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Rhodium-Catalyzed Synthesis of 1,2-Dihydropyridine by Tandem Reaction of 4-(1-Acetoxyallyl)-1-sulfonyl-1,2,3-triazole

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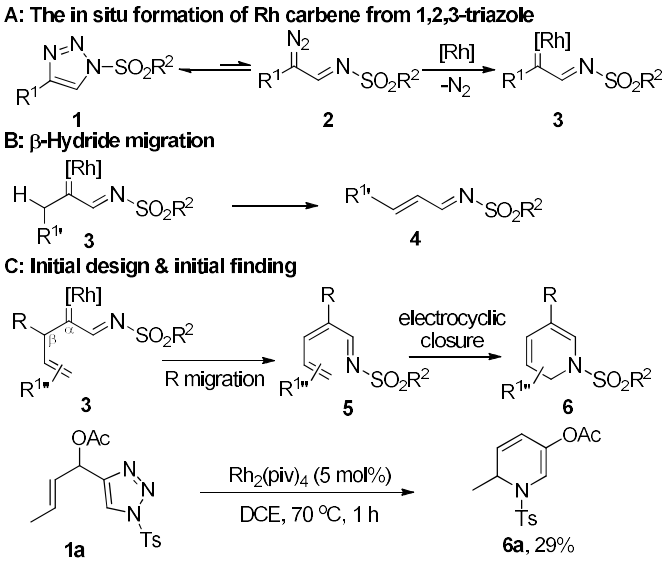
A tandem reaction of 4-(1-acetoxyallyl)-1-sulfonyl-1,2,3-triazole including formation of α-imino rhodium carbene, 1,2-migration of acetoxy group and six electron electrocyclic ring closure was reported. The migration of OAc group with excellent chemoselectivity was the crucial process leading to the formation of 1,2-dihydropyridine specifically in up to 90% yield. Several transformations of the dihydropyridine product were also achieved illustrating the potential of the protocol in organic synthesis. Based on the observation of the intermediate, a plausible mechanism was proposed.

Metal carbene, such as gold and rhodium carbene and so on, has been viewed as one of the most powerful tools in organic synthesis.[1] First reported by the group of Fokin and Gevorgyan in 2008, α-imino rhodium carbene **3** can be obtained very easily by taking advantage of the ring-chain tautomerization between readily available 1-sulfonyl-1,2,3-triazole **1** and α-diazo imine **2** (Scheme 1A).[2] Because of the 1,3-dipole feature, plenty of annulations for the generation of various (hetero)cycles were reported subsequently providing great flexibility in construction of such structures.[3,4]

1,2-Hydride migration is a well-known unpleasant process in the chemistry of α-imino rhodium carbene **3** (Scheme 1B). The undesired **4** was always generated as a side-product, resulting in low efficiency in annulation of **3** with other substrates.[4s] Although the crucial 1,3-dipole feature was disappeared in **4**, one good thing is that a new carbon-carbon double bond was generated. As a widely used building block in organic synthesis, the α,β-unsaturated imine **4**[5] would enrich the chemistry of α-imino rhodium carbene **3**. Based on this idea, we initially proposed our design as indicated in Scheme 1C.[6] In order to improve the efficiency of the 1,2-migration, a good migrating group R (R = OAc in this work) was loaded at the β-position of **3**, and an additional γ,δ-carbon carbon double bond was also installed. From the newly designed intermediate **3**, the 6π-electron electrocyclic ring closure precursor **5** could be generated much easier through a 1,2-migration of OAc, and **5** would be converted into *m*-oxygen dihydropyridine **6** very easily under heating conditions.



Scheme 1 Proposal and initial finding.

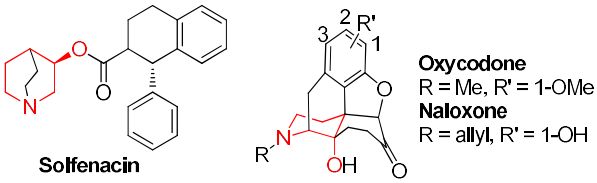


Fig. 1 Drugs containing multi-functionalized *m*-oxygen piperidine skeleton.

Fortunately, when we tried the reaction initially using **1a** with 5 mol% $Rh_2(piv)_4$ in DCE at 70 °C for 1 h, the desired **6a** was generated in 29% yield (Scheme 1C). It is well known that piperidine derivatives are vital motifs in many natural products,

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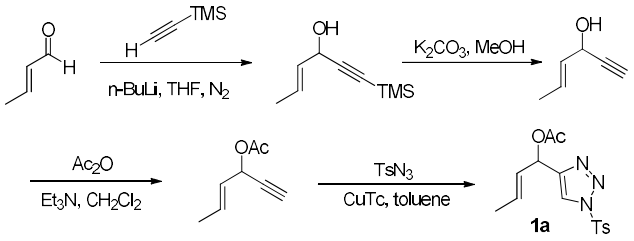
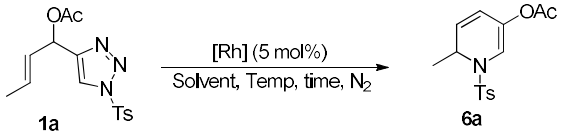
bioactive molecules and drugs (Fig. 1).[7] Considering the importance of the *m*-substituted piperidine derivatives as well as the convenience of the protocol in the synthesis of such multi-functionalized skeleton, we studied the tandem reaction of 1,2,3-triazoles for the synthesis of the *m*-substituted dihydropyridines, and reported the primary results herein.



Scheme 2 Synthesis of **1a**.

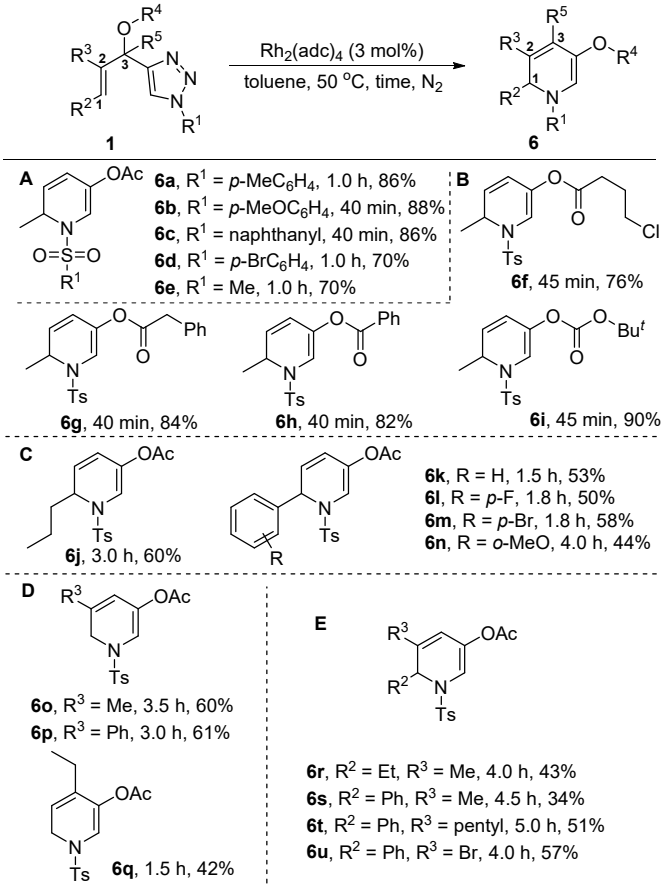
Table 1 Optimization of Reaction Conditions[a]



Entry	Catalyst	Solvent	Temp(°C)	time(h)	Yield[b](%)
1	$Rh_2(piv)_4$	DCE	70	1	29
2	$Rh_2(OAc)_4$	DCE	70	1	34
3	$Rh_2(oct)_4$	DCE	70	1	15
4	$Rh_2(esp)_2$	DCE	70	1	48
5	$Rh_2(adc)_4$	DCE	70	1	66
6	$Rh_2(dpf)_4$	DCE	70	5	0
7	$Rh_2(tpa)_4$	DCE	70	2.5	44
8[c]	$Rh_2(adc)_4$	DCE	70	0.5	75
9[c]	$Rh_2(adc)_4$	toluene	70	1.5	80
10[c]	$Rh_2(adc)_4$	$CHCl_3$	reflux	1.5	72
11[c]	$Rh_2(adc)_4$	TCE	70	1.5	67
12[c]	$Rh_2(adc)_4$	THF	70	2	52
13[c]	$Rh_2(adc)_4$	MeCN	70	4	37
14[c]	$Rh_2(adc)_4$	toluene	50	1	86
15[d,e]	--	toluene	50	1	--

[a] General reaction conditions: **1a** (67.0 mg, 0.2 mmol), rhodium(II) catalyst (0.01 mmol, 5 mol%), solvent (2.0 mL), N_2 atmosphere. [b] Isolated yield. [c] Rhodium(II) catalyst (0.006 mmol, 3 mol%). [d] No rhodium(II) catalyst was used. [e] **1a** was recovered in 85% yield. Ts = tosyl, OAc = acetate, oct = octanoate, piv = pivalate, esp = α,α,α',α'-tetramethyl-1,3-benzenedipropionate, adc = 1-adamantanecarboxylate, dpf = *N*,*N*'-diphenylformamidinate, tpa = triphenylacetate, DCE = 1,2-dichloroethane, THF = tetrahydrofuran, TCE = 1,1,2-trichloroethane.

Firstly, 1-(1-tosyl-1H-1,2,3-triazol-4-yl)but-2-en-1-yl acetate (**1a**), synthesized as displayed in Scheme 2 (see the Supporting Information for details),[8] was selected as the model substrate to optimize the reaction conditions for the generation of the **6a** (Table 1). Some rhodium salts (5 mol%) were tested as catalysts under N_2 atmosphere in distilled DCE at 70 °C (entries 1-7). Most rhodium salts we screened worked in this transformation. **1a** was consumed completely along with 29-66% **6a** being isolated except for $Rh_2(dpf)_4$ (entry 6). $Rh_2(adc)_4$ was selected as the most efficient catalyst giving **6a** in 66% yield (entry 5). Decreasing the amount of $Rh_2(adc)_4$ from 5 mol% to 3 mol% led to an increased yield (75%) in a shorter reaction time (entry 8). Screening solvents, such as toluene, $CHCl_3$, TCE, THF and MeCN (entries 9-13) proved that toluene was more suitable and the yield of **6a** was promoted to 80% (entry 9). The yield of **6a** was further increased to 86% when the reaction temperature was reduced to 50 °C (entry 14). When the reaction was carried out in the absence of rhodium catalyst, no desired product **6a** was isolated and substrate **1a** was recovered in 85% yield (entry 15), indicating the vital role of rhodium catalyst in this transformation. Accordingly, the optimized reaction conditions for the generation of **6** were established as indicated in entry 14.

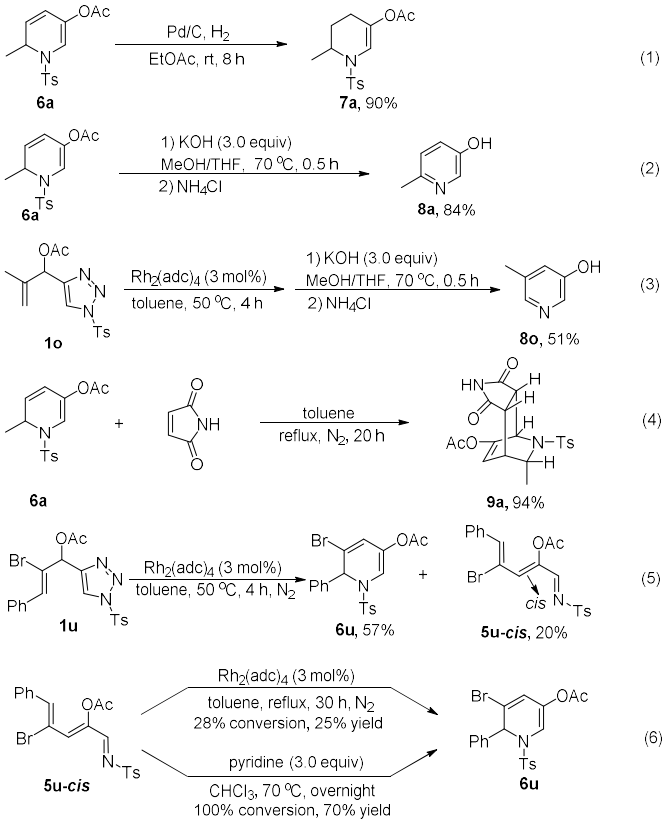


Scheme 3 Reaction Scope.

As displayed in Scheme 3, the scope of the transformation was evaluated under optimized reaction conditions. In general, variation of sulfonyl groups in 1,2,3-triazole **1** did not influence the yields of **6** greatly (Scheme 3A). Arylsulfonyl-substituted 1,2,3-triazoles produced the corresponding dihydropyridines conveniently in pretty good yields (**6a**-**c**, 86-88% yields) except for **6d**, which was generated in 70% yield. Methylsulfonyl-substituted 1,2,3-triazole performed not as good as the arylsulfonyl-substituted ones, and the product **6e** was generated in 70% yield. A range of ester groups were then tested (Scheme 3B), 76-90% yields of the corresponding products were obtained, and the best yield was achieved when Boc group was employed as the protecting group (**6i**, 90%).

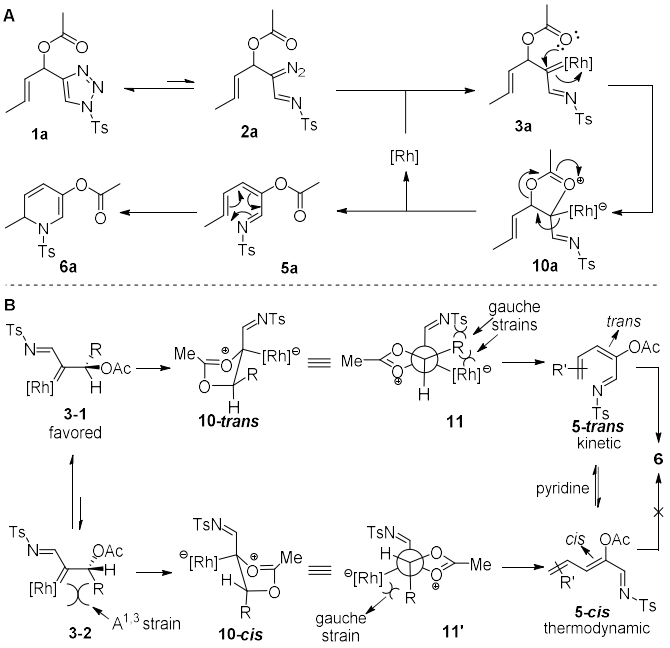
Next, we evaluated the scope of the reaction with respect to the substituents on the allyl group. When the methyl group in **1a** was replaced by propyl or aryl group (Scheme 3C), decreased yields (**6j-n**, 44-60%) were obtained. Position of substituent also influenced the efficiency of the transformation (Scheme 3D), **6o** and **6p** were formed in 60% and 61% yield respectively, whereas **6q** was isolated in only 42% yield. When more substituents were introduced into the substrate (Scheme 3E), highly functionalized dihydropyridine (**6r-u**) were obtained in 34-57% yields.

When OAc was replaced by hydroxy, methoxy or hydrogen(**1v-y**), no corresponding dihydropyridines were isolated, indicating the importance of OAc group in this transformation; 4-phenyl-1,2,3-trizaole (**1z**) was inert in this reaction, 93% of **1z** was recovered without generation of the desired product after treated under standard conditions for 4.0 h (See Supporting Information).



In order to illustrate the potential of the protocol in organic synthesis, product **6** was employed in several transformations. For example, **6a** could be reduced to tetrahydropyridine **7a** easily in 90% yield at rt (eq 1).[9] Treatment of **6a** with KOH in a mixed solvent at 70 °C delivered aromatization product hydroxyl pyridine **8a** in 84% yield (eq 2).[10] **8o** was synthesized in one pot from **1o** in 51% overall yield (eq 3). Actually, the structure of **6** was determined by the comparison of the analytical data of **8o** with that reported in literature.[11] Furthermore, as an electron-rich diene, **6a** could react with maleic imide generating D-A product **9a** in 94% yield (eq 4), and the relative configuration of **9a** was determined by H-H noesy data (See Supporting Information).

During our evaluation of the substrate scope, it was found that along with the formation of **6u**, uncyclized product **5u** was also isolated in 20% yield when triazole **1u** was treated under the standard conditions (eq 5). When **5u** was heated in toluene at 50 °C, no desired product **6u** was obtained; increasing the temperature to reflux did produce **6u** but only in 25% yield after 30 h (eq 6). It was inferred that in the case of **1u**, both **5u-*trans*** and **5u-*cis*** was formed and only **5u-*trans*** was converted to cyclic product **6u** through electrocyclic closure, leaving **5u-*cis*** being isolated. According to Murakami's report,[12] pyridine could help to establish an equilibrium between *cis* and *trans* of α,β-unsaturated imine, so **5u-*cis*** was heated with 3 equiv pyridine in $CHCl_3$ at 70 °C, and the desired **6u** was isolated in 70% yield (eq 6). Further NMR monitoring of the reaction of **1a** also provided additional evidence for the formation of **5a** (See Supporting Information for detail).



Scheme 4 Proposed Mechanism.

According to the above facts as well as literatures,[6,12] a plausible mechanism was proposed in Scheme 4A. Dimroth-type rearrangement of **1a** produced α-imino diazo compound **2a**, from which carbene **3a** was delivered in the presence of rhodium catalyst. Subsequently, the nucleophilic carbonyl oxygen atom in OAc group attacked the rhodium carbene resulting in the generation of the cyclic intermediate **10a**. Ring opening of **10a** produced the OAc migration product **5a** along with the rebirth of rhodium catalyst. The following electrocyclic ring closure of **5a** produced the final desired dihydropyridine **6a**.

Noticeably, in Murakami and his coworkers' report,[12] penta-2,4-dien-1-imine and 1,2-dihydropyridine could be synthesized by reaction of triazole and 2-(siloxy)furan. The synthesis of both products could be controlled by rhodium catalyst, but the selectivity for 1,2-dihydropyridine was not so good. They solved the problem by adding 3 equiv pyridine and heating for 24 h. From the proposed mechanism of our

reaction, the cis/trans selectivity could be controlled by $A^{1,3}$ strain and gauche strain (Scheme 4B). In intermediate **3**, because of the $A^{1,3}$ strain between [Rh] and R group, conformation **3-1** was favored than **3-2**, and after addition of the oxygen in carbonyl to C=Rh double bond, **10-*trans***, rather than **10-*cis***, should be generated easier. An antiperiplanar relationship between C-Rh bond and the leaving C-O bond in **11** led to the formation of kinetic controlled intermediate **5-*trans***.

In conclusion, a convenient protocol for the generation of 1,2-dihydropyridines was achieved by the rhodium-catalyzed tandem reaction of 4-(1-acetoxyallyl)-1-sulfonyl-1,2,3-triazole. The crucial intermediate penta-2,4-dien-1-imine was obtained by 1,2-migration of an ester group with excellent chemoselectivity. The ready access to the substrates, the mild reaction conditions and the versatility of the dihydropyridines should enhance the synthetic potential of this transformation.

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