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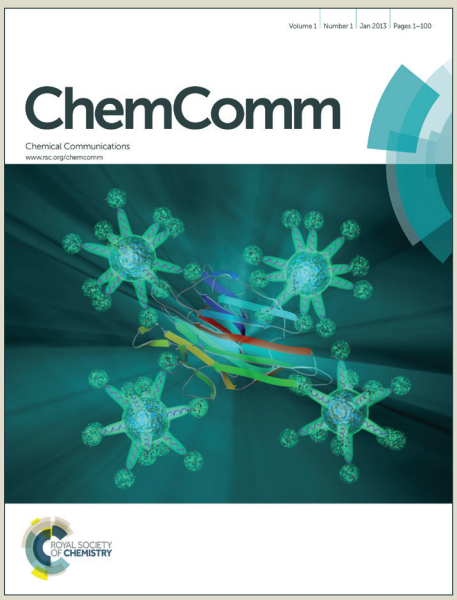

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ARTICLE TYPE

Unprecedented Synthesis of Aza-Bridged Benzodioxepine Derivatives using a Tandem Rh(II)-Catalyzed 1,3-Rearrangement/[3+2] Cycloaddition of Carbonyltriazoles

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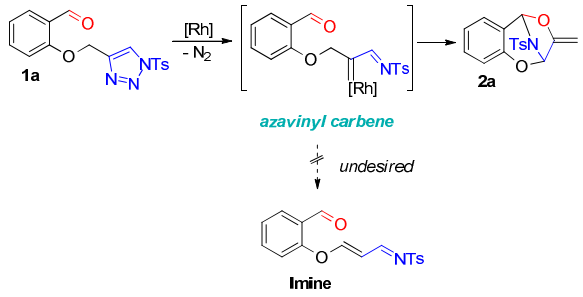
Rh(II)-catalyzed novel tandem intramolecular cycloisomerizations of aldehydes or ketones with 1-sulfonyl 1,2,3-triazoles have been disclosed, providing a facile protocol to access a series of functionalized aza-bridged benzodioxepine heterocycles.

Transition metal catalyzed ring-opening reaction of 1-sulfonyl 1,2,3-triazoles have immerged as a powerful tool that has been used widely in organic synthesis in recent years.[1] As demonstrated by Fokin, Gevorgyan, Murakami and Davies, the *in situ* formed Rh-azavinyl carbenes derived from 1-sulfonyl-1,2,3-triazoles,[2] can be used in numerous useful transformations, including cyclopropanation or rearrangement with unsaturated double bonds,[3] transannulations,[4] X-H (X = heteroatoms) bond insertions,[5] C-H functionalizations[6] and carbene induced 1,2-migration or other reactions.[7] Most strikingly, the construction of a variety of novel N-containing heterocycles, that are otherwise difficult to be established using traditional methods, can be easily accomplished *via* this Rh-catalyzed ring-opening process.[1] As part of our ongoing research interest in design of new methodologies for synthesis of heterocycles, we have developed the C-H functionalization of pyrroyl-/indolyltriazoles[6b] as well as the intramolecular rearrangement of methylene cyclopropane tethered triazoles,[7e] both through the key azavinyl carbene intermediates. Encouraged by the achievements contributed by others and our group, we envisaged that an intramolecular annulation reaction could take place between aldehyde/ketone tethered 1-sulfonyl 1,2,3-triazoles. Therefore, substrate **1a**, which can be easily prepared from the CuAAC[8] reaction of 2-(prop-2-yn-1-yloxy)benzaldehyde, was synthesized and treated in the presence of a dirhodium catalyst. To our delight and surprise, the reaction proceeded smoothly, giving an unprecedented 8-aza bridged benzodioxepine derivative **2a**, which was unambiguously determined by X-ray diffraction, rather than the undesired imine product (Scheme 1).[9] On the basis of the obtained structure, it is easy to see that an rearrangement takes place, revealing that the azavinyl carbene intermediate may undergo a cascade reaction process such as a C-O bond cleavage and the subsequent recyclization. Herein, we wish to report a novel intramolecular formal [3+2] cycloaddition of carbonyltriazoles, affording an easy access to 8-aza bridged benzodioxepines.

Scheme 1. Unprecedented Synthesis of Aza-Bridged Benzodioxepines.



Our initial work started with the investigation of the optimized reaction conditions using **1a** as the model substrate. As can be seen from Table 1, when the reaction was catalyzed by $Rh_2(Piv)_4$ (2 mol%) in DCE (1,2-dichloroethane) for 3 h at different temperature, the corresponding product **2a** was obtained in only 20-32% yields (Table 1, entries 1-3). Changing solvent to toluene and performing the reaction at 70 °C, 110 °C and 120 °C, the yields of **2a** increased from 37% to 64% (Table 1, entries 4-6). It was found that DCM (dichloromethane) was better than DCE and toluene as the solvent for this reaction, delivering **2a** in 75% yield (Table 1, entry 7). Prolonging the reaction time to 4 h, the yield of **2a** increased to 80% yield (Table 1, entry 8). However, increasing the loadings of $Rh_2(Piv)_4$ catalyst did not benefit the formation of **2a** (Table 1, entries 9 and 10). Other rhodium carboxylate complexes such as $Rh_2(OAc)_4$, $Rh_2(esp)_2$, and $Rh_2(Oct)_4$ were also employed as the catalysts but turned out to be less effective than $Rh_2(Piv)_4$ (Table 1, entries 11-13). When the reaction was conducted at 70 °C for 5 h in DCM using $Rh_2(Piv)_4$ as catalyst, the reaction gave the corresponding product

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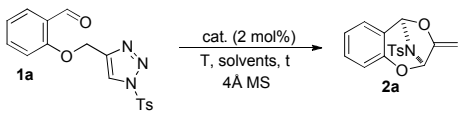
2a in 55% yield (Table 1, entry 14). Other Rh(I) and Rh(III) complexes, such as $[Rh(CO)_2Cl]_2$ and $[Cp^*RhCl_2]_2$, were also tested, giving **2a** in only 4% and 15% yields, respectively (Table 1, entries 15 and 16). In addition, the reaction did not take place in the absence of catalyst under otherwise identical standard reaction conditions (Table 1, entry 17). Notably, upon conducting the reaction at gram scale, **2a** could be still produced in 78% yield (Table 1, entry 8).

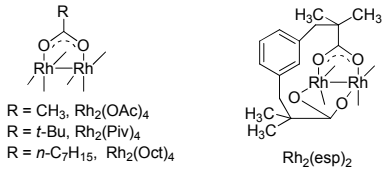
Table 1. Optimization of the Reaction Conditions of Rhodium-Catalyzed Tandem Reaction of **1a**



entry	cat.	T (°C)	solvent	time	yield (%)[b] 2
1	$Rh_2(Piv)_4$	60	DCE	3 h	32
2	$Rh_2(Piv)_4$	80	DCE	3 h	20
3	$Rh_2(Piv)_4$	90	DCE	3 h	30
4	$Rh_2(Piv)_4$	70	Toluene	3 h	37
5	$Rh_2(Piv)_4$	110	Toluene	3 h	60
6	$Rh_2(Piv)_4$	120	Toluene	3 h	64
7	$Rh_2(Piv)_4$	90	DCM	3 h	75
8	**$Rh_2(Piv)_4$**	**90**	**DCM**	**4 h**	**80** (78)[c]
9	$Rh_2(Piv)_4$[d]	90	DCM	4 h	59
10	$Rh_2(Piv)_4$[e]	90	DCM	4 h	58
11	$Rh_2(OAc)_4$	90	DCM	4 h	61
12	$Rh_2(esp)_2$	90	DCM	4 h	59
13	$Rh_2(Oct)_4$	90	DCM	4 h	61
14	$Rh_2(Piv)_4$	70	DCM	5 h	55
15	$[Rh(CO)_2Cl]_2$	90	DCM	4 h	15[f]
16	$[Cp^*RhCl_2]_2$	90	DCM	4 h	4[f]
17	-[g]	90	DCM	4 h	0[h]

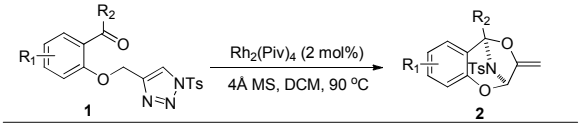
[a] Reaction conditions: **1a** (0.2 mmol), Rh cat. (2 mol%) and 4Å MS (30 mg) were stirred in 2 mL of solvent. [b] Yields of isolated product. [c] 3 mmol scale, 1.07 g of **1a**, **2a** (770 mg, 78%). [d] Catalyst loading was 3 mol%. [e] Catalyst loading was 5 mol%. [f] NMR spectroscopic yield. [g] The reaction was conducted without catalyst. [h] No reaction takes place.

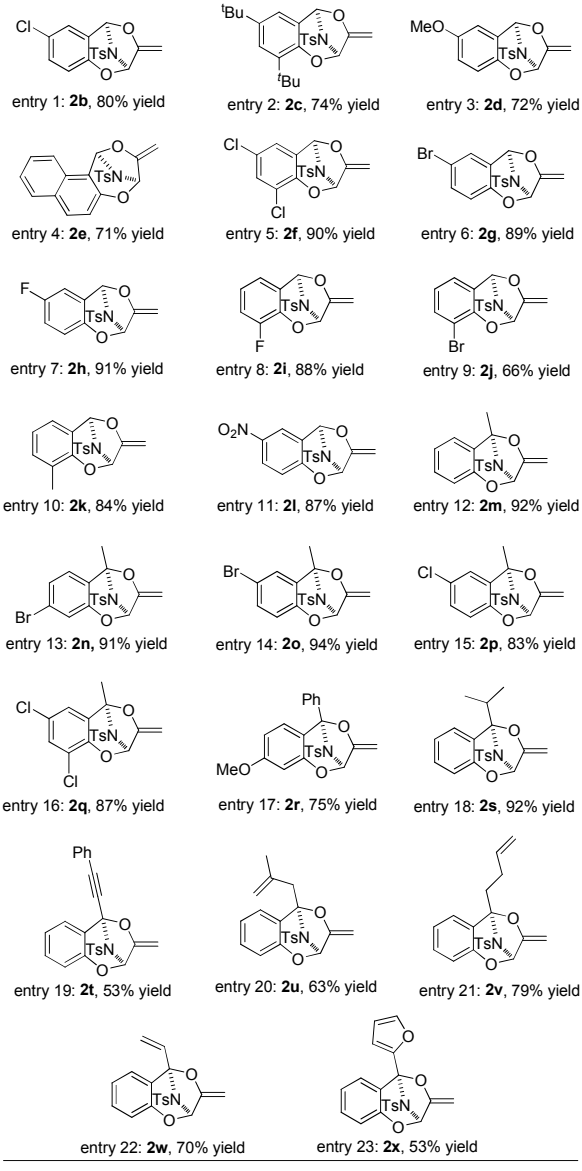
Rhodium(II) carboxylate catalysts employed in this study.



With the optimized reaction conditions in hand (Table 1, entry 8), we next turned our effort to examine the substrate scope and limitation of this method and the results are summarized in Table 2. As for aldehyde substrates **1b**-**1l**, the reactions proceeded smoothly to give the corresponding 8-azo bridged benzodioxepines **2b**-**2l** in moderate to excellent yields (Table 2, entries 1-11). The electronic properties of the substituents on the benzene ring did not have significant influence on the reaction outcomes, even for strongly electron-withdrawing F and NO_2 groups (Table 2, entries 7-8 and 11). As for ketone substrates **1m**-**1x**, a variety of functional groups (R^2) such as alkyl, alkenyl, phenyl, alkyne or furyl groups were all compatible very well under the standard reaction conditions, delivering the corresponding products **2m**-**2x** in 53-94% yields (Table 2, entries 12-23), indicating that our method has broad functional group tolerance.

Table 2. Substrate Scope of Rhodium-Catalyzed Tandem Reaction of Carbonlytriazoles **1**



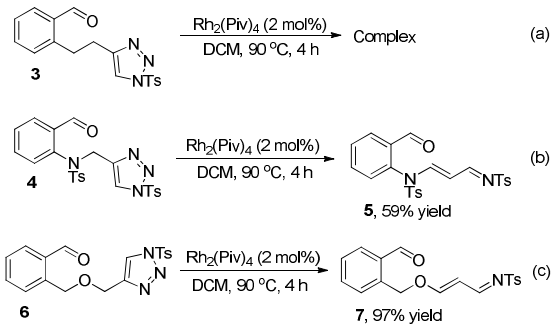


[a] Reaction conditions: 0.2 mmol of **1**, 2 mol% of $Rh_2(Piv)_4$ and 4Å MS (30 mg) were stirred in dry DCM in a 10 mL of sealed tube. [b] Yields of isolated products.

To clarify the reaction mechanism, several control experiments were conducted. When triazole **3** with a carbon tether was treated with $Rh_2(Piv)_4$ (2 mol%) under the standard reaction conditions, the reaction gave complex product mixtures (Scheme 2, a); While substrate **4** with a NTs tether readily underwent a 1,2-H shift to give the corresponding imine product **5** through a β-H elimination (Scheme 2, b); Upon treatment of substrate **6** with a longer

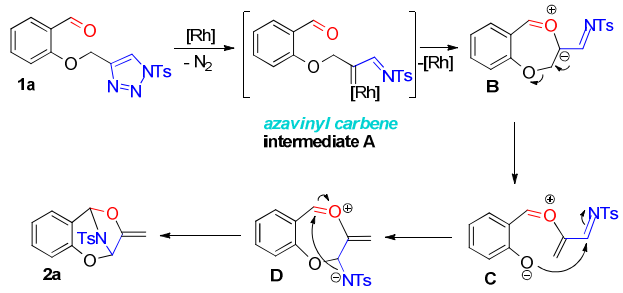
carbon chain also resulted in the formation of the imine product **7** in 97% yield under identical conditions (Scheme 2, c).

Scheme 2. Control experiments



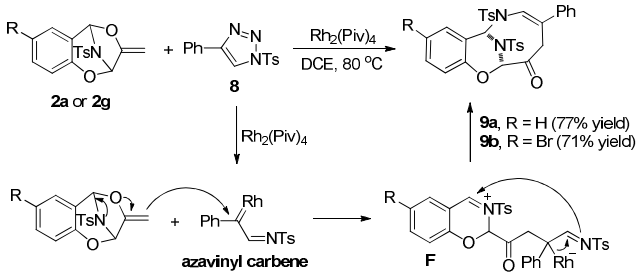
Based on the control experiments, a plausible mechanism for this reaction is outlined in Scheme 3 using **1a** as a model. Upon treating with Rh(II) catalyst, azavinyl carbene intermediate **A** is formed, which undergoes an intramolecular nucleophilic attack by the carbonyl group to give intermediate **B**. The C-O bond is cleaved to give intermediate **C** perhaps due to that the newly generated anion can be stabilized by the aromatic ring. Intermediate **C** can afford another zwitterionic intermediate **D** through 1,2-addition, which undergoes recyclization to produce the corresponding product **2a**. This formal [3+2] cycloaddition is a stepwise process. This interesting late stage cascade process is the first example in the aza-vinyl Rh-carbene chemistry.

Scheme 3. Proposed Mechanism for the Synthesis of **2**.



Considering that an exocyclic double bond was contained in product **2**, several useful transformations were conducted. Upon treatment of **2a** or **2g** with 4-phenyl-1-tosyl 1,2,3-triazole **8** and $Rh_2(Piv)_4$, a ten-membered ring system was constructed, affording the corresponding 2,8-epiminobenzo[b][1,5]oxazecin derivatives **9a** or **9b** in 77% and 71% yields, respectively (Scheme 3). Their structures have been unambiguously determined by X-ray diffraction of **9a** (Figure 1).[10] This interesting reaction may proceed through a formal [7+3] cycloaddition of **2** with Rh(II) azavinyl carbene intermediate. First, the carbene intermediate accepts a nucleophilic attack from **2** to give a zwitterionic intermediate **F**, and then, the Rh-species initiates another nucleophilic attack to deliver the product **9** via a ring-closing reaction (Scheme 4).

Scheme 4. Synthetic application for the synthesis of **9**.



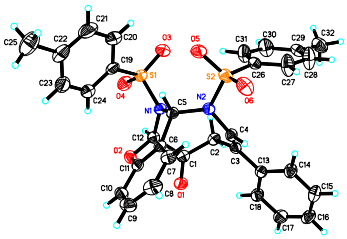
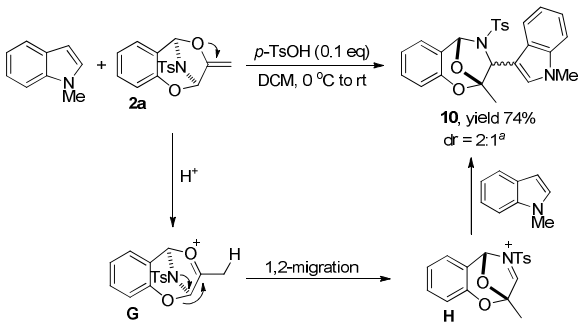


Figure 1. X-ray structure of **9a**.

Moreover, the intermolecular reaction of **2a** with *N*-methyl indole also went through smoothly in DCM under acidic condition. After protonation of **2a**, a cationic intermediate **G** is formed, followed by a 1,2-migration to generate cationic intermediate **H**. Finally, a Friedel-Crafts type reaction takes place to afford the corresponding 2,5-epoxybenzo[f][1,4]oxazepine derivative **10** as a pair of diastereoisomers (dr = 2:1) in 74% yield (Scheme 5). The structure of major diastereoisomer of **10** has been also unambiguously determined by X-ray diffraction.[11]

Scheme 5. Synthetic application for the synthesis of **10**.



[a] Determined by ^{1}H NMR spectroscopy, see Supporting Information.

In summary, a novel protocol to effectively construct 8-aza-benzodioxepine derivatives **2** has been developed. Due to the rapid assembly of structural complexity, this method is synthetically valuable and useful. A prevalent Rh-azavinyl carbene is formed as the key intermediate. Thus, this protocol may enrich the chemistry with regard to the utilization of 1-sulfonyl 1,2,3-triazoles in the construction of N-containing heterocycles. The substrates scope is broad and many valuable functional groups are tolerated. Since benzodioxepine containing compounds usually have special immunotoxicity effects and antioxidant activity,[12] this novel synthetic method provides a convenient access to these substances. Furthermore, a series of interesting derivatizations of products **2** to structurally more complex *N*-heterocycles well demonstrates the versatile applications of this methodology. The biological evaluation of the

corresponding heterocycles and more detailed mechanistic investigation are currently underway in our laboratory.[13]

We are grateful for the financial support from the National Basic Research Program of China (973)-2015CB856603, Shanghai Municipal Committee of Science and Technology (11JC1402600), and the National Natural Science Foundation of China (20472096, 21372241, 21361140350, 20672127, 21102166, 21121062, 21302203 and 20732008).

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[10] The crystal data of **9a** have been deposited in CCDC with number 1001752. For detail, see Supporting Information.

[11] The crystal data of **10** have been deposited in CCDC with number 1001749. For detail, see Supporting Information.

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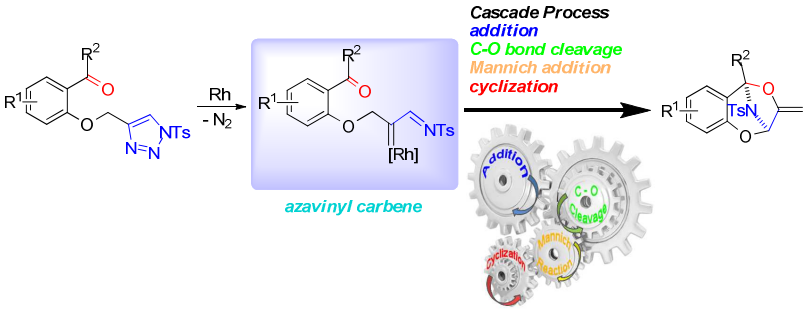
[13] Another paper entitled as "Intramolecular Annulation of Aromatic Rings with *N*-Sulfonyl 1,2,3-triazoles: Divergent Synthesis of 3-Methylene-2,3-dihydrobenzofurans and 3-Methylene-2,3-dihydroindoles" has been submitted to *Chem. Commun.* in which the controllable synthesis of 3-methylene-2,3-dihydrobenzofurans and 3-methylene-2,3-dihydroindoles has been developed through Rh-catalyzed intramolecular annulation of aromatic rings with azavinyl carbenes.

5

N-Bridged Heterocycles

Yong-Sheng Zhang, Xiang-Ying Tang,* and Min Shi* _____ **Page – Page**



Unprecedented Synthesis of Aza-Bridged Benzodioxepine Derivatives using a Tandem Rh(II)-Catalyzed 1,3-Rearrangement/[3 + 2] Cycloaddition of Carbonyltriazoles