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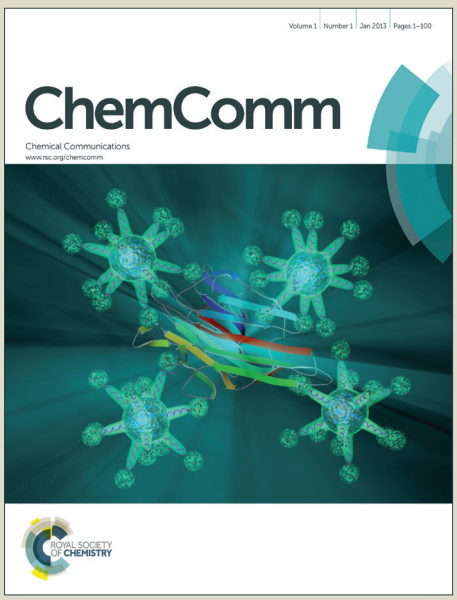

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Rh(II)-Catalyzed Cycloadditions of 1-Tosyl 1,2,3-Triazoles with *2H*-Azirines: Switchable Reactivity of Rh-Azavinylcarbene as [2C]- or Aza-[3C]-Synthon

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The Rh(II)-catalyzed formal [3+2] and [3+3] cycloadditions of 1-tosyl 1,2,3-triazoles with 2*H*-azirines have been developed, which enable the efficient synthesis of polysubstituted 3-aminopyrroles and 1,2-dihydropyrazines, respectively. The reported [3+2] cycloaddition represents the first application of 1-sulfonyl 1,2,3-triazole as [2C]-component in relevent cycloaddition reactions.

Readily generated from 1-sulfonyl 1,2,3-triazole through denitrogenation upon treatment with Rh(II)-catalyst, Rh-azavinylcarbene (Rh-AVC) has evolved into a versatile reactive intermediate in organic synthesis over the past several years.[1] On one hand, it displays typical reactivity of metallocarbene derived from diazo compound,[2] and has been employed as [1C]-synthon in various reactions including cyclopropanation,[3] X-H (X = C, O or N) insertion,[4] ylide formation and rearrangement[5] and others[6] (eqn (1), Fig. 1a). On the other hand, owing to its dipolar nature, it could also function as aza-[3C]-synthon in a wide range of cycloadditions, such as [3+2],[7] [3+3],[8] [4+3][9] and others multicomponent cycloadditions (eqn (2), Fig. 1a).[10] Despite such progresses, the utilization of Rh-AVC as [2C]-synthon in cycloaddition reactions has never been explored so far (eqn (3), Fig. 1a).

2*H*-azirines represent a type of highly strained three-membered cyclic imines that have been employed as versatile precursors for the synthesis of various heterocycles.[11] For an example, Park and co-workers recently reported an interesting formal [3+3] cycloadditions of vinyl carbenoids with 2*H*-azirines, which resulted in the formation of polysubstituted pyridines.[12] Inspired by this semial work, we envisioned that it was feasible to unite the two 1,3-diplolarophiles

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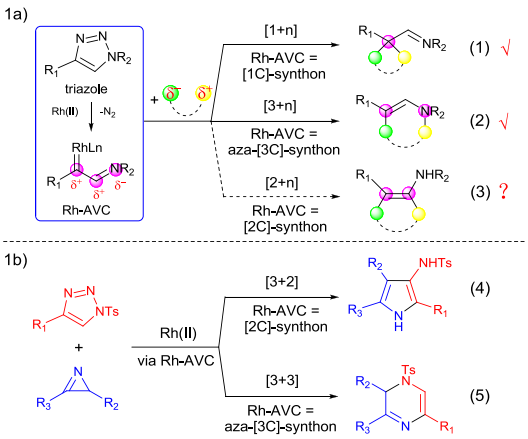
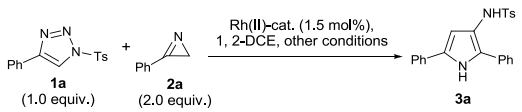


Fig. 1 1a) The graphic illustration of versatile reactivities of Rh-AVC; 1b) The cycloaddition developed in current work.

Rh-AVC and 2*H*-azirine in a single transformation to realize a formal aza-[3+3] cycloaddition, which would afford an efficient method for the synthesis of 1,2-dihydropyrazines (eqn (5), Fig. 1b) as well as related heterocycles (e.g. pyrazine). As a part of our continuing interests on the development of novel Rh-AVC promoted transformations,[9a,13] we report herein the successful implementation of this design, which lead to the development of unprecedented Rh(II)-catalyzed formal [3+2] and [3+3] cycloadditions of 1,2,3-triazoles with 2*H*-azirines (Fig. 1b). Of note, the putative Rh-AVC intermediate in the [3+2] cycloadditions serves as [2C]- instead of [1C]- or aza-[3C]-synthon.[14]

The readily accessible triazole **1a** and 3-phenyl-2*H*-azirine **2a** were empyed as substrates in the inital study.[15] Thus, **1a** and **2a** were treated with 1.5 mol% $Rh_2(OAc)_4$ in 1,2-DCE at 140 °C for 4 h, which resulted in the formation of a product in 48% yield. Careful analysis of its spectrosopic data suggested that it was not the expected [3+3] adduct, but a 3-amino-pyrrole derivative **3a** (entry 1, Table 1). The structural assignment of **3a** was further confirmed by the X-ray crystallographic study of its derivative **3a'** (structure not shown, for details, see Supporting Information).[16]

Table 1. Condition screening of cycloaddition of **1a** with **2a**.[a]



Entry	Cat.	Solvent	Other conditions	Yield of **3a** (%)[b]
1	$Rh_2(OAc)_4$	1,2-DCE	140 °C, 4 h	48
2	$Rh_2(OAc)_4$	1,2-DCE	120 °C, 10 h	38
3	$Rh_2(OAc)_4$	1,2-DCE	160 °C, 1 h	57
4	$Rh_2(oct)_4$	1,2-DCE	160 °C, 1 h	45
5	Rh_2(*S*-ptad)$_4$	1,2-DCE	160 °C, 1 h	trace
6	Rh_2(*S*-dosp)$_4$	1,2-DCE	160 °C, 1 h	trace
7	$Rh_2(esp)_2$	1,2-DCE	160 °C, 1 h	81
8	$Rh_2(esp)_2$	1,2-DCE	160 °C, 1 h, 4Å MS	62
9	$Rh_2(esp)_2$	1,2-DCE	160 °C, MW, 15 min	50

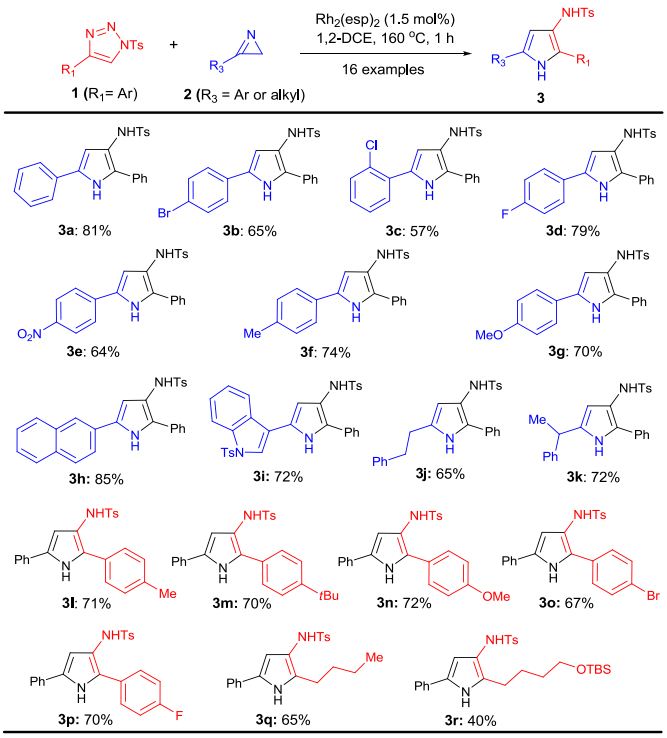
[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.6 mmol) and Rh(II)-cat. (0.0045 mmol) in 1,2-DCE (0.8 mL). [b] Isolated yield. DCE = dichloroethane, oct = octanoate, (*S*)-ptad = N-phthaloyl-(*S*)-adamantylglycine, (*S*)-dosp = 4-(dodecyl-phenyl)sulfonyl-(2*S*)-prolinate, esp = *a,a,a',a'*-tetramethyl-1,3-benzenedipropanoate, MS = molecular sieves, MW = microwave.

The initial discovery deserves further investigation, since it represents a formal [3+2] cycloaddition, wherein the triazole partner served as [2C]- instead of the proposed aza-[3C]-component. Moreover, the resulting 3-amino-pyrrole derivative represent valuable structural motif distributed in natural products and bioactive molecules.[17] To improve the efficiency of the transformation, we conducted a systematic condition screening (Table 1). It was shown that lower temperature was detrimental to the reaction (entry 2), while higher temperature afforded **3a** in improved yield (entry 3). The Rh(II)-catalyst also had notable influence on the reaction. While $Rh_2(oct)_4$ displayed reactivity similar to $Rh_2(OAc)_4$, the sterically hindered Rh_2(*S*-ptad)$_4$ and Rh_2(*S*-dosp)$_4$ failed to yield the desired product (entries 4-6). Gratifyingly, $Rh_2(esp)_2$, a dirhodium complex with tethered carboxylate ligands,[18] exhibited superior reactivity by giving **3a** in 81% yield (entry 7). We also attempted to perform the reaction in the presence of 4Å MS or microwave irradiation, however, both of them resulted in inferior yields (entries 8 and 9).

The generality of the cycloaddition was then evaluated with various monosubstituted 2*H*-azirines (Table 2). First of all, an array of 3-aryl-2*H*-azirines were examined with **1a** as the reaction partner. Gratifyingly, all of the substrates bearing either electron withdrawing (4-Br, 2-Cl, 4-F or 4-NO_2) or donating (4-Me or 4-MeO) substituents gave the corresponding products (**3a-g)** in good yields. The 2-naphthyl- or 3-indol-derived 2*H*-azirines also tolerated well. Besides, the reaction could also extend to 3-alkyl-2*H*-azirines, as shown in the cases leading to **3j** and **3k**. Moreover, the variant on the 1,2,3-triazole partners was also evaluated. Not surprisingly, a variety of 4-aryl-substituted 1,2,3-triazoles proved to be suitable substrates by affording the desired products (**3l-p**) in satisfying yields. Comparably, although the cycloadditions could also be applied to 4-alkyl-substituted substrates, only moderate yield of products (**3q** and **3r**) were obtained.

Furthermore, we explored 2,3-disubstituted substrates in the reactions. Interestingly, we found that when 2,3-diphenyl-2*H*-azirines **4a** was submitted to the optimized condition, a mixture of tetrasubstituted 3-amino-pyrrole **5a** and 2,3,5-trisubstituted 1,2-dihydropyrazine **6a** were obtained in 36% and 48% yields, respectively (entry 1, Table 3). The structure of **6a** was confirmed by the X-ray crystallographic study.[16] This result showed that the introduction of aromatic substitute on the C-2 position of 2*H*-azirine largely inverted its reactivity. Although

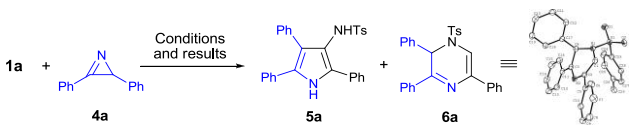
Table 2. Scope of Rh(II)-catalyzed cycloadditions of 1-tosyl 1,2,3-triazoles with monosubstituted 2*H*-azirines.[a, b]



[a] Reaction conditions: **1a** (0.30 mmol), **2** (0.60 mmol) and Rh(II)-catalyst (0.0045 mmol) in 1,2-DCE (0.8 mL). [b] Isolated yield.

the efficiency of the reaction was excellent, the poor selectivity discounted its synthetic utility. Thus, we sought to improve the reaction with the futher condition optimization. Fortunately, we found that simply changing the solvent from 1,2-DCE to toluene notably increased the selectivity of [3+3] vs [3+2] from 1.3:1 to 6.3:1, with **6a** obtained in 82% yield (condition B, entry 2).[19] Furthermore, the use of substoichiometric amounts of $ClCH_2COOH$ in the reaction could invert the selectivity of the reaction.[20] As a result, **5a** was isolated in 86% yield, along with only a small amount of **6a** (11%) (condition C, entry 3).

Table 3. Condition screening of cycloaddition of **1a** with **4a**.[a]

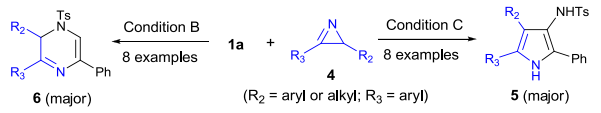


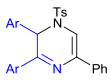
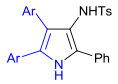
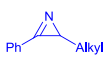
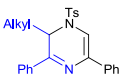
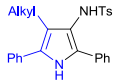
Entry	Conditions	Yield of Products[b]
1	A: $Rh_2(esp)_2$ (1.5 mol%), 1,2-DCE, 160 °C, 1 h	**5a**: 36%; **6a**: 48%
2	B: $Rh_2(esp)_2$ (1.5 mol%), toluene, 160 °C, 1 h	**5a**: 13%; **6a**: 82%
3	C: $Rh_2(esp)_2$ (1.5 mol%), $ClCH_2CO_2H$ (50 mol%), 1,2-DCE, 160 °C, 0.5 h	**5a**: 86%; **6a**: 11%

[a] Reaction conditions: **1a** (0.30 mmol), **4a** (0.60 mmol) and Rh(II)-catalyst (0.0045 mmol) in the solvent (0.8 mL). [b] Isolated yield.

The above discovery was encouraging, since it enabled the divergent synthesis of two different heterocycles from common precursor simply by tuning reaction conditions. To test its generality, several other symmetric 2,3-diaryl-2*H*-azirines (**4b-d**) were evaluated under the dual condition systems (Table 4). To our delight, all of them afforded the expected [3+3] adducts (**6b-d**) under condition B and [3+2] adducts (**5b-d**) under condition C (entries 2-4)

Table 4. Scope of Rh(II)-catalyzed cycloadditions of **1a** with 2,3-diaryl-2*H*-azirines and 2-alkyl-3-Ph-2*H*-azirines.[a]



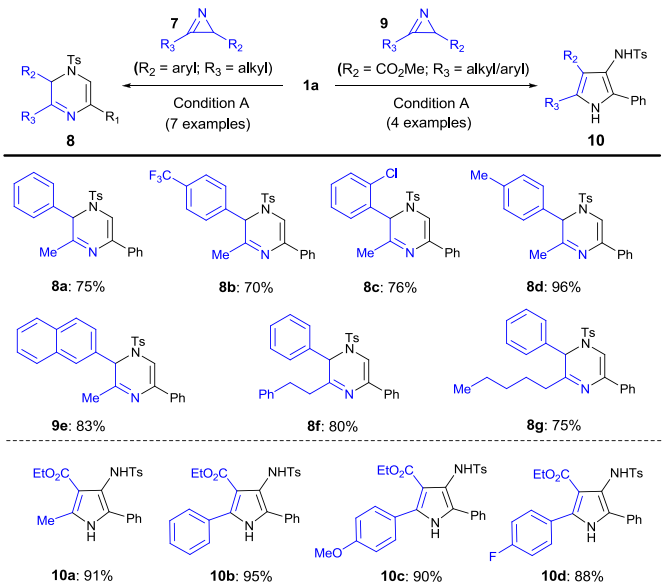
Entry	2*H*-azirine	Product (yield)[b] Condition B	Condition C
			
1	**4a**: Ar = Ph	**6a**: 82% (**5a**: 13%)	**5a**: 86% (**6a**: 11%)
2	**4b**:Ar = 4-F-Ph	**6b**: 80% (**5b**: 14%)	**5b**: 74% (**6b**: 14%)
3	**4c**: Ar = 4-Cl-Ph	**6c**: 85% (**5c**: 11%)	**5c**: 69% (**6c**: 21%)
4	**4d**: Ar = 4-Me-Ph	**6d**: 84% (**5d**: 9%)	**5d**: 70% (**6d**: 10%)
			
5	**4e**: alkyl = Me	**6e**: 83% (**5e**: 13%)	**5e**: 60% (**6e**: 8%)
6	**4f**: alkyl = CH_2CH_2Ph	**6f**: 79% (**5f**: 10%)	**5f**: 50% (**6f**: 20%)
7	**4g**: alkyl = $(CH_2)_4Me$	**6g**: 80% (**5g**: 12%)	**5g**: 65% (**6g**: 20%)
8	**4h**: alkyl = (CH)MePh[c]	**6h**: 84% (**5h**: 10%)[c]	**5h**: 58% (**6h**: 20%)

[a] Condition B: **1a** (0.30 mmol), **4** (0.6 mmol) and Rh-catalyst (0.0045 mmol) in toluene (0.8 mL); Condition C: **1a** (0.30 mmol), **4** (0.6 mmol), $ClCH_2CO_2H$ (0.15 mmol) and Rh-catalyst (0.0045 mmol) in 1,2-DCE (1.0 mL). [b] Isolated yield. [c] Obtained as a mixture of diastereoisomers (1:1).

with excellent yields and good selectivity. Besides, a variety of 2-alkyl-3-Ph-2*H*-azirines (**4e-h**) were also tested. Gratifyingly, all of them exhibited propensity similar to the 2,3-diaryl-2*H*-azirines, affording satisfying results (entries 5-8).

To further explore the substitute effect of 2*H*-azirines on the reaction outcomes, an array of 2-aryl-3-alkyl-2*H*-azirines (**7a-g**) were evaluated (Table 5). Unlike the above-mentioned 2,3-disubstituted 2*H*-azirines, this type of substrates only yielded the [3+3] adducts (**8a-g**) in good yields under the condition A. Comparable results were obtained with condition B employed,

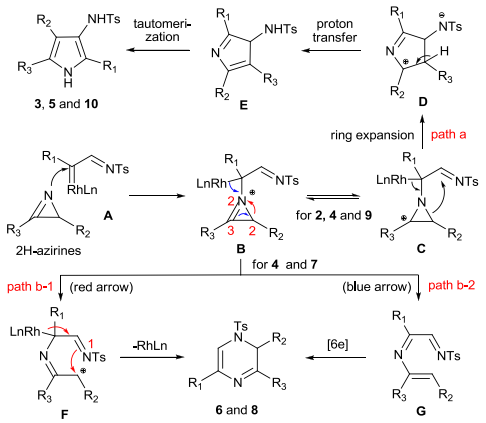
Table 5. Scope of Rh(II)-catalyzed cycloadditions of **1a** with 2-aryl-3-alkyl-2*H*-azirines and 2-carboxylate-3-aryl/alkyl-2*H*-azirines.[a]



[a] Condition A: **1a** (0.30 mmol), **8** or **10** (0.60 mmol) and Rh(II)-catalyst (0.0045 mmol) in 1,2-DCE (0.8 mL) at 160 °C for 1 h. [b] Isolated yield.

however, the usage of condition C failed to invert the selectivity of the reactions. In sharp contrast, when several 2-carboxylate-3-aryl/alkyl-2H-azirines **9a-d** were employed, they displayed propensity close to monosubstituted substrates, affording [3+2] adducts **10a-d** in excellent yields (Table 5).

All the above-mentioned outcomes suggested that the structural feature of 2*H*-azirine partner plays an important role in determining the reaction pathways. Given that, the plausible mechanism of the titled reactions is depicted in Scheme 1. The nucleophilic attack of 2*H*-azirine to the Rh-AVC **A** leads to azirinium ylide **B**. At this point, there are several possibilities for **B** to evolve into the final products. On one hand, it could convert into **C** via resonant equilibrium, which then undergoes ring expansion to generate the zwitterionic intermediate **D**. After proton transfer followed by isomerization, D could advance to the pyrrole product (path a). On the other hand, **B** could divert into carboncation **F** via cleavage of the C2-N2 bond. **F** then undergoes cyclization to give the 1,2-dihydropyrazine (path b-1).[21] Alternatively, **B** could also transform to the 1,4-azatriene **G** which further evolves into 1,2-dihydropyrazine product via 6π electrocyclization (path b-2). Notably, the above mechanistic considerations are in good agreement with the experimental results. For examples, for 2*H*-azirines **2** and **9** (R_2 = H or CO_2Et), the formation of carbocation **F** is disfavored, and thus path b-1 is excluded. While path b-2 could be envisioned in this scenario,[22] path a more readily takes place to afford the thermodynamically more stable pyrrole product. In contrast, for 2-aryl-3-alkyl-2*H*-azirines **7**, the intermediate **B** prefers to advance into the more stable benzylic carbocation **F**, thus leading to [3+3] adducts via path b-1. For 2*H*-azirines **4**, both pathways may take place concurrently due to the comparable stability of the intermediates **F** and **C**.



Scheme 1 Proposed mechanism of Rh(II)-catalyzed cycloadditions of 1,2,3-triazoles with 2*H*-azirines.

Conclusions

In summary, the Rh(II)-catalyzed formal [3+2] and [3+3] cycloadditions of 1-tosyl 1,2,3-triazoles with *2H*-azirines have been developed, which enable the efficient synthesis of polysubstituted 3-amino-pyrroles and 1,2-dihydropyrazines. The selectivity of the cycloadditions is mainly determined by the structural feature of *2H*-azirine partners, and in some cases, could be controlled by tuning the reaction conditions. The reported [3+2] cycloaddition represents a proof-of-concept case that utilizes 1-sulfonyl 1,2,3-triazole as [2C]-component in cycloaddition reactions, which may inspire the development of some other new transformations. Such efforts are undertaken in our lab and will be reported in due course.

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21 While the direct nucleophilic attack of the nitrogen atom of the imine moiety to the C-2 position of azirine could also afford the 1,2-dihydropyrazine products, the observed notable electronic effect on the C-2 position is agreement with the mechanism via carbocation intermediate **F** (path b-1).

22 Actually, formal [3+3] adducts were obtained with similar substrates in references 14a and 14b, indicating that the reaction pathways of the cycloadditions of 1-sulfonyl 1,2,3-triazoles and *2H*-azirines are very sensitive to the substrates and reaction conditions.

