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Authors: Yingting Li, Yan Zhu, Guangliang Tu, Jingyu Zhang, and Yingsheng Zhao

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Rhodium(III)-Catalyzed Oxidative Annulation of Acrylic Acid with Alkynes: An Easy Approach to the Synthesis of α-Pyrones

Yu-Ting Li, [a] Yan zhu,[a] Guang-Liang Tu,[a] Jing-Yu Zhang* [b] and Ying-Sheng Zhao*[a]

Abstract: A highly efficient Rhodium(III)-catalyzed direct oxidative annulation of acrylic acid with alkynes to form the α-pyrone was developed. Various substituted acrylic acids were compatible in this transformation, affording the corresponding products in moderate to excellent yields under mild conditions.

Introduction

C–H functionalization reactions have provided a straightforward way to access useful synthetic units in the past decades, which greatly enriched the route to prepare highly important compounds in organic synthesis[1]-[6]. The α-pyrone is a key skeleton in various natural products and bioactive compounds, such as aurovertin B (**A**), yangonin (**B**), desmethoxyyangonin (**C**) and myxopyronin B (**D**) (Figure 1)[7]-[9].

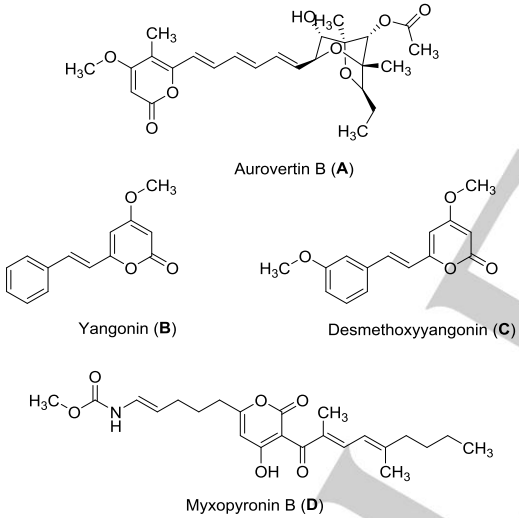
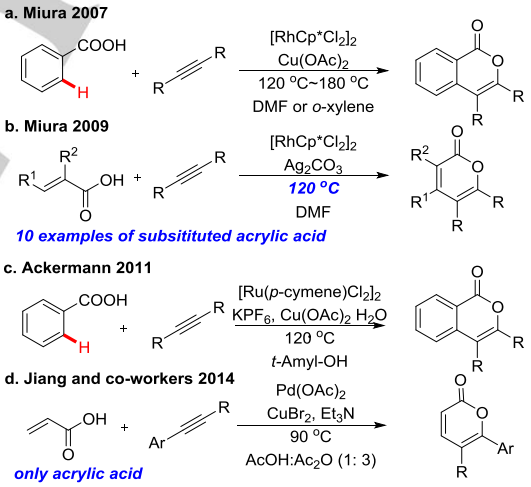


Figure 1. Bioactive compounds with α-pyrone skeleton.

Various approaches to the synthesis of these α-pyrone-based compounds have been well explored[10]-[11]. Considerable developments have already been achieved by the groups of Miura, Ackermann, Jiang, Tanka and Sundararaju through the oxidative annulation of carboxylic acid and alkynes (Scheme 1)[12]-[16]. These methods provided an atom-economical route to prepare the α-pyrone and isocoumarin derivatives. For example, the groundbreaking work was first reported by the group of Miura through the Rhodium(III)-catalyzed oxidative annulation of carboxylic acid and alkynes using the copper acetate as the oxidant (Scheme 1a)[13]. Later, the same group succeeded in expanding the substrates to the acrylic acid derivatives, when the silver carbonate was used as the oxidant (Scheme 1b)[14]. The group of Ackermann demonstrated that the Ruthenium(II) complex is an effective catalyst for this oxidative [4+2] cyclization reaction (Scheme 1c)[15]. In 2014, Jiang and co-workers disclosed a Palladium-catalyzed oxidative annulation of acrylic acid with alkynes, where only unsubstituted acrylic acid was compatible in the transformation (Scheme 1d)[16]. Although such great results have already been achieved, the substrates scope of acrylic acids were relatively less explored.

Scheme 1. The synthesis of α-pyrone derivatives.



Herein we report our recent development of a highly efficient rhodium(III)-catalyzed oxidative annulation of acrylic acid with alkynes under mild conditions. Various acrylic acids were tolerated in this transformation, affording the corresponding products in good to excellent yields. More impressively, sorbic acid was also compatible, leading to the corresponding α-pyrones in good yields.

Results and Discussion

At the beginning of our study, we firstly treated acrylic acid **1a** with diphenylacetylene **2a** in the presence of $[RhCp^*Cl_2]_2$ (1 mol%) and AgOAc (1 equiv) in DCE at 80 °C under air for 8 h (Table 1). To our delight, the α-pyrone **3a** was obtained in 51%

[a] Y.-T. Li, Y. Zhu, G.-L. Tu, and Prof. Dr. Y.-S. Zhao
Key Laboratory of Organic Synthesis of Jiangsu Province and College of Chemistry, Chemical Engineering and Materials Science
Soochow University
Jiangsu, Suzhou 215123, China
E-mail: yszhao@suda.edu.cn
[b] Dr. J.-Y. Zhang
College of Physics, Optoelectronics and Energy & Collaborative Innovation Center of Suzhou Nano Science and Technology
Soochow University
Jiangsu, Suzhou 215123, China
E-mail: jyzhang@suda.edu.cn

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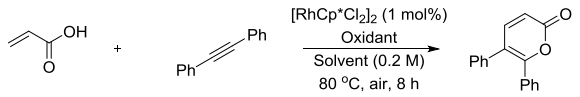
yield. A series of silver salts including AgOTf, Ag_2O, AgF, and Ag_2CO_3 were all further tested. The result showed that Ag_2CO_3 was the best oxidant, leading to the product **3a** in 58% yield. We next explored the effect of solvents such as DMF, 1,4-dioxane, MeOH, *t*-Amyl-OH, HFIP and toluene on this transformation. Gratifyingly, a satisfactory yield of **3a** was achieved when HFIP was used as the solvent. It is worth noting that the reaction proceeded well with merely 0.5 equiv of Ag_2CO_3. We next tried to use other oxidants instead of the silver salts. For example, when a catalytic amount of $AgSbF_6$ (10 mol%) with $Cu(OAc)_2$▪H_2O (0.3 equiv) and K_2CO_3 (1 equiv) were used instead of silver carbonate, a dramatical drop in yield of **3a** was observed. The utility of several other oxidants such as $Cu(OAc)_2/O_2$, O_2 and benzoquinone were further explored, however, none of them could afford the product **3a** in good yields. Moreover, the control experiment revealed that the rhodium catalyst is essential for this reaction (see supporting information).

Table 1. Optimization of reaction conditions[a]



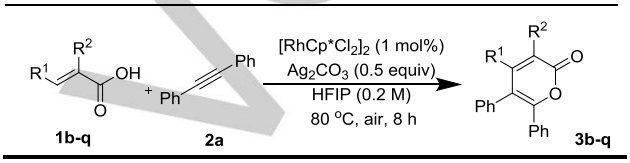
1a **2a** **3a**

Entry	Oxidant	Solvent	Yield (%)[b]
1	AgOAc (1.0 equiv)	DCE	51
2	AgOTf (1.0 equiv)	DCE	N.D.
3	Ag_2O (1.0 equiv)	DCE	36
4	AgF (1.0 equiv)	DCE	34
5	Ag_2CO_3 (1.0 equiv)	DCE	58
6	Ag_2CO_3 (1.0 equiv)	DMF	16
7	Ag_2CO_3 (1.0 equiv)	1,4-dioxane	Trace
8	Ag_2CO_3 (1.0 equiv)	MeOH	77
9	Ag_2CO_3 (1.0 equiv)	*t*-Amyl-OH	Trace
10	Ag_2CO_3 (1.0 equiv)	HFIP	95
11	Ag_2CO_3 (1.0 equiv)	toluene	Trace
12	**Ag_2CO_3 (0.5 equiv)**	**HFIP**	**95**
13	Ag_2CO_3 (0.3 equiv)	HFIP	49
14	$AgSbF_6$ (10 mol%) + $Cu(OAc)_2$▪H_2O (1.0 equiv)	HFIP	23
15[c]	$AgSbF_6$ (10 mol%) + $Cu(OAc)_2$▪H_2O (0 .3 equiv)	HFIP	66
16[c]	$AgSbF_6$ (10 mol%) + benzoquinone (1.0 equiv)	HFIP	N.D.
17[c]	$AgSbF_6$ (10 mol%)	HFIP	38
18[d]	Ag_2CO_3 (0.5 equiv)	HFIP	52

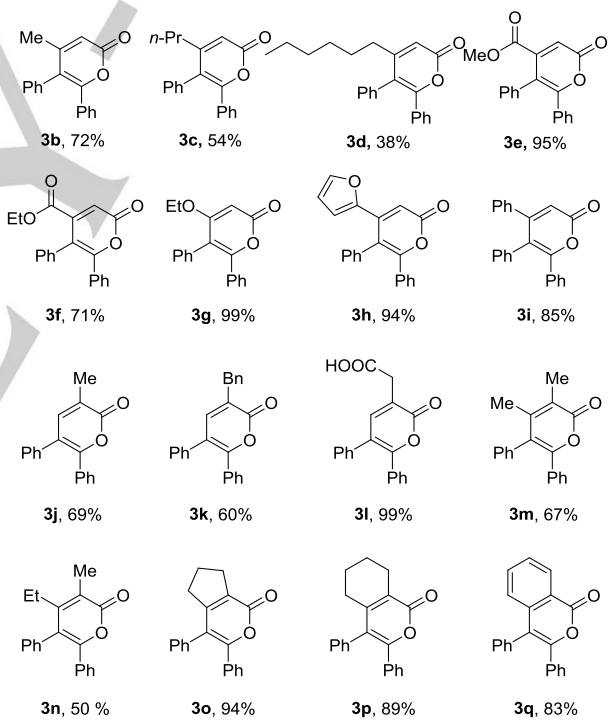
[a] Reaction condition: **1a** (0.2 mmol), **2a** (0.21 mmol), $[RhCp^*Cl_2]_2$ (1 mol%), oxidant, solvent (0.2 M). [b] GC yield. [c] K_2CO_3 (1.0 equiv) was added, In oxygen atmosphere. [d] Reduced $[RhCp^*Cl_2]_2$ load to 0.5 mol%, prolonged time to 24 h.

With optimized reaction conditions in hand, various acrylic acid derivatives were subjected to the standard reaction to investigate the functional group tolerance (Table 2). Generally, the β-substituted acrylic acids all reacted well, affording the corresponding products (**3b**–**3i**) in moderate to good yields. The acrylic acids substituted with sterically hindered functional groups all provided the corresponding products (**3b**–**3d**) in lower yields. Interestingly, electron withdrawing functional groups have shown a promoting effect for this transformation, leading to the corresponding products (**3e**–**3i**) in excellent yields. The α-substituted acrylic acid derivatives were next explored, which all provided the corresponding products (**3j**–**3l**) in good yields. It is worth mentioning that the presence of free carboxylic acid, furan, ester and oxethyl were all compatible to this reaction, affording the corresponding products in good to excellent yields, highlighting the excellent functional group tolerance of this method. When the α- and β-substituted acrylic acids were tested, the corresponding products (**3m**–**3q**) were obtained in good to excellent yields.

Table 2. The scope of acrylic acid derivatives[a], [b]



1b-q **2a** **3b-q**



3b, 72% **3c,** 54% **3d,** 38% **3e,** 95%

3f, 71% **3g**, 99% **3h**, 94% **3i**, 85%

3j, 69% **3k**, 60% **3l**, 99% **3m**, 67%

3n, 50 % **3o**, 94% **3p**, 89% **3q**, 83%

[a] Reaction conditions: **1b–1q** (0.2 mmol), **2a** (0.21 mmol), $[RhCp^*Cl_2]_2$ (1 mol%), Ag_2CO_3 (0.5 equiv), and HFIP (0.2 M). [b] Isolated yields.

The scope of the alkynes was further explored under the optimized reaction condition as illustrated in Table 3. Both hex-3-yne and oct-4-yne performed well, generating the cyclized products in excellent yields, respectively. Unsymmetrical alkylphenylacetylenes could be coupled with acrylic acid, providing a mixture of substituted pyrones (**4c**–**4e**). We next coupled hex-3-yne with various substituted acrylic acids to obtain the corresponding α-pyrones in good to excellent yields (**4f**–**4l**).

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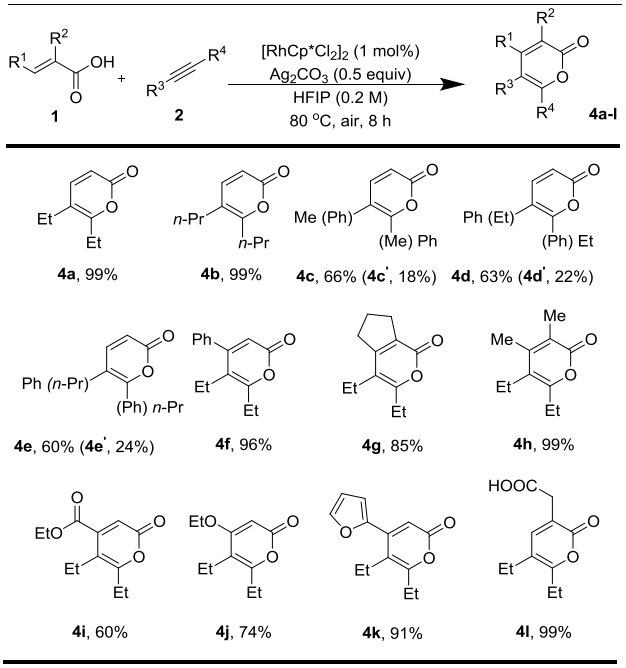
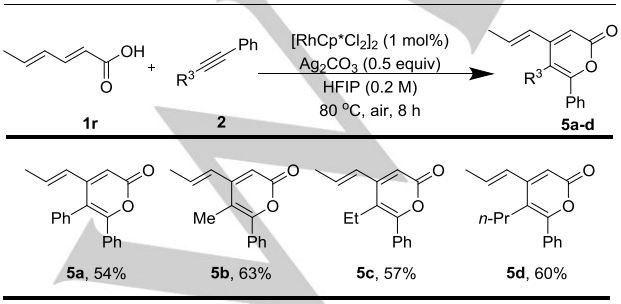
Table 3. The scope of the alkynes[a], [b]



[a] Reaction condition: **1** (0.2 mmol), **2b–2f** (0.21 mmol), $[RhCp^*Cl_2]_2$ (1 mol%), Ag_2CO_3 (0.5 equiv), and HFIP (0.2 M). [b] Isolated yields.

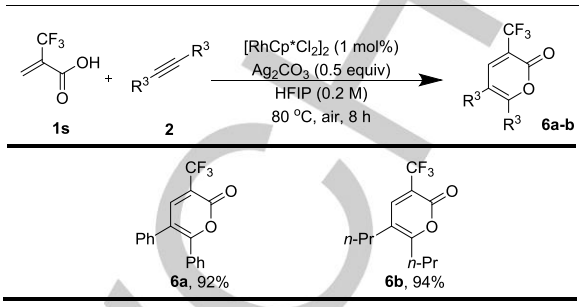
Sorbic acid, used as a food preservative, was firstly employed in this work as a substrate in the oxidative annulation of the acrylic acid derivative with alkyne. It was successfully coupled with diphenylacetylene (**2a**) under standard reaction conditions to generate α-pyrone derivative (**5a**) in good yields. Interestingly, when unsymmetrical alkynes were coupled with sorbic acid, only the products **5b–5d** were formed without the generation of any regioisomers (Scheme 2). It is probable that the steric hindrance effect causes **5b**-**5d** to be the only product. Trifluoromethyl functional group is highly important in organic compounds. For the first time, we successfully introduced a trifluoromethyl group into α-pyrone derivatives using 2-(trifluoromethyl)acrylic acid as the substrate, highlighting the synthetic utility of this method (Scheme 3). To further demonstrate the synthetic significance of this new method, gram-scale reactions were performed in which **3a**, **3f** and **3g** were obtained in good yields by prolonging the reaction time to 24 h (Scheme 4).

Scheme 2. Reactions of sorbic acid with alkynes[a], [b]



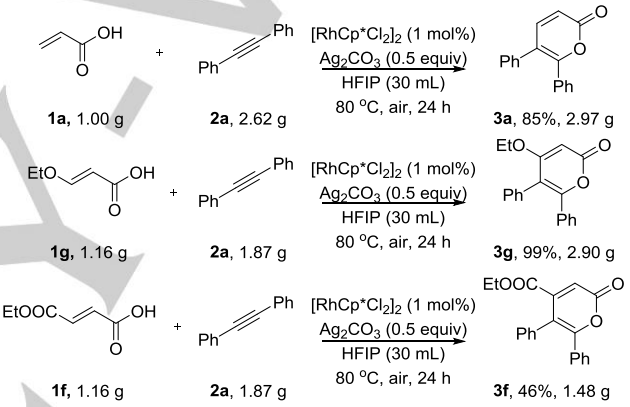
[a] Reaction conditions: **1r** (0.2 mmol), **2** (0.21 mmol), $[RhCp^*Cl_2]_2$ (1 mol%), Ag_2CO_3 (0.5 equiv), and HFIP (0.2 M). [b] Isolated yields.

Scheme 3. Reactions of 2-(trifluoromethyl)acrylic acid with alkynes[a], [b]



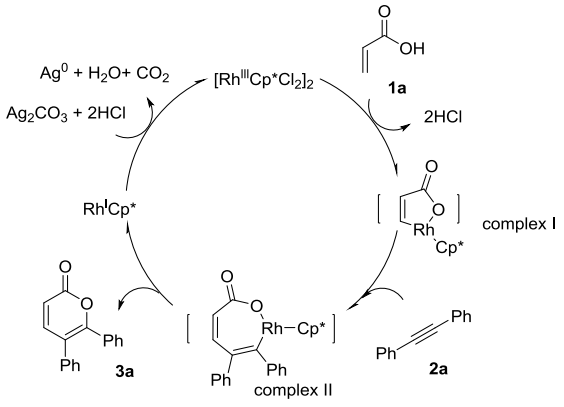
[a] Reaction conditions: **1s** (0.2 mmol), **2** (0.21 mmol), $[RhCp^*Cl_2]_2$ (1 mol%), Ag_2CO_3 (0.5 equiv), and HFIP (0.2 M). [b] Isolated yields.

Scheme 4. Gram-scale reactions



Based on the previous reports[13]-[14], a plausible catalytic cycle was proposed for this annulation reaction (Scheme 5). The carboxyl acid **1a** combines with Rhodium(III) catalyst precursor, followed by an ortho C–H activation, to provide complex I. The complex I coordinates with alkyne **2a** and follows regioselective migratory insertion to form the key intermediate complex II, which furnishes the desired product **3a** after reductive elimination.

Scheme 5. Proposed catalytic cycle.



Conclusions

In conclusion, we have developed an atom-efficient strategy for the synthesis of α-pyrones via the oxidative annulation of acrylic acid with alkynes under mild conditions by employing Rhodium(III) as the catalyst. Various acrylic acids were tolerated in this transformation, affording the corresponding products in good to excellent yields. More impressively, the sorbic acid was also compatible, leading to the corresponding α-pyrones in good yields.

Experimental Section

General Procedure for Rhodium(III)-Catalyzed Oxidative Annulation of Acrylic Acid with Alkynes:

A mixture of **1** (0.20 mmol, 1.0 equiv), **2** (0.21 mmol, 1.05 equiv), $[RhCp^*Cl_2]_2$ (1.2 mg, 1 mol%), Ag_2CO_3 (27.6 mg, 0.10 mmol, 0.5 equiv) and 1 mL HFIP in a 15 mL glass vial under air atmosphere was heated at 80 ^oC with vigorous stirring for 8 hours. The reaction mixture was then cooled to room temperature, and filtered through celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (Ethyl acetate/Petroleum ether = 1:10 to 1:5) to give the product α-Pyrone derivatives .

Acknowledgements

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Keywords: Rhodium(III)-catalyzed • oxidative annulation • acrylic acid • α-pyrone • C–H functionalization

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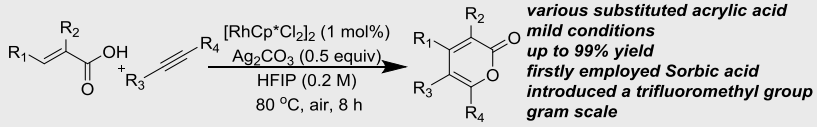

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