Heterocycles

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Synthesis of 2*H*-Azirines by Iridium-Catalyzed Decarboxylative Ring Contraction of Isoxazol-5(4*H*)-ones

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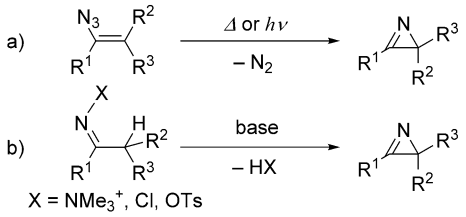
Abstract: *A phosphine-free iridium-catalyzed reaction of isoxazol-5(4H)-ones (isoxazolones) has been developed, and affords 2H-azirines through decarboxylation and ring contraction. This method provides an efficient and environmentally benign protocol which could replace the conventional approaches used to synthesize 2H-azirines.*

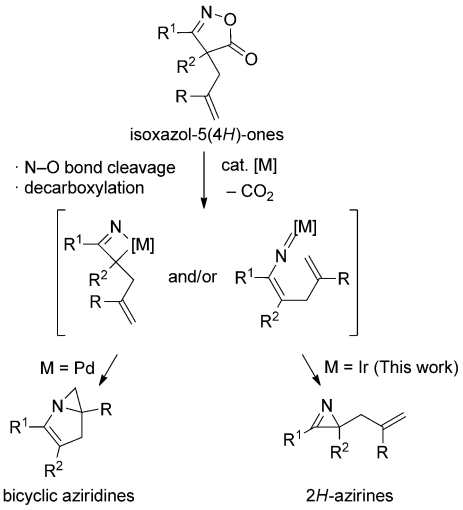
2*H*-Azirines, which are three-membered, nitrogen-containing, unsaturated heterocyclic compounds bearing a C=N bond, are highly strained molecules. They are the structural motifs seen in some antibiotic molecules.[1] The reactivity of 2*H*-azirines is characterized by their high ring-strain energy, which can cause various ring-opening reactions, such as hydrolytic formation of aminocarbonyl compounds,[2] transition-metal-catalyzed cycloaddition with unsaturated molecules,[3] and various nucleophilic addition reactions leading to aziridines.[4] Synthetic approaches to 2*H*-azirines are limited to a few types of reactions: denitrogenative cyclization of alkenyl azides (Scheme 1a) or base-mediated eliminative



Scheme 1. Conventional synthetic approaches to 2*H*-azirines. Ts = 4-toluenesulfonyl.

cyclization reactions of oxime esters, N-haloimines, or hydrazonium salts (Scheme 1b; Neber reaction).[1e] Both reactions require the generation of N-alkenylnitrene equivalents as intermediates. In the former case, great care should be taken when using explosive azide compounds as reagents. In the latter case, undesired reactions of 2*H*-azirines with bases or protic solvents should be carefully avoided.[5–7]

We have developed some reactions of isoxazol-5(4*H*)-ones (isoxazolones) as new types of thermally stable N-alkenylnitrene equivalents in which a palladium catalyst efficiently catalyzes either the intramolecular aziridination or aza-Wittig-type condensation with aldehydes.[8,9] The key intermediates in these reactions are considered to be vinylimido complexes of palladium or azapalladacyclobutenes, which are formed by the oxidative addition of N–O bonds of isoxazolones to palladium, followed by decarboxylation (Scheme 2). The reductive elimination of these plausible



Scheme 2. Palladium- and iridium-catalyzed reactions of isoxazol-5-(4*H*)-ones.

intermediates seems possible, and should afford 2*H*-azirines as products. However, when we used palladium catalysts in our investigations, the generation of 2*H*-azirines could not be detected. We now report on an iridium-catalyzed decarboxylative ring-contraction reaction of isoxazolones, a reaction which affords 2*H*-azirines selectively.

In a preliminary reaction, the isoxazolone **1a** (bearing a methallyl group) reacted with a catalyst precursor [{IrCl(coe)$_2$}$_2$] (5 mol%) and PPh_3 (20 mol%) as a ligand in 1,4-dioxane at 100 °C for 3 hours. The corresponding 2*H*-azirine **2a** was obtained in 56% yield at a 67% conversion of **1a** (Table 1, entry 1).[10] Then various polar and nonpolar solvents were examined under these reaction conditions. The yields, based on the consumed isoxazolone **1a**, were low when the following solvents were used: toluene, 1,2-dichloroethane, and DMF (entries 2–4). Acetonitrile resulted in very low conversion (entry 5). Examination of ether-type solvents revealed the following: cyclopentyl methyl ether (CPME) resulted in a high yield of **2a** (85% yield) at full conversion of **1a**, whereas 1,2-dimethoxyethane (DME) and 2-MeTHF were as effective as 1,4-dioxane.

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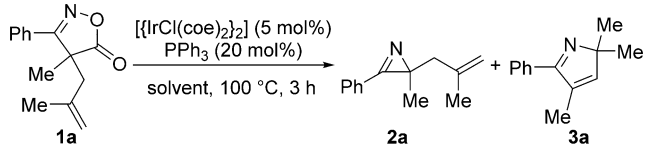
Table 1: Solvent effect in the iridium-catalyzed decarboxylative formation of **2a**.[a]

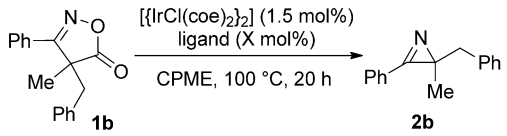


Entry	Solvent	Conv. [%][b]	**2a** Yield [%][b]	**3a** Yield [%][b]
1	1,4-dioxane	67	56	6
2	toluene	91	53	2
3	1,2-dichloroethane	66	17	5
4	DMF	63	21	2
5	MeCN	14	14	0
6	DME	48	43	4
7	2-MeTHF	66	64	0
8	CPME	100	85	4

[a] Isoxazolone (**1a**; 45.9 mg, 0.20 mmol) was reacted with [{IrCl(coe)$_2$}$_2$] (9.0 mg, 10 μmol) in solvent (2.0 mL) at 100 °C for 3 h. [b] Conversions and yields were determined by ^{1}H NMR spectroscopy. coe = cyclooctene, CPME = cyclopentyl methyl ether, DME = 1,2-dimethoxyethane, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

Table 2 summarizes the results of the examination of ligands in which the reactions of the simple isoxazolone **1b** were performed with a reduced amount of catalyst, that is, 3 mol% of the iridium catalyst.[11] The conversions of **1b** were low when using triarylphosphines having either methoxy or trifluoromethyl groups on the aromatic *para*-positions (entries 2 and 3). Various bis(phosphine) ligands were also examined, but conversions remained low, despite the good yield based on the recovered starting isoxazolone (entries 4–8). It emerged that the phosphine ligands merely decreased the catalytic activity. The azirine **2b** was isolated in the highest yield (91%) with no ligand addition (entry 9). An iridium/diene complex [{IrCl(cod)}$_2$] was also effective, but less so than the [{IrCl(coe)$_2$}$_2$] we used (entry 10). The structure of **2b** was confirmed by X-ray crystallographic analysis (Figure 1).[12]

Table 2: Ligand effect in the iridium-catalyzed decarboxylative formation of the 2*H*-azirine **2b**.[a]



Entry	Ligand [mol%]	Conv. [%][b]	Yield [%][b]
1	PPh_3 (6)	70	70
2	$P(4\text{-}MeOC_6H_4)_3$ (6)	31	23
3	$P(4\text{-}CF_3C_6H_4)_3$ (6)	17	16
4	dppe (3)	83	80
5	dppp (3)	51	57
6	dppb (3)	54	55
7	dppf (3)	33	35
8	*rac*-binap (3)	89	79
9	none	100	91 (91)[c]
10	none[d]	100	75

[a] Isoxazolone (**1b**; 44.3 mg, 0.20 mmol) was reacted with [{IrCl(coe)$_2$}$_2$] (2.7 mg, 3.0 μmol) and a ligand in CPME (2.0 mL) at 100 °C for 20 h. [b] Conversions and yields were determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product. [d] [{IrCl(cod)}$_2$] was used instead of [{IrCl(coe)$_2$}$_2$]. cod = 1,5-cyclooctadiene, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, dppb = bis(diphenylphosphino)butane, dppe = bis(diphenylphosphino)ethane, dppf = bis(diphenylphosphino)ferrocene, dppp = 1,3-bis(diphenylphosphino)propane.

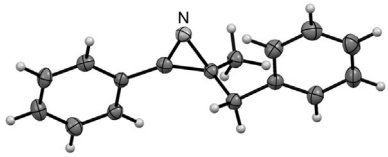
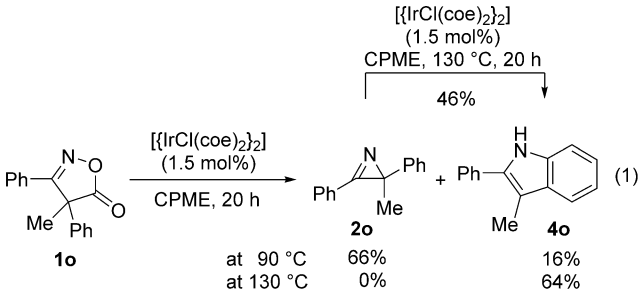


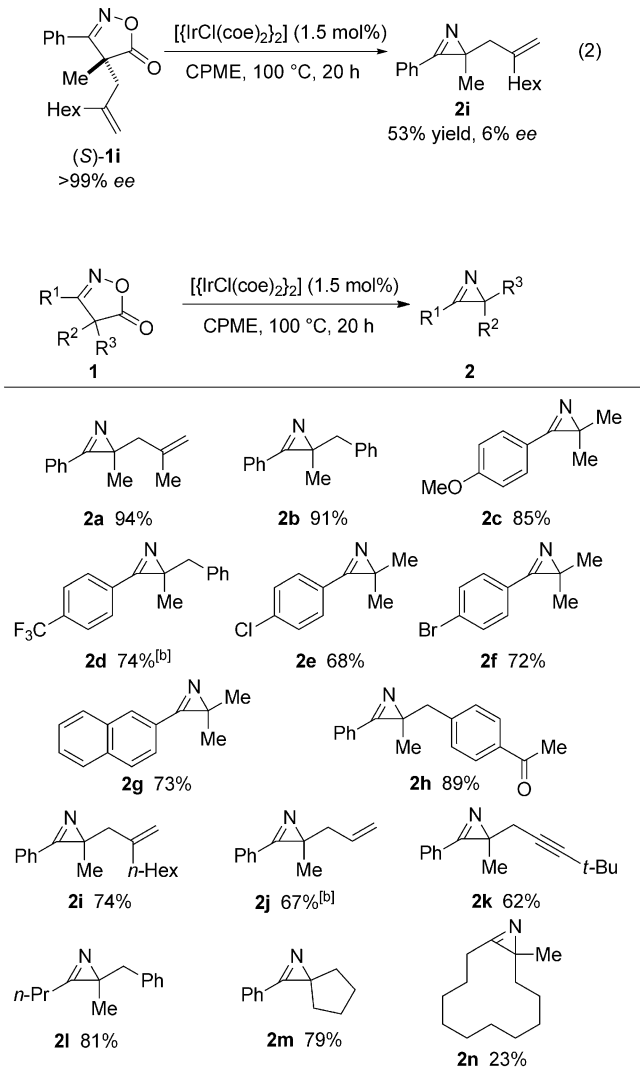
Figure 1. ORTEP illustration of azirine **2b** by X-ray crystallographic analysis. Thermal ellipsoids shown at 50% probability.

Under the optimized reaction conditions, the iridium-catalyzed decarboxylative ring-contraction reaction of isoxazolones having various substituents and various functional groups afforded the corresponding 2*H*-azirines in good yields (Scheme 3). As aromatic moieties (R^1) the following groups could be used: phenyl, *p*-methoxy-, *p*-trifluoromethyl-, *p*-chloro-, and *p*-bromophenyl, as well as 2-naphthyl groups. The yields of the 2*H*-azirines were in the range 68–91% (**2b–g**). When isoxazolones possess reactive sites such as carbonyl, alkene, and alkyne moieties, the yields were still moderate to high (62–94%), and indicates that these reactive moieties can be tolerated (**2a**,**h–k**). The azirine **2l**, which is substituted with all aliphatic groups, was also obtained in high yield. The spirocyclic azirine **2m** was obtained in high yield (79%), and the bicyclic azirine **2n** was also obtained, albeit in low yield (23%).

It is noteworthy that the reaction of the isoxazolone **1o**, which possesses a phenyl group on the 4-position, afforded the 2*H*-azirine **2o** in 66% yield, as well as indole **4o** in 16% yield [Eq. (1)]. At 130 °C, however, **4o** was obtained as a major product in 64% yield. The isolated **2o** also reacted at 130 °C in the presence of an iridium catalyst to afford **4o** in 46% yield.[13,14]

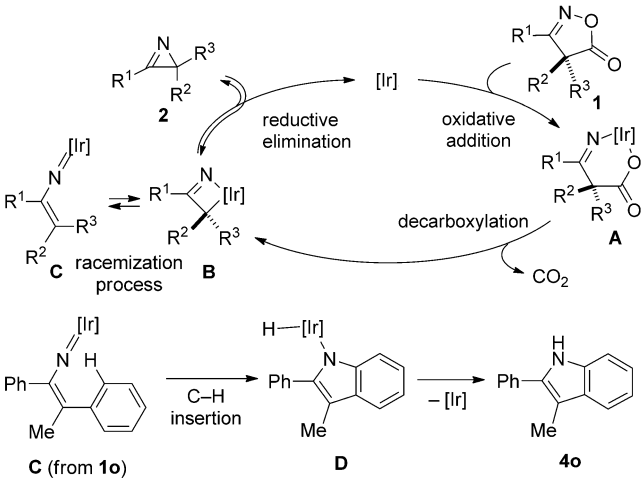


To investigate the reaction mechanism involving chiral information of the starting isoxazolones and the product azirines, the optically pure isoxazolone (*S*)-**1i** was prepared separately[15] and subjected to the iridium-catalyzed reaction [Eq. (2)]. The enantiomeric excess of the azirine **2i** was only 6% *ee*, thus indicating that chirality transfer hardly occurred in this reaction system.



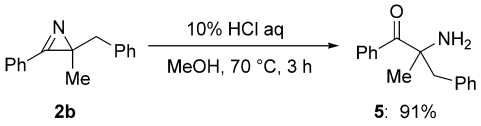
Scheme 3. Iridium-catalyzed decarboxylative ring contraction of the isoxazolone **1** to afford the 2*H*-azirine **2**. Isoxazolone (**1**; 0.20 mmol) was reacted with [{IrCl(coe)$_2$}$_2$] (2.7 mg, 3.0 μmol) in CPME (2.0 mL) at 100 °C for 20 h. Yield of isolated product is shown. [a] Reaction temperature was 130 °C.

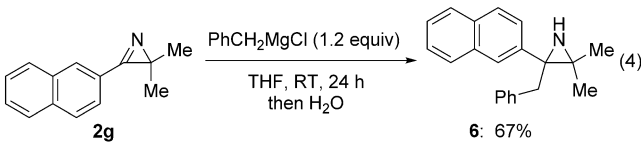
Scheme 4 shows a proposed catalytic cycle for the present reaction with isoxazolones (**1**). The cycle commences with the oxidative addition of an N–O bond of **1** to an iridium(I) species.[16,17] The adduct **A** liberates carbon dioxide immediately to generate the azairidacyclobutene **B**. If azirine **2** is produced by the irreversible reductive elimination from **B**, then the chirality of **1** must be completely maintained. However, significant deterioration of the product *ee* value was observed, as shown in Equation (2). Therefore, the reductive elimination step would be the reversible pathway and **B** is likely to be in equilibrium with the achiral imido (nitrene) complex **C**. Formation of **4o** from both **1o** and **2o** [Eq. (1)] also supports the reversible formation of these intermediates and azirine **2o**. The iridium imido complex **C** undergoes the intramolecular insertion of an aromatic C–H bond, thus leading to the intermediate **D**, which then forms indole **4o** by reductive elimination.



Scheme 4. A proposed catalytic cycle for iridium-catalyzed formation of 2*H*-azirines.

The potentially useful transformation of 2*H*-azirines obtained in the present reaction has been demonstrated. The 2*H*-azirine **2b** readily underwent a hydrolytic ring-opening reaction under acidic aqueous conditions to afford the α-aminoketone **5** in 91 % yield [Eq. (3)]. The nucleophilic addition with benzylmagnesium chloride to **2g**, followed by hydrolysis, afforded the tetrasubstituted NH aziridine **6** in 67 % yield [Eq. (4)].





In conclusion, by using a phosphine-free iridium catalyst, we have developed a decarboxylative ring-contraction reaction of isoxazolones which affords highly strained 2*H*-azirines. Advantages of the present synthetic reaction include the thermal stability and availability of the isoxazolones, as compared to the conventional synthetic approaches in which highly reactive and thermally unstable precursors are used. It is noteworthy that decarboxylation provides a driving force towards small-ring formation in terms of both enthalpy and entropy.[18] Formation of the indole and the disappearance of chiral information of the starting isoxazolone supports the proposed catalytic cycle. We expect that the present approach may also be useful in process chemistry because the sole reaction by-product is carbon dioxide, as neither salts nor organic wastes are produced.

Acknowledgements

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Keywords: decarboxylation · iridium · nitrogen heterocycles · reaction mechanisms · small-ring systems

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[10] The 2*H*-pyrrole **3a** was also obtained as a by-product, but in $<6\%$ yield in all cases, thus indicating that a nitrene intermediate could react with the reactive site, such as an alkene moiety, in this reaction system.

[11] Other transition metal catalysts, for example $[Pd(PPh_3)_4]$, $[RhCl(PPh_3)_3]$, and $[RuCl_2(PPh_3)_3]$, did not exhibit catalytic activity towards 2*H*-azirine formation (yields of **2b** were $<5\%$).

[12] CCDC 1452316 contains the supplementary crystallographic data of azirine **2b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[13] Conversion from **2o** into **4o** was not observed at all in the reaction of the isolated azirine **2o** without an iridium catalyst at 130 °C.

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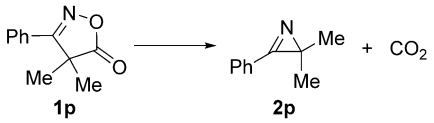
[18] Thermodynamic parameters between the reactant (isoxazolone **1p**) and the products (azirine **2p** and carbon dioxide) at 25 °C (298 K) were estimated with DFT calculations at B3LYP/6-31G(d,p) level ($\Delta G^{298} = -14.0$ kcal mol^{-1}, $\Delta H^{298} = -1.8$ kcal mol^{-1}, $\Delta S^{298} = 41.0$ cal mol^{-1}·K). These values indicate that the decarboxylation process will stabilize the products in both enthalpy and entropy, despite the formation of highly strained 2*H*-azirines (calculated strain energy = ca. 45–48 kcal mol^{-1}[1d]).



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