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Hoveyda−Grubbs II Catalyst: A Useful Catalyst for One-Pot Visible-Light-Promoted Ring Contraction and Olefin Metathesis Reactions

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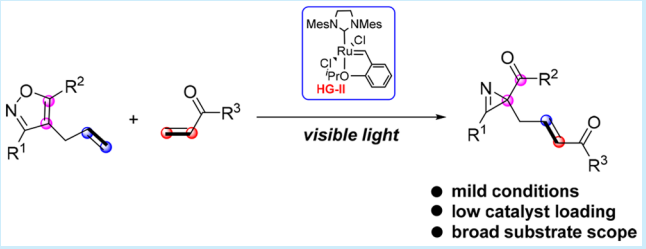
Supporting Information

ABSTRACT: A one-pot reaction to synthesize functionalized 2*H*-azirines through visible-light-mediated ring contraction and olefin metathesis of isoxazoles is described. Hoveyda−Grubbs II catalyst was found to function as a photocatalyst for these transformations, allowing these processes to be carried out in a one-pot manner. This study offers a new entry for the application of Grubbs catalysts as efficient photocatalysts and the possibilities of carrying out other photoreactions and olefin metathesis in a one-pot process.



Olefin metathesis is an extremely useful reaction for the synthesis of both linear and cyclic alkenes.[1] It has been shown that ruthenium complexes such as Grubbs catalyst I (**G-I**),[2] Grubbs catalyst II (**G-II**),[3] Hoveyda−Grubbs I (**HG-I**),[4] and Hoveyda−Grubbs II (**HG-II**)[5] are useful catalysts to effect this important transformation (Figure 1). Therefore, the ability

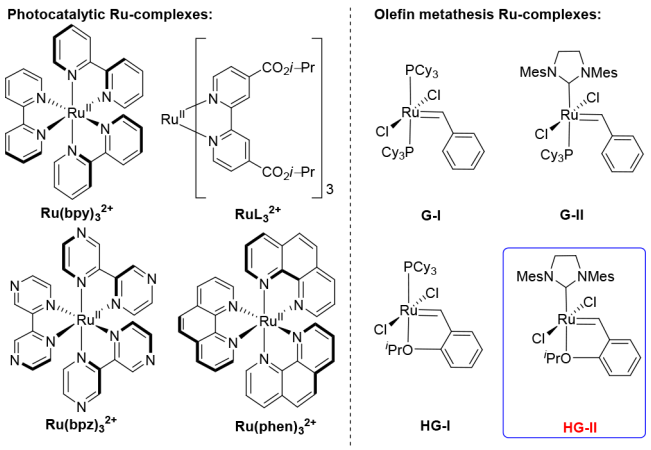


Figure 1. Ruthenium complex promoted reactions.

to carry out various transformations that can include olefin metathesis in a one-pot manner using ruthenium complexes will be useful in organic synthesis. Recently, there has been great interest in the development of a new organic method under visible-light promotion.[6] We envisage that the ruthenium complexes used in olefin metathesis may also be able to function as photocatalysts since many ruthenium complexes have been used as latent initiators under UV-light irradiation.[7] Herein, we demonstrate for the first time a one-pot reaction of olefin metathesis and ring contraction of isoxazoles using Hoveyda−Grubbs II catalyst to construct synthetically useful functionalized 2*H*-azirines[8] under visible-light irradiation (Figure 2).

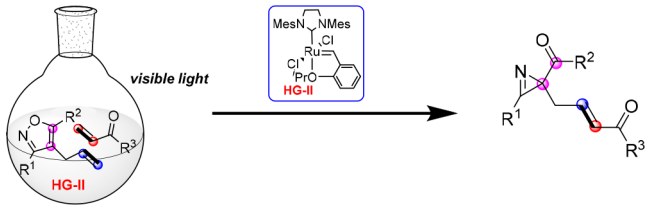


Figure 2. One-pot ring contraction and olefin metathesis reaction.

Ring contraction of isoxazoles is a useful strategy for the synthesis of 2*H*-azirines.[9] This can normally be realized using UV irradiation, high temperature, or iron-catalyzed processes with well-defined substrates.[10] Ohe and co-workers recently have shown that transition metals can also efficiently mediate the isomerization of isoxazoles.[8] We first explored the possibility of the ring contraction of 3-cyclohexyl-5-amino-isoxazole **1a** under visible light in the presence of Ru catalysts (Table 1, entries 1−6). Interestingly, the desired product 3-cyclohexyl-2*H*-azirine-2-carboxamide **2a** was obtained when **HG-II** catalyst was employed, while **G-I** and **G-II** catalysts failed to promote the reaction. Surprisingly, other known

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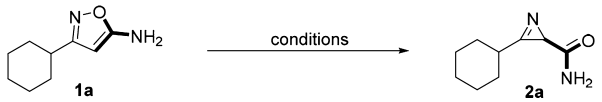
Table 1. Optimization of Reaction Conditions[a]



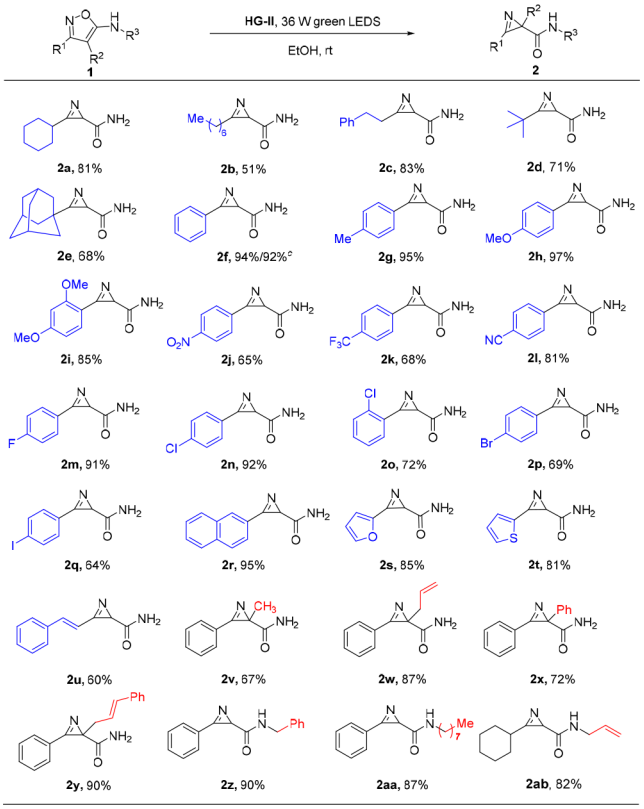
entry	catalyst	solvent	conditions	yield[b] (%)
1	**G-I**	CH_3CN	green LED	0
2	**G-II**	CH_3CN	green LED	0
3	**HG-I**	CH_3CN	green LED	58
4	**HG-II**	CH_3CN	green LED	65
5	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	CH_3CN	green LED	5
6	$Ru(bpy)_3(PF_6)_2$	CH_3CN	green LED	3
7	$Ru(bpy)_3(PF_6)_2$	CH_3CN	blue LED	0
8	**HG-II**	DCE	green LED	53
9	**HG-II**	CH_2Cl_2	green LED	60
10	**HG-II**	toluene	green LED	58
11	**HG-II**	MeOH	green LED	54
12	**HG-II**	EtOH	green LED	85/81[c]
13	**HG-II**	EtOH	green LED	49[d]
14	**HG-II**	EtOH	blue LED	72
15	**HG-II**	EtOH	white LED	67
16	**HG-II**	EtOH	dark	0
17		EtOH	180 °C	0
18		EtOH	green LED	0

[a]Conditions: a mixture of **1a** (0.1 mmol, 1 equiv), catalyst (1 mol %), and solvent (1 mL) was sealed in a Schlenk tube under an argon atmosphere, and the mixture was stirred until the **1a** was consumed completely. [b]Yields were determined by ^1H NMR vs an internal standard. [c]Isolated yield. [d]5 mol % of PCy_3 was added. DCE = dichloroethane.

ruthenium photocatalysts in the reaction displayed low reactivities under either green LEDs or blue LEDs (Table 1, entries 5−7). Further screening of the solvent effect revealed that EtOH was the optimal solvent, affording the desired product **2a** in 81% isolated yield (Table 1, entry 12). It is worth noting that when a small amount of PCy_3 was added into the reaction, the product was obtained in lower yield (49% instead of 85%) (Table 1, entry 13). Considering that no reaction was observed when **G-I** and **G-II** catalysts were used in the reaction, it indicated that the nucleophilic PCy_3 ligand might have inhibited the reaction. Different wavelengths of visible light were also tested. Product **2a** was obtained under blue and white LEDs in 72% and 67% yields, respectively (Table 1, entries 14 and 15). However, a control experiment carried out without a light source resulted in no desired product (Table 1, entry 16). This result showed that visible light is essential for the transformation. Control experiments performed in the absence of Ru catalyst or under a light source or high temperature (Table 1, entries 17 and 18) also led to no desired product **2a**.

With the optimized reaction conditions in hand, we proceeded to examine the substrate scope of the reaction (Scheme 1). Overall, numerous functional groups were tolerated, and the corresponding products were obtained in good to excellent yields. Alkyl-substituted substrates difficult to prepare using reported methods can be successfully obtained using our reaction conditions (**2a−e**). Bulky groups such as *tert*-butyl (**2d**) and adamantyl (**2e**) also proceeded well under the reaction conditions to give the corresponding products in 71% and 68% yields, respectively. It is worth noting that the reaction of **1f** can be scaled up to 10 mmol without a decrease in yield, affording the 3-phenyl-2*H*-azirine-2-carboxamide **2f** in 92% yield. The electronic effect was then studied in the

Scheme 1. Ring Contraction of Isoxazoles[a,b]



[a]Conditions: 0.2 mmol of **1** and 1 mol % of **HG-II** in EtOH (2 mL) were stirred under irradiation of 36 W green LEDs at room temperature. [b]Isolated yields. [c]10 mmol scale.

reaction. The aryl-substituted compounds with electron-donating groups proceeded well (**2g−i**) and gave the desired small rings in excellent yields (85−97%). The reaction using electron-withdrawing aryl groups also underwent smooth reaction but with decreased yields (**2j−l**). Different halogen substituents (F, Cl, Br, and I) on the aryl group also worked well under the standard conditions, affording the desired products in good to excellent yields (**2m−q**). It is worth noting that the chloro, bromo, and iodo functional groups are useful in coupling reactions.[11] A naphthalene substrate worked efficiently to give the corresponding 2*H*-azirine in 95% yield (**2r**). Heterocyclic compounds such as thienyl and furyl groups were also well tolerated and generated the products in 85% and 81% yields, respectively (**2s** and **2t**). Conjugated double bonds survived in the presence of Hoveyda−Grubbs II catalyst reaction conditions, albeit in decreased yield (**2u**). Notably, when R^2 = alkyl, allyl, and aryl groups (**2v−x**), the reaction proceeded smoothly to furnish 2*H*-azirine-2-carboxamides bearing all-carbon quaternary centers. Rather than simple primary carboxamides, secondary amides were found to be obtained in excellent yield (**2z**, **2aa**, and **2ab**).

After establishing the catalytic system, we then turned our attention to synthesize useful 2-allyl-2*H*-azirines[12] through the one-pot reaction of ring contraction and olefin metathesis of isoxazoles under visible-light irradiation. The reactions proceeded smoothly to give functionalized 2*H*-azirines in the presence of conjugated alkenes **3** in dichloromethane with increased catalyst loading in a one-pot manner (Scheme 2). In the one-pot reaction, dichloromethane was used as solvent

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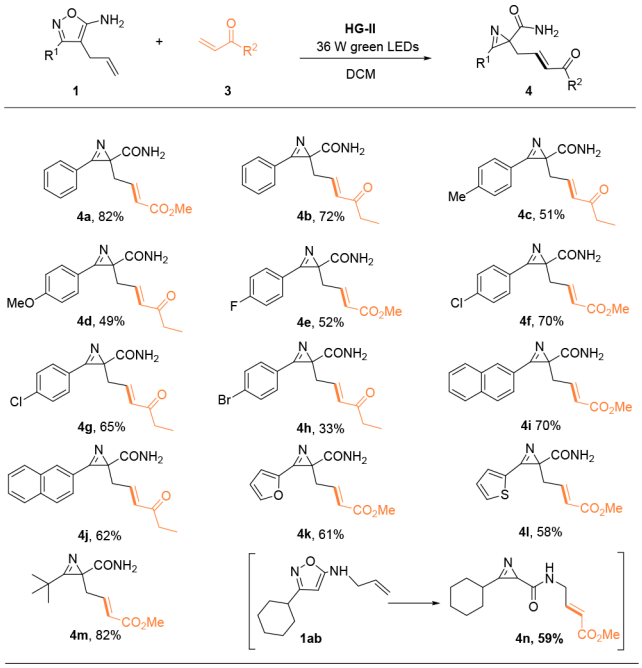
Scheme 2. One-Pot Reaction of Isoxazoles[a,b]

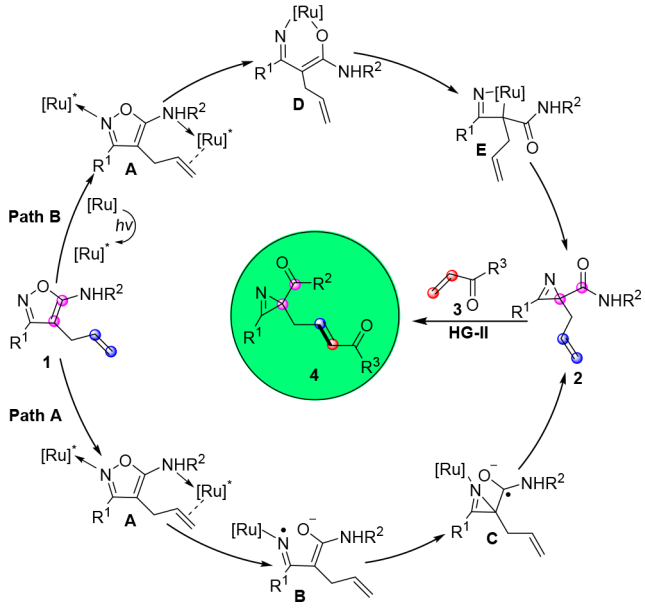


[a]Conditions: **1** (0.2 mmol), **3** (2.0 mmol), and 2 × 5 mol % **HG-II** in CH_2Cl_2 (2 mL) were stirred under irradiation of 36 W green LEDs at room temperature. [b]Isolated yields.

because halogenic solvents are common solvent used in olefin metathesis reaction. Notably, increased catalyst loading is essential for this one-pot transformation since using 1 mol % of **HG-II** will cause the reaction to stop at the ring-contraction step. This is probably the reason why substrates that bear an allyl moiety in Scheme 1 (**2w,ab**) were transformed to the 2*H*-azirines efficiently without homometathesis side reaction of the terminal alkene side chain. Both methyl acrylate and vinyl ketone **3** reacted efficiently under the reaction conditions (**4a**–**j**). Unfortunately, styrene, acrylamide, and acrylonitrile were not suitable for this one-pot catalytic system. Isoxazoles **1** with different substitutents (Me, MeO, and halogens) on the phenyl group gave moderate to good yields (**4c**–**h**). A naphthalene substrate worked well with both the methyl acrylate and vinyl ketone **3** to give the corresponding 2*H*-azrines in 70% and 62% yields, respectively (**4i** and **4j**). Heterocycles including thienyl and furyl groups survived uner the reaction conditions and resulted in promising yields (**4k** and **4l**). Interestingly, a bulky group was also incorporated successfully to afford 2-vinyl-2*H*-azirine in 82% yield (**4m**). Next, we explored the one-pot reaction of substrates having a double bond attached to the amino group. The secondary vinyl amides could be obtained in 59% yield (**4n**). Notably, this one-pot reaction of isoxazoles facilitates ring contraction first, followed by cross-metathesis with an alkene cross-partner (see the Supporting Information).

Encouraged by the above results, we became interested in the reaction mechanism. The well-known visible-light promoted reactions normally proceeded through a single-electron-transfer (SET) pathway in the presence of a ruthenium catalyst. Thus, a possible radical reaction pathway was proposed for the visible light-promoted ring contraction reactions (Scheme 3, path A). Initially, **HG-II** is probably activated from the ground state to the excited state under light irradiation. Both the nitrogen atoms of the isoxazole ring and amino group coordinate with

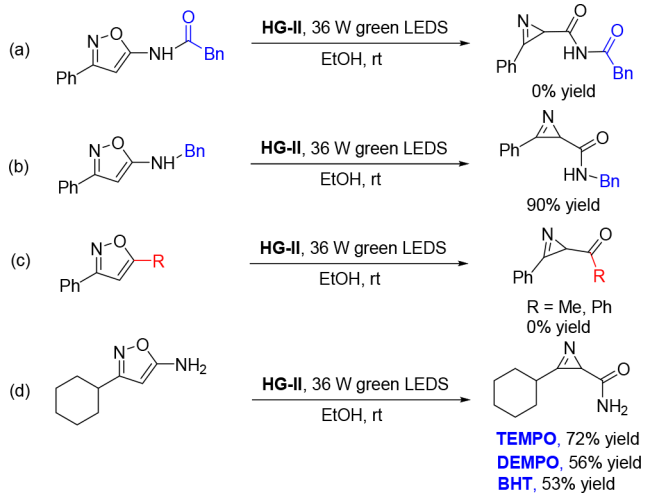
Scheme 3. Proposed Mechanism



the Ru complex in the excited state, giving intermediate **A**, which subsequently undergoes N–O bond cleavage through an SET process to afford **B**. The C–N bond then is formed by radical addition to give intermediate **C**, which transfers one electron to Ru to afford the corresponding 2*H*-azirine **2** and the ground state Ru. On the other hand, the activated ruthenium complex may directly insert into the N–O bond and afford intermediate **D** (Scheme 3, path B),[8b] which subsequently leads to four-membered ring **E**. After a reductive elimination process, the small ring product **2** was obtained through C–N bond formation. In either case, 2-vinyl-2*H*-azirine **2** then reacts with alkene **3** to give the functionalized 2*H*-azirine **4** through an olefin metathesis process.

To provide further understanding of the possible reaction pathway, some control experiments were explored (Scheme 4). We found that the amino group was essential to the reaction. When the amino group was substituted with an electron-withdrawing group, it failed to give the corresponding 2*H*-azirines. On the other hand, with a benzyl-substituted substrate,

Scheme 4. Mechanism Study



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the desired product was obtained in 90% yield (Scheme 4a,b). If an amino group at the 2-position of isoxazole was replaced by a methyl or phenyl group, the reaction was completely suppressed (Scheme 4, c). These results showed that the amino group may be coordinated with the ruthenium catalyst. When the reaction was carried out in the presence of radical trapping reagents such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), 5,5-dimethyl-1-pyrroline *N*-oxide (DEMPO), and butylated hydroxytoluene (BHT) (Scheme 4d), the desired product was obtained in slightly decreased yields (72, 56, and 53%). Although the mechanism is not fully understood, path B is preferred.

In summary, we have shown that Hoveyda−Grubbs II catalyst can be used to catalyze a one-pot photochemical ring contraction/olefin metathesis. Representative examples involving the visible-light-mediated one-pot ring contraction of substituted isoxazoles followed by olefin metathesis has been demonstrated. This study opens the door for the application of Hoveyda−Grubbs catalysts as efficient photocatalysts and the possibility of carrying out other photoreactions and olefin metathesis in a one-pot manner.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00971.

Experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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