

Communication

Dearomatization of 3-Aminophenols for Synthesis of Spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones via Hydride Transfer Strategy-Enabled [5+1] Annulations

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Abstract: The Sc(OTf)₃-catalyzed dearomatative [5+1] annulations between readily available 3-aminophenols and *O*-alkyl *ortho*-oxybenzaldehydes were developed for synthesis of spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones. The “two-birds-with-one-stone” strategy was disclosed by the dearomatization of phenols and direct α -C(sp³)-H bond functionalization of oxygen through cascade condensation/[1,5]-hydride transfer/dearomatative-cyclization process. In addition, the anti-fungal activity assay and derivatizations of products were conducted to further enrich the utility of the structure.

Keywords: dearomatization; spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones; C(sp³)-H bond functionalization; antifungal activity



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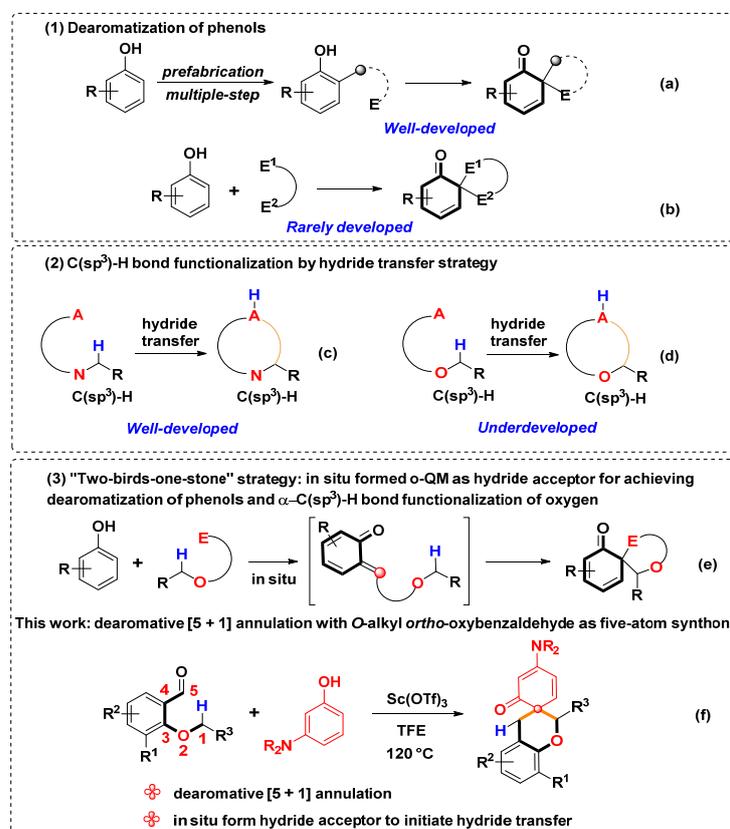
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1. Introduction

Aromatic compounds as bulk and fundamental chemical feedstocks play a prominent role in organic synthesis [1–3]. Dearomatization is the high-value-added transformation of aromatic compounds to generate structurally diverse three-dimensional polycyclic molecules [4–7]. Due to the high significance of dearomatization in assembling sophisticated polycyclic architectures with enhanced sp³-character, much more attention has been paid to dearomatization chemistry [4–16]. Among the dearomatization reactions, phenol is one of the most studied structures which could be facily converted into cyclohexadienone, and many strategies have been developed to achieve dearomatization of phenols [13–16]. For example, *ortho*-substituted phenols were commonly used to undergo oxidant-promoted oxidative dearomatization or transition-metal-catalyzed allylation, alkylation, amination to generate cyclohexadienones (Scheme 1a) [17–19]. Although great progress has been made in these transformations, the *ortho*-substituted phenols have to be prefabricated, which brings limitations in practical production. Notably, the employment of phenols and dielectrophiles as starting materials for direct dearomatization of phenols was a highly atom- and step-economic strategy (Scheme 1b). Until now, the dearomatization of phenols by employment of the phenols without pre-installed substituents at the dearomatization site via direct formation of two chemical bonds was a huge challenge.

Hydride transfer/cyclization has attracted intense interest as an efficient strategy with the breaking and formation of a number of bonds in one operation for construction of privileged molecules [20–38]. Among the diverse transformations, the α -C(sp³)-H bond functionalization of amine occupied the majority (Scheme 1c) [23–35], while the application of an α -C(sp³)-H bond of oxygen as hydride donor was relatively challenging, which might be attributed to (1) lower reactivity of the α -C(sp³)-H bond of oxygen

than that of *tert*-amine; (2) the in situ-formed acyclic oxocarbenium intermediate tends to hydrolyze [36–38]. This disadvantage led to few acceptors being available for initiating the α -C(sp³)-H bond functionalization of oxygen (Scheme 1d).



Scheme 1. (a) Dearomatization of phenols. (b) Direct dearomatization of phenols. (c) The α -C(sp³)-H bond functionalization of amine. (d) The α -C(sp³)-H bond functionalization of oxygen. (e) In situ formed *o*-QM as hydride acceptor for achieving dearomatization of phenols and α -C(sp³)-H bond functionalization of oxygen. (f) Dearomative [5 + 1] annulation with *O*-alkyl *ortho*-oxybenzaldehyde as five-atom synthon.

Aromatization is an important thermodynamic driving force for organic transformation [39–42]. Inspired by the above-mentioned challenge, we designed to utilize the in situ-assembled *ortho*-quinone methides (*o*-QMs) from phenols and aldehydes as hydride acceptors for driving hydride transfer with the potent propensity of aromatization. In addition, the formal [5+1] annulation that undergo dearomatization/rearomatization/dearomatization process would achieve the direct dearomatization of phenols and α -C(sp³)-H bond functionalization of oxygen (Scheme 1e).

As a continuation of our interest in developing hydride transfer-involved reactions for the rapid construction of privileged heterocyclic skeletons [7,22,34,35,42], herein we report the "two-birds-with-one-stone" strategy to dearomatize phenols and functionalize α -C(sp³)-H bond of oxygen. This dearomative [5+1] annulation provided a variety of cy spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones from 3-aminophenols and *O*-alkyl *ortho*-oxybenzaldehydes through Sc(OTf)₃-catalyzed cascade condensation/[1,5]-hydride transfer/dearomative-cyclization process (Scheme 1f). It is worth mentioning that the direct dearomatization of phenols combined with the functionalization of an α -C(sp³)-H bond of oxygen via a hydride transfer strategy was achieved unprecedentedly. In addition, the antifungal activity assay preliminarily showed the potential of these products in the prevention and control of agricultural pathogens.

2. Results and Discussion

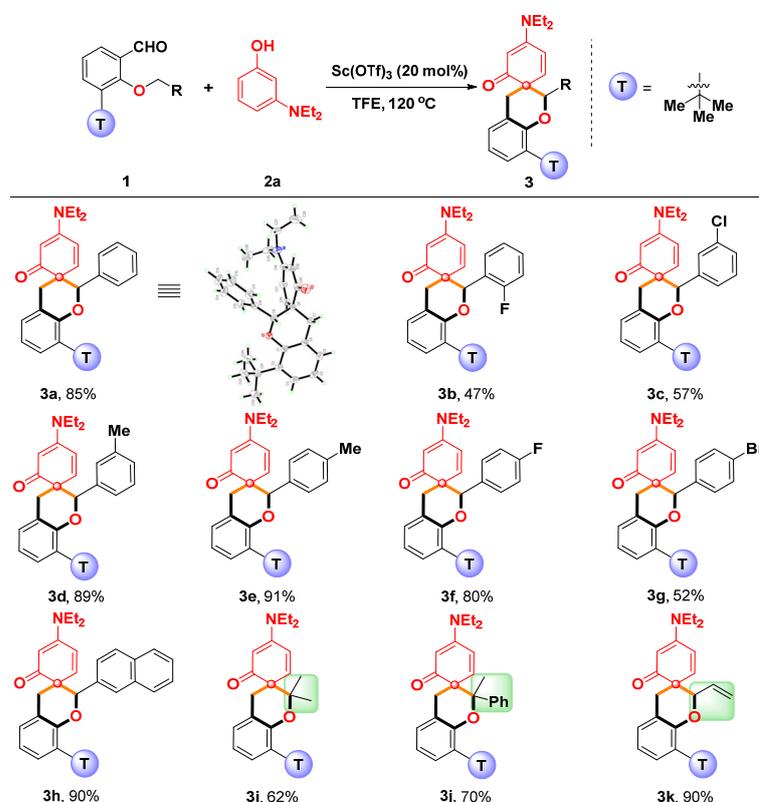
At the outset of the reaction, the *O*-benzyl salicylaldehyde-derived substrate **1a** and phenol **2a** were selected as model substrates to examine the reaction (Table 1). Firstly, Lewis acids Sc(OTf)₃, Mg(OTf)₂, and Zn(OTf)₂ were applied as catalysts in DCE to promote the desired transformation. To our delight, the expected cyclohexadienone-fused spirochromane **3a** was obtained through the Lewis acids-catalyzed cascade condensation/[1,5]-hydride transfer/dearomatization-cyclization, and a 52% yield was isolated with Sc(OTf)₃ as catalyst (entry 1). Next, various Brønsted acids were also applied to evaluate the reaction. As shown, Brønsted acids showed slightly weaker catalytic activity than Lewis acids (entries 4–7). Subsequently, diverse solvents were investigated with Sc(OTf)₃ as catalyst to further improve the yield of the product. Delightedly, fluorinated alcohol TFE (2,2,2-trifluoroethanol) was efficient in mediating the dearomatization/aromatization-dearomatization process to afford the product **3a** in 84% yield and excellent diastereoselectivity (entries 8–13). Moreover, HFIP (1,1,1,3,3,3-Hexafluoro-2-propanol) was also a good reaction medium for the transformation (entry 14). Then, the ratios of substrates, reaction temperature, and the loading of catalyst were meticulously screened. The results showed that the adjustment of the ratio of **1a** and **2a** and reaction temperature was unavailing for improving the reaction efficiency (entries 15–19). The examination of the loading of catalyst indicated that 20 mol% of Sc(OTf)₃ was the suitable dosage for the reaction (entries 20–22). At last, the optimal reaction conditions were determined to be those described in entry 21 of Table 1.

Table 1. Optimization of the reaction conditions ¹.

Entry	Catalyst	Ratio (1a:2a)	Solvent	Temp. (°C)	Time (h)	Yield (%) ²
1	Sc(OTf) ₃	1:1.5	DCE	120	5	52
2	Mg(OTf) ₂	1:1.5	DCE	120	5	22
3	Zn(OTf) ₂	1:1.5	DCE	120	5	40
4	TfOH	1:1.5	DCE	120	5	No
5	TsOH	1:1.5	DCE	120	5	22
6	CSA	1:1.5	DCE	120	5	20
7	TFA	1:1.5	DCE	120	5	16
8	Sc(OTf) ₃	1:1.5	TFE	120	5	84
9	Sc(OTf) ₃	1:1.5	MeOH	120	12	Trace
10	Sc(OTf) ₃	1:1.5	EtOH	120	5	20
11	Sc(OTf) ₃	1:1.5	<i>n</i> -BuOH	120	12	No
12	Sc(OTf) ₃	1:1.5	Toluene	120	12	No
13	Sc(OTf) ₃	1:1.5	EA	120	12	No
14	Sc(OTf) ₃	1:1.5	HFIP	120	5	65
15	Sc(OTf) ₃	1:1	TFE	120	5	71
16	Sc(OTf) ₃	1:1.2	TFE	120	5	82
17	Sc(OTf) ₃	1:2	TFE	120	5	77
18	Sc(OTf) ₃	1:1.5	TFE	80	5	70
19	Sc(OTf) ₃	1:1.5	TFE	100	5	71
20 ³	Sc(OTf) ₃	1:1.5	TFE	120	5	78
21 ⁴	Sc(OTf) ₃	1:1.5	TFE	120	5	85
22 ⁵	Sc(OTf) ₃	1:1.5	TFE	120	5	82

¹ Reaction conditions (unless otherwise noted): **1a** (0.1 mmol, 26.8 mg), **2a** (x mmol), catalyst (30 mol%), solvent (1 mL), under air; TFE = 2,2,2-Trifluoroethanol, HFIP = 1,1,1,3,3,3-Hexafluoro-2-propanol. ² Isolated yield after column chromatography; dr > 20:1, dr was determined by ¹H NMR. ³ Sc(OTf)₃ (10 mol%). ⁴ Sc(OTf)₃ (20 mol%). ⁵ Sc(OTf)₃ (40 mol%).

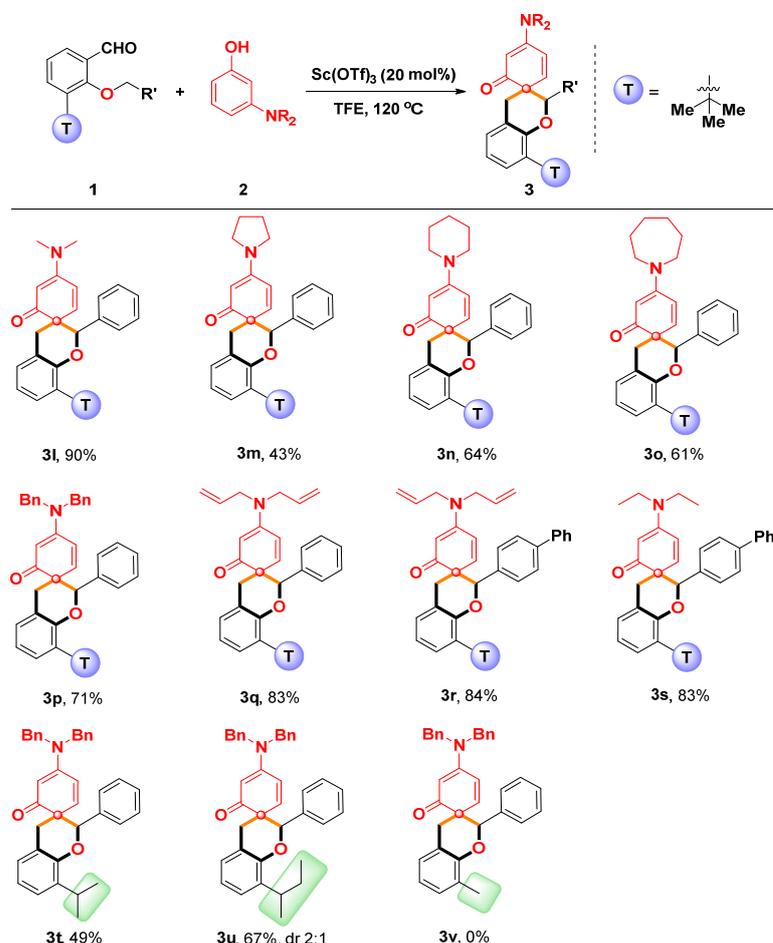
With the optimal reaction conditions in hand, the generality of the dearomative [5+1] annulation with respect to diverse *O*-alkyl *ortho*-oxybenzaldehydes **1** was investigated (Scheme 2). Notably, substrates **1** carrying electron-withdrawing or -donating groups on the phenyl ring of the benzyl moiety were applicable for the [5+1] annulation with phenol **2a** to afford the corresponding products **3a–g** in moderate to excellent yields and excellent diastereoselectivities. Moreover, among the diverse substituents, the electron-withdrawing group had some effect on the reaction efficiency, delivering slightly lower yields of products (**3b**, **3c**, **3f**, **3g**). Apart from 2-phenyl spirochromane, the 2-naphthyl spirochromane **3h** could also be obtained in 90%. Moreover, isopropyl could act as hydride donor to conduct the hydride transfer-involved dearomative [5+1] annulation to provide the gem-dimethyl-substituted spirochromane **3i**. In addition, the methyl-substituted benzyl and allyl-derived *ortho*-oxybenzaldehydes **1** were good reaction partners with phenol to perform the dearomative [5+1] annulation for giving the diversity-enriched spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones **3j** and **3k** in 70% and 90% yields, respectively.



Scheme 2. The scope of *O*-alkyl *ortho*-oxybenzaldehydes for the dearomative [5+1] annulations. Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), Sc(OTf)₃ (20 mol%), TFE (1 mL), at 120 °C under air for 5 h; isolated yield after column chromatography; dr > 20:1, dr was determined by ¹H NMR.

Next, further investigation of the substrate scope with regard to phenols was performed for dearomatization of diverse phenols (Scheme 3). Various types of phenols were applied to react with *O*-alkyl *ortho*-oxybenzaldehydes **1**. For example, non-substituted phenol was unavailable for the transformation, and electron-rich sesamol gave several unascertained products. Moreover, *m*-aminophenols showed excellent activity for reacting with *O*-alkyl *ortho*-oxybenzaldehydes. For instance, dimethylamine, pyrrolidine, piperidine, and azepine-substituted phenols were applicable for the transformation, affording the corresponding spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones **3l–o** in moderate to excellent yields. In addition, dibenzylamine- and diallylamine-substituted phenols were also available for the reaction which further enriched the diversity of the substituents of products. The wide tolerance of the substituents on the phenols made the product more feasible for late-stage functionalization. On the other hand, the *ortho tert*-butyl could

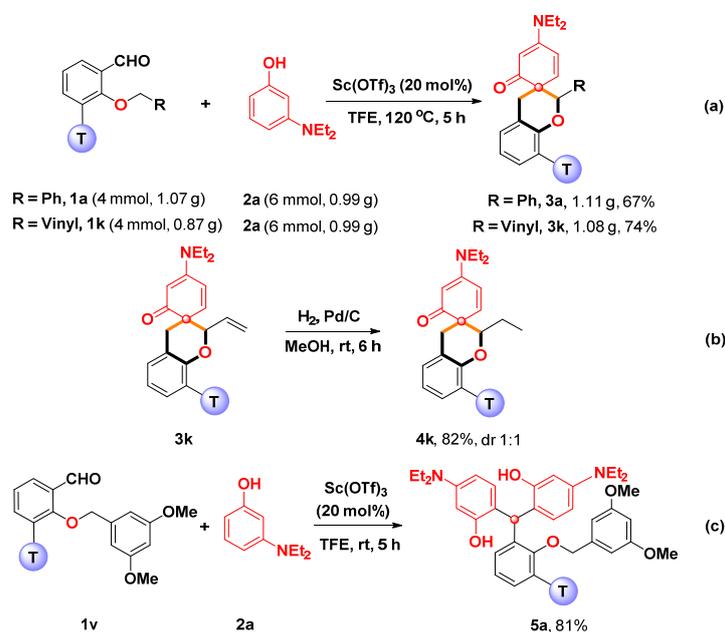
be replaced by *iso*-propyl or *sec*-butyl, delivering the corresponding products **3t** or **3u** in slightly lower yields than product **3a**.



Scheme 3. The substrate scope of the dearomative [5+1] annulations. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), Sc(OTf)₃ (20 mol%), TFE (1 mL), at 120 °C under air for 5 h; isolated yield after column chromatography; dr > 20:1, dr was determined by ¹H NMR.

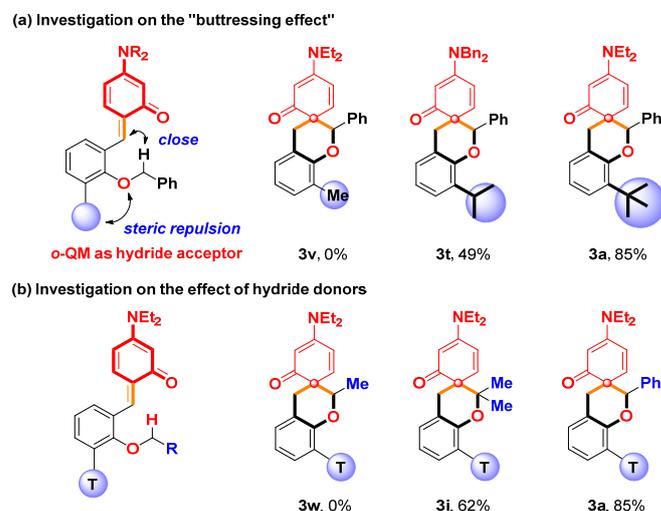
Then, the practicality of this protocol was demonstrated by the gram-scale synthesis of products **3**. As shown in Scheme 4a, the reaction efficiency was almost unaffected in a 4 mmol scale to give the corresponding products **3a** and **3k** in 67% and 74% yields, respectively (Scheme 4a). In addition, in order to illustrate the biological activity of the product, the antifungal activity assay was performed (See Supporting Information). Compounds **3a**, **3j**, **3k**, **3q**, **3t** and **3u** were evaluated for their antifungal activities against four economically important phytopathogenic fungi: *Rhizoctonia solani*, *Alternaria solani*, *Alternaria mali*, and *Sclerotium rolfsii*. The results showed that most of the tested compounds possessed in vitro antifungal activity at a concentration of 200 mg/L. Especially, compound **3a** exhibited remarkable antifungal potency among all target compounds, with inhibition rates of 40.21, 60.35, 53.56 and 29.09% at a concentration of 200 mg/L, respectively, against *Rhizoctonia solani*, *Alternaria solani*, *Alternaria mali*, and *Sclerotium rolfsii*. The results preliminarily showed the potential of these products in the prevention and control of agricultural pathogens. Moreover, the selective reduction in the terminal alkene by H₂/Pd/C was performed to provide the 2-ethyl spirochromane **4k** in 82% yield (Scheme 4b). This transformation remedied the deficiency that was unable to furnish 2-ethyl spirochromane by the direct dearomative [5+1] annulation. Apart from spirochromanes, polyarylated methane **5a** could also be provided by twice nucleophilic addition with the employment of the

O-alkyl *ortho*-oxybenzaldehyde **1v** (Scheme 4c). This transformation indicated that the latter nucleophilic addition and hydride transfer were competitive reaction pathways.



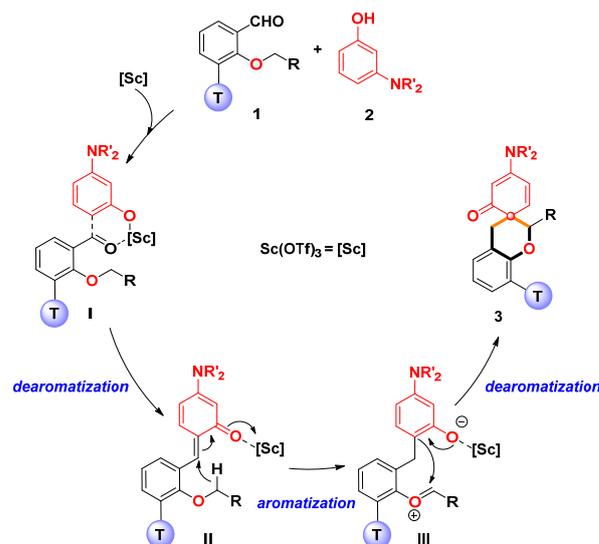
Scheme 4. (a) Gram-scale synthesis of products **3a** and **3k**. (b) Derivatization of Product **3k**. (c) Synthesis of polyarylated methane **5a**.

Subsequently, the key factor for the hydride transfer/dearomative-cyclization was investigated (Scheme 5). In a hydride transfer reaction, the distance between hydride donor and hydride acceptor was decisive for the occurrence, and the conclusion was verified by the investigation on the “buttressing effect”. As shown in Scheme 5a, remarkable enhancement of the reactivity by the bulky group *ortho* to the alkoxy group could be clearly observed, which might be due to the steric repulsion between the *ortho* group and the alkoxy group shortening the distance between hydride donor and hydride acceptor. Then, the investigation into the effect of hydride donors demonstrated that the transfer ability of the hydride donors was a key factor as well (Scheme 5b). The examination of the α -C(sp³)-H bond of ethyl, *iso*-propyl, and benzyl adjacent to oxygen showed the difference in the activity, which might be dependent on the transfer ability of the hydride donors and the stability of the cations generated upon hydride transfer.



Scheme 5. The investigation into the influence factor for the hydride transfer process.

Based on the above experiments and precedent reports [37,38], a plausible mechanism was proposed to rationalize the dearomative [5+1] annulation (Scheme 6). First, the catalyst scandium-aggregated *O*-alkyl *ortho*-oxybenzaldehyde **1** and phenol **2** to mediate the Friedel–Crafts hydroxyalkylation condensation. Then, the adduct dehydrated immediately to generate an *o*-QM intermediate **II**. The propensity for aromatization of *o*-QM as a driving force initiated the α -hydride of oxygen transfer to yield the zwitterionic intermediate **III**. Next, the dearomative cyclization of **III** took place to furnish the cyclohexadienone-fused spirochromane **3**.



Scheme 6. Proposed mechanism.

3. Materials and Methods

3.1. General Information

Unless otherwise noted, all reagents and solvents were purchased from the commercial sources (from Adamas-beta, Shanghai, China) and used as received. Thin layer chromatography (TLC) was used to monitor the reaction on a Merck 60 F254 precoated silica gel plate (0.2 mm thickness). TLC spots were visualized by UV-light irradiation on a Spectroline Model ENF-24061/F 254 nm. The products were purified by flash column chromatography (200–300 mesh silica gel) eluted with the gradient of petroleum ether and ethyl acetate. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker 500 MHz or 400 MHz NMR spectrometer (CDCl_3 , $\text{DMSO}-d_6$ or $\text{Methanol}-d_4$ solvent). The chemical shifts were reported in parts per million (ppm), downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.26, singlet), dimethyl sulfoxide-*d*₆ (δ 2.54, singlet) or methanol-*d*₄ (δ 3.31, quintuplet). Multiplicities were afforded as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet) or m (multiplets). The number of protons for a given resonance is indicated by nH. Coupling constants were reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were referenced to the appropriate residual solvent peak. High-resolution mass spectral analysis (HRMS) was performed on Waters XEVO G2 Q-TOF. The *ortho*-substituted benzaldehydes were prepared according to the literature [43].

3.2. General Procedure for the Dearomative [5+1] Annulation

A sealed tube was charged with *O*-alkyl *ortho*-oxybenzaldehyde **1** (0.1 mmol), phenol **2** (0.15 mmol), $\text{Sc}(\text{OTf})_3$ (20 mol%), and TFE (1.0 mL). The mixture was stirred at 120 °C for 5 h. Upon completion of the reaction, as indicated by TLC analysis, the mixture was concentrated in vacuum and the residue was directly purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 1:3) to afford the desired spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones **3a–u**.

3.3. Gram-Scale Synthesis and Derivatization of Products 3

A round-bottom flask was charged with *O*-alkyl *ortho*-oxybenzaldehydes **1a** (4.0 mmol, 1.07 g) or **1k** (4.0 mmol, 0.87 g), phenol **2a** (6.0 mmol, 0.99 g), Sc(OTf)₃ (20 mol%), and TFE (40.0 mL). The mixture was stirred at 120 °C for 5 h. Upon completion of the reaction, as indicated by TLC analysis, the mixture was concentrated in vacuum and the residue was directly purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 1:3) to afford the desired spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones **3a** in 67% yield or **3k** in 74% yield, respectively.

A reaction tube was charged with cyclohexadienone-fused spirochromane **3k** (0.1 mmol, 36.6 mg) and 30% by wt Pd/C (10% by wt relative to **3k**) in 1.0 mL of MeOH. The tube was equipped with a magnetic stir bar, and the suspension was sealed with a septum under an atmosphere of H₂ supplied via a balloon for 6 h. Upon completion of the reaction, as indicated by TLC analysis, the suspension was filtered through a pad of Celite. The filtrate was concentrated in vacuum. The residue was directly purified by flash column chromatography on silica gel (ethyl acetate: petroleum ether, 1:3) to give the desired product **4k** in 82% yield and 1:1 diastereoselectivity.

3.4. The Procedure for Synthesis of Product 5a

A tube was charged with *O*-alkyl *ortho*-oxybenzaldehyde **1v** (0.1 mmol, 32.8 mg), phenol **2a** (0.22 mmol, 36.4 mg), Sc(OTf)₃ (20 mol%), and TFE (1.0 mL). The mixture was stirred at room temperature for 5 h. Upon completion of the reaction, as indicated by TLC analysis, the mixture was concentrated in vacuum and the residue was directly purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 1:15) to afford the polyarylated methane **5a** in 81% yield.

3.5. Investigation on the “Buttressing Effect”

A tube was charged with *O*-alkyl *ortho*-oxybenzaldehydes **1** bearing methyl, isopropyl, or tertbutyl (0.1 mmol), phenol **2** (0.15 mmol), Sc(OTf)₃ (20 mol%), and TFE (1.0 mL). The mixture was stirred at 120 °C for 5 h. Upon completion of the reaction, as indicated by TLC analysis, the mixture was concentrated in vacuum and the residue was directly purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 1:3) to afford the desired spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones **3v**, **3t**, or **3a**. A remarkable enhancement of the reactivity by the bulky group ortho to the alkoxy group could be clearly observed, which might be due to the steric repulsion between ortho group and alkoxy group shortening the distance between hydride donor and hydride acceptor.

3.6. Investigation on the Effect of Hydride Donors

A tube was charged with *O*-ethyl, *O*-isopropyl, or *O*-benzyl *ortho*-oxybenzaldehydes **1** (0.1 mmol), phenol **2** (0.15 mmol), Sc(OTf)₃ (20 mol%), and TFE (1.0 mL). The mixture was stirred at 120 °C for 5 h. Upon completion of the reaction, as indicated by TLC analysis, the mixture was concentrated in vacuum and the residue was directly purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 1:3) to afford the desired spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones **3w**, **3i**, or **3a**. A remarkable enhancement of the reactivity by the bulky group ortho to the alkoxy group could be clearly observed, which might be due to the steric repulsion between ortho group and alkoxy group shortening the distance between hydride donor and hydride acceptor. The examination of the α-C(sp³)-H bond of ethyl, *iso*-propyl, and benzyl adjacent to oxygen showed the difference in the activity, which might be dependent on the transfer ability of the hydride donors and the stability of the cations generated upon hydride transfer.

3.7. Characterization of Products

8-(tert-butyl)-4'-(diethylamino)-2-phenylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3a**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (35.3 mg, 85% yield) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ 7.30 (m, 2H), 7.17–7.08 (m, 4H), 6.95 (d, $J = 7.4$ Hz, 1H), 6.82 (d, $J = 7.6$ Hz, 1H), 6.56 (d, $J = 10.4$ Hz, 1H), 6.26 (dd, $J = 10.4, 2.1$ Hz, 1H), 5.24 (s, 1H), 4.93 (d, $J = 2.0$ Hz, 1H), 3.85 (d, $J = 16.5$ Hz, 1H), 3.16–3.01 (m, 4H), 2.62 (d, $J = 16.6$ Hz, 1H), 1.30 (s, 9H), 0.93 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.4, 156.2, 152.6, 142.2, 137.9, 137.1, 127.9, 127.6, 127.1, 124.4, 121.0, 120.4, 119.0, 97.4, 83.5, 49.9, 45.0, 36.9, 34.8, 29.9. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{28}\text{H}_{33}\text{NNaO}_2^+$: 438.2404, found: 438.2408.

8-(tert-butyl)-4'-(diethylamino)-2-(2-fluorophenyl)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3b**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (20.4 mg, 47% yield) as a yellow solid.

^1H NMR (500 MHz, CDCl_3) δ 7.41 (t, $J = 6.9$ Hz, 1H), 7.21 (d, $J = 6.7$ Hz, 1H), 7.18 (d, $J = 7.7$ Hz, 1H), 7.02 (m, 2H), 6.99–6.94 (m, 1H), 6.89 (t, $J = 7.6$ Hz, 1H), 6.71 (d, $J = 10.4$ Hz, 1H), 6.43 (dd, $J = 10.4, 1.8$ Hz, 1H), 5.61 (s, 1H), 5.05 (d, $J = 1.4$ Hz, 1H), 3.97 (d, $J = 16.6$ Hz, 1H), 3.21 (d, $J = 6.2$ Hz, 4H), 2.70 (d, $J = 16.6$ Hz, 1H), 1.34 (s, 9H), 1.04 (t, $J = 6.7$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 194.5, 160.2 (d, $J = 248.7$ Hz), 156.0, 152.5, 142.2, 137.8, 129.5 (d, $J = 3.8$ Hz), 129.3 (d, $J = 8.8$ Hz), 127.9, 124.5 (d, $J = 12.5$ Hz), 124.4, 122.6 (d, $J = 3.8$ Hz), 120.8, 120.5, 119.0, 115.3, 115.2, 96.7, 77.6, 49.2, 44.9, 36.8, 34.7, 29.7. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{28}\text{H}_{32}\text{FNNaO}_2^+$: 456.2309, found: 456.2311.

8-(tert-butyl)-2-(3-chlorophenyl)-4'-(diethylamino)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3c**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (25.6 mg, 57% yield) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ 7.40 (s, 1H), 7.28 (s, 1H), 7.23–7.19 (m, 2H), 7.17 (t, $J = 7.7$ Hz, 1H), 7.04 (d, $J = 7.4$ Hz, 1H), 6.91 (t, $J = 7.6$ Hz, 1H), 6.62 (d, $J = 10.4$ Hz, 1H), 6.40 (dd, $J = 10.4, 2.2$ Hz, 1H), 5.28 (s, 1H), 5.05 (d, $J = 2.1$ Hz, 1H), 3.92 (d, $J = 16.6$ Hz, 1H), 3.22 (d, $J = 6.4$ Hz, 4H), 2.71 (d, $J = 16.7$ Hz, 1H), 1.39 (s, 9H), 1.05 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 194.8, 156.1, 152.3, 141.7, 139.1, 137.9, 132.8, 128.4, 127.9, 127.7, 127.3, 126.1, 124.5, 120.8, 120.6, 119.3, 97.3, 82.7, 49.7, 45.0, 36.5, 34.7, 29.8. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{28}\text{H}_{32}\text{ClNaNO}_2^+$: 472.2014, found: 472.2010.

8-(tert-butyl)-4'-(diethylamino)-2-(m-tolyl)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3d**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (38.2 mg, 89% yield) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ 7.16 (m, 3H), 7.08 (t, $J = 7.5$ Hz, 1H), 7.00 (d, $J = 7.3$ Hz, 2H), 6.86 (t, $J = 7.6$ Hz, 1H), 6.61 (d, $J = 10.4$ Hz, 1H), 6.32 (dd, $J = 10.4, 2.2$ Hz, 1H), 5.25 (s, 1H), 4.99 (d, $J = 2.2$ Hz, 1H), 3.90 (d, $J = 16.6$ Hz, 1H), 3.28–3.01 (m, 4H), 2.67 (d, $J = 16.6$ Hz, 1H), 2.27 (s, 3H), 1.36 (s, 9H), 0.99 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.2, 156.1, 152.5, 142.1, 137.7, 136.9, 136.2, 128.2, 128.2, 127.8, 126.8, 124.5, 124.3, 120.8, 120.2, 118.8, 97.3, 83.4, 49.7, 44.9, 36.8, 34.7, 29.7, 21.4. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{29}\text{H}_{35}\text{NNaO}_2^+$: 452.2560, found: 452.2558.

8-(tert-butyl)-4'-(diethylamino)-2-(p-tolyl)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3e**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (39.1 mg, 91% yield) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ 7.29 (d, $J = 1.9$ Hz, 1H), 7.27 (s, 1H), 7.22–7.16 (m, 1H), 7.04 (m, 3H), 6.89 (t, $J = 7.6$ Hz, 1H), 6.65 (d, $J = 10.4$ Hz, 1H), 6.36 (dd, $J = 10.4, 2.2$ Hz, 1H), 5.30 (s, 1H), 5.02 (d, $J = 2.2$ Hz, 1H), 3.93 (d, $J = 16.6$ Hz, 1H), 3.20 (d, $J = 6.7$ Hz, 4H), 2.70 (d, $J = 16.6$ Hz, 1H), 2.30 (s, 3H), 1.40 (s, 9H), 1.03 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.3, 156.1, 152.6, 142.2, 137.7, 137.0, 134.1, 127.8, 127.6, 127.3, 124.3, 120.8, 120.2, 118.9, 97.3, 83.3, 49.8, 44.85, 36.8, 34.7, 29.7, 21.1. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{29}\text{H}_{35}\text{NNaO}_2^+$: 452.2560, found: 452.2556.

8-(tert-butyl)-4'-(diethylamino)-2-(4-fluorophenyl)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3f**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (34.6 mg, 80% yield) as a yellow solid.

^1H NMR (500 MHz, CDCl_3) δ 7.40–7.31 (m, 2H), 7.18 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.02 (dd, $J = 7.5, 1.6$ Hz, 1H), 6.95–6.85 (m, 3H), 6.62 (d, $J = 10.5$ Hz, 1H), 6.36 (dd, $J = 10.5, 2.3$ Hz, 1H), 5.30 (s, 1H), 5.02 (s, 1H), 3.89 (dt, $J = 16.5, 1.1$ Hz, 1H), 3.20 (q, $J = 7.2$ Hz, 4H), 2.69 (d, $J = 16.6$ Hz, 1H), 1.37 (s, 9H), 1.03 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 195.2,

162.3 (d, $J = 244.0$ Hz, 1H), 156.2, 152.5, 142.1, 137.9, 129.2 (d, $J = 8.0$ Hz, 1H), 127.9, 124.5, 120.9, 120.6, 119.2, 113.9 (d, $J = 21.0$ Hz, 1H), 97.3, 82.8, 49.8, 45.0, 36.9, 34.8, 29.8. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{28}H_{32}FNNaO_2^+$: 456.2309, found: 456.2311.

2-(4-bromophenyl)-8-(tert-butyl)-4'-(diethylamino)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3g**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (25.6 mg, 52% yield) as a white solid.

1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, $J = 8.5$ Hz, 2H), 7.20 (s, 1H), 7.18 (s, 1H), 7.11 (d, $J = 7.4$ Hz, 1H), 6.95 (d, $J = 7.4$ Hz, 1H), 6.82 (t, $J = 7.6$ Hz, 1H), 6.53 (d, $J = 10.4$ Hz, 1H), 6.28 (dd, $J = 10.4, 2.2$ Hz, 1H), 5.20 (s, 1H), 4.95 (d, $J = 2.1$ Hz, 1H), 3.82 (d, $J = 16.6$ Hz, 1H), 3.14 (d, $J = 5.4$ Hz, 4H), 2.62 (d, $J = 16.7$ Hz, 1H), 1.29 (s, 9H), 0.97 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.7, 156.9, 153.1, 142.6, 138.6, 137.0, 131.0, 130.0, 128.6, 125.3, 122.3, 121.6, 121.4, 120.0, 98.1, 83.5, 50.5, 45.8, 37.5, 35.5, 30.6. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{28}H_{32}BrNNaO_2^+$: 516.1509, found: 516.1496.

8-(tert-butyl)-4'-(diethylamino)-2-(naphthalen-2-yl)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3h**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (41.8 mg, 90% yield) as a white solid.

1H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.84–7.80 (m, 1H), 7.80–7.76 (m, 1H), 7.70 (d, $J = 8.5$ Hz, 1H), 7.55 (dd, $J = 8.5, 1.7$ Hz, 1H), 7.45–7.41 (m, 2H), 7.22 (d, $J = 7.0$ Hz, 1H), 7.06 (d, $J = 7.0$ Hz, 1H), 6.92 (t, $J = 7.6$ Hz, 1H), 6.74 (d, $J = 10.4$ Hz, 1H), 6.34 (dd, $J = 10.5, 2.2$ Hz, 1H), 5.50 (s, 1H), 4.98 (d, $J = 2.2$ Hz, 1H), 3.98 (d, $J = 16.6$ Hz, 1H), 3.05 (s, 4H), 2.75 (d, $J = 16.6$ Hz, 1H), 1.41 (s, 9H), 0.83 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 156.1, 152.6, 142.1, 137.9, 134.8, 133.0, 132.5, 128.3, 127.9, 127.3, 126.6, 126.4, 125.8, 125.6, 125.5, 124.4, 120.9, 120.4, 119.1, 97.2, 83.43, 49.94, 44.8, 37.0, 34.8, 29.8. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{32}H_{35}NNaO_2^+$: 488.2560, found: 488.2550.

8-(tert-butyl)-4'-(diethylamino)-2,2-dimethylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3i**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (22.8 mg, 62% yield) as a yellow oil.

1H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.00–6.92 (m, 1H), 6.82 (t, $J = 7.6$ Hz, 1H), 6.48 (d, $J = 10.5$ Hz, 1H), 6.42 (dd, $J = 10.5, 2.3$ Hz, 1H), 5.31 (d, $J = 2.3$ Hz, 1H), 3.69–3.58 (m, 1H), 3.39 (q, $J = 7.1$ Hz, 4H), 2.46 (d, $J = 16.9$ Hz, 1H), 1.47 (s, 3H), 1.39 (s, 9H), 1.33 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 156.4, 151.1, 146.1, 138.1, 127.7, 124.3, 120.9, 119.6, 117.8, 97.4, 79.1, 77.2, 50.2, 44.9, 34.8, 33.8, 30.4, 29.7, 24.6, 21.6. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{24}H_{33}NNaO_2^+$: 390.2404, found: 390.2409.

8-(tert-butyl)-4'-(diethylamino)-2-methyl-2-phenylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3j**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (30.0 mg, 70% yield) as a yellow oil.

1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.46 (m, 2H), 7.23 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.20–7.12 (m, 3H), 7.03 (dd, $J = 7.5, 1.6$ Hz, 1H), 6.91 (t, $J = 7.6$ Hz, 1H), 6.50 (d, $J = 10.5$ Hz, 1H), 6.08 (dd, $J = 10.5, 2.3$ Hz, 1H), 5.08 (d, $J = 2.3$ Hz, 1H), 3.83 (d, $J = 17.1$ Hz, 1H), 3.09 (d, $J = 7.4$ Hz, 4H), 2.58 (d, $J = 17.2$ Hz, 1H), 1.86 (s, 3H), 1.45 (s, 9H), 0.93 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 156.1, 150.7, 144.6, 142.3, 138.9, 127.9, 126.7, 126.7, 126.4, 124.7, 121.3, 120.4, 118.1, 98.5, 83.3, 50.9, 44.9, 34.9, 33.4, 30.2, 29.7, 20.1. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{29}H_{35}NNaO_2^+$: 452.2560, found: 452.2563.

8-(tert-butyl)-4'-(diethylamino)-2-vinylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3k**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:5) afforded the product (32.9 mg, 90% yield) as a white solid.

1H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, $J = 7.5$ Hz, 1H), 6.95 (d, $J = 7.3$ Hz, 1H), 6.84 (t, $J = 7.6$ Hz, 1H), 6.58–6.42 (m, 2H), 5.86–5.71 (m, 1H), 5.51 (d, $J = 17.2$ Hz, 1H), 5.33 (d, $J = 2.0$ Hz, 1H), 5.19 (d, $J = 10.8$ Hz, 1H), 4.81 (d, $J = 5.2$ Hz, 1H), 3.67 (d, $J = 16.4$ Hz, 1H), 3.39 (dd, $J = 14.1, 7.0$ Hz, 4H), 2.61 (d, $J = 16.4$ Hz, 1H), 1.42 (s, 9H), 1.23 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 156.6, 152.0, 143.1, 137.6, 133.3, 127.6, 124.4, 120.8, 120.1, 118.3, 117.2, 96.6, 80.8, 48.1, 44.9, 37.6, 34.7, 29.6. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{24}H_{31}NNaO_2^+$: 388.2247, found: 388.2244.

8-(tert-butyl)-4'-(dimethylamino)-2-phenylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3l**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (34.8 mg, 90% yield) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.31 (dd, *J* = 7.3, 2.4 Hz, 2H), 7.18–7.13 (m, 3H), 7.12–7.07 (m, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 10.5 Hz, 1H), 6.32 (dd, *J* = 10.4, 2.3 Hz, 1H), 5.30 (s, 1H), 4.92 (d, *J* = 2.3 Hz, 1H), 3.77 (d, *J* = 16.5 Hz, 1H), 2.79 (s, 6H), 2.59 (d, *J* = 16.5 Hz, 1H), 1.30 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 195.9, 158.1, 152.6, 142.4, 137.9, 137.5, 127.7, 127.7, 127.6, 127.3, 124.5, 120.9, 120.4, 118.7, 97.6, 82.9, 50.0, 39.9, 38.3, 34.8, 29.9. HRMS (ESI): [M+Na]⁺ calcd. for C₂₆H₂₉NNaO₂⁺: 410.2091, found: 410.2094.

8-(tert-butyl)-2-phenyl-4'-(pyrrolidin-1-yl)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3m**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (17.7 mg, 43% yield) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.34 (dd, *J* = 7.5, 1.7 Hz, 2H), 7.20–7.15 (m, 3H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 10.3 Hz, 1H), 6.23 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.35 (s, 1H), 4.87 (d, *J* = 1.8 Hz, 1H), 3.78 (d, *J* = 16.5 Hz, 1H), 3.32 (m, 2H), 3.03 (m, 2H), 2.60 (d, *J* = 16.5 Hz, 1H), 1.82 (s, 4H), 1.31 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 195.3, 155.7, 152.6, 142.7, 137.9, 137.7, 127.7, 127.7, 127.6, 127.3, 124.5, 121.0, 120.3, 119.9, 97.3, 82.8, 50.3, 48.0, 47.8, 38.6, 34.8, 29.9, 25.3, 24.6. HRMS (ESI): [M+Na]⁺ calcd. for C₂₈H₃₁NNaO₂⁺: 436.2247, found: 436.2251.

8-(tert-butyl)-2-phenyl-4'-(piperidin-1-yl)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3n**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:5) afforded the product (27.3 mg, 64% yield) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.42–7.36 (m, 2H), 7.24 (m, 3H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 10.4 Hz, 1H), 6.40 (d, *J* = 10.4 Hz, 1H), 5.32 (s, 1H), 5.13 (s, 1H), 3.91 (d, *J* = 16.5 Hz, 1H), 3.24 (t, *J* = 5.2 Hz, 4H), 2.71 (d, *J* = 16.6 Hz, 1H), 1.63–1.54 (m, 2H), 1.44–1.32 (m, 13H). ¹³C NMR (125 MHz, CDCl₃) δ 196.2, 157.4, 152.6, 141.6, 137.8, 137.1, 127.8, 127.6, 127.5, 127.1, 124.4, 120.8, 120.4, 119.1, 99.1, 83.4, 49.9, 48.2, 36.9, 34.7, 29.8, 25.2, 24.3. HRMS (ESI): calcd. for C₂₉H₃₃NO₂ [M+Na]⁺: 450.2404, found: 450.2404. HRMS (ESI): [M+Na]⁺ calcd. for C₂₉H₃₃NNaO₂⁺: 450.2404, found: 450.2408.

4'-(azepan-1-yl)-8-(tert-butyl)-2-phenylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3o**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (26.9 mg, 61% yield) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.46–7.37 (m, 2H), 7.28–7.16 (m, 4H), 7.05 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 10.4 Hz, 1H), 6.41 (dd, *J* = 10.5, 2.3 Hz, 1H), 5.34 (s, 1H), 5.07 (d, *J* = 2.2 Hz, 1H), 3.95 (d, *J* = 16.5 Hz, 1H), 3.67–3.07 (m, 4H), 2.71 (d, *J* = 16.6 Hz, 1H), 1.58 (s, 4H), 1.40 (s, 9H), 1.28 (s, 4H). ¹³C NMR (125 MHz, CDCl₃) δ 195.5, 157.2, 152.6, 142.2, 137.9, 137.2, 127.9, 127.7, 127.6, 127.1, 124.4, 120.9, 120.4, 118.8, 97.6, 83.5, 49.9, 36.9, 34.8, 29.9. HRMS (ESI): [M+Na]⁺ calcd. for C₃₀H₃₅NNaO₂⁺: 464.2560, found: 464.2566.

8-(tert-butyl)-4'-(dibenzylamino)-2-phenylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3p**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (38.3 mg, 71% yield) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.42 (m, 3H), 7.37–7.27 (m, 8H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.91 (m, 5H), 6.67 (d, *J* = 10.4 Hz, 1H), 6.43 (dd, *J* = 10.4, 2.1 Hz, 1H), 5.32 (s, 1H), 5.24 (d, *J* = 2.1 Hz, 1H), 4.41 (s, 4H), 3.96 (d, *J* = 16.6 Hz, 1H), 2.77 (d, *J* = 16.7 Hz, 1H), 1.40 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 196.4, 158.3, 152.6, 142.9, 137.9, 137.1, 128.9, 127.9, 127.7, 127.6, 127.3, 126.3, 124.5, 120.7, 120.6, 119.2, 98.7, 83.8, 50.4, 36.4, 34.8, 29.9. HRMS (ESI): [M+Na]⁺ calcd. for C₃₈H₃₇NNaO₂⁺: 562.2717, found: 562.2724.

8-(tert-butyl)-4'-(diallylamino)-2-phenylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3q**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (36.4 mg, 83% yield) as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 7.36 (m, 2H), 7.23 (m, 3H), 7.19 (d, $J = 7.7$ Hz, 1H), 7.03 (d, $J = 7.5$ Hz, 1H), 6.89 (t, $J = 7.6$ Hz, 1H), 6.62 (d, $J = 10.4$ Hz, 1H), 6.28 (dd, $J = 10.4, 2.3$ Hz, 1H), 5.73–5.51 (m, 2H), 5.29 (s, 1H), 5.11 (d, $J = 10.4$ Hz, 2H), 5.07 (d, $J = 2.2$ Hz, 1H), 4.81 (d, $J = 17.2$ Hz, 2H), 3.91 (d, $J = 16.6$ Hz, 1H), 3.72 (s, 4H), 2.70 (d, $J = 16.7$ Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.1, 157.6, 152.5, 142.1, 137.8, 136.9, 127.8, 127.5, 127.4, 127.0, 124.4, 120.7, 120.4, 119.2, 117.1, 98.1, 83.5, 52.2, 50.0, 36.6, 34.7, 29.8. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{30}\text{H}_{33}\text{NO}_2^+$: 462.2404, found: 462.2409.

2-([1,1'-biphenyl]-4-yl)-8-(tert-butyl)-4'-(diallylamino)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3r**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (43.3 mg, 84% yield) as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 7.64–7.53 (m, 2H), 7.47 (d, $J = 8.2$ Hz, 2H), 7.50–7.39 (m, 4H), 7.37–7.31 (m, 1H), 7.20 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.04 (dd, $J = 7.6, 1.5$ Hz, 1H), 6.89 (t, $J = 7.6$ Hz, 1H), 6.64 (d, $J = 10.4$ Hz, 1H), 6.30 (dd, $J = 10.4, 2.3$ Hz, 1H), 5.59 (s, 2H), 5.33 (s, 1H), 5.12–5.01 (m, 3H), 4.81–4.77 (m, 2H), 3.93 (d, $J = 16.4$ Hz, 1H), 3.71 (s, 4H), 2.71 (d, $J = 16.6$ Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.1, 157.7, 152.6, 142.2, 140.9, 140.3, 137.9, 136.2, 128.8, 127.9, 127.9, 127.2, 126.9, 125.8, 124.5, 120.8, 120.5, 119.4, 98.3, 83.4, 77.3, 50.2, 36.7, 34.8, 29.9. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{36}\text{H}_{37}\text{NNaO}_2^+$: 538.2717, found: 538.2715.

2-([1,1'-biphenyl]-4-yl)-8-(tert-butyl)-4'-(diethylamino)spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3s**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (40.7 mg, 83% yield) as a white oil.

^1H NMR (500 MHz, CDCl_3) δ 7.63–7.55 (m, 2H), 7.52–7.41 (m, 6H), 7.39–7.32 (m, 1H), 7.23 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.07 (dd, $J = 7.5, 1.6$ Hz, 1H), 6.93 (t, $J = 7.6$ Hz, 1H), 6.69 (d, $J = 10.4$ Hz, 1H), 6.39 (dd, $J = 10.5, 2.3$ Hz, 1H), 5.39 (s, 1H), 5.07 (d, $J = 2.3$ Hz, 1H), 3.98 (dd, $J = 16.5, 1.0$ Hz, 1H), 3.19 (q, $J = 7.0$ Hz, 4H), 2.74 (d, $J = 16.6$ Hz, 1H), 1.43 (s, 9H), 1.01 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.3, 156.3, 152.6, 142.2, 141.0, 140.3, 137.9, 136.3, 128.8, 128.0, 127.9, 127.2, 126.9, 125.8, 124.5, 120.9, 120.5, 119.1, 97.5, 83.3, 49.9, 45.0, 36.8, 34.8, 29.9. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{34}\text{H}_{37}\text{NNaO}_2^+$: 514.2717, found: 514.2719.

4'-(dibenzylamino)-8-isopropyl-2-phenylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3t**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:5) afforded the product (25.7 mg, 49% yield) as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 7.41–7.35 (m, 3H), 7.34–7.25 (m, 8H), 7.13–7.08 (m, 1H), 6.99 (dd, $J = 8.0, 1.3$ Hz, 1H), 6.90 (t, $J = 7.6$ Hz, 1H), 6.88–6.83 (m, 4H), 6.56 (d, $J = 10.5$ Hz, 1H), 6.36 (dd, $J = 10.5, 2.3$ Hz, 1H), 5.31 (s, 1H), 5.23 (d, $J = 2.3$ Hz, 1H), 4.36 (d, $J = 13.0$ Hz, 4H), 3.90 (dd, $J = 16.5, 1.2$ Hz, 1H), 3.38–3.30 (m, 1H), 2.71 (d, $J = 16.6$ Hz, 1H), 1.22 (dd, $J = 14.5, 6.9$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.5, 158.3, 150.8, 142.7, 137.3, 136.4, 128.9, 127.7, 127.6, 127.5, 127.3, 127.2, 126.3, 124.0, 120.7, 119.8, 119.2, 98.7, 83.5, 77.3, 50.3, 36.3, 26.9, 23.1, 22.3. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{37}\text{H}_{35}\text{NNaO}_2^+$: 548.2560, found: 548.2568.

8-(sec-butyl)-4'-(dibenzylamino)-2-phenylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**3u**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:5) afforded the product (36.1 mg, 67% yield, dr 2:1) as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 7.41–7.34 (m, 3H), 7.35–7.20 (m, 8H), 7.09–7.04 (m, 1H), 7.02–6.94 (m, 1H), 6.98–6.89 (m, 1H), 6.87–6.80 (m, 4H), 6.55 (m, 1H), 6.39–6.30 (m, 1H), 5.31 (d, $J = 3.1$ Hz, 1H), 5.23 (t, $J = 2.8$ Hz, 1H), 4.58–4.23 (m, 4H), 3.96–3.84 (m, 1H), 3.16–3.09 (m, 1H), 2.71 (d, $J = 16.6$ Hz, 1H), 1.66–1.48 (m, 2H), 1.20 (m, 3H), 0.86 (t, $J = 7.4$ Hz, 2H), 0.79 (t, $J = 7.4$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.6, 196.6, 158.4, 158.4, 151.2, 151.2, 142.9, 142.8, 137.3, 135.2, 135.2, 128.9, 128.6, 127.7, 127.6, 127.6, 127.5, 127.5, 127.3, 127.3, 127.1, 126.3, 124.8, 120.7, 119.8, 119.7, 119.2, 119.1, 98.7, 98.7, 83.6, 83.4, 77.3, 50.3, 36.3, 33.9, 33.3, 30.7, 29.5, 20.9, 20.3, 12.4, 12.2. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{38}\text{H}_{37}\text{NNaO}_2^+$: 562.2717, found: 562.2723.

8-(tert-butyl)-4'-(diethylamino)-2-ethylspiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-one (**4k**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:3) afforded the product (30.1 mg, 82% yield, dr 1:1) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.13 (m, 2H), 6.93 (m, 2H), 6.79 (m, 2H), 6.02 (m, 1H), 5.64 (m, 1H), 5.30 (m, 1H), 5.21 (m, 2H), 5.04 (m, 1H), 4.37 (m, 1H), 3.44–3.21 (m, 7H), 3.19–3.02 (m, 2H), 2.75 (m, 2H), 2.42 (m, 4H), 2.01–1.93 (m, 2H), 1.78–1.59 (m, 4H), 1.41 (m, 16H), 1.18 (m, 13H). ^{13}C NMR (100 MHz, CDCl_3) δ 198.7, 163.1, 162.9, 137.1, 134.4, 128.1, 127.9, 124.3, 121.5, 121.3, 119.9, 119.3, 116.4, 98.5, 98.3, 82.3, 79.4, 44.2, 42.3, 42.0, 34.8, 34.7, 34.5, 34.0, 29.7, 29.6, 23.5, 22.8, 22.6, 22.6, 12.2. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{24}\text{H}_{33}\text{NNaO}_2^+$: 390.2404, found: 390.2411.

6,6'-((3-(tert-butyl)-2-((3,5-dimethoxybenzyl)oxy)phenyl)methylene)bis(3-(diethylamino)phenol) (**5a**). Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1:15) afforded the product (51.8 mg, 81% yield) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ 7.29 (m, 1H), 7.14 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.09 (t, $J = 7.7$ Hz, 1H), 6.94 (d, $J = 8.3$ Hz, 2H), 6.56 (d, $J = 2.4$ Hz, 2H), 6.44 (t, $J = 2.3$ Hz, 1H), 6.22 (d, $J = 7.9$ Hz, 4H), 5.76 (s, 1H), 5.19 (s, 2H), 4.75 (s, 2H), 3.81 (s, 6H), 3.31 (q, $J = 7.1$ Hz, 8H), 1.50 (s, 9H), 1.15 (t, $J = 7.0$ Hz, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.9, 155.5, 148.6, 139.3, 135.4, 130.7, 129.4, 125.7, 124.4, 114.3, 105.2, 104.6, 100.3, 100.0, 76.6, 55.3, 44.3, 37.4, 35.4, 31.3, 12.7. HRMS (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{40}\text{H}_{52}\text{N}_2\text{NaO}_5^+$: 663.3768, found: 663.3778.

3.8. In Vitro Antifungal Activities

Each target compound was dissolved in acetone to prepare the stock solution (2.5 g/L). The stock solution was added into the PDA medium, and the concentration of target compound in the medium was 200.0 mg/L. Pure acetone without the target compound was utilized as the blank control, and difenoconazole and thifluzamide were co-assayed as the reference compound. Fresh dishes with a diameter of 6 mm were taken from the edge of the PDA-cultured fungi colonies and inoculated on the above three PDA media. Each treatment was tested for three replicates, and the antifungal effect was averaged. The relative inhibitory rate I (%) of all the tested compounds was calculated through the equation: I (%) = $[(C - T)/(C - 5)] \times 100$. In this equation, I is the inhibitory rate and C and T are the colony diameter of the blank control (mm) and treatment (mm), respectively. Mycelia growth of four crop pathogenic fungi after treatment with the target compounds on PDA medium is illustrated in the Supplementary Materials Figure S1.

4. Conclusions

In conclusion, we have developed the $\text{Sc}(\text{OTf})_3$ -catalyzed dearomative [5+1] annulation between readily available 3-aminophenols and *O*-alkyl *ortho*-oxybenzaldehydes for synthesis of spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones. The "two-birds-with-one-stone" strategy was disclosed by the dearomatization of phenols and direct $\alpha\text{-C}(\text{sp}^3)\text{-H}$ bond functionalization of oxygen for providing a variety of spiro[chromane-3,1'-cyclohexane]-2',4'-dien-6'-ones through cascade condensation/[1,5]-hydride transfer/dearomative-cyclization process. The antifungal activity assay and derivatizations of products were conducted to further enrich the utility of the structure. This work offers aromatization of the in situ-formed *o*-QM as hydride acceptor for initiating the hydride transfer-involved dearomatization, which would further enhance the utility of hydride transfer strategy in dearomatization chemistry.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules29051012/s1>. Online supplementary information contains ^1H and ^{13}C NMR spectra for all compounds prepared in this study. CCDC 2310751 contains supplementary crystallographic data for this paper.

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