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Ruthenium-Catalyzed Alkyne Oxidation with Part-Per-Million Catalyst Loadings

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Abstract: Using a catalytic system of the (cymene)-ruthenium dichloride dimer, [Ru(cymene)Cl_2]$_2$, (0.001 mol%) and iodine (10 mol%), a variety of alkynes bearing different functional groups were oxidized with *tert*-butyl hydroperoxide (TBHP; 70% solution in water) under mild conditions to give 1,2-diketones in good to excellent yields. Two noteworthy features of the method are the extremely high catalyst productivity (TON up to 420,000) and scale-up to 1 mol. Preliminary mechanism investigations showed that iodonium ion and water were involved in the transformation.

Keywords: alkynes; 1,2-diketones; oxidation; ruthenium

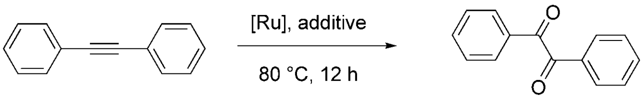
Oxidations are fundamental reactions in organic synthesis. Traditionally, these reactions are carried out with stoichiometric oxidizing agents and thus large amounts of wastes are inevitable.[1] With growing environmental concerns, much attention has been paid to the development of the transition metal catalytic systems.[2] In spite of significant achievements, most systems reported so far necessitate expensive transition metal catalysts with high loadings, which may result in problems of metal contamination and/or catalyst recycling. From the practical point of view, an efficient and robust catalytic system is still a highly sought-after goal for many oxidation reactions.

1,2-Diketones are frequently found as structural motifs in molecules of biological and/or medicinal interest,[3] and have been used as important synthetic intermediates in organic synthesis.[4] Oxidation of alkynes constitutes one of the most straightforward routes towards their synthesis, and significant successes have been made in this area over the past two decades.[5,6] However, for practical applications there still remains several issues to be addressed, such as substrate scope, chemoselectivity, and mildness of reaction conditions. Recently, we have realized, for the first time, the Wacker-type oxidation of alkynes with $PdBr_2$/$CuBr_2$ as the catalyst system and molecular oxygen as the terminal oxidant, affording high conversions and good chemoselectivity for diarylalkyne substrates.[5m] However, a shortcoming of the system is the relative high catalyst loading (5% $PdBr_2$ and 10% $CuBr_2$). Herein, we report a new and highly efficient catalytic system that allows for alkynes oxidation in the presence of an extremely low loading (ppm level) of a transition metal catalyst.

Initially, our study focused on the ruthenium catalyzed oxidation of 1,2-diphenylethyne (**1a**).[7,8] Benzil **2a** was obtained in low yield in the presence of the catalytic Ru complex using TBHP as the oxidant (Table 1, entry 12). Surprisingly, simply adding iodine improved the yield in a remarkable manner. Further screening of a wide array of conditions indicates that 0.001 mol% [Ru(cymene)Cl_2]$_2$/10 mol% iodine/1.8 equiv. *tert*-butyl hydroperoxide (70% solution in water) in dioxane at 80 °C constitutes the optimal conditions, furnishing the desired oxidation product **2a** in excellent yield (93%, Table 1, entry 1). The reaction was found to proceed with high selectivity, and no overoxidation product (carboxylic acids) was detected. It is noteworthy that the reaction is not affected by atmospheric moisture and, therefore, can be conducted under an air atmosphere.

Table 1 provides information on the impact of several key reaction parameters (catalysts, additives, and solvents, etc.) on the efficiency of this new alkyne oxidation process. Switching the dioxane to other solvents resulted in significant drops in yield (Table 1, entries 2–9). In the absence of the ruthenium catalyst, only a trace amount of the oxidation product **2a** was isolated (Table 1, entries 10 and 11). Replacement of

Table 1. Optimization of reaction conditions.[a]



1a **2a**

Entry	Catalyst	Additive	Oxidant	Solvent	Yield [%][b]
1	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	dioxane	93
2	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	DMF	<5
3	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	DME	37
4	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	EA	71
5	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	*i*-PrOH	20
6	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	MeCN	<5
7	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	CH_3NO_2	31
8	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	toluene	<5
9	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	DCE	18
10	–	I_2	TBHP	dioxane	<5
11	–	–	TBHP	dioxane	<5
12	$[Ru(cymene)Cl_2]_2$	–	TBHP	dioxane	10
13	$RuCl_3$	I_2	TBHP	dioxane	90
14	RuO_4	I_2	TBHP	dioxane	<5
15	$[Ru(cymene)Cl_2]_2$	I_2	$NaIO_4$	dioxane	<5
16	$[Ru(cymene)Cl_2]_2$	I_2	benzoquinone	dioxane	<5
17	$[Ru(cymene)Cl_2]_2$	I_2	H_2O_2	dioxane	<5
18	$[Ru(cymene)Cl_2]_2$	I_2	NaClO	dioxane	<5
19	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	dioxane	90[c]
20	$[Ru(cymene)Cl_2]_2$	I_2	TBHP	dioxane	42[d]

[a] All reactions were carried out in the scale of 0.2 mmol at 80 °C in 1.0 mL of dioxane in the presence of 0.001 mol% Ru catalyst and 10 mol% I_2 under air atmosphere for 12 h unless noted otherwise.

[b] Isolated yield.

[c] The reaction was carried out in the scale of 1 mol.

[d] 0.0001 mol% $[Ru(cymene)Cl_2]_2$ was used.

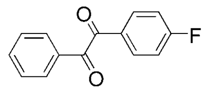
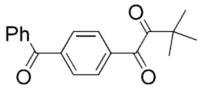
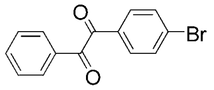
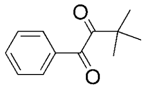
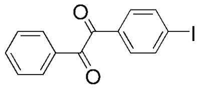
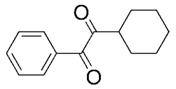
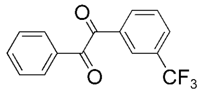
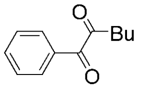
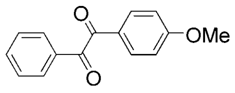
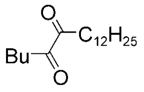
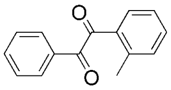
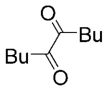
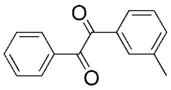
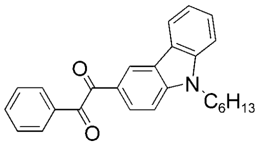
TBHP by other common oxidants did not lead to the desired product (Table 1, entries 15–18).[8a] A high yield was obtained using $RuCl_3$ which afforded **2a** in 90% yield (Table 1, entry 13), while the use of RuO_4[9] gave only a trace amount of **2a** (Table 1, entry 14). Finally, a moderate yield was observed even with ultralow catalyst loadings (1.0 ppm, Table 1, entry 20), and up to 420,000 catalyst turnovers were achieved.[10] To the best of our knowledge, such a TON should be among the highest values reported for ruthenium-catalyzed oxidation reactions so far.

In the literature, most transition metal-catalyzed oxidations were conducted on a millimole scale. To further highlight the synthetic utility of our new protocol, the oxidation of **1a** was scaled up to a 1 mol (178 g) scale, affording the benzil smoothly in 90% yield (Table 1, entry 19).[11]

Encouraged by these results, we proceeded to examine the scope of this new alkyne oxidation reaction catalyzed by the $[Ru(cymene)Cl_2]_2/I_2$ system. As shown in Table 2, a variety of 1,2-disubstituted alkynes were selectively oxidized to the corresponding 1,2-diketones in high to excellent yields under the optimized reaction conditions. This transformation showed good functional group tolerance, in which halide, ketone, benzylic C–H bond, trifluoromethyl, carbazole, ether etc., were tolerated. Both electron-withdrawing and electron-donating substituted alkynes were selectively oxidized to the corresponding 1,2-ketones. Particular noteworthy is that a carbazole-bearing alkyne is also amenable to the present protocol and the corresponding 1,2-diketone was obtained in excellent yield (Table 2, entry 14). Alkyl-substituted alkynes are usually poor substrates for transition metal-catalyzed oxidation. Nevertheless, in this reaction the reactivity of alkynes bearing one or two aliphatic substituents was found to be similar to that of diarylalkynes in this reaction (Table 2, entries 8–13).

With these results in hand, we next turned our attention to the reaction mechanism. Initially, we suspected that deoxybenzoin or benzoin might be involved in catalytic cycle. However, when the oxidation of deoxybenzoin was conducted under the typical conditions, no oxidation product **2a** was detected [Scheme 1, Eq. (1)]. Additionally, when the reaction was performed with benzoin as the substrate, **2a** was only obtained in poor yields either in the presence or absence of ruthenium catalyst [Scheme 1, Eq. (2)].

Table 2. Scope of the alkynes oxidation.[a]

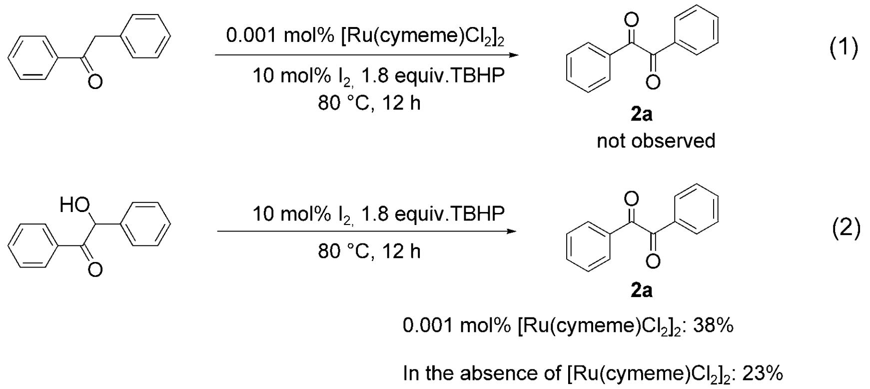
Entry	Product	Yield [%][b]	Entry	Product	Yield [%][b]
1		91	8		87
2		92	9		74
3		94	10		86
4		77	11		70
5		93	12		79
6		95	13		79
7		94	14		96

[a] All reactions were carried out in the scale of 0.2 mmol at 80 °C in 1.0 mL of dioxane in the presence of 0.001 mol% Ru catalyst under air atmosphere for 12 h unless noted otherwise.

[b] Isolated yield.

Considering the necessity of the ruthenium species for the alkyne oxidation (Table 1, entries 10 and 11), benzoin was also excluded as an intermediate in this transformation.

When the addition of iodine to dec-5-yne was followed by ^{13}C NMR spectroscopy,[12] a shift to lower field was observed for the signals of all the carbons, in agreement with the formation of an iodonium ion



Scheme 1. Preliminary investigations on mechanism.

(see Supporting Information). Under otherwise identical conditions, replacement of aqueous TBHP with TBHP in decane (5.0–6.0 M, <4% water) in the reaction of **1a** only led to the isolation of a small amount of benzil **2a**. On addition of $H_2{}^{18}O$ to the above reaction, the desired product was obtained in 89% yield and ^{18}O was found to be incorporated into the diketone (^{16}O:$^{18}O \approx 56{:}44$ by MS), which confirmed that water participated as a reagent.

In conclusion, we have disclosed a general, practical, and simple Ru-catalyzed reaction for transforming alkynes into 1,2-diketones. Salient features of the method are extremely high catalyst productivity (TON up to 420,000) and amenability to scale-up, thus implying the feasibility for industrial/practical applications. Importantly, no residual ruthenium impurity was detected by ICP mass analysis in the 1,2-diketone products after recrystallization or column chromatographic purification. Further investigations, especially on details of the mechanism, are ongoing in our laboratory.

Experimental Section

General Procedures for Oxidation of Alkynes

Into a test tube were added alkyne (0.2 mmol) and I_2 (5.1 mg, 0.02 mmol). Dioxane (1.0 mL) was added *via* syringe. A $[Ru(cymene)Cl_2]_2$ solution (10 μL, 0.0002 mol/L in distilled dioxane, 10 ppm) and 100 μL *tert*-butyl hydroperoxide were added into the tube. The reaction mixture was placed under air, stirred, and heated to 80 °C for 12 h. It was then quenched with saturated Na_2SO_3 solution (consumption of residual TBHP) and reaction mixture was extracted with ethyl acetate (3 × 4 mL). The organic layer was separated and dried with Na_2SO_4. Removal of solvent followed by flash column chromatographic purification afforded the products.

Acknowledgements

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