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Rh^{II}-Catalyzed [3+2] Cycloaddition of 2*H*-Azirines with *N*-Sulfonyl-1,2,3-Triazoles

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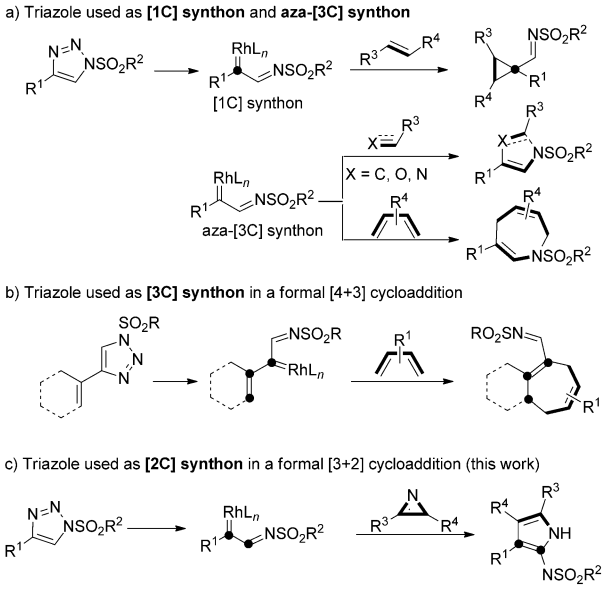
Abstract: Rh^{II}-catalyzed intermolecular [3+2] cycloaddition of 2*H*-azirines with *N*-sulfonyl-1,2,3-triazoles is disclosed, in which a series of fully functionalized pyrroles is produced via rhodium azavinyl carbene intermediates. A distinct feature of this reaction is that the azavinyl carbene serves as a [2C] equivalent, instead of as [1C] or aza-[3C] synthons, which have been reported previously in cyclopropanations and [3+*n*] cycloadditions. Moreover, this methodology has also been successfully applied in the total synthesis of URB447 as well as the formal synthesis of Atorvastatin (Lipitor).

Pyrroles and their derivatives are one of the most important classes of nitrogen-containing heterocycles with diverse biological properties and synthetic applications.[1] For example, highly functionalized pyrroles are subunits of heme, chlorophyll, bile pigments, vitamin B12, and pyrrole alkaloids derived from nature.[2] Another well-known man-made representative is Atorvastatin (Lipitor), which is used primarily for lowering blood cholesterol and for the prevention of events associated with cardiovascular disease.[3] Motivated by these significance effects, intensive investigations have been conducted to develop practical, useful, and step-economic methodologies to the pyrrole architecture.[4] Accordingly, the discovery of novel strategies for the synthesis of fully functionalized pyrroles with good functional-group tolerance through simple operation is highly desirable.

N-sulfonyl-1,2,3-triazoles, the precursors of Rh–azavinyl carbenes, have been the focus of research interest in recent years, as introduced by the leading groups of Fokin, Gevorgyan, Murakami, and Davies.[5] Since these initial studies, a variety of useful transformations have been reported.[6,7] As [1C], [3C], or aza-[3C] equivalents, azavinyl carbenes are particularly attractive for use in cyclopropanations, [3+*n*] and [4+3] cycloadditions (Scheme 1A and B) to produce cyclic derivatives, especially N-heterocycles. However, to the best of our knowledge,



Scheme 1. Cycloadditions of Rh–azavinyl carbenes with unsaturated compounds.

the use of an azavinyl carbene as a [2C] synthon in a formal cycloaddition reaction has not yet been achieved. As the major part of our research efforts in developing new methodologies for the construction of heterocycles, we previously developed the intramolecular C–H functionalization of pyrroyl-/indolyltriazoles and the tandem ring extension/intermolecular Diels–Alder cycloaddition of methylene cyclopropane tethered triazoles.[8] To continue our research in this area, we have started to develop new synthetic methods for heterocycles through azavinyl carbene chemistry. Herein, we report a novel Rh^{II}-catalyzed intermolecular [3+2] cycloaddition of 2*H*-azirines[9] with *N*-sulfonyl-1,2,3-triazoles, which serve as [2C] equivalents (Scheme 1C).

2*H*-azirines, easily derived from the corresponding ketones through the Neber reaction,[10] have been investigated intensively in the synthesis of heterocycles.[9] Notably, Park and coworkers[11] have demonstrated an elegant synthesis of pyridines by a vinyl carbene-mediated ring-opening of 2*H*-azirines, in which the vinyl carbene served as a [3C] synthon. Interestingly, in our work, upon treatment of 4-phenyl-1-tosyl-1*H*-1,2,3-triazole, **1a**, with ethyl 3-methyl-2*H*-azirine-2-carboxylate, **2a**, in the presence of a dirhodium complex, a fully substituted pyrrole derivative, **3aa**, was obtained and its structure was unambiguously determined by X-ray diffraction, confirming that

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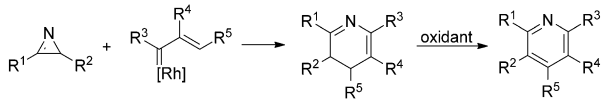
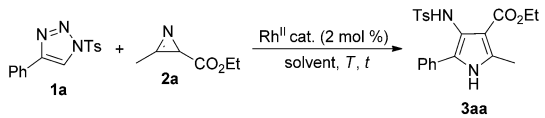


Scheme 2. Park's pyridine synthesis.

only two carbon atoms of the azavinyl carbene were incorporated into the pyrrole ring (Scheme 2).[12]

Based on our previous work, solvents usually were critical in Rh-catalyzed ring-opening reactions of triazoles;[8] therefore, solvent effect was first investigated and it was revealed that CH_2Cl_2 was the best solvent to promote the formation of **3 aa**, giving 51% yield (Table 1, entries 1–5). Next, by using CH_2Cl_2 as solvent, the performance of various rhodium complexes was investigated. Changing catalysts from the initially used $[Rh_2(Piv)_4]$ to $[Rh_2(Oct)_4]$, $[Rh_2(OAc)_4]$, or $[Rh_2(esp)_2]$ (Piv = Pivalate, Oct = Octanoate, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate), we found that **3 aa** was produced in the highest yield (56%) when $[Rh_2(esp)_2]$ was used (Table 1, entries 6, 8, and 9). Conversely, $[Rh_2(tfa)_4]$ (tfa = trifluoroacetate) showed very low catalytic activity in the reaction (Table 1, entry 7). After evaluation of the reaction temperature (Table 1, entries 10–12), it was found that the yield of **3 aa** increased to 69% if conducting the reaction at 70 °C (Table 1, entry 11). When the reaction was carried out at 60 °C, the reaction time needed to be prolonged to 48 h, affording **3 aa** in 57% yield (Table 1, entry 12).

Table 1. Optimization of the reaction conditions.[a]

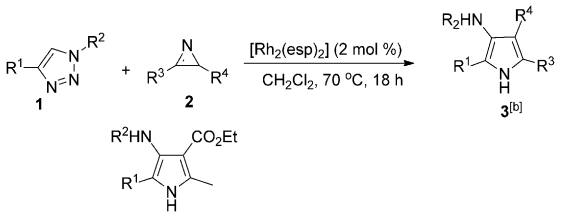


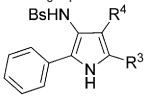
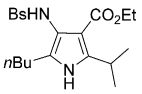
Entry	Cat.	Solvent	*T* [°C]	*t* [h]	Yield[b] [%]
1	$[Rh_2(Piv)_4]$	DCE	90	2	33
2	$[Rh_2(Piv)_4]$	toluene	90	2	25
3	$[Rh_2(Piv)_4]$	$CHCl_3$	90	2	0
4	$[Rh_2(Piv)_4]$	hexane	90	2	40
5	$[Rh_2(Piv)_4]$	CH_2Cl_2	90	2	51
6	$[Rh_2(Oct)_4]$	CH_2Cl_2	90	2	46
7	$[Rh_2(tfa)_4]$	CH_2Cl_2	90	2	trace
8	$[Rh_2(OAc)_4]$	CH_2Cl_2	90	2	47
9	$[Rh_2(esp)_4]$	CH_2Cl_2	90	2	56
10	$[Rh_2(esp)_4]$	CH_2Cl_2	80	10	59
11	$[Rh_2(esp)_4]$	CH_2Cl_2	70	18	69
12	$[Rh_2(esp)_4]$	CH_2Cl_2	60	48	57

[a] Conditions: **2a** (0.20 mmol), **1a** (0.30 mmol), Rh cat. (2 mol%), and solvent (2.0 mL) were heated in a sealed tube until consumption of **2a** was apparent by TLC. [b] Isolated yields. DCE = 1,2-dichloroethane.

With the optimized reaction conditions in hand (Table 1, entry 11), we next examined the substrate scope and limitations of this reaction by using various triazoles, **1**, and different 3-alkyl-2*H*-azirines, **2**, (Table 2). For substrates **1 b–d**, in which the nitrogen atom was protected by Bs (4-bromobenzene-1-sulfony), Ms (methanesulfonyl), and benzenesulfonyl groups, the reactions proceeded smoothly to give the corresponding products, **3 ba–3 da**, in 77–80% yields (Table 2, entries 1–3). Employing different aryl-ring-substituted (R^1) triazoles, **1 e–1 h**, as substrates, the reactions went on smoothly to deliver the desired products, **3 ea–3 ha**, in 65–90% yields, and the electronic properties of the substituents did not have significant impact on the reaction outcomes (Table 2, entries 4–7). When a triazole substituted with a *n*-butyl group (R^1) was employed as the substrate, the corresponding pyrrole derivative, **3 ic**, was obtained in low yield, because another byproduct, **3 i′**, was also formed in 30% yield by a carbene-induced 1,2-H shift (Table 2, entry 8).[13] Next, a series of 3-alkyl-2*H*-azirines, **2**, were also examined, and we found that different substituents at R^3 (methyl, ethyl, or isopropyl groups) and R^4 (ester, carbonyl, or aryl groups) were all well tolerated under the standard reaction conditions and the desired products, **3 bb–3 bg**, were obtained in 60–92% yields (Table 2, entries 9–14). R^3 could also be a phenyl substituent, instead of alkyl groups. For instance, when 3-phenyl-2*H*-azirines with ethyl ester, H, or methyl substituents (R^4) were employed as substrates, the reactions all proceeded smoothly to yield pyrrole derivatives, **3 bl–3 bn**, in

Table 2. Scope of the Rh^{II}-catalyzed tandem rearrangement.[a]



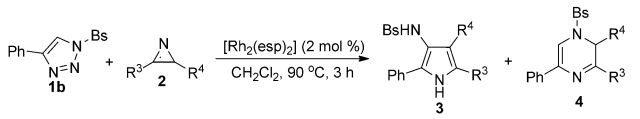
Entry	R^1	R^2	Product	Yield [%]
1	C_6H_5	Bs	**3ba**	80
2	C_6H_5	Ms	**3ca**	77
3	C_6H_5	SO_2Ph	**3da**	78
4	4-Me-C_6H_4	Bs	**3ea**	90
5	3-Me-C_6H_4	Bs	**3fa**	73
6	4-MeO-C_6H_4	Bs	**3ga**	74
7	4-F-C_6H_4	Bs	**3ha**	65
8			**3ic**	23[c]
				
	R^3	R^4		
9	Et	CO_2Et	**3bb**	81
10	*i*Pr	CO_2Et	**3bc**	92
11	Me	CO_2tBu	**3bd**	73
12	Me	CO_2Bn	**3be**	75
13	Me	COPh	**3bf**	86
14	Me	4-Cl-C_6H_4	**3bg**	60
15	C_6H_5	CO_2Et	**3bl**	81[d]
16	C_6H_5	H	**3bm**	77[d]
17	C_6H_5	Me	**3bn**	80

[a] Conditions: **1** (0.3 mmol), **2** (0.2 mmol), $[Rh_2(esp)_2]$ (2 mol%), anhydrous CH_2Cl_2 (2.0 mL) were heated at 70 °C in a sealed tube for 18 h. [b] Isolated yields. [c] Another imine byproduct, **3i′**, derived from a carbene-induced 1,2-H shift was obtained in 30% yield. [d] The reaction was run in CH_2Cl_2 (2.0 mL) at 90 °C in a sealed tube for 3 h.

77–81% yields (Table 2, entries 15–17). In addition, the identification of **3bm** was further established by single-crystal X-ray analysis.[14]

To further evaluate the generality of this method, we synthesized several 3-aryl-2*H*-azirines and treated them with **1b** in the presence of $[Rh_2(esp)_2]$,[15] and the results are shown in Table 3. Very surprisingly, 2*H*-pyrazine derivatives, **4**, could be

Table 3. 3-Aryl-2*H*-azirines **2** variations.[a,b]

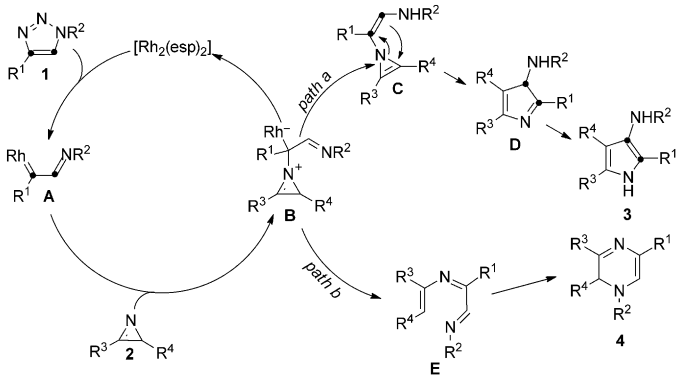


Entry	R^3	R^4	Product	Yield [%]	Product	Yield [%]
1	Ph	CO_2tBu	**3bh**	80	**4bh**	7
2	4-NO_2-C_6H_4	CO_2tBu	**3bi**	48	**4bi**	35
3	4-Br-C_6H_4	CO_2tBu	**3bj**	36	**4bj**	55
4	4-Br-C_6H_4	CO_2Et	**3bk**	81	**4bk**	12

[a] Conditions: **1** (0.3 mmol), **2** (0.2 mmol), $[Rh_2(esp)_2]$ (2 mol%), anhydrous CH_2Cl_2 (2.0 mL) were heated at 90 °C for 3 h. [b] Isolated yields.

obtained along with pyrrole derivatives, **3**. For substrates **2h**–**2j**, in which R^4 was *tert*-butyl ester and R^3 was a phenyl group substituted with Ph, *para*-NO_2, or *ortho*-Br, the reactions all produced products **3bh**–**3bj** along with **4bh**–**4bj** in high total yields (Table 3, entries 1–3). Substrate **2k**, with a less sterically bulky ethyl ester (R^4) and a *para*-Br–phenyl group (R^3), led to the formation of **3bk** and **4bk** in 81% and 12% yields, respectively (Table 3, entry 4). The structures of the pyrrole and 2*H*-pyrazine derivatives were further confirmed by X-ray diffraction analysis of **3bj**[16] and pyrazine **4bj'**, which was derived from the deprotection of **4bj**.[17,18] The electronic and steric effects observed in this reaction indicate that the electronegativity or steric hindrance of substituents in substrates, **2**, produce a combined impact on the reaction outcomes. Therefore, we hypothesize that the two reaction pathways share a common cationic intermediate, which controls the product's distribution.

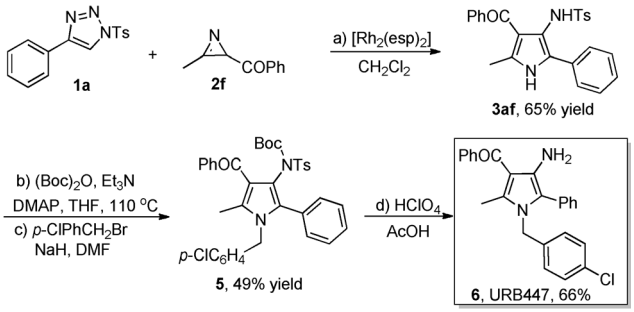
A plausible mechanism for the formation of pyrrole and 2*H*-pyrazine is outlined in Scheme 3. *N*-sulfonyltriazole **1** generates



Scheme 3. Proposed mechanism.

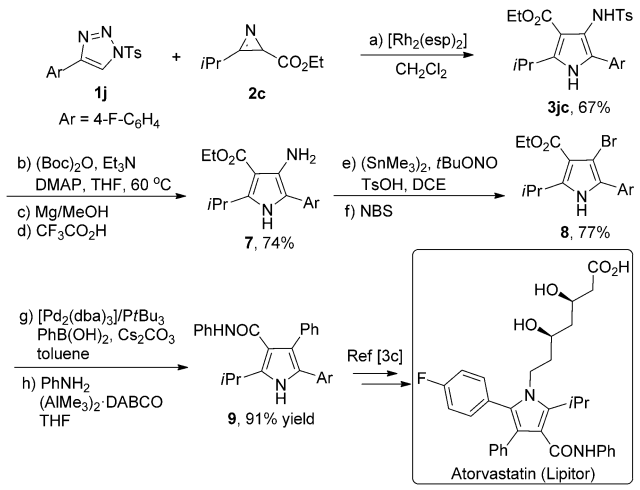
an azavinyl carbene intermediate, **A**, in the presence of the Rh^{II} catalyst. This Fisher-type carbine, **A**, readily accepts nucleophilic attack from the nitrogen atom of 2*H*-azirine, giving the key zwitterionic intermediate, **B**, which is shared by both reaction pathways. For pyrrole synthesis (path a), intermediate **B** undergoes a proton elimination and proto-demetalation to produce aza cyclopropene intermediate **C**. Following a ring expansion, intermediate **D** is obtained. Aromatization of intermediate **D** results in the final pyrrole product, **3**. On the other hand, if the reaction goes through path b, a ring-opening process of intermediate **B** takes place to produce intermediate **E**, which then delivers the final pyrazine derivatives after a 6π electrocyclization.[11] The reactivity of intermediate **B** is greatly affected by the properties of R^3 and R^4. In most cases, path a is the dominate process. However, if R^3 is electronegative or R^4 is a sterically bulky group, the azirine ring is more unstable or strained and the ring-opening process is also possible; that can account for the formation of both **3** and **4** in these reactions.

To demonstrate the synthetic utility of this Rh^{II}-catalyzed [3+2] cycloaddition, we turned our efforts to synthesizing URB447 ([4-amino-1-(4-chlorobenzyl)-2-methyl-5-phenyl-1*H*-pyrrol-3-yl](phenyl)methanone), which is a mixed CB_1 antagonist/CB_2 agonist and can be used to lower food intake and body-weight gain in mice without it entering the brain or antagonizing central CB_1-dependent responses.[19] The formal [3+2] cycloaddition of triazole **1a** and azirine **2f** afforded the fully substituted pyrrole derivative **3af**. This was followed by selective protection and then alkylation with 4-chlorobenzyl bromide to deliver intermediate **5** in 49% yield. Finally, the target molecule URB447, **6**, was synthesized by removal of the tosyl (Ts) and Boc groups in a single step upon heating **5** in $HClO_4$ and AcOH at 90 °C (Scheme 4).



Scheme 4. Total synthesis of URB447.

Additionally, the formal synthesis of Atorvastatin (Lipitor) was performed. As shown in Scheme 5, the reaction of **1j** and **2c** afforded **3jc** in 67% yield. Then, after deprotection the free amine, derivative **7** was obtained (74% yield from **3jc**). We next tried to convert the free amine group to the corresponding bromide by means of deamination[20] and bromination. It turned out to be successful and the desired bromide, **8**, was delivered in 77% yield from **7**. The following Suzuki coupling and transamidation[21] with aniline delivered 4-acylamino pyrrole derivative **9**, which is the key synthetic intermediate to the



Scheme 5. Formal synthesis of Lipitor.

target Atorvastatin (Lipitor).[3c] The ^{1}H and ^{13}C NMR spectroscopy data of the synthesized URB447 and precursor of Lipitor were in good agreement with those reported in the literature.[3b,19]

In summary, we have developed a practical synthesis of fully substituted pyrroles by means of formal [3+2] cycloaddition of *N*-sulfonyl-1,2,3-triazoles with 2*H*-azrines. This is the first example where *N*-sulfonyl-1,2,3-triazoles are used as [2C] synthons in a formal cycloaddition reaction. Notably, the potential of this novel protocol has been demonstrated by successful total synthesis of URB447 as well as the formal synthesis of Atorvastatin (Lipitor). The substrate scope is broad and a wide range of functional groups are tolerated, which gives promising usefulness to this pyrrole synthesis for the construction of other important pyrrole-containing drugs. Further potential applications and mechanistic investigations of this methodology are currently underway in our laboratory.

Acknowledgements

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Keywords: 2*H*-azirines · azavinyl carbenes · pyrroles · rhodium · triazoles

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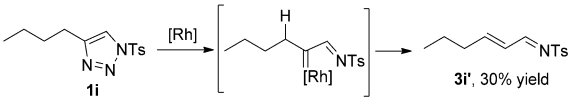
[12] CCDC-960827 (**3 aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For more details, see the Supporting Information.

[13] The carbene-induced 1,2-H shift product, **3 i′**, was formed in 30% yield together with **3 ic**;

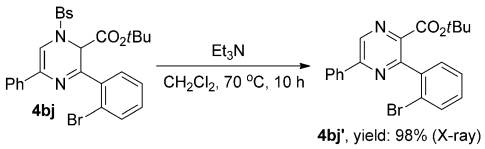


[14] CCDC-996017 (**3 bm**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For more details, see the Supporting Information.

[15] For 3-aryl-2*H*-azirines, it was found that running the reaction as 90 °C gave better results as compared to 70 °C. For details, see Table S1 in the Supporting Information.

[16] CCDC-982806 (**3 bj**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For more details, see the Supporting Information.

[17] After removal of the Bs group under basic conditions, **4 bj** was converted to pyzarine **4 bj′** in 98% yield;



[18] CCDC-988488 (**4 bj′**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For more details, see the Supporting Information.

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Synthetic Methods

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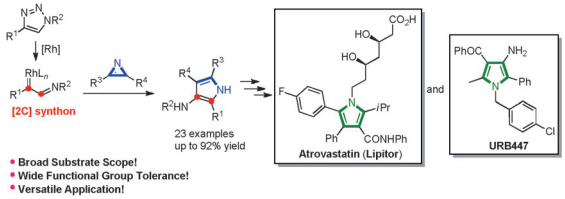
Rh^{II}-Catalyzed [3+2] Cycloaddition of 2*H*-Azirines with *N*-Sulfonyl-1,2,3-Triazoles



Fully functional: A novel Rh^{II}-catalyzed intermolecular [3+2] cycloaddition of 2*H*-azrines with *N*-sulfonyl-1,2,3-triazoles is disclosed. The reaction, in which aza-vinyl carbene serves as a [2C] equivalent, produces a series of fully functionalized pyrroles via rhodium azavinyl carbene intermediates.