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Ru-Catalyzed Redox-Neutral Cleavage of the N−O Bond in Isoxazolidines: Isatogens to Pseudoindoxyls via a One-Pot [3 + 2]-Cycloaddition/N−O Cleavage

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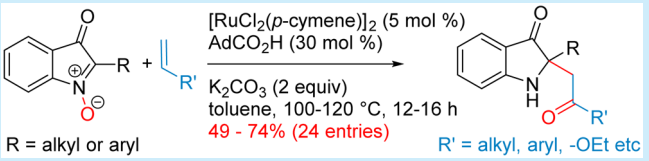
Supporting Information

ABSTRACT: A novel metal-catalyzed oxygen atom transfer reaction onto olefins is reported. By taking isatogens as substrates, a one-pot [3 + 2]-cycloaddition of nitrone with olefins followed by the Ru-catalyzed redox-neutral N−O bond cleavage of intermediate isoxazolidine has been executed as a simple method for the synthesis of 2,2-disubstituted pseudoindoxyls.



Catalytic internal redox-neutral reactions are often characterized by atom economy and reaction efficiency,[1] and the metal-catalyzed internal reorganization of oxygen atoms, employing nucleophilic oxygen atom donors such as nitro, *N*-oxides, nitrone, sulfoxides, and epoxides; olefins and alkynes as acceptors have been particularly well explored in the context of the synthesis of various heterocyclic units and also in target oriented synthesis.[2] Oxygen-bearing directing groups have also been employed to develop redox-neutral C−H activation reactions, which, at the outset, make this "C−H activation and functionalization protocol" even more green by avoiding any external oxidants.[3−8] While, the N−O bond, as a part of nitro, nitrone, and *N*-oxides, is most frequently used in such internal oxygen atom transfer processes, hydroxylamine derivatives have been commonly employed as oxidizing directing groups in redox-neutral C−H activation processes.

Isoxazolidines (derived from the classical [3 + 2]-cycloaddition of a nitrone with olefin) that bear such an oxidizing N−O bond have particularly attracted our attention,[9] for reductive cleavage of the N−O bond leading to a *β*-aminoalcohol substructural unit is commonly practiced. There are a couple of processes for the conversion of isoxazolidines directly to the *β*-aminoketones, which, in general, employ a suitably positioned leaving group that departs after the reductive N−O bond cleavage, leading to a *β*-aminoketone.[10,11] Thus, the catalytic redox neutral N−O bond cleavage would be an interesting proposal for the preparation of *β*-aminoketones, yet, surprisingly, this has not yet been explored.[12] We hypothesized such a proposal could expedite our total synthesis of pseudoindoxyl natural products employing the isatogens (a cyclic nitrone) as key intermediates.[13] The isatogens readily undergo cycloaddition with olefins leading to tricyclic oxazolidines.[14] The catalytic redox neutral N−O bond cleavage of these tricyclic oxazolidines should lead to 2,2-disubstituted pseudoindoxyl derivatives (Figure 1).[15] Apart from their potential as valuable intermediates in the synthesis of natural products such as austamide, hinckdentine, brevianimide, and

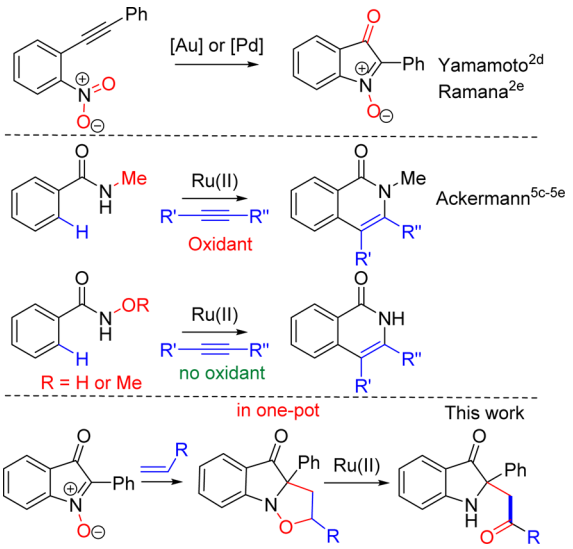


Figure 1. Selected examples on the internal oxygen transfer and redox-neutral processes involving N−O bonds and proposed novel redox-neutral N−O cleavage of isoxazolidine.

aristotelone, these pseudoindoxyl compounds display large Stoke shifts.[16,17] Thus, a protocol that combines both the cycloaddition and redox neutral N−O bond cleavage in one pot could provide a simple means for fluorescence labeling.

With this proposition in mind, an examination of various metal complexes commonly employed in redox-neutral C−H activation reactions has revealed a widespread use of ruthenium complexes in this domain, which provided a starting point for our exploration. Table 1 saliently describes the exploratory experiments that were conducted in this context. In general, the reactions were carried out in a sealed tube employing 1 equiv of

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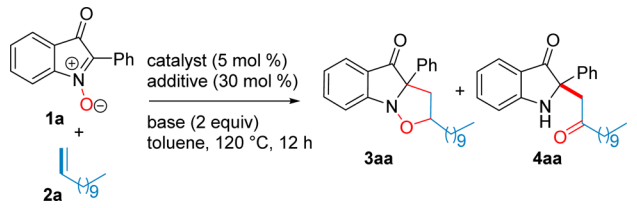
Table 1. Optimization of Catalysts and Additives[a]



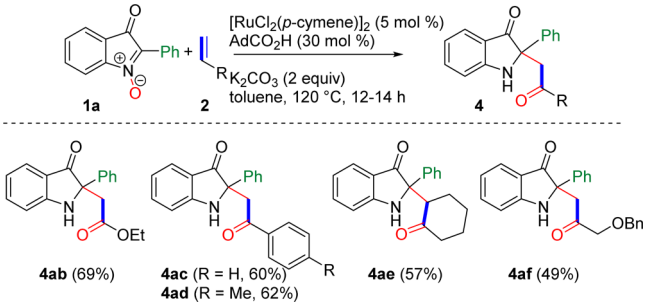
entry	catalyst	additive	base	yield (%)[b] 3	4
1	$RuCl_2(PPh_3)_3$	$AdCO_2H$	K_2CO_3	62	12
2	**$[RuCl_2(p\text{-cymene})]_2$**	$AdCO_2H$	K_2CO_3	**0**	**74**
3	$Ru_3(CO)_{12}$	$AdCO_2H$	K_2CO_3	0	58
4	–	$AdCO_2H$	K_2CO_3	82	0
5	$[RuCl_2(p\text{-cymene})]_2$	–	–	0	63[c]
6	$[RuCl_2(p\text{-cymene})]_2$	$AdCO_2H$	–	0	66[c]
7	$[RuCl_2(p\text{-cymene})]_2$	–	K_2CO_3	14	54[c]
8	$[RuCl_2(p\text{-cymene})]_2$	CH_3CO_2H	K_2CO_3	0	69
9	$[RuCl_2(p\text{-cymene})]_2$	$AdCO_2H$	$NaHCO_3$	0	67

[a]Reaction conditions: **1** (1 equiv), **2** (5 equiv), toluene (3 mL), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AdCO_2H$ (30 mol %) and K_2CO_3 (2 equiv), 120 °C, 12 h in a sealed tube. [b]Isolated yields. [c]48 h.

isatogen and 5 equiv of olefin in toluene at 120 °C in the presence of 5 mol % of catalyst along with 30 mol % of adamantane carboxylic acid ($AdCO_2H$) and 2 equiv of K_2CO_3.[5c] Under these conditions, when $RuCl_2(PPh_3)_3$ was employed as a catalyst, the cycloaddition product **3aa** (62%) was obtained as the major product along with substantial amounts of the expected β-amino ketone **4aa** (12% yield). This early result was promising and suggested that the proposed N−O bond cleavage with a concomitant C−O bond oxidation was possible. Gratifyingly, when $[RuCl_2(p\text{-cymene})]_2$ was employed as a catalyst, the *keto* compound **4aa** was obtained exclusively in 74% yield. Even the reaction with the $Ru_3(CO)_{12}$ complex delivered **4aa** as the only product, although the yield was not comparable and thus the reaction also required prolonged heating. As expected, the cycloaddition product **3aa** was obtained exclusively when $AdCO_2H$ and K_2CO_3 were employed without using the catalyst. Control experiments revealed that the thermal cycloaddition of **1a** and **2a** proceeds at 110 °C within 8 h providing **3aa** in 78% yield [see Supporting Information for complete details]. Interestingly, only when complex **A** ($[RuCl_2(p\text{-cymene})]_2$) alone was present, the reaction seemed to be facile even in the absence of both a base and an additive. However, it required more than 2 days for the complete consumption of the intermediate cycloaddition product and a nominal decrease in the isolated yield was noticed. A similar result was obtained when the reaction was carried out in the absence of a base. However, when conducted in the absence of an additive, the N−O cleavage reaction was incomplete even after 2 days and substantial amounts of an intermediate cycloaddition product were isolated. A preliminary screening of other additives revealed that $AdCO_2H$ was superior. When other bases were examined, such as $NaHCO_3$, there was not much improvement in yield, when compared to K_2CO_3.

Next, the compatibility of different alkenes in this one-pot protocol was scrutinized. Scheme 1 summarizes the results. Treatment of **1a** with ethylvinyl ether **2b** provided the corresponding C2-(ethyl acetate) pseudoindoxyl derivative **4ab** in 69% yield. Regarding the reactions with vinylbenzene

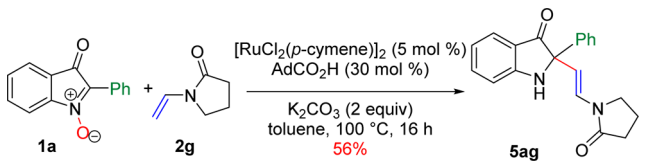
Scheme 1. Olefins Scope in One-Pot Cycloaddition and Ru-Catalyzed Redox-Neutral N−O Cleavage



derivatives, with styrene **2c** and 4-methylstyrene **2d**, the reactions provided the corresponding β-aminoketone products **4ac** and **4ad** in 60% and 62% yield, respectively. Additionally, the reaction with cyclohexene **2e** produced a neat conversion and **4ae** was obtained in good yield. However, with allylated benzylether **2f**, the corresponding **4af** was obtained in 49% yield along with several unidentified products.

During this survey, the reaction with vinylpyrrolidone **2g** proved interesting (Scheme 2). Instead of the expected redox

Scheme 2. A One-Pot Cycloaddition and Ru-Catalyzed N−O Bond Cleavage with *N*-Vinyl Pyrrolidone



product; the intermediate N−O cleavage product underwent dehydration, resulting in **5ag** with a net C2-alkenylation of starting isatogen. This apparent regioselective sp^2 C−H activation and functionalization of vinylpyrrolidone involving an oxidizing-directing group was remarkable and opens up new possibilities and queries, especially in C−H activation protocols employing pyridine-/quinolone-*N*-oxides.[18]

After examining the various facets of the current protocol, we next proceeded to generalize this one-pot reaction, employing a broad range of isatogens with selected alkenes. Diverse isatogens having different C2-substituents (aryl or alkyl) and different substituents on both the aromatic rings were employed in this context. As summarized in Scheme 3, the 2-hexylisatogen **1b**, on reaction with ethylvinyl ether **2b** and styrene **2c**, underwent the [3 + 2]-cycloaddition with a redox neutral cascade, providing the C2-alkylated pseudoindoxyl **4bb** and **4bc** in 66% and 60% yields. Control experiments with **1b** revealed that its cycloaddition with styrene **2c** proceeds at 80 °C, whereas the key N−O cleavage required heating at 100 °C. Next, treatment of the 2-phenylisatogen having an electron-withdrawing substituent (e.g., chloro) at the *para*-position to the carbonyl group was investigated, with 1-dodecene **2a**, ethylvinyl ether **2b**, and styrene **2c**. All proceeded smoothly, giving the corresponding C2-alkylated products **4ca**, **4cb**, and **4cc** in very good yields. A similar trend was observed with the isatogen **1d** having an electron-donating substituent (e.g., methoxy), indicating that the electronic influence on the keto does not alter the reaction outcome. Subsequently, the reaction of the isatogen **1e** having the electron-withdrawing $-NO_2$ group at the *para*-position of the C2-aryl of the nitrone unit

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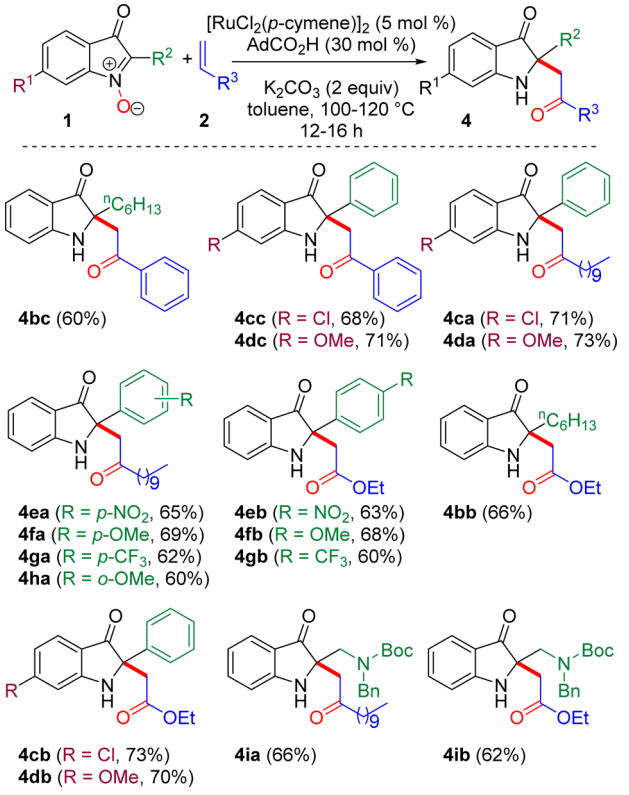
Scheme 3. Scope of One-Pot Cycloaddition/Ru-Catalyzed Redox-Neutral N−O Cleavage



was examined. The reaction worked magnificently with the alkenes 1-dodecene **2a** and ethylvinyl ether **2b**, providing the corresponding alkylation products **4ea** and **4eb** in fairly good yields. A similar trend was noticed in the case of the isatogen **1f**, where the $-NO_2$ group was replaced with the electron-donating −OMe group. Again, **4fa** and **4fb** were isolated in excellent yields. Gratifyingly, even the reactions of the isatogen **1g** (where the $-CF_3$ group is present at the same *para*-position) with 1-dodecene and with the ethylvinyl ether delivered **4ga** and **4gb** in good yields. Furthermore, the effect of steric hindrance was examined by performing the reaction of 2-(*o*-MeOPh) isatogen **1h** with 1-dodecene under the standard conditions. This procured the C2-alkylated pseudoindoxyl **4ha** in 60% yield. Also, the reaction with the isatogen **1i** proceeded smoothly with 1-dodecene and ethyl vinyl ether, thus revealing the compatibility of the *N*-Boc group under the present reaction conditions. Compound **1i** delivered the corresponding *β*-aminoketo and ester compounds **4ia**, **4ib** in 66% and 62% yields, respectively.

Mechanistically it is believed that, under the conditions employed, reduction of the initial Ru(II) to Ru(0) does not occur. Hence, we assume that the reaction starts with oxidative insertion of the ruthenium into the N−O bond followed by formation of a Ru(IV)−H after the *β*-hydride elimination. A final reductive elimination of Ru(II) positions the H on the nitrogen.[19]

In conclusion, the catalytic redox neutral N−O bond cleavage of isoxazolidines has been installed as a novel tool in the armory of organic synthesis. Its compatibility with the preceding cycloaddition has been developed as a simple protocol for the synthesis of 2,2-disubstituted pseudoindoxyl scaffolds having proven potential as intermediates in the total synthesis of natural products and applications in inorganic materials chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for the new compounds are provided in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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