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Rh^{III}-Catalyzed [4 + 1] Annulations of 2-Hydroxy- and 2-Aminobenzaldehydes with Allenes: A Simple Method toward 3-Coumaranones and 3-Indolinones

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Supporting Information

ABSTRACT: A novel method for the regio- and stereoselective synthesis of substituted 3-coumaranones from salicylaldehydes and allenes using a rhodium(III) catalyst has been developed. This procedure gives access to new 2-vinyl-substituted 3-coumaranone compounds. The method involves a Rh^{III}-catalyzed aldehyde C−H activation and annulation reactions. Moreover, this Rh^{III}-catalyzed [4 + 1] annulation reaction has been applied to 2-aminobenzaldehydes to afford 2,2-disubstituted 3-indolinones.

3-Coumaranones (benzofuran-3(2*H*)-one) are an important structural motif found in many natural and bioactive compounds (Figure 1).[1,2] They are also an important building

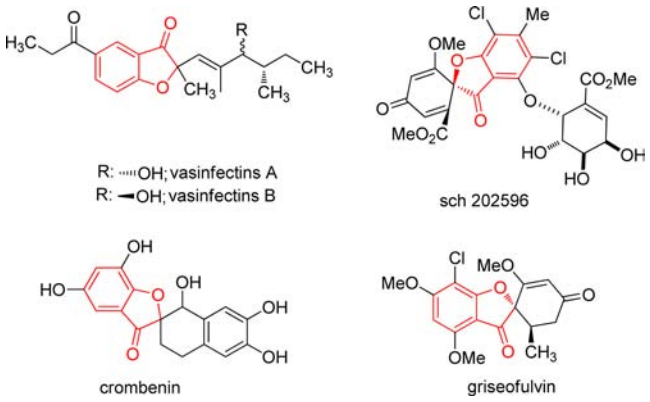

Figure 1. Examples of natural products containing the 3-coumaranone motif.

block in the synthesis of heterocycles and molecules with medicinal properties.[3] Classical methods to synthesize 3-coumaranone derivatives mainly involve the $AlCl_3$-mediated cyclization of 2-phenoxyacetyl chlorides or the base-mediated Dieckmann reaction of ethyl 2-(2-formylphenoxy)acetates.[4] However, these methods are not widely used due to the limited availability of starting compounds, and harsh acid or base reaction conditions required. Therefore, the development of a facile synthetic method to synthesize 3-coumaranone derivatives with a broad substrate scope is highly desired.[5] Herein, we report a convenient method for the synthesis of 3-coumaranones from readily available salicylaldehydes and allenes through rhodium(III)-catalyzed aldehyde C−H activation and [4 + 1] annulation reactions. Furthermore, our method gives access to 2-vinyl-substituted 3-coumaranones, and to the best of our knowledge, there is currently no direct method available for their synthesis in the literature.

Transition-metal-catalyzed C−H activation reactions have emerged as a promising avenue in organic synthesis.[6] In particular, coordination-assisted C−H bond cleavage followed by coupling with π-components is an attractive strategy for the synthesis of carbocyclic and heterocyclic compounds.[7] In addition to aromatic $C(sp^2)$−H and aliphatic $C(sp^3)$−H bond functionalization, aldehyde $C(sp^2)$−H activation has also become increasingly popular in recent years.[8] Owing to our interest in the area of transition-metal-catalyzed C−H functionalization,[9] we developed a method based on an *o*-hydroxyl-group-assisted aldehyde $C(sp^2)$−H cleavage followed by coupling with allenes to afford 2-vinyl-substituted 3-coumaranones.

Treatment of salicylaldehyde (**1a**) and buta-2,3-dien-1-ylbenzene (**2a**) in the presence of 2.0 mol % of $[RhCl_2Cp^*]_2$, and 2.1 equiv of $Cu(OAc)_2$ in *N*,*N*-dimethylformamide (DMF) (2 mL) at 90 °C for 15 h gave (*E*)-2-methyl-2-styrylbenzofuran-3(2*H*)-one (**3aa**) in 88% isolated yield. The product was characterized using ^1H and ^{13}C NMR, along with high resolution-mass spectrometry (HR-MS). The choice of solvent and oxidant play a crucial role in the reaction. Among the various tested solvents, the formation of product **3aa** was less effective in MeOH, CH_3CN, THF, and $(CH_3)_2CO$. In addition, the catalytic reaction was ineffective when other oxidants (AgOAc, Ag_2O, and O_2) were used instead of $Cu(OAc)_2$. Nonetheless, using a catalytic amount of $Cu(OAc)_2$ (0.2 equiv) and O_2 in the reaction gave 11% product yield. The controlled experiment revealed that no product was formed in the absence of $[RhCl_2Cp^*]_2$ (see the Supporting Information for detailed optimization studies).

After obtaining the optimal reaction conditions, we examined the reaction of various substituted salicylaldehydes **1b**−**p** with

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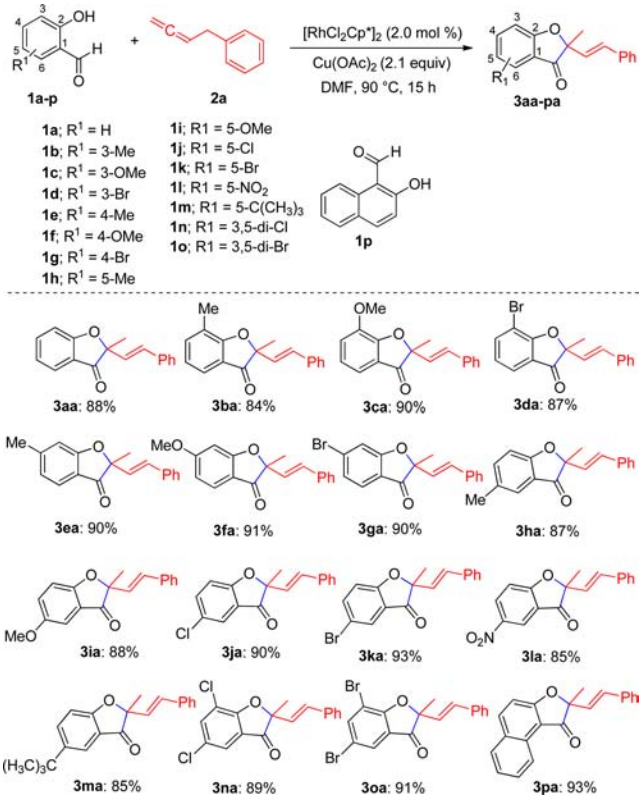
2a (Scheme 1). Reaction of 3-Me-, 3-OMe-, and 3-Br-substituted salicylaldehydes 1b−d with 2a afforded the

Scheme 1. Scope of Salicylaldehydes in the Synthesis of Substituted 3-Coumaranones[a,b]

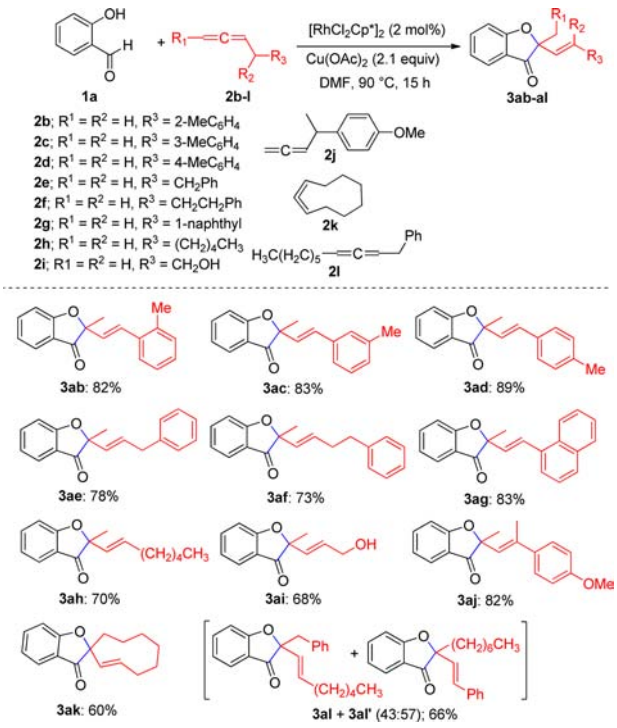


[a]Reaction conditions: salicylaldehyde **1** (0.40 mmol), allene **2a** (0.60 mmol), $[RhCl_2Cp^*]_2$ (0.008 mmol), and $Cu(OAc)_2$ (0.840 mmol) in DMF (2 mL) at 90 °C for 15 h. [b]Isolated yields.

products **3ba−da** in 84%, 90%, and 87% yields, respectively. Similarly, 4-substituted salicylaldehydes (**1e−g**) gave the desired products **3ea−ga** in excellent yields. Next, we tested various 5-substituted salicylaldehydes (**1h−m**) under the same reaction conditions to afford the desired products (**3ha−ma**) in 85−93% yields. The reaction of 3,5-disubstituted salicylaldehydes (**1n** and **1o**) also provided the desired products **3na** and **3oa** in high yields. Using the optimized reaction conditions, 2-hydroxy-1-naphthaldehyde (**1p**) and **2a** reacted to give the corresponding [4 + 1] annulation product **3pa** in 93% yield.

Next, we investigated the scope of the allenes for the rhodium(III)-catalyzed [4 + 1] annulation reaction (Scheme 2). 2-Me-, 3-Me-, and 4-Me-substituted benzyl allenes (**2b−d**) reacted with **1a** to give the desired cycloaddition products **3ab−ad** in 82−89% yields. Similarly, 5-phenyl-1,2-pentadiene (**2e**) and 6-phenyl-1,2-hexadiene (**2f**) gave the expected products **3ae** and **3af** in 78% and 73% yields, respectively. 1-Naphthyl-substituted allene **2g** afforded the product **3ag** in 83% yield, whereas alkyl allene **2h** gave the product **3ah** in 70% yield under similar reaction conditions. Penta-3,4-dien-1-ol (**2i**) reacted with **1a** to give 2-allyl alcohol substituted 3-coumaranone (**3ai**) in 68% yield. The catalytic reaction also proceeded well with 1-methoxy-4-(penta-3,4-dien-2-yl)benzene (**2j**) to afford the product **3aj** in 82% yield. Cyclic internal allene **2k** underwent [4 + 1] cycloaddition with **1a** to furnish the spiro 3-coumaranone derivative **3ak** in good yield (60%).

Scheme 2. Scope of Allenes in the Synthesis of Substituted 3-Coumaranones[a,b]



[a]Reaction conditions: salicylaldehyde **1** (0.40 mmol), allene **2a** (0.60 mmol), $[RhCl_2Cp^*]_2$ (0.008 mmol), and $Cu(OAc)_2$ (0.840 mmol) in DMF (2 mL) at 90 °C for 15 h. [b]Isolated yields.

Meanwhile, the unsymmetrical internal allene **2l** gave two regioisomeric products **3al** + **3al′** in 66% combined yield.

The reaction of substituted 2-aminobenzaldehydes with allenes using the Rh^{III} catalyst was also examined.[8k,10] Treatment of 2-(tosylamino)benzaldehyde (**4a**) with **2a**, under the reaction conditions aforementioned, gave (*E*)-2-methyl-2-styryl-1-tosylindolin-3-one (**5aa**) in a meager 7% yield. However, increasing the reaction temperature to 130 °C provided a maximum yield of 45%. After performing detailed optimization studies, we found that the reaction of **4a** (0.18 mmol), **2a** (0.36 mmol), $[RhCp^*Cl_2]_2$ (0.0036 mmol), and $Cu(OAc)_2$ (0.36 mmol) in CH_3NO_2 at 130 °C for 15 h afforded **5aa** in 82% isolated yield (see the Supporting Information for details). It is worth mentioning that the indolin-3-one skeleton is an important structural moiety found in many natural products.[11]

To study the scope of the Rh^{III}-catalyzed formation of 3-indolinone derivatives, we examined the reaction of different substituted 2-aminobenzaldehydes with allenes under the optimized reaction conditions (Scheme 3). Thus, the reaction of **4a** with *o*-, *m*-, and *p*-methylbenzylallenes (**2b−d**) afforded the desired [4 + 1] annulation products **5ab−ad** in good yields. Similarly, allenes **2e** and **2f** reacted with **4a** to give products **5ae** and **5af** in 63% and 56% yields, respectively. Bromo-substituted 2-aminobenzaldehyde **4b** was also effectively transformed to the corresponding indolinone **5ba** in 60% yield. A sterically demanding methyl group at the *ortho* position (relative to the aldehyde moiety) of **4c** did not adversely affect the cyclization reaction, giving **5ca** in 68% yield. Moreover, we also examined the effect of different amino protecting groups in the Rh^{III}-catalyzed [4 + 1] annulation reaction. The reaction of 3-OMe

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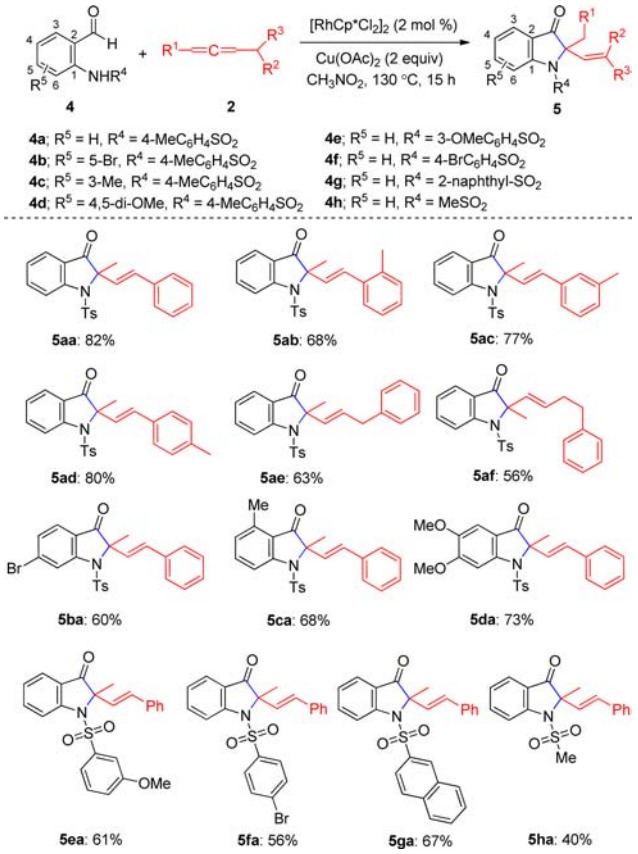
Scheme 3. Scope of the Rh^{III}-Catalyzed [4 + 1] Annulation of 2-Aminobenzaldehydes and Allenes[a,b]

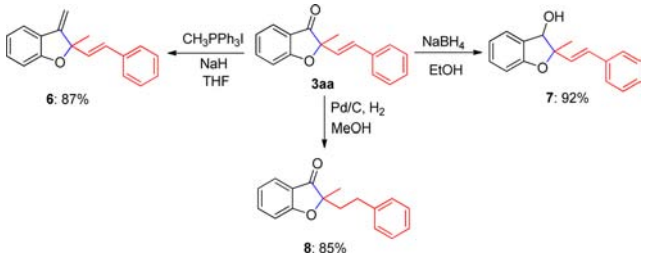


[a]Reaction conditions: 2-aminobenzaldehyde **4** (0.18 mmol), allene **2** (0.36 mmol), $[RhCl_2Cp^*]_2$ (0.0036 mmol), and $Cu(OAc)_2$ (0.36 mmol) in CH_3NO_2 (2 mL) at 130 °C for 15 h. [b]Isolated yields.

and 4-Br benzenesulfonyl-protected substrates **4e** and **4f** with **2a** afforded the desired products **5ea**–**fa** in good yields. Similarly, 2-naphthylsulfonyl-protected aminoaldehyde **4g** coupled with **2a** to give **5ga** in 67% yield. However, the treatment of *N*-(2-formylphenyl)methanesulfonamide (**4h**) with **2a** gave **5ha** in only 40% yield. Unfortunately, acetyl- and pivaloyl-protected aminobenzaldehydes failed to undergo the [4 + 1] cyclization reaction.

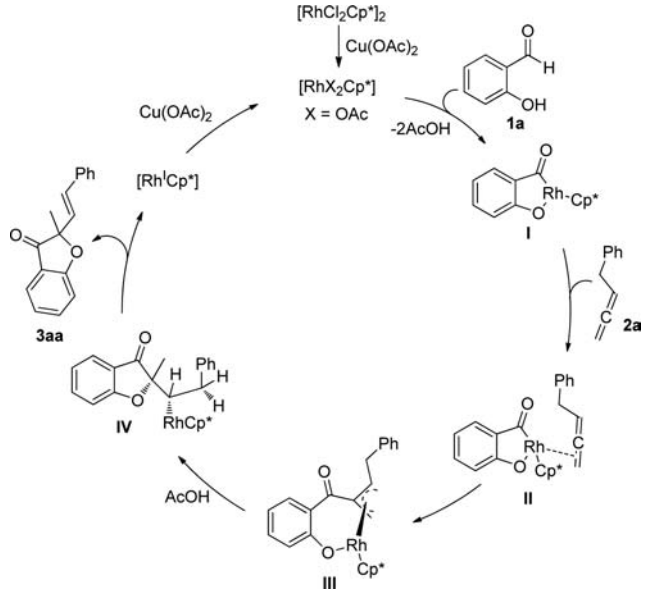
Since the synthesized 3-coumaranone and 3-indolinone derivatives contain multiple functional groups, they can be used in diversity-oriented synthesis (DOS) to generate useful structurally diverse compounds. As demonstrated in Scheme 4, the Wittig reaction between the keto group of **3aa** and methyltriphenylphosphonium afforded dihydrobenzofuran derivative **6** in 87% yield. Similarly, 2-methyl-2-styryl-2,3-dihydrobenzofuran-3-ol (**7**) was obtained by the reduction of **3aa** with $NaBH_4$. A selective reduction of the alkenyl C–C double bond of **3aa** using Pd/C and H_2 generated 2-methyl-2-phenethylbenzofuran-3(2*H*)-one (**8**) in 85% yield.

Scheme 4. Diversity-Oriented Synthesis of Compounds 6–8 from 3aa



On the basis of our experimental results and known literature, a plausible catalytic cycle of the [4 + 1] annulation reaction of salicylaldehydes and allenes is presented in Scheme 5 (using **1a** and **2a** as examples).[8,12] The formation of the

Scheme 5. Proposed Reaction Mechanism



$[Rh^{III}]$ monomer from the $[Rh^{III}]$ dimer precatalyst initiates the catalytic cycle. Coordination of the OH group on the salicylaldehyde to the Rh^{III} complex, followed by an aldehyde $C(sp^2)$–H bond cleavage, formed the five-membered rhodacycle **I**. Subsequently, coordination of the allene **2a** to the rhodium(III) center of **I**, followed by a regioselective intramolecular insertion of the allene into the carbon–rhodium bond of **II**, provides the rhodium–π-allyl complex **III**. A consecutive intramolecular insertion of the oxygen–rhodium bond into the π-allyl complex affords the intermediate **IV**. The final product **3aa** is delivered by a β-hydride elimination process from the intermediate **IV**. The resulting Rh–H complex undergoes reductive elimination to give $[Cp^*Rh^I]$, which is then oxidized by $Cu(OAc)_2$ to regenerate an active $[Cp^*Rh^{III}]$ catalytic species.

In summary, we have developed a novel method for the Rh^{III}-catalyzed synthesis of 2,2-disubstituted 3-coumaranones from substituted salicylaldehydes and allenes. The reaction leads to the formation of 2-vinyl-substituted 3-coumaranones under mild reaction conditions with a broad substrate scope. A possible mechanism involves the phenolic hydroxyl group directed aldehyde $C(sp^2)$–H activation and annulation cycle. Our method has also been applied to 2-aminobenzaldehydes to give 2-vinyl-substituted 3-indolinones. A detailed mechanistic study and the application of this synthetic strategy to asymmetric systems are now in progress.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01825.

General experimental procedures, characterization details, ^{1}H and ^{13}CNMR spectra of new compounds, and X-ray data (PDF)

X-ray data for compound **3ga** (CIF)

X-ray data for compound **5ea** (CIF)

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Notes

The authors declare no competing financial interest.

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