Rh(II)-catalyzed Isomerization of 2-Aryl-2*H*-azirines to 2,3-Disubstituted Indoles

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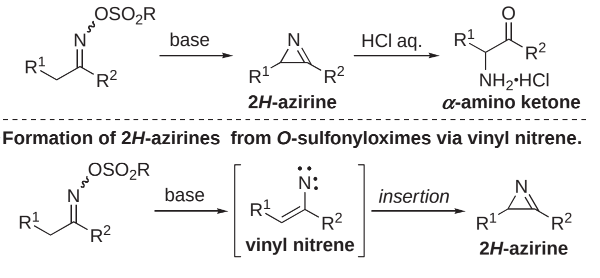
Various 2,3-disubstituted indoles are synthesized by $Rh_2(OCOCF_3)_4$-catalyzed isomerization of 2-aryl-2*H*-azirines.

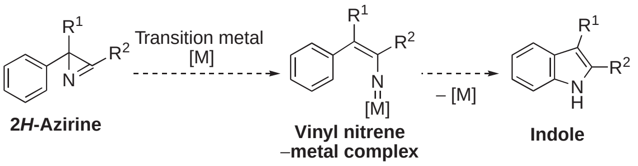
Introduction of an amino group to organic molecules by direct amination of C–H bonds would be an extremely attractive tool for the synthesis of amino compounds. Recently, considerable advances have been made in C–H amination by the use of transition-metal catalysts, where various amide derivatives are used as the nitrogen donors.[1] In this communication, we present an intramolecular C–H amination (aromatic substitution) reaction to prepare 2,3-disubstituted indoles[2] by a catalytic isomerization of 2-aryl-2*H*-azirines with $Rh_2(OCOCF_3)_4$.

The Neber reaction of *O*-sulfonyloximes has been recognized as one of the preparative methods for α-amino ketones via 2*H*-azirines as intermediates (Scheme 1).[3] One of the plausible reaction pathways of the formation of 2*H*-azirines from *O*-sulfonyloximes involves initial removal of an α-proton followed by loss of the sulfonate to afford vinyl nitrenes, which are converted into 2*H*-azirines via the insertion to the C–C double bond.[4] It is also known that 2-aryl-2*H*-azirines can be converted to indoles by the aryl C–H amination through the formation of vinyl nitrene intermediates by pyrolysis, whereas the application is quite limited.[5] Accordingly, we intended to develop a metal-catalyzed method for the transformation of 2-aryl-2*H*-azirines to indoles.

It was expected that the treatment of 2*H*-azirines with appropriate transition-metals would form vinyl nitrene–metal complexes, which in turn might undergo intramolecular C–H amination to furnish the corresponding azaheterocyclic compounds.[6] On the basis of the above considerations, we assumed that the vinyl nitrene–metal complexes generated from 2-aryl-2*H*-azirines would undergo the successive aromatic substitution to give indoles (Scheme 2). There has been only one report on a metal-catalyzed transformation of 2,2-diphenyl-2*H*-azirines to indoles by the use of a catalytic amount of $PdCl_2(PhCN)_2$.[7] This reaction was carried out under high dilution conditions (0.003 M) in benzene, and the application was not investigated. We, therefore, started to screen metal-catalysts for the transformation of 2-aryl-2*H*-azirines to indoles.



Scheme 1. Neber reaction.

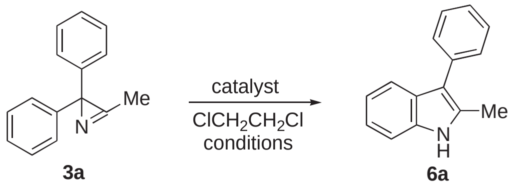


Scheme 2. Metal-catalyzed indole formation.

Firstly, 2,2′-diphenyl-3-methyl-2*H*-azirine (**3a**)[8] was treated with various metal complexes, and dirhodium(II) carboxylates were found to catalyze the isomerization to indole **6a** (Table 1).[9] When 2*H*-azirine **3a** was treated with a catalytic amount of $Rh_2(OCOCH_3)_4$ in 1,2-dichloroethane (0.2 M) at 60 °C for 9 h, the reaction proceeded as expected to give 2-methyl-3-phenylindole (**6a**) in 12% yield with 82% recovery of **3a** (Entry 1). 2*H*-Azirine **3a** was not transformed to indole **6a** at all in the absence of the rhodium catalyst in refluxing 1,2-dichloroethane (Entry 2). $Rh_2(OCOCF_3)_4$ was found to catalyze this reaction efficiently to give indole **6a** in 85% yield at 60 °C for 1 h (Entry 4). Furthermore, $Rh_2(OCOCF_3)_4$-catalyzed reaction proceed even at room temperature (Entry 5), and the catalyst loading was reduced to a 0.02 molar amount to afford indole **6a** in 90% yield (Entry 6).

We turned our attention to the scope of this catalytic indole formation with a diverse array of 2-aryl-2*H*-azirines (Table 2). 3-Alkenyl- and 3-alkynyl-2,2-diphenyl-2*H*-azirines **3b** and **3c** could isomerize to the corresponding indoles **6b** and **6c** in good yields without affecting the alkenyl and alkynyl moieties (Entries 1 and 2). From C2-monosubstituted 2*H*-azirine **3d**, however, the desired indole did not obtained at all (Entry 3).

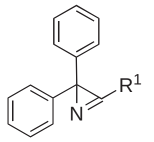
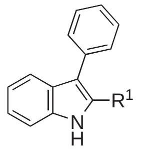
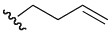
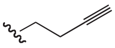
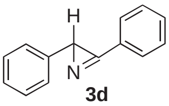
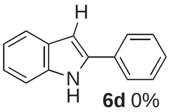
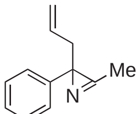
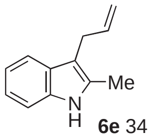
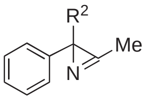
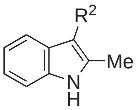
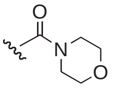
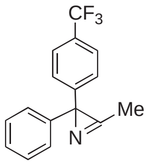
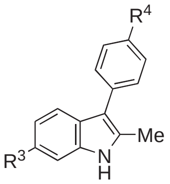
Table 1. Rh(II)-catalyzed isomerization of 2*H*-azirine **3a** to indole **6a**



Entry	Catalyst (mol amt.)	Conditions[a]	Yield[b]/%
1	$Rh_2(OCOCH_3)_4$ (0.05)	60 °C, 9 h	12 (82)[c]
2	none	reflux, 8 h	0 (99)[c]
3	$Rh_2(OCOCPh_3)_4$ (0.05)	60 °C, 9 h	2 (89)[c]
4	$Rh_2(OCOCF_3)_4$ (0.05)	60 °C, 1h	85
5	$Rh_2(OCOCF_3)_4$ (0.05)	rt, 17 h	85
6	$Rh_2(OCOCF_3)_4$ (0.02)	60 °C, 2h	90

[a]All reactions were performed under 0.2 M concentration. [b]Isolated yield. [c]Recovery yield of **3a**.

Table 2. $Rh(OCOCF_3)_4$-catalyzed isomerization of 2-aryl-2*H*-azirines **3** to indoles **6**[a]

Entry	2*H*-Azirines **3**	Conditions	Indoles **6**[b]
			
1	**3b** R^1 = 	60 °C, 5 h	**6b** 80%
2	**3c** R^1 = 	reflux, 3 h	**6c** 83%
3[c]	 **3d**	reflux, 8 h	 **6d** 0%
4[d]	 **3e**	reflux, 11 h	 **6e** 34%
			
5	**3f** R^2 = 	reflux, 3 h	**6f** 91%
6	**3g** R^2 = CN	reflux. 9 h	**6g** 84%
7	 **3h**	60 °C, 5 h	 88% (**6h**:**6h'** = 2:1)[e] **6h** (R^3 = H, R^4 = CF_3) **6h'** (R^3 = CF_3, R^4 = H)

[a]All reactions were performed with 0.05 mol amt. of $Rh_2(OCOCF_3)_4$ in $ClCH_2CH_2Cl$ (0.2 M). [b]Isolated yields. [c]Benzene was used as a sovent. [d]2*H*-Azirine **3e** was recorved in 14% yield. [e]The ratio was judged from ^1H NMR spectroscopy.

2,3-Dialkyl-substituted indole **6e** was obtained in 34% yield due to the product instability under these reaction conditions (Entry 4). This method was applied successfully to the synthesis of indoles bearing an electron-withdrawing group at C2 such as aminocarbonyl and cyano groups (Entries 5 and 6). The rhodium catalyst was vital for this conversion, because pyrolysis of **3g** in refluxing 1,2-dichloroethane in the absence of the rhodium catalyst gave a complex mixture without formation of indole **6g**. Electronic effect of aryl groups did not exhibit a significant influence in the cyclization. That is, the isomerization of 2*H*-azirine **3h** having a trifluoromethyl group on one of the phenyl rings proceeded smoothly to give a mixture of indoles **6h** and **6h′** in 88% yield in 2:1 ratio (Entry 7).

The isomerization of **3a** with a 0.05 molar amount of $PdCl_2(PhCN)_2$ proceeded slowly to give indole **6a** in 84% yield for 23 h under 0.2 M concentration in benzene, presumably owing to low solubility of the palladium catalyst. The reaction of alkenyl and alkynyl 2*H*-azirines **3b** and **3c** with the same palladium catalyst in 1,2-dichloroethane (0.2 M) gave the desired indoles **6b** and **6c** only in 14 and 7% yields, respectively, under the reaction conditions shown in Table 2, Entries 1 and 2.[10]

Thus $Rh_2(OCOCF_3)_4$ is found to be the effective catalyst for the isomerization of 2*H*-azirines **3** to indoles **6**.

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This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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7 K. Isomura, K. Uto, H. Taniguchi, *J. Chem. Soc., Chem. Commun.* **1977**, 664.

8 The details of the synthetic procedures of 2*H*-azirines were depicted in the Supporting Information, which is available electronically on the CSJ-Journal web site, http://www.csj.jp/journals/chem-lett/index.html.

9 The isomerization of 2*H*-azirine **3a** to indole **6a** with other transition metals did not gave satisfactory results. For example, $PtCl_2$ (8%), $Cu(acac)_2$ (0%), $Pd(OAc)_2$ (10%), and $Pd(BF_4)_2(CH_3CN)_2$ (0%).

10 The starting materials, 2*H*-azirine **3b** and **3c** were recovered in 55 and 31%, respectively along with some unidentified side products.

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