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Iridium-Catalyzed Cyclization of Isoxazolines and Alkenes: Divergent Access to Pyrrolidines, Pyrroles, and Carbazoles

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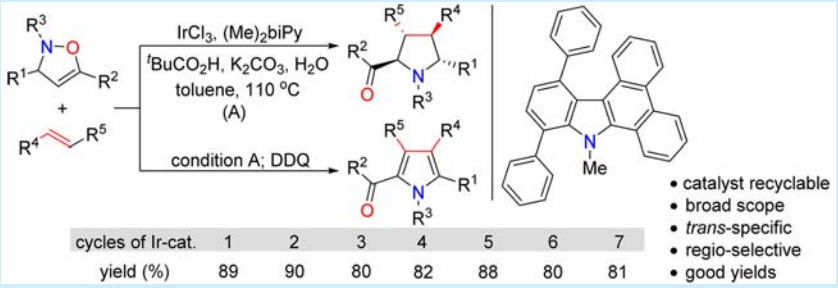
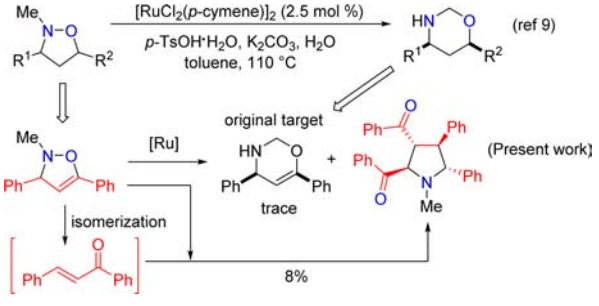
Supporting Information



ABSTRACT: A heterogeneous iridium-complex-catalyzed N−O-cleaving rearrangement/cyclization of 2,3-dihydroisoxazoles with alkenes has been developed. It provides divergent access to multiple substituted pyrrolidines, pyrroles, and carbazoles. The iridium catalyst remains highly catalytic active after seven cycles. The gram-scale synthesis afforded a carbazole with strong bluish-violet fluorescence.

Pyrrolidine and pyrrole heterocycles are core structures widely existing in natural products and bioactive molecules.[1] They are also important building blocks or intermediates in organic synthesis or pharmaceuticals. Research on diverse methods of synthesis of such heterocycles has always been a hot topic, attracting chemists to the challenge.[2] Although many methods have been well-established,[3−7] the synthesis of multiply substituted pyrrolidines and pyrroles is more or less a challenge for traditional methods. We previously reported a Ru-catalyzed N−O-cleaving rearrangement of *N*-methyl isoxazolidines that provides feasible access to 1,3-oxazinanes and 1,3-amino alcohols (Scheme 1).[8] Compared with isoxazolines, although 2,3-dihydroisoxazoles[9,10] bear a relatively weak N−O bond,[11] the N−O-cleaving isomerization of 2,3-dihydroisoxazoles has barely been reported.[12] Unfortunately, 2,3-dihydroisoxazoles were found to be unsuccessful in forming six-membered rearrangement products. However, an 8% yield of pyrrole was observed by NMR spectroscopy. We rationalized that the pyrrole was formed from the cyclization of 2,3-dihydroisoxazole and chalcone, where the chalcone was generated via the isomerization of 2,3-dihydroisoxazole (Scheme 1, bottom). Thus, the addition of extra chalcone resulted in successful access to pyrroles. In this work, a recyclable iridium-catalyst-promoted N−O-bond-cleaving cyclization of 2,3-dihydroisoxazoles has been developed, providing feasible access to pyrrolidines, pyrroles, and a carbazole with strong bluish-violet fluorescence.

Scheme 1. N−O Cleavage: From Isoxazolidines to 2,3-Dihydroisoxazoles



Initially, 2,3-dihydroisoxazole **1a** and chalcone **2a** were subjected to the catalysis of 2.5 mol % $[RuCl_2(p\text{-cymene})]_2$ in toluene, and the desired product **3a** was obtained in 60% yield (Table 1, entry 1). The in situ-generated Ir-4,4′-$(Me)_2$biPy complex gave **3a** in 80% yield (entry 3), whereas the in situ-generated Ru catalyst afforded **3a** in 74% yield (entry 2). The replacement of 2,4,6-trimethylbenzoic acid (TMBA) by $^tBuCO_2H$ gave rise to an increase in the yield to 84%. Higher temperature further increased the yield to 89% (entry 5). The reactions in the absence of iridium or bipyridines were unsuccessful (entries 6 and 7).

Next, various chalcones and 1,2-dihydroisozole **1a** were subjected to the standard reaction conditions, and the corresponding pyrrolidines were obtained in good yields (Scheme 2). Both aryl- and heteroaryl-substituted enones **2** afforded the desired pyrrolidines **3** in 71−86% yield (**3a**, **3e**, **3g**,

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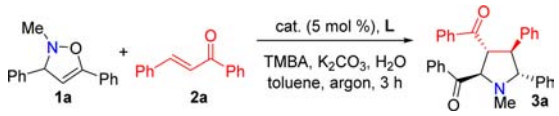
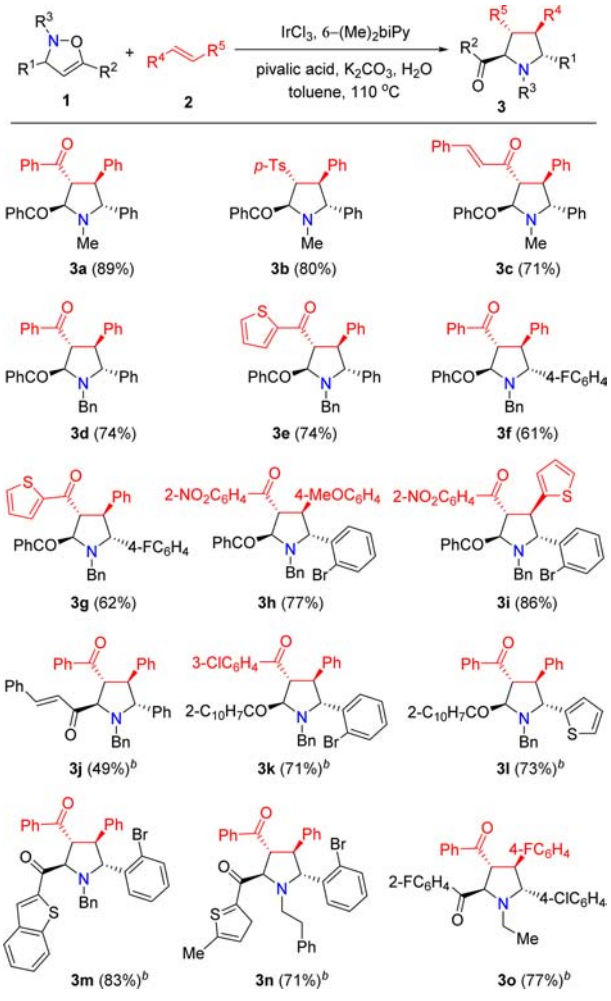
Table 1. Reaction Conditions[a]



entry	cat.	L	T (°C)	yield of **3a** (%)[b]
1[c]	[Ru]	biPy	90	60
2	$RuCl_3$	4,4′-$(Me)_2$biPy	90	74
3	$IrCl_3$	4,4′-$(Me)_2$biPy	90	80
4[d]	$IrCl_3$	6,6′-$(Me)_2$biPy	90	84
5[d]	$IrCl_3$	6,6′-$(Me)_2$biPy	110	89
6	none	none	90	trace
7[d]	none	6,6′-$(Me)_2$biPy	90	4[e]

[a]Conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), cat. (5 mol %), 2,4,6-trimethylbenzoic acid (TMBA) (0.15 mmol), toluene (2 mL), H_2O (18 μL), K_2CO_3 (69 mg). [b]Determined by ^1H NMR spectroscopy. [c]$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %). [d]Pivalic acid instead of TMBA. [e]With 96% of **1a** recovered.

Scheme 2. Scope of Pyrrolidines[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $IrCl_3$ (0.05 mol %), pivalic acid (0.075 mmol), K_2CO_3 (0.5 mol), H_2O (18 μL), toluene (2 mL), 110 °C, argon. [b]On a 0.25 mol scale.

3h, and **3i**). Besides carbonyl groups, tosylstyrene and a dienone were also suitable alkenes for construction of **3b** and **3c** in 80% and 71% yield, respectively. A wide scope of alkyl substituents such as methyl, benzyl, phenylethyl, and ethyl groups were examined, and the corresponding pyrrolidines were obtained in up to 89% yield (**3a**, **3d**, **3n**, and **3o**). When substrates bearing alkyl substituents were subjected to the reaction conditions, no target products were observed. This is a limitation for this method.

The molecular structure of **3a** was determined by single-crystal X-ray diffraction (Figure 1). All of the substituents are *trans* to each other.

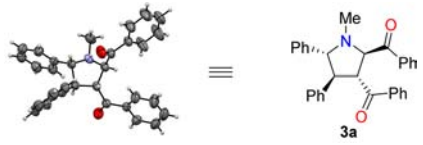
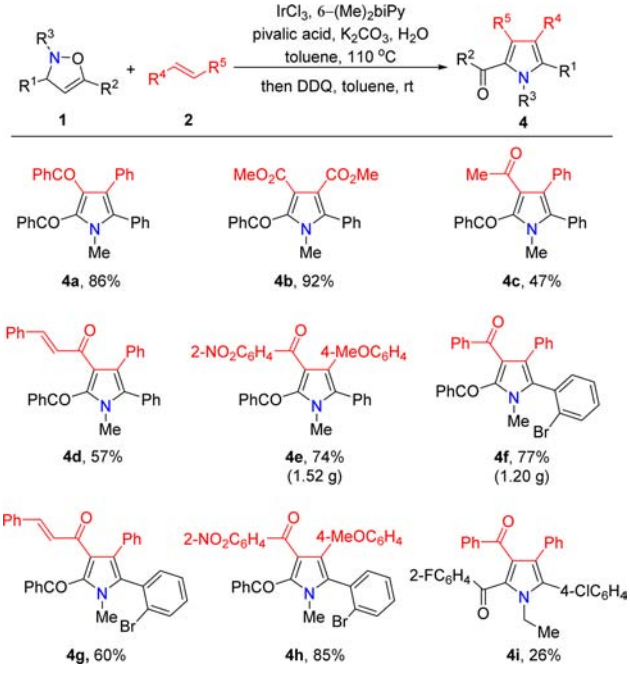


Figure 1. Molecular structure of **3a**.

This N−O-cleaving rearrangement/cyclization reaction was next applied to the one-pot direct synthesis of multiply substituted pyrroles (Scheme 3). Various 4-oxazolines and

Scheme 3. Scope of Pyrroles[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $IrCl_3$ (0.05 mol %), pivalic acid (0.075 mmol), K_2CO_3 (0.5 mol), H_2O (18 μL), toluene (2 mL), 110 °C, argon; then DDQ (1.0 mmol), 110 °C, argon.

alkenes were subjected to the cyclization/oxidation conditions and afforded the desired pyrroles in up to 92% yield. A methyl group is a stable N substituent that is tolerated in the DDQ oxidation. Gram-scale syntheses gave **4e** and **4f** in 74% and 77% yield, respectively.

The catalytic system was found to be suspended in the solution, inspiring us to recycle the catalyst. After seven cycles, the catalyst still performed well, giving an 81% yield (Scheme 4). For the expensive iridium catalyst, the recyclability is very important for industrial applications.

Pyrrole structures are the cores of carbazoles. Thus, this method was applied in the synthesis of carbazoles (Scheme 5). **4f** was subjected to the $Pd(NCPh)_2Cl_2$-catalyzed C−H bond

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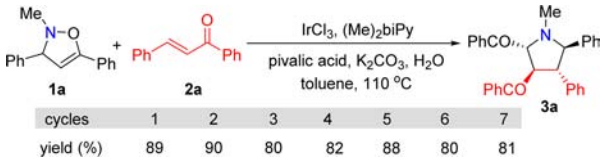
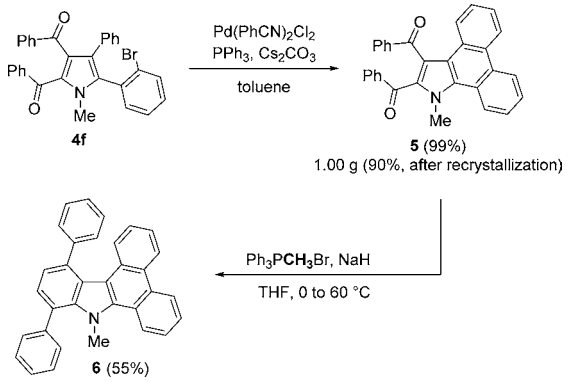
Scheme 4. Catalyst Recycling Experiments



cycles	1	2	3	4	5	6	7
yield (%)	89	90	80	82	88	80	81

Scheme 5. Synthesis of Carbazole 6



activation and coupling reaction,[13] furnishing **5** in 99% yield. In the further purification, 1.0 g of product was obtained in 90% yield after recrystallization in the gram-scale synthesis. The Wittig olefination of diketone **5** afforded polycyclic carbazole **6** in 55% overall yield. Compound **6** has strong bluish-violet fluorescence (λ = 430 nm), suggesting a potential utilization in photoelectric materials such as fluorescent probes and organic electroluminescent materials.

In conclusion, a recyclable iridium-catalyst-catalyzed N–O-cleaving rearrangement/cyclization of 2,3-dihydroisoxazoles has been developed. Multiply substituted pyrrolidines and pyrroles were readily obtained in up to 89% and 92% yield, respectively. A carbazole with strong bluish-violet fluorescence that has potential utilization in photoelectric materials such as fluorescent probes and organic electroluminescent materials was also synthesized. The recyclable iridium catalyst maintained high catalytic activity after seven cycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02905.

Experimental details and spectroscopic data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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