Synthetic Methods

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Ruthenium(II)-Catalyzed Synthesis of Spirobenzofuranones by a Decarbonylative Annulation Reaction

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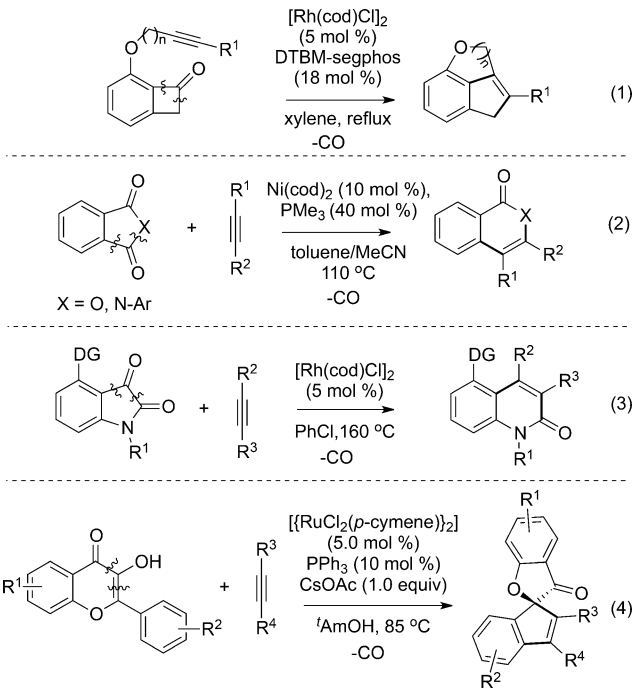
Abstract: *The first decarbonylative insertion of an alkyne through C–H/C–C activation of six-membered compounds is reported. The Ru-catalyzed reaction of 3-hydroxy-2-phenylchromones with alkynes works most efficiently in the presence of the ligand PPh_3 to provide spiro-indenebenzofuranones. Unlike previously reported metal-catalyzed decarbonylative annulation reactions, in the present decarbonylative annulation reaction, the annulation occurs before extrusion of carbon monoxide.*

The cycloaddition reaction of π-systems is the most common strategy to synthesize cyclic compounds.[1] In recent years, transition-metal-catalyzed activation of inert C–H/C–C bonds, followed by insertion of π-systems has developed as the method of choice to synthesize complex carbacycles and heterocycles.[2] In particular, metal-catalyzed decarbonylative activation of the C–C bonds of strained four-membered cyclobutanones and insertion of π-systems have been typically used for the synthesis of ring structures [Scheme 1, Eq. (1)].[3] Kondo, Mitsudo, and co-workers reported the first example of an intermolecular decarbonylative addition reaction of strained cyclobutenediones and cyclobutenones with norbornene and ethylene.[3e,f] Concurrently, the low-valent metal complex $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) has been used for the decarbonylative activation of the C–N/C–O/C–C bonds of carbonyl-containing cyclic compounds and the subsequent annulation reactions with alkynes [Scheme 1, Eq. (2)].[4] Although decarbonylative addition reactions with higher-valent metals are mainly limited to strained rings,[3] recently, Zheng and Dong have reported a directing-group-assisted decarbonylative cyclization reaction of less-strained five-membered isatins with alkynes for the synthesis of 2-quinolinone derivatives [Scheme 1, Eq. (3)].[5] Nevertheless, less-strained six-membered rings, to our knowledge, have never been studied for the decarbonylative C–C/C–H activation and π-insertion reaction. In all of the above-mentioned metal-catalyzed decarbonylative cyclization reactions, insertion of the π-system occurs after the extrusion of carbon monoxide by means of C–C/C–N/C–O activation. Herein, in continuation of our studies on metal-catalyzed novel transformations,[6] we describe an unprecedented decarbonylative alkyne insertion reaction, in which insertion of the π-system occurs before the extrusion of carbon monoxide by means of C–H/C–C activation. Notably, this decarbonylative cycloaddition reaction of 3-hydroxy-2-phenylchromones with alkynes provides a discrete procedure for the synthesis of spiro-indenebenzofuranones. Spirobenzofuranones are important motifs that are widely distributed in bioactive compounds, pharmaceuticals, and natural products.[7] In particular, spiro-cyclopentanebenzofuranone and spiro-dihydroindenebenzofuranone are the substructures of some recently isolated bioactive natural products (Figure 1).[7c–d] Therefore, an efficient method to synthesize this substructure is essential.



Scheme 1. Examples of decarbonylative annulation reactions.

Initially, the reaction conditions for the decarbonylative annulation reaction were optimized by using hydroxychromone **1a** and alkyne **2a** (see Table 1 and the Supporting Information). Of the catalysts screened to perform this reaction, $[RuCl_2(p\text{-cymene})_2]$ provided the highest yield of the annulated product **3aa** in the presence of additive CsOAc

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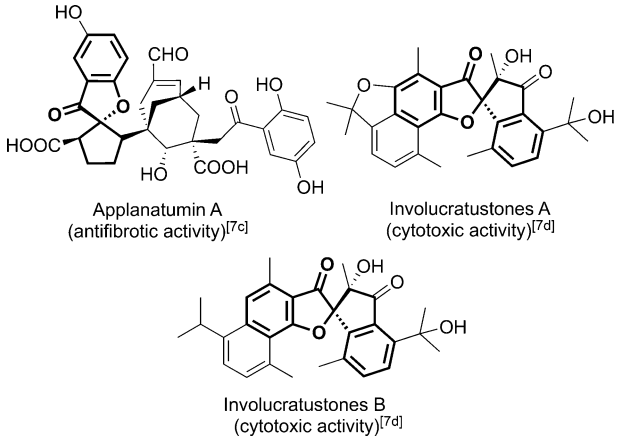
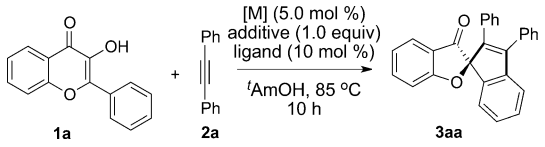


Figure 1. Representative examples of related natural products.

Table 1: Optimization of the reaction conditions for the synthesis of **3aa**.[a]

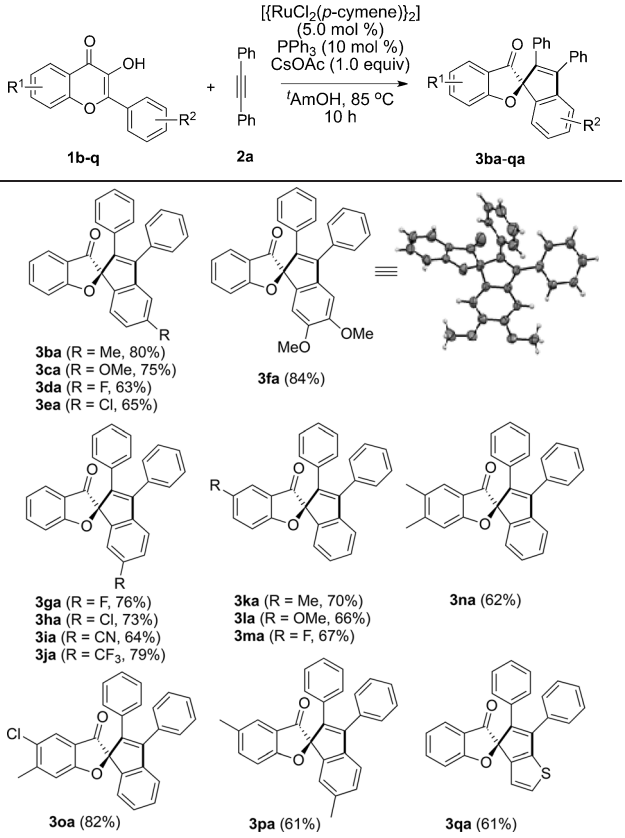


Entry	Catalyst	Additive	Ligand	**3aa** [%][b]
1	$[RuCl_2(p\text{-cymene})_2]$	$Cu(OAc)_2$	–	21
2	$[RuCl_2(p\text{-cymene})_2]$	CsOAc	–	56
3	$[RuCl_2(p\text{-cymene})_2]$	AgOAc	–	34
4	$[RuCl_2(p\text{-cymene})_2]$	$CuBr_2$	–	0
5	$[RuCl_2(p\text{-cymene})_2]$	CsOAc	$P(Cy)_3$	76
6	$[RuCl_2(p\text{-cymene})_2]$	CsOAc	PPh_3	85
7	$[RuCl_2(p\text{-cymene})_2]$	CsOAc	Dppe[c]	56
8	$[RuCl_2(p\text{-cymene})_2]$	CsOAc	(±)-BINAP[d]	62

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst (5.0 mol%), additive (1.0 mmol), ligand (10 mol%), and *t*AmOH (5.0 mL) at 85 °C under air for 10 h; unless otherwise mentioned. [b] Yields of isolated products. [c] 1,4-Bis(diphenylphosphino)ethane. [d] (±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene.

(Table 1, entry 2). Screening of some monodentate and bidentate phosphine ligands revealed PPh_3 as the best ligand to afford **3aa** in 85% yield (see Table 1, entries 5–8 and the Supporting Information). The optimized conditions were then first utilized to study the scope of various 2-aryl-3-hydroxychromones **1b–q** for this annulation reaction with **2a**. As shown in Table 2, different electron-donating and electron-withdrawing *para* substituents, such as methyl, methoxy, fluoro, and chloro substituents on the 2-phenyl ring (**1b–e**), tolerate the reaction conditions to afford good yields of spiro compounds **3ba–ea**. Similarly, a substrate with a methoxy substituent present at both the *meta* and *para* positions of the 2-phenyl ring (**1f**) provided a good yield of **3fa**. Substrates that have electron-withdrawing substituents, such as F, Cl, CN, and CF_3, at the *meta* position of the 2-phenyl ring (**1g–j**), were also found to be good substrates for this reaction to provide spiro compounds **3ga–ja**. Next, the scope of 2-aryl-3-hydroxy chromones that have substituents on the fused aromatic ring (**1k–m**) was studied. All of the representative chromone derivatives substituted with a methyl, methoxy, or

Table 2: Scope of chromones **1b–q** with **2a**.[a]

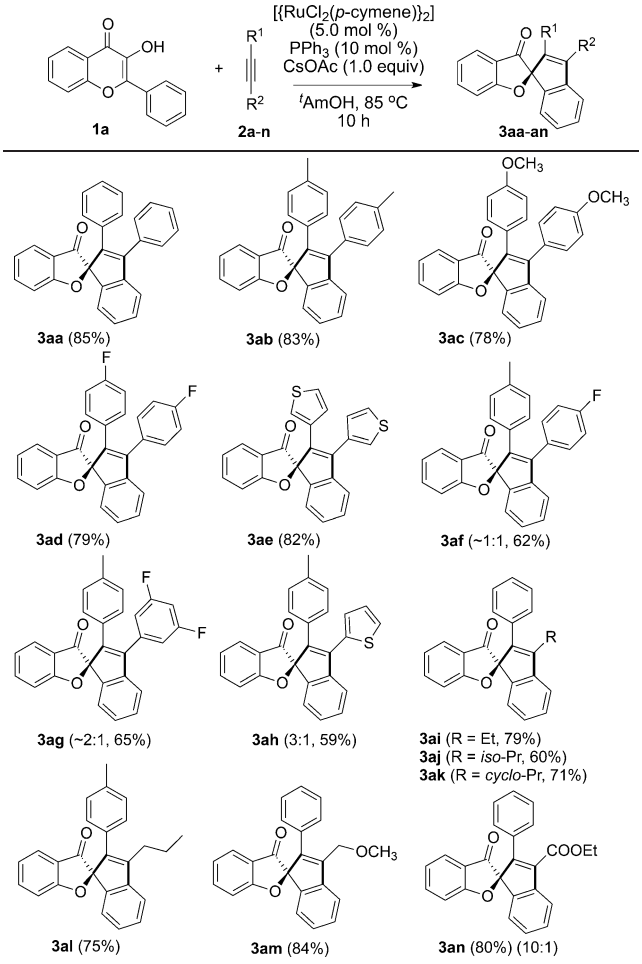


[a] Reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol), Ru catalyst (5.0 mol%), PPh_3 (10 mol%), and CsOAc (1.0 equiv) in *t*AmOH (5.0 mL) was heated at 85 °C for 10 h under air.

fluoro substituent (**1k–m**) proved to be good substrates to afford **3ka–ma**. The disubstituted chromones substituted on the fused aryl ring (**1n**, **1o**) or substituted both on the fused phenyl ring and 2-phenyl ring (**1p**) were also found to be good substrates for the reaction to provide **3na–pa**. The 2-heteroaryl-substituted chromone **1q** also tolerated the reaction conditions well to afford **3qa** in good yield. However, other 2-heteroaryl-substituted chromones, such as 2-(furan-2-yl)-3-hydroxy-4*H*-chromen-4-one and 3-hydroxy-2-(pyridin-4-yl)-4*H*-chromen-4-one, tested for this annulation reaction were not found to be good substrates. The annulation reactions of **1g–j** and **1p** with **2a** were highly regioselective.

Next, the scope of alkynes **2a–n** for this annulation reaction was studied with **1a** (Table 3). The diaryl-substituted alkynes substituted with electron-donating and electron-withdrawing groups, such as methyl, methoxy, and fluoro substituents on the phenyl rings (**2b–d**) provided very good yields of **3ab–ad**. The diheteroaryl-substituted alkyne **1e** also tolerated the reaction conditions to provide **3ae**. The unsymmetrical diaryl-substituted and arylheteroaryl-substituted alkynes **2f–h** provided a mixture of isomers **3af–ah**. The annulation reactions of unsymmetrical arylalkyl-substituted alkynes **2i–m** with **2a** were highly regioselective and provided single isomers of the spiro compounds **3ai–am**. Similarly, the aryl- and ester-group-containing alkyne **2n** also proved to be a very good substrate for this reaction to afford the

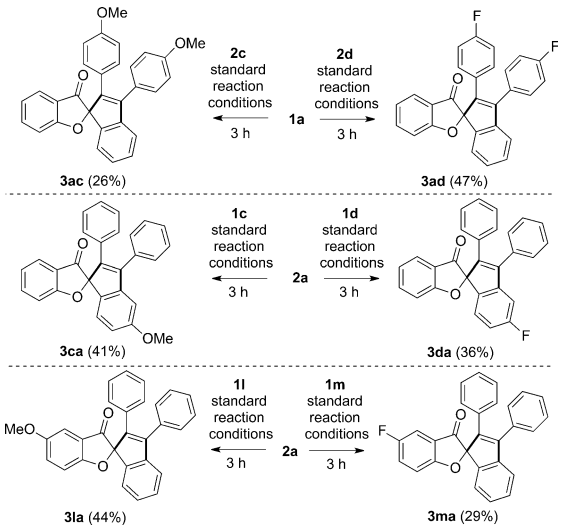
Table 3: Scope of alkynes **2a–n** with **1a.**[a]



[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), Ru catalyst (5.0 mol%), PPh_3 (10 mol%), and CsOAc (1.0 equiv) in *t*AmOH (5.0 mL) was heated at 85 °C for 10 h under air.

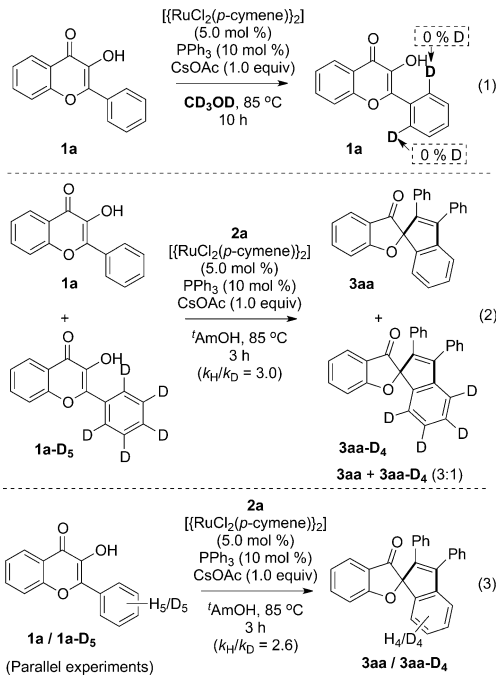
regioselective product **3an** (10:1). However, under the standard reaction conditions, attempts to synthesize spiro compounds with dialkyl-substituted symmetrical and unsymmetrical alkynes were unsuccessful. The structure of the compounds were determined by spectroscopic studies and finally confirmed by single X-ray crystallographic studies of compound **3fa**.[8] Previous studies on transition-metal-catalyzed annulation reactions showed that the alkyne-insertion phenomenon was mainly controlled by electronic effects rather than steric effects.[2f–h] Thus, similar to the previous reports, it is difficult to envisage the regioselectivity of the unsymmetrical diaryl-substituted alkynes in the present reaction, though with some of the unsymmetrical diaryl alkynes good regioselectivity was observed.[2f–h] Nevertheless, the annulation pattern of unsymmetrical arylalkyl-substituted alkynes in the present reaction is similar to the previously reported transition-metal-catalyzed annulation reactions, in which the electron-rich carbon center of the alkyne favorably binds with the metal to furnish the final annulated products regioselectively.[2f–i,5]

The competitive experiment performed between the electron- rich alkyne **2c** and electron-poor alkyne **2d** with **1a** showed that **2d** reacted faster than **2c** (**3ac**:**3ad** = 1:1.8, Scheme 2). Similarly, another competitive reaction between



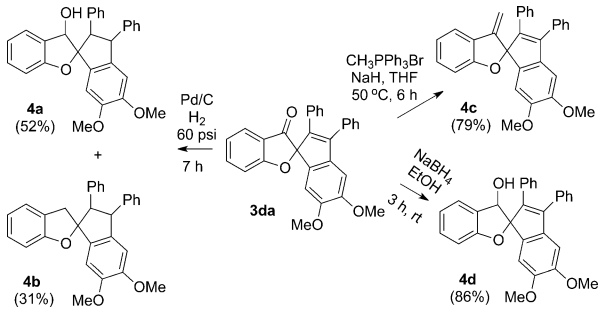
Scheme 2. Competitive experiments.

electron-rich chromone **1l** and electron-poor chromone **1m** with **2a** displayed preferential conversion of **1l** into the corresponding product **3la** (**3la**:**3ma** = 1.5:1, Scheme 2). The reaction of **1a** alone in CD_3OD under the standard conditions did not afford the D/H exchanged product [Scheme 3, Eq. (1)], which indicates a nonreversible Ru–C bond formation. To determine the k_H/k_D value, the intermolecular competitive experiment between **1a** and **1a-D$_5$** with **2a** was performed and it was found that $k_H/k_D = 3$ [Scheme 3, Eq. (2)]. The competitive parallel experiments, performed



Scheme 3. Isotopically labeled experiments.

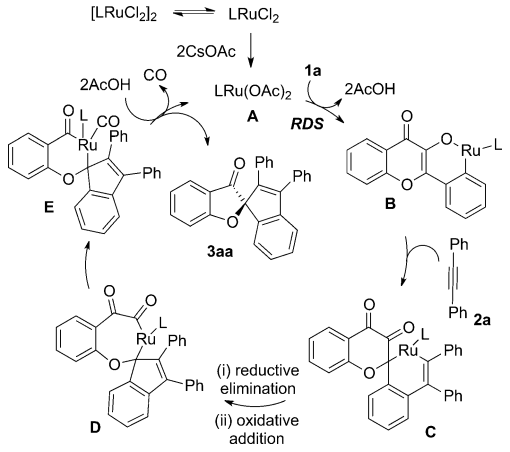
using substrates **1a** and **1a-D$_5$** with **2a** provided $k_H/k_D = 2.6$ [Scheme 3, Eq. (3)].[9] These results indicate the Ru–C bond-formation step might be the rate-determining step of this reaction. Furthermore, the elimination of CO from the reaction mixture was proven by a phosphomolibdic acid/$PdCl_2$ test (see Figure SI-1, in the Supporting Information).[10] In this test, the evolved CO is oxidized to CO_2 in the presence of phosphomolibdic acid $[H_3PO_4(Mo^{VI}O_3)_{12}]$ and $PdCl_2$. During this process, phosphomolibdic acid, which is yellow in color gets reduced into a mixed valence molybdate complex (Mo^{V} Mo^{VI}), which is blue–green in color. To demonstrate the synthetic utility of this method, some other transformations of spirobenzofuranone **3da** were performed (Scheme 4). Hydrogenation of **3da** in the presence of Pd/C



Scheme 4. Transformation of spirobenzofuranone.

provided a mixture of spirobenzofurans **4a** and **4b**, which were separated by silica-gel column chromatography. The Wittig reaction of **3da** and methyltriphenylphosphonium bromide provided a good yield of spirobenzofuran **4c**. Similarly, selective reduction of the keto functionality of **3da** with $NaBH_4$ afforded spirobenzofuran **4d**.

Based on these studies as well as literature precedent,[3e,4,5,11] a possible mechanism is proposed in Scheme 5. The active catalyst **A** first forms Ru^{II} complex **B** by elimination of two molecules of acetic acid; this could be the rate-determining step. Insertion of alkyne **2a** into the C–Ru bond of complex **B** affords complex **C**. Reductive elimination of the metal from **C**, followed by carbonyl-group-assisted oxidative addition of the eliminated Ru^0 species into the C(4°)–C(carbonyl) bond could afford complex **D**.[11b–c] Next, decarbonylation and reductive elimination of the metal in the presence of acetic acid affords **3aa** and regenerates the active catalyst **A**.



Scheme 5. Possible reaction mechanism.

In summary, we have developed a novel Ru^{II}-catalyzed decarbonylative π-insertion reaction of less-strained six-membered ring compounds. This annulation reaction of 3-hydroxy-2-phenyl chromones and disubstituted alkynes proceeds by means of C–H/C–C activation, alkyne insertion, and decarbonylation reactions, providing good yields of spiroindenebenzofuranones, which are the key skeleton of some recently isolated bioactive natural products.

Experimental Section

Typical experimental procedure: A solution of 3-hydroxy-2-phenyl-chromone (**1**, 0.3 mmol), alkyne (**2**, 0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol%), PPh_3 (10 mol%), and CsOAc (1.0 equiv) in *t*AmOH (5.0 mL) was stirred at 85 °C under open air for 10 hours. The solvent was removed in vacuo and the crude reaction mixture was poured into water and extracted with dichloromethane (2 × 20 mL). The organic layer was then washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product obtained was purified by silica-gel (100–200 mesh) column chromatography using EtOAc/hexane (1:9) as the eluent to afford spirobenzofuranone **3**.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: annulation · benzofuranones · C–H activation · decarbonylation · ruthenium catalysis

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Communications

Synthetic Methods

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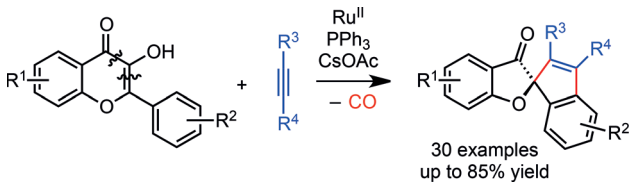
Ruthenium(II)-Catalyzed Synthesis of Spirobenzofuranones by a Decarbonylative Annulation Reaction



Ruthenium(II)-catalyzed C–H/C–C activation, alkyne insertion, and decarbonylation reactions of 3-hydroxy-2-phenyl chromones and disubstituted alkynes afforded good yields of spiro-indenebenzofuranones.

