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Scope and Mechanism of the Ruthenium-Catalyzed Dehydrative C−H Coupling of Phenols with α,β-Unsaturated Carbonyl Compounds: Expedient Synthesis of Chromene and Benzoxacyclic Derivatives

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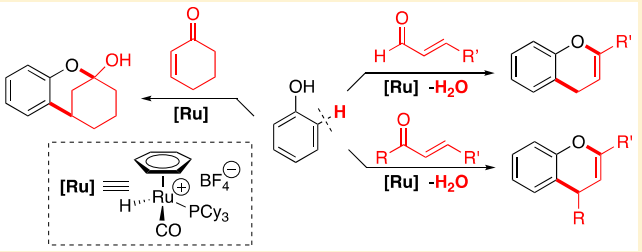
Supporting Information

ABSTRACT: Chromene and benzoxacyclic derivatives were efficiently synthesized from the ruthenium-catalyzed dehydrative C−H coupling reaction of phenols with α,β-unsaturated carbonyl compounds. The cationic ruthenium−hydride complex was found to be an effective catalyst for the coupling and annulation of phenols with enals to form chromene products. The coupling of phenols with linear enones afforded 2,4-disubstituted chromene derivatives, whereas the analogous coupling with cyclic enones yielded 9-hydroxybenzoxazole products. The reaction of 3,5-dimethoxyphenol with PhCH═CHCDO resulted in the chromene product with a significant H/D exchange to both benzylic and vinyl positions. The most significant carbon isotope effect from the coupling of 3,5-dimethoxyphenol with 4-methoxycinnamaldehyde was observed on the α-olefinic carbon of the chromene product (C(2) = 1.067). A Hammett plot from the coupling of 3,5-dimethoxyphenol with *para*-substituted *p*-X-C_6H_4CH═CHCHO displayed a linear correlation, with a strong promotional effect by an electron-withdrawing group (ρ = +1.5; X = OCH_3, CH_3, H, F, Cl). Several biologically active chromenone derivatives were synthesized by using the catalytic coupling method. The catalytic method provides an expedient synthetic protocol for the coupling of phenols with α,β-unsaturated carbonyl compounds without employing reactive reagents or forming any wasteful byproducts.



INTRODUCTION

Motivated by their prominent presence in a variety of natural products and pharmaceuticals as well as in petroleum and biomass feedstocks, considerable research efforts have been focused on the development of catalytic coupling methods for the utilization of phenols and related arenes.[1] In recent decades, transition-metal-catalyzed C−H coupling methods have been extensively investigated as step-efficient and sustainable ways to functionalize phenols without forming wasteful byproducts or employing any reactive reagents.[2] Chelate assistance has been shown to be a highly effective strategy for promoting regioselective C−H *ortho*-arylation, alkenylation, and acylation of phenols,[3] and a number of sophisticated heteroatom directing groups have been successfully used for achieving *meta*- and *para*-selective C−H functionalization reactions of phenol derivatives.[4] Late transition-metal-catalysts have been shown to be particularly effective in mediating C−H coupling and functionalization reactions of phenol derivatives with heteroatom-containing substrates.[5]

Chromenes and chromenones are an important class of bicyclic oxygen heterocycles that are present in a large number of natural products as well as in pharmaceutical and agricultural agents with a broad spectrum of pharmacological and biological activities.[6] In efforts to increase synthetic efficiency as well as to overcome the drawbacks associated with traditional synthetic methods, a number of transition-metal-catalyzed coupling methods have been developed for the synthesis of chromene derivatives over the years, and recent selected notable examples include Au- and Pd-catalyzed intramolecular cyclization of propargyl ethers,[7] Co-catalyzed coupling reaction of hydrazones with terminal alkynes,[8] and Re-catalyzed cyclocondensation of phenols with propargylic alcohols.[9] Soluble organoruthenium catalysts have also been employed for the synthesis of chromene derivatives.[10] Chiral palladium catalysts have been successfully utilized for enantioselective cyclization of allylphenols and asymmetric synthesis of chromene-containing natural products.[11] As demonstrated in the synthesis of chromene derivatives via Pd-catalyzed intramolecular C−H alkenylation of allylic and homoallylic ethers,[12] transition-metal-catalyzed C−H coupling reactions have emerged as step-efficient methods to synthesize oxygen heterocyclic derivatives.[13]

While searching for suitable substrates for the dehydrative C−H coupling methods, we previously reported that the cationic ruthenium−hydride complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**) effectively catalyzes dehydrative C−H coupling reactions of phenols with aldehydes and ketones to form alkylation and alkenylation products.[14,15] In an effort to

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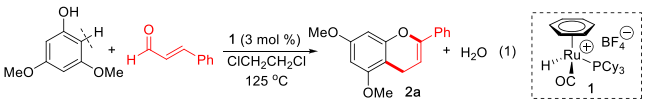
extend synthetic utility of the catalytic coupling methods, we have been investigating the coupling reactions of phenols with α,β-unsaturated carbonyl compounds as a means for achieving sustainable synthesis of substituted benzo-fused oxacyclic products. Herein, we delineate full details on the scope and mechanism for the ruthenium-catalyzed dehydrative C−H coupling of phenols with α,β-unsaturated aldehydes and ketones, which demonstrates the synthetic utility in forming chromene and benzo-fused oxacycle derivatives. The salient feature of the catalytic method is that chromene and related benzoxacyclic core structures are efficiently constructed from the direct intermolecular C−H coupling of phenols with α,β-unsaturated aldehydes and ketones without employing any reactive reagents or forming wasteful byproducts.

RESULTS AND DISCUSSION

Reaction Scope. We recently reported that the cationic ruthenium−hydride complex **1** is a uniquely active catalyst for mediating the dehydrative C−H coupling of phenols with α,β-unsaturated carbonyl compounds to form chromene derivatives.[15] To fully explore substrate scope of the catalytic method, we first performed the optimization study for the coupling reaction of 3,5-dimethoxyphenol with cinnamaldehyde (eq 1). Initial catalyst screenings showed that the Ru−H

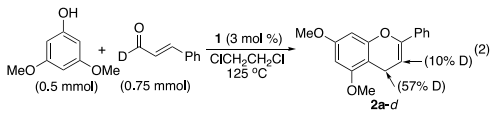


complex **1** exhibited the highest catalytic activity among screened Ru catalysts, and the subsequent solvent and temperature optimization efforts established the standard conditions for the coupling reaction as 3,5-dimethoxyphenol (0.50 mmol), cinnamaldehyde (0.75 mmol), and **1** (3 mol %) in 1,2-dichloroethane (2 mL) at 125 °C for 16−24 h (Table S1, Supporting Information (SI)).

We explored the substrate scope of the coupling reaction by using the standard conditions (Table 1). An electron-rich 3,5-dimethoxyphenol was found to be a suitable substrate for the coupling with aryl-substituted enals to give the chromene derivatives **2a**−**g**. The coupling of 3,5-dimethoxyphenol with both cyclohexenecarbaldehyde and 3-methylbutenal formed the corresponding chromene products **2i**,**i** in high yields. In contrast, the coupling with α-substituted cinnamaldehydes resulted in a 1:1 mixture of the double bond isomers **2j**,**k**. A number of phenols with electron-donating groups predictively reacted with cinnamaldehyde to form the 2-phenyl-substituted chromene products **2l**−**p**. The coupling of 1- and 2-naphthols and 9-phenanthrol with cinnamaldehyde led to the formation of the chromene products **2q**−**t**. For the coupling with electron-donating aryl-substituted enals, (*E*)-3-(4-(dimethylamino)phenylacrylaldehyde and (*E*)-3-(furan-2-yl)-acrylaldehyde, a mixture of chromene and the hydrogenated products was obtained **2u**,**v**. The analogous treatment with biologically active citral and β-cyclocitral yielded the annulation product **2w**,**x** in a single step. The coupling with a chiral aldehyde, (1*R*)-myrtenal, led to a diastereoselective coupling product **2y** (dr = 5:1), whereas the coupling with 6-methylchromone-3-carboxaldehyde afforded the corresponding polycyclic enol ether product **2z**. The structure of these chromene products was fully characterized by spectroscopic methods, and the molecular structure of **2c** was also confirmed by X-ray crystallography (Figure S6, SI). It should be noted that the coupling of 3,5-dimethoxyphenol with an electron-rich crotonaldehyde led to a substituted coumarin derivative instead of the chromene product.

We next surveyed the enone substrate scope for the dehydrative C−H coupling method (Table 2). Thus, the treatment of 3,5-dimethoxyphenol with linear enones having both electron-donating and -withdrawing aryl substituents under the standard reaction conditions cleanly formed the desired 2,4-disubstituted chromene products **3a**−**g**. The analogous treatment of aliphatic 1-(cyclohex-1-en-1yl)-ethanone and linear 4-methylpent-3-en-2-one gave the corresponding chromene derivatives **3h**,**i** in good to moderate yields. The coupling of 3,5-dimethoxyphenol with substituted 3,4-dihydronaphthalenone yielded the polycyclic xanthene analogue **3k**, and the coupling of 3,4,5-trimethoxyphenol with linear enones smoothly formed the chromene derivatives **3l**,**m**. The coupling with a thiophene-substituted enone (*E*)-4-(thiophen-2-yl)but-3-en-2-one afforded a 4:1 mixture of the chromene products **3n**/**3n**′. In contrast, the coupling with cyclic enones such as 2-cyclohexenone and 2-cycloheptenone selectively yielded the bicyclic hemiketal products **3o** and **3p**, respectively, with >95% diastereoselectivity, in which an opposite regioselectivity pattern on the addition of these cyclic enones has been observed compared to the linear enones.[11b] The acetate derivatives **3q** and **3r** were obtained in high yields by the addition of acetic anhydride to the reaction mixture **3q**,**r**. The analogous treatment of 3,5-dimethoxyphenol with 3-methylene-2-norbornanone led to the clean formation of its chromene derivative **3s**. The treatment of 2,6-bis(phenylmethylene)cyclohexanone and its bismethoxyphenyl analogue gave the selective formation of its dehydrative annulation products **3t** and **3u**, respectively. The molecular structures of **3a** and **3u** were confirmed by X-ray crystallography (Figures S7 and S8, SI). In general, the coupling reaction of phenols with an electron-withdrawing group has been found to be very sluggish, leading to low product yields even after a prolonged reaction time.

Deuterium Labeling Study. We performed the following set of deuterium labeling experiments to probe the mechanism of the coupling reaction. To examine the possible H/D exchange pattern, we prepared cinnamaldehyde-*d* from the reduction of methyl cinnamate by following a literature procedure.[16] Thus, the treatment of 3,5-dimethoxyphenol (0.5 mmol) with PhCH=CHCDO (99% D, 0.75 mmol) in the presence of **1** (3 mol %) in 1,2-dichloroethane (2 mL) was heated at 125 °C for 16 h, which led to 92% conversion of the product **2a**-*d* as analyzed by both GC-MS and NMR (eq 2).



The ^{1}H and ^{2}H NMR spectra of the isolated product **2a**-*d* showed a largely retained deuterium on the benzylic position (57% D) with a small amount of deuterium incorporation on the vinyl position (10% D) (Figure S1, SI). In a complementary deuterium labeling experiment, a mixture of 1-naphthol-d_8 (98% D, 0.5 mmol) with cinnamaldehyde (0.75 mmol) in the presence of **1** (3 mol %) in 1,2-dichloroethane (2 mL) was heated at 125 °C for 24 h, which led to 86% conversion of the product **2q**-*d* as analyzed by both GC-MS and NMR (eq 3). In this case, ^{1}H and ^{2}H NMR of **2q**-*d*

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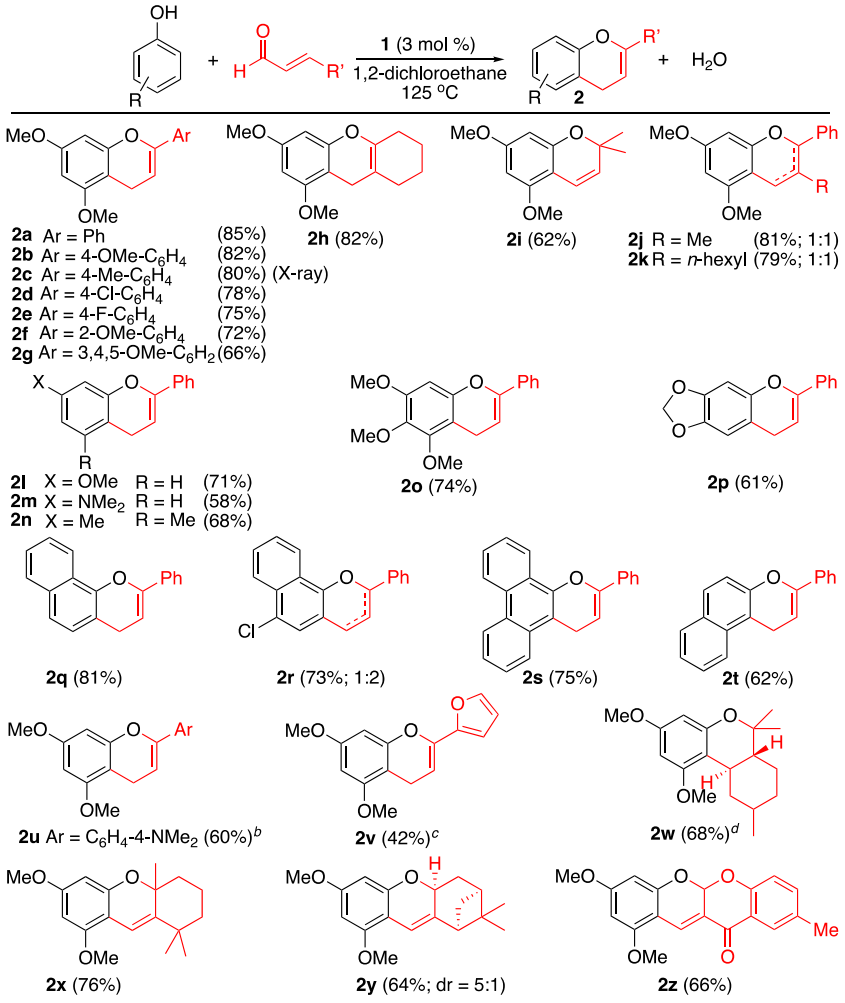
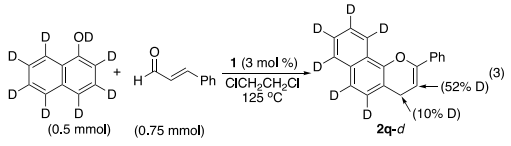
Table 1. Dehydrative C−H Coupling of Phenols with Enals[a]

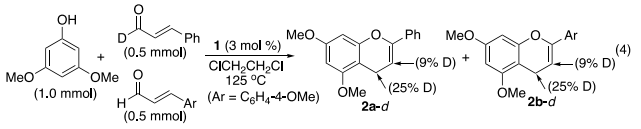


[a]Reaction conditions: phenol (0.5 mmol), aldehyde (0.75 mmol), **1** (3 mol %), 1,2-dichloroethane (2 mL), 125 °C, 16−24 h. [b]The hydrogenated product was formed in 21% yield. [c]The hydrogenated product was formed in 38% yield. [d]Citral substrate was used.



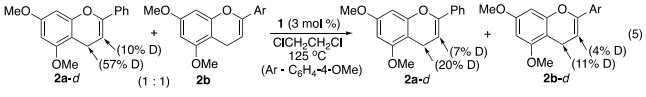
showed an opposite trend of the deuterium labeling pattern, with a substantial amount of deuterium on the vinyl position (52% D) and a small amount on the benzylic position (10% D) (Figure S2, SI).

We next performed the crossover experiment to discern the possible source of the H/D exchange pattern on the vinyl position of the chromene products. Thus, the treatment of 3,5-dimethoxyphenol (1.0 mmol) with a 1:1 mixture of deuterated PhCH═CHCDO (>99% D, 0.5 mmol) and nondeuterated 4-OMe-C_6H_4CH═CHCHO (0.5 mmol) in the presence of **1** (3 mol %) in 1,2-dichloroethane (2 mL) at 125 °C for 22 h led to 92% product conversion as analyzed by both GC-MS and NMR (eq 4). The ^{1}H and ^{2}H NMR of isolated products **2a**-*d* and **2b**-*d* showed an identical amount of deuterium incorporation to benzylic (25% D) and vinyl positions (9% D) for both products (Figure S3, SI). An extensive H/D crossover between two products is consistent with a rapid



intermolecular H/D exchange process during the coupling reaction.

We performed another control experiment to distinguish if the observed H/D exchange process occurred during or after the reaction. Thus, a 1:1 mixture of the deuterium-labeled **2a**-*d* with unlabeled **2b** in the presence of **1** (3 mol %) in 1,2-dichloroethane (2 mL) was heated in an oil bath at 125 °C for 24 h (eq 5). The ^{1}H and ^{2}H NMR analysis of the mixture



showed a considerably lower amount of deuterium on both the benzylic (20% D) and the vinyl (7% D) positions of **2a**-*d*, as a significant amount of deuterium has been transferred to the benzylic (11% D) and vinyl (4% D) positions of **2b**-*d* (Figure S4, SI). The observed control experiment result suggests that a significant intermolecular H/D exchange process occurred

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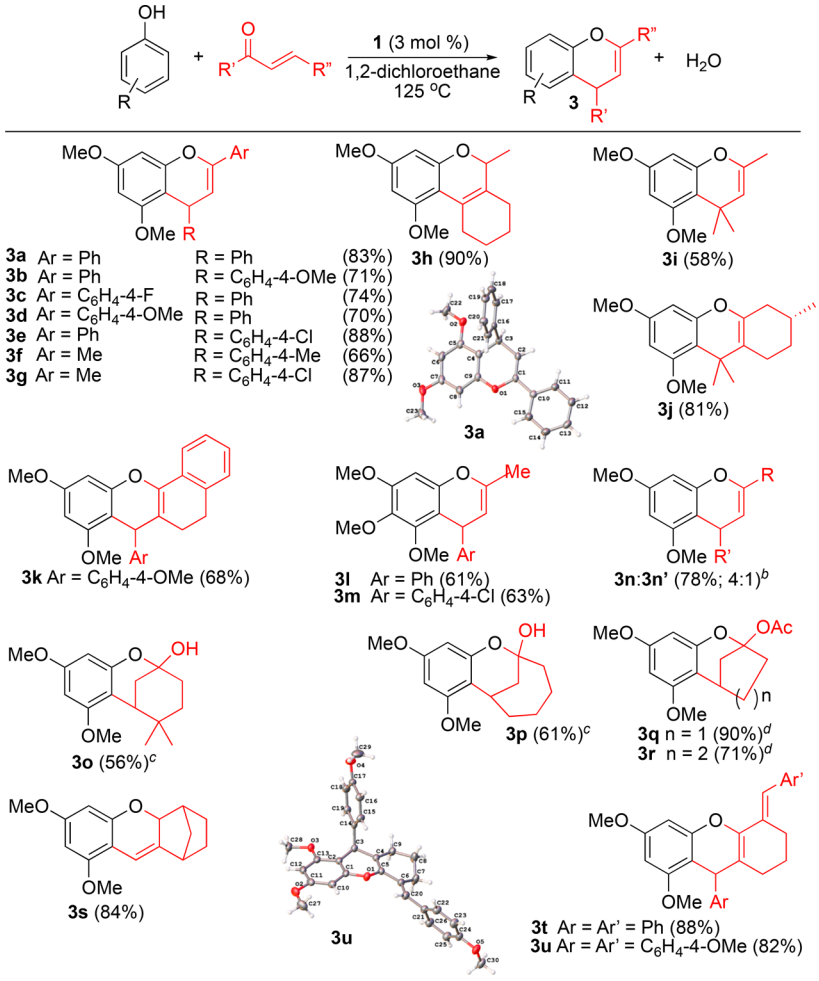
Table 2. Dehydrative C−H Coupling of Phenols with Enones[a]



[a]Reaction conditions: phenol (0.5 mmol), enone (0.75 mmol), **1** (3 mol %), 1,2-dichloroethane (2 mL), 125 °C, 22−30 h. [b]**3n**: R = Me, R′ = 2-thiophenyl. **3n′**: R = 2-thiophenyl, R′ = Me. [c]The reaction was run at 105 °C. [d]The reaction was run with Ac_2O (0.5 mmol) at 105 °C for 24 h.

after the product formation and that the crossover H/D exchange could be explained via Ru-catalyzed olefin isomerization reactions. The observed deuterium labeling results also indicate that the aldehydic C−H bond does not get broken, but an extensive H/D exchange process between the *ortho*-C−H phenol substrate and the vinyl hydrogen of cinnamaldehyde occurs during the coupling reaction. Approximately 10% of deuterium incorporation on the vinyl position can be explained from the olefin isomerization of the chromene product under the reaction conditions. In support of this hypothesis, we previously observed a facile olefin isomerization reaction rate mediated by the Ru−H catalysts.[17]

Carbon Isotope Effect Study. To discern the rate-limiting step of the coupling reaction, we next measured the carbon isotope effect by employing Singleton's high-precision NMR technique.[18] Thus, the coupling reaction of 3,5-dimethoxyphenol with 4-methoxycinnamaldehyde and **1** (3 mol %) under the standard conditions was run for 24 h to obtain the product **2b** at high conversion. The analogous reaction was run for 0.5 h to obtain the product at low conversion. The isolated product **2b** in each case was analyzed by high-precision $^{13}C\{^1H\}$ NMR spectroscopy (eq 6). The most pronounced carbon isotope effect was observed on the α-vinyl carbon of the product **2b** when the ^{13}C ratio of the

product from a high conversion was compared with the product obtained at a low conversion (^{13}C(avg 92% conversion)/^{13}C(avg 19% conversion) at C(2) = 1.067; average of two runs) (Table S2, SI). The observed carbon isotope effect on the vinyl carbon is consistent with the C−O bond formation as the turnover-limiting step of the catalytic coupling reaction.

Hammett Study. The observed carbon isotope effect strongly suggests that the C−O bond formation is the rate-limiting step of the coupling reaction. To probe the electronic influence on the C−O bond formation step, we compared the coupling reaction rate of 3,5-dimethoxyphenol with a series of *para*-substituted benzaldehydes *p*-X-C_6H_4CH=CHCHO (X = OCH_3, CH_3, H, F, Cl). The Hammett plot showed a linear correlation with σ_p, in which the coupling reaction is promoted by an electron-withdrawing group (Figure 1). A relatively strong promotional effect by the electron-withdrawing group of the cinnamaldehyde substrate (ρ = +1.5 ± 0.4) suggests a substantial cationic character build-up on the vinyl carbon in

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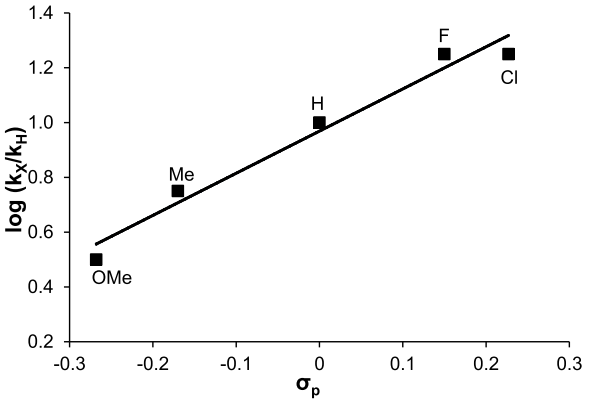
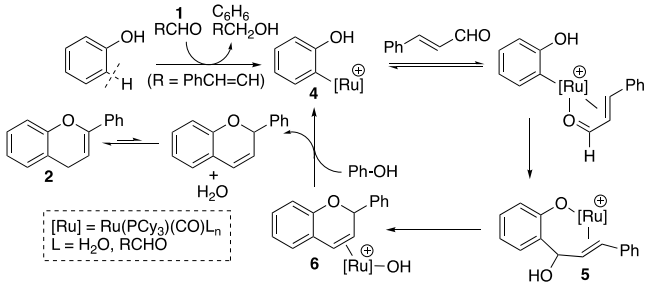


Figure 1. Hammett plot from the reaction of 3,5-dimethoxyphenol with *p*-X-$C_6H_4CH{=}CHCHO$ (X = OCH_3, CH_3, H, F, Cl).

the transition state, where the nucleophilic attack of the phenoxy group would be facilitated by the electrophilic vinyl carbon. Strong Hammett linear free energy relationships have been observed in a number of transition-metal-catalyzed arene C−H and related coupling reactions.[19]

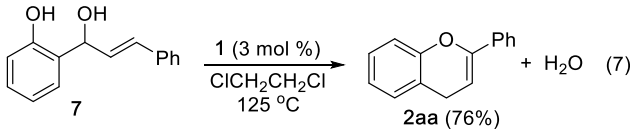
Proposed Mechanism. A plausible mechanistic rationale for the coupling reaction of phenol with cinnamaldehyde has been compiled on the basis of these experimental results (Scheme 1). We propose that the catalytically active cationic

Scheme 1. Proposed Mechanism of the C−H Coupling Reaction of Phenol with Cinnamaldehyde



Ru−aryl species **4** is initially formed from an *ortho*-C−H metalation of phenol followed by H_2 elimination. In support of this, we detected the formation of both free benzene and cinnamyl alcohol in the crude reaction mixture. The coordination of the aldehyde substrate followed by the nucleophilic addition of the aryl group to the carbonyl group of the cinnamaldehyde substrate would generate the cationic Ru−phenoxy species **5**. The subsequent annulation of the phenoxy group and the hydroxy group elimination would form the chromene-coordinated Ru−hydroxo species **6**. The coordination and *ortho*-C−H activation of phenol with concomitant elimination of water byproduct is envisaged for the regeneration of the *ortho*-metalated species **4**. The observed H/D exchange patterns on the coupling product support a notion that a rapid H/D exchange process is facilitated by the olefin isomerization on the benzylic position of the chromene product **2**. We previously observed a similar H/D exchange pattern and negligible deuterium isotope effect from related C−H coupling reactions of phenols.[14]

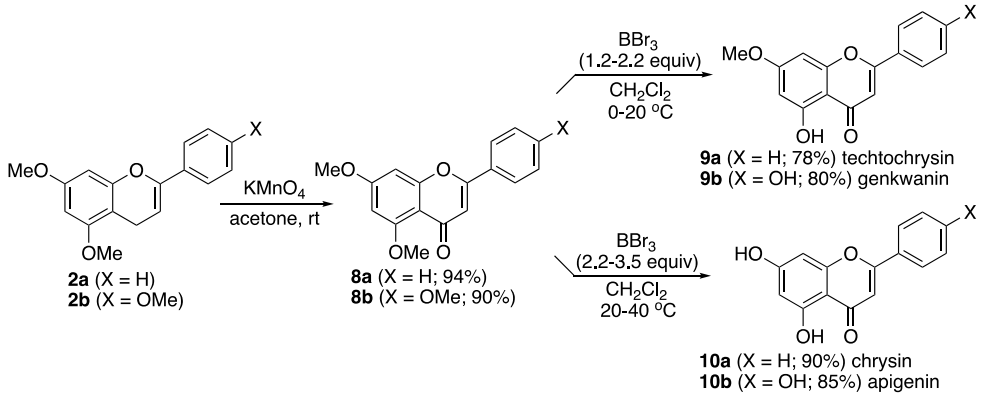
The observation of the carbon isotope effect on the vinyl carbon of **2b** provides strong support for the turnover-limiting C−O bond formation step. A relatively high positive ρ value from the Hammett correlation of *para*-substituted cinnamaldehydes also corroborates the carbon KIE data, in that the C−O bond formation step is strongly promoted by the electrophilic nature of the vinyl carbon. Overall, the proposed mechanistic pathway shares similar mechanistic features with the previously reported ruthenium-catalyzed dehydrative coupling reaction of phenol with ketones, where both of these coupling reactions involve *ortho*-arene C−H activation and the subsequent nucleophilic addition of arenes to carbonyl



substrates, and they are driven by the formation of water byproduct.[14b] From a synthetic point of view, the ruthenium-catalyzed C−H coupling/annulation protocol provides an alternate strategy to classical acid catalysis, where aldol-type condensation of 2-hydroxyacetophenone followed by cyclization protocols has been commonly utilized for the synthesis of chromene derivatives.[20]

The proposed mechanistic pathway suggests that the phenolic intermediate **5** could be independently generated from the reaction of a phenol-substituted allylic alcohol with the ruthenium catalyst **1**. To establish its participation for the coupling reaction, we prepared the substrate (*E*)-2-(1-hydroxy-3-phenylallyl)phenol (**7**) by following a literature procedure.[21] The treatment of **7** with the ruthenium catalyst **1** under the standard reaction conditions smoothly led to the chromene

Scheme 2. Synthesis of Biologically Active Flavenones



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product **2aa** in 76% isolated yield (eq 7). The result indicates that the cationic Ru−phenoxy complex **5**, which would be formed from the deprotonation of phenolic proton and the coordination of the olefinic group of the substrate **7**, is the key species for the formation of the chromene product **2**.

Synthesis of Biologically Active Flavenones. Flavenones (chromenones) are an important subgroup of flavonoids that have been shown to exhibit a range of biological activities *in vivo*.[22] To further demonstrate the synthetic utility of the catalytic coupling method, we synthesized a number of biologically active flavenone derivatives by using the dehydrative coupling method (Scheme 2). For example, the oxidation reaction of **2a**,**b** with $KMnO_4$ (1.2 equiv) in acetone at room temperature for 16 h selectively formed chromenone products **8a**,**b**. The selective deprotection from the treatment of **8a**,**b** with 1.2 equiv of BBr_3 in CH_2Cl_2 at 0 °C cleanly yielded the flavone derivatives techtochrysin (**9a**) and genkwanin (**9b**). The analogous treatment with an excess amount of BBr_3 (2−3 equiv) in CH_2Cl_2 at an increased temperature led to the formation of fully deprotected flavenones, chrysin (**10a**) and apigenin (**10b**) in high yields.

CONCLUSION

In summary, the cationic ruthenium−hydride complex **1** has been shown to mediate regioselective dehydrative C−H coupling reactions of phenols with *α*,*β*-unsaturated carbonyl compounds to give chromene and benzo-fused oxazole derivatives. A broad substrate scope and synthetic utility for the catalytic method has been demonstrated by using biologically active carbonyl substrates. The observed H/D exchange results support a mechanism involving a nucleophilic addition of *ortho*-metalated phenol substrate to the carbonyl substrate followed by annulation and isomerization steps. Both carbon isotope effect and Hammett study support a mechanism via a turnover-limiting C−O bond formation step. An expedient synthesis of several biologically active chromenones has been achieved to demonstrate the synthetic utility of the catalytic method. The catalytic method provides a sustainable synthetic protocol for the synthesis of chromene and benzoxacyclic core structures from the intermolecular dehydrative C−H coupling reaction of readily available phenols with *α*,*β*-unsaturated carbonyl compounds without employing any reactive reagents or forming wasteful by-products.

EXPERIMENTAL SECTION

General Information. All operations were carried out in a nitrogen-filled glovebox or by using standard high-vacuum and Schlenk techniques unless otherwise noted. Solvents were freshly distilled over appropriate drying reagents. Benzene, toluene, and hexanes were distilled from purple solutions of sodium and benzophenone, and 1,2-dichloroethane was dried over calcium hydride prior to use. All organic substrates were received from commercial sources and were used without further purification. Column chromatography was performed on Dynamic Absorbents silica gel 60A (32−63 *μ*m particle size), and thin layer chromatography was performed on Agela TLC plates precoated with silica gel MF254. The NMR spectra were recorded on a Varian 300 or 400 MHz FT-NMR spectrometer, and the data are reported in parts per million (ppm) relative to TMS. Mass spectra were recorded with an Agilent 6850 GC-MS spectrometer with a HP-5 (5% phenylmethylpolysiloxane) column (30 m, 0.32 mm, 0.25 *μ*m). High-resolution mass spectra (HRMS) were obtained at the Mass Spectrometry/ICP Lab, Department of Chemistry and Biochemistry, University of Wisconsin—Milwaukee, Milwaukee, WI.

General Procedure for the Coupling Reaction of a Phenol with a Carbonyl Compound. In a glovebox, a phenol (0.5 mmol), a carbonyl compound (0.75 mmol), and complex **1** (9 mg, 3 mol %) were dissolved in 1,2-dichloroethane (2 mL) in a 25 mL Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar. The tube was brought out of the glovebox, and it was stirred in an oil bath preset at 125 °C for 16−24 h. The reaction tube was taken out of the oil bath, and it was cooled to room temperature. After the tube was open to air, the solution was filtered through a short silica gel column by eluting with CH_2Cl_2 (10 mL), and the filtrate was analyzed by GC-MS. Analytically pure product was isolated by column chromatography on silica gel (230−460 mesh, hexanes/EtOAc). The product was completely characterized by NMR and MS spectroscopic methods.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.9b00629.

Experimental procedures, characterization data for organic products (PDF)

Molecular structure (XYZ)

Accession Codes

CCDC 1954240−1954242 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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