Heterocycles

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Expedient Synthesis of Fused Azepine Derivatives using a Sequential Rhodium(II)-Catalyzed Cyclopropanation/1-Aza-Cope Rearrangement of Dienyltriazoles**

*Erica E. Schultz, Vincent N. G. Lindsay, and Richmond Sarpong**

Abstract: *A general method for the formation of fused dihydroazepine derivatives from 1-sulfonyl-1,2,3-triazoles bearing a tethered diene is reported. The process involves an intramolecular cyclopropanation of an α-imino rhodium(II) carbenoid, leading to a transient 1-imino-2-vinylcyclopropane intermediate which rapidly undergoes a 1-aza-Cope rearrangement to generate fused dihydroazepine derivatives in moderate to excellent yields. The reaction proceeds with similar efficiency on gram scale. The use of catalyst-free conditions leads to the formation of a novel [4.4.0] bicyclic heterocycle.*

Azepine and azepane derivatives are found in numerous bioactive natural products and other compounds of pharmaceutical interest (Figure 1).[1,2] While a vast array of methods have been developed through the years for their synthesis,[1] only a few approaches exist for the preparation of their ring-fused analogues.[1b] The ubiquity of these units in a variety of biologically relevant compounds, such as alkaloids, makes the development of new stereoselective strategies to access polycyclic, substituted azepines, and azepanes in a single operation from readily available acyclic precursors highly desirable. The [3,3] sigmatropic rearrangement of 1,2-divinylcyclopropane derivatives is a well-established strategy to access seven-membered ring compounds in a stereospecific manner.[3] The analogous transformation where one of the vinyl groups is replaced by a C=N group is known to lead to azepine derivatives through a similar mechanism. While 2-aza-Cope rearrangements of this type are quite common for 2-azepinone synthesis using an isocyanate intermediate (formed in situ),[4] examples of the corresponding 1-aza-Cope rearrangement, which directly leads to 2,5-dihydro[1-*H*]azepines, remain scarce.[5] Indeed, the preparation of the *cis*-1-imino-2-vinylcyclopropanes (IVCs) required for such a rearrangement to occur is hampered by the multiple steps needed for their synthesis, thus discouraging the use of this approach for the formation of azepine derivatives.[5b,6]

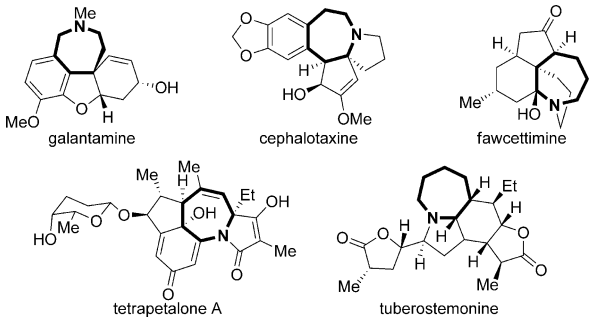
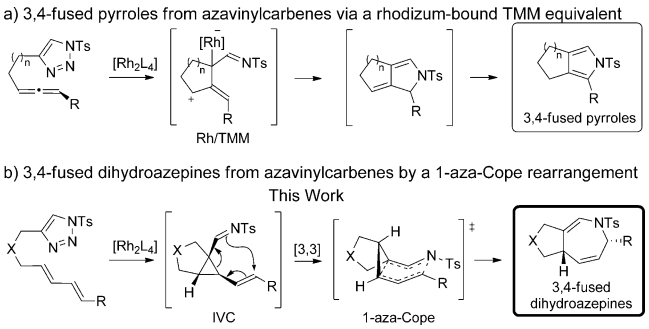


Figure 1. Natural products containing fused azepine derivatives.

In recent years, 1-sulfonyl-1,2,3-triazoles have emerged as stable and readily available azavinylcarbene equivalents for a variety of useful transformations.[7,8] We have recently shown that these carbenes can be utilized in the synthesis of 3,4-fused pyrroles upon reaction with a tethered allene functionality, through a Rh/TMM intermediate (Scheme 1a).[9] To access fused azepine derivatives through an analogous approach, we envisioned the reaction of an α-imino metallocarbene with a tethered *E*,*E*-1,3-diene would instead generate a *cis*-1-imino-2-vinylcyclopropane (IVC), which is ideally substituted for a subsequent 1-aza-Cope rearrangement (Scheme 1b). Herein, we report our studies on the synthesis of 3,4-fused dihydroazepines, which is complementary to a recent report by Tang et al. that appeared during the completion of this work.[10] In their report, Tang et al. achieve an elegant divergent synthesis of nitrogen heterocycles by



Scheme 1. Synthesis of fused heterocycles using azavinylcarbene equivalents. TMM = trimethylenemethane, Ts = 4-toluenesulfonyl.

[*] E. E. Schultz,[+] V. N. G. Lindsay,[+] Prof. R. Sarpong
Department of Chemistry, University of California, Berkeley
Berkeley, CA 94720 (USA)
E-mail: rsarpong@berkeley.edu

[+] These authors contributed equally to this work.

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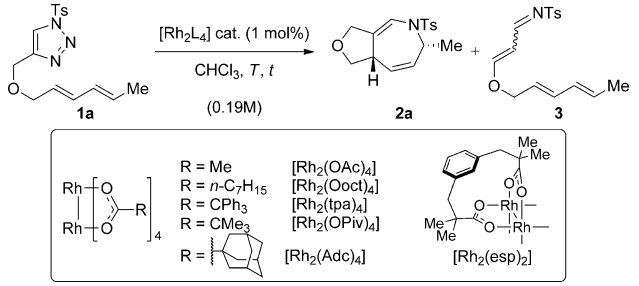
intermolecular reaction of triazoles with 1,3-dienes to provide access to azepine or pyrroline derivatives, with the pyrroline products being favored over extended reaction times.

Herein, we report a general method for the expedient synthesis of fused azepine derivatives as the sole products from dienyltriazoles. Our mechanistic studies strongly suggest that the reaction proceeds by a sequential intramolecular rhodium(II)-catalyzed cyclopropanation/1-aza-Cope rearrangement. The stereospecific nature of each step in this transformation is critical and allows a highly diastereoselective process, leading to fused 2,5-dihydro[1*H*]azepines in good to excellent yields.

Applying the reaction conditions we previously developed for the formation of 3,4-fused pyrroles from allenyltriazoles to the dienyltriazole **1a** (Table 1),[9a] we were delighted to observe the formation of the dihydroazepine **2a** in 54% yield (entry 1). A major byproduct observed in the reaction was the α,β-unsaturated N-tosylimine **3**, resulting from a competing 1,2-hydride shift from the rhodium(II) carbenoid intermediate.[11] To combat this challenge, we investigated a variety of more sterically encumbered rhodium(II) complexes (entries 3–6).[12] Gratifyingly, we found that $[Rh_2(Adc)_4]$ affords the desired dihydroazepine in increased yield (entry 6). Varying the nature of the solvent and the concentration of the reactants did not significantly improve the yield.[13] Decreasing the temperature to 60°C and increasing the reaction time to 16 hours afforded **2a** in 74% isolated yield (entry 7), along with a minimal amount of **3**.

By using the optimized reaction conditions, a range of dienyltriazole substrates is transformed into the corresponding 3,4-fused dihydroazepines (Table 2). A variety of aryl-substituted substrates, including phenyl, electron-rich and electron-poor dienyls are tolerated (entries 2–4). In addition, internal substitution of the diene portion is compatible with the transformation, albeit proceeding in slightly lower yield to the dihydroazepine (entry 2 versus 5). Furthermore, dienyltriazole substrates bearing N-tosylamine or diester groups

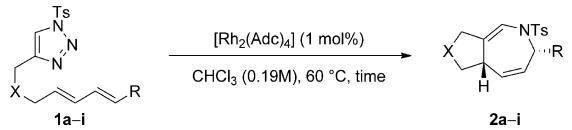
Table 1: Catalyst optimization for the intramolecular rhodium(II)-catalyzed dihydroazepine formation.[a]

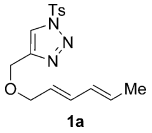
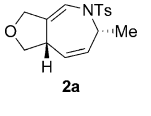
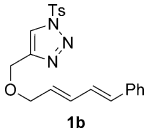
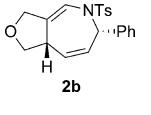
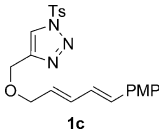
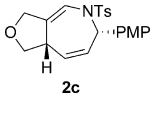
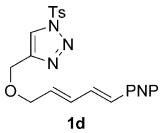
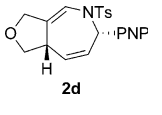
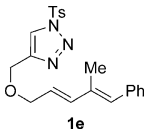
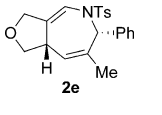
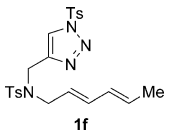
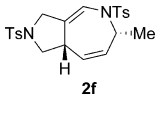
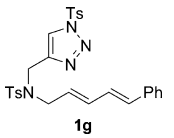
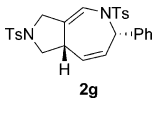
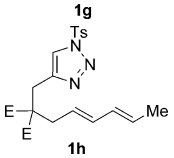
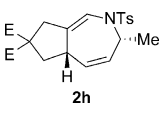
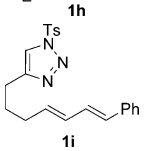
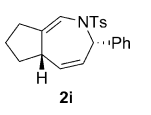


Entry	$[Rh_2L_4]$	*T* [°C]	*t*	**2a** Yield [%][b,c]
1	$[Rh_2(Ooct)_4]$	140[d]	0.25 h	54 (34)
2	$[Rh_2(OAc)_4]$	140[d]	0.25 h	47 (48)
3	$[Rh_2(tpa)_4]$	140[d]	0.25 h	18 (70)
4	$[Rh_2(OPiv)_4]$	140[d]	0.25 h	58 (18)
5	$[Rh_2(esp)_2]$	140[d]	0.25 h	66 (33)
6	$[Rh_2(Adc)_4]$	140[d]	0.25 h	68 (17)
7	$[Rh_2(Adc)_4]$	60	16 h	74 (14)

[a] Only one diastereomer of the dihydroazepine product **2a** was observed by ^{1}H NMR spectroscopy in all cases. [b] Yield of the isolated product. [c] Yield of imine **3**, as determined by NMR spectroscopy, is given within parentheses. [d] Reaction was performed in a microwave apparatus. Adc = 1-adamantanecarboxylate, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, Ooct = octanoate, Piv = pivaloyl.

Table 2: Substrate scope of the intramolecular $[Rh_2(Adc)_4]$-catalyzed dihydroazepine formation.[a]

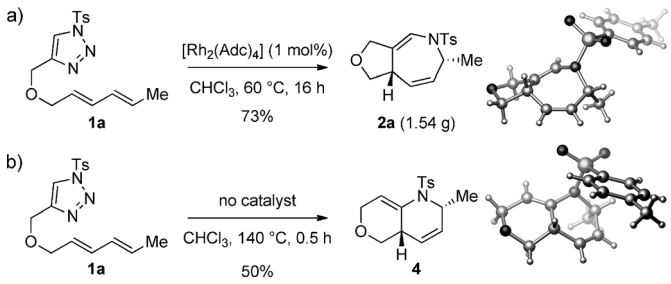


Entry	Substrate	Product	*t* [h]	Yield [%][b]
1	 **1a**	 **2a**	16	74
2	 **1b**	 **2b**	0.5	92
3	 **1c**	 **2c**	0.5	61
4	 **1d**	 **2d**	16	69
5	 **1e**	 **2e**	16	63
6	 **1f**	 **2f**	0.5	72
7	 **1g**	 **2g**	0.5	72
8	 **1h**	 **2h**	0.5	45 (60)[c]
9	 **1i**	 **2i**	0.5	92

[a] Only one diastereomer of the dihydroazepine product was observed by ^{1}H NMR spectroscopy in all cases. [b] Yield of isolated product. [c] Yield within parentheses is that obtained when $[Rh_2(Ooct)_4]$ was used at 140°C in the microwave for 0.25 h. PMP = 4-$MeOC_6H_4$, PNP = 4-$O_2NC_6H_4$, E = CO_2Me.

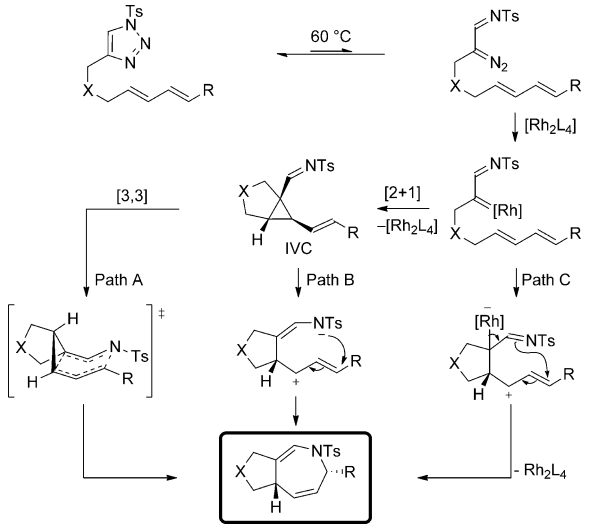
instead of the ether tether furnish the corresponding 3,4-fused dihydroazepines in moderate to good yields (entries 6–8). In the case of **1h**, the observed yield of the corresponding product (**2h**) was significantly lower as a result of side-reactions, presumably arising from intramolecular attack of the proximal ester groups on the rhodium carbene intermediate. Importantly, the all-carbon tethered dihydroazepine **2i**, corresponding to a portion of tetrapetalone A (Figure 1), could be accessed in excellent yield using the optimized reaction conditions (entry 9). In all cases, only one diastereomer of the dihydroazepine product is observed. Notably, dienyltriazole substrates which would yield a 6-7-fused dihydroazepine product afford only the corresponding 1,2-hydride-shift product. It is noteworthy that the 1-aza-Cope rearrangement was found to proceed significantly more slowly for substrates **1d** and **1e**, where the IVC intermediates were observed by NMR spectroscopy after 0.5 hours, and complete conversion was only achieved after 16 hours.

Finally, the reaction is amenable to a gram-scale synthesis of dihydroazepines, as exemplified with **2a** (Scheme 2a). Interestingly, we also found that in the absence of a rhodium(II) catalyst under more forcing conditions, a distinct heterocyclic product (**4**) was formed in 50% yield, presumably arising from a ketenimine intermediate (Scheme 2b).[14] For both types of products (that is, **2a** and **4**), the structure and relative configuration was confirmed by X-ray analysis.[15]



Scheme 2. Gram-scale synthesis of the dihydroazepine **2a** and metal-free access to [4.4.0] bicycle **4**.

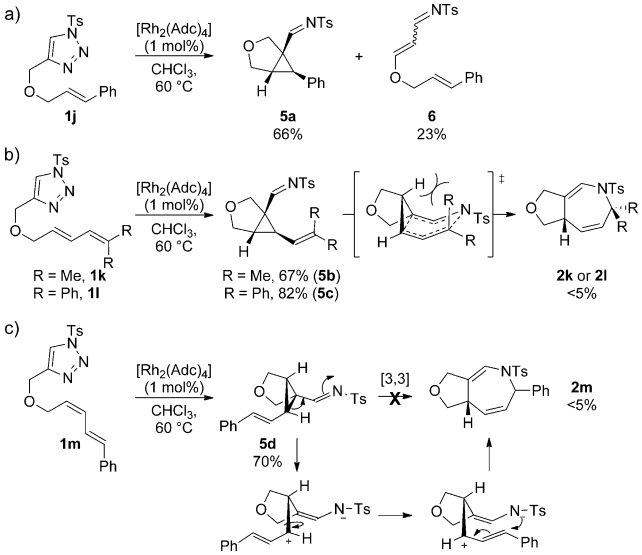
The rhodium(II)-catalyzed dihydroazepine formation can, in principle, occur through three distinct mechanistic pathways (Scheme 3). First, the azavinyl-substituted rhodium carbenoid species formed by reaction of the dienyltriazole with the rhodium catalyst could undergo a [2+1] cycloaddition with the proximal alkenyl group to generate a *cis*-IVC, which could undergo a [3,3] sigmatropic rearrangement to directly afford the dihydroazepine product (Path A). Alternatively, the IVC intermediate could undergo ring-opening to a zwitterionic intermediate, thus generating an allyl cation capable of ring-closure by an intramolecular N attack of the azanide thus formed on the distal alkenyl moiety (Path B). Similarly, the rhodium carbenoid which is formed initially could be attacked by the dienyl moiety to generate a rhodium-bound zwitterion, which is able to cyclize by an analogous mechanism (Path C). While the stereospecificity of Path A should lead to a single diastereomer of the product bearing the predicted stereochemistry as shown,



Scheme 3. Different possible mechanistic pathways for the dihydroazepine formation.

either Path B or C could give rise to a mixture of both isomers. Notably, the single diastereomer **2a** obtained from the reaction, as determined by X-ray analysis, is consistent with the [2+1]/[3,3] sequence depicted in Path A (Scheme 2a).

To obtain further insight, several other triazoles were synthesized and evaluated (Scheme 4). To gain support for the intermediacy of iminocyclopropanes, the alkenyltriazole **1j** (Scheme 4a), which lacks the distal alkenyl group required for the subsequent 1-aza-Cope to occur, was submitted to the standard reaction conditions. The iminocyclopropane **5a** was obtained as a single diastereomer in 66% yield (determined by NMR spectroscopy). Although 1-sulfonyl-1,2,3-triazoles are known to lead to iminocyclopropanes by intermolecular cyclopropanation with alkenes,[7,8a,b] to our knowledge, the analogous intramolecular cyclopropanation has never been reported. Thus the viability and stereoselectivity of such



Scheme 4. Experimental mechanistic insights: [3,3] sigmatropic rearrangement versus zwitterionic pathways.

a mechanistic step is confirmed by this observation. The sterically encumbered dienyltriazoles **1k** and **1l** (Scheme 4b) led to the formation of IVC intermediates (**5b** and **5c**, respectively), which do not undergo the subsequent 1-aza-Cope rearrangement. This lack of reactivity is likely due to an unfavorable interaction with the *cis*-R group in the transition state of the [3,3] rearrangement, significantly slowing the rate of this pathway.[16,17] The fact that none of the dihydroazepine was observed in this particular case strongly suggests that a concerted mechanism is operative for the rearrangement, as the increased flexibility of a ring-opened zwitterionic intermediate (as shown in Path B or C) should still allow the cyclization to occur. Notably, the formation of such zwitterionic intermediates should not be hampered by the steric hinderance of the distal alkenyl moiety in either **1k** or **1l**. Possibly as a result of a similar steric effect, it is noteworthy that 1,1-disubstituted dienes, which would generate a quaternary center in the product, only reacted sluggishly. Finally, the *Z*,*E*-dienyltriazole **1m** (Scheme 4c), which leads to a *trans*-IVC (**5d**), was also found to be unreactive toward dihydroazepine formation. This observation can be attributed to the inability of such an intermediate to engage in a concerted 1-aza-Cope rearrangement. The corresponding zwitterionic intermediate formed from **1m** should be identical to the case of the *E*,*E*-dienyltriazole **1b**, which in contrast to **1m**, leads to dihydroazepine formation in excellent yield in only 0.5 hours (Table 2, entry 2). These results strongly support a sequential intramolecular rhodium(II)-catalyzed cyclopropanation/1-aza-Cope rearrangement as the operative pathway for dihydroazepine formation (Scheme 3, Path A). Moreover, if a zwitterionic intermediate is involved in the process, the formation of the corresponding five-membered heterocycle (pyrroline) would be expected to be competitive, as the generation of five-membered ring compounds from this type of zwitterionic intermediate is typically a fast process.[3f,8g,10] Notably, this type of product was not observed in any case throughout this study, again lending support to Path A.

In summary, a general approach for the synthesis of fused dihydroazepines from dienyltriazoles is reported. A range of substrates have been found to participate in the transformation, and several mechanistic investigations strongly support a sequential intramolecular rhodium(II)-catalyzed cyclopropanation/1-aza-Cope rearrangement as the operative mechanistic pathway. The reaction can be scaled with similar efficiency, and the use of catalyst-free conditions provides access to a novel [4.4.0] bicyclic heterocycle. Given the ubiquity of these scaffolds in biologically relevant compounds, this work should prove valuable for the synthesis of new and useful fused azepine-based building blocks.

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Keywords: azavinylcarbene · dihydroazepine · heterocycles · rearrangements · rhodium

[1] For reviews on the synthesis, properties, and natural occurrences of azepine derivatives, see: a) J. J. Vaquero, A. M. Cuadro, B. Herradón, *Modern Heterocyclic Chemistry*, Wiley-VCH, Weinheim, **2011**, pp. 1865–1988; b) J. B. Bremner, S. Samosorn, *Comprehensive Heterocyclic Chemistry III*, *Vol. 13* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven, R. Taylor), Elsevier, Oxford, **2008**, pp. 1–43; c) G. R. Proctor, J. Redpath, *The Chemistry of Heterocyclic Compounds*, *Vol. 56* (Ed.: E. C. Taylor), Wiley-Interscience, Chichester, **1996**.

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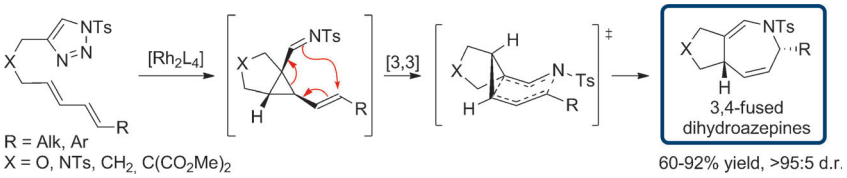
Communications

Heterocycles

E. E. Schultz, V. N. G. Lindsay,
R. Sarpong* ——— ■■■■–■■■■

Expedient Synthesis of Fused Azepine Derivatives using a Sequential Rhodium(II)-Catalyzed Cyclopropanation/1-Aza-Cope Rearrangement of Dienyltriazoles



A general method for the formation of fused dihydroazepines from 1-sulfonyl-1,2,3-triazoles bearing a tethered diene is reported. The process involves an intramolecular cyclopropanation of an α-imino rhodium(II) carbenoid, leading to a transient 1-imino-2-vinylcyclopropane intermediate which rapidly undergoes a 1-aza-Cope rearrangement to generate the products in moderate to excellent yields. Ts = 4-toluenesulfonyl.