# Rhodium(II)-Catalyzed Stereocontrolled Synthesis of Dihydrofuran-3-imines from 1-Tosyl-1,2,3-triazoles

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S *Supporting Information*

ABSTRACT: Rhodium(II) acetate catalyzes the denitrogenative transformation of 5-substituted and 4,5-disubstituted 1-sulfonyl-1,2,3-triazoles with pendent allyl and propargyl ether motifs to oxonium ylides that undergo [2,3]-sigmatropic rearrangement to give substituted dihydrofuran-3-imines in high yield and diastereoselectivity.
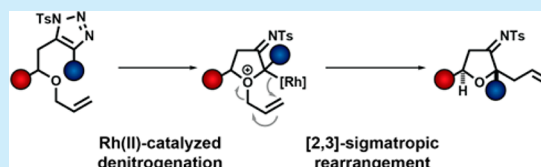
The manipulation of highly reactive species is an attractive strategy for organic chemists because it allows rapid generation of molecular complexity. In the presence of a suitable transition-metal catalyst, 1-sulfonyl-1,2,3-triazoles (1-STs) are under Dimroth-type equilibrium $1 \rightleftharpoons 1'$,[1] and denitrogenative decomposition results in the controlled formation of reactive carbenoid[2] species **2** (Scheme 1a).

Scheme 1. Overview

a) 1-Sulfonyl-1,2,3-Triazoles as Carbenoid Precursors

b) Dihydrofuran-3-one Formation by Diazoketone Decomposition

c) This Work
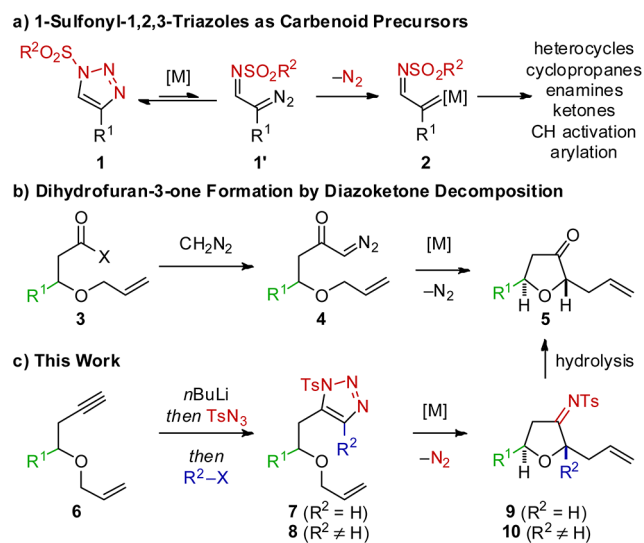
The careful design of novel reaction conditions has resulted in the ability to steer these intermediates toward a range of interesting products with excellent yield and selectivity.[3−5] Despite the wealth of chemistry that has been developed in this area, the focus has been the use of 4-substituted 1-STs (i.e., **1**), and there are few examples of reactions using 1-STs with substitution at the 5-position or with 4,5-disubstitution.[4]

The tetrahydrofuran motif is ubiquitous across many natural product classes and important bioactive compounds.[6] One area in which the use of carbenoids has been exploited to great effect is the synthesis of 2,5-*trans*-disubstituted dihydrofuran-3-ones **5**

from α-diazoketones **4** (Scheme 1b).[7] Despite the value of products accessible from this reaction, the requirement for diazomethane to synthesize the substrates (i.e., **3 → 4**) has limited its use to those with specialist training and equipment.[8] Furthermore, the corresponding reaction with α-diazoketones derived from higher diazoalkanes has not been reported,[9] limiting the level of substitution which can be achieved in the products **5**.

This paper describes the rhodium(II)-catalyzed transformation of 5- and 4,5-substituted-1-STs **7** bearing allyl and propargylic ethers into stereodefined dihydrofuran-3-imines **9** (Scheme 1c). The imines themselves are valuable products,[10] or they can be hydrolyzed under mild conditions to offer complementary access to 2,5-*trans*-disubstituted dihydrofuran-3-ones **5**. Furthermore, this reaction is shown to be effective for trisubstituted 1,2,3-triazoles **8** to give products **10** with controlled formation of a tetrasubstituted stereocenter.

The substitution pattern of the substrate required for this study **7a** cannot be formed using metal-catalyzed cycloaddition[11] but can be readily accessed by treatment of the corresponding alkyne **6a** with *n*-BuLi and TsN₃ (Scheme 2).[12,13] A careful screen of catalysts and conditions showed rhodium(II) acetate to be most effective at promoting the loss of nitrogen at elevated temperatures, resulting in selective formation of a single product that was identified as the 2,5-*trans*-disubstituted dihydrofuran-3-imine **9a**.[13] The *N*-tosylimine was unstable to purification by chromatography, but Rh₂(OAc)₄ could be removed by filtration through Celite to

## Scheme 2. 1-ST Synthesis and Reactivity
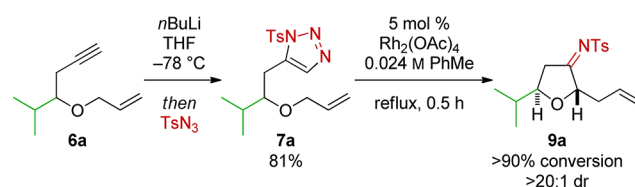
give the product of denitrogenative rearrangement **9a**. The *N*-tosylimine is a valuable functional group[10] for further functionalization: the imine **9a** could be hydrolyzed to the corresponding ketone **5a** by stirring with wet basic alumina (Brockmann III)[14] and also was an excellent substrate for reduction or nucleophilic attack which allowed facile generation of highly decorated tetrahydrofuran products **11a–13a** (Scheme 3).

Scheme 3. Reactivity of *N*-Tosylimine 9a
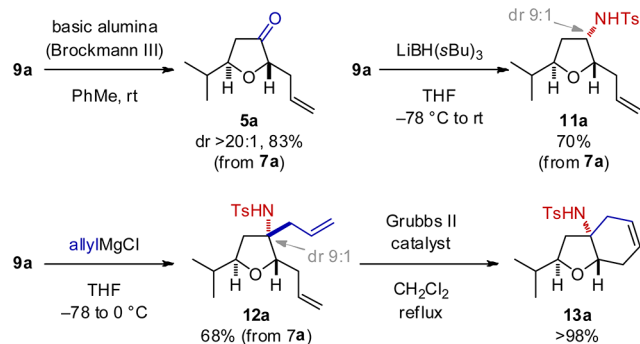
To probe the scope of this reaction, a range of 1-STs was subjected to denitrogenative rearrangement. In each case, the corresponding *N*-tosylimino dihydrofuran was formed with good to excellent 2,5-*trans*-distereoselectively. The imines were hydrolyzed to give the corresponding dihydrofuran-3-one products **5** in high overall yield, and although hydrolysis was conducted under basic conditions, there was no erosion in dr (Table 1). The diastereoisomeric control was dictated by the

Table 1. Diastereoselective Formation of Dihydrofuran-3-ones with a Variety of Substituents
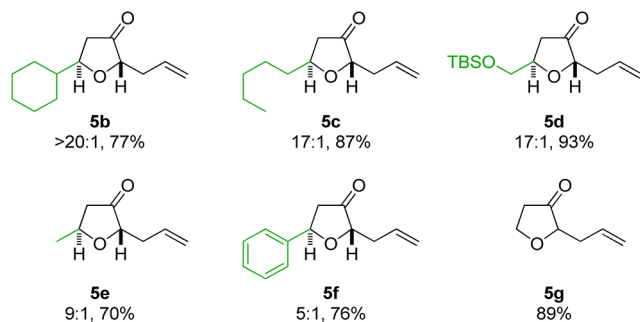

substituent adjacent to the allyl ether and correlated with its steric bulk: an isopropyl or cyclohexyl group provided excellent selectivity (**5a/b**, >20:1) which was lower in the case of the methyl group (**5e**, 9:1). An exception to this trend was observed in the case of the substrate bearing a phenyl substituent where there was a reduction in selectivity (**5f**, 5:1).

This method provided the same 2,5-*trans*-substituted tetrahydrofuran-3-ones **5**, but with significantly superior yield and diastereoselectivity, as the corresponding rhodium(II)-catalyzed reactions of α-diazoketones.[7] The yields and selectivities were comparable to those obtained from the reaction of α-diazoketones with copper(II) catalysts.[7]

Several *trans*-2,5-disubstituted tetrahydrofuran-3-ones have been used as building blocks for natural product synthesis.[15] To demonstrate an application of this process on large scale, the enantiomerically pure 1-ST **7h** was formed from (*S*)-glycidol in

short order (Scheme 4). Rhodium(II)-catalyzed denitrogenation of the 1-ST **7h** occurred on a 6.0 g (10.4 mmol) scale with

Scheme 4. Large-Scale Preparation of 5h
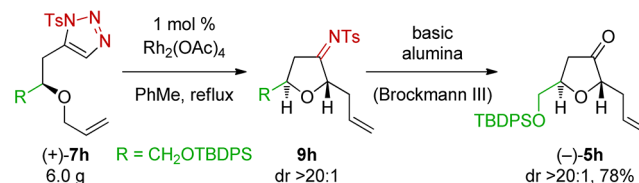
steady nitrogen release over the course of the reaction using a reduced amount of catalyst (1 mol %) at the expense of a slightly longer reaction time (1 h). Hydrolysis of the imine **9h** using basic alumina generated the dihydrofuran-3-one building block **5h** as exclusively (>20:1) the 2,5-*trans* diastereoisomer.

In addition to rearrangement of an allyl group, when the ether motif was switched to a propargylic ether, the substrate **14** underwent rhodium(II)-catalyzed cyclization and hydrolysis to give the corresponding 2-allenyldihydrofuran-3-one **15** in good yield and selectivity (Scheme 5).

Scheme 5. Rearrangement of a Propargylic Ether
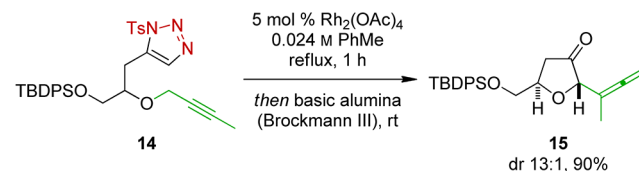
It was particularly interesting to see if this approach to oxonium ylide formation and rearrangement could be extended to 4,5-disubstituted 1-STs **8**, which would produce a class of dihydrofuran-3-ones **16** with controlled formation of a tetrasubstituted center because the 2-methyl-2,5-disubstituted tetrahydrofuran motif is found in several natural product families.[16] Notably, the analogous sequence using α-diazo-ketone substrates starting from higher diazoalkanes has not been reported.[9] Using the reaction between lithiated alkynes and TsN$_3$ to form 1-STs allowed regiocontrolled modular formation of trisubstituted 1,2,3-triazoles **8** when the reaction was quenched with a suitable electrophile (Scheme 6). Rhodium(II) acetate was able to promote denitrogenation and rearrangement to form the 2,2-disubstituted dihyrofuran-3-one products **16a–c**. Initially, using the same conditions as described above (5 mol % Rh$_2$(OAc)$_4$, PhMe, reflux) gave **16b** in only 33% yield, but the use of 1,2-dichloroethane as solvent
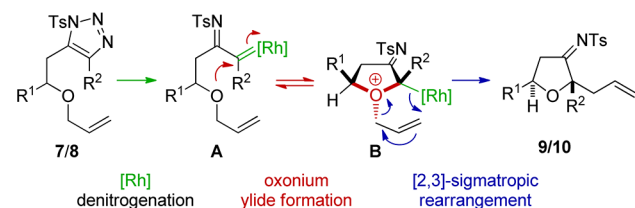
Scheme 6. Rearrangement of Disubstituted 1-STs
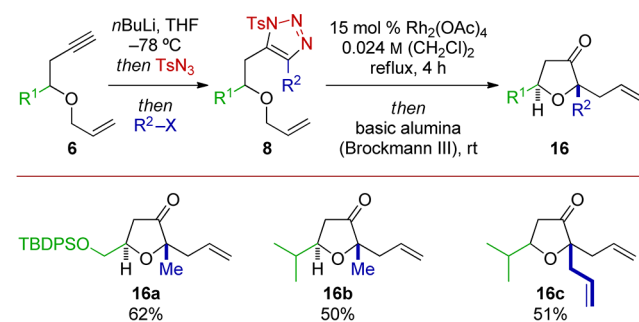
along with 15 mol % of $Rh_2(OAc)_4$ and reduced reaction temperature gave significant improvement.

The mechanism for these reactions is proposed to proceed by $Rh_2(OAc)_4$-catalyzed denitrogenation of the 1-ST **7/8** to form a rhodium carbenoid[2] **A** (Scheme 7). The oxygen lone

Scheme 7. Proposed Mechanism

pair interacts with the carbenoid to form an oxonium species **B** which undergoes [2,3]-sigmatropic rearrangement, transferring the allyl group to form a new C–C bond. This aspect of the mechanism is supported by the formation of an allene **15** from a propargylic ether **14** (Scheme 5). The diastereoselectivity is proposed to arise from the minimization of steric clash between migrating group and the bulk of the substituent R^1. The improvement in yield and diastereoselectivity compared to the corresponding rhodium(II)-catalyzed reactions of α-diazoketones is ascribed to increased steric demand of the *N*-tosylimine in addition to electronic factors. Finally, it is noteworthy that the proposed organometallic intermediates **A/B** ($R^2 \neq H$) generate the observed products given the potential for competitive 1,2-hydrogen shift,[4c] which would give byproducts stabilized by conjugation.

In summary, 1-STs bearing allyloxy and propargyloxy substituents are readily accessed from simple acyclic alkynes. Upon treatment with $Rh_2(OAc)_4$ at elevated temperatures, these 1-STs undergo denitrogenative rearrangement to give decorated dihydrofuran-3-imines with excellent diastereoselectivity. Following hydrolysis, 4-substituted 1-STs were converted to 2,5-*trans*-disubstituted dihydrofuran-3-ones, giving an alternative to the formation and rearrangement of α-diazoketones that avoids the use of diazomethane. This process was also successfully applied to 4,5-disubstituted 1-STs which resulted in the diastereoselective formation of products with a 2-tetrasubstituted center. Studies are currently underway to expand this method, fully elucidate the mechanism, and investigate its application to the synthesis of important bioactive molecules.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental protocols, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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