Rhodium Catalysis Hot Paper

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A Complete Switch of the Directional Selectivity in the Annulation of 2-Hydroxybenzaldehydes with Alkynes**

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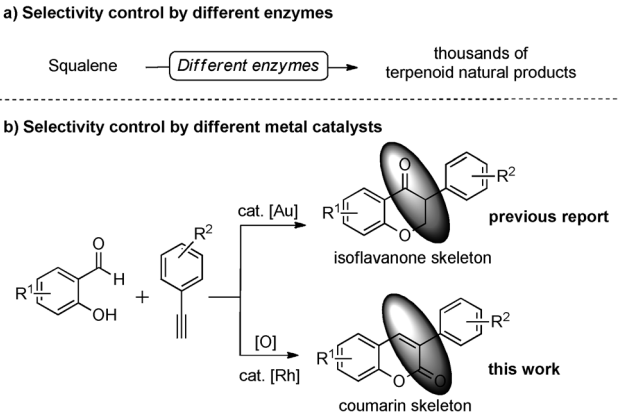
Abstract: *Controlling reaction selectivity is an eternal pursuit for chemists working in chemical synthesis. As part of this endeavor, our group has been exploring the possibility of constructing different natural product skeletons from the same simple starting materials by using different catalytic systems. In our previous work, an isoflavanone skeleton was obtained from the annulation of a salicylaldehyde and an alkyne when a gold catalyst was employed. In this paper, it is shown that a coumarin skeleton can be efficiently obtained through an annulation reaction with the same starting materials, that is, terminal alkynes and salicylaldehydes, by simply switching to a rhodium catalyst. A plausible reaction mechanism is proposed for this new annulation based on isotopic substitution experiments.*

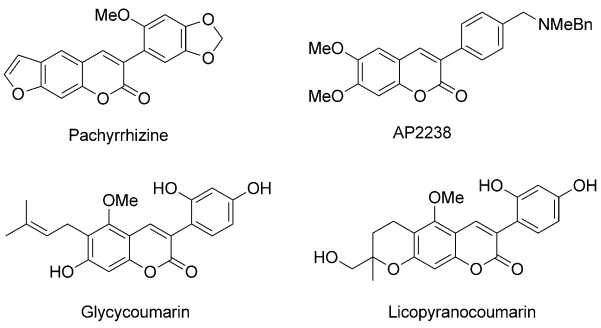
Controlling reaction selectivity is an ultimate goal for chemists working in chemical synthesis.[1] Selectivity is defined as the rate of a reaction along a particular pathway divided by the sum of the rates along all possible reaction pathways. In nature, enzymes have miraculous abilities to control reaction selectivity by converting the same simple starting materials into a diverse range of products. For example, squalene, a common intermediate in biosynthesis, can be transformed selectively into a wide variety of terpenoids when subjected to different enzymes (Scheme 1 a). Inspired by the abilities of enzymes, chemists have been developing abiological means to control reaction selectivity, mimicking nature.[2] As a part of this endeavor, our group has been exploring the possibility of constructing different natural product skeletons from the same reaction of salicylaldehydes and terminal alkynes by employing different catalysts (Scheme 1 b). Previously, we have developed an expedient route for the synthesis of isoflavanone skeletons by a gold-catalyzed annulation of salicylaldehyde with phenylacetylene.[3] Herein, we report that a complete switch of the reaction selectivity, which was achieved by replacing the gold with a rhodium catalyst, in the annulation of the same starting materials provides a direct and efficient access to coumarin skeletons.



Scheme 1. Controlling the reaction selectivity for the synthesis of different natural product skeletons with different catalysts.

Coumarin and its derivatives are widely found in nature.[4] They represent important heterocyclic structures with a broad range of biological activities.[5] Coumarin has also been used as a medium in dye lasers[6] and as a sensitizer in earlier photovoltaic technologies.[7] The 3-aryl coumarin moiety is the key structural motif of many complex natural products and pharmaceutical compounds with important biological activities (Scheme 2), such as pachyrrhizine (mosquitocidal activity),[8] AP2238 (anti-Alzheimer drug candidate),[9] glycycoumarin (anti-HIV activity), and licopyranocoumarin (anti-HIV activity).[10]

Our investigation commenced with the reaction of salicylaldehyde and phenylacetylene in the presence of $[Rh(PPh_3)_3Cl]$ (5 mol%) in acetonitrile at 50 °C under an



Scheme 2. Representative natural products and pharmaceutical compounds with a 3-aryl coumarin framework. Bn = benzyl.

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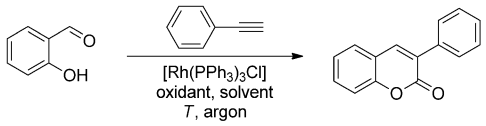
Table 1: Annulation of salicylaldehyde with phenylacetylene under various conditions.[a]



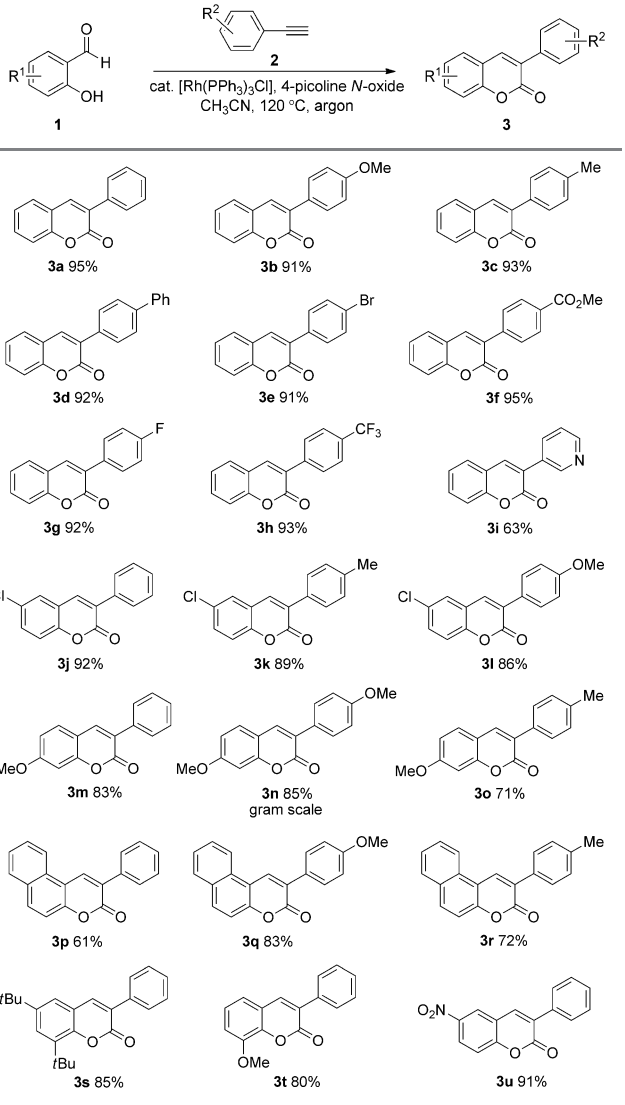
Entry	Oxidant	*T* [°C]	Ratio[e]	Yield [%]
1	4-picoline *N*-oxide	50	1:1.3:1.3	15
2	4-picoline *N*-oxide	80	1:1.3:1.3	38
3	4-picoline *N*-oxide	120	1:1.3:1.3	60
4	4-picoline *N*-oxide	150	1:1.3:1.3	60
5	4-methoxypyridine *N*-oxide	120	1:1.3:1.3	44
6	4-nitropyridine *N*-oxide	120	1:1.3:1.3	9
7	pyridine *N*-oxide	120	1:1.3:1.3	58
8	isoquinoline *N*-oxide	120	1:1.3:1.3	60
9	2-picoline *N*-oxide	120	1:1.3:1.3	40
10[b]	4-picoline *N*-oxide	120	1:1.3:1.3	3
11[c]	4-picoline *N*-oxide	120	1:1.3:1.3	20
12[d]	4-picoline *N*-oxide	120	1:1.3:1.3	32
13	4-picoline *N*-oxide	120	1:1.3:2	39
14	4-picoline *N*-oxide	120	2:1:1.3	41
15	4-picoline *N*-oxide	120	1:2:1.3	67
16	4-picoline *N*-oxide	120	1:3:1.3	87
17	4-picoline *N*-oxide	120	1:4:1.3	96

[a] All reactions were conducted on a 0.2 mmol scale with $[Rh(PPh_3)_3Cl]$ (5 mol%) in a sealed tube in acetonitrile (1 mL); all yields were determined by ^1H NMR spectroscopy using nitromethane as an internal standard. [b] Cesium carbonate was added. [c] Zinc chloride was added. [d] Water (1.0 equiv) was added. [e] The ratio of salicylaldehyde, phenylacetylene, and oxidant.

argon atmosphere (Table 1). Gratifyingly, the desired annulation product 3-phenylcoumarin was formed in 15% yield (Table 1, entry 1). Encouraged by this result, we then examined different temperatures and found that a higher temperature was beneficial to this reaction (entries 2–4), with the best result obtained at 120°C (entry 3). Further increasing the temperature to 150°C gave a similar result (entry 4). Next, an investigation of different oxidants revealed that a better yield can be obtained by utilizing an oxidant with a weakly electron-donating group, 4-picoline N-oxide (entry 3). Both more strongly electron-donating groups (entry 5) and an electron-withdrawing group on the *N*-oxide (entry 6) resulted in lower yields. Similar results were obtained when pyridine *N*-oxide and isoquinoline *N*-oxide were used as the oxidants (entries 7 and 8). When 2-picoline *N*-oxide was used, the yield also decreased (entry 9). Addition of either a weak base (cesium carbonate) or a Lewis acid (zinc chloride) led to lower yields (entries 10 and 11). The addition of one equivalent of water to this reaction was detrimental to the yield (entry 12). Increasing the amount of oxidant was also harmful to this transformation (entry 13). After optimizing the ratio of the different reagents, we found that increasing the amount of phenylacetylene promoted the reaction tremendously whereas an excess amount of salicylaldehyde would decrease the yield (entries 14–17). When four equivalents of phenylacetylene were used, the desired annulation product was obtained in 96% yield. Other solvents and rhodium catalysts were found to be less effective for this transformation (see the Supporting Information).

With the optimized reaction conditions established, the substrate scope was explored at 120°C under argon using $[Rh(PPh_3)_3Cl]$ (5 mol%) as the catalyst and 4-picoline *N*-oxide (1.3 equiv) as the oxidant in acetonitrile for five hours. As shown in Table 2, the reaction proceeded efficiently

Table 2: Rhodium-catalyzed annulations of aldehydes with alkynes.[a]

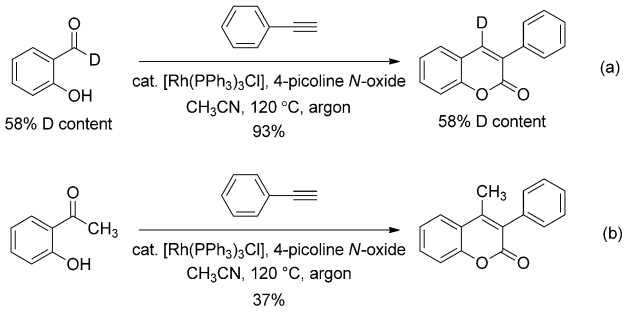


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $[Rh(PPh_3)_3Cl]$ (5 mol%), and 4-picoline *N*-oxide (0.26 mmol) in acetonitrile (1 mL). All reactions were carried out at 120°C in a sealed tube under argon for 5 hours; yields of isolated products are given.

with different aryl acetylenes and salicylaldehyde derivatives. Various substituents on the aryl acetylene had little effect on the outcome of the reaction, and different 3-aryl coumarins were obtained in excellent yields in all cases (Table 2, **3a**–**3h**). It is noteworthy that the use of a heteroaryl alkyne, 3-ethynylpyridine, also led to the corresponding product in good yield without any complication from the strongly coordinating pyridinyl nitrogen atom (**3i**). On the other hand, the presence of an electron-withdrawing group (**3j**–**3l**)

on the 2-hydroxybenzaldehyde appeared to be more beneficial than the presence of an electron-donating group (**3m**–**3o**). 2-Hydroxy-naphthaldehyde also reacted smoothly with several acetylenes to afford the corresponding products in good to high yields (**3p**–**3r**). A bulky or an electron-donating substituent (**3s** and **3t**) at the *ortho* position of the 2-hydroxybenzaldehyde did not affect the reaction adversely, and good yields were obtained in both cases. A good yield was also obtained with a strongly electron-withdrawing group on the 2-hydroxyaldehyde coupling partner (**3u**). However, aliphatic alkynes were not viable substrates for the current annulation under the standard reaction conditions, which is similar to what was observed for the gold-catalyzed annulation.[3] For aliphatic alkynes, owing to the absence of the conjugating effect of the aryl group, the intermediate **B** or **E** (Scheme 4) generated in the process might not survive long enough to undergo cyclization; instead, protonation of the intermediate leads to side product formation. For example, the reaction of salicylaldehyde with 1-decyne under the standard reaction conditions generated the acylated side product 2-formylphenyl decanoate in 51% yield.

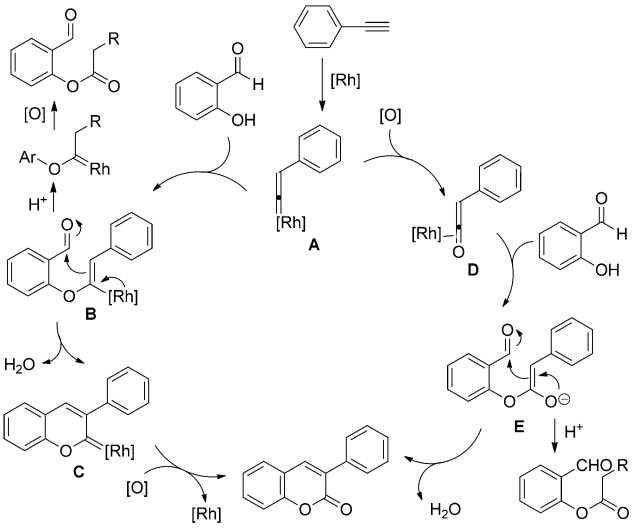
To explore the reaction mechanism, deuterium-labeled salicylaldehyde [D]-**1**[11] (58% D) was used as the substrate under the standard reaction conditions. We found that the isolated product also possesses 58% deuterium at the C4 position (Scheme 3a), which unambiguously demonstrated



Scheme 3. Investigation of the mechanism for the annulation of 2-hydroxycarbonyl compounds with phenylacetylene.

that no C–H/D insertion of salicylaldehyde occurred in this reaction,[12] and that the carbon atom of the C4 position originated from the carbonyl moiety of the salicylaldehyde. This conclusion was further supported by the reaction of 2′-hydroxyacetophenone with phenylacetylene under the standard reaction conditions, which gave a 4-methylcoumarin derivative (also a very useful structural motif; Scheme 3b), while the corresponding annulation product was obtained in a lower yield.

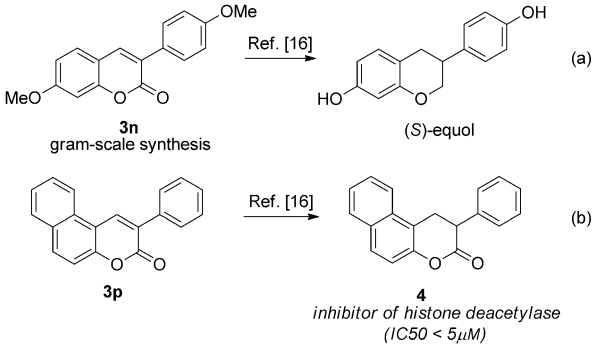
Based on these experimental results, a tentative mechanism was proposed (Scheme 4). Initially, phenylacetylene reacts with the rhodium catalyst to form vinylidene intermediate **A**.[13] Subsequently, nucleophilic addition of salicylaldehyde to **A** generates intermediate **B**, which undergoes an intramolecular Aldol-type reaction immediately followed by dehydration, which then results in metal carbene intermediate **C**. Finally, oxidation of **C**[14] produces the desired product



Scheme 4. Tentative mechanism for the rhodium-catalyzed annulation of salicylaldehyde with phenylacetylene.

3-phenylcoumarin and regenerates the rhodium catalyst. Alternatively, it is also possible that oxidation of vinylidene intermediate **A** occurs in the second step to give a rhodium ketene intermediate **D**, as proposed by Lee and co-workers.[15] Then, nucleophilic addition of salicylaldehyde to rhodium ketene **D** forms intermediate **E**, which also undergoes an intramolecular Aldol-type reaction followed by dehydration to give the desired product 3-phenylcoumarin.

The products readily generated by this method are very useful in synthesizing natural products and bioactive molecules. For example, compounds **3n** and **3p** can be readily transformed into the natural product (*S*)-equol and bioactive molecule **4**, respectively (Scheme 5).[16] To test whether the



Scheme 5. 3-Aryl coumarins for the synthesis of natural products and bioactive compounds.

reaction could be readily scaled up, compound **3n** was synthesized on a 1.35 gram scale in 80% yield. The product crystallized from the reaction mixture upon cooling, and thus this transformation provides a convenient large-scale synthesis of this compound.

In conclusion, we have developed a novel annulation of simple *ortho*-hydroxybenzaldehydes with terminal alkynes

catalyzed by a rhodium species. The cyclization generated products with a 3-aryl coumarin motif, which have many applications in the synthesis of pharmaceutical compounds and photosensitizers. The reaction perfectly complements the gold-catalyzed annulation, as an endeavor to control the selectivity of reactions with the same starting materials to construct different natural product skeletons by using different metal catalysts. An extension of this catalytic method to broaden its scope and further mechanistic studies are in progress.

Experimental Section

Typical experimental procedure: A solution of $[Rh(PPh_3)_3Cl]$ (9.25 mg, 0.01 mmol), 4-picoline *N*-oxide (29 mg, 0.26 mmol), salicylaldehyde (0.2 mmol), and alkyne (0.8 mmol) in distilled acetonitrile (1 mL) was stirred in a sealed tube at 120 °C for 5 hours under argon. The reaction mixture was cooled to room temperature, and the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (TLC) on silica gel with the appropriate mixture of hexane and ethyl acetate to give the 3-aryl coumarin derivative.

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Communications

Rhodium Catalysis

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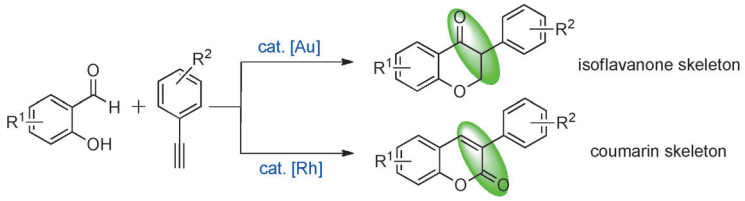
A Complete Switch of the Directional Selectivity in the Annulation of 2-Hydroxybenzaldehydes with Alkynes



Rodeo rhodium: Different natural product skeletons can be obtained from the same simple starting materials by using different catalytic systems. The gold-catalyzed annulation of terminal alkynes and salicylaldehydes yielded isoflavanones, whereas the rhodium-catalyzed version led to coumarin skeletons.