic routes for the preparation of substrates.[43] Moreover, such dearomatization reactions often encounter competitive O-alkylation pathways. Therefore, it remains desirable to develop new reaction systems for achieving intermolecular dearomative spiroannulation reactions of phenol derivatives under mild non-oxidative conditions.



Scheme 1. Dearomative spiroannulation reactions of phenolic compounds.

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Ortho-Quinone methides (*o*-QMs), versatile reactive intermediate in organic chemistry, have been postulated over 100 years ago for explaining unusual observations in some cycloadditions and biological processes.[44-46] In the past decades, remarkable applications of *o*-QMs with various reaction partners have been studied.[47-51] According to the reported results, the inherent reactivity of *o*-QMs depends on their rapid rearomatization tendency, including two reaction pathways, namely 1,4-addition of nucleophiles and cycloannulation reaction with 2π partners or dipoles (Scheme 1b). To our knowledge, there has been little literature precedence in terms of the application of the dearomatization of 2-phenol precursors of *o*-QMs, except for recent examples described by Adler, Ishihara and Johnson, work in which the oxidative spiroepoxidation of 2-alkylarenols was achieved.[52-54] As part of our recent development of reactions involving *o*-QMs[55-59], we studied the reactions of *o*-QMs with nitrile oxides as reaction partners. Our original aim was to construct the 7-member ring by the [4+3] cycloaddition. Surprisingly, a model reaction using 2-(tosylmethyl)sesamol **1** as the precursor of *o*-QM did not give the expected 7-membered ring product **3**, but instead the dearomatizative spiro product **4a** in good yield (Scheme 2a). This discovery clearly showed that suitable ring strain could overcome the extraordinary thermodynamic driving force caused by aromaticity as well as the dimerization, forcing the reaction pathway of these *o*-QMs to dearomatization. Following this finding, we herein described a one-pot, three-component tandem reaction of phenol with aldehydes and chlorobenzaldehyde oxime by the use of piperidine as a traceless additive (Scheme 1c). This catalyst-free reaction system provides a new strategy for the synthesis of valuable spiro decene-6-ones with moderate yields and excellent diastereoselectivities. The mild conditions also allow for a broad substrate scope, as well as good functional group tolerance.

Results and Discussion

Initially, *o*-QM precursor **1** and oxime chloride **2a** were combined in DCM with an inorganic base. The ^{1}H NMR spectra results showed that a dearomatized spiro product **4a** with high diastereoselectivity was obtained, instead of the expected [4+3] cycloaddition product **3** (Scheme 2a). According to Jurd's report,[60] the hydroxyl group in Mannich base **5** forms strong hydrogen bonds with the nitrogen atom, making it easy to dissociate and produce *o*-QM in both protic and aprotic solvents. Encouragingly, we successfully carried out the reaction without the need for an additional base when Mannich base **5** was used instead of *o*-QM precursor **1** (Scheme 2b, 60% yield). We realized that the required Mannich base **5** could be generated *in situ* by reacting sesamol **6a** with equimolar amounts of an aromatic aldehyde and piperidine. Therefore, the reaction system could be treated with oxime chloride **2a** to obtain the dearomatized product without the need for separation and purification (Scheme 2c). As a result, we have achieved a one-pot, two-step dearomatizing spiroannulation of a phenolic compound with benzaldehyde and an oxime chloride via the *o*-QM intermediate, with piperidine serving as a traceless additive.

To improve the efficiency of the reaction, we optimized the reaction conditions by searching for a suitable traceless amine to generate *o*-QM precursors *in situ*. The key results of our reaction optimization are summarized in Table 1, using sesamol **6a**, benzaldehyde **7a** and *p*-methyl chlorobenzaldehyde oxime **2a** as the model substrates for the dearomative spiroannulation reaction. The reaction was carried out with pyrrolidine as a traceless additive in $CHCl_3$ at room temperature, and the desired product **4a** was obtained in a yield of 31% (Table 1, Entry 1). Substituting pyrrolidine with piperidine increased the reaction yield to 45% (Table 1, Entry 2). However, further attempts to improve the reaction yield using morpholine and 1,2,3,4-tetrahydroisoquinoline were ineffective (Table 1, Entry 3 and 4). We then tested the effect of the solvent on the reaction, and the yield decreased to 38% when the reaction was conducted in DCM (Table 1, Entry 5).

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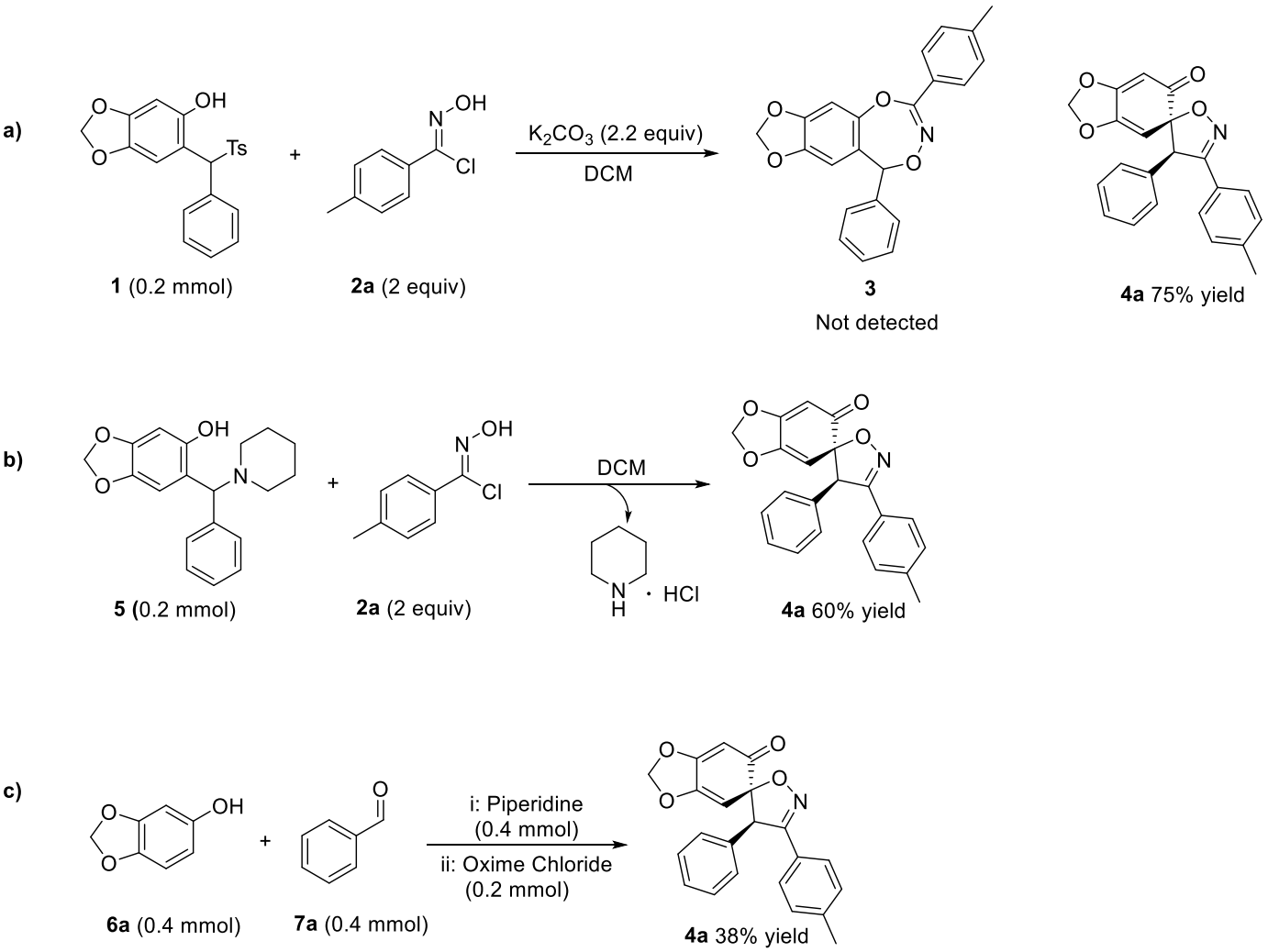
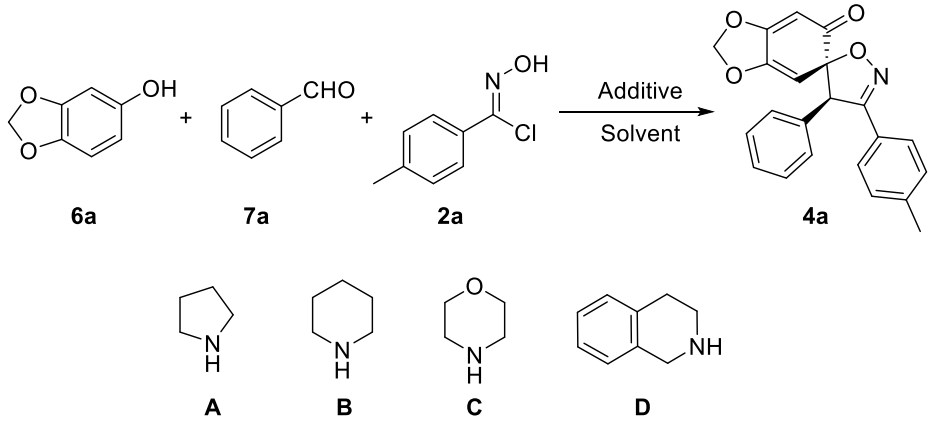
Toluene and THF were also not suitable for the reaction yield (Table 1, Entry 6 and 7). Finally, we obtained a satisfying yield of 64% by prolonging the reaction time (Table 1, Entry 8).



Scheme 2. Our design process of the one-pot two-step dearomative spiroannulation reaction.

Table 1. Condition optimizations.[a]



Entry	Solvent	Additive	Yield %

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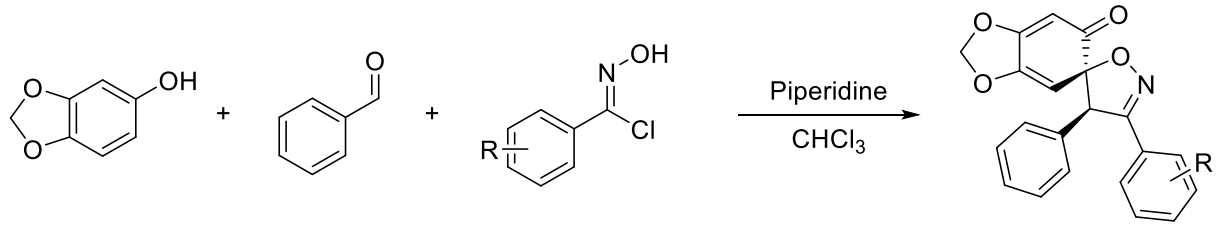
1	$CHCl_3$	**A**	31
2	$CHCl_3$	**B**	45
3	$CHCl_3$	**C**	18
4	$CHCl_3$	**D**	21
5	$CHCl_2$	**B**	38
6	Toluene	**B**	9
7	THF	**B**	20
8[b]	$CHCl_3$	**B**	64

Details of the reaction conditions: [a] Substrate **6a** (0.4 mmol), **7a** (0.4 mmol) and additive (0.4 mmol) were dissolved in $CHCl_3$ (10 µL), and the reaction was stirred at room temperature for 4 hours. Then substrate **2a** (0.2 mmol) was added with $CHCl_3$ (3 mL). The reaction mixture was stirred and monitored by TLC until completion (about 24 hours). The yield was obtained by column chromatography. [b] After substrate **2a** was added, the resulting mixture was stirred for 48 hours.

After obtaining the optimized conditions, we proceeded to examine the substrate scope of the dearomative spiroannulation reaction with various types of nitrile oxide precursors (Scheme 3). The oximes derived from both electron-donating and -withdrawing substituted aromatic aldehydes performed well, with yields ranging from 51-64% (**4a**-**4l**). The introduction of a methyl or methoxy group at the *meta*- or *para*-positions of the benzene ring resulted in higher yields (59-64%, **4b**-**4d**). Naphthaldehyde-derived oximes were tolerable, affording the corresponding spiro ring products in 52-56% yield (**4e**-**4f**). The installation of electron-withdrawing substituents on the benzene ring did not affect the reaction efficiency, with yields of 51-62% being obtained for the products **4h**-**4l**.



6a **7a** **2** **4**

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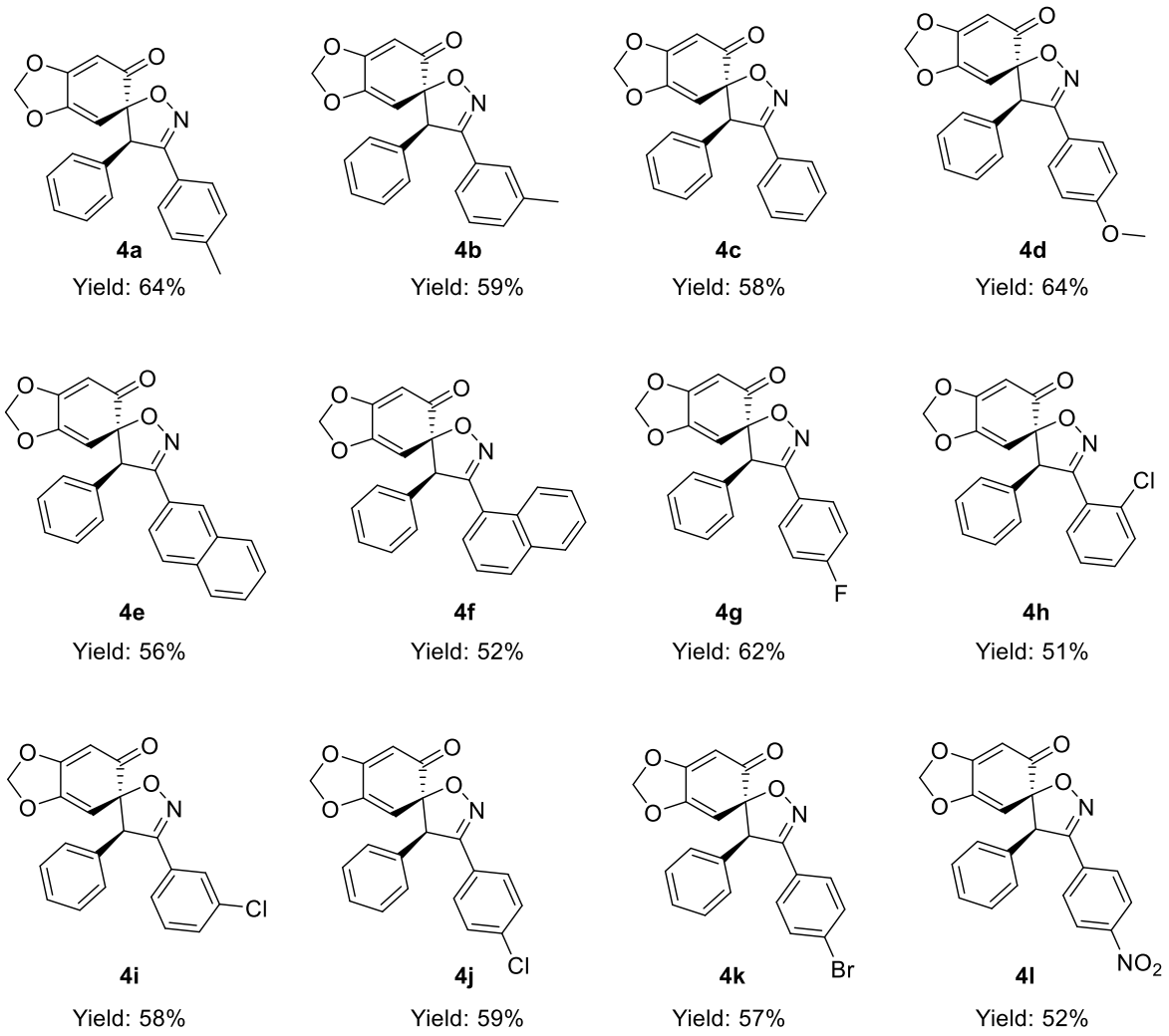

Scheme 3. Substrate scope of the dearomatization reaction: **6a** (0.4 mmol, 55 mg), **7a** (0.4 mmol, 42mg) and piperidine (0.4 mmol, 34 mg) were dissolved in 10 μL $CHCl_3$, and the reaction was stirred at room temperature for 4 hours. Then substrate **2** (0.2 mmol) was added with $CHCl_3$ (3 mL). The reaction mixture was stirred and monitored by TLC until completion (about 24 hours). The yields obtained after column chromatography are listed.

The focus of our extension was on the performance of other phenol and benzaldehyde starting materials. Moderate to good yields of spiro products **4m**-**4p** (Scheme 4) were obtained in reactions involving methyl- and methoxy-substituted benzaldehydes (47-71%). Naphthaldehyde also underwent the reaction smoothly, with corresponding products **4q**-**4r** obtained in good yields (61-79%). Different electron-deficient substituted benzaldehydes were tolerable, with the products obtained in moderate to good yields depending on the position of the substituent (**4s**-**4v**, 43-70% yields). Notably, the dearomative spiroannulation reaction was successfully extended to 3,4-dimethoxyphenol and 1-naphthalenol, leading to desired products **4w**-**4x** with moderate yields (42-53%). Of value was that the structure of **4m** (CCDC Number: 2298602) was unambiguously confirmed by X-ray crystallographic analysis (see the SI for more information).

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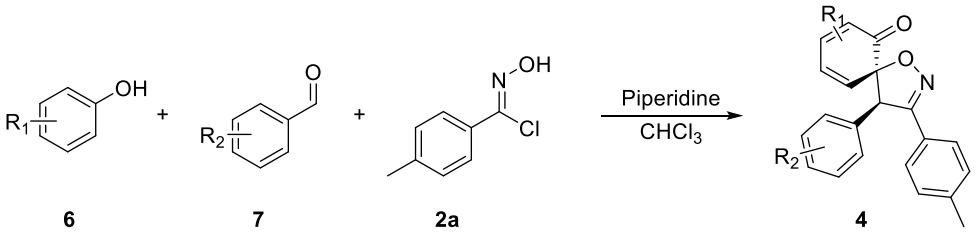

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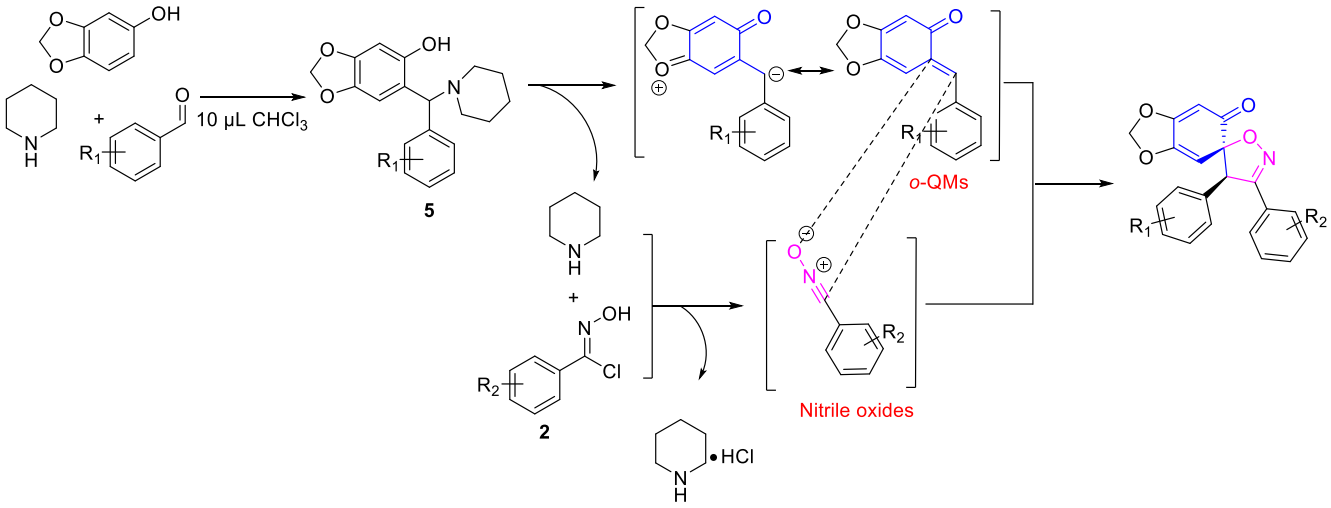
Scheme 4. Substrate scope of the dearomatization reaction: **6** (0.4 mmol), **7** (0.4 mmol) and piperidine (0.4 mmol, 34 mg) were dissolved in 10 µL $CHCl_3$, and the reaction was stirred at room temperature for 4 hours. Then substrate **2a** (0.2 mmol, 34 mg) was added with $CHCl_3$ (3 mL). The reaction mixture was stirred and monitored by TLC until completion (about 24 hours). The yields shown were calculated after column chromatography.

A plausible mechanism for the reaction is shown in Scheme 5. The first step involves the formation of a Mannich base **5** from sesamol **6a**, an aromatic aldehyde and piperidine. This intermediate may undergo a proton transfer to form the highly reactive *o*-QM intermediate in solution, which reacts with the oxime chloride to form a nitrile oxide. The piperidine then leaves as a traceless additive to generate the highly reactive nitrile oxide intermediate, which rapidly reacts with *o*-QM through a [3+2] cycloaddition reaction to yield the dearomatized spiro product **4**. The 3+2 reaction probably proceeds via a concerted mechanism between the *in situ* generated *o*-QMs and nitrile oxides, which is supported by the high diastereoselectivity observed in the products. Moreover, the high regioselectivity of the [3+2] cycloaddition probably lies in the strong +M effect of oxygen in the sesamol **6a** which causes the benzylic position to be nucleophilic.[61]



Scheme 5. Proposed mechanism of the one-pot tandem dearomatization reaction.

To explore the synthetic utility of this method, the reaction was conducted on a gram scale, providing 50% yield of the desired product **4a** (Scheme 6a). Scheme 6b shows that the reaction product **4a** can be further reductively derivatized. $NaBH_4$ reduction of **4a** resulted in partial hydrogenation of the spiro ring system. NMR spectra results showed that the carbonyl group was reduced to hydroxyl group, giving compound **8** in 80% yield. This reduction may find use in the synthesis of bioactive compounds with spirocyclic motifs. On the other hand, Pd/C-catalyzed hydrogenation of **4a** cleaved the C-O bond and gave a new oxime

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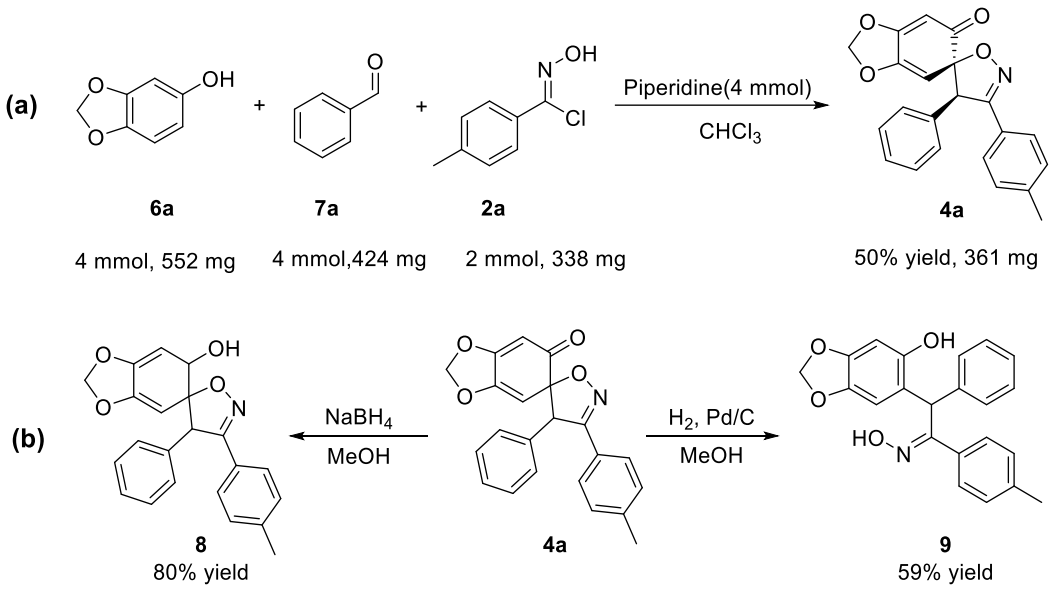
derivative **9** in 59% yield. The ^{1}HNMR spectrum shows that the peaks at 10.35 and 9.30 ppm correspond to signals of two hydroxyl groups.



Scheme 6. Scale-up experiment and reductive derivatizations.

Conclusions

In conclusion, we have successfully described the discovery of a one-pot, three-component tandem reaction involving phenols, aldehydes and chlorobenzaldehyde oximes, mediated by *in situ*-generated *ortho*-quinone methides (*o*-QMs), with piperidine acting as a traceless additive. This method allowed for the synthesis of a range of isoxazoline-based spiro-*ortho*-quinones bearing an all-carbon quaternary center at the α-position, with moderate to good yields. Future investigations are focused on extending the scope of this method towards asymmetric synthesis of such compounds.

Experimental Section

General. All the commercial compounds were bought from Alfa Aesar, Acros Organics, J&K Scientific and Sigma-Aldrich. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometer using $CDCl_3$ solvent (reported in δ ppm). The mass spectra were recorded on LTQ-Orbitrap instrument (ESI) (Thermo Fisher Scientific, USA).

General synthetic procedure for the cascade reaction: at room temperature, substrates **1** (0.2 mmol), **2** (0.2 mmol), and piperidine (0.2 mmol) were dissolved in 10 μL $CHCl_3$, and the reaction was stirred for 4 hours. Substrate **3** (0.4 mmol) in $CHCl_3$ (3 mL) was then added. The mixture was stirred until the reactants were consumed (about 12 hours). After the solvent was removed under reduced pressure, the residue was

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subjected to flash chromatography on silica gel (Hexanes/EtOAc = 10/1-5/1) to afford the desired products **4** (with characteristics as described below).

4'-Phenyl-3'-(*p*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4a). Yield: 64% (46 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.13 – 7.04 (m, 4H), 5.77 (s, 1H), 5.75 (s, 1H), 5.62 (s, 1H), 5.08 (s, 1H), 4.96 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.67, 162.44, 158.76, 146.29, 140.17, 134.51, 129.25, 129.00, 128.18, 127.63, 125.67, 102.06, 100.08, 95.90, 87.60, 61.96, 21.40; HRMS Calculated For $C_{22}H_{17}NO_4$, $[M+H]^+$: 360.1230, found: 360.1236.

4'-Phenyl-3'-(*m*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4b). Yield: 59% (42 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 1H), 7.35 – 7.24 (m, 4H), 7.14 – 7.07 (m, 4H), 5.76 (s, 1H), 5.74 (s, 1H), 5.61 (s, 1H), 5.07 (s, 1H), 4.95 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.68, 162.49, 159.05, 146.37, 138.23, 134.42, 130.83, 129.28, 128.97, 128.38, 128.22, 128.16, 124.94, 102.12, 99.93, 95.86, 87.68, 61.86, 21.32; HRMS Calculated For $C_{22}H_{17}NO_4$, $[M+H]^+$: 360.1230, found: 360.1238.

3',4'-Diphenyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4c). Yield: 58% (40 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 2H), 7.36 – 7.23 (m, 6H), 7.15 – 7.07 (m, 2H), 5.78 (s, 1H), 5.75 (s, 1H), 5.62 (s, 1H), 5.10 (s, 1H), 4.96 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.62, 162.49, 158.82, 146.37, 134.36, 129.95, 129.30, 128.99, 128.53, 128.26, 127.68, 102.10, 99.95, 95.90, 87.77, 61.85; HRMS Calculated For $C_{21}H_{15}NO_4$, $[M+H]^+$: 346.1074, found: 346.1079.

3'-(4-Methoxyphenyl)-4'-phenyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4d). Yield: 64% (48 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 2H), 7.36 – 7.27 (m, 3H), 7.13 – 7.07 (m, 2H), 6.81 – 6.74 (m, 2H), 5.78 (s, 1H), 5.75 (s, 1H), 5.62 (s, 1H), 5.06 (s, 1H), 4.96 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.72, 162.40, 160.86, 158.39, 146.27, 134.57, 129.26, 129.25, 129.00, 128.18, 121.03, 113.98, 102.03, 100.12, 95.91, 87.49, 62.06, 55.25; HRMS Calculated For $C_{22}H_{17}NO_5$, $[M+H]^+$: 376.1179, found: 376.1194.

3'-(Naphthalen-2-yl)-4'-phenyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4e). Yield: 56% (40 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.82 – 7.74 (m, 3H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.35 – 7.28 (m, 3H), 7.19 – 7.14 (m, 2H), 5.79 (s, 1H), 5.77 (s, 1H), 5.65 (s, 1H), 5.23 (s, 1H), 5.00 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.61, 162.49, 159.02, 146.43, 134.46, 133.89, 132.81, 129.34, 129.00, 128.53, 128.35, 128.29, 128.17, 127.69, 127.08, 126.40, 126.03, 124.46, 102.11, 99.94, 95.94, 87.92, 61.79; HRMS Calculated For $C_{25}H_{17}NO_4$, $[M+H]^+$: 396.1230, found: 396.1248.

3'-(Naphthalen-1-yl)-4'-phenyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4f). Yield: 52% (37 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (dd, *J* = 8.6, 0.5 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.69 – 7.60 (m, 1H), 7.58 – 7.48 (m, 1H), 7.40 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.31 – 7.21 (m, 4H), 7.15 – 7.07 (m, 2H), 5.79 (s, 1H), 5.75 (s, 1H), 5.67 (s, 1H), 5.35 (s, 1H), 5.09 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.84, 162.54, 159.39, 146.50, 134.37, 133.95, 131.33, 130.60, 129.17, 129.04, 128.54, 128.46, 128.20, 127.47, 126.85, 126.25, 125.53, 124.71, 102.11, 99.99, 96.07, 86.73, 64.37; HRMS Calculated For $C_{25}H_{17}NO_4$, $[M+H]^+$: 396.1230, found: 396.1249.

3'-(4-Fluorophenyl)-4'-phenyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4g). Yield: 62% (45 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.37 – 7.28 (m, 3H), 7.09 (dd, *J* = 7.8, 1.5 Hz, 2H), 6.98 – 6.90 (m, 2H), 5.78 (s, 1H), 5.75 (s, 1H), 5.62 (s, 1H), 5.05 (s, 1H), 4.95 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.61, 163.59 (d, *J* = 251.49 Hz), 162.56, 157.93, 146.47, 134.09, 129.64 (d, *J* = 8.08 Hz), 129.39, 128.96, 128.41, 124.75 (d, *J* = 4.04 Hz), 115.73 (d, *J* = 21.21 Hz), 102.16, 99.74, 95.86, 87.82, 61.84; HRMS Calculated For $C_{21}H_{14}FNO_4$, $[M+H]^+$: 364.0980, found: 364.1004.

3'-(2-Chlorophenyl)-4'-phenyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4h). Yield: 51% (39 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 1H), 7.35 – 7.30 (m, 1H), 7.30 – 7.18 (m, 5H),

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7.08 – 7.01 (m, 2H), 5.78 (s, 1H), 5.73 (s, 1H), 5.67 (s, 1H), 5.60 (s, 1H), 5.13 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.32, 162.51, 158.05, 146.17, 133.40, 133.17, 131.49, 130.78, 130.74, 129.23, 128.98, 128.18, 127.78, 126.78, 102.05, 100.10, 96.31, 87.95, 63.65; HRMS Calculated For $C_{21}H_{14}ClNO_4$, $[M+H]^+$: 380.0684, found: 380.0715.

3'-(3-Chlorophenyl)-4'-phenyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4i). Yield: 58% (44 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.57 (m, 1H), 7.41 – 7.30 (m, 4H), 7.29 – 7.25 (m, 1H), 7.21 – 7.15 (m, 1H), 7.14 – 7.04 (m, 2H), 5.79 (s, 1H), 5.77 (s, 1H), 5.62 (s, 1H), 5.04 (s, 1H), 4.94 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.33, 162.49, 157.90, 146.60, 134.56, 133.88, 130.33, 129.99, 129.80, 129.44, 128.93, 128.49, 127.54, 125.78, 102.17, 99.51, 95.88, 88.01, 61.44; HRMS Calculated For $C_{21}H_{14}ClNO_4$, $[M+H]^+$: 380.0684, found: 380.0705.

3'-(4-Chlorophenyl)-4'-phenyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4j). Yield: 59% (45 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 2H), 7.37 – 7.29 (m, 3H), 7.25 – 7.21 (m, 2H), 7.13 – 7.04 (m, 2H), 5.79 (s, 1H), 5.76 (s, 1H), 5.62 (s, 1H), 5.05 (s, 1H), 4.95 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.45, 162.53, 157.94, 146.51, 135.95, 134.01, 129.41, 128.94, 128.88, 128.85, 128.44, 127.04, 102.16, 99.66, 95.88, 87.94, 61.63; HRMS Calculated For $C_{21}H_{14}ClNO_4$, $[M+H]^+$: 380.0684, found: 380.0699.

3'-(4-Bromophenyl)-4'-phenyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4k). Yield: 57% (48 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 4H), 7.36 – 7.29 (m, 3H), 7.12 – 7.04 (m, 2H), 5.79 (s, 1H), 5.76 (s, 1H), 5.62 (s, 1H), 5.05 (s, 1H), 4.95 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.44, 162.54, 158.04, 146.52, 133.99, 131.80, 129.41, 129.09, 128.94, 128.45, 127.48, 124.33, 102.16, 99.64, 95.89, 87.96, 61.57; HRMS Calculated For $C_{21}H_{14}BrNO_4$, $[M+H]^+$: 424.0179, found: 424.0196.

3'-(4-nitrophenyl)-4'-phenyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4l). Yield: 52% (41 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.09 (m, 2H), 7.76 – 7.69 (m, 2H), 7.39 – 7.31 (m, 3H), 7.09 (dd, J = 7.6, 1.6 Hz, 2H), 5.82 (s, 1H), 5.79 (s, 1H), 5.64 (s, 1H), 5.09 (s, 1H), 4.96 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.08, 162.65, 157.38, 148.27, 146.85, 134.68, 133.47, 129.63, 128.88, 128.77, 128.34, 123.81, 102.29, 99.09, 95.90, 88.61, 61.13. HRMS Calculated For $C_{21}H_{14}N_2O_6$, $[M+H]^+$: 391.0925, found: 391.0942.

4'-(*o*-Tolyl)-3'-(*p*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4m). Yield: 71% (53 mg). Colorless crystal, melting point : 126 °C . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 2H), 7.24 – 7.13 (m, 3H), 7.11 – 7.03 (m, 3H), 6.95 (d, *J* = 7.5 Hz, 1H), 5.75 (d, *J* = 1.6 Hz, 2H), 5.61 (s, 1H), 5.31 (s, 1H), 4.88 (s, 1H), 2.28 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.75, 162.23, 159.00, 146.19, 140.16, 136.01, 133.05, 130.87, 129.28, 129.12, 128.05, 127.56, 126.82, 125.73, 102.08, 100.07, 95.71, 87.15, 58.02, 21.42, 20.21; HRMS Calculated For $C_{23}H_{19}NO_4$, $[M+H]^+$: 374.1387, found: 374.1411.

4'-(*m*-Tolyl)-3'-(*p*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4n). Yield: 47% (35 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 2H), 7.23 – 7.16 (m, 1H), 7.11– 7.03 (m, 3H), 6.93 – 6.97 (m, 2H), 5.76 (s, 1H), 5.74 (s, 1H), 5.60 (s, 1H), 5.01 (s, 1H), 4.97 (s, 1H), 2.29 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.75, 162.44, 159.06, 146.36, 140.12, 139.02, 134.37, 129.52, 129.24, 129.09, 129.03, 127.62, 126.10, 125.76, 102.09, 100.02, 95.81, 87.54, 61.82, 21.45, 21.41; HRMS Calculated For $C_{23}H_{19}NO_4$, $[M+H]^+$: 374.1387, found: 374.1406.

3',4'-di-*p*-Tolyl-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4o). Yield: 55%. White foam (41 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 7.9 Hz, 2H), 5.77 (s, 1H), 5.75 (s, 1H), 5.61 (s, 1H), 5.04 (s, 1H), 4.98 (s, 1H), 2.31 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.86, 162.51, 158.90, 146.21, 140.10, 137.95, 131.37, 129.97, 129.23, 128.84, 127.62, 125.77, 102.11, 100.20, 95.82, 87.58, 61.69, 21.41, 21.15; HRMS Calculated For $C_{23}H_{19}NO_4$, $[M+H]^+$: 374.1387, found: 374.1401.

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4'-(4-Methoxyphenyl)-3'-(*p*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4p).: Yield: 54% (42 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.76 (s, 1H), 5.74 (s, 1H), 5.59 (s, 1H), 5.03 (s, 1H), 4.98 (s, 1H), 3.76 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.92, 162.52, 159.34, 158.91, 146.18, 140.12, 130.08, 129.23, 127.63, 126.37, 125.74, 114.63, 102.10, 100.22, 95.84, 87.60, 61.41, 55.23, 21.41; HRMS Calculated For $C_{23}H_{19}NO_5$, $[M+H]^+$: 390.1336, found: 390.1356.

4'-(Naphthalen-2-yl)-3'-(*p*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4q). Yield: 61% (50 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.74 (m, 3H), 7.60 (s, 1H), 7.52 – 7.44 (m, 4H), 7.20 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 5.69 (s, 1H), 5.66 (s, 1H), 5.62 (s, 1H), 5.24 (s, 1H), 4.97 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.72, 162.52, 158.91, 146.45, 140.23, 133.48, 132.93, 132.08, 129.29, 129.23, 128.22, 128.00, 127.79, 127.66, 126.62, 126.53, 126.48, 125.68, 102.12, 99.93, 95.90, 87.69, 62.09, 21.39; HRMS Calculated For $C_{26}H_{19}NO_4$, $[M+H]^+$: 410.1387, found: 410.1406.

4'-(Naphthalen-1-yl)-3'-(*p*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4r). Yield: 79% (65 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.86 (m, 1H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.53 (dd, *J* = 6.4, 3.3 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.31 (m, 1H), 7.18 (d, *J* = 7.1 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 5.93 (d, *J* = 6.0 Hz, 1H), 5.70 (s, 1H), 5.66 (s, 1H), 5.53 (s, 1H), 4.81 (s, 1H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.70, 162.45, 158.74, 146.24, 140.20, 134.05, 131.74, 130.62, 129.27, 129.22, 128.74, 127.77, 127.62, 126.91, 126.13, 125.74, 125.58, 122.66, 101.93, 100.15, 95.88, 87.75, 56.81, 21.40; HRMS Calculated For $C_{26}H_{19}NO_4$, $[M+H]^+$: 410.1387, found: 410.1401.

4'-(4-Fluorophenyl)-3'-(*p*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4s).: Yield: 50%(38 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2 Hz, 2H), 7.11 – 7.05 (m, 4H), 7.04 – 6.97 (m, 2H), 5.78 (s, 1H), 5.76 (s, 1H), 5.60 (s, 1H), 5.07 (s, 1H), 4.93 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.56, 162.51, 162.43 (d, *J* = 249.47 Hz), 158.70, 146.47, 140.38, 130.64 (d, *J* = 8.08 Hz), 130.33 (d, *J* = 4.04 Hz), 129.33, 127.59, 125.43, 116.33 (d, J = 22.22 Hz), 102.23, 99.65, 95.91, 87.49, 61.15, 21.41; HRMS Calculated For $C_{22}H_{19}FNO_4$, $[M+H]^+$: 378.1136, found: 378.1163.

4'-(4-Chlorophenyl)-3'-(*p*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4t). Yield: 69% (54 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.11 – 7.01 (m, 4H), 5.79 (s, 1H), 5.78 (s, 1H), 5.62 (s, 1H), 5.06 (s, 1H), 4.93 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.43, 162.52, 158.55, 146.56, 140.45, 134.20, 133.07, 130.32, 129.53, 129.37, 127.57, 125.34, 102.26, 99.52, 95.93, 87.45, 61.21, 21.42; HRMS Calculated For $C_{22}H_{19}ClNO_4$, $[M+H]^+$: 378.1136, found: 378.1163.

4'-(4-Bromophenyl)-3'-(*p*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4u). Yield: 70% (61 mg).White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 8.4 Hz, 5H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 5.78 (s, 1H), 5.76 (s, 1H), 5.60 (s, 1H), 5.04 (s, 1H), 4.92 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.34, 162.48, 158.48, 146.58, 140.45, 133.61, 132.48, 130.65, 129.37, 127.58, 125.33, 122.37, 102.24, 99.49, 95.94, 87.38, 61.24, 21.43; HRMS Calculated For $C_{22}H_{19}BrNO_4$, $[M+H]^+$: 438.0335, found: 438.0351.

4'-(3-Bromophenyl)-3'-(*p*-tolyl)-4'*H*,6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazol]-6-one (4v). Yield: 43% (38 mg).White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 3H), 7.29 – 7.27 (m, 1H), 7.23 – 7.16 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 1H), 5.80 (s, 1H), 5.79 (s, 1H), 5.62 (s, 1H), 5.01 (s, 1H), 4.93 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.21, 162.42, 158.52, 146.74, 140.47, 136.90, 131.85, 131.49, 130.82, 129.38, 127.62, 127.58, 125.28, 123.41, 102.21, 99.30, 95.93, 87.44, 61.19, 21.43; HRMS Calculated For $C_{22}H_{19}BrNO_4$, $[M+H]^+$: 438.0335, found: 438.0349.

8,9-Dimethoxy-4-phenyl-3-(*p*-tolyl)-1-oxa-2-azaspiro[4.5]deca-2,7,9-trien-6-one (4w). Yield: 42% (32 mg).White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.26 (m, 3H), 7.13 – 7.01 (m, 4H), 5.44 (s, 1H), 5.01 (s, 1H), 4.62 (s, 1H), 3.85 (s, 3H), 3.24 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ

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196.49, 165.60, 157.89, 148.46, 140.15, 134.71, 129.24, 129.08, 128.85, 128.08, 127.62, 125.80, 103.57, 98.08, 88.01, 62.29, 56.82, 55.30, 21.40; HRMS Calculated For $C_{23}H_{21}NO_4$, $[M+H]^+$: 376.1543, found: 376.1569.

4-Phenyl-3-(*p*-tolyl)-1'*H*,4*H*-spiro[isoxazole-5,2'-naphthalen]-1'-one (4x). Yield: 53% (39 mg). White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.59 – 7.50 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.18 (d, *J* = 7.1 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 5.94 (s, 1H), 5.68 (d, *J* = 15.5 Hz, 2H), 5.54 (s, 1H), 4.81 (s, 1H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.69, 162.44, 158.73, 146.23, 140.19, 134.05, 131.74, 130.63, 129.27, 129.22, 128.74, 127.77, 127.62, 126.90, 126.13, 125.74, 125.58, 122.66, 101.93, 100.15, 95.89, 87.74, 56.80, 21.40; HRMS Calculated For $C_{26}H_{21}NO_2$, $[M+H]^+$: 366.1489, found: 366.1498.

Synthetic procedure for the compound 8. To a solution of **4d** (72 mg, 0.2 mmol) in MeOH (4 mL) was added $NaBH_4$ (16 mg, 0.4 mmol) at 0 °C. Then, the reaction mixture was stirred for 4 h. After the completion of the reaction indicated by TLC, the solvent was evaporated and the residue was purified by column chromatography on silica gel to give product **8** (61mg, 80% yield).

4'-Phenyl-3'-(*p*-tolyl)-6*H*-spiro[benzo[*d*][1,3]dioxole-5,5'-isoxazolidin]-6-one (8). White foam. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.27 – 7.24 (m, 1H), 7.10 – 7.04 (m, 4H), 5.51 (s, 1H), 5.49 (s, 1H), 5.14 (d, *J* = 4.0 Hz, 1H), 4.68 (s, 1H), 4.53 – 4.49 (m, 1H), 4.42 (s, 1H), 2.81 (d, *J* = 6.2 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 160.15, 147.76, 147.23, 140.36, 135.03, 129.35, 129.16, 128.70, 127.94, 127.36, 125.87, 100.10, 93.81, 92.54, 92.37, 72.75, 60.54, 21.42; HRMS Calculated For $C_{22}H_{19}NO_4$, $[M+H]^+$: 362.1387, found: 362.1386.

Synthetic procedure for the compound 9. 4d (72 mg, 0.2 mmol) and 10% palladium on charcoal (5 mg) were dissolved in methanol (4 mL). The mixture was hydrogenated with H_2 from a balloon for 12 h. The reaction mixture was then filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **9** (45mg, 59% yield).

(*E*)-2-(6-Hydroxybenzo[*d*][1,3]dioxol-5-ygl)-2-phenyl-1-(*p*-tolyl)ethan-1-one oxime (9): White foam. ^{1}H NMR (700 MHz, DMSO) δ 10.85 (s, 1H), 9.30 (s, 1H), 7.35 (d, J = 8.0 Hz, 3H), 7.29 – 7.25 (m, 2H), 7.24 (d, *J* = 7.3 Hz, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.41 (d, *J* = 2.4 Hz, 2H), 5.85 (d, *J* = 4.7 Hz, 2H), 5.57 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (176 MHz, DMSO) δ 157.03, 149.44, 146.15, 141.59, 139.80, 137.92, 132.74, 129.70, 128.79, 128.56, 128.48, 126.62, 120.18, 109.56, 100.98, 97.89, 49.79, 21.30; HRMS Calculated For $C_{22}H_{19}NO_4$, $[M+H]^+$: 362.1387, found: 362.1384.

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Supplementary Material

All reaction conditions in the manuscript, copies of all ^{1}H and ^{13}C NMR spectra of all products, HRMS spectra of new compounds and basic crystallographic data of **4a** are available in the supplementary material.

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