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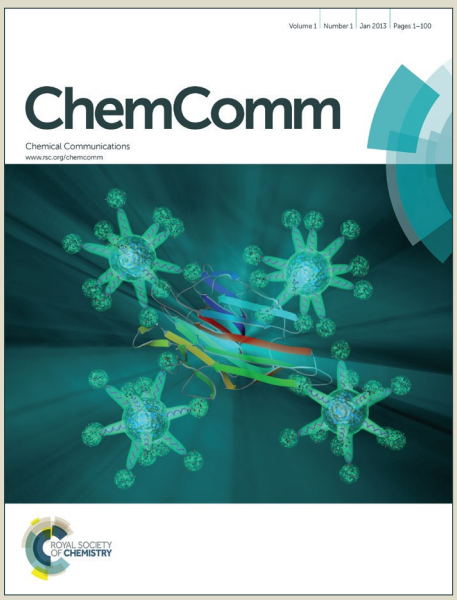

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Rh(II)-Catalyzed Formation of Pyrrolo[2,3-b]quinolines from Azide-methylenecyclopropanes and Isonitriles

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Azide-methylenecyclopropanes (azide-MCPs) underwent intermolecular cyclization with isonitriles catalyzed by Rh^{II} complex has been disclosed in this paper, producing a series of pyrrolo[2,3-b]quinolines in moderate to good yields via carbodiimide intermediates. Moreover, synthetic applications of these products to construct structurally novel and useful heterocycles have also been achieved.

Nitrogen-containing heterocycles, especially pyrrole and quinoline ring systems, are ubiquitous heterocycles in nature.[1] Pyrrolo[2,3-b]quinolines, special tricyclic *N*-heterocycles, are common cores prevalently in many medicinally and biologically important molecules,[2] such as blebbistatin (myosin II inhibitor)[3] and PGP-4008 (P-gp-specific MDR modulator)[4] (Figure 1). Furthermore, proliferation inhibition of DU-145 cell which also containing pyrrole-fused quinoline skeleton showed the best IC_{50} value (0.114 μM) and can be used as a classical cell line of prostate cancer (Figure 1).[5] These previous findings have stimulated our interest to develop facile synthetic approach to access pyrrolo[2,3-b]quinoline structure motif owing to its biological profile and fascinating molecular architecture.

Methylenecyclopropanes (MCPs), as highly strained but readily accessible molecules, are important building blocks in organic synthesis. Due to their special electronic properties and high ring strain, MCPs are very reactive towards transition metals or Lewis acids, facilitating a variety of ring-opening reactions to give efficient access to enhanced molecular complexity.[6,7] According to our previous work, the intramolecular reactions of carbenes or nitrenes with MCPs lead to cyclobutane or azetidine.[8] For example, in the presence

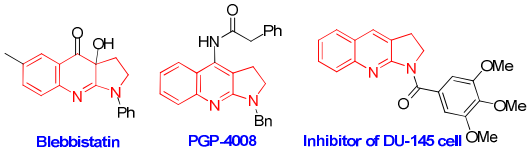
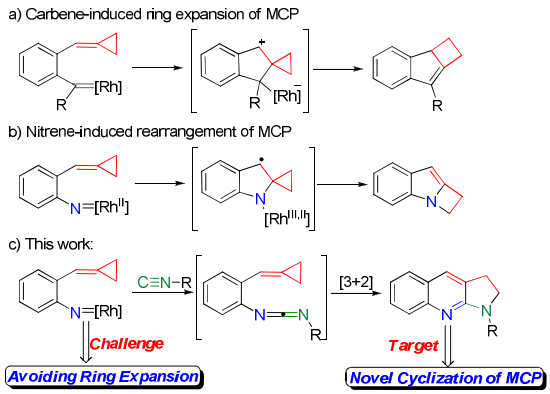


Figure 1 Represented important pyrrolo[2,3-b]quinolines.

of Rh^{II} catalyst, the intramolecular rearrangement of MCPs with carbenes furnished cyclobutane derivatives after ring expansion (Scheme 1, a).[8d] Moreover, the intramolecular reaction of Rh nitrenes with MCPs delivered indole-fused azetidines via radical intermediates (Scheme 1, b).[8e] To this regard, the multicomponent cascade reaction of nitrenes with MCPs should be very attractive because the incorporation of nitrogen atom can potentially give rise to *N*-heterocycles. Furthermore, extended application to intercept the *in situ* generated rhodium nitrene to embed the 3C synthon of MCPs into other ring systems, especially heterocycles instead of the indole-fused azetidines formation, seems to be challenging and interesting.



Scheme 1 Ring-opening patterns of MCPs with carbenes and nitrenes: ring expansion (a, b) and cyclization with isonitriles (c).

According to the previously reported results, the addition of azides to isonitriles with loss of N_2 could afford a

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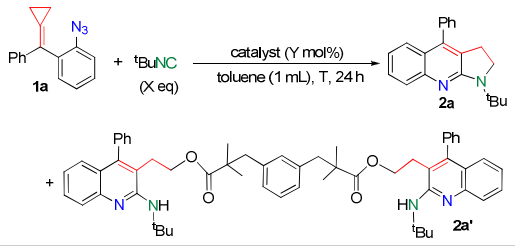
carbodiimide catalyzed by metal–isonitrile complexes.[9] On the basis of this hypothesis, azide tethered MCPs[8e] were synthesized and treated with a dirhodium complex to investigate the reaction of carbodiimide with MCP moiety. We were glad to find that the metal nitrenes could be intercepted by isonitriles and subsequent formal [3+2] cyclization took place, affording pyrrole-fused quinoline skeletons (Scheme 1, c). The synthetic potential of this novel method is very high, herein, we wish to report our preliminary results on the synthesis of these pyrrolo[2,3-b]quinolines.

Table 1 Optimization of the reaction conditions of rhodium-catalyzed tandem reaction of **1a**



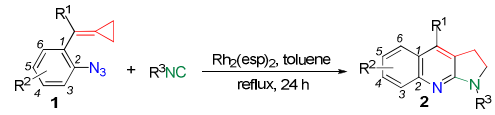
entry[a]	catalyst	X	Y	T/°C	yield/%[b] 2a	2a'
1	$Rh_2(OAc)_4$	3	5	110	50	-
2	$Rh_2(Piv)_4$	3	5	110	63	-
3	$Rh_2(TFA)_4$	3	5	110	57	-
4	$Rh_2(esp)_2$	3	5	110	68	10
5	$Rh_2(esp)_2$	5	5	110	72	6
6	$Rh_2(esp)_2$	5	5	80	53	8
7	$Rh_2(esp)_2$	5	5	50	47	8
8	$Rh_2(esp)_2$	5	10	110	46	32
9	***$Rh_2(esp)_2$***	***5***	***3***	***110***	***80***	***4***
10	$Rh_2(esp)_2$	5	0	110	-	-

[a] Reaction conditions: **1a** (0.1 mmol). [b] Isolated yield. Piv = pivalate, esp = a,a,a',a'-tetramethyl-1,3-benzenedipropionic acid.

We initially investigated the reaction of 1-azido-2-(cyclopropylidene(phenyl)methyl)benzene **1a** with tert-butyl isonitrile by variation of catalysts, temperature and the employed amounts of isonitriles (X equiv) and catalysts (Y mol %) (Table 1). When $Rh_2(OAc)_4$, $Rh_2(Piv)_4$, $Rh_2(TFA)_4$ and $Rh_2(esp)_2$ (5 mol %) were used as catalysts and ^{t}BuNC (3.0 equiv) was added, **2a** could be furnished in 50-68% yields (Table 1, entries 1-4). $Rh_2(esp)_2$ was chosen as the best catalyst in this reaction. The structure of **2a'** has been unambiguously determined by X-ray diffraction.[10] Increasing the employed amounts of ^{t}BuNC to 5.0 equiv improved the yield of **2a** to 72% (Table 1, entry 5). Carrying out the reaction at lower temperatures (80 and 50 °C), **2a** could be afforded in 47-53% yields (Table 1, entries 6-7). Using $Rh_2(esp)_2$ (10 mol %), the yield of **2a** reduced to 46% and the yield of **2a'** promoted to 32% (Table 1, entry 8). To our delight, when $Rh_2(esp)_2$ (3 mol %) was used, the main product **2a** was isolated in 80% yield along with **2a'** in only 4% yield (Table 1, entry 9). In the absence of $Rh_2(esp)_2$, no reaction occurred (Table 1, entry 10).

We next examined the substrate scope of this reaction and the results are shown in Table 2. The reaction of substrate **1a** with several other isonitriles furnished the desired products **2b**-**2d** in 56–73% yields (Table 2, entries 1-3). Tert-butyl isonitrile showed the best reactivity and was chosen to test other substrates **1**. When substrates **1b** (R^1 = 4-MeC_6H_4, R^2 = H), **1c** (R^1 = 4-BrC_6H_4, R^2 = H), **1d** (R^1 = 2-ClC_6H_4, R^2 = 5-Cl) or **1e** (R^1 = Ph, R^2 = 4-OMe) were employed as substrates, the corresponding products **2e**-**2h** were obtained in 60-80% yields (Table 2, entries 4-7). It was also found that the electronic property of aromatic ring did not have significant impact on the reaction outcomes. Treatment of methyl (R^1) substituted MCP with tert-butyl isonitrile and benzyl isonitrile under the standard conditions afforded the desired products **2i** and **2j** in 70% and 64% yields, respectively (Table 2, entries 8-9). Substrate **1g**, in which R^1 = R^2 = H, was also suitable for this reaction, giving the corresponding products **2k-2m** in 71-77% yields (Table 2, entries 10-12). The structure of **2d** has been further confirmed by X-ray diffraction. Its ORTEP drawing is shown in Figure 2 and the CIF data are presented in the Supporting Information.[11]

Table 2 Substrate scope of rhodium-catalyzed intermolecular reaction of azide-MCPs **1** with isonitriles



entry[a]	substrate	R^1	R^2	R^3	product	yield/%[b]
1	**1a**	Ph	H	Bn	**2b**	71
2	**1a**	Ph	H	Cy	**2c**	73
3	**1a**	Ph	H	Ph	**2d**	56
4	**1b**	4-MeC_6H_4	H	^{t}Bu	**2e**	62
5	**1c**	4-BrC_6H_4	H	^{t}Bu	**2f**	80
6	**1d**	2-ClC_6H_4	5-Cl	^{t}Bu	**2g**	77
7	**1e**	Ph	4-OMe	^{t}Bu	**2h**	60
8[c]	**1f**	Me	H	^{t}Bu	**2i**	70
9	**1f**	Me	H	Bn	**2j**	64
10	**1g**	H	H	PMB	**2k**	71
11	**1g**	H	H	^{t}Bu	**2l**	77
12	**1g**	H	H	Cy	**2m**	72

[a] Reaction conditions: **1** (0.2 mmol), isonitrile (1.0 mmol), catalyst (3 mol%), solvent (2.0 mL). [b] Isolated yield. [c] Catalyst (5 mol%).

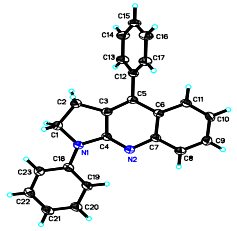
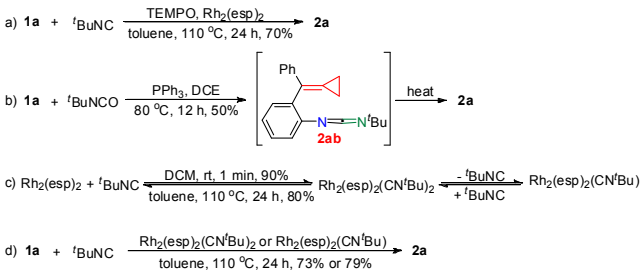


Figure 2 ORTEP drawing of **2d**.

To investigate the mechanism of this Rh^{II}-catalyzed intermolecular reaction of azide-MCPs with isonitriles, several control experiments were performed as shown in Scheme 2. Thus far, it has been already demonstrated that single electron transfer (SET) could take place in dirhodium nitrene, resulting in nitrogen radical species.[12,8e] However, the addition of TEMPO (2.0 equiv) did not inhibit the formation of **2a** (70% yield), rendering unlikely the intervention of a radical pathway

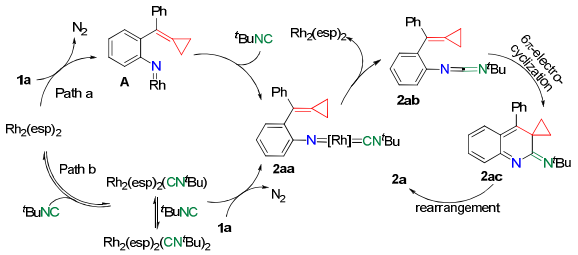


Scheme 2 Control experiments.

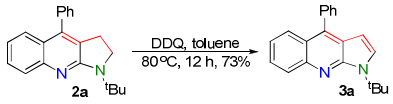
(Scheme 2, a). According to the previous report, a carbodiimide intermediate can be afforded through tandem Staudinger reduction and aza-Wittig reaction.[13] Therefore, upon treating substrate **1a** with PPh_3 and ^{t}BuNCO in DCE at 80 °C for 12 h, product **2a** was isolated in 50% yield, indicating that product **2a** might be afforded from carbodiimide intermediate **2ab** via a thermal-induced rearrangement (Scheme 2, b). $Rh_2(esp)_2$–isonitrile complexes were also investigated herein. Stirring the mixture of $Rh_2(esp)_2$ and tert-butyl isonitrile (20.0 eq) in DCM for 1 min, $Rh_2(esp)_2(CN^tBu)_2$ was isolated in 90% yield.[14] Moreover, upon heating in toluene at 110 °C for 24 h, it could be transformed back to $Rh_2(esp)_2$ in 80% yield. Interestingly, $Rh_2(esp)_2(CN^tBu)_2$ could be easily transformed to a more stable $Rh_2(esp)_2(CN^tBu)$ once exposed to the air for 24 h (Scheme 2, c).[15] Both $Rh_2(esp)_2(CN^tBu)_2$ and $Rh_2(esp)_2(CN^tBu)$ could be used as catalysts under the otherwise identical conditions, giving product **2a** in 73% and 79% yields, respectively (Scheme 2, d).

According to the above results, two plausible pathways accounting for this intermolecular cascade reaction are outlined in Scheme 3. In path a, the denitrogenation process gives Rh-nitrene **A**, which reacts with ^{t}BuNC to afford the key intermediate **2aa**. Alternatively (path b), the reaction of $Rh_2(esp)_2$ with ^{t}BuNC gives $Rh_2(esp)_2(CN^tBu)_2$, which is not very stable and decomposes to $Rh_2(esp)_2(CN^tBu)$ at the same time. Upon regeneration of the catalyst, key intermediate **2aa** also can be afforded from azide-MCP **1a**. After the regeneration of rhodium catalysts, **2aa** is transformed to carbodiimide **2ab**. A consecutive 6π-electrocyclization occurs to afford intermediate **2ac**, which subsequently undergoes a thermal-induced rearrangement to produce product **2a**.[16]

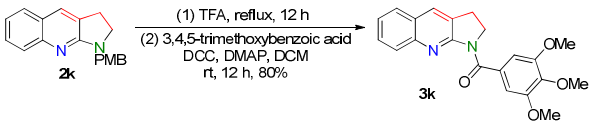
To further demonstrate the potential application of this protocol, several derivatizations of products **2** were conducted. Dehydrogenation of **2a** would provide the corresponding pyrrolo[2,3-b]quinoline **3a** (Scheme 4). After removal of PMB and further condensation with 3,4,5-trimethoxybenzoic acid,



Scheme 3 A plausible reaction mechanism.



Scheme 4 Aromatization of product **2a**.



Scheme 5 Synthesis of DU-145 cell inhibitor.

product **2k** could be converted to DU-145 cell inhibitor **3k** (Scheme 5), which may be used as novel anti-cancer agents in prostate cancer therapy (Figure 1).[5]

In summary, facile synthesis of pyrrolo[2,3-b]quinolines in moderate to good yields has been established through Rh^{II}-catalyzed intermolecular cyclization from azide-MCPs and isonitriles via carbodiimide intermediates. The product **2a** can be smoothly oxidized to the corresponding quinoline derivative. Significantly, this protocol afforded an easy access to product **3k**, which may be used as novel anti-cancer agents in prostate cancer therapy. The potential utilization and extension of the substrate scope of this synthetic methodology are currently under investigation.

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15 For more details, see the Supporting Information.

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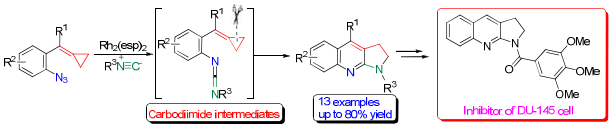
Rh(II)-Catalyzed Formation of Pyrrolo[2,3-b]quinolines from Azide-methylenecyclopropanes and Isonitriles



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