VIP Rhodium(II) Catalysis

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Ring Expansion and Rearrangements of Rhodium(II) Azavinyl Carbenes**

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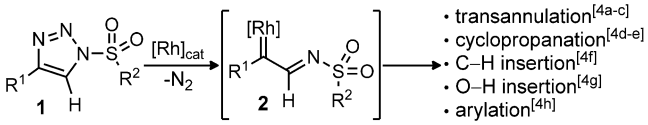
Dedicated to Professor Michael P. Doyle on the occasion of his 70th birthday

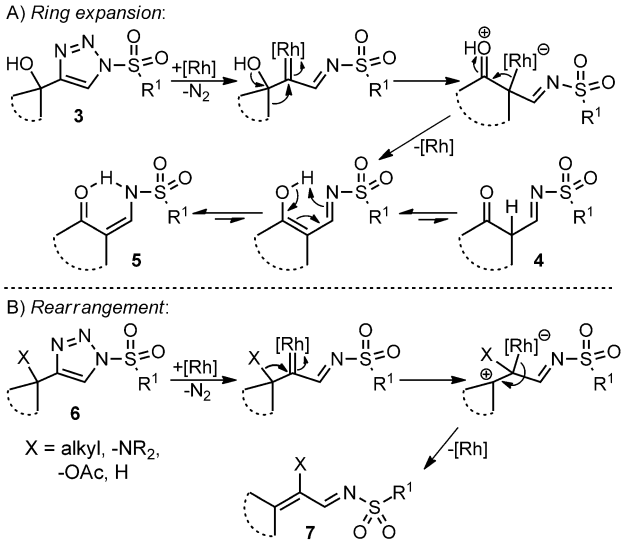
The ring expansion and rearrangement of diazo compounds, specifically rhodium carbenes (derived from the corresponding diazo species), is an efficient and operationally simple method for the construction of structurally unique frameworks.[1] Products derived from these reactions normally consist of large carbocyclic rings (7, 8, and 9 membered) and multiple substituted olefins, which are ubiquitous in natural products and drug molecules.[2] Indeed, these robust methods have found widespread use in organic synthesis, both for the synthesis of complex natural products and in pharmaceutical research.[3] Bolstered by our recent success utilizing readily available and stable 1-sulfonyl-1,2,3-triazoles **1** as direct precursors to rhodium(II) azavinyl carbenes **2** (Scheme 1),[4,5] we hypothesized that these diazo progenitors



Scheme 1. Utility of Rhodium(II) Azavinyl Carbenes.

could be effective in these ring expansion/rearrangement reactions, to deliver unique products that are not accessible via conventional diazo compounds (Scheme 2). Herein, we report the rhodium(II)-catalyzed ring-expansion and rearrangement reactions of azavinyl carbenes (**2**), to access various enaminones and substituted olefins, which, in the case of the expanded enaminones can be further reacted to form a variety of heterocycles and ketone-based products.[6,7]

We began our investigations with the synthesis of various 1-sulfonyl triazoles bearing cyclic, tertiary alcohols at the 4-position (Table 1) from the corresponding sulfonyl azide and commercially available or easily synthesized propargylic



Scheme 2. Rhodium(II)-catalyzed ring expansion and rearrangement of azavinyl carbenes.

alcohols.[8] These unique triazoles species (**3**) were submitted to a rhodium-catalyzed denitrogenative ring-expansion reaction to form the homologated product. To this end, we reacted triazole **3a** with 0.5 mol% of rhodium(II) octanoate dimer in chloroform. When the reaction was heated to a minimum of 70 °C, a rapid evolution of gas occurred and the reaction proceeded to completion within 15 min. The ring-expanded product **5a** was formed in 91 % yield (Table 1, entry 1). A *Z*-substituted enaminone (**5**) was exclusively formed owing to a facile but selective tautomerization of the acidic α-proton (the tautomeric ketoimine **4** was not observed). Of note, no reaction was observed without the addition of a rhodium(II) catalyst, even under forcing conditions (> 100 °C).

When these reaction conditions were applied to different sulfonyl triazoles similarly satisfying results were obtained (Table 1, yields 66–98 %). Various cyclic substituents were smoothly and rapidly (15 min) converted into the expanded enaminone products, to yield 6, 7, and 8-membered rings (**5a**–**5c**, 91–94 %). Triazoles bearing electron-withdrawing, electron-donating, and aliphatic sulfonyl groups easily underwent this homologation process to yield the enaminone products (**5d**–**5f**, 66–95 %) in good to excellent yields. Furthermore, heteroatoms within the ring structure did not affect the efficiency of this reaction; reactions of both ether **3g** and amide **3h** gave the expected products in excellent yields (**5g** and **5h**, 92–98 %). Interestingly, the strained adamantane **3i**

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Table 1: Ring expansion of various 1-sulfonyl 4-tertiary alcohol triazoles **3** yielding products **5**.[a]

Entry	Triazole	*T* [°C]/*t* [min]	Product	Yield [%]
1	**3a**: *n* = 1	70/15	**5a**: *n* = 1	91
2	**3b**: *n* = 2	70/15	**5b**: *n* = 2	93
3	**3c**: *n* = 3	70/15	**5c**: *n* = 3	94
4	**3d**: *R* = *p*-OMeC$_6$H$_4$	70/60	**5d**: *R* = *p*-OMeC$_6$H$_4$	95
5	**3e**: *R* = *p*-IC$_6$H$_4$	70/5	**5e**: *R* = *p*-IC$_6$H$_4$	71
6	**3f**: *R* = *i*Pr	70/20	**5f**: *R* = *i*Pr	66
7	**3g**	70/30	**5g**	92
8	**3h**	70/45	**5h**	98
9	**3i**	70/60	**5i**	89
10	**3j**	70/30	**5j**	95

[a] Reaction conditions: 1-sulfonyl triazole (1.0 mmol, 1.0 equiv), rhodium(II) octanoate (0.5 mol%), $CHCl_3$ (2.0 mL), 70°C, μw, 5–60 min. All yields shown are of the isolated products. Ts = *p*-toluenesulfonyl.

and fluorene **3j** triazoles underwent this homologation reaction effectively (89% and 95% respectively) but instead of the expected enaminone moiety, they delivered peculiar enone/imine products **5i** and **5j**, respectively. It should be noted that owing to the stability of the 1-sulfonyl triazoles in Table 1 and the robust nature of the process, no special precautions were taken regarding the exclusion of air and moisture. Performing these reactions in a microwave reactor allows for the reaction progress to be monitored by the expulsion of dinitrogen; conventional heating is also effective for this process.

Having shown that 1-sulfonyl triazoles bearing a tertiary alcohol at the 4-position (e.g. **3**) can readily undergo ring expansion reactions, we sought to explore the use of azavinyl carbenes in rhodium-catalyzed rearrangements.[1g–n] We believed that 1-sulfonyl triazoles bearing a quaternary center at C4 (e.g. **6**) would undergo rearrangement to the corresponding substituted olefin (**7**) upon formation of the rhodium(II) azavinyl carbene. To investigate this hypothesis, we synthesized 1-sulfonyl triazole **6a** bearing the requisite *tert*-butyl group at C4 and submitted it to the general reaction conditions. Gratifyingly, upon heating to 70°C in the presence of 0.5 mol% of rhodium(II) octanoate, the rapid evolution of gas occurred (20 min) and **6a** was smoothly converted into the expected tetra-substituted olefin **7a** in 91% yield (Table 2, entry 1).

Table 2: Rearrangements of 1-sulfonyl triazoles **6** to give substituted alkenes **7**.[a]

Entry	Triazole	*T* [°C]/*t* [min]	Product	Yield [%]
1	**6a**	70/20	**7a**	91
2	**6b**	70/60	**7b**	96
3	**6c**	70/30	**7c**	92
4	**6d**	70/30	**7d**	96
5	**6e**	70/60	**7e**	92
6	**6f**	70/80	**7f**	71

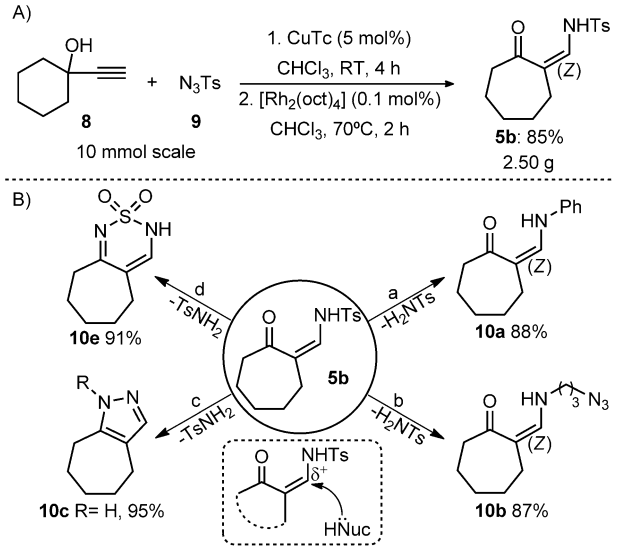
[a] Reaction conditions: 1-sulfonyl triazole (1.0 mmol, 1.0 equiv), rhodium(II) octanoate (0.5 mol%), $CHCl_3$ (2.0 mL), 70°C, μw, 20–80 min. All yields shown are of the isolated products. Boc = *tert*-butyloxycarbonyl.

We next examined the migratory aptitude of different atoms and functional groups. When cyclohexyl triazole **6b** was submitted to the reaction conditions, a facile hydride shift occurred, leading to the formation of alkene **7b** in 96% yield. In contrast to triazoles **3a–e**, the reaction of the triazole **6c** bearing a tertiary nontethered alcohol at the 4-position led to the nonregioselective migration of the alkyl group to give enaminone **7c** in a 3:1 ratio of isomers (*Z*/*E* ratio). Furthermore, for acetoxy triazoles **6d** and **6e** the exclusive migration of the acetoxy group, led to formation of the acetyl enols **7d** and **7e** in excellent yields (96% and 92% respectively). Finally and most interestingly, reaction of piperazine triazole **6f** under our general conditions led to the selective migration of the nitrogen group to give the stable imine enamine **7f** in good yield (71%). We believe that this selective nitrogen transfer is likely to proceed through an

attack of the nitrogen lone pair of the pendant piperazine onto the rhodium carbene center, thus forming an aziridinium ylide intermediate, which upon loss of the rhodium catalyst leads to the observed product. This rearrangement is, to the best of our knowledge, unknown, which we account to the difficulty in preparation of the diazo starting material. All of the triazoles shown in Table 2 are formed from the commercially available or easily prepared alkynes and tosyl azide, thus allowing for the simple synthesis of active diazo progenitors, which would be inaccessible utilizing traditional diazo chemistry.

The copper(I)-catalyzed synthesis of 1-sulfonyl triazoles and their subsequent rhodium(II)-catalyzed ring expansion or rearrangement can be combined into a sequential one-pot procedure, thus eliminating the requirement for purification of the starting 1-sulfonyl triazole. This efficient procedure was demonstrated on a 10 mmol scale for the conversion of commercial alkyne **8** and tosyl azide **9** into the 7-membered enaminone **5b**, to deliver 2.5 g of material in an overall 85% yield using only 0.1 mol% of the rhodium catalyst for the ring-expansion step (Scheme 3a). With this unique enaminone (**5b**) building block in hand, we sought to transform it into useful ketone and heterocyclic-based products. As enaminones are well-studied and versatile intermediates in organic synthesis,[9] the subsequent functionalization was easily accomplished. Indeed, enaminone **5b** can easily undergo transamination by the addition of an amine nucleophile with loss of tosyl amine, to give products **10a** and **10b** at room temperature in excellent yields (88% and 87%, respectively). When enaminone **5b** was reacted with hydrazines, pyrazoles **10c** and **10d** were formed as single regioisomers, at room temperature and in high yields (95% and 82%, respectively). Additionally, this transamination/cyclization procedure was further demonstrated by the reaction of enaminone **5b** with sulfamide to obtain heterocycle **10e** in 91% yield (Scheme 3b).

The facile rhodium(II)-catalyzed ring-expansion and rearrangement reactions of 4-substituted 1-sulfonyl-1,2,3 triazoles shown here are experimentally simple and useful transformations for the synthesis of enaminones and olefins in high yield and selectivity.[10] Furthermore, the exocyclic enaminone products can be readily transformed to various heterocycles and ketone derivatives.



Scheme 3. A) One-pot large-scale synthesis of **5b**. Reaction conditions: **8** (10 mmol, 1 equiv), **9** (10 mmol, 1 equiv), CuTc (5 mol%), $CHCl_3$ (15 mL), RT, 4 h; then rhodium(II) octanoate (0.1 mol%), 70°C, 2 h. B) Functionalization of **5b**. Reaction conditions: a) $PhNH_2$ (3 equiv), MeOH, RT, 6 h; b) 3-azidopropan-1-amine (2 equiv), MeOH, RT, 2 h; c) hydrazine hydrate (5 equiv), MeOH, RT, 1 h; d) phenyl hydrazine hydrochloride (1.1 equiv), MeOH, RT, 5 h; e) sulfamide (1.1 equiv), *p*-TsOH (10 mol%), MeOH, 70°C, 36 h. See the Supporting Information for reaction details.

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