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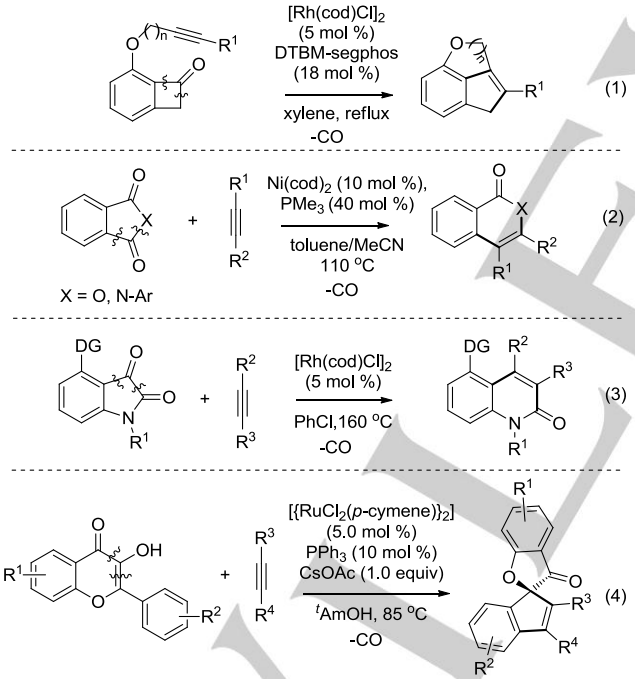
Ru(II)-Catalyzed Synthesis of Spiro Benzofuranones via Decarbonylative Annulation Reaction

P. P. Kaishap[a], G. Duarah[a], B. Sarma[b], D. Chetia[c] and S. Gogoi[a]*

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

Cycloaddition reaction of π-systems is the most common strategy to synthesize cyclic compounds.[1] In recent years, the transition-metal-catalyzed activation of inert C-H/C-C bonds, followed by insertion of π-systems has grown as the method of choice to synthesize complex carbacycles and heterocycles.[2] In particular, the metal-catalyzed decarbonylative activation of C-C bonds of strained four membered cyclobutanones and insertion of π-systems have been usually used for the synthesis of ring structures (Scheme 1, eqn 1).[3] Kondo and Mitsudo have reported the first example of intermolecular decarbonylative addition reaction of strained cyclobutenediones and cyclobutenones with norbornene and ethylene.[3e-f] Concurrently, the low valent metal complex $Ni(COD)_2$ has been used for the decarbonylative activation of C-N/C-O/C-C bonds of carbonyl containing cyclic compounds and subsequent annulation reactions with alkynes (Scheme 1, eqn 2).[4] While the decarbonylative addition reactions with higher valent metals are mainly limited to strained rings,[3] very recently, G. Dong and co-workers 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, eqn 3).[5] Nevertheless, the less strained six-membered rings, to the best of our knowledge, have never been studied for the decarbonylative C-C/C-H activation and π-insertion reaction. In all the above mentioned, reported metal-catalyzed decarbonylative cyclization reactions, insertion of the π-systems occur after the extrusion of carbon monoxide via C-C/C-N/C-O activations. Herein, in continuation of our studies on metal-catalyzed novel transformations,[6] we describe an unprecedented decarbonylative alkyne insertion reaction, where insertion of the π-system occur before the extrusion of carbon monoxide via C-H/C-C activations. Notably, this decarbonylative cycloaddition reaction of 3-hydroxy-2-phenylchromones with alkynes provides a discrete procedure for the synthesis of spiro-indenebenzofuranones. Spiro-benzofuranones are the 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 of the recently isolated bioactive natural products (Figure 1).[7c-d] Therefore, an efficient method to synthesize this substructure is very essential.



Scheme 1. Examples of decarbonylative annulation reactions

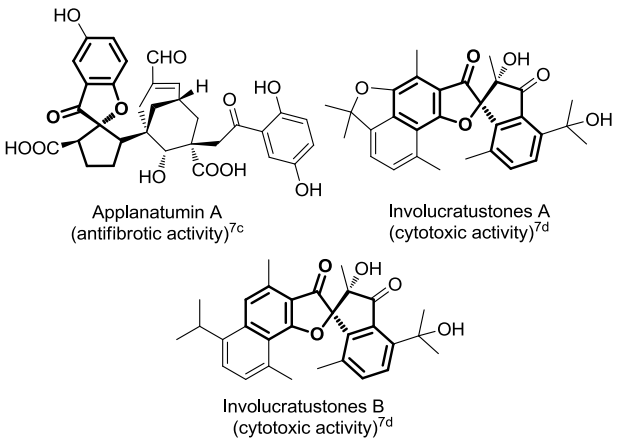


Figure 1. Representative examples of related natural products

Initially, the reaction conditions for the decarbonylative annulation reaction were optimized using hydroxychromone **1a** and alkyne **2a** (Table 1 and SI). Among the catalysts screened

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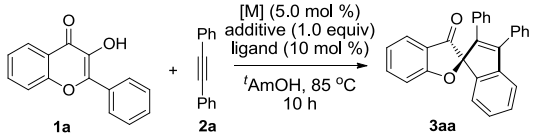
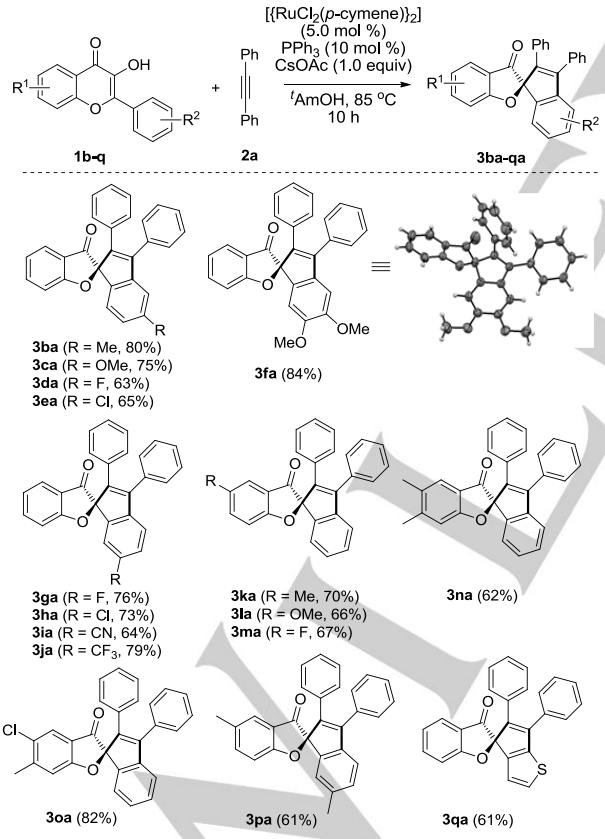
Table 1. Optimization of the reaction conditions for **3aa**[a]



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] Isolated yields. [c] 1,4-Bis(diphenylphosphino)ethane. [d] (±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene.

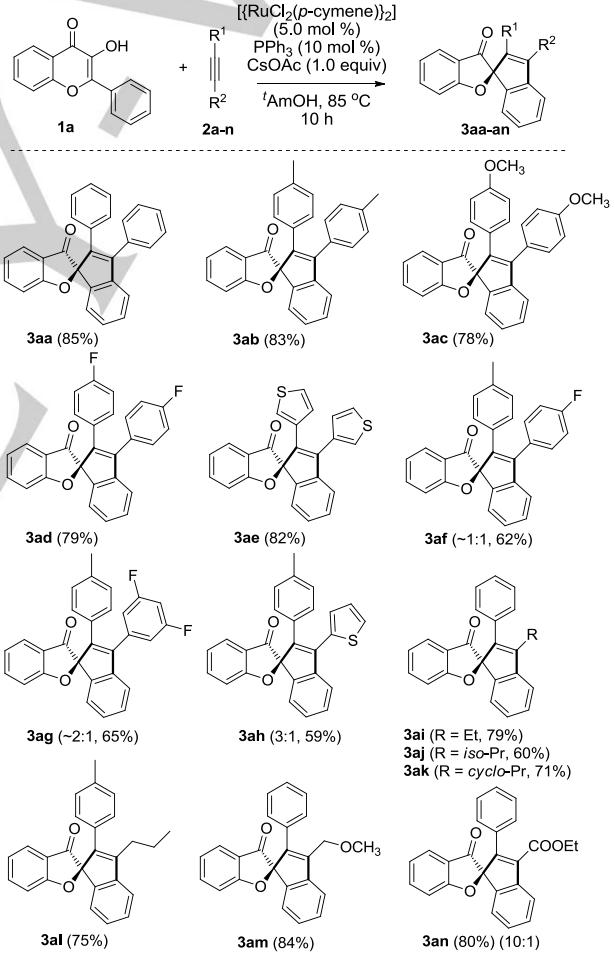
Table 2: Scope of chromones **1b**-**q** with **2a**[a]



[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 ^{o}C for 10 h under air.

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 (entry 2). Screening of some monodented and bidented phosphine ligands revealed PPh_3 as the best ligand to afford **3aa** in 85% yield (entries 5-8 & SI). This optimized condition was 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 on the 2-phenyl ring of **1b**-**e**, tolerate the reaction condition to afford good yields of spiro compounds **3ba**-**ea**. Similarly, methoxy substituent present at both *meta* and *para* position of the 2-phenyl ring of **1f** provided good yield of **3fa**. The substrates that have electron withdrawing substituents such as F, Cl, CN and CF_3 at *meta* position of 2-phenyl ring of **1g**-**j**, were also found to be good substrates for this reaction to provide spiro compounds **3ga**-**ja**. Then, the scope of 2-aryl-3-hydroxy chromones that have substituents on the fused aromatic ring **1k**-**m** was studied. All the representative chromone derivatives substituted with a methyl, methoxy and fluoro substituent **1k**-**m** turned out to be good substrates to afford **3ka**-**ma**. The disubstituted chromones substituted on the fused aryl ring **1n**-**o**

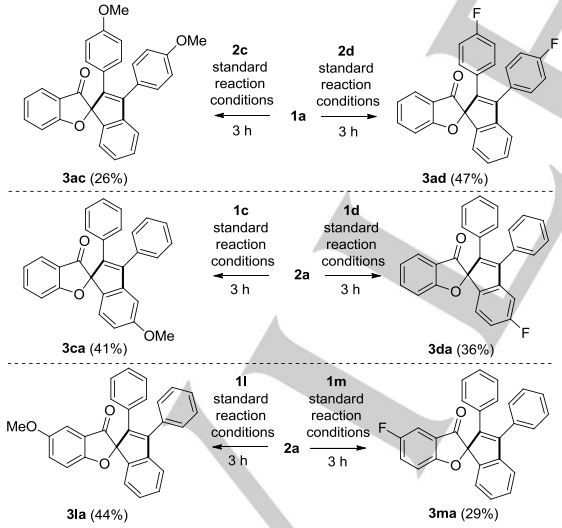
Table 3: Scope of alkynes **2a-n** with **1a**[a]



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

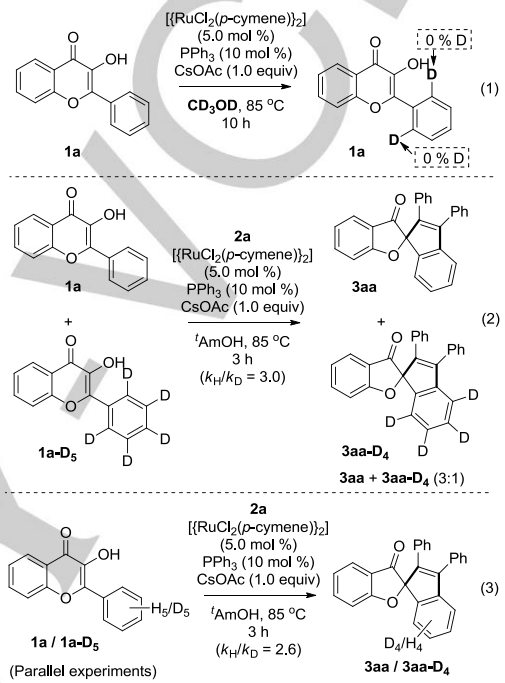
or substituted both on the fused phenyl ring and 2-phenyl ring **1p** were also found to be good substrates for the reaction to provide **3na**-**pa**. The 2-heteroaryl substituted chromone **1q** also tolerated the reaction condition well to afford **3qa** in good yield. However, other 2-heteroaryl 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,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 on the phenyl rings **2b**-**d** provided very good yields of **3ab**-**ad**. The diheteroaryl substituted alkyne **1e** also tolerated the reaction condition 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 to provide single isomers of the spiro compounds **3ai**-**am**. Similarly, the aryl and ester group containing alkyne **2n** also turned out to be very good substrate for this reaction to afford regioselective product **3an** (10:1). However, under the standard reaction condition, attempts to synthesize the spiro compounds with dialkyl substituted symmetrical and unsymmetrical alkynes met with failure. 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 the transition-metal-catalyzed annulation reactions showed that the alkyne insertion phenomenon was mainly controlled by electronic effect rather than steric effect.[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, where the electron rich carbon center of the alkyne favorably binds with the metal to furnish regioselectivity into the final annulated products.[2f-i][5]



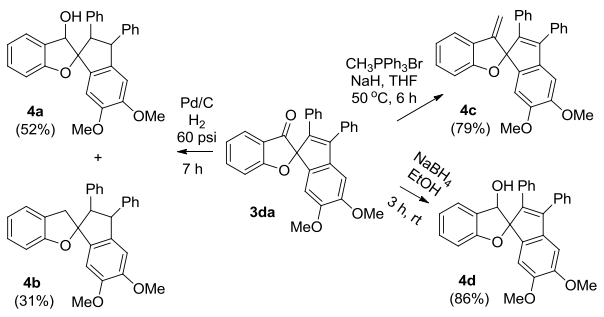
Scheme 2. Competitive experiments

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 electron-rich chromone **1l** and electron-poor chromone **1m** with **2a** displayed preferential conversation of **1l** into its corresponding product **3la** (**3la**:**3ma** = 1.5:1, Scheme 2). The reaction of **1a** alone in CD_3OD under standard condition could not afford the D/H exchanged product (Scheme 3, eqn 1), which indicates a nonreversible Ru-C bond formation. To determine the k_H/k_D, the intermolecular competitive experiment between **1a** and **1a-D$_5$** with **2a** was performed which provided k_H/k_D = 3 (Scheme 3, eqn 2). The competitive parallel experiments, performed using substrates **1a** and **1a-D$_5$** with **2a** provided k_H/k_D = 2.6 (Scheme 3, eqn 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 proved by phosphomolibdic acid-$PdCl_2$ test (Figure SI-1, SI).[10] In this test, the evolved CO is oxidized to CO_2 in the presence of phosphomolibdic acid $[H_3PO_4(Mo^{VI}O_3)_{12}]$



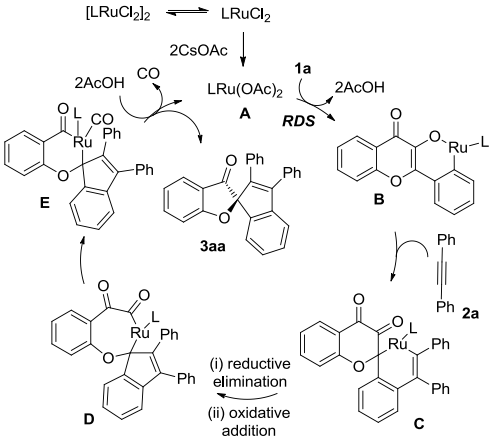
Scheme 3. Isotopically labeled experiments

and $PdCl_2$. During this process, phosphomolibdic acid which is yellow in color gets reduced into 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 spiro benzofuranone **3da** were carried out (Scheme 4). Hydrogenation of **3da** in the presence of Pd/C provided a mixture of spiro benzofurans **4a** and **4b** which were separated by silica gel column chromatography. The Wittig reaction of **3da** and methyltriphenylphosphonium bromide provided good yield of spiro benzofuran **4c**. Similarly, selective reduction of keto functionality of **3da** with $NaBH_4$ afforded spiro benzofuran **4d**.



Scheme 4. Transformation of spiro benzofuranone

Based on these studies as well as literature evidences,[4,5,11] a possible mechanism is proposed in Scheme 5. The active catalyst **A** first forms Ru(II) complex **B** by eliminating two molecules of acetic acid which might be the rate determining step. Insertion of alkyne **2a** in between 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) into C(4^o)-C(carbonyl) bond might 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 compound. This annulation reaction of 3-hydroxy-2-phenyl chromones and di-substituted alkynes proceeds via C-H/C-C activation, alkyne insertion and decarbonylation reactions, providing good yields of spiro-indenebenzofuranones which are the key skeleton of some of the 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 ^{o}C under open air for 10 hours. The solvent was removed under vacuo and the crude reaction mixture was poured into water and extracted with dichloromethane (20 mL x 2). The organic layer was then washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuo and the crude product obtained was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane (1:9) as the eluant to afford spiro benzofuranone **3**.

Acknowledgements

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Keywords: Decarbonylation • annulation reaction • spiro-benzofuranone • C-H activation • ruthenium catalysis

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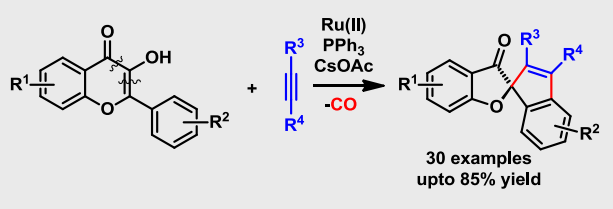

Ru(II)-Catalyzed C-H/C-C activation, alkyne insertion and decarbonylation reaction of 3-hydroxy-2-phenyl chromones and di-substituted alkynes afforded good yields of spiro-indenebenzofuranones.

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Ru(II)-Catalyzed Synthesis of Spiro Benzofuranones via Decarbonylative Annulation Reaction