Heterocycle Synthesis

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Rhodium(II)-Catalyzed Intramolecular Annulation of 1-Sulfonyl-1,2,3-Triazoles with Pyrrole and Indole Rings: Facile Synthesis of N-Bridgehead Azepine Skeletons**

Jin-Ming Yang, Cheng-Zhi Zhu, Xiang-Ying Tang, and Min Shi**

Abstract: *A convenient and efficient synthetic method has been developed to construct highly functionalized N-bridgehead azepine skeletons, which are of great importance in biological and pharmaceutical industry. The reaction proceeds through a rhodium(II) azavinyl carbene intermediate, which initiated the intramolecular C–H functionalization with pyrrolyl and indolyl rings. A variety of azepine derivatives were obtained in moderate to good yields under mild reaction conditions with high chemoselectivity. Several interesting derivatizations of the resulting products demonstrate that this method is synthetically valuable and useful.*

The azepine skeleton is a privileged structural motif in many biologically active and medicinally valuable molecules.[1] In addition, polyheterocyclic frameworks built on the azepine backbone lead to relatively rigid structures which might be expected to show substantial selectivity in their interactions with enzymes or receptors.[2] Among these poly-heterocycles, the structurally diverse and biologically interesting N-bridgehead azepine skeletons are of great importance because of their well-represented and wide distribution in nature. Representative examples, such as *Cephalotaxus* alkaloids,[3] *Stemona* alkaloids,[4] ant venom/frog alkaloids,[5a] and the antitumor antibiotics anthramycin,[5b] all have N-bridgehead azepine skeletons (Figure 1). Construction of N-bridgehead azepine units usually requires multistep approaches.[3–5] Therefore, it is not surprising that much attention has to be paid to developing a more general and efficient strategy to afford such azacyclic skeletons.

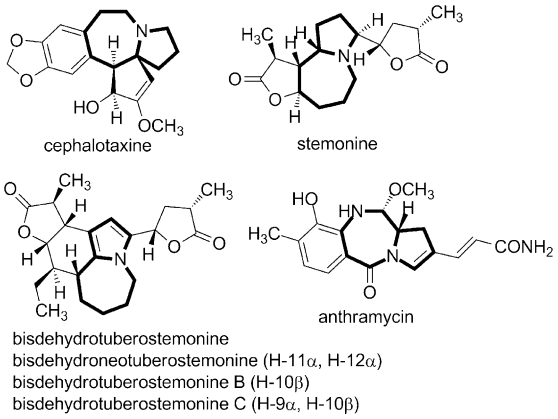

Figure 1. Selected examples of naturally occurring compounds and drugs containing N-bridgehead azepine unit.

1-Sulfonyl-1,2,3-triazoles, stable precursors of rhodium(II) azavinyl carbenes, provide opportunities for a series of novel carbene-induced transformations such as transannulation with unsaturated compounds, X–H (X = C, N, or O) bond functionalization, 1,2-migration, and so on.[6] To date, the research groups of Fokin,[7] Gevorgyan,[8] Davies,[9] Murakami,[10] and others[11] have intensively investigated the diverse reactivities of this carbenoid intermediate. In the case of a rhodium imino carbene intermediate, it has enabled the development of many useful transformations, including cyclopropanation,[7b] cycloaddition,[7a,h,8a] C–H insertion,[7d] O–H/N–H insertion,[7i,10b,d] and arylation with boronic acids.[7e] In 2013, the groups of Sarpong[11b] and Gevorgyan[8b] independently reported intramolecular transannulation of allenyl and alkynyl triazoles to form 3,4-fused pyrroles. Very recently, Murakami and co-workers[10h] synthetized tricyclic 3,4-fused dihydroindoles by a rhodium-catalyzed dearomatizing [3+2] annulation reaction of 4-(3-arylpropyl)-1,2,3-triazoles. Notably, Davies and co-workers recently also reported a catalytic enantioselective formal [3+2] cycloaddition of 1-sulfonyl-1,2,3-triazoles with C3-substituted indoles (Scheme 1 a).[9c]

Encouraged by the finding of Davies and co-workers, and on the basis of our previous work of gold-catalyzed cycloisomerization of 1,6-diynes[12a] and 1,1-bis(indolyl)-5-alkynes,[12b] we successfully the prepared stable pyrrolyl and indolyl triazoles **A** through copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[13] and investigated its performance in rhodium(II)-catalyzed annulation. One major challenge that needed to be tackled in the desired reaction was the carbene-induced 1,2 H migration. Given the intramolecular

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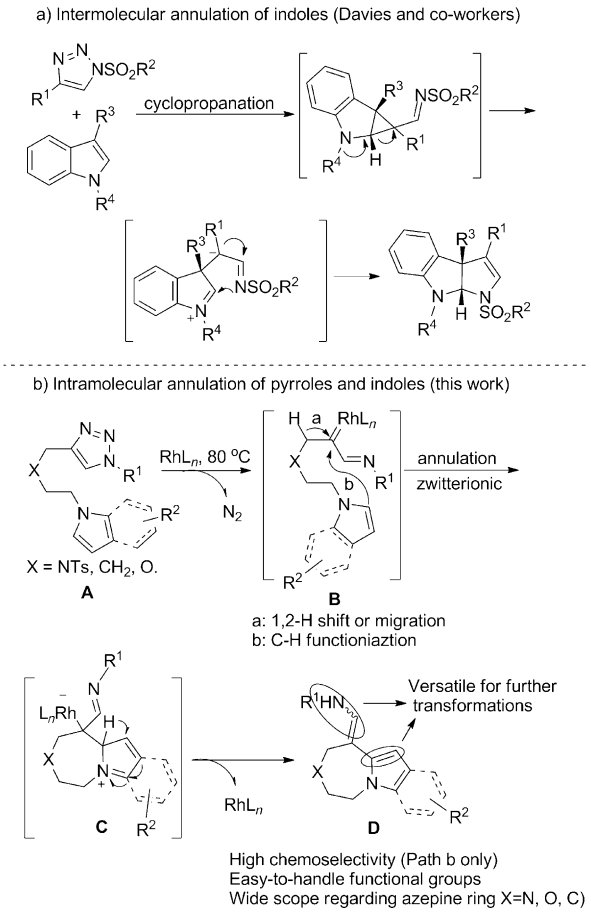
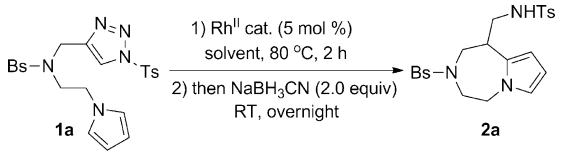


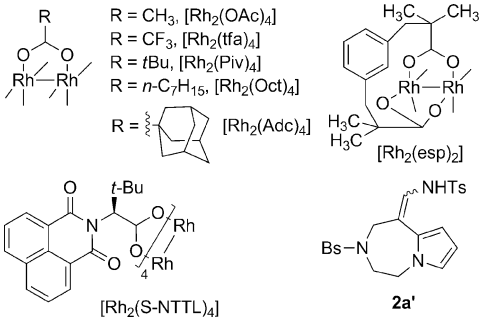
Scheme 1. Previous work and our work on the annulation of pyrroles and indoles.

Table 1: Optimization of the reaction conditions.



Entry[a]	[Rh]	Solvent	Yield [%][b]
1	$[Rh_2(Oct)_4]$	DCE	86
2	$[Rh_2(Piv)_4]$	DCE	80
3	$[Rh_2(esp)_4]$	DCE	77
4	$[Rh_2(OAc)_4]$	DCE	78
5	$[Rh_2(Adc)_4]$	DCE	80
6	$[Rh_2(tfa)_4]$	DCE	0
7	$[Rh_2(S\text{-}NTTL)_4]$	DCE	70
8	$[Rh_2(Oct)_4]$	toluene	78
9	$[Rh_2(Oct)_4]$	cyclohexane	–[c]
10	$[Rh_2(Oct)_4]$	$CHCl_3$	–[c]

[a] Reaction conditions: **1a** (0.1 mmol), cat. (5 mol%), dry solvent (1.0 mL). [b] Yield of isolated product. [c] Not determined. DCE = 1,2-dichloroethane.

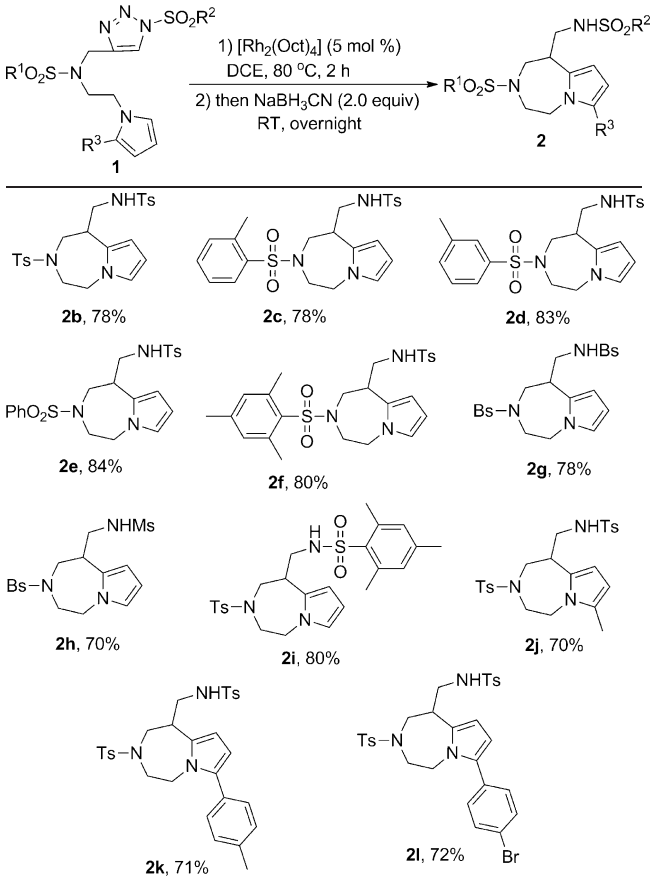


annulations reported by the groups of Murakami,[10h] Gevorgyan,[8b] and Sarpong,[11b] the fused ring systems are all restricted to five- and six-membered rings. The seven-membered ring has not yet been achieved, presumably because the longer chain will greatly reduce the chance for intramolecular reaction, and the 1,2 H migration will become dominant. To our great delight, upon treatment of **A** with a dirhodium catalyst, an interesting N-bridgehead azepine skeleton product (**D**) was obtained as the sole product (Scheme 1b), thus stemming from tandem triazole ring opening and denitrogenation to generate the key imino carbene intermediate **B**[7] and the subsequent annulation[14] with regeneration of the dirhodium catalyst. We envisaged that as a result of the highly electrophilic pyrrole or indole, the 1,2 H migration was suppressed. This transformation results in important skeletal units, azepines, which are found in numerous natural products, and in compounds having important chemical, biological, and medicinal properties (Figure 1).

Initially, we started our investigation by using the model substrate **1a** and 5 mol% $[Rh_2(OAc)_4]$ in dry 1,2-DCE (1,2-dichloroethane) at 80°C, and the desired enamine **2a′** was obtained as two isomers in high overall yield (90%) after 2 hours (Table 1). The structure of *E*-**2a′** has been unequivocally confirmed by X-ray diffraction (see the Supporting Information).[15] To our delight, a one-pot treatment of the formed enamine with 2.0 equivalents of $NaBH_3CN$ resulted in a smooth reduction of **2a′** to afford the alkylamine **2a** in 86% yield (entry 1). Other catalysts, such as $[Rh_2(Piv)_4]$, $[Rh_2(esp)_2]$, $[Rh_2(OAc)_4]$, and $[Rh_2(Adc)_4]$ gave no better results than that of $[Rh_2(Oct)_4]$ (entries 2–5). When **1a** was treated with $[Rh_2(tfa)_4]$ no reaction occurred (entry 6). The use of chiral the rhodium(II) tetracarboxylate catalyst $[Rh_2(S\text{-}NTTL)_4]$[16] afforded the racemic product **2a** in 70% yield (entry 7). Next we turned our attention to examining the solvent effects. Toluene was substantially less effective than 1,2-dichloroethane (entry 8), and the use of cyclohexane and chloroform, which have been reported as the optimum solvents for carbenoid transformations from triazoles,[7c,h,9c] provided poor results (entries 9 and 10).

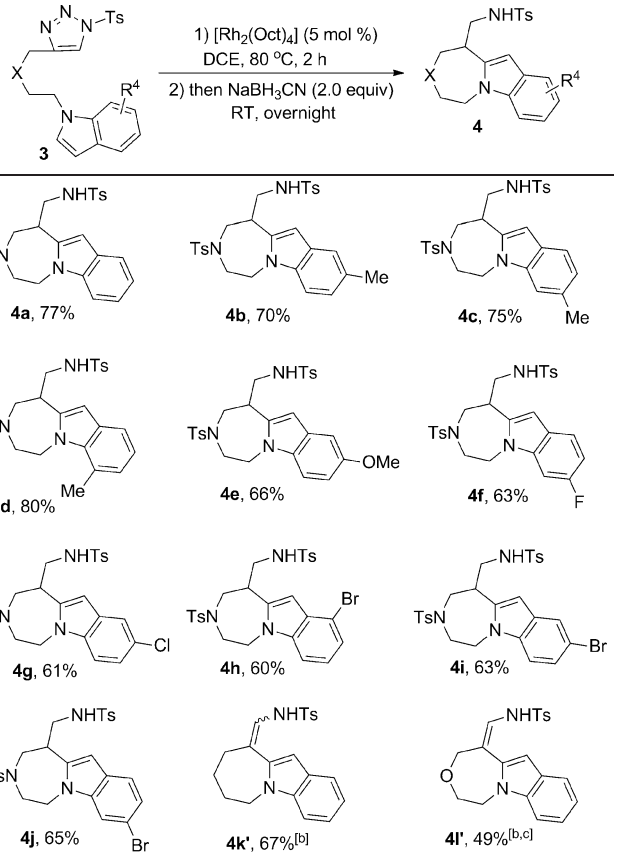
With these optimized one-pot, reaction conditions in hand, we turned our attention to determining the scope and limitations of the reaction in the presence of $[Rh_2(Oct)_4]$. As summarized in Table 2, all of the reactions proceeded smoothly to afford the corresponding products **2b–f** in 78–84% yields when sulfonyl group was *p*-methylbenzenesulfonyl (Ts), *o*-methylbenzenesulfonyl, *m*-methylbenzenesulfonyl, benzenesulfonyl, and mesitylenesulfonyl (Mes), thus indicating that the electronic and steric effects of the sulfonyl group did not have significant impact on the reaction outcome. Next, the scope of this transformation with respect to the sulfonyl moiety (R^2) of the triazole was examined. The

Table 2: Reaction scope: N-pyrrolyl substrates.

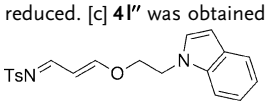


Reaction conditions: **1** (0.1 mmol), $[Rh_2(Oct)_4]$ (5 mol%), anhydrous DCE (1.0 mL). Yields are those of the isolated products.

Table 3: Reaction scope: N-indolyl substrates.[a]



[a] Reaction conditions: **3** (0.1 mmol); $[Rh_2(Oct)_4]$ (5 mol%), anhydrous DCE (1.0 mL). Yields are those of the isolated products. [b] Substrates were used only in the first step, and the two resulting isomers were not reduced. [c] **4l″** was obtained in 43% yield.



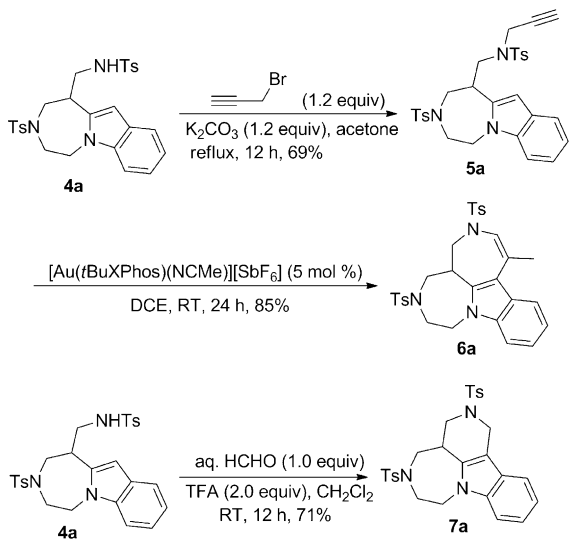
p-bromobenzenesulfonyl (Bs), mesyl (Ms), and mesitylenesulfonyl (Mes) derivatives **2g–i** could be obtained, using this method, in moderate to good yields. Furthermore, substituted pyrrole derivatives bearing methyl, *p*-methylphenyl, and *p*-bromophenyl groups were also suitable for this reaction, thus giving the corresponding cyclized products **2j–l** in reasonable yields. Thus, the reaction was highly general with respect to the R^1, R^2, and R^3 groups.

Next, the further examinations were performed to extend the scope of this cyclization to indolyl triazoles (**3**; Table 3), thus affording the N-bridgehead azepines **4** under the optimized reaction conditions (Table 1, entry 1). As can be seen from Table 3, the substrate bearing no substituent gave the desired product **4a** in 77% yield. Meanwhile, substrates bearing either electron-donating (5-Me, 6-Me, 7-Me, 5-OMe) or electron-withdrawing (6-F, 5-Cl, 4-Br, 5-Br, 6-Br) groups on the indole core all afforded the corresponding products **4b–e** and **4f–j** in moderate to good yields. Moreover, the carbon-tethered substrate **3k** was also suitable for this cyclization reaction, thus providing the desired isomers **4k′** in 67% overall yield.[17] Only when the substrate was tethered by an oxygen atom, were the (*E*)-isomer **4l′** obtained in low yield along with the β-hydride elimination byproduct **4l″** (*trans* only, $J = 12.4$ Hz, see ^{1}H NMR spectroscopy in the Supporting Information) in 43% yield. The structures of **4h** and **4l′** have been unequivocally confirmed by X-ray diffraction.[15]

Considering the easy-to-handle functional groups of the product, further transformations of **4a** to construct polycyclic azepines were investigated (Scheme 2). The propargyl-substituted product **5a** could be obtained in 69% yield by treatment with potassium carbonate and propargyl bromide, and subsequently gave the polycyclic indole **6a** in 85% yield in the presence of [Au(*t*BuXPhos)(NCMe)][SbF_6] (XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) (5 mol%).[18] Moreover, the corresponding tetracyclic [1,4]diazepino[4,5-*a*]indole skeleton **7a** could be synthesized in dichloromethane at room temperature by the Pictet–Spengler reaction in 71% yield.[19]

A kinetic isotope effect (KIE) study suggested that the C–H bond cleavage was not involved in the rate-determining step (for more details, see the Supporting Information).

In conclusion, we have developed a highly efficient and accessible rhodium(II)-catalyzed intramolecular annulation of pyrrolyl and indolyl triazoles. A variety of N-bridgehead azepine derivatives are obtained in moderate to good yields



Scheme 2. Transformations of **4a** into **5a**, **6a**, and **7a**. TFA = trifluoroacetic acid.

under mild reaction conditions with high chemoselectivity and wide scope with respect to the azepine ring (N, O, C). The reaction mechanism is proposed on the basis of isotopic labeling and control experiments. Further applications of this chemistry and more detailed mechanistic investigations are underway in our laboratory.

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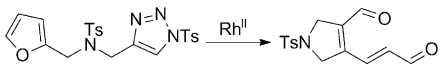
Keywords: annulation · heterocycles · reaction mechanisms · rhodium · synthetic methods

[1] *The Chemistry of Heterocyclic Compounds*, *Vol. 43* (Eds.: A. Weissberger, E. C. Taylor), Wiley-Interscience, New York, **1984**.
[2] R. M. Shaheen, D. W. Davis, W. Liu, B. K. Zebrowski, M. R. Wilson, C. D. Bucana, D. J. McConkey, G. McMahon, L. M. Ellis, *Cancer Res.* **1999**, *59*, 5412 – 5416.
[3] For reviews on *Cephalotaxus* alkaloids, see: a) S. M. Weinreb, M. F. Semmelhack, *Acc. Chem. Res.* **1975**, *8*, 158 – 164; b) L. Huang, Z. Xue in *The Alkaloids*, *Vol. 23* (Ed.: A. Brossi), Academic Press, New York, **1984**, p. 157; c) M. A. Jalil Miah, T. Hudlicky, J. W. Reed in *The Alkaloids*, *Vol. 51* (Ed.: G. A. Cordell), Academic Press, New York, **1998**, p. 199.
[4] For recent reviews on *Stemona* alkaloids, see: a) H. Greger, *Planta Med.* **2006**, *72*, 99 – 113; b) R. Alibés, M. Figueredo, *Eur. J. Org. Chem.* **2009**, 2421 – 2435; c) R. A. Pilli, G. B. Rosso, M. C. F. de Oliveira, *Nat. Prod. Rep.* **2010**, *27*, 1908 – 1937.
[5] a) J. W. Daly, T. F. Spande, H. M. Garraffo, *J. Nat. Prod.* **2005**, *68*, 1556 – 1575; b) T. Kaneko, H. Wong, T. W. Doyle, W. C. Rose, W. T. Bradner, *J. Med. Chem.* **1985**, *28*, 388 – 392.
[6] For recent reviews on ring-opening reactions of triazoles, see: a) B. Chattopadhyay, V. Gevorgyan, *Angew. Chem.* **2012**, *124*, 886 – 896; *Angew. Chem. Int. Ed.* **2012**, *51*, 862 – 872; b) A. V. Gulevich, V. Gevorgyan, *Angew. Chem.* **2013**, *125*, 1411 – 1413; *Angew. Chem. Int. Ed.* **2013**, *52*, 1371 – 1373; for the first example of a transannulation reaction of pyridotriazoles, see: c) S. Chuprakov, F. W. Hwang, V. Gevorgyan, *Angew. Chem.* **2007**, *119*, 4841 – 4843; *Angew. Chem. Int. Ed.* **2007**, *46*, 4757 – 4759.
[7] a) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 14972 – 14974; b) S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher, V. V. Fokin, *J. Am. Chem. Soc.* **2009**, *131*, 18034 – 18035; c) N. Grimster, L. Zhang, V. V. Fokin, *J. Am. Chem. Soc.* **2010**, *132*, 2510 – 2511; d) S. Chuprakov, J. A. Malik, M. Zibinsky, V. V. Fokin, *J. Am. Chem. Soc.* **2011**, *133*, 10352 – 10355; e) N. Selander, B. T. Worrell, S. Chuprakov, S. Velaparthi, V. V. Fokin, *J. Am. Chem. Soc.* **2012**, *134*, 14670 – 14673; f) N. Selander, B. T. Worrell, V. V. Fokin, *Angew. Chem.* **2012**, *124*, 13231 – 13234; *Angew. Chem. Int. Ed.* **2012**, *51*, 13054 – 13057; g) M. Zibinsky, V. V. Fokin, *Angew. Chem.* **2013**, *125*, 1547 – 1550; *Angew. Chem. Int. Ed.* **2013**, *52*, 1507 – 1510; h) S. Chuprakov, S. W. Kwok, V. V. Fokin, *J. Am. Chem. Soc.* **2013**, *135*, 4652 – 4655; i) S. Chuprakov, B. T. Worrell, N. Selander, R. K. Sit, V. V. Fokin, *J. Am. Chem. Soc.* **2014**, *136*, 195 – 202.
[8] a) B. Chattopadhyay, V. Gevorgyan, *Org. Lett.* **2011**, *13*, 3746 – 3749; b) Y. Shi, V. Gevorgyan, *Org. Lett.* **2013**, *15*, 5394 – 5396.
[9] a) J. S. Alford, H. M. L. Davies, *Org. Lett.* **2012**, *14*, 6020 – 6023; b) B. T. Parr, S. A. Green, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 4716 – 4718; c) J. E. Spangler, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 6802 – 6805; d) B. T. Parr, H. M. L. Davies, *Angew. Chem.* **2013**, *125*, 10228 – 10231; *Angew. Chem. Int. Ed.* **2013**, *52*, 10044 – 10047; e) J. S. Alford, J. E. Spangler, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 11712 – 11715.
[10] a) T. Miura, M. Yamauchi, M. Murakami, *Chem. Commun.* **2009**, 1470 – 1471; b) T. Miura, T. Biyajima, T. Fujii, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 194 – 196; c) T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 17440 – 17443; d) T. Miura, T. Tanaka, T. Biyajima, A. Yada, M. Murakami, *Angew. Chem.* **2013**, *125*, 3975 – 3978; *Angew. Chem. Int. Ed.* **2013**, *52*, 3883 – 3886; e) T. Miura, T. Tanaka, K. Hiraga, S. G. Stewart, M. Murakami, *J. Am. Chem. Soc.* **2013**, *135*, 13652 – 13655; f) T. Miura, K. Hiraga, T. Biyajima, T. Nakamuro, M. Murakami, *Org. Lett.* **2013**, *15*, 3298 – 3301; g) T. Miura, T. Tanaka, A. Yada, M. Murakami, *Chem. Lett.* **2013**, *42*, 1308 – 1310; h) T. Miura, Y. Funakoshi, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 2272 – 2275.
[11] a) R. Liu, M. Zhang, G. Winston-McPherson, W. Tang, *Chem. Commun.* **2013**, *49*, 4376 – 4378; b) E. E. Schultz, R. Sarpong, *J. Am. Chem. Soc.* **2013**, *135*, 4696 – 4699.
[12] a) D.-H. Zhang, L.-F. Yao, Y. Wei, M. Shi, *Angew. Chem.* **2011**, *123*, 2631 – 2635; *Angew. Chem. Int. Ed.* **2011**, *50*, 2583 – 2587; b) L. Huang, H.-B. Yang, D.-H. Zhang, Z. Zhang, X.-Y. Tang, Q. Xu, M. Shi, *Angew. Chem.* **2013**, *125*, 6899 – 6903; *Angew. Chem. Int. Ed.* **2013**, *52*, 6767 – 6771.
[13] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708 – 2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596 – 2599; b) E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless, S. Chang, *Angew. Chem.* **2007**, *119*, 1760 – 1763; *Angew. Chem. Int. Ed.* **2007**, *46*, 1730 – 1733; c) J. Raushel, V. V. Fokin, *Org. Lett.* **2010**, *12*, 4952 – 4955; d) J. C. Culhane, V. V. Fokin, *Org. Lett.* **2011**, *13*, 4578 – 4580; e) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302 – 1315; f) B. T. Worrell, J. A. Malik, V. V. Fokin, *Science* **2013**, *340*, 457 – 460.
[14] a) H. M. L. Davies, E. Saikali, W. B. Young, *J. Org. Chem.* **1991**, *56*, 5696 – 5700; b) H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong, M. J. Fall, *J. Am. Chem. Soc.* **1996**, *118*, 6897 – 6907; c) H. M. L. Davies, G. Ahmed, M. R. Churchill, *J. Am. Chem. Soc.* **1996**, *118*, 10774 – 10782; d) H. M. L. Davies, S. J. Hedley, *Chem. Soc. Rev.* **2007**, *36*, 1109 – 1119.
[15] The molecular structures of the products *E*-**2a′**, **4h**, **4l′**, and **9a** have been determined by means of X-ray crystallographic studies. Their ORTEP drawings and the corresponding CIF

data have been presented in the Supporting Information. We also developed intramolecular annulation of 1-sulfonyl-1,2,3-triazoles with furan ring.



8a **9a**

[16] a) P. Müller, Y. F. Allenbach, E. Robert, *Tetrahedron: Asymmetry* **2003**, *14*, 779 – 785; b) P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferry, H. D. Flack, *Org. Lett.* **2004**, *6*, 1725 – 1728; c) D. Marcoux, A. B. Charette, *Angew. Chem.* **2008**, *120*, 10309 – 10312; *Angew. Chem. Int. Ed.* **2008**, *47*, 10155 – 10158; d) D. Marcoux, S. Azzi, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 6970 – 6972; e) A. DeAngelis, V. W. Shurtleff, O. Dmitrenko, J. M. Fox, *J. Am. Chem. Soc.* **2011**, *133*, 1650 – 1653. See also Refs. [7b,c].

[17] The structure of compound **4k** was confirmed by NOE experiments; see Supporting Information for more details.

[18] a) C. Ferrer, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 1123 – 1127; *Angew. Chem. Int. Ed.* **2006**, *45*, 1105 – 1109; b) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358 – 1373.

[19] a) E. D. Cox, J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797 – 1842; b) J.-F. Rousseau, R. H. Dodd, *J. Org. Chem.* **1998**, *63*, 2731 – 2737.

Communications

Heterocycle Synthesis

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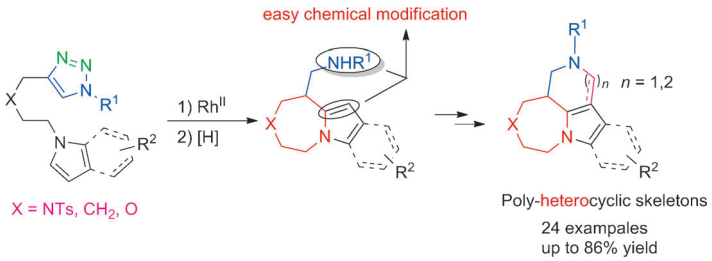
M. Shi* ——————— ■■■■–■■■■

Rhodium(II)-Catalyzed Intramolecular Annulation of 1-Sulfonyl-1,2,3-Triazoles with Pyrrole and Indole Rings: Facile Synthesis of N-Bridgehead Azepine Skeletons



Heads up: A convenient and efficient synthetic method of highly functionalized N-bridgehead azepine skeletons was developed using a rhodium(II)-catalyzed intramolecular annulation of pyrrolyl and indolyl triazoles. Several interesting transformations of the products into poly-heterocyclic products and the reaction mechanism are disclosed. Ts = 4-toluenesulfonyl.