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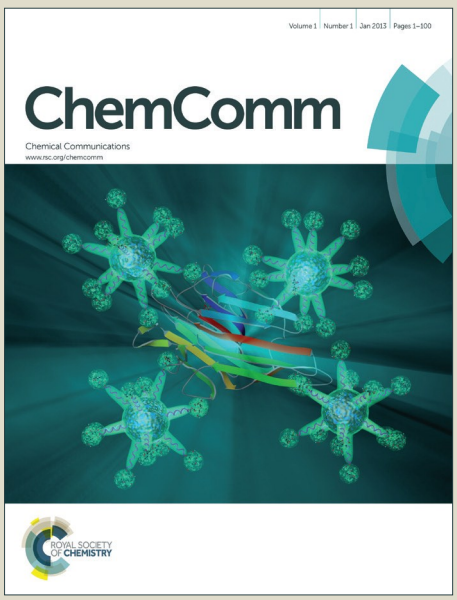

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Substrate-Controlled Rh(II)-Catalyzed Single-Electron-Transfer (SET): Divergent Synthesis of Fused Indoles†

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Rh(II)-catalyzed diversified ring expansions controlled by single-electron-transfer (SET) have been disclosed in this paper, producing a series of indole-fused azetidines and 1*H*-carbazoles or related derivatives in moderate to good yields via $Rh_2^{III,II}$ nitrene radical intermediates. The direction of ring expansion branches according to different ring size of methylenecycloalkanes.

The indole ring system is one of the most ubiquitous heterocycles in nature.[1] Fused indoles, polycyclic indole derivatives, are common cores found in a number of naturally occurring products.[2] For example, the insecticidal alkaloid Okaramine B carries indole-fused azetidine moiety.[3] Valparicine, containing a 1*H*-carbazole core, shows pronounced cytotoxic effects against KB and Jurkat cells.[4] Moreover, another 1*H*-carbazole derivative, namely, akuammiline alkaloid Scholarisine A, is used in traditional Chinese medicine to treat various respiratory diseases (Figure 1).[5] Their importance in medicinal chemistry has stimulated the development of new synthetic methods to create such structural motifs. Herein, we report a new protocol for facile construction of the above azetidine and 3*H*-indole akuammiline via ring expansion of methylenecycloalkanes. This method allows two types of ring expansions according to ring size: three-membered ring compounds furnish the azetidine ring; while larger sized substrates deliver 3*H*-indole fused cycloalkanes.

To rapid generation of molecular complexity from simple starting materials is the permanent pursuit in organic synthesis. To this regard, the ring-expansion (or 1,2-shift) strategy offers an excellent solution because it can facilitate easy formation of polycyclic derivatives, which are otherwise difficult to be

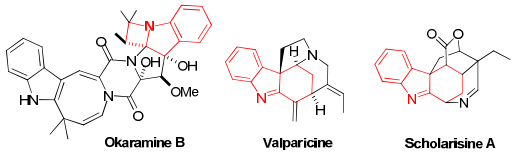
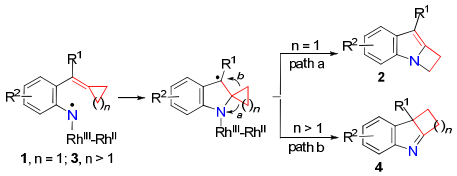


Figure 1 Represented important fused indoles



Scheme 1 Rearrangements of cycloalkyl radicals.

accessed by traditional methods. Our group has a long interest to investigate the ring expansion of methylenecyclopropanes (MCPs).[6,7] We then envisaged that a nitrogen radical species could induce the ring expansion of MCPs or methylenecycloalkanes, giving azetidine or 1*H*-carbazole derivatives. Notably, to the best of our knowledge, this is the first example of ring expansion of MCPs to a nitrogen atom to afford azetidines (Scheme 1).[7]

It has been reported that single-electron-transfer (SET) can take place between nitrene and dirodium(II) dimer, resulting in $Rh_2^{III,II}$ species which is the catalyst resting state in intermolecular amination reactions.[8] Furthermore, computational calculations suggested that such reactions were catalyzed by a triplet mixed-valent $Rh_2^{III,II}$ nitrene radical via the SET oxidation of the $Rh_2^{II,II}$ dimer.[9] On the basis of these results, azide tethered MCPs **1** were treated with a dirhodium complex (Scheme 1). We were glad to find that it underwent a ring expansion to give indole fused azetidines **2**. Moreover, we also found that the expansion of larger sized rings **3** under rhodium catalysis would go different direction to give 1*H*-carbazoles and related derivatives **4**.

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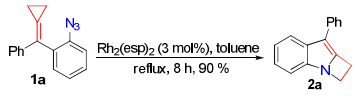
† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of new compounds, and CCDC 949600, 1003610. See DOI: 10.1039/b000000x/

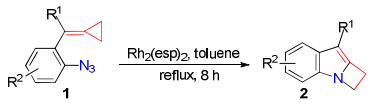


Scheme 2 Rhodium-catalyzed intramolecular reaction of **1a**.

We initially investigated the reaction of 1-azido-2-(cyclopropylidene(phenyl)methyl)benzene **1a** catalyzed by $Rh_2(esp)_2$ in toluene under reflux for 8 h. To our delight, the indole fused azetidine **2a** could be furnished in 90% yield (Scheme 2). Its structure has been unambiguously determined by X-ray diffraction (for more details about the optimization of this reaction, please see Table S1 in the Supporting Information).[10]

We next examined the substrate scope of this reaction. As for substrates **1b**-**1e**, in which R^1 = 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4 or 4-$MeOC_6H_4$, R^2 = H, the reactions proceeded smoothly to furnish the desired products **2b**-**2e** in 75-86% yields (Table 1, entries 1-4). In the cases of substrates **1f**-**1i** bearing halogen substituted aryl rings (R^1), the corresponding products **2f**-**2i** were obtained in 79-83% yields (Table 1, entries 5-8). Alternatively, R^2 could be other substituents such as 5-Cl or 4-MeO, and the desired products **2j**-**2l** were formed in 72-83% yields (Table 1, entries 9-11). The electronic property of R^1 and R^2 did not have significant impact on the reaction outcomes. When substrate **1m**, in which R^1 = Me, R^2 = H, was treated with $Rh_2(esp)_2$ under the standard reaction conditions, the corresponding product **2m** was afforded in 42% yield (Table 1, entry 12). The reaction of substrate **1n** (R^1 = R^2 = H) did not take place under the standard reaction conditions, suggesting that the derived radical intermediate shown in Scheme 1 is not stable enough when R^1 = H (Table 1, entry 12).

Table 1 Substrate scope of rhodium-catalyzed intramolecular tandem reaction of azide-MCPs **1**

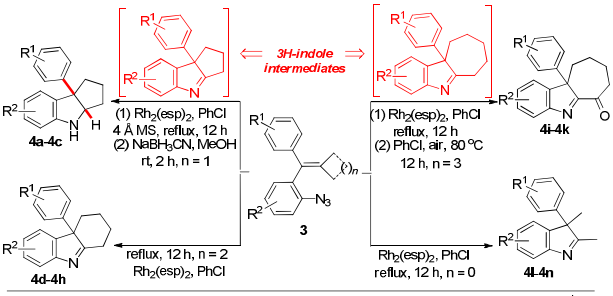


entry[a]	substrate	R^1	R^2	product	yield/%[b]
1	**1b**	2-MeC_6H_4	H	**2b**	77
2	**1c**	3-MeC_6H_4	H	**2c**	75
3	**1d**	4-MeC_6H_4	H	**2d**	86
4	**1e**	4-$MeOC_6H_4$	H	**2e**	78
5	**1f**	4-FC_6H_4	H	**2f**	82
6	**1g**	4-BrC_6H_4	H	**2g**	81
7	**1h**	4-ClC_6H_4	H	**2h**	83
8	**1i**	2-ClC_6H_4	H	**2i**	79
9	**1j**	2-ClC_6H_4	5-Cl	**2j**	77
10	**1k**	Ph	5-Cl	**2k**	83
11	**1l**	Ph	4-OMe	**2l**	72
12	**1m**	Me	H	**2m**	42
13	**1n**	H	H	**2n**	0

[a] Reaction conditions: **1** (0.2 mmol), catalyst (3 mol %), solvent (1.0 mL). [b] Isolated yield. esp = a,a,a',a'-tetramethyl-1,3-benzenedipropionic acid.

Next, we turned our interest in constructing 1*H*-carbazoles and related derivatives. Different ring sized methylenecycloalkanes as well as dimethyl substituted alkenes were investigated. These reactions did not occur under the standard reaction conditions (under reflux in toluene), but went on smoothly in chlorobenzene under reflux for 12 h, affording a series of 3*H*-indoles in good yields. When n = 1, the reactions of methylenecyclobutanes **3a**-**3c** proceeded smoothly, giving hexahydrocyclopenta[b]indoles **4a**-**4c** in 59–60% yields after reduction by $NaBH_3CN$, owing to the instability of the corresponding 3*H*-indole intermediates (Table 2, entries 1-3).[11] In the cases of substrates **3d**-**3h** (n = 2) bearing halogen, methyl and methoxy substituted aromatic ring (R^1), the corresponding tetrahydro-1*H*-carbazoles **4d**-**4h** were obtained in 62-80% yields (Table 2, entries 4-8). Specifically, as for methylenecyclohexanes **3i**-**3k**, the reactions proceeded smoothly and the desired products were easily oxidized by air to afford ketones **4i**-**4k** in 62-75% yields (Table 2, entries 9-11).[12] When substrates **3l**-**3n** bearing two methyl substituents were treated with $Rh_2(esp)_2$ under the standard reaction conditions, the products **4l**-**4n** were produced after 1,2-alkyl migration in 81-88% yields (Table 2, entries 12-14). Moreover, **3a**, **3d**, **3i** and **3l** could be converted to the corresponding products in less than 10% yield in the absence of Rh(II) complex, indicating that Rh(II) catalyst can promote the reaction efficiently.

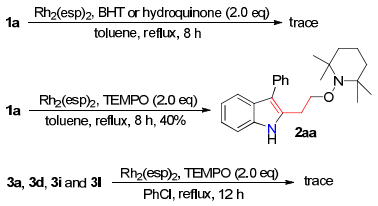
Table 2 Substrate scope of rhodium-catalyzed intramolecular tandem reaction of azide-styrenes **3**



entry[a]	substrate	n	R^1	R^2	product	yield/%[b]
1	**3a**	1	H	H	**4a**	60 (6)[c]
2	**3b**	1	4-Cl	H	**4b**	59
3	**3c**	1	H	5-Cl	**4c**	60
4	**3d**	2	H	H	**4d**	73 (8)[c]
5	**3e**	2	4-Br	H	**4e**	62
6	**3f**	2	4-Cl	H	**4f**	68
7	**3g**	2	3-Me	H	**4g**	80
8	**3h**	2	4-OMe	H	**4h**	72
9	**3i**	3	H	H	**4i**	75 (10)[c]
10	**3j**	3	4-Br	H	**4j**	62
11	**3k**	3	H	5-Cl	**4k**	62
12	**3l**	-	H	H	**4l**	88 (10)[c]
13	**3m**	-	3-Me	H	**4m**	81
14	**3n**	-	H	5-Cl	**4n**	86

[a] Reaction conditions: **3** (0.1 mmol), catalyst (5 mol %), solvent (1.0 mL). [b] Isolated yield. [c] No catalyst.

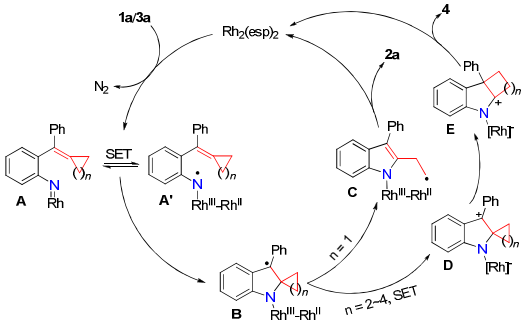
To investigate the mechanism, control experiments were conducted (Scheme 3). When radical inhibitors such as TEMPO, 2,6-di-*tert*-butyl-4-methylphenol (BHT) or hydroquinone (2.0 equiv) were added, the reaction outcomes of **1a** were significantly interrupted. To our delight, among them the radical trapping product **2aa** could be isolated in 40% yield. These results indicated that the reaction might indeed start from the $Rh_2^{III,II}$ nitrene radical intermediate and went through a radical pathway. Owing to the instability of azide groups at high temperature, trapping the reaction systems of **3a**, **3d**, **3i** and **3l** with TEMPO only gave complex mixtures along with trace of the desired products. Furthermore, the yields of product **2a** (R^1 = Ph, 90%), **2m** (R^1 = Me, 42%) and **2n** (R^1 = H, 0%) in Table 1 descended in order, clarifying the radical



Scheme 3 Radical trapping experiments.

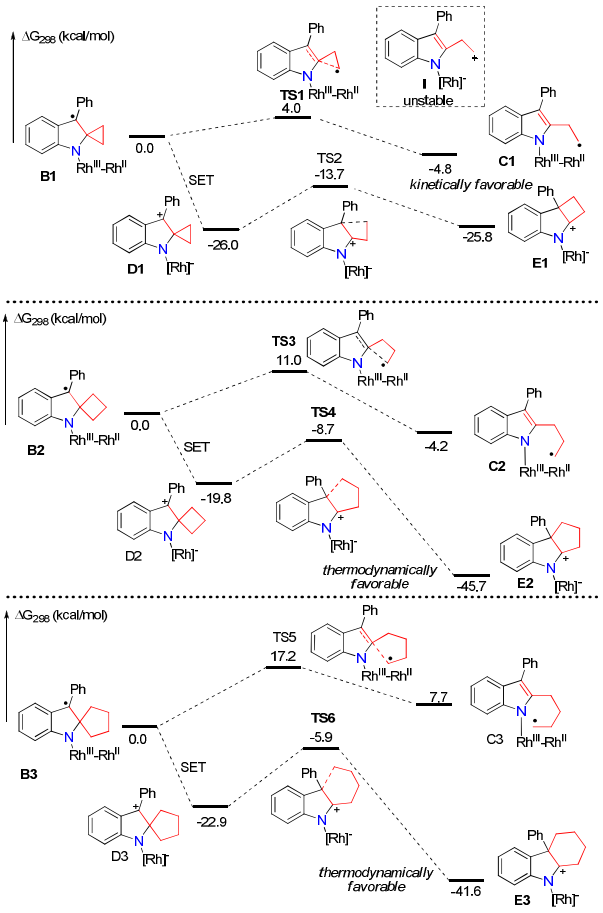
process because the stability of these three radical intermediates decreased in turn.

Based on above experiments and previous reports, a plausible mechanism is outlined in Scheme 4. Coordination of azide to $Rh_2(esp)_2$ complex and extrusion of N_2 give the Rh-nitrene **A**.[13] Next, intramolecular single electron transfer (SET) takes place, resulting in nitrogen centered radical specie **A'**.[8,9,14] The following radical addition to C=C bond in MCP moiety forms intermediate **B**, which undergoes ring-opening process to furnish homoallylic radical **C**. Subsequent SET from radical to Rh^{III} and ring-closure give rise to **2a** together with the regeneration of the Rh(II) catalyst. When n = 2-4, ring-opening can not take place and intermediate **B** undergoes another SET to afford spirocyclic cationic intermediate **D**. While a 1,2-alkyl shift from **D** can occur to afford the fused indole **E** which produces the corresponding 3*H*-indole product **4** and regenerates the Rh(II) catalyst.



Scheme 4 A plausible reaction mechanism.

In order to understand why the ring size of substrate can affect the reaction outcome, we did the DFT calculations on the key step in the reaction. All calculations have been performed at BPW91/BS1 level[15] with Gaussian 09 program.[16] The Rh_2-nitrene intermediate **A'** suggested in Scheme 4 was first investigated theoretically, and its $Rh_2^{III,II}$-nitrene radical character was proved (for details, see Supporting Information). Subsequently, we investigated the ring-opening process of **B** to generate intermediate **C**, and another possible reaction pathway starting from **B** which involves to form intermediate **D** via the SET and following 1,2-alkyl migration to give intermediate **E**. The relative energies of all intermediates and transitional states along the reaction pathways using different substrates are shown in Scheme 5. For the substrate involving three-membered ring, the intermediate **B1** can undergo a ring-opening process to generate another radical intermediate **C1**



Scheme 5 DFT studies on the key reaction step.

via transition state **TS1** with an energy barrier of 4.0 kcal/mol. Alternatively, the intermediate **B1** can undergo SET to a more stable zwitterionic intermediate **D1** which undergoes a 1,2-alkyl migration to form intermediate **E1** by passing through **TS2** with an energy barrier of 12.3 kcal/mol. In this case, the energy barrier of ring-opening process to form radical intermediate **C1** is much lower, thus this process is kinetically favorable, which may account for why experimentally obtained product is **2**. In addition, one possible intermediate **I** is also investigated theoretically. However, this intermediate is unstable and could not be located. Similarly, the substrates involving four-membered ring and five-membered ring are also investigated. In these two cases, the energy barriers for two reaction pathways are very close (11.0 kcal/mol vs. 11.1 kcal/mol, 17.2 kcal/mol vs. 17.0 kcal/mol), however, the intermediates **E2** and **E3** are very thermodynamically stable. Thus, for substrates involving four-membered ring and five-membered ring, the favored pathway is 1,2-alkyl migration, furnishing products **4**.

In summary, we have disclosed in this paper that styryl azides could smoothly undergo intramolecular rearrangement in the presence of Rh^{II} complex, producing a series of indole-fused azetidines and 1*H*-carbazoles or related derivatives in moderate to good yields via $Rh_2^{III,II}$ nitrene radical. The

products **2** and **4** have important structural motif in organic and medicinal chemistry. DFT calculations on the key step explain that cyclization and SET pathways are controlled by designed radical clock. The potential utilization and extension of the substrate scope of this synthetic methodology are currently under investigation.

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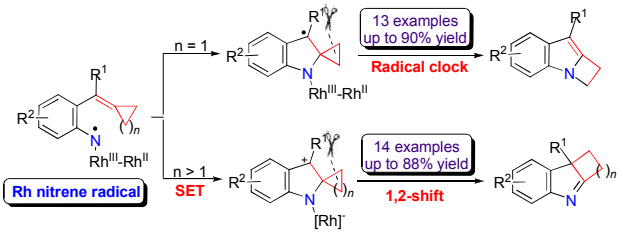
Substrate-Controlled Rh(II)-Catalyzed Single-Electron-Transfer (SET): Divergent Synthesis of Fused Indoles



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