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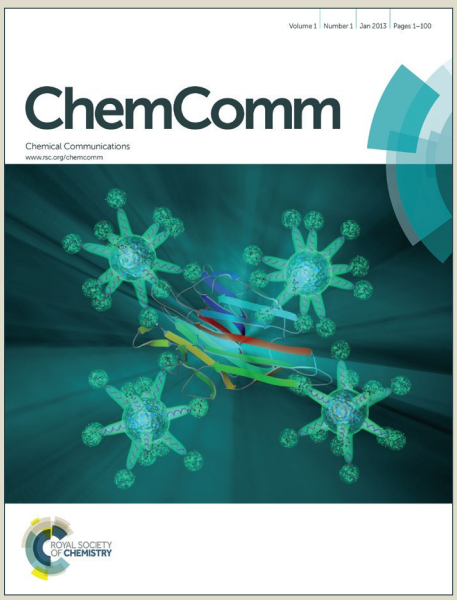

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ARTICLE TYPE

Ru(II)-Catalyzed C-H Activation and Annulation of Salicylaldehydes with Monosubstituted and Disubstituted Alkynes

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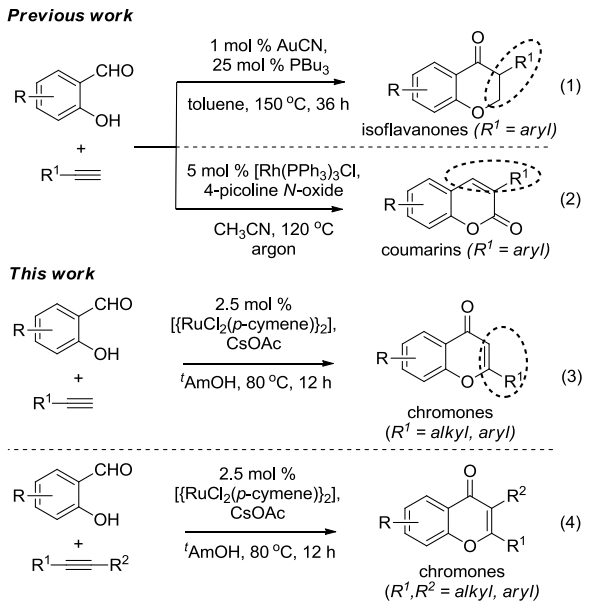
The Ru(II)-catalyzed C-H activation and annulation reaction of salicylaldehydes and disubstituted alkynes affords chromones in high yields. This reaction works with terminal alkynes also and tolerates wide range of sensitive functional groups. The selectivity pattern of this Ru(II)-catalyzed annulation reaction is different from the known Au(I), Rh(III)-catalyzed annulation reactions of salicylaldehydes and terminal alkynes.

Chromones represent the core structures of flavonoids, isoflavonoids, wide range of biologically active compounds and drug molecules.[1] Because of their tremendous significance in medicinal chemistry and drug discovery,[1a] there is a continuous interest in the development of simple and general synthetic routes to access derivatives of this heterocyclic scaffold.[1a,2] In recent years, the transition metal catalyzed C-H activation and annulation reactions have emerged as a powerful tool for the efficient construction of various important heterocycles.[3] The Rh(III)-catalyzed, Co(I)-diphosphine-catalyzed C-H activation and annulation reactions of salicylaldehydes with disubstituted alkynes have been reported for the synthesis of 2,3-disubstituted chromones.[4] However, the Rh-catalyzed reaction was very low yielding when dialkyl and arylalkyl substituted alkynes were used as the coupling partners.[4a] Again, the high cost of the Rh(III) catalyst is a limitation of this approach. The Co(I)-diphosphine-catalyzed method was also not efficient for dialkyl substituted alkynes, though the reaction condition was suitable to retain a silyl group of the alkyne in the heterocycle.[4b]

Apart from accelerating the rate of a reaction, a catalyst can influence the selectivity of a chemical reaction. In nature, the enzymes have the ability to convert the same starting material into a wide range of products by controlling the reaction selectivity. Taking the advantage of the reaction selectivity of the catalysts, chemists have been working on the development of new catalyst systems which could transform the same simple starting compounds into valuable products similar to the enzymes.[5] Very recently, Li and coworkers developed two catalytic systems to control the selectivity of the reaction of simple starting materials salicylaldehydes and terminal aryl alkynes.[6] These starting materials on Au-catalyzed annulation reaction afforded isoflavanone skeleton (eqn 1, Scheme 1),[6a] whereas replacing Au with Rh catalyst, the same starting materials provided coumarin skeleton by switching the selectivity of the reaction (eqn 2, Scheme 1).[6b] In continuation of our work on the metal catalyzed C-H/C-C bond activation and functionalization reactions,[7] herein, we describe that the newly developed Ru(II) catalytic system efficiently catalyzes the oxidative alkyne annulation reaction of dialkyl, diaryl, arylalkyl substituted alkynes with salicylaldehydes to afford biologically important chromones (eqn 4). Furthermore, we describe that the terminal alkynes are also suitable substrates for this Ru(II)-catalyzed annulation reaction and the selectivity pattern of this Ru(II)-catalyzed reaction is different from the reported Au- with Rh-catalyzed reactions of salicylaldehydes and terminal alkynes (eqn 3).



Scheme 1. Synthesis of various important scaffolds controlling the selectivity of the reaction using different catalysts

Initially, the performance of the $[RuCl_2(p\text{-cymene})]_2$ catalyst was studied for the oxidative coupling reaction of salicylaldehyde **1a** with phenylacetylene **2a** (Table 1). Among the additives tested for this reaction, only CsOAc provided the highest yield of **3aa** (entries 1-4). The reaction did not work in the absence of additive (entry 5). Screening of other solvents and additives could not

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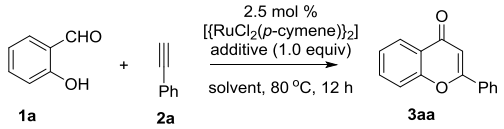
Table 1. Optimization study for chromone synthesis[a]

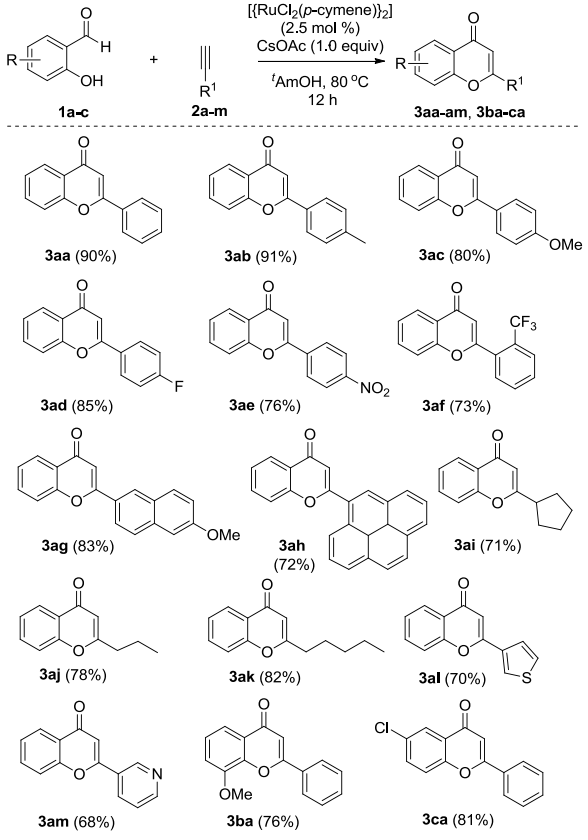


1a 2a 3aa

entry	additive	solvent	yield (%)[b]
1	$Cu(OAc)_2$	^{t}AmOH	0
2	AgOAc	^{t}AmOH	23
3	CsOAc	^{t}AmOH	90
4	$CuBr_2$	^{t}AmOH	0
5	-	^{t}AmOH	-
6	CsOAc	MeOH	67[c]
7	CsOAc	H_2O	58
8	CsOAc	MeCN	78
9	CsOAc/KPF_6	^{t}AmOH	65
10	CsOAc/$AgSbF_6$	^{t}AmOH	73

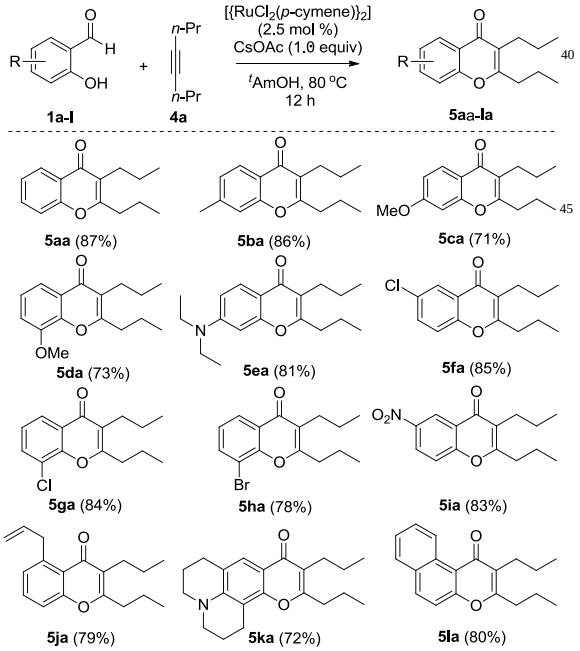
[a]Reaction conditions: Salicylaldehyde (**1a**, 1.0 mmol), alkyne (**1a**, 1.0 mmol), Ru catalyst (2.5 mol %) and additive (1.0 equiv) in solvent (6.0 mL) was heated at 80 °C for 12 h under air.

Table 2. Scope of terminal alkynes[a]



[a]*Reaction conditions:* Salicylaldehyde (1.0 mmol), alkyne (1.0 mmol), Ru catalyst (2.5 mol %), and CsOAc (1.0 equiv) in ^{t}AmOH (6.0 mL) was heated at 80 °C for 12 h under air.

Table 3. Scope of salicylaldehydes with **4a**[a]



[a]Reaction conditions: Salicylaldehyde (1.0 mmol), alkyne (1.0 mmol), Ru catalyst (2.5 mol %), and CsOAc (1.0 equiv) in ^{t}AmOH (6.0 mL) was heated at 80 °C for 12 h under air.

further improve the yield of the reaction (entries 6-10). With the optimized reaction conditions in hand, we first tested the scope of the annulation reaction of salicylaldehyde **1a** with terminal alkynes **2a-m**. As shown in Table 2, terminal aryl alkynes substituted with electron-donating and electron-withdrawing groups such as methyl, methoxy, fluoro, nitro trifluoromethyl groups at C-4, C-2 positions were well tolerated, providing good yields of chromones **3aa-af**. In contrast to the previously reported metal catalyzed annulation reactions of salicylaldehydes and terminal alkynes,[2] which worked only with aryl/heteroaryl substituted alkynes, in the present annulation reaction, the terminal alkynes substituted with cycloalkyl and alkyl substituents also turned out to be good substrates to provide chromones **3ai-ak**. Similarly, terminal fused aryl and heteroaryl alkynes also tolerated the reaction conditions to afford **3ag-ah**, **3al-am**. The electron rich and poor salicylaldehydes **1b-c** were also tested with **2a**. Both the aldehydes **1b-c** reacted well with **2a** irrespective of the substituents present to provide good yields of **3ba-ca**.

Next, the scope of the annulation reaction of aliphatic disubstituted alkyne **4a**, which was not a good substrate in the previously reported annulation reactions[6] was studied with salicylaldehydes **1a-i**. As shown in Table 3, salicylaldehydes substituted with electron-donating and electron-withdrawing groups such as methyl, methoxy, diethylamino and chloro groups at C-3, C-4, C-5 positions were well tolerated, providing good yields of chromones **5ba-ga**. Similarly, useful sensitive fuctional groups such as bromo, nitro and allyl were well tolerated to provide chromones **5ha-ja**, which could be easily subjected for further transformations. 9-Formyl-8-hydroxyjulolidine (**1k**) and 2-hydroxy-1-naphthaldehyde (**1l**)

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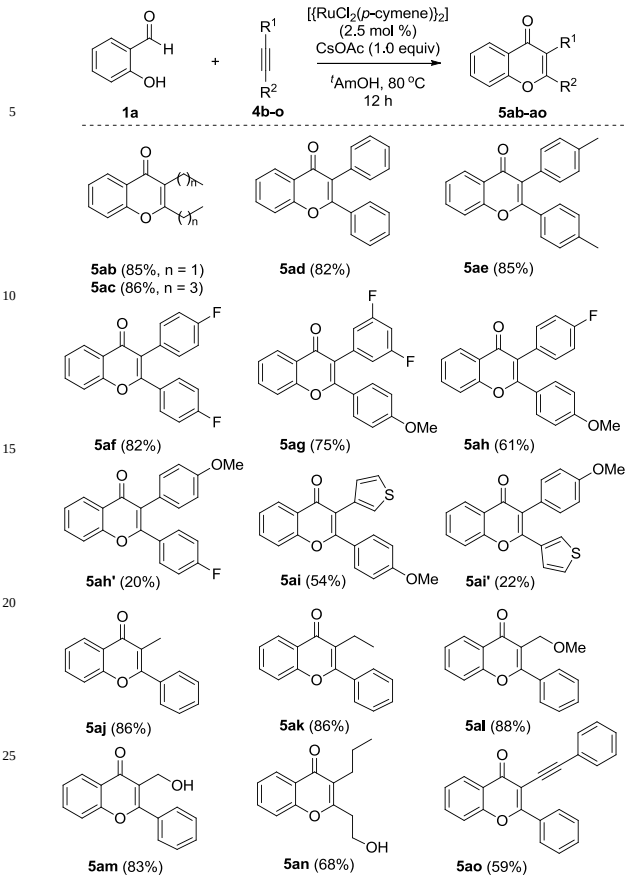
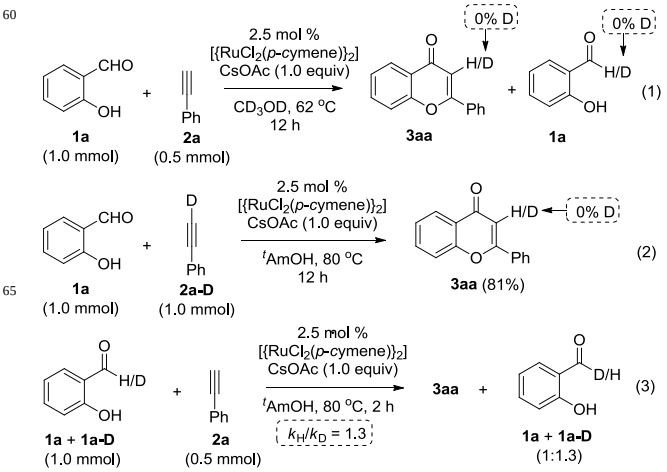
Table 4. Scope of disubstituted alkynes with **1a**[a]



[a]Reaction conditions: Salicylaldehyde (1.0 mmol), alkyne (1.0 mmol), Ru-catalyst (2.5 mol %), and CsOAc (1.0 equiv) in ^{t}AmOH (6.0 mL) was heated at 80 ^{o}C for 12 h under air.

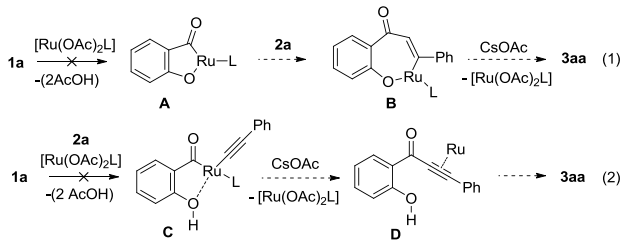
were also found to be good substrates for this reaction. The annulated product **5ka** is a promising compound in the production of laser-compatible NIR marker dyes.[8]

Subsequently**,** the scope of disubstituted alkynes (**4b-o**) was studied for the annulation reaction with **1a** (Table 4). All the tested symmetrical dialkyl, diaryl and diheteroaryl substituted alkynes were found to be good substrates for this annulation reaction (**5ab-af**). Except alkyne **4g**, all other tested unsymmetrical alkynes **4h-i** provided both the isomers of chromones **5ah-ah′**, **5ai-ai′** with **1a**, which were easily separated by silica gel column chromatography. The major isomers formed with these unsymmetrical alkynes possess the electron rich substituents closer to the oxygen atom of the heterocycle. The arylalkyl disubstituted alkynes **5j-l** provided only one isomer of the product (**5aj-al**).[4e] Free hydroxyl group containing alkynes **4m-n** and dialkyne **4o** tolerated the reaction conditions to provide chromones **5am-ao**.[6b] The reaction of **1a** with 1-phenyl-2-trimethylsilylacetylene under the optimized reaction conditions provided the silyl deprotected product **3aa**. The reaction between **1a** and **2a** performed under standard conditions in CD_3OD using an excess of **1a** did not show D/H exchange in the aldehyde C-H of the recovered starting material **1a** (eqn 1, Scheme 2), which indicates an irreversible C-H bond ruthenation step. Furthermore, the product **3aa** obtained from this reaction did not show H/D exchange in the C-H of the pyranone ring. The intermolecular competition experiment performed between **1a**+**1a**-D (1:1) and **2a**, provided 1:1.3 mixture of unreacted **1a**+**1a-D** in two hours (k_H/k_D = 1.3, eqn 2). Furthermore, the rates of individual reactions of **1a** and **1a-D** with alkyne **2a** were also determined (k_H/k_D = 1.4), which indicates that C-H bond cleavage might be involved in the rate-limiting step.



Scheme 2. Experiments with isotopically labeled compounds

A plausible mechanism for formation of **3aa** through formation of Ru complex **A** and seven membered ruthenocycle **B** (eqn 1, Scheme 3) is ruled out as retention of deuterium atom was not observed when the reaction between **1a** and **2a-D** was performed under standard conditions (eqn 2, Scheme 2). Another possibility of formation of **3aa** through intermediate **D** (eqn 2, Scheme 3) is also ruled out as the D/H exchange in the product **3aa** was not observed when the reaction between **1a** and **2a** was performed in CD_3OD (eqn 1, Scheme 2). These studies suggest a greater level of mechanistic complexity of this annulation reaction.



Scheme 3. Plausible reaction mechanism

In summary, we have developed a novel Ru(II)-catalyzed annulation reaction of salicylaldehydes with disubstituted and terminal alkynes. The dialkyl and arylalkyl substituted alkynes which were not suitable substrates for the reported Rh- and Co-catalyzed reactions with salicylaldehydes, turned out to be good substrates for this inexpensive Ru(II)-catalyzed reaction. Unlike the previously reported Au(I)- and Rh(III)-catalyzed reactions of salicylaldehydes with terminal aryl alkynes which afford isoflavanones and coumarins, this Ru(II)-catalyzed reaction affords chromones. Moreover, the Ru(II)-catalyzed reaction works with terminal aliphatic alkynes. Because of some of the noteworthy features of this reaction, such as the broad substrate scope, valuable products, high functional group tolerance, less catalyst loading and high regioselectivity with unsymmetrical

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alkynes, this reaction should be of synthetic utility.

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Notes and references

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.† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of synthesized compounds. See DOI:

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