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# Synthesis of 6-Substituted Piperidin-3-ones via Rh(II)-Catalyzed Transannulation of *N*-Sulfonyl-1,2,3-triazoles with Electron-Rich Aromatic Nucleophiles

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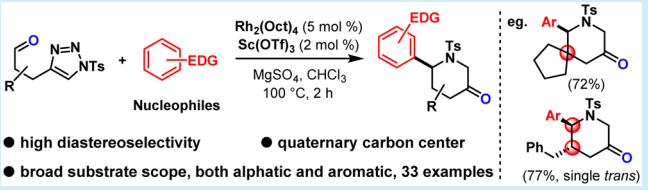
Supporting Information

**ABSTRACT:** A highly diastereoselective rhodium(II)-catalyzed transannulation of aldehyde-tethered *N*-sulfonyl triazoles with electron-rich aromatic nucleophiles is reported for the first time to afford functionalized 6-substituted piperidin-3-ones. The reaction has a broad substrate scope including both aliphatic and aromatic *N*-sulfonyl-1,2,3-triazoles together with various aromatic nucleophiles. The addition of a catalytic amount of Lewis acid has proven to be crucial for the yield improvement. By employing this methodology, hardly accessible piperidin-3-ones bearing quaternary carbons could be obtained.




The piperidin-3-one is a frequently encountered intermediate in the synthesis of alkaloid natural products and pharmaceutical agents.[1] This moiety could be easily converted into diversely functionalized compounds, such as piperidin-3-ol, a versatile building block in organic synthesis,[2] as well as piperidin-3-amine via reductive amination.[3] However, a practical and efficient access to piperidin-3-one remains scarce. The aza-Achmatowicz reaction is a general method for the preparation of this scaffold, which requires multiple steps and affords 6-alkoxy or hydroxyl piperidin-3-ones (eq 1 in Figure 1).[4] Other methods including ring expansion of cyclopropanes,[5] [1, 2]-shift of ammonium ylides,[6] and modification of amino acids[7] usually need particular precursors to generate specific piperidin-3-ones. Recently, Zhou et al. reported an iridium-catalyzed hydrogenation of 3-hydroxypyridinium salts, but this reaction is restricted to the formation of 6-*H*-piperidin-3-ones (eq 2 in Figure 1).[8] Moreover, to the best of our knowledge, the synthesis of piperidin-3-ones bearing quaternary carbons are still unexplored. In this context, the search for a step-economical and efficient system to generate structural diversity of piperidin-3-ones is of great value.

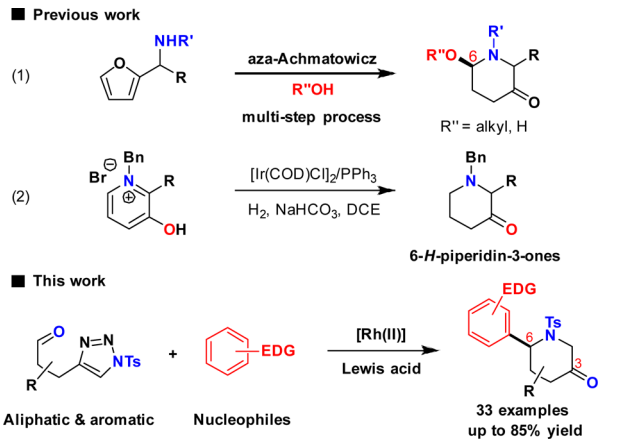



**Figure 1.** Different strategies for the construction of piperidin-3-ones.

The *N*-sulfonyl triazole chemistry has attracted much attention in recent years.[9] Disclosed initially by Fokin, Gevorgyan and co-workers,[10] the *N*-sulfonyl-1,2,3-triazoles have emerged as stable and readily available precursors of α-imino metal carbenes[11] and have proven to be an excellent nitrogen source for the construction of numerous heterocycles.[9d] The Shi and Huang groups independently reported the synthesis of a mixture of 1,2-dihydroisoquinolines and 1-indanones from *N*-sulfonyl 1,2,3-triazoles bearing an ether tether upon treatment with a rhodium(II) catalyst.[12] Quite recently, Li and co-workers disclosed the rhodium-catalyzed intramolecular reaction of benzyl bromide and *N*-sulfonyl triazoles to afford versatile 4-bromo-1,2-dihydroisoquinolines, and a bromonium ylide was proposed as the key intermediate.[13]

In continuation of our interest in the development of novel carbene transformations involving *N*-sulfonyl triazoles,[14] we present herein a diastereoselective rhodium(II)-catalyzed intermolecular transannulation of *N*-sulfonyl triazoles with electron-rich aromatic nucleophiles to construct diversely functionalized 6-substituted piperidin-3-ones, including these with quaternary carbons.

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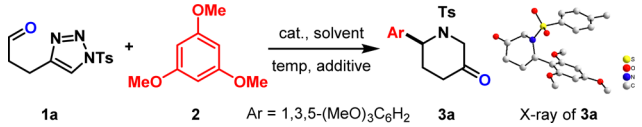
In alignment with our previous work, the reaction of *N*-sulfonyl triazole **1a** and 1,3,5-trimethoxybenzene **2** in chloroform at 120 °C in the presence of catalytic $Rh_2(Oct)_4$ was selected as a model system (Table 1).[14b] To our delight, the

**Table 1. Optimization of the Reaction Conditions**[a]



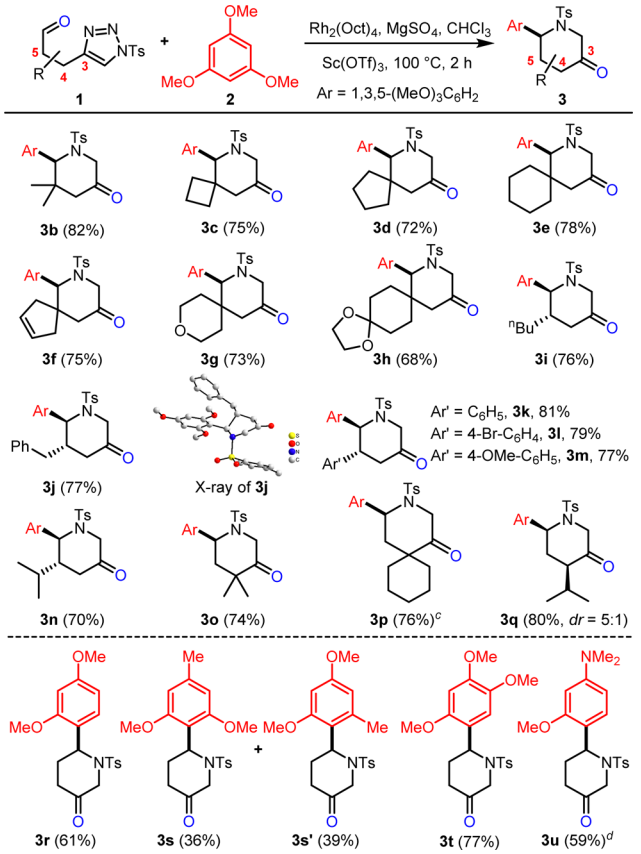

| entry | catalyst | solvent | temp (°C) | additive | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $Rh_2(Oct)_4$ | $CHCl_3$ | 120 | none | 10 |
| 2 | $Rh_2(Oct)_4$ | $CHCl_3$ | 120 | $MgSO_4$ | 35 |
| 3 | $Rh_2(Oct)_4$ | $CHCl_3$ | 100 | $MgSO_4$ | 47 |
| 4 | $Rh_2(Oct)_4$ | $CHCl_3$ | 80 | $MgSO_4$ | 39 |
| 5 | $Rh_2(OAc)_4$ | $CHCl_3$ | 100 | $MgSO_4$ | 20 |
| 6 | none | $CHCl_3$ | 100 | $MgSO_4$ | 0 |
| 7 | $Rh_2(Oct)_4$ | DCE | 100 | $MgSO_4$ | 28 |
| 8 | $Rh_2(Oct)_4$ | toluene | 100 | $MgSO_4$ | 25 |
| **9** | **$Rh_2(Oct)_4$** | **$CHCl_3$** | **100** | **$MgSO_4$/Sc(OTf)$_3$ (2 mol %)** | **78** |
| 10 | $Rh_2(Oct)_4$ | $CHCl_3$ | 100 | $MgSO_4$/Cu(OTf)$_2$ (2 mol %) | 71 |
| 11 | $Rh_2(Oct)_4$ | $CHCl_3$ | 100 | $MgSO_4$/Yb(OTf)$_3$ (2 mol %) | 69 |
| 12 | $Rh_2(Oct)_4$ | $CHCl_3$ | 100 | $MgSO_4$/Sc(OTf)$_3$ (10 mol %) | 50 |

[a]All reactions were carried out in 0.04 M solvent with 5 mol % catalyst and 5.0 equiv of nucleophile under a nitrogen atmosphere. [b]Isolated yields.

desired 6-substituted piperidin-3-one **3a** was detected albeit in just 10% yield (entry 1), and its structure was further confirmed by X-ray crystallographic analysis.[15] The addition of anhydrous magnesium sulfate into the reaction mixture would improve the yield up to 35%, suggesting that water could compete with the aromatic nucleophile to take part in the reaction (entry 2). Screening the reaction temperature showed that 100 °C was the best choice (entries 3 and 4), and the product was obtained in 47% yield. Replacing $Rh_2(Oct)_4$ with other rhodium(II) catalysts, such as $Rh_2(OAc)_4$, gave a lower yield (entry 5). When the reaction was carried out without a metal catalyst, no desired product could be detected, indicating that $Rh_2(Oct)_4$ played an essential role (entry 6). Other solvents, for instance, 1,2-dichloroethane or toluene, all gave unsatisfactory yields (entries 7 and 8). Lewis acids have been used as efficient promoters for some *N*-sulfonyl triazole reactions,[14b,16] so we tested different kinds of Lewis acids. Delightedly, the yield of **3a** was dramatically improved, and when 2 mol % Sc(OTf)$_3$ was employed, a yield of 78% was obtained (entries 9−11). Further increasing the amount of Sc(OTf)$_3$ up to 10 mol %, in contrast, made the yield drop to 50% (entry 12).

With the optimized reaction conditions secured, we explored the scope and generality of the reaction with a variety of aliphatic *N*-sulfonyl triazoles. As shown in Scheme 1, the substrates with either dimethyl groups or different rings, including four-, five-, and six-membered rings, at the C5 position could be transformed into the corresponding products **3b−e** in excellent yields. Functional groups, such as a double bond and heteroatom, could also be tolerated under the reaction conditions to give **3f−h**. Especially, all these formed products contain quaternary carbons, which could not be

**Scheme 1. Substrate Scope of Aliphatic *N*-Sulfonyl-1,2,3-triazoles**[a,b]




[a]Reaction conditions: **1** (0.20 mmol), aromatic nucleophile (1.0 mmol), $Rh_2(Oct)_4$ (10 μmol), Sc(OTf)$_3$ (4.0 μmol), and $MgSO_4$ (0.40 g) in $CHCl_3$ (5.0 mL) at 100 °C for 2 h. [b]Isolated yields. [c]Reaction for 6 h. [d]Without Sc(OTf)$_3$.

accessed by a normal aza-Achmatowicz reaction. When the C5 position of the substrate was monosubstituted by *n*-butyl, benzyl, various phenyl, or isopropyl groups, the desired products **3i−n** were obtained as single *trans*-isomers. The relative stereochemistry of **3j** was established by X-ray crystallographic analysis.[15] The C4 position of the substrate could be substituted with a variety of groups as well, including dimethyl groups, cyclohexane, and an isopropyl group, to give products **3o−q** in good yields. Besides 1,3,5-trimethoxybenzene, other electron-rich aromatic compounds could also serve as good nucleophiles. For 1,3-dimethoxy- and 1,2,4-trimethoxybenzene, the products **3r** and **3t** were isolated in 61% and 77% yields respectively, while 1,3-dimethoxy-5-methylbenzene gave isomers **3s** and **3s′** in nearly equal yields. When 3-dimethylaminoanisole was employed, the desired product **3u** was obtained in just 59% yield in the absence of a Lewis acid.[17] The aromatic nucleophiles with less electron-rich substituent groups, such as anisole and *N*,*N*-dimethylaniline, did not give the corresponding products. It is noteworthy that, during all the above cases, *β*-H elimination or [1, 2]-alkyl migration,[18] which potentially occurs along with alphatic rhodium carbenoid intermediates, was not observed.[19]

Later, the aromatic *N*-sulfonyl triazoles were found to be suitable substrates for this transannulation (Scheme 2). When 2-triazole-benzaldehyde was employed as the substrate, the product **5a** was isolated in 84% yield, and the structure of **5a**



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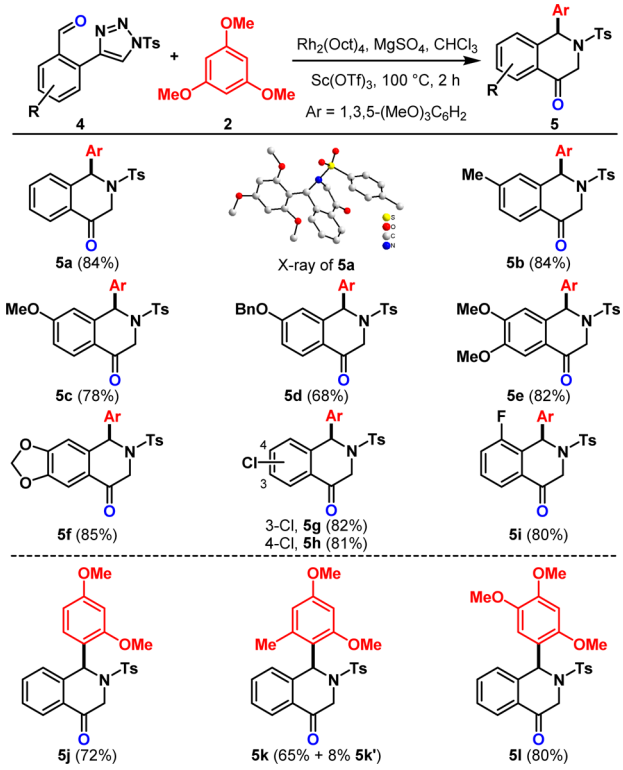
**Scheme 2. Substrate Scope of Aromatic *N*-Sulfonyl-1,2,3-triazoles**[a,b]

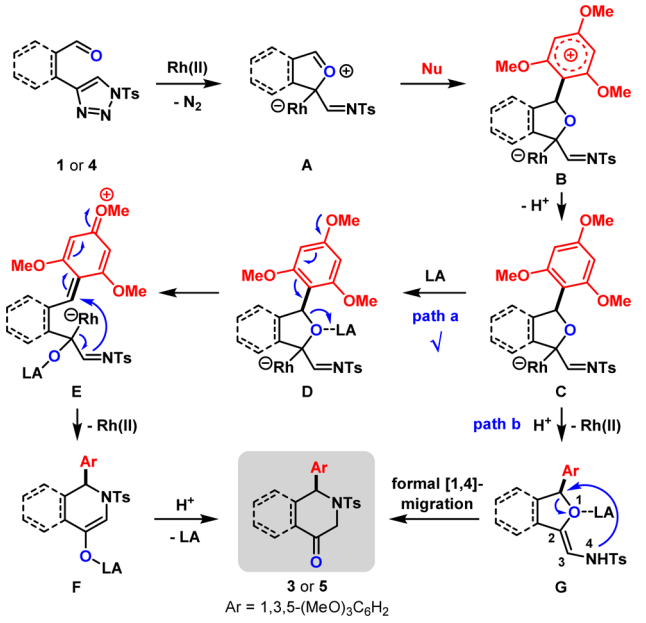



[a]Reaction conditions: **4** (0.20 mmol), aromatic nucleophile (1.0 mmol), $Rh_2(Oct)_4$ (10 $\mu$mol), $Sc(OTf)_3$ (4.0 $\mu$mol), and $MgSO_4$ (0.40 g) in $CHCl_3$ (5.0 mL) at 100 °C for 2 h. [b]Isolated yields.

was confirmed by X-ray crystallographic analysis.[15] The effect of substituents on the phenyl ring was evaluated. Both electron-donating (Me−, MeO−, BnO−, 3,4-$(MeO)_2$−, or $-OCH_2O-$) and electron-withdrawing (Cl− or F−) groups were tolerated well to give the desired products **5b−i** in excellent yields. The 1,3-dimethoxy- and 1,2,4-trimethoxybenzene could also be efficiently used as nucleophiles affording **5j** and **5l** in 72% and 80% yields, respectively. For 1,3-dimethoxy-5-methylbenzene, the major product was **5k**, along with minor isomer **5k′** which was generated from the nucleophilic attack of the *N*-sulfonyl triazole via the C2 position of 1,3-dimethoxy-5-methylbenzene. The ratio of the isomers was proposed due to the stronger electron effect of the *para*-methoxyl group compared to the *ortho*-methoxyl group.

Based on the above results, a proposed mechanism is illustrated in Scheme 3. Upon treatment with the rhodium(II) catalyst, *N*-sulfonyl triazole **1** or **4** decomposes into the corresponding $\alpha$-imino metal carbene, which could be further trapped by the intramolecular aldehyde to form oxonium ylide **A**.[14b,20] Nucleophilic addition of an electron-rich aromatic nucleophile to the oxonium intermediate affords zwitterion **B**, which releases a proton to generate intermediate **C**. There are two plausible pathways for the subsequent transformations. In path a, the oxygen atom bearing lone pair electrons coordinates to the Lewis acid, and subsequent C−O bond cleavage takes place under the simultaneous action of the electron-rich aromatic ring to give zwitterion **E**. Release of the rhodium catalyst and recombination of the nitrogen atom with the benzylic carbon center deliver the cycloadduct **F**, which after protonation would isomerize into 6-substituted piperidin-3-one

**Scheme 3. Proposed Mechanism**




**3** or **5**. On the other hand, path b involving demetalation, followed by a formal [1, 4]-migration and isomerization to product **3** or **5**, could also not be ruled out. However, previous reports show that a formal [1, 3]-migration is possible for intermediate **G**.[14c,21] In this case, path a is more favorable.

In conclusion, a novel rhodium(II)-catalyzed intermolecular transannulation of aldehyde-tethered *N*-sulfonyl triazoles with electron-rich aromatic nucleophiles has been developed for the first time. This methodology provides a step-economical and practical access to functionalized 6-substituted piperidin-3-ones, especially to these with quaternary carbons, which are not easily obtained through other methods. A mechanism involving oxonium ylide formation, Lewis acid assisted C−O cleavage, C−N recombination, and enol isomerization has been proposed. The broad substrate scope for both aliphatic and aromatic *N*-sulfonyl triazoles together with the high diastereoselectivity make this reaction promising for the construction of useful scaffolds in biomedical research and drug discovery.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01180.

Experimental procedures and spectra copies (PDF)

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### Notes

The authors declare no competing financial interest.



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(15) CCDC 1539648 (**3a**), CCDC 1539578 (**3j**), and CCDC 1539582 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

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