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Ruthenium-Catalyzed Oxidation of Alkenes at Room Temperature: A Practical and Concise Approach to α-Diketones

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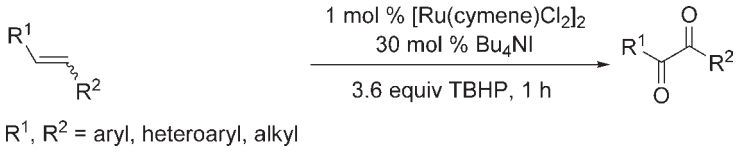
ABSTRACT



R^1, R^2 = aryl, heteroaryl, alkyl

The catalytic oxidation of alkenes to α-diketones is unprecedented. A new oxidation of alkenes, catalyzed by a ruthenium complex, which allows an efficient route to α-diketones using TBHP as an oxidant is described. This methodology is highly functional group tolerant, is practically convenient, requires no additional ligand, and operates under mild conditions with short reaction times. Based upon experimental observations, a plausible mechanism is proposed.

The oxidation of alkenes is an important transformation in both academia and industry. This investigation into alkene oxidation is, therefore, an area of considerable ongoing interest. For example, epoxidation,[1] dihydroxylation,[2] aminohydroxylation,[3] and the Wacker reaction[4] have all been widely applied in organic synthesis. To the best of our knowledge, the catalytic oxidation of alkenes to α-diketones is unprecedented.

α-Diketones have attracted a great deal of attention due to their rich applications across many fields of science.[5] A typical method for the preparation of α-diketones is the oxidation of substituted alkynes.[6] The methodology, however, has limitations with respect to selectivity, scope, yield, practicality, and functional group tolerance.

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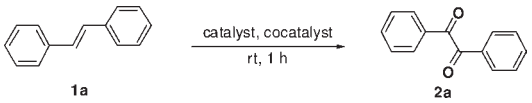
The introduction of two oxygen atoms across an alkene is conceptually the most direct route to α-diketones but has remained largely unexplored, and stoichiometric quantities of oxidant are typically required.[7] These reactions generate large amounts of waste, which leads to environmental and economic issues associated with recycling or removal of the reduction byproducts. For the synthesis of complex, functionalized α-diketones, the tandem alkene dihydroxylation−oxidation procedure has proved most popular with respect to functional group tolerance and mild reaction conditions.[8] Khan et al., in their pioneering work, reported a Ru-catalyzed conversion of vicinal dihaloalkenes to α-diketones using $NaIO_4$.[9] In this communication, we describe the first catalytic oxidation of alkenes to α-diketones in moderate to excellent yields.

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	cocatalyst	oxidant	solvent	yield[b]
1	$Ru(cymene)Cl_2$	Bu_4NI	TBHP	toluene/MeCN/H_2O	91%
2	$Ru(cymene)Cl_2$	Bu_4NI	TBHP	toluene/H_2O	47%
3	$Ru(cymene)Cl_2$	Bu_4NI	TBHP	MeCN/H_2O	79%
4	$Ru(cymene)Cl_2$	Bu_4NI	TBHP	toluene/MeCN	83%
5	$Ru(cymene)Cl_2$	Bu_4NI	TBHP	DCE/H_2O	17%
6	$Ru(cymene)Cl_2$	Bu_4NI	TBHP	DME/H_2O	23%
7	$Ru(cymene)Cl_2$	Bu_4NI	TBHP	DMSO/H_2O	N.D.[c]
8	$Ru(cymene)Cl_2$	Bu_4NI	TBHP	CH_3NO_2/H_2O	27%
9	$Ru(cymene)Cl_2$	Bu_4NI	TBHP	Dioxane/H_2O	23%
10	$Ru(cymene)Cl_2$	Bu_4NI	TBHP	^{i}PrOH/H_2O	N.D.[c]
11	–	Bu_4NI	TBHP	toluene/MeCN/H_2O	N.D.[c]
12	$[Ru(cymene)Cl_2]_2$	Bu_4NCl	TBHP	toluene/MeCN/H_2O	N.D.[c]
13	$[Ru(cymene)Cl_2]_2$	Bu_4NBr	TBHP	toluene/MeCN/H_2O	N.D.[c]
14	$PdCl_2$	Bu_4NI	TBHP	toluene/MeCN/H_2O	N.D.[c]
15	$Pd(OAc)_2$	Bu_4NI	TBHP	toluene/MeCN/H_2O	N.D.[c]
16	$[Ru(cymene)Cl_2]_2$	Bu_4NI	O_2	toluene/MeCN/H_2O	N.D.[c]
17	$[Ru(cymene)Cl_2]_2$	Bu_4NI	NaClO	toluene/MeCN/H_2O	N.D.[c]
18	$[Ru(cymene)Cl_2]_2$	Bu_4NI	oxone	toluene/MeCN/H_2O	N.D.[c]
19	$[Ru(cymene)Cl_2]_2$	Bu_4NI	$(^tBuO)_2$	toluene/MeCN/H_2O	N.D.[c]
20	$[Ru(cymene)Cl_2]_2$	Bu_4NI	H_2O_2	toluene/MeCN/H_2O	N.D.[c]
21	$RuCl_3$	Bu4NI	TBHP	toluene/MeCN/H2	86%
22	$[Ru(benzene)Cl_2]_2$	Bu_4NI	TBHP	toluene/MeCN/H_2O	88%
23	$[Ru(cymene)Cl_2]_2$	Bu_4NI	TBHP	toluene/MeCN/H_2O	83%[d]
24	$[Ru(cymene)Cl_2]_2$	Bu_4NI	TBHP	toluene/MeCN/H_2O	N.D.[e]

[a] 0.5 mmol of **1a**, 0.005 mmol (1 mol %) of $[Ru(cymene)Cl_2]_2$, 0.15 mmol (30 mol %) of Bu_4NI, and 3.6 equiv of TBHP in toluene/MeCN/H_2O at room temperature unless otherwise noted. [b] Isolated yield. [c] Not detected. [d] 100 mmol of **1a**. [e] 1,2-Diphenylethyne was used as substrate.

Several groups have reported Ru-catalyzed *oxo*-functionalizations of alkenes, such as epoxidation,[10] dihydroxylation,[11] ketohydroxylation,[12] and oxidative cleavage.[13] This suggested that controlling selectivity could be a big challenge. (*E*)-1,2-Diphenylethene (**1a**) was selected as a model substrate to establish the reaction conditions. Through optimizing the reaction conditions, we determined that 1 mol % $[Ru(cymene)Cl_2]_2$/30 mol % Bu_4NI/3.6 equiv of *t*-BuOOH (70% in aqueous solution) in toluene/MeCN/H_2O at room temperature for 1 h furnished the desired oxidation product benzil **2a** (Table 1, entry 1) in excellent yield (91%). The transformation proceeded with high selectivity, and only trace amounts of benzaldehyde (< 5%) were observed. Gratifyingly, the reaction was little affected by atmospheric moisture and could, therefore, be performed under air.

The influence of catalyst, cocatalyst, oxidant, and solvent on the efficiency of this alkene oxidation is shown in Table 1. No product **2a** was obtained in the absence of a Ru catalyst (entry 11). When other Ru precursors, such as $RuCl_3$ and $[Ru(benzene)Cl_2]_2$, were used as catalysts, comparable yields were achieved (entries 21 and 22). Switching the catalyst to $PdCl_2$ or $Pd(OAc)_2$ did not provide the desired product **2a** (entry 14 and 15). Solvent

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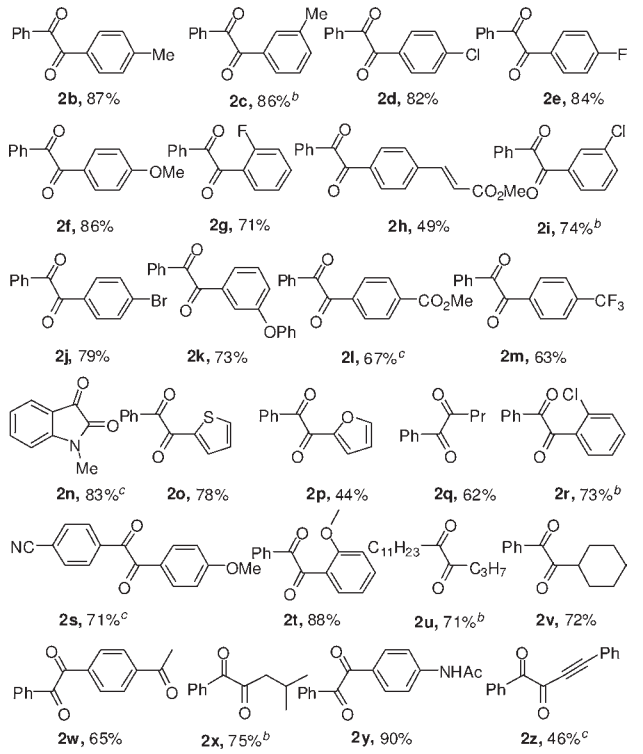
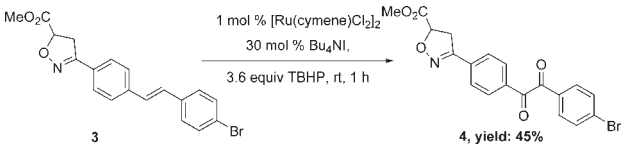


Figure 1. Ru-catalyzed alkenes oxidation for α-diketones. (a) 0.5 mmol of alkenes, 0.005 mmol (1 mol %) of $[Ru(cymene)Cl_2]_2$, 0.15 mmol (30 mol %) of Bu_4NI, and 3.6 equiv of TBHP in toluene/$MeCN/H_2O$ at room temperature unless otherwise noted. (b) Mixures of *trans*- and *cis*-alkenes. (c) 35 °C.

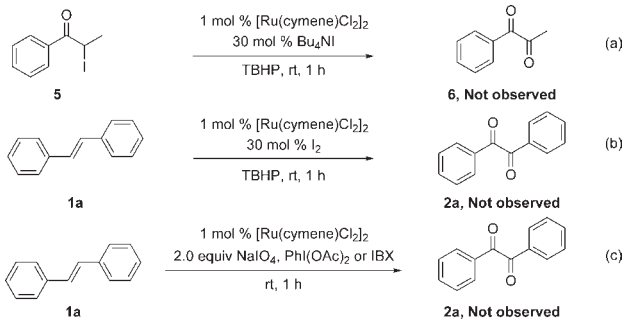
choice also had a dramatic effect on the reaction efficiency (entries 2−10). Interestingly, the replacement of Bu_4NI with Bu_4NCl or Bu_4NBr resulted in negligible conversion (entries 12 and 13). Employing TBHP as the stoichiometric oxidant also proved crucial, since no product **2a** was observed when other common oxidants were tested (entries 16−20). No product **2a** was detected when 1,2-diphenylethyne was used as a substrate (entry 24).[6p] Finally, the oxidation of **1a** was conducted on a larger scale (100 mmol) and the benzil **2a** was obtained in 83% yield (entry 23).

With the optimized conditions in hand, the scope of this reaction was assessed with a representative selection of alkenes. As shown in Figure 1, a variety of functional groups, including F, Cl, Br, ether, ester, CN, ketone, CF_3, amide, and triple bond, were tolerated under the reaction conditions. Generally, alkenes with electron-donating substituents provided the corresponding products in higher yield than those bearing electron-withdrawing substituents. Both *trans*- and *cis*-alkenes were successfully applied in this oxidation reaction (Products **2c**, **2i**, **2r**, **2u**, and **2x**). Moreover, sterically demanding alkenes can also be employed, producing the desired products in satisfactory yields (Products **2g**, **2r**, and **2t**). It is noteworthy that heterocyclic alkenes, such as thiophene and furan, can be transformed into their corresponding α-diketone products (Products **2o** and **2p**). The oxidation of *N*-methylindole, as

Scheme 1. Synthetic Application of the Methodology



Scheme 2. Investigation on Reaction Mechanism



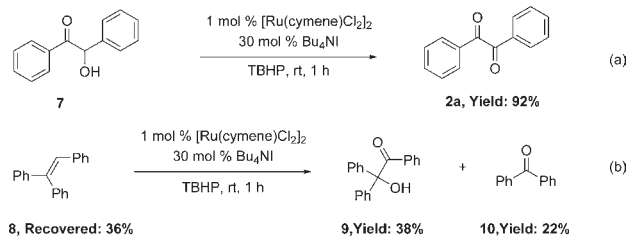
anticipated, produced *N*-methylisatin **2n** in high yield under the slightly modified conditions. Notably, an electron-poor double bond was also tolerated in this alkene oxidation process (Product **2h**). For some substrates, moderate yields were observed due to competing oxidative cleavage (Products **2h**, **2p**, and **2z**). Finally, the reaction was not limited to diarylalkenes and preliminary results demonstrated that alkenes with alkyl substituents also afforded the desired products in satisfactory yield (Products **2q**, **2u**, **2v**, and **2x**).

To further showcase the utility of such a highly active, mild, and chemoselective alkene oxidation, its application in complexe synthesis was investigated. α-Diketones **4**, an intermediate for an anti-inflammatory drug, was constructed in moderate yield (Scheme 1). In sharp contrast, three steps were necessary for the preparation of compound **4** in the literature.[5g]

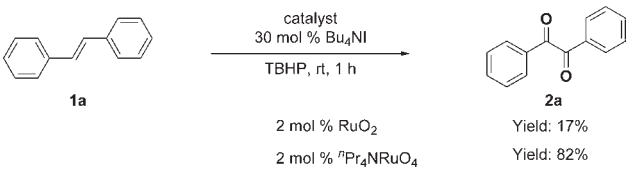
Notably, no product **2a** was obtained in the absence of Bu_4NI. Therefore, we suspected that an α-iodo ketone might serve as an intermediate in this transformation. Unexpectedly, no desired α-diketone **6** was detected when α-iodo ketone **5** was subjected to the reaction conditions (Scheme 2a). A brown color was observed under the optimized conditions, which is consistent with the generation of iodine *in situ*. However, replacement of Bu_4NI with iodine did not lead to the product **2a** (Scheme 2b). Further investigations were carried out to elucidate the role of iodide. When hypervalent iodine reagents, such as $NaIO_4$, $PhI(OAc)_2$ or IBX, were used as oxidants, no product **2a** was observed (Scheme 2c).

With 0.1 mol % $[Ru(cymene)Cl_2]_2$, a trace amount of benzoin **7** was detected in the reaction, implying an

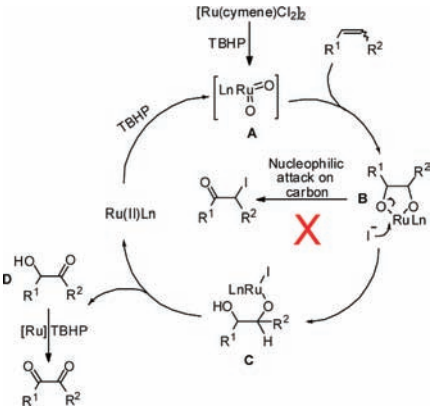
Scheme 3. Possible Reaction Intermediate



Scheme 4. Investigation on Reaction Mechanism



Scheme 5. Plausible Catalytic Cycle



α-hydroxyl ketone might be an intermediate in the alkene oxidation transformation. We subjected benzoin **7** to the optimal reaction conditions, leading to benzil **2a** in excellent yield (Scheme 3a). When triphenylethylene **8** was used as a substrate, the corresponding α-hydroxyl ketone **9** and oxidative cleavage product benzophenone **10** were observed (Scheme 3b). In addition, the addition of TEMPO to the reaction did not have a significant influence on performance, suggesting a free radical pathway may be unlikely.

Murahashi et al.[14] and Che et al.[15] reported that the ruthenium(II) complex reacts with *t*-BuOOH to form Ru(II)OOBu-*t*, which subsequently undergoes cleavage of the O–O bond to give an oxoruthenium species. Drago et al. also discovered that the ruthenium(II) complex could be oxidized by TBHP to generate *cis*-dioxoruthenium species.[16] Recently, several groups have developed an alkene *cis*-dihydroxylation, which proceeds via a [3 + 2] cycloaddition reaction between the *cis*-dioxoruthenium complex and the alkene.[11,15,16] Further experiments were carried out to investigate the exact nature of the ruthenium catalyst in this transformation. When commercially available *trans*-dioxoruthenium specie RuO_2 was used as a catalyst, only a 17% yield was observed. In sharp contrast, *cis*-dioxoruthenium complex $^nPr_4NRuO_4$ resulted in benzil **2a** in 82% yield (Scheme 4). Based upon the above results, we suspect, not conclude, *cis*-dioxoruthenium species might act as the active catalyst in this transformation.

A tentative mechanism is proposed in Scheme 5. The reaction of the ruthenium catalyst with TBHP forms a *cis*-dioxoruthenium intermediate **A**. A [3 + 2] cycloaddition between intermediate **A** and the alkene generates intermediate **B**. The nucleophilic attack of iodide on ruthenium of intermediate **B**, not on carbon, affords intermediate **C**. Intermediate **C** then undergoes *β*-hydrogen elimination, leading to α-hydroxyl ketone **D**, and the subsequent oxidation of **D** would produce the desired α-diketone. Finally, oxidation of the resulting Ru(II) species facilitated by TBHP forms *cis*-dioxoruthenium intermediate **A**, completing the cycle.

In summary, we have successfully constructed α-diketones via a novel Ru-catalyzed alkene oxidation. We believe that the excellent functional group tolerance, mild conditions, practical convenience, short reaction times, and ligand-free nature of this protocol would prove it to be a valuable synthetic tool in organic chemistry and drug discovery. Further investigations into the detailed mechanism and the reaction scope are ongoing in our laboratory.

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Supporting Information Available. Experimental details, ^1H, and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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