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Ruthenium-Catalyzed C−H Activation of Salicylaldehyde and Decarboxylative Coupling of Alkynoic Acids for the Selective Synthesis of Homoisoflavonoids and Flavones

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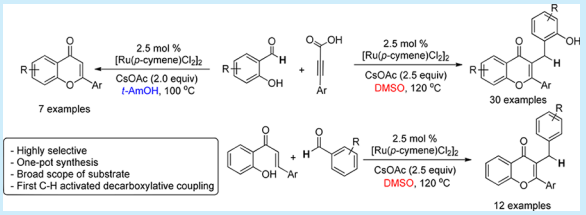
Supporting Information

ABSTRACT: Homoisoflavonoids were formed in DMSO exclusively, and flavones were formed in *t*-AmOH when salicylaldehyde and alkynoic acids reacted with $[Ru(p\text{-cymene})Cl_2]_2$ and CsOAc. They were formed through C−H activation of salicylaldehyde and decarboxylative coupling of alkynoic acid. This reaction system showed good yields, broad substrate scope, and good functional group tolerance. It was found that chalcone was an intermediate in the formation of both homoisoflavonoid and flavone.



Flavonoids are heterocyclic compounds that contain oxygen atoms and have chromone as a core structure. As their analogues, homoisoflavonoids are a type of flavone with benzyl moieties at the C-3 position. Homoisoflavonoids have been found in natural products and are known to play important roles in biological processes, such as symbiotic nitrogen fixation, plant pigmentation, and UV filtration (Figure 1).[1] In addition, their

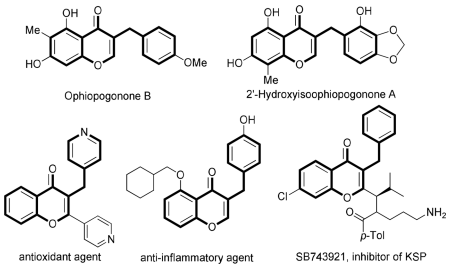


Figure 1. Representative biologically active structures of homoisoflavonoids.

biological properties, e.g., anti-inflammatory, antioxidant, anticancer, antiangiogenic, antidiabetic, antiallergic, antiviral, and antimicrobial activities, have been reported.[2] Nevertheless, little effort toward the development of efficient synthetic routes has been put forth.

The synthetic methods that have been reported thus far are categorized into three groups: (1) the cyclization of dihydrochalcone with one-carbon extension reagents such as Vilsmeier reagent,[3] methanesulfonyl chloride/DMF,[4] ethylformate/sodium,[5] and DMF/2,4,6-trichloro-1,3,5-triazine;[6] (2) the condensation of 4-chromanones with arylaldehydes, followed by rearrangement of the double bond via a base or rhodium;[7] and (3) the cyclization of 1-(*o*-hydroxyphenyl)-1,3-diketone in the presence of anhydrides, strong acids, or bases.[8] However, these methods have drawbacks with respect to the requisite multiple steps for the preparation of dihydrochalcone, 4-chromanone, and 1,3-diketone. To address these problems, new synthetic routes have to be developed.

As part of our ongoing studies for the expansion of decarboxylative coupling reactions,[9] we found that a homoisoflavonoid was unexpectedly formed when phenylpropiolic acid and salicylaldehyde were reacted in the presence of a ruthenium catalyst. This type of homoisoflavonoid is a key skeleton for the synthesis of isoxazole, pyrazole, and 3-benzylchroman-4-one.[10] Furthermore, only one multistep synthetic route was reported for the synthesis of *cis*-homopterocarpans from a homoisoflavonoid that contains a hydroxyl group.[11] Therefore, we envisioned that this Ru-catalyzed C−H activation of salicylaldehyde and decarboxylative coupling of alkynoic acid afforded a selective tool for the synthesis of homoisoflavonoid and flavone. To the best of our knowledge, no report exists of one-pot and metal-catalyzed synthesis of homoisoflavonoid from readily available starting materials. In particular, arylpropiolic acids readily prepared from the coupling reaction of aryl halides and propiolic acid without column chromatography procedure.[9d,e] Herein, we report an efficient and simple method for the synthesis of homoisoflavonoid and flavone.

To find the optimal conditions, phenylpropiolic acid and salicylaldehyde were chosen as standard substrates. The results are summarized in Table 1. The reactions with $[Ru[p\text{-cymene}]Cl_2]_2$ in DMSO, DMF, and NMP provided the homoisoflavonoid **3aa** with 68%, 34%, and 28% yields, respectively, and no **4aa** was found in the reaction mixtures (entries 1−3). However, when the reactions were conducted in *t*-AmOH, *i*-PrOH, and CH_3CN, flavone **4aa** formed with 61%, 28%, and 15% yields, respectively (entries 4−6). Reaction attempts with other bases, such as NaOAc and KOAc, were not successful in increasing the yields of **3aa** (entries 7 and 8). The

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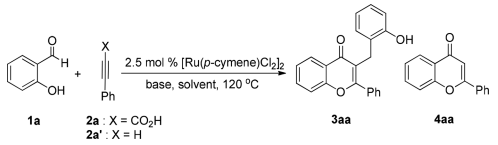
Table 1. Optimization Conditions for the Synthesis of 3aa and 4aa[a]



entry	catalyst	base	solvent	yield[b] (%) 3aa	4aa
1	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	DMSO	68	0
2	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	DMF	34	0
3	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	NMP	28	0
4	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	*t*-AmOH	0	61
5	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	*i*-PrOH	0	28
6	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	CH_3CN	0	15
7	$[Ru(p\text{-cymene})Cl_2]_2$	NaOAc	DMSO	22	0
8	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	DMSO	19	0
9	$[Ru(p\text{-cymene})Cl_2]_2$	Na_2CO_3	DMSO	45	0
10	$[Ru(p\text{-cymene})Cl_2]_2$	K_2CO_3	DMSO	34	0
11	$[Ru(p\text{-cymene})Cl_2]_2$	Cs_2CO_3	DMSO	41	0
12	$[Ru(p\text{-cymene})Cl_2]_2$	CsOPiv	DMSO	10	0
13	$Ru(Phen)_3]Cl_2$	CsOAc	DMSO	8	0
14	$[Ru(Bipy)_3]Cl_2$	CsOAc	DMSO	10	0
15	$RuCl_3$	CsOAc	DMSO	30	0
16[c]	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	DMSO	55	0
17[d]	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	DMSO	**84**	0
18[e]	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	DMSO	22	0
19		CsOAc	DMSO	0	0
20	$[Ru(p\text{-cymene})Cl_2]_2$		DMSO	0	0
21[f]	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	DMSO	59	0

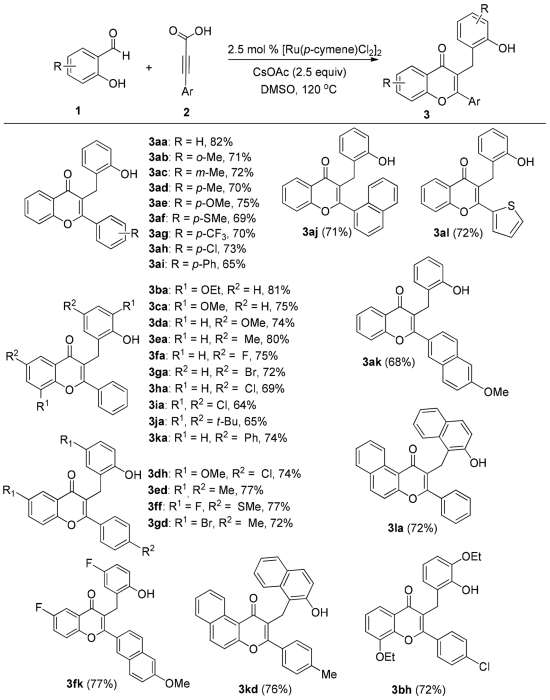
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), base (0.3 mmol), and Ru (0.0075 mmol) were reacted at 120 °C. [b]Isolated yield. [c]The ratio of **1a**/**2a**/base was 2/1/2. [d]The ratio of **1a**/**2a**/base was 1/1.5/2.5. [e]Reaction temperature was 70 °C. [f]**2a′** was used instead of **2a**.

yields from the reactions with other bases, such as Na_2CO_3, K_2CO_3, Cs_2CO_3, and CsOPiv, were lower than those with CsOAc (entries 9−12). Reactions with other ruthenium catalysts, such as $[Ru(Phen)_3]Cl_2$, $[Ru(Bipy)_3]Cl_2$, and $RuCl_3$, resulted in 8%, 10%, and 30% yields, respectively (entries 13−15). When the amount of **1a** increased, the yield decreased (entry 16). However, the amount of both **2a** and the base increased, and the yield increased to 84% (entry 17). The reaction at 70 °C showed lower yield; however, the selectivity did not change (entry 18). Neither **3aa** nor **4aa** were formed in the absence of either the ruthenium catalyst or base (entries 19 and 20).

Interestingly, the use of **2a′** as an alkyne source in DMSO also provided **4aa** with 59% yield (entry 21). These results implied that the solvent is a key factor in controlling the selective formation of homoisoflavonoid and flavone. In addition, it was noteworthy that neither **3aa** nor **4aa** formed when other catalysts, such as $Pd(OAc)_2$, CuI, $[Ir(OMe)(1,5\text{-cod})]_2$, and $[Rh(nbd)Cl]_2$, were used.

With this optimization in hand, a variety of substituted arylpropiolic acids were evaluated in the reaction with salicylaldehyde for the formation of homoisoflavonoid (Scheme 1). As expected, **3aa** was obtained in 82% isolated yield. The structure was confirmed by X-ray crystallography.[12] Methyl-substituted phenylpropiolic acids afforded the desired products **3ab**, **3ac**, and **3ad** in the range of 70−72% yields. Arylpropiolic acids bearing OMe, SMe, CF_3, Cl, and Ph groups in the para

Scheme 1. Synthesis of Homoisoflavonoid from Salicylaldehyde Derivatives and Arylpropiolic Acids[a]



[a]Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), CsOAc (2.5 mmol), and $[Ru(p\text{-cymene})Cl_2]_2$ (0.025 mmol) were reacted in DMSO at 120 °C for 12 h.

position of the phenyl ring provided the corresponding homoisoflavonoids **3ae**, **3af**, **3ag**, **3ah**, and **3ai** in good yields. Naphthyl propiolic acid derivatives and thiophene-yl propiolic acid gave **3aj**, **3ak**, and **3al** in 71%, 68%, and 72% yields, respectively. Next, several substituted salicylaldehydes were allowed to react with phenylpropiolic acid under the optimized conditions. 3-Ethoxy-, 3-methoxy-, 5-methoxy-, and 3-methyl-substituted salicylaldehyde gave the corresponding homoisoflavonoids **3ba**, **3ca**, **3da**, and **3ea** in 81%, 75%, 74%, and 80% yields, respectively. Halo-substituted salicylaldehyde exhibited good yields in the formation of homoisoflavonoids. 3,5-Di-*tert*-butyl- and 5-phenyl-substituted salicylaldehyde provided the corresponding products **3ja** and **3ka** in 65% and 74% yields, respectively. 2-Hydroxy-1-naphthaldehyde also gave the homoisoflavonoid **3la** in 72% yield. When substituted arylpropiolic acids and substituted salicylaldehydes were reacted, the desired homoisoflavonoids (**3dh**, **3ed**, **3ff**, **3gd**, **3fk**, **3kd**, and **3bh**) were formed in good yields in the range of 70−76%. However, we failed to get the desired product in the reaction with alkyl substitued alkyne carboxylic acids. From these results, we found the following: (1) the steric effect of substituents might be minor regarding the yield of homoisoflavonoid, and (2) the electronic effect was not found in the substituents of arylpropiolic acids.

During the investigation of the scope of substrates, we failed to obtain the desired homoisoflavonoid **3ma** from the reaction of 5-nitrosalicylaldehyde with phenylpropiolic acid; however, the chalcone-type compound **5ma** was obtained with 40% yield, as shown in Scheme 2. This result supported that chalcone was formed through decarboxylative hydroacylation and might be the intermediate in the formation of homoisoflavonoid, and electron-withdrawing groups in salicylaldehyde suppressed the cyclization step.

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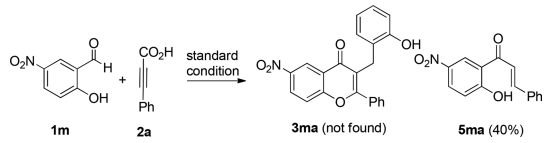
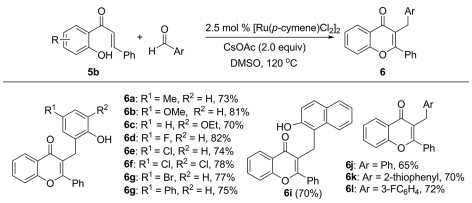
Scheme 2. Formation of Chalcone-Type Product



On the basis of this result, when salicylaldehyde was treated with 2′-hydroxychalcone under standard conditions, homoisoflavonoid **3aa** was formed exclusively, with 92% yield. This inspired us to develop a new route for the synthesis of homoisoflavonoid from 2′-hydroxychalcone. As shown in Scheme 3, numerous aldehydes were allowed to react with 2′-hydroxychalcone in the presence of Ru and CsOAc. Reactions with salicylaldehyde having different substituents, such as methyl, methoxy, ethoxy, fluoro, chloro, bromo, and phenyl, afforded the corresponding products **6a**−**h** in the range of 70−82% yield. The reactions with 2-hydroxy-1-naphthaldehyde, benzaldehyde, 2-thiophenecarboxaldehyde, and 3-fluorobenzaldehyde afforded the corresponding homoisoflavonoids **6i**, **6j**, **6k**, and **6l** in 70%, 65%, 70%, and 72% yields. However, we failed to obtain the desired product in the reaction with alkylaldehydes such as hexanaldehyde, 2-hydroxy-5-nitrobenzaldehyde, and 2,4-dihydroxybenzaldehyde.

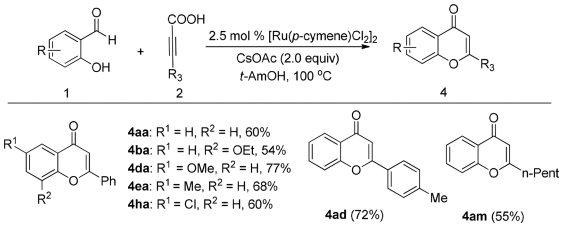
Scheme 3. Synthesis of Homoisoflavonoid from 2′-Hydroxychalcone and Aldehydes[a]



[a]Reaction conditions: **5b** (1.0 mmol), aldehyde (1.0 mmol), CsOAc (2.0 mmol), and $[Ru(p\text{-cymene})Cl_2]_2$ (0.025 mmol) were reacted in DMSO at 120 °C for 12 h.

As we expected, flavones were readily obtained when substituted salicylaldehyde and arylpropiolic acids were reacted with $[Ru[p\text{-cymene}]Cl_2]_2$ and CsOAc in *t*-AmOH. As shown in Scheme 4, **4aa** was successfully isolated with 60% yield. These are the same results as those for the reaction with phenylacetylene, which were reported by Gogoi.[13] The reactions with the substituted salicylaldehyde and phenylpropiolic acid afforded the desired products **4ba**, **4da**, **4ea**, and **4ha** in good yields. When salicylaldehyde was reacted with *p*-tolylpropiolic acid and octynoic acid, **4ad** and **4am** occurred in 72% and 55% yields, respectively.

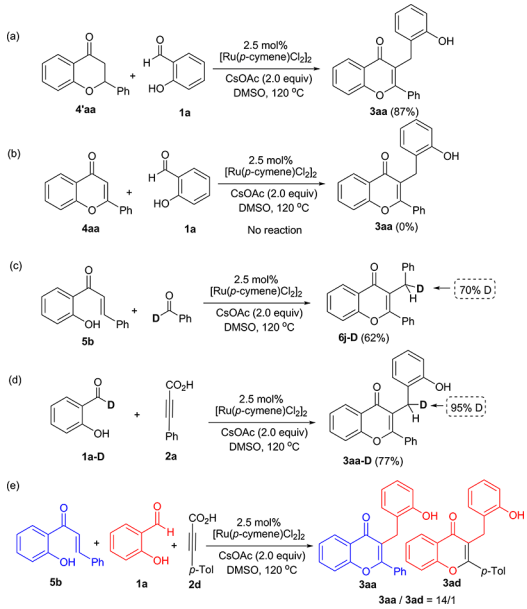
Scheme 4. Synthesis of Flavone from Salicylaldehyde and Arylpropiolic Acids[a]



[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), CsOAc (2.0 mmol), and $[Ru(p\text{-cymene})Cl_2]_2$ (0.025 mmol) were reacted in *t*-AmOH at 100 °C for 12 h.

To study the reactivity of salicylaldehyde and the reaction pathway, several experiments were conducted. When chromanone **4aa′** was reacted with salicylaldehyde under the optimal conditions, **3aa** was formed with 87% yield; however, flavone **4aa** did not provide **3aa**. These results implied that the chromanone was the intermediate in the formation of homoisoflavonoid (Scheme 5a,b).

Scheme 5. Control Experiments



The reaction of chalcone **5b** with deuterated benzaldehyde under optimized reaction conditions afforded **6j-D** in 62% yield (Scheme 5c). The reaction between **1a-D** and **2a** provided **3aa-D** in 77% yield with 95% monodeuteration (Scheme 5d). From these results, we suggest that one of the benzyl protons in homoisoflavonoid comes from aldehyde. When salicylaldehyde and chalcone were competitively reacted with *p*-tolylpropiolic acid under the optimal conditions, **3aa**, which was formed from chalcone, was produced more than was **3ad**, which was formed from salicylaldehyde (Scheme 5e). It was found that the reaction with salicylaldehyde and chalcone was faster than the reaction with salicylaldehyde and *p*-tolylpropiolic acid. In addition, salicylaldehyde showed higer reactivity than benzaldehyde in the competitive reaction (see Supporting Information Scheme S1).

On the basis of these results, the plausible reaction pathway was proposed, as shown in Scheme 6. In the presence of ruthenium and a base, salicylaldehyde reacts with arylpropiolic acid to provide the chalcone intermediate **A**.[14] This intermediate is converted to flavone **B** in *t*-AmOH;[15] however, chromanone was formed in DMSO and further reacts with aldehyde to give the intermediate **E** through dehydration in DMSO as ruthenium catalyzed cross aldol reaction.[16] Finally, intermediate **E** was transformed to homoisoflavonoid through rearrangement.[7] We found that both ruthenium catalyst and base are important in the formation of homoisoflavonoid and flavone.[17]

In conclusion, homoisoflavonoid and flavone were selectively obtained from the reaction with salicylaldehyde and arylpropiolic

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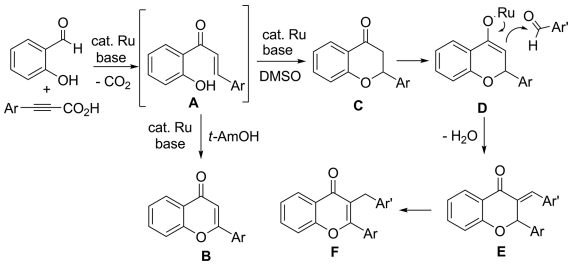
Scheme 6. Proposed Mechanism



acid in the presence of a ruthenium catalyst and base. When the reaction was conducted in DMSO, numerous homoisoflavonoids were exclusively obtained in good yields. In contrast, several flavones were dominantly formed in the *t*-AmOH solvent. It was found that chalcone was an intermediate in the formation of both homoisoflavonoid and flavone, and chromanone was an intermediate for the formation of homoisoflavonoid. It also was confirmed that homoisoflavonoid formation proceeds via decarboxylative C−H activation and a chelation-assisted hydroacylation pathway. From the competitive experiment, we found that the high reactivity of chalcone toward aldehyde drove the reaction to selectively produce homoisoflavonoid. This is the first simple and one-pot selective metal-catalyzed synthetic method for homoisoflavonoid and flavone from salicylaldehyde and readily accessible arylpropiolic acid, which could be utilized for the preparation of a number of bioactive materials. Further investigations on the mechanism are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03325.

Experimental procedures, X-ray crystallographic data, NMR spectroscopic and MS data for all new compounds (PDF)

Accession Codes

CCDC 1576196 contains 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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(12) For X-ray crystallography data, see the Supporting Information.

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(14) We failed to detect any intermediate for the formation of **A**. It is not clear when decarboxylation and C−H activation took place in the formation of chalcone **A**. In addition, we found that the suggested complexes in ref 13 were not the intermediates in this transformation.

(15) We proposed that further aldol condensation might be block in *t*-AmOH. See Table S2.

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(17) The role of ruthenium and base in the formation of homoisoflavonoid and flavone was studied in both *t*-AmOH and DMSO. See more details in the Supporting Information.

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