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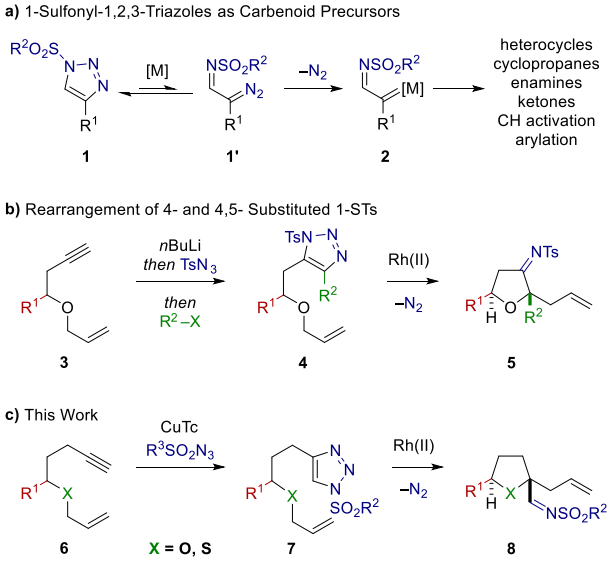
Rhodium(II)-Catalyzed Stereocontrolled Synthesis of 2-Tetrasubstituted Saturated Heterocycles from 1-Sulfonyl-1,2,3-triazoles

Alistair Boyer

Rhodium(II) acetate catalyzes the denitrogenative transformation of 4-substituted 1-sulfonyl-1,2,3-triazoles with pendent allyl and propargyl ethers and thioethers to onium ylides that undergo [2,3]-sigmatropic rearrangement to give 2-tetrasubstituted heterocycles with high yield and diastereoselectivity.

Heteroaliphatic ring-containing compounds are of high-value with high sp^3 content and a stereo-defined 3D architecture.[1] Tetrahydrofurans with substitution at the 2- and 5- positions are recurring motifs across several natural product families and synthetic analogues of medicinal importance that exhibit remarkable bioactivity.[2] Their sulfur-containing analogues, tetrahydrothiophenes, also can be found at the heart of bioactive compounds as well as valuable catalysts and ligands.[3] Although there are several efficient methods for the synthesis of these aliphatic hetereocycles, it is recognized that the stereocontrolled construction of heterocycles with tetrasubstituted centers represents an increased challenge.[4]

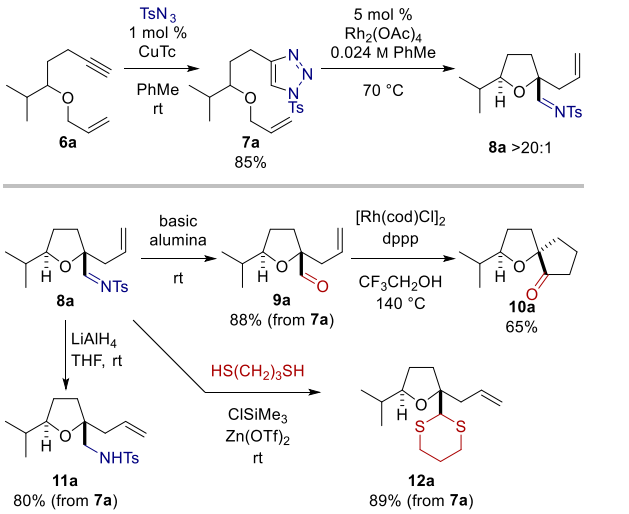
Scheme 1. Overview.



Following the pioneering work of Fokin, Gevorgyan and Murakami,[5] the 1-sulfonyl triazole (1-ST) motif has been widely adopted as a metal carbenoid[6] precursor and the resulting rich chemistry which can be achieved therewith (Scheme 1a). The reactivity of 1-STs is driven by the presence of the electron-withdrawing sulfonyl group which, under certain circumstances, promotes Dimroth equilibration of the heterocycle (**1**⇌**1′**).[7] Typically, this equilibrium is reached in the presence of a transition metal catalyst at elevated temperatures and the catalyst triggers denitrogenation to form the corresponding metal carbenoid **2**. Using this approach, several novel methods of accessing value-added products have recently emerged.[5,8-11] Previously, this strategy was applied to the diasetereoselective synthesis of functionalized dihydrofuran-3-one imines **5** from 1-STs with a β-allyloxy group at the 5-position of the triazole (**4**, Scheme 1b).[10] Herein, the development of a complimentary reaction[11] is described where a rhodium(II) catalyst promotes denitrogenation from 1-STs **7** bearing a γ-allyloxy group at the 4-position to deliver saturated hetereocycles with a 2-tetrasubstituted center **8** (Scheme 1c). Importantly, these products would be inaccessible using rhodium catalysts with traditional α-diazo aldehyde starting materials.[12]

The substitution pattern of the triazoles (**7**) required for this study was readily achieved by copper-catalyzed cycloaddition between simple alkyne precursors **6** and a sulfonyl azide.[13] Rhodium(II) acetate was effective in promoting the loss of nitrogen from the 1-ST **7a** at elevated temperatures, resulting in selective formation of a single product that was identified as the 2,5-*cis*-disubstituted tetrahydrofuran **8a** (Scheme 2).[14] These conditions are similar to those applied to the isomeric substrates,[10] although in this case a lower temperature was required to promote the reaction (70 *vs* 90°C).

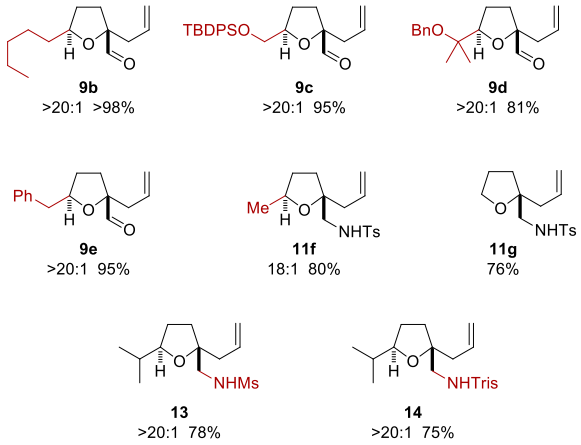
Scheme 2. 1-ST synthesis and reactivity.



The *N*-tosylimine **8a** was unstable to purification by silica gel chromatography. However, the *N*-tosylimine is known to be a valuable functional group for further transformation.[15] In this case, the crude imine **8a** was: hydrolyzed to the corresponding aldehyde **9a** by stirring with wet basic alumina (Brockmann III);[16] reduced to the sulfonamide **11a**; or directly transformed into the corresponding 1,3-dithiane **12a**. These functional groups are useful for further manipulation as demonstrated by the formation of the spirocyclic compound **10a** by intramolecular hydroacylation.[17]

To probe the scope of this reaction, a range of 1-STs was subjected to denitrogenative rearrangement and in each case, the corresponding tetrahydrofur-2-yl methyl imine **8** was formed. The imines were hydrolyzed to give the corresponding aldehydes **9b-e**, or reduced to give sulfonamides **11f,g** in high overall yield (Figure 1). The diastereocontrol was excellent with all substituents effectively controlling the formation of the new tetrasubstituted center (dr 18:1 to >20:1). Substrates with a selection of substituted sulfonyl groups could be used in the transformation with no significant erosion of yield or diastereoselectivity (**13**,**14**).

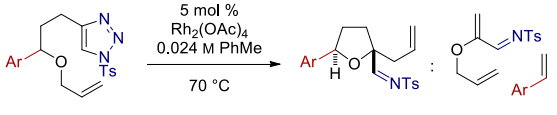
Figure 1. Example products accessible by Rh(II)-catalyzed denitrogenation and rearrangement.



9b >20:1 >98% **9c** >20:1 95% **9d** >20:1 81% **9e** >20:1 95% **11f** 18:1 80% **11g** 76% **13** >20:1 78% **14** >20:1 75%

The reaction conditions required to promote denitrogenation and rearrangement (**7**→**8**) were found to be orthogonal to the copper-catalyzed formation of the 1-ST precursors (**6**→**7**). Accordingly, following conversion of the alkyne substrates to the corresponding 1-STs, the reaction mixture was diluted, rhodium(II) acetate was added and the mixture heated to 70 °C, followed by hydrolysis to form the heterocyclic aldehydes in an efficient one pot-protocol (**6**→**7**→**8**→**9**).[14]

Scheme 3. Fragmentation of substrates with aromatic substituents.

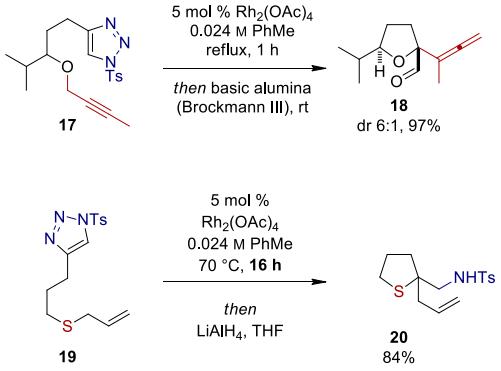


	7	**8**		**15**	**16**
h	Ar = Ph	1	:	5	
i	Ar = 4-$NO_2C_6H_4$	1	:	11	
j	Ar = 4-$MeOC_6H_4$	1	:	>20	

By way of contrast, substrates bearing an aromatic substituent **7h-j** only formed a trace of the tetrahydrofuran product **8** under the reaction conditions (Scheme 3). Instead, the major products were the unsaturated imine **15** and a styrene **16** which derived from fragmentation of the substrate. Altering the electronic character of the aromatic group did not have a significant effect and in each case fragmentation was the major outcome.

In addition to rearrangement of an *O*-allyl group, the *O*-propargyl motif was also investigated. The substrate **17** underwent rhodium(II)-catalyzed cyclization followed by hydrolysis to give the corresponding 2-allenyl tetrahydrofuran **18** with good yield and diastereoselectivity (Scheme 4).

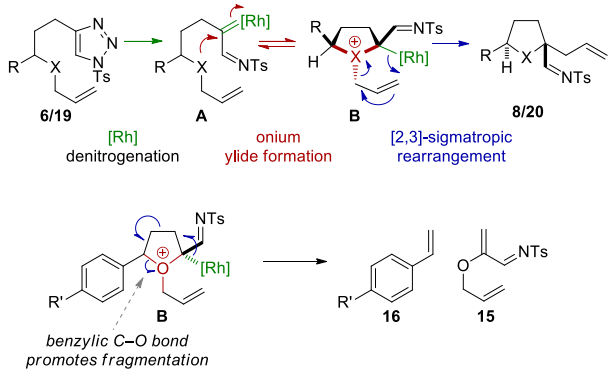
Scheme 4. Formation of an allenyl tetrahydrofuran 18 and tetrahydrothiophene **20**.



Finally, the reaction was evaluated with a substrate **19** containing a sulfur heteroatom.[18] Denitrogenation and rearrangement proceeded to give the substituted tetrahydrothiophene product **20** in good yield although the reaction was somewhat retarded, requiring 16 h for consumption of starting material to be complete.

All of these reactions are proposed to proceed by a common mechanism which is analogous to the reaction of the isomeric 1-STs[10] which, in turn, was inspired by the decomposition of α-diazoketones.[19]

Scheme 5. Proposed Mechanism.



First, rhodium(II)-catalyzed denitrogenation of the 1-ST gives the corresponding rhodium carbenoid **A** (Scheme 5). Nucleophilic attack of one of the heteroatom lone pairs on the carbenoid results in the formation of an onium species **B** whose charge is neutralized following [2,3]-sigmatropic rearrangement of the allyl/propargyl motif to form a new C–C bond. This aspect of the mechanism is supported by the formation of an allene **18** from the butynyl ether **17** (Scheme 4). The stereochemistry observed in the products can be attributed to the minimization of steric clash between the migrating group and the substituent R. It is important to note that an analogous mechanism in which the metal plays a reduced role is also conceivable.

In the case of substrates with an aromatic substituent, the presence of a benzylic C–O bond opens up an alternative and

favored pathway in which the charge within the intermediate **B** is neutralized by fragmentation leading to a styrene **15** and an unsaturated imine **16**.[20]

In summary, 1-STs bearing 4-γ-allyloxy and 4-γ-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 tetrahydrofurans and a tetrahydrothiophene with excellent yield and diastereoselectivity. The *N*-tosylimine products are valuable compounds and were shown to be precursors to aldehydes, sulfonamides and 1,3-dithianes which demonstrates further value of the products. Studies are currently underway to further investigate the mechanism of this process and study application to the synthesis of important bioactive molecules.

CORRESPONDING AUTHOR

Email: alistair@boyer-research.com
Website: www.boyer-research.com
Address: School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, UK

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REFERENCES

1. (a) Lovering, F.; Bikker, J.; Humblet, C.; *J. Med. Chem.* **2009**, *52*, 6752-6756; (b) Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D.; *Drug Discovery Today* **2011**, *16*, 164-171.
2. (a) Dutton, C. J.; Banks, B. J.; Cooper, C. B.; *Natural Product Reports* **1995**, *12*, 165-181; (b) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M.; *Chem. Rev.* **2013**, *113*, 4567-4610; (c) Bartroli, J.; Carceller, E.; Merlos, M.; Garcia-Rafanell, J.; Forn, J.; *J. Med. Chem.* **1991**, *34*, 373-386; (d) Yang, G. X.; Chang, L. L.; Truong, Q.; Doherty, G. A.; Magriotis, P. A.; de Laszlo, S. E.; Li, B.; MacCoss, M.; Kidambi, U.; Egger, L. A.; McCauley, E.; Van Riper, G.; Mumford, R. A.; Schmidt, J. A.; Hagmann, W. K.; *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1497-1500.
3. (a) Aloup, J.-C.; Bouchaudon, J.; Farge, D.; James, C.; Deregnaucourt, J.; Hardy-Houis, M.; *J. Med. Chem.* **1987**, *30*, 24-29; (b) Konosu, T.; Takeda, N.; Tajima, Y.; Yasuda, H.; Oida, S.; *Chem Pharm Bull* **1990**, *38*, 1258-1265; (c) Aggarwal, V. K.; Winn, C. L.; *Acc. Chem. Res.* **2004**, *37*, 611-620; (d) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K.; *Chem. Rev.* **2007**, *107*, 5841-5883; (e) Clark, J. S.; Boyer, A.; Aimon, A.; Engel García, P.; Lindsay, D. M.; Symington, A. D. F.; Danoy, Y.; *Angew. Chem. Int. Ed.* **2012**, *51*, 12128-12131; (f) Uson, R.; Laguna, A.; Laguna, M.; Briggs, D. A.; Murray, H. H.; Fackler, J. P.; *Inorg. Synth.* **1989**, *26*, 85-91.
4. (a) Jalce, G.; Franck, X.; Figadère, B.; *Tetrahedron: Asymmetry* **2009**, *20*, 2537-2581; (b) Wolfe, J. P.; Hay, M. B.; *Tetrahedron* **2007**, *63*, 261-290; (c) Piccialli, V.; *Synthesis* **2007**, *2007*, 2585-2607; (d) Pilgrim, B. S.; Donohoe, T. J.; *J. Org. Chem.* **2013**, *78*, 2149-2167.
5. (a) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V.; *Angew. Chem. Int. Ed.* **2007**, *46*, 4757-4759; (b) Chuprakov, S.; Gevorgyan, V.; *Org. Lett.* **2007**, *9*, 4463-4466; (c) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V.; *J. Am. Chem. Soc.* **2008**, *130*, 14972-14974; (d) Miura, T.; Yamauchi, M.; Murakami, M.; *Chem. Commun.* **2009**, 1470-1471.
6. (a) Padwa, A.; Weingarten, M. D.; *Chem. Rev.* **1996**, *96*, 223-270; (b) Doyle, M. P.; McKervey, M. A.; Ye, T.; *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**.
7. Gilchrist, T. L.; Gymer, G. E. in *Adv. Heterocycl. Chem., Vol. Volume 16* (Eds.: A. R. Katritzky, A. J. Boulton), Academic Press, **1974**, pp. 33-85.
8. Selected reviews: (a) Hein, J. E.; Fokin, V. V.; *Chem. Soc. Rev.* **2010**, *39*, 1302-1315; (b) Chattopadhyay, B.; Gevorgyan, V.; *Angew. Chem. Int. Ed.* **2012**, *51*, 862-872; (c) Davies, H. M. L.; Alford, J. S.; *Chem. Soc. Rev.* **2014**, *43*, 5151-5162.
9. (a) Chattopadhyay, B.; Gevorgyan, V.; *Org. Lett.* **2011**, *13*, 3746-3749; (b) Zibinsky, M.; Fokin, V. V.; *Angew. Chem. Int. Ed.* **2013**, *52*, 1507-1510; (c) Chuprakov, S.; Kwok, S. W.; Fokin, V. V.; *J. Am. Chem. Soc.* **2013**, *135*, 4652-4655; (d) Schultz, E. E.; Sarpong, R.; *J. Am. Chem. Soc.* **2013**, *135*, 4696-4699; (e) Parr, B. T.; Green, S. A.; Davies, H. M. L.; *J. Am. Chem. Soc.* **2013**, *135*, 4716-4718; (f) Spangler, J. E.; Davies, H. M. L.; *J. Am. Chem. Soc.* **2013**, *135*, 6802-6805; (g) Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M.; *Org. Lett.* **2013**, *15*, 3298-3301; (h) Alford, J. S.; Spangler, J. E.; Davies, H. M. L.; *J. Am. Chem. Soc.* **2013**; (i) Miura, T.; Tanaka, T.; Hiraga, K.; Stewart, S. G.; Murakami, M.; *J. Am. Chem. Soc.* **2013**, *135*, 13652-13655; (j) Shi, Y.; Gevorgyan, V.; *Org. Lett.* **2013**, *15*, 5394-5396; (k) Miura, T.; Funakoshi, Y.; Murakami, M.; *J. Am. Chem. Soc.* **2014**, *136*, 2272-2275; (l) Kwok, S. W.; Zhang, L.; Grimster, N. P.; Fokin, V. V.; *Angew. Chem. Int. Ed.* **2014**, *53*, 3452-3456; (m) Kim, C.-E.; Park, S.; Eom, D.; Seo, B.; Lee, P. H.; *Org. Lett.* **2014**, *16*, 1900-1903; (n) Yang, J.-M.; Zhu, C.-Z.; Tang, X.-Y.; Shi, M.; *Angew. Chem. Int. Ed.* **2014**, *53*, 5142-5146; (o) Shang, H.; Wang, Y.; Tian, Y.; Feng, J.; Tang, Y.; *Angew. Chem. Int. Ed.* **2014**, *53*, 5662-5666; (p) Chen, K.; Zhu, Z.-Z.; Zhang, Y.-S.; Tang, X.-Y.; Shi, M.; *Angew. Chem. Int. Ed.* **2014**, *53*, 6645-6649; (q) Medina, F.; Besnard, C.; Lacour, J.; *Org. Lett.* **2014**, *16*, 3232-3235; (r) Ran, R.-Q.; He, J.; Xiu, S.-D.; Wang, K.-B.; Li, C.-Y.; *Org. Lett.* **2014**, *16*, 3704-3707.
10. Boyer, A.; *Org. Lett.* **2014**, *16*, 1660-1663.
11. For a related non-diastereoselective process applied to the synthesis of spirocyclic compounds, see: Fu, J.; Shen, H.; Chang, Y.; Li, C.; Gong, J.; Yang, Z.; *Chem. Eur. J.* **2014**, *20*, 12881-12888.
12. Sezer, Ö.; Anaç, O.; *Helv. Chim. Acta* **1994**, *77*, 2323-2334.
13. (a) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S.; *Angew. Chem. Int. Ed.* **2007**, *46*, 1730-1733; (b) Raushel, J.; Fokin, V. V.; *Org. Lett.* **2010**, *12*, 4952-4955.
14. Further details are included in the Supporting Information.
15. (a) Appel, R.; Mayr, H.; *J. Am. Chem. Soc.* **2011**, *133*, 8240-8251; (b) Charette, A. B. in *Chiral Amine Synthesis*, Wiley-VCH, Weinheim, **2010**, pp. 1-49; (c) Weinreb, S. M.; *Top. Curr. Chem.* **1997**, *190*, 131-184.
16. Boultwood, T.; Affron, D. P.; Trowbridge, A. D.; Bull, J. A.; *J. Org. Chem.* **2013**, *78*, 6632-6647.
17. (a) Willis, M. C.; *Chem. Rev.* **2009**, *110*, 725-748; (b) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2007**, *46*, 9331-9334.
18. (a) Miura, T.; Tanaka, T.; Yada, A.; Murakami, M.; *Chem. Lett.* **2013**, *42*, 1308-1310; (b) Yadagiri, D.; Anbarasan, P.; *Chem. Eur. J.* **2013**, *19*, 15115-15119.
19. (a) Pirrung, M. C.; Werner, J. A.; *J. Am. Chem. Soc.* **1986**, *108*, 6060-6062; (b) Roskamp, E. J.; Johnson, C. R.; *J. Am. Chem. Soc.* **1986**, *108*, 6062-6063; (c) Clark, J. S.; *Tetrahedron Lett.* **1992**, *33*, 6193-6196; (d) West, F. G.; Eberlein, T. H.; Tester, R. W.; *J. Chem. Soc., Perkin Trans. 1*

1993, 2857-2859; (e) Eberlein, T. H.; West, F. G.; Tester, R. W.; *J. Org. Chem.* **1992**, *57*, 3479-3482; (f) West, F. G.; Naidu, B. N.; Tester, R. W.; *J. Org. Chem.* **1994**, *59*, 6892-6894; (g) Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C. J.; Fox, D. N. A.; *Tetrahedron Lett.* **1998**, *39*, 97-100; (h) Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L.; *Angew. Chem. Int. Ed.* **2007**, *46*, 437-440; (i) D. M. Hodgson, D. Angrish, S. P. Erickson, J. Kloesges, C. H. Lee, *Org. Lett.* **2008**, *10*, 5553-5556; (j) Jackson, K. L.; Henderson, J. A.; Motoyoshi, H.; Phillips, A. J.; *Angew. Chem. Int. Ed.* **2009**, *48*, 2346-2350; (k) Clark, J. S.; Berger, R.; Thomas, L. H.; Hayes, S. T.; Morrison, A. J.; Gobbi, L.; *Angew. Chem. Int. Ed.* **2010**, *49*, 9867-9870; (l) D. M. Hodgson, S. Man, *Chem. Eur. J.* **2011**, *17*, 9731-9737; (m) Clark, J. S.; Berger, R.; Hayes, S. T.; Senn, H. M.; Farrugia, L. J.; Thomas, L. H.; Morrison, A. J.; Gobbi, L.; *J. Org. Chem.* **2013**, *78*, 673-696; (n) Murphy, G. K.; Stewart, C.; West, F. G.; *Tetrahedron* **2013**, *69*, 2667-2686; (o) Clark, J. S.; Hansen, K. E.; *Chem. Eur. J.* **2014**, *20*, 5454-5459.

20. Alternatively, the fragmentation may proceed by homolysis of the oxonium ylide.