Nitrogen Heterocycles

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Rhodium(II)-Catalyzed Intramolecular Cycloisomerizations of Methylenecyclopropanes with *N*-Sulfonyl 1,2,3-Triazoles**

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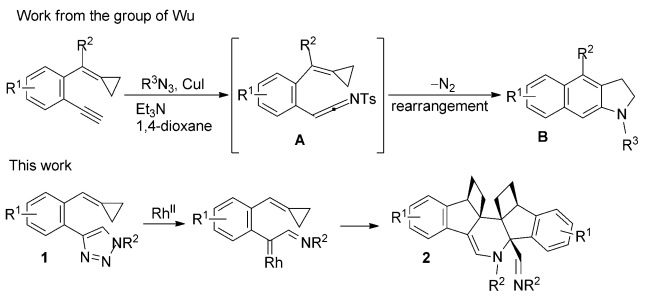
Abstract: *A novel rhodium(II)-catalyzed tandem cycloisomerization of methylenecyclopropanes (MCPs) with N-sulfonyl 1,2,3-triazoles is disclosed. The reaction produces a series of highly functionalized polycyclic N heterocycles via a rhodium imino carbene intermediate. A distinct feature of this divergent synthesis is that different types of substrates control the reaction pathways. Moreover, several interesting transformations of these products to construct diazabicyclo[3.2.1]octane derivatives are also reported.*

Methylenecyclopropanes (MCPs), as highly strained but readily accessible molecules, are important building blocks in organic synthesis. In the presence of transition metals or Lewis acids, MCPs can undergo a variety of ring-opening reactions, thus giving efficient access to enhanced molecular complexity.[1,2] As an important research branch, transition-metal-catalyzed intermolecular reactions of carbenes or nitrenes with MCPs have drawn great attention during the last decade.[3] For example, Kuznetsova and co-workers found that diazo compounds could undergo cyclopropanation with MCPs in the presence of $[Rh_2(OAc)_4]$ to give polyspirocyclic cyclopropanes in good yields.[3a] The groups of Meijere and Kamikawa also reported [4+1] and [3+1+1] cycloadditions, respectively, of MCPs with Fischer carbenes to generate cyclopentanone derivatives.[3b,c] Moreover, Yu and co-workers first reported intermolecular reaction of MCPs with *N*-aminophthalimide (precursor of nitrene) to give ring-expansion products.[3d] Later, we also disclosed similar transformations of MCPs with other nitrenes.[3e,f] Surprisingly, although intermolecular versions of such reactions have been studied for years, examples of the intramolecular reaction of the MCP moiety with metal carbenes are very rare.

N-sulfonyl-1,2,3-triazoles, which can be easily prepared from copper(I)-catalyzed azide–alkyne cycloadditions (CuAAC) have recently received much attention.[4] In general, they are used as precursors of α-imino metal carbenes which can trigger many types of useful transformations.[5] For instance, transannulation of *N*-sulfonyl-1,2,3-triazoles with unsaturated compounds such as nitriles, alkynes, allenes, isocyanates, furans, aldehydes, imines, and indoles produced a series of useful N heterocycles,[6] which are the most important class of compounds in the pharmaceutical and agrochemical industries.[7] In addition, these α-imino metal carbenes can also undergo cyclopropanation,[8] C–H insertion,[9] O–H or N–H insertion,[10] and arylation with boronic acids.[11] Recently, rhodium(II)-catalyzed intramolecular reactions of *N*-sulfonyl-1,2,3-triazoles have aroused the interest of chemists and become increasingly popular.[12] For example, the groups of Murakami and Fokin independently reported the rhodium(II)-catalyzed denitrogenative rearrangement of 1-(*N*-sulfonyl-triazol-4-yl)alkanols.[12a,b] Another example was reported by Davies and co-workers. They disclosed an intramolecular rhodium(II)-catalyzed cyclization of 4-alkenyl-1-sulfonyl-1,2,3-triazoles to 2,3-fused pyrroles and substituted indoles.[12c] The rapid development of the chemistry of *N*-sulfonyl-1,2,3-triazoles motivated us to link these novel azavinyl carbenes with methylenecyclopropanes.

In 2011, the group of Wu discovered a novel cascade reaction of 2-ethynylaryl methylenecyclopropane with sulfonylazide catalyzed by CuI to generate fused indolines (Scheme 1).[13] It is believed that the ketenimine **A** is the key intermediate. However, if the *N*-sulfonyl-1,2,3-triazole moiety is considered a precursor of the α-imino carbene, we reasoned that the reaction pathway should be quite different and interesting. In fact, at the beginning of this research, we found that *N*-sulfonyl-triazole MCPs (**1**) could undergo a tandem cycloisomerization/aza-Diels–Alder process, thus



Scheme 1. Formation of N-heterocyclic compounds from 2-ethynylaryl MCPs and *N*-sulfonyl-triazole MCPs. Ts = 4-toluenesulfonyl.

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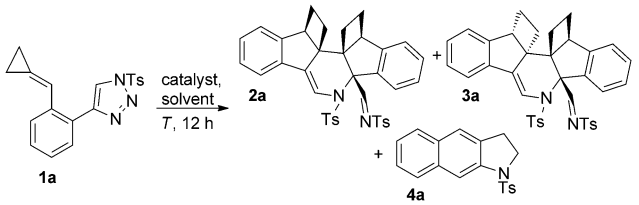
affording the polycyclic N-heterocycle **2** (Scheme 1). The 1,2-diamino-containing **2** exists in many medicinally and biologically important molecules such as biotin,[14b] balanol,[14c] and oxaliplatin.[14d] In addition, vicinal diamines and their derivatives are widely used as ligands in transition-metal catalysis.[14] In contrast, the cyclobutane moieties in **2** can be very useful building blocks as they appear in many natural products[15] such as dictazole,[15c] sceptrin,[15d] and piperarborenines.[15e] Moreover, the four-membered-ring usually gives the molecule special bioactivities. For example, the cyclobutane pyrimidine dimer (CPD) interferes with base pairing during DNA replication, thus leading to mutations.[16] Given these facts, herein, we report our preliminary results on this novel protocol to construct the corresponding products **2**.

We initially investigated the cascade reaction of 1-(cyclopropylidenemethyl)-2-(1-tosyl-1,2,3-triazol-4-yl)benzene (**1a**) using a variety of the rhodium(II) catalysts, solvents, and temperatures (Table 1). The reaction of **1a** catalyzed by $[Rh_2(OAc)_4]$ in 1,2-dichloroethane (DCE) at 80 °C gave the product **4a** (reported by Wu) in 56% yield (Table 1, entry 1).[13] By changing catalysts to $[Rh_2(esp)_2]$, $[Rh_2(oct)_4]$, and $[Rh_2(Piv)_4]$ a pair of diastereoisomers, **2a** and **3a**, were obtained simultaneously (Table 1, entries 2–4). $[Rh_2(Piv)_4]$ was the best catalyst in this transformation and **2a** could be obtained in 61% yield together with **3a** in 21% yield. Their structures have been unambiguously determined by X-ray diffraction.[17] By decreasing the reaction temperature to 25 °C, no reaction took place (Table 1, entry 5). Carrying out the reaction at 60 °C afforded **2a** and **3a** in 45 and 20% yield, respectively, (Table 1, entry 6). When the reaction was conducted at 100 °C or 120 °C in 1,1,2,2-tetrachloroethane (TCE), **2a** and **4a** were obtained (at 100 °C: 50 and 20% yield, respectively; at 120 °C: 46 and 28% yields, respectively). However, **3a** was not observed, thus indicating that **3a** might be converted into **2a** at higher temperature (Table 1, entries 7 and 8). By changing the solvent to 1,4-dioxane, **4a** was isolated as the sole product, presumably because of the coordinative property of the oxygen atom in 1,4-dioxane (Table 1, entry 9). To our delight, treatment of **1a** in cyclohexane in a sealed tube at 120 °C afforded **2a** in 80% yield (Table 1, entry 10). Furthermore, carrying out the reaction at 110 °C in toluene led to the formation of **2a** in 86% yield (Table 1, entry 11). In the absence of the rhodium(II) catalyst, **4a** was isolated in 80% yield as the sole product from a thermally induced rearrangement (Table 1, entry 12).

With the best reaction conditions in hand, we next examined the substrate scope of this reaction and the results are shown in Table 2. For the substrates **1b–d**, the reactions proceeded smoothly to furnish the desired products **2b–d** in 74–81% yields (Table 2, entries 1–3). In addition, in the cases of substrates **1e–i**, the reactions proceeded efficiently to give the products **2e–i** in 71–83% yields (Table 2, entries 4–8). These results suggest that the electronic property of the aromatic ring does not have a significant impact on the reaction outcome. With two MeO groups at the 4- and 5-positions on the ring, the reaction still proceeded efficiently to afford **2j** in 70% yield (Table 2, entry 9). As for substrates **1k** and **1l**, in which R^1 = 6-F or 3-F, the reaction proceeded smoothly to furnish **2k** (60%) and **2l** (73%), respectively (Table 2, entries 10 and 11). Other sulfonyl groups such as Bs, Tris, or Ms were also tested, thus giving the corresponding products **2m–o** in 67–81% yields (Table 2, entries 12–14).

To further evaluate the generality of this method, the thiophene- or cycloalkane-tethered MCPs **1p** and **1q** were

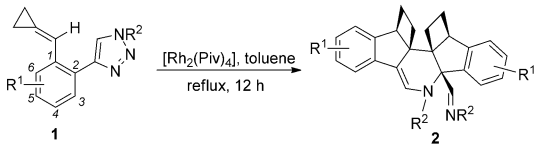
Table 1: Optimization of the reaction conditions of the rhodium(II)-catalyzed tandem reaction of **1a**.



Entry[a]	Catalyst	Solvent	T [°C]	Yield [%][b]		
				2a	3a	4a
1	$[Rh_2(OAc)_4]$	DCE	80	–	–	56
2	$[Rh_2(esp)_2]$	DCE	80	37	9	–
3	$[Rh_2(oct)_4]$	DCE	80	30	12	–
4	$[Rh_2(Piv)_4]$	DCE	80	61	21	–
5[c]	$[Rh_2(Piv)_4]$	DCE	25	–	–	–
6	$[Rh_2(Piv)_4]$	DCE	60	45	20	–
7	$[Rh_2(Piv)_4]$	TCE	100	50	–	20
8	$[Rh_2(Piv)_4]$	TCE	120	46	–	28
9	$[Rh_2(Piv)_4]$	1,4-dioxane	100	–	–	65
10	$[Rh_2(Piv)_4]$	cyclohexane	120	80	–	–
11	$[Rh_2(Piv)_4]$	toluene	110	86	–	–
12	–	toluene	110	–	–	80

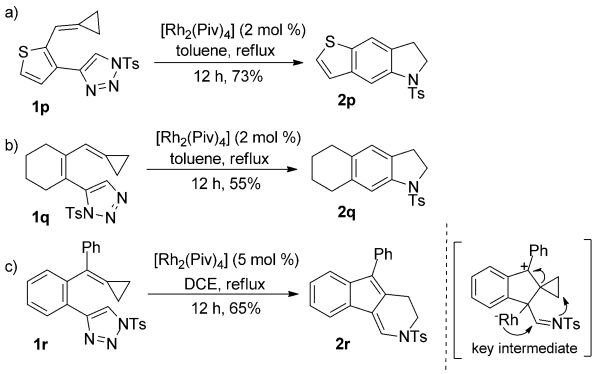
[a] Reaction conditions: **1a** (0.1 mmol), catalyst (2 mol%), solvent (1.0 mL). [b] Yield of isolated product. [c] The reaction did not take place and the starting material **1a** was recovered. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, oct = octanoate, Piv = pivalate.

Table 2: Substrate scope of rhodium-catalyzed tandem reaction of *N*-sulfonyl-triazole MCPs **1**.



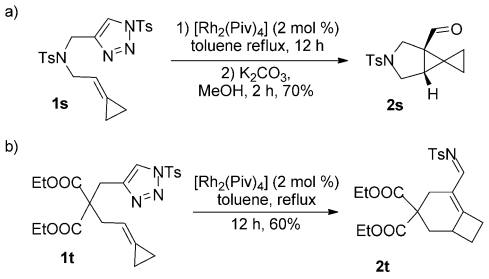
Entry[a]	Substrate	R^1	R^2	2	Yield [%][b]
1	**1b**	4-Me	Ts	**2b**	74
2	**1c**	4-F	Ts	**2c**	74
3	**1d**	4-Cl	Ts	**2d**	81
4	**1e**	5-F	Ts	**2e**	76
5	**1f**	5-Cl	Ts	**2f**	83
6	**1g**	5-CF_3	Ts	**2g**	79
7	**1h**	5-Me	Ts	**2h**	77
8	**1i**	5-OMe	Ts	**2i**	71
9	**1j**	4-OMe, 5-OMe	Ts	**2j**	70
10[c]	**1k**	6-F	Ts	**2k**	73
11[c]	**1l**	3-F	Ts	**2l**	60
12	**1m**	H	Bs	**2m**	67
13[d]	**1n**	H	Tris	**2n**	74
14	**1o**	H	Ms	**2o**	81

[a] Reaction conditions: **1** (0.1 mmol), $[Rh_2(piv)_4]$ (2 mol%), solvent (1.0 mL). [b] Yield of isolated product. [c] The reaction mixtures were heated for 24 h. [d] Tris = 2,4,6-(iPr)$_3$C$_6$H$_2$SO$_2$. Bs = bromobenzenesulfonyl, Ms = methanesulfonyl, Tris = 2,4,6-triisopropylbenzenesulfonyl.



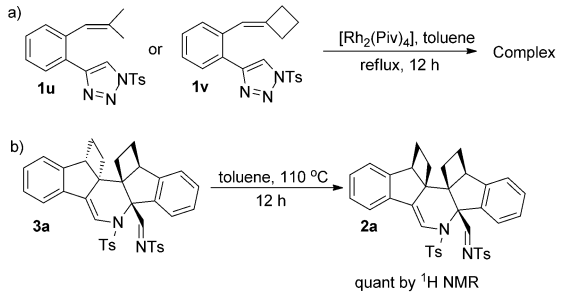
Scheme 2. Further substrate scope study.

synthesized and treated under the standard reaction conditions, thus affording the corresponding fused indolines **2p** (73%) and **2q** (55%; Scheme 2a,b). It is possible that thermally induced rearrangements of these two special substrates are faster than the generation of their rhodium(II) azavinyl carbene intermediates. As for substrate **1r**, which has a phenyl substituent on the MCP moiety, formal [3+3] cyclization took place to give **2r** in 65% yield (Scheme 2c). When the N-tethered MCP **1s** was used as a substrate, the tricyclic aldehyde **2s** was formed in 70% yield after cyclopropanation and detosylation (Scheme 3a). Interestingly, the reaction of the substrate **1t** delivered the *trans*-α,β-unsaturated imine product **2t** in 60% yield (Scheme 3b).[18] The structures of **2r**, **2s**, and **2t** have been unambiguously determined by X-ray diffraction.[19] These results have demonstrated the divergent reaction pathways of MCPs with azavinyl carbenes.



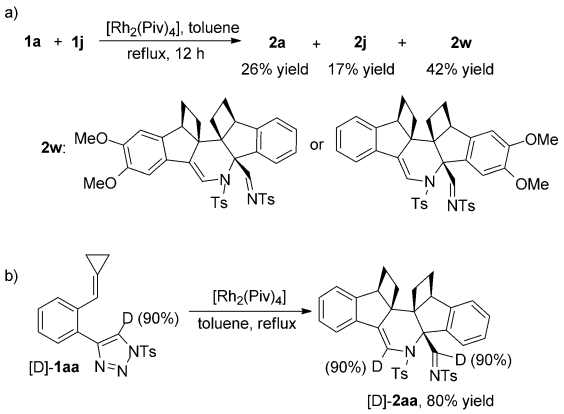
Scheme 3. Investigations of alkyl-substituted substrates.

To investigate the mechanism of this rhodium(II)-catalyzed tandem reaction, several control experiments were performed (Schemes 4 and 5). The substrates **1u** and **1v**, which have no cyclopropane moiety, could not be converted into the desired products under the standard reaction conditions, thus indicating that the strained small ring is essential in this rhodium(II)-catalyzed tandem reaction (Scheme 4a). Upon heating in toluene at 110 °C overnight, **3a**, the diastereoisomer of **2a**, could be converted into **2a** quantitatively, thus indicating that retro-Diels–Alder reaction may occur in this cascade reaction (Scheme 4b). Exposure of **1a** and **1j** to the reaction conditions produced not only



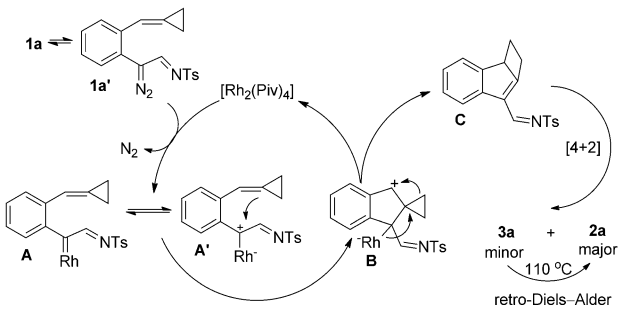
Scheme 4. Control experiments for **1u**, **1v**, and **3a**.

products **2a** (26% yield) and **2j** (17% yield), but also the crossover cycloaddition product **2w** in 42% yield, thus confirming the intermolecular Diels–Alder reaction (Scheme 5a). Furthermore, we also performed a deuterium-labeling experiment to show that hydrogen migration does not exist for this tandem reaction (Scheme 5b).



Scheme 5. Crossover deuterium-labeling experiments.

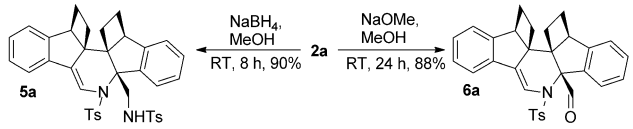
Based on the above results and the previously reported literature, a plausible mechanism for this reaction is outlined in Scheme 6. The *N*-sulfonyltriazole **1a** exists in equilibrium with its diazoimine tautomer **1a′**, which can be efficiently intercepted by a transition-metal catalyst to give rise to the highly reactive rhodium(II) azavinyl carbene **A**. The intermediate **A** exists in equilibrium with its diazoimine tautomer **A′**, and undergoes an electrophilic attack from the MCP to



Scheme 6. A plausible reaction mechanism.

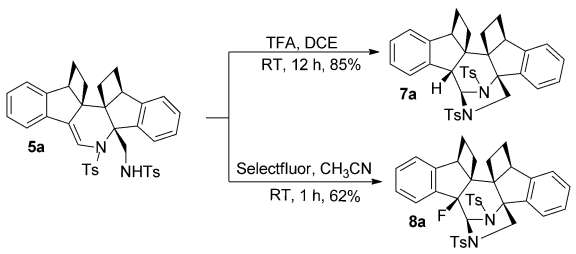
furnish the intermediate **B**. Subsequent ring expansion and elimination of the rhodium(II) catalyst generates the α,β-unsaturated imine intermediate **C**, which is very reactive and induces an intermolecular aza-Diels–Alder reaction to give polycyclic the N-heterocycles **2a** and **3a**. When the product mixture is heated at 110 °C, the thermodynamically more stable product **2a** can be isolated as the sole product because of the retro-Diels–Alder reaction process. For the synthesis of **2r**, a similar reaction pathway may take place via the key intermediate pictured in Scheme 2c. The formal [3+3] cyclization is more favorable, probably because of the steric hindrance of the phenyl group on MCP. Moreover, similar reaction mechanisms for the formation of **2s** and **2t** are shown in the Supporting Information.

The imino group of the polycyclic N heterocycles could be easily converted into an amine and aldehyde upon reduction and hydrolysis, respectively (Scheme 7). As a result, the corresponding amine **5a** and aldehyde **6a** were obtained in 90 and 88% yields, respectively.

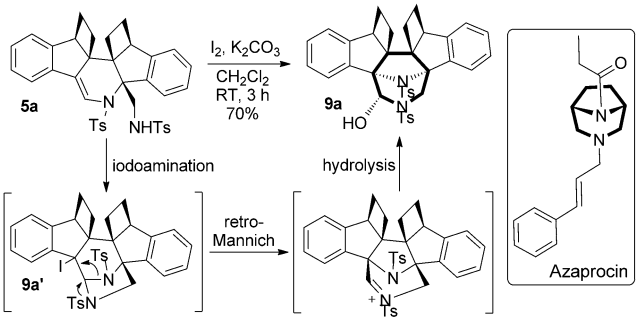


Scheme 7. Transformation of compound **2a** into **5a** and **6a**.

Further transformations of the polycyclic sulfonamide **5a** were also conducted. In the presence of TFA and selectfluor, **5a** underwent hydroamination and fluoroamination, respectively, thus giving the corresponding 2,8-diazabicyclo-[3.2.1]octane derivatives **7a** (85%) and **8a** (62%; Scheme 8). To our delight, upon treatment of **5a** with I_2 and K_2CO_3, the 3,8-diazabicyclo[3.2.1]octane derivative **9a** was obtained in 70% yield (Scheme 9). This interesting reaction pathway may contain a cascade iodoamination, retro-Mannich reaction,[20] and hydrolysis. Significantly, diazabicyclo-[3.2.1]octanes, especially 3,8-diazabicyclo[3.2.1]octane derivatives, usually have valuable biological properties.[21] For example, Azaprocin is an opioid analgesic with approximately ten times the potency of morphine, and a fast onset and short duration of action.[21a,b] Therefore, the compounds **7a**, **8a**, and **9a** are all potential drug candidates. Considering that the synthetic methods to these diazabicyclo[3.2.1]octane derivatives are extremely limited, our synthetic methodology offers



Scheme 8. Transformation of compound **5a** into **7a** and **8a**. TFA = trifluoroacetic acid.



Scheme 9. Transformation of compound **5a** into **9a**.

an easier access to these compounds. Moreover, the structures of **7a** and **9a** have been all unambiguously determined by X-ray diffraction.[22]

In summary, several intramolecular tandem reactions of MCPs with rhodium(II) azavinyl carbenes have been realized. Different reaction pathways depending on different types of substrates have been well investigated. The mechanisms have been also elucidated by performing control and deuterium-labeling experiments. A series of interesting annulations of **5a** to structurally more complex polycyclic N heterocycles demonstrates the versatile utilization of this methodology to give efficient access to enhanced molecular complexity. The potential application and extension of the substrate scope of this synthetic methodology are currently underway in our laboratory.

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