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COMMUNICATION

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Synthesis of Piperidine Derivatives by Rhodium-Catalyzed Tandem Reaction of *N*-Sulfonyl-1,2,3-Triazole and Vinyl Ether

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Abstract. A chemoselective tandem reaction of 4-acyloxymethylene-1-sulfonyl-1,2,3-triazole and vinyl ether was reported, producing polysubstituted piperidine derivatives in up to 96% yield. The key intermediate *N*-sulfonyl 1-azadiene generated by migration of the OAc group to the α-imino rhodium carbene was isolated and a plausible mechanism was proposed. Several related ring systems were constructed from the highly functionalized products.

Keywords: Heterocycles; Annulation; Rearrangement; Carbenes; 1,2,3-Triazole.

Many alkaloids, bearing the motif of piperidine, show various biological activities (Figure 1).[1] For instance, pipermethystine, 3α,4α-epoxy-5β-piper-methystine and awaine were all isolated from the aerial part of the same plant of piperaceae, and the first two compounds exhibited great anti-anxiety effect.[2] In addition, piperidine derivative vesicare has been reported to be an important muscarinic receptor antagonists[3] and butorphanol can be used as an anesthetic.[4]

Because of the importance of the piperidine scaffold, many efficient synthetic protocols for piperidine derivatives, such as hydrogenation of pyridine salts,[5] cyclocondensation of δ-haloimines,[6] displacement reaction of pyran,[7] reduction of dihydropyridines[8] and so on, have been developed. Additionally, aza-Diels-Alder reaction of azadiene was an efficient strategy.[9] Due to the electron-withdrawing nature of nitrogen, 1-azadiene are representative electron deficient dienophile in the common Diels-Alder reaction for the synthesis of six-membered rings.[9f] Alternatively, Boger,[10] Otani,[11] Arrayás[12] and other researches[13] have disclosed that azadiene substituted by strong electron-withdrawing group on nitrogen atom could be employed as diene part in inverse-electron-demand Diels-Alder reaction with electron-donor group substituted electron abundant olefin (Scheme 1A).[9a-b]

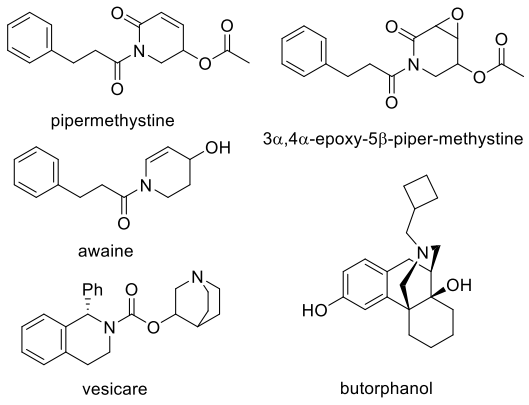
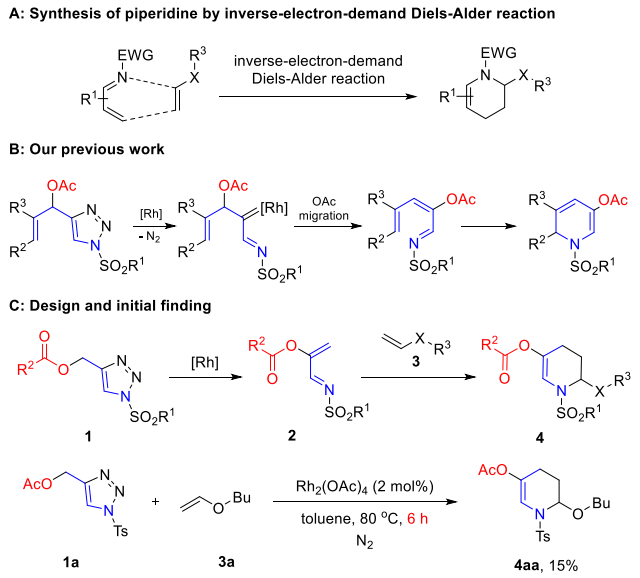


Figure 1. Piperidine framework in bioactive molecules.

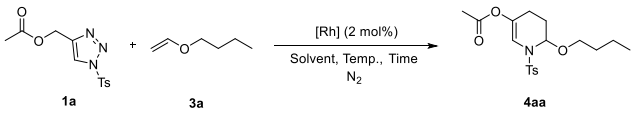
Owing to the pioneering work of Fokin and Gevorgyan,[14] α-imino rhodium carbene can be generated very easily from readily available 1-sulfonyl-1,2,3-triazole. The following research

works showed that α-imino rhodium carbene could undergo a series of synthetically useful transformations via [3+2],[15] [3+3] transannulation,[16] ring expansion[17] and so forth.[18,19] Recently, we reported a tandem reaction of 4-(1-acetoxyallyl)-1-sulfonyl-1,2,3-triazole, which produced piperidine derivatives effectively via formation of α-imino rhodium carbene, 1,2-migration of an acetoxy group and electrocyclization (Scheme 1B).[20a] To make the methodology more flexible, we started to study the corresponding intermolecular reaction. We envisioned that triazole **1**, which could be easily obtained from propargyl alcohol in two steps, might yield 1-azadiene **2**[20b] by rhodium catalyzed 1,2-migration of acetoxy group, the subsequent aza-Diels-Alder reaction of **2** with electron rich olefin would deliver polysubstituted piperidine derivative as indicated in the top of Scheme 1C. The chemoselectivity of this reaction is a major issue, since Lee's group[21] reported the rhodium catalyzed reaction of 1-sulfonyl-1,2,3-triazole and vinyl alkyl ether, giving pyrrole derivatives in 2014. To test our hypothesis, we tried the reaction by heating (1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl acetate (**1a**) and 1.0 equiv 1-(vinyloxy)butane (**3a**) in toluene at 80 °C for 6 h with 2 mol% $Rh_2(OAc)_4$ as catalyst, and the desired **4aa** was generated in 15% yield (Scheme 1C, see also Table 1, entry 1). Remarkably, excellent chemoselectivity was observed and no pyrrole derivatives were detected in this reaction. Herein, we report our achievement in the synthesis of polysubstituted piperidine by tandem reaction of 4-acyloxymethylene-1-sulfonyl-1,2,3-triazole and vinyl ether.



Scheme 1. Background and initial finding.

Table 1. Optimization of reaction conditions.[a]



Entry	[Rh]	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1[c]	$Rh_2(OAc)_4$	toluene	80	6	15
2[d]	$Rh_2(OAc)_4$	toluene	80	6	82
3	**$Rh_2(OAc)_4$**	**toluene**	**80**	**3.5**	**87**
4	$Rh_2(piv)_4$	toluene	80	4.5	75
5	$Rh_2(adc)_4$	toluene	80	4.5	79
6	$Rh_2(oct)_4$	toluene	80	4.5	81
7	$Rh_2(s\text{-}nttl)_4$	toluene	80	6	76
8	$Rh_2(s\text{-}ntv)_4$	toluene	80	7	83
9	$Rh_2(dpf)_4$	toluene	80	5	0
10	$Rh_2(OAc)_4$	THF	reflux	5.5	38
11	$Rh_2(OAc)_4$	DCE	80	4	72
12	$Rh_2(OAc)_4$	TCE	80	4	79
13	$Rh_2(OAc)_4$	DCM	reflux	30.5	65
14	$Rh_2(OAc)_4$	toluene	60	22	74
15	$Rh_2(OAc)_4$	toluene	reflux	4	82

[a] General conditions: **1a** (0.2 mmol), **3a** (3.0 equiv), Rh(II) catalyst (2 mol%), solvent (1.5 mL), N_2 atmosphere.
[b] Isolated yield.
[c] **3a** (1.0 equiv) was used.
[d] **3a** (2.0 equiv) was used.
Ts = tosyl, OAc = acetate, piv = pivalate, adc = 1-adamantanecarboxylate, oct = octanoate, nttl = *N*-1,8-naphthoyl-*tert*-leucine, ntv = *N*-1,8-naphthoylvaline, dpf = *N*,*N*'-diphenylformamidinate , THF = tetrahydrofuran, DCE = 1,2-dichloroethane, TCE = 1,1,2-trichloroethane, DCM = dichloromethane.

Based on the aforementioned initial result, series of reactions were carried out to define the optimal reaction conditions (Table 1). Considering the volatility of vinyl ether, the amount of **3a** was increased (entries 2-3). Dramatic promotion in the yield of the desired piperidine was observed and 3.0 equiv of **3a** was acceptable giving **4aa** in good yield (87%). Other Rh(II) catalysts, such as $Rh_2(piv)_4$, $Rh_2(adc)_4$, $Rh_2(oct)_4$, $Rh_2(s\text{-}nttl)_4$ and $Rh_2(s\text{-}ntv)_4$, were also efficient in the transformation, delivering **4aa** in 75-83% yields (entries 4-8), however, $Rh_2(dpf)_4$ was completely unreactive and **1a** was recovered in 90% yield (entry 9). Screening of solvent revealed that THF was not a good choice in the transformation in which only 38% yield of **4aa** was isolated (entry 10); chlorinated solvents such as 1,2-dichloroethane (DCE) and 1,1,2-trichloroethane (TCE) were less efficient than toluene and the desired product was generated in 72% and 79% yields respectively (entries 11-12), when the reaction was run in dichloromethane (DCM), 65% yield was obtained after a sluggish transformation (entry 13). Decreasing the reaction temperature would slow down the reaction (60 °C, 22 h, 74% yield, entry 14),

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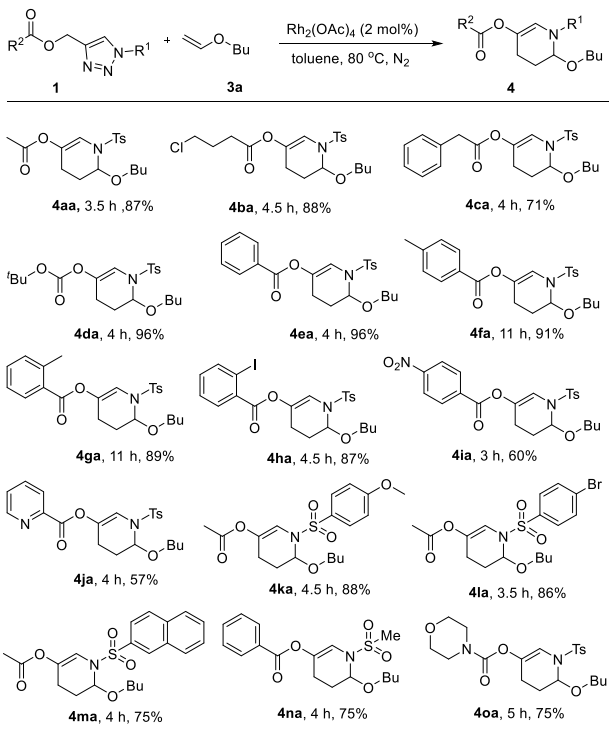
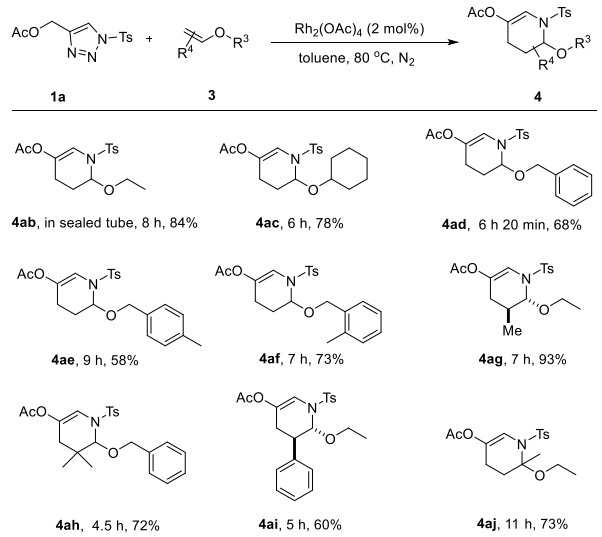
whereas elevating the reaction temperature brought no additional improvement for the yield (entry 15). As a result, the optimal reaction conditions were established as indicated in entry 3.



Scheme 2. Synthesis of piperidines using various triazoles. Reactions were carried out with **1** (0.2 mmol), **3a** (3.0 equiv), Rh(II) catalyst (2 mol%) in toluene (1.5 mL) under nitrogen atmosphere at 80 °C.



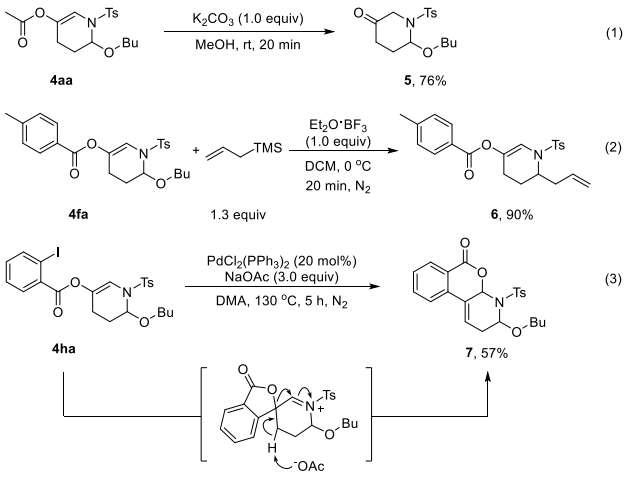
Scheme 3. Synthesis of piperidines using different vinyl ethers. Reactions were carried out with **1a** (0.2 mmol), **3** (3.0 equiv), Rh(II) catalyst (2 mol%) in toluene (1.5 mL) under nitrogen atmosphere at 80 °C. For **4ah** and **4ai**, 1-azadiene was first generated in 1 h at 80 °C, then vinyl ether was added and the mixture was stired at 130 °C for 3.5-4 h.

Under the optimal reaction conditions, we next surveyed the substrate scope of various triazoles **1** (Scheme 2). Aliphatic acetates were well compatible in the reaction, and **4aa**-**ca** were generated smoothly in good yields (71-88%). To our delight, **4da** was isolated in excellent yield (96%) with a Boc protecting group. Depending on the substituents in the aryl rings, benzoate derivatives exhibited very different reactivities under standard conditions. For instance, benzoate performed very effectively giving **4ea** in excellent yield (96%); *p*- and *o*-methyl benzoates delivered the corresponding piperidines **4fa** and **4ga** in similar yields (91% and 89% respectively), indicating that steric effect had slight influence on the transformation; iodide was also well tolerated in the reaction and **4ha** was formed in 87% yield. However, strong electron-withdrawing group had a negative effect on the conversion. Nitro substituted **4ia** was generated in moderate yield (60%), picolinate **4j** transformed to the desired piperidine **4ja** in 57% yield. The influence of sulfonyls was also investigated, and **4ka**-**na** were obtained in similar yields ranging from 75% to 88%. Specially, carbamate substituted triazole **1o** was synthesized, and after heated with **3a** under standard conditions, the desired carbamate substituted piperidine **4oa** was generated in 75% yield.

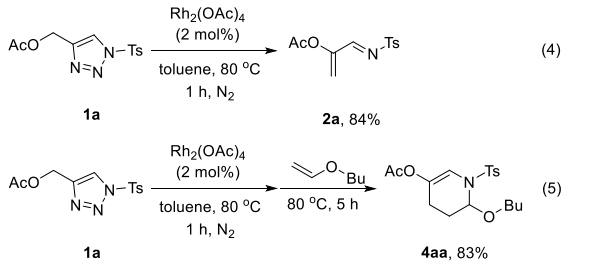
Different vinyl ethers were successively tested in the transformation under standard conditions (Scheme 3). Considering the low boiling point and for insuring the complete consumption of **1a**, vinyl ethyl ether (**3b**) was heated with **1a** in a sealed tube for a prolonged reaction time, and the desired **4ab** was produced in 84% yield. Cyclohexyl and benzyl ethers were also suitable substrates in the reaction and furnished piperidines **4ac**-**af** in moderate to good yields (58-78%) although after a longer reaction time. The commercially available more steric 2-methylvinyl ethyl ether (**3g**, *cis*:*trans* = 1:4) was proved to be an excellent reaction partner and a multi substituted *trans*-piperidine **4ag** was generated in 93% yield. The reactivity of the even more steric vinyl ethers was poor, and the problem was solved by elevating the temperature to 130 °C, giving the desired piperidines **4ah** in 72% yield. Under the same reaction conditions, *trans*-**4ai** was obtained in 60% yield from the corresponding *trans*-vinyl ether **3i**. 1-Methylvinyl ethyl ether was transformed to **4aj** in fairly good yield (73%).

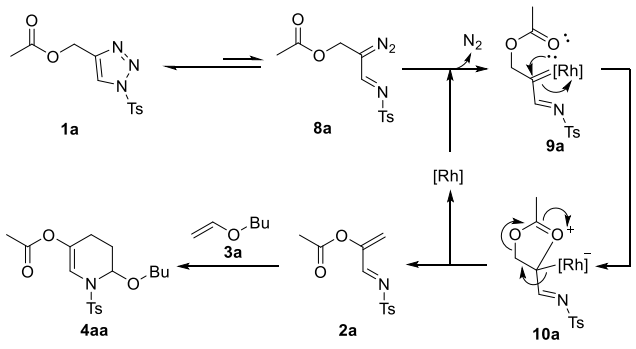
As multiple functionalized piperidine derivatives, the product **4** could be further converted into related cyclic compounds. For instance, the acyl group of **4aa** could be easily removed by K_2CO_3 in methanol at rt, and cyclic α-aminocarbonyl **5** could be obtained in 76% yield within only 20 min (eq 1). The ether group of **4fa** would be replaced by allyl group conveniently after treated with $Et_2O{\cdot}BF_3$ and allyltrimethylsilane in DCM at 0 °C, delivering β-aminoalkene derivative **6** in excellent yield (90%) (eq 2). The carbon carbon double bond in the ring of **4ha** could couple with the carbon iodine bond of the benzene ring by catalysis of $PdCl_2(PPh_3)_2$ in

N,*N*-dimethylacetamide (DMA), and after a consequent migration of benzoate group, isochromeno[3,4-b]pyridine skeleton **7** was smoothly constructed in 57 % yield (eq 3).



To detect the mechanism of the transformation, triazole **1a** was treated with 2 mol% of $Rh_2(OAc)_4$ in toluene at 80 °C (eq 4), *N*-sulfonyl 1-azadiene **2a** could be isolated in 84% yield after 1.0 h. If 3 equiv of vinyl ether **3a** was added to the reaction mixture after the formation of **2a**, the desired **4aa** could be obtained in 83% yield (eq 5). Unlike the sulfur substituted 1-azadiene,[16a] dimerization of **2a** was not detected even after the in situ generated **2a** was stirred at 130 °C, and **2a** was decomposed gradually.





Scheme 4. Proposed mechanism for the reaction.

Based on the above experimental facts as well as literatures,[17a,20a,22] a plausible mechanism for this reaction was outlined in Scheme 4. Firstly, A Dimroth-type rearrangement of **1a** gave rise to α-diazo imine **8a**,[23] then the irreversible conversion of **8a** with Rh(II) provided α-imino rhodium carbenoid **9a** along with release of molecular nitrogen. Subsequently, the nucleophilic carbonyl oxygen atom in the OAc group attacked the rhodium carbene carbon resulting in the generation of cyclic intermediate **10a**. Ring opening of **10a** produced OAc migration product **2a** together with the liberation of the rhodium catalyst, from which polysubstituted piperidine **4aa** was obtained through an intermolecular aza-Diels–Alder reaction with **3a**.

In conclusion, we have developed a convenient synthetic protocol accessing polysubstituted piperidine easily from acyloxy substituted 1-sulfonyl-1,2,3-triazole and vinyl ether in moderate to excellent yields, and several related ring systems were constructed. A tandem process including rhodium carbene formation, 1,2-migration of acyloxy and inverse-electron-demand Diels–Alder reaction occurred in the procedure. Common functional groups were well tolerated and the chemoselectivity of this transformation was excellent, no pyrrole was detected at all. Further investigations of other migrating groups and dienophiles as well as the application of the strategy in bioactive molecule synthesis were underway in the lab.

Experimental Section

General procedure for synthesis of piperidines 4: Under a nitrogen atmosphere, dry toluene (1.5 mL) was added to reaction flask charged with $Rh_2(OAc)_4$ (0.004 mmol) 1-sulfonyl-1,2,3-triazole **1** (0.2 mmol), vinyl ether **3** (0.6 mmol) at room temperature. Then the reaction mixture was stirred at 80 °C for the indicated time in Scheme 2 and 3. The reaction mixture was cooled to room temperature and filtered through a short plug of silica gel. The filtrate was concentrated and the residue was purified by flash chromatography with PE/EtOAc (8:1) as eluent to give the corresponding product **4**.

Acknowledgements

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