Organic LETTERS

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Rh(II)/Mg(O^{t}Bu)$_2$-Catalyzed Tandem One-Pot Synthesis of 1,4-Oxazepines and 1,4-Oxazines from *N*-Sulfonyl-1,2,3-triazoles and Glycidols

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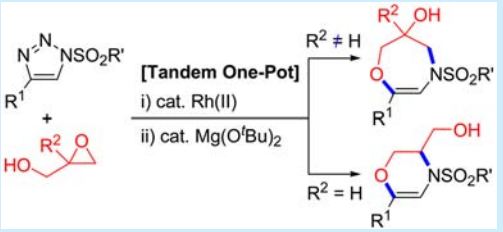
Supporting Information

ABSTRACT: A novel, one-pot route for the synthesis of nonaromatic ring-fused 1,4-oxazepines and 1,4-oxazines has been developed. The reaction features a sequential rhodium(II)-catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles with glycidols, followed by a regioselective Lewis acid Mg(O^{t}Bu)$_2$-catalyzed intramolecular ring-opening reaction. It has been found that the regioselectivity in the epoxide ring-opening was largely determined by the substituents on the glycidols. Thus, substituted glycidols ($R^2 \neq H$) afforded seven-membered oxazepine derivatives selectively, while unsubstituted glycidols ($R^2 = H$) afforded six-membered oxazine derivatives. Plausible reaction pathways are elucidated and supported by experiments with several glycidols bearing different substituents around the epoxide functionality.

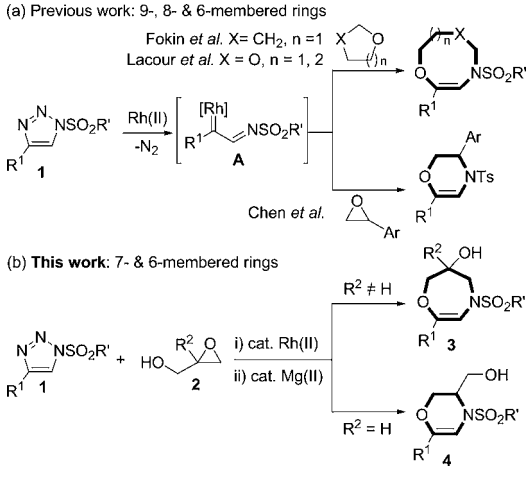


1,4-Oxazepine and 1,4-oxazine moieties are ubiquitous in natural products and bioactive compounds.[1,2] Although synthetic methods are known for these *N,O*-heterocycles, most of them afford the aromatic ring fused heterocycles.[3] In contrast, only a few particular strategies enable the construction of a non-aryl-fused seven-membered 1,4-oxazepine unit.[4] Thus, development of a novel catalytic method for the construction of these *N,O*-heterocycles would enable facile access to a relatively underexplored chemical space.

In recent years, rhodium(II)-catalyzed transannulations of *N*-sulfonyl-1,2,3-triazoles into other heterocyclic compounds have received considerable attention.[5] Among them, Fokin and co-workers found the insertion of rhodium(II)-carbene intermediate (**A**) into the C−O bond of THF, resulting in an eight-membered *N,O*-heterocyclic oxazocine (Scheme 1a, X = CH_2, *n* = 1).[6a] Quite recently, Lacour and co-workers extended this chemistry by reacting triazoles **1** with 1,3-dioxolanes or 1,3-dioxanes for the preparation of eight- and nine-membered dioxazocines and dioxazonines (X = O, *n* = 1 and 2).[6b] Chen and co-workers, meanwhile, reported the regioselective insertion of intermediate **A** into oxiranes to produce six-membered 1,4-oxazines,[6c] limited to the use of aryl-substituted epoxides only. To the best of our knowledge, there are no reports on the transformation of triazole **1** into seven-membered 1,4-oxazepines. In this context, we report the selective transannulation of triazoles **1** into seven-membered 1,4-oxazepines **3** and six-membered 1,4-oxazines **4** through insertion of **A** into the O−H bond of glycidol **2**, followed by the Lewis acid catalyzed intramolecular ring-opening reaction, which was found to be regioselective with respect to the R^2 substituent on the glycidol **2** (Scheme 1b).

As part of our continuing interest in rhodium-catalyzed transformation of triazole **1**,[7] we were prompted to examine the

Scheme 1. Rh(II)-Catalyzed Transannulations of *N*-Sulfonyl Triazoles 1 with Cyclic Ethers to *N,O*-Heterocyclic Compounds

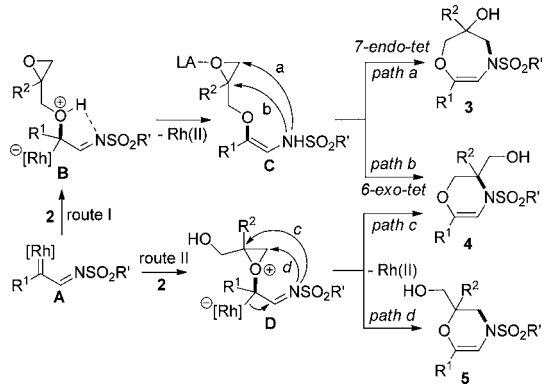


reaction between α-imino rhodium(II)−carbene intermediate **A** and glycidol **2** for the construction of 1,4-oxazepine and/or 1,4-oxazine scaffolds. Two reaction pathways could be anticipated (Scheme 2): intermediate **A** generated from rhodium-catalyzed denitrogenative rearrangement of **1** may undergo 1,3-insertion into the O−H bond to generate hydroxonium ylide **B** (route I)[8] or react with the epoxide to generate oxonium ylide **D** (route II).[6,9] In the route I pathway, 1,3-insertion product **C** could then undergo ring-opening in a *7-endo-tet* manner to afford 1,4-

Received: November 6, 2016
Published: December 1, 2016

DOI: 10.1021/acs.orglett.6b03328
Org. Lett. 2016, 18, 6432−6435

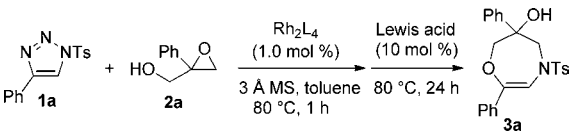
Scheme 2. Possible Reaction Pathways



oxazepine **3** (path a) or in a *6-exo-tet* manner to yield 1,4-oxazine **4** (path b). On the other hand, if the reaction follows route II, the ring opening of oxonium ylide **D** could furnish the two regioisomeric oxazines **4** and **5** through path c and path d, respectively. As the reactivity of intermediate **A** toward substrates bearing both hydroxyl and epoxide functionalities has not yet been investigated, we aimed to scrutinize which of the aforementioned pathways would be in operation in the reaction between *N*-sulfonyl-1,2,3-triazoles and glycidols under rhodium(II) catalysis in furnishing value-added *N*,*O*-heterocycles.

Our investigation commenced with *N*-tosylated triazole **1a** and phenyl-substituted glycidol **2a** as model substrates. As shown in Table 1, a judicious combination of catalysts was important for the efficacy of this reaction. In the reaction using 1.0 mol % of $Rh_2(^tBuCO_2)_4$ as the sole catalytic agent, triazole **1a** was consumed without affording the desired product (entry 1, Table 1). In this reaction, it was found that although the transitory intermediate **C** is observable via TLC and crude ^1H NMR, **C** was nevertheless subject to rapid nonspecific decomposition, underlining the need for Lewis acid activation of the epoxide ring to enable the subsequent ring-opening reaction. After screening different Lewis acids as a secondary catalytic additive to facilitate the anticipated epoxide ring-opening event (entries 2−10, Table 1), it was found that the use of 10 mol % of $Mg(O^tBu)_2$ was particularly propitious, affording 1,4-oxazepine **3a** in 46% yield (entry 9, Table 1). Use of other Lewis acids such as $Sc(OTf)_3$, $BF_3{\cdot}Et_2O$, $Ni(ClO_4)_2$, and $Mg(OTf)_2$ was unsuccessful (entries 2−4 and 8, Table 1) and use of $Zn(OAc)_2$, SmI_2, or MgI_2 (entries 5−7, Table 1) afforded inferior yields. We were pleased to discover that the elevation of the reaction temperature to 110 °C following the addition of $Mg(O^tBu)_2$ furnished the desired product in 81% yield (entry 10, Table 1). The nonsequential coaddition of rhodium(II) and Lewis acid catalysts afforded the desired product in a depressed 36% yield (entry 11, Table 1). The use of rhodium(II) catalysts with different ligand appendages such as $Rh_2(OAc)_4$, $Rh_2(oct)_4$, $Rh_2(S\text{-PTAD})_4$, $Rh_2(S\text{-DOSP})_4$, $Rh_2(S\text{-NTTL})_4$, and $Rh_2(esp)_4$ failed to improve the reaction (entries 12−17). Additionally, a solvent and additive screening conducted during the preliminary stages of this investigation established the use of toluene with added 3 Å molecular sieves to be particularly optimal.

Table 1. Optimization of Reaction Conditions[a]



entry	Rh_2L_4	Lewis acid	**3a**[b] (%)
1	$Rh_2(^tBuCO_2)_4$	–	–
2	$Rh_2(^tBuCO_2)_4$	$Sc(OTf)_3$	–
3	$Rh_2(^tBuCO_2)_4$	$BF_3{\cdot}Et_2O$	–
4	$Rh_2(^tBuCO_2)_4$	$Ni(ClO_4)_2$	–
5	$Rh_2(^tBuCO_2)_4$	$Zn(OAc)_2$	6
6	$Rh_2(^tBuCO_2)_4$	SmI_2	28
7	$Rh_2(^tBuCO_2)_4$	MgI_2	28
8	$Rh_2(^tBuCO_2)_4$	$Mg(OTf)_2$	–
9	$Rh_2(^tBuCO_2)_4$	$Mg(O^tBu)_2$	46
10[c]	$Rh_2(^tBuCO_2)_4$	$Mg(O^tBu)_2$	81 (60)[d]
11[e]	$Rh_2(^tBuCO_2)_4$	$Mg(O^tBu)_2$	36
12[c]	$Rh_2(OAc)_4$	$Mg(O^tBu)_2$	<5
13[c]	$Rh_2(oct)_4$	$Mg(O^tBu)_2$	29
14[c]	$Rh_2(S\text{-PTAD})_4$	$Mg(O^tBu)_2$	–
15[c]	$Rh_2(S\text{-DOSP})_4$	$Mg(O^tBu)_2$	27
16[c]	$Rh_2(S\text{-NTTL})_4$	$Mg(O^tBu)_2$	63
17[c]	$Rh_2(esp)_4$	$Mg(O^tBu)_2$	39

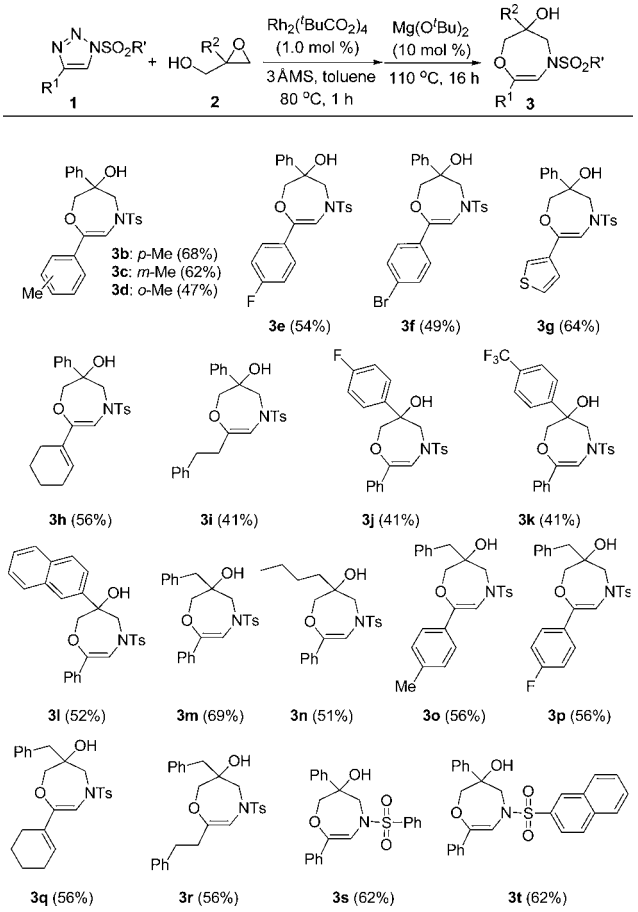
[a]Conditions: **1a** (0.50 mmol), **2a** (0.60 mmol), Rh_2L_4 (1.0 mol %), 3 Å MS (ca. 100 mg) in toluene (3.1 mL, 0.16 M). [b]NMR yield with CH_2Br_2 as an internal standard. [c]After addition of Lews acid (10 mol %), the reaction was conducted at 110 °C for 16 h. [d]Isolated yield in parentheses. [e]Both Rh(II) and Lewis acid catalyst were added at the initial stage.

With the optimal reaction conditions in hand, we next explored the scope of this reaction with various 1,2,3-triazoles and glycidols (Scheme 3). The reaction of *N*-tosylated 4-phenyl-substituted triazoles bearing a methyl group at the *para*- (**1b**) and *meta*- (**1c**) positions with phenyl-substituted glycidol **2a** furnished the corresponding 1,4-oxazepines **3b** and **3c** in good yield. Although the yields were diminished, use of triazole **2d** bearing an *o*-methyl-substituted 4-phenyl moiety also furnished the desired product **3d**. 4-Phenyltriazoles with electron-withdrawing fluoride and bromide substituents on the *para* position afforded the corresponding 1,4-oxazepines **3e** and **3f** in moderate yields. The reactions of heteroaromatic 3-thiophene-yl **1g**, cyclohexenyl **1h**, and even alkyl-substituted triazole **1i** were effective in furnishing 1,4-oxazepines **3g−i** in high to moderate yields. The present protocol showed broad scope with respect to glycidols. Thus, the reaction of **1a** with glycidol bearing aryl (**2b−d**), benzyl (**2e**), and butyl (**2f**) substituents all afforded the corresponding 1,4-oxazepines **3j−n** in moderate to good yields. Benzyl-substituted glycidol **2e** was further reacted with a variety of 4-substituted triazoles having phenyl, cyclohexenyl, and alkyl appendages to successfully furnish aryl/alkyl-, alkene/alkyl-, and alkyl/alkyl-substituted 1,4-oxazepines **3o−r**. Variations of the *N*-sulfonyl group were explored in the successful reaction of *N*-benzenesulfonated and *N*-naphthalene-2-sulfonated 1,2,3-triazoles with **2a**, which provided **3s** and **3t** in good yields. In all reactions considered thus far, 1,4-oxazines were not detected, indicating that in reactions employing glycidols bearing a highly hindered tertiary carbon the intramolecular epoxide ring-opening event occurs via sterically less substituted carbon through *7-endo-tet* cyclization.

Interestingly, the use of unsubstituted glycidol **2g** in the reaction with triazole **1a** did not afford the corresponding 1,4-oxazepine, leading instead to a mixture of inseparable regioisomeric oxazines **4a** and **5a** (**4a**/**5a** = 7/1, NMR analysis) in 74% yield. Fortunately, the inseparable **4a** and **5a** could easily be separated after further elaboration to the corresponding *p*-nitrobenzoates **6a** and **7a** (see the SI). As shown in Scheme 4,

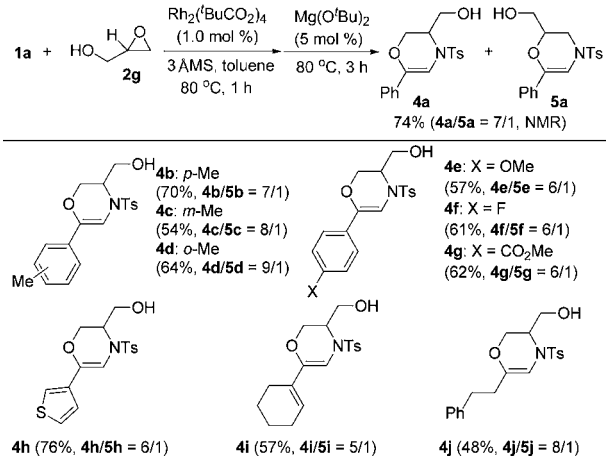
DOI: 10.1021/acs.orglett.6b03328
Org. Lett. 2016, 18, 6432−6435

Scheme 3. Synthesis of 1,4-Oxazepines 3[a]



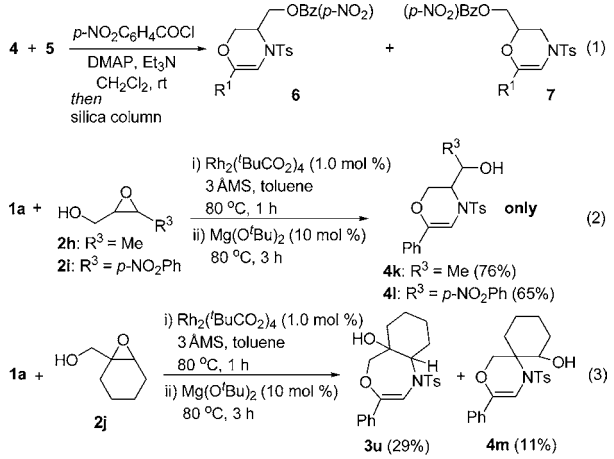
[a]Conditions: **1** (0.30 mmol), **2g** (0.36 mmol), $Rh_2(^tBuCO_2)_4$ (1.0 mol %), and 3 Å MS (ca. 60 mg) in toluene (1.8 mL, 0.16 M). After 1 h reaction at 80 °C, $Mg(O^tBu)_2$ (2.6 mg, 5 mol %) was added, and then the mixture was reacted for 16 h at 110 °C. Isolated yield.

Scheme 4. Rh(II)-Catalyzed Transannulations of Triazoles 1 to Oxazines[a]



[a]Conditions: **1a** or **1** (0.50 mmol), **2g** (0.60 mmol), and 3 Å MS (ca. 100 mg) in toluene (3.1 mL, 0.16 M). After 1 h of reaction at 80 °C, $Mg(O^tBu)_2$ (8.5 mg, 10 mol %) was added, and then the mixture was reacted for 16 h at 110 °C. Yields are isolated yields, and **4**/**5** ratios were determined by ^1H NMR analysis.

this reactivity was quite general when unsubstituted glycidol **2g** was reacted with various triazoles and could afford the 1,4-oxazines **4b**−**j** along with regioisomeric **5b**−**j** in good yields with up to **4**/**5** = 9/1 ratio. For all cases, the major isomer **4** could also easily be separated after formation of the corresponding *p*-nitrobenzoates **6** (eq 1). Formation of the regioisomeric oxazines



4a and **5a** in the reaction of **1a** with **2g** strongly suggests that substituents on the glycidol moiety play a decisive role in influencing the reaction pathway. In order to gain more insight, a mixture of *cis*/*trans* glycidols **2h** (ca. *cis*/*trans* = 1:1), **2i** (*trans* only), and a racemic cyclohexene oxide **2j** bearing substituents on different positions around the epoxide functionality have been investigated in their reaction with **1a**.

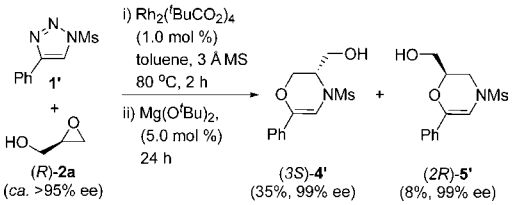
Interestingly, the reaction of triazole **1a** with methyl-substituted epoxide **2h** or *p*-nitrophenyl-substituted **2i** furnished only oxazines **4k** and **4l** in good yields (eq 2). In contrast, reaction with cyclohexene oxide **2j** afforded a mixture of oxazepine **3u** and spiro-oxazine **4m** (**3u**/ **4m** = ca. 3:1 ratio) (eq 3). We propose the following reaction pathways to account for our observations: in the reaction between α-imino rhodium(II)−carbene **A** with glycidol **2**, 1,3-insertion reaction of **A** into the O−H bond via ylide **B** takes place to produce unstable vinyl ether **C** (route I in Scheme 2), which then undergoes Lewis acid catalyzed epoxide ring opening. Regioselectivity of this event is determined by the nature of the R^2 substituent. When $R^2 \neq H$, the ring opening occurs at the sterically less hindered carbon in a 7-*endo*-*tet* fashion (path a, route I in Scheme 2), affording 1,4-oxazepine **3**. In contrast, when unsubstituted glycidols ($R^2 = H$) are used (such as **2g**, **2h**, and **2i**), the kinetically favorable 6-*exo*-*tet* ring opening pathway is enabled (path b, route I in Scheme 2), resulting in 6-membered oxazine **4** as the major product. For glycidols with nonterminal epoxides (such as **2h** and **2i** where $R^3 \neq H$), this is the only reaction pathway available. We propose an additional, competing reaction pathway to account for the minor regioisomers observed in the reaction of unsubstituted glycidols (where $R^2 = H$ and $R^3 = H$). In this situation, intermediate **A** could also react with the sterically unhindered oxygen atom of the epoxide to form ylide **D**, and subsequent ring opening via the sterically less hindered carbon furnishes **5** as a minor product (route II, path d in Scheme 2). In all cases, the hydroxyl functionality is more reactive than the epoxide functionality with respect to intermediate **A**, although C−O insertion into the epoxide can also take place as a minor event when using unsubstituted glycidols such as **2g**.

To investigate if the chemistry presented is amenable to asymmetric synthesis, we performed the reaction using a

DOI: 10.1021/acs.orglett.6b03328
Org. Lett. 2016, 18, 6432−6435

commercially available chiral glycidol (*R*)-**2a** (ca. >95% ee) and *N*-mesyl-1,2,3-triazole **1′** as starting materials. Although the yield was moderate, the separable *N*-mesyl-substituted regioisomeric 1,4-oxazine (3*S*)-**4′** and (2*R*)-**5′** were synthesized with complete transfer of chirality via S_N2 opening of the epoxide (Scheme 5).

Scheme 5. Transfer of Chirality in Preparation of 1,4-Oxazines



In summary, we have developed a novel Rh(II)/$Mg(O^tBu)_2$-catalyzed tandem one-pot reaction for the synthesis of 1,4-oxazepine and 1,4-oxazine derivatives from *N*-sulfonyl-1,2,3-triazoles and glycidols through sequential O−H insertion of rhodium(II) carbene and subsequent Lewis acid catalyzed regioselective epoxide ring-opening reaction. It has been found that electrophilic α-imino Rh(II)−carbene intermediates show higher reactivity toward alcohol functionality and readily undergo 1,3-insertion into the O−H bond, although direct reaction with the epoxide can also take place when using unsubstituted glycidols. The present protocol represents an effective method for preparation of non-aryl-fused *N*,*O*-heterocycles including 7-membered 1,4-oxazepines, which are not readily accessible from known methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03328.

Detailed experimental procedures, characterization data, and ^1H and ^{13}C NMR for all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Samsung Science and Technology Foundation (SSTF-BA1401-10). We thank Dr. Kris Rathwell for critical reading of this manuscript.

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DOI: 10.1021/acs.orglett.6b03328
Org. Lett. 2016, 18, 6432−6435