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Intramolecular Transannulation of Alkynyl Triazoles via Alkyne−Carbene Metathesis Step: Access to Fused Pyrroles

Yi Shi and Vladimir Gevorgyan*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607, United States

vlad@uic.edu

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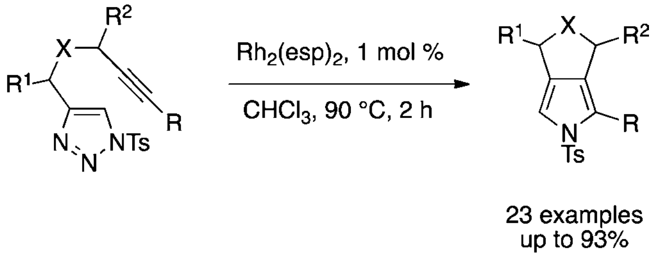
ABSTRACT



An intramolecular Rh-catalyzed transannulation reaction of alkynyl triazoles has been developed. This method allows efficient construction of various 5,5-fused pyrroles, including tetrahydropyrrolo and spiro systems. The method demonstrates excellent functional group compatibility. A rhodium carbene−alkyne metathesis mechanism is proposed for this transformation.

Rhodium-imino carbenes **B**, which are easily generated from *N*-sulfonyl-1,2,3-triazoles (**A**),[1,2] open wide opportunities for formation of diverse heterocycles **C** through various transannulation reactions (eq 1).[3−7] We have recently reported a transannulation of triazoles with terminal alkynes into pyrroles **E**, which operates via an ylide mechanism (**D**).[5]

Apparently, the ylide path limits this method to terminal alkynes, which disqualifies the possibility of an intramolecular transannulation reaction toward valuable fused pyrroles. Inspired by a recent report by May,[8] in which a carbene−alkyne metathesis[9] has been employed as a key step in an efficient synthesis of bridged polycyclic ring systems, we hypothesized that this key step can potentially be employed in an intramolecular transannulation reaction. Thus, iminocarbene **F** would undergo a carbene−alkyne metathesis to form a new Rh carbene intermediate **G**. A subsequent nucleophilic attack of the N atom at the Rh carbene and the following tautomerization would

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(1) For synthesis of *N*-sulfonyl-1,2,3-triazoles, see: (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. (b) Fokin, V. V.; Raushel, J. *Org. Lett.* **2010**, *12*, 4952. (c) Liu, Y.; Wang, X.; Xu, J.; Zhang, Q.; Zhao, Y.; Hu, Y. *Tetrahedron* **2011**, *67*, 6294.

(2) For reviews, see: (a) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862. (b) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371.

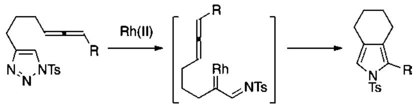
(3) For reports on transannulation of pyridotriazoles, see: (a) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757. (b) Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463.

(4) For the first report on transannulation of *N*-sulfonyl-1,2,3-triazoles, see: Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972.

(5) Chattopadhyay, B.; Gevorgyan, V. *Org. Lett.* **2011**, *13*, 3746.

(6) (a) Zibinsky, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1507. (b) Chuprakov, S.; Kwok, S. W.; Fokin, V. V. *J. Am. Chem. Soc.* **2013**, *135*, 4652. (c) Parr, B. T.; Green, S. A.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 4716. (d) Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6802. (e) Miura, T.; Biyajima, T.; Fujii, T.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 194. (f) Funakoshi, Y.; Morimoto, M.; Biyajima, T.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17440. (g) Miura, T.; Tanaka, T.; Hiraga, K.; Stewart, S. G.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 13652.

(7) When our work was underway, Sarpong reported an intramolecular transannulation of triazoles with allenes to form 6,5-fused pyrrole systems efficiently. Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.* **2013**, *135*, 4696.



(8) Jansone-Popova, S.; May, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 17877.

(9) For earlier reports on the carbene−alkyne metathesis mechanism in Rh-catalyzed reactions of diazocarbonyl compounds, see: (a) Padwa, A.; Kassir, J. M.; Semones, M. A.; Weingarten, M. D. *Tetrahedron Lett.* **1993**, *34*, 7853. (b) Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M.; Xu, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2637.

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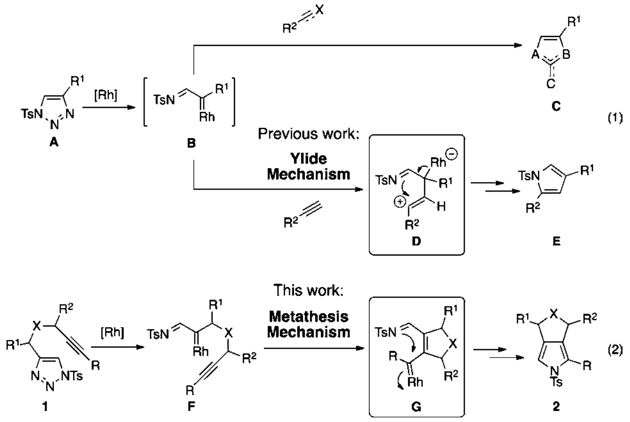
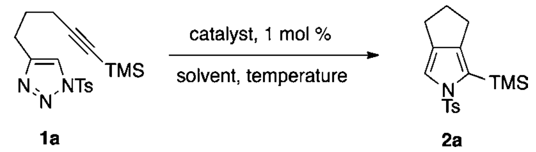
produce a fused pyrrole **2** (eq 2).[10,11] Herein we report that indeed this concept can be realized. Hence, a novel, general, and efficient method for the construction of 5,5-fused pyrrole units[12] from easily available alkynyl triazoles has been developed.



To test the above hypothesis, alkynyl triazole **1a** was subjected to the reaction with rhodium octanoate. To our delight, the desired 5,5-fused pyrrole **2a** was formed in 60% yield (Table 1, entry 1). A brief optimization indicated reaction conditions of entry 9 to be sufficient for this transformation.

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	t/°C	yield/%[b]
1	$Rh_2(Oct)_4$	$ClCH_2CH_2Cl$	80	62[d] (60[c])
2	$Rh_2(Oct)_4$	$CHCl_3$	80	63[d]
3	$Rh_2(Oct)_4$	dioxane	80	19
4	$Rh_2(Oct)_4$	THF	80	trace
5	$Rh_2(Oct)_4$	PhMe	80	0
6	$Rh_2(S\text{-NTTL})_4$	$CHCl_3$	80	41[d]
7	$Rh_2(esp)_2$	$CHCl_3$	80	63[d]
8	$Rh_2(S\text{-DOSP})_4$	$CHCl_3$	80	46[d]
9	$\mathbf{Rh_2(esp)_2}$	$\mathbf{CHCl_3}$	**90**	**78**[e]
10	$Rh_2(esp)_2$	$CHCl_3$	70	76[d,f]
11	$Rh_2(esp)_2$	$CHCl_3$	60	78 (78[c,f])
12	$Rh_2(esp)_2$	$CHCl_3$	50	59[g]

[a] **1a** (0.1 mmol) and Rh(II) (1 mol %) were dissolved in solvent (1.0 mL) and heated at the indicated temperature for 12 h. [b] GC yield. [c] Isolated yield. [d] Desilylation of product was observed. [e] Heated for 2 h. [f] Heated for 15 h. [g] Heated for 42 h.

Next, the scope of this transformation has been examined. First, we tested a series of aryl substituents at the alkyne moiety (Figure 1, **b**–**m**). It was found that a variety of groups, including OMe (**d**, **j**), F (**g**), Br (**f**), CO_2Me (**h**), CF_3 (**i**), and protected diol (**e**), were perfectly tolerated under these reaction conditions to produce the corresponding fused pyrroles **2d**–**m** in reasonable to excellent yields.

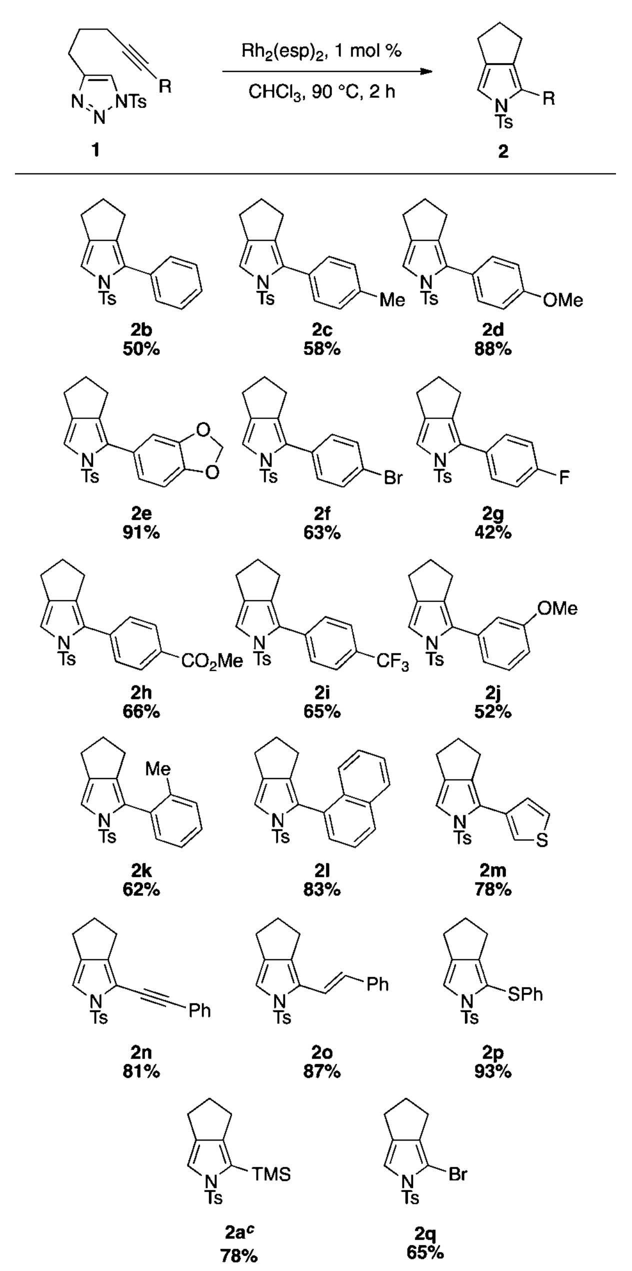


Figure 1. Transannulation of alkynyl triazoles: R substituent variations.[a,b] [a] **1** (0.2 mmol) and $Rh_2(esp)_2$ (1 mol %) were dissolved in $CHCl_3$ (3.0 mL) and heated at 90 °C for 2 h. [b] Isolated yields. [c] Heated at 60 °C for 15 h.

Likewise, naphthalene- (**2l**) and heterocycle-substituted pyrroles (**2m**) were obtained in good yields. It was also

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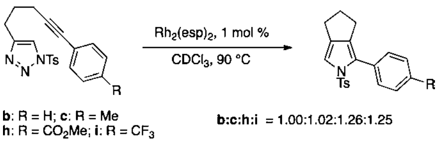
(10) The relative rate comparison indicated that the triazoles bearing an electron-deficient aryl group (**1h** and **1i**) reacted faster than those having electron-neutral (**1b**) or electron-rich (**1c**) aryl groups. This result does not support an ylide mechanism, which strongly favors electron-rich alkynes.[5]



b: R = H; **c**: R = Me
h: R = CO_2Me; **i**: R = CF_3

b:**c**:**h**:**i** = 1.00:1.02:1.26:1.25

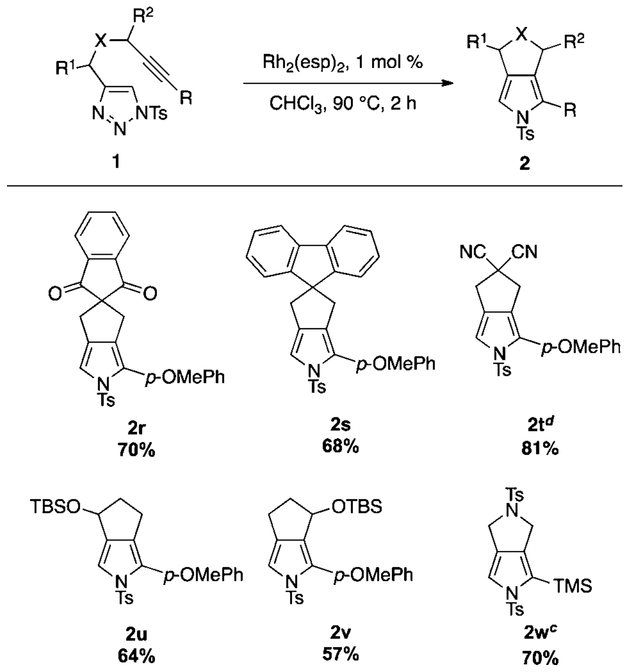


Figure 2. Transannulation of alkynyl triazoles: tether variations[a,b] [a] **1** (0.2 mmol) and Rh$_2$(esp)$_2$ (1 mol %) combined in CHCl$_3$ (3.0 mL) and heated at 90 °C for 2 h. [b] Isolated yields. [c] Heated at 60 °C for 15 h. [d] Heated at 90 °C for 15 h.

found that triazoles, bearing *ortho*- or *meta*-substituted aryl groups, could also participate in this transannulation reaction to give fused pyrroles **2j**, **k**.

Further investigation indicated that this reaction is not limited to aryl alkynes. Thus, we found that alkynyl (**n**) or alkenyl (**o**) groups can also be efficiently utilized in this transformation to produce the corresponding pyrroles possessing an unsaturated unit at the C-2 position. Notably, the reaction of alkynyl triazole bearing a phenylthio group proceeded smoothly to afford thiopyrrole **2p** in excellent yield. Moreover, TMS (**2a**) and Br (**2q**) groups were compatible with these reaction conditions, thus providing opportunities for further functionalization of the obtained pyrroles .[13,14]

We also investigated the scope of the reaction with respect to a triazole–alkyne tether (Figure 2). It was found that substrates possessing a C-3[15] tether reacted well, including those possessing ketone (**2r**), nitrile (**2t**), and protected alcohol (**2u**, **2v**) functional groups to produce the corresponding fused pyrroles in good yields. Notably, this method also allows efficient access to polycyclic spiro systems **2r**, **2s**. Furthermore, a substrate with a nitrogen tether underwent a smooth transannulation reaction to give a bicyclic tetrahydropyrrolo-pyrrole skeleton **2w**.

In summary, we developed an efficient rhodium-catalyzed intramolecular transannulation reaction of alkynyl *N*-tosyltriazoles, which involves a Rh-carbene–alkyne metathesis step. This new method provides expeditious access to various 5,5-fused pyrroles from easily available starting materials. It can also be used for the efficient construction of spiro systems, as well as fused tetrahydropyrrolo-pyrrole cores.

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Supporting Information Available. Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Although a direct [3 + 2] cycloaddition path cannot be completely ruled out at this point, our numerous unsuccessful attempts on the transannulation of tosyltriazoles with a number of electron-deficient alkynes and alkenes do not support this possibility.

(12) For 5,5-fused pyrrole cores found in biologically active molecules, see for example: (a) Portevin, B.; Tordjman, C.; Pastoureau, P.; Bonnet, J.; Nanteuil, G. D. *J. Med. Chem.* **2000**, *43*, 4582. (b) Oesterlin, R.; Bell, M. R.; Hlavac, A. G.; McGarry, R. H.; Gelotte, K. O. *J. Med. Chem.* **1980**, *23*, 945.

(13) For transformations of 2-silyl-pyrroles, see: (a) Aikawa, K.; Hioki, Y.; Mikami, K. *Chem.—Asian J.* **2010**, *5*, 2346. (b) Maitin, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379. (c) Ito, H.; Sensui, H.-O.; Arimoto, K.; Miura, K.; Hosomi, A. *Chem. Lett.* **1997**, *7*, 639.

(14) For transformations of 2-bromo-pyrroles, see: (a) Chen, W.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 6025. (b) Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194. (c) Korsager, S.; Taaning, R. H.; Skrydstrup, T. *J. Am. Chem. Soc.* **2013**, *135*, 2891. (d) Strotman, N. A.; Chobanian, H. R.; Guo, Y.; He, J.; Wilson, J. E. *Org. Lett.* **2010**, *12*, 3578.

(15) Attempts on employment of alkynyltriazoles possessing C-2 or C-4 tethers were not successful.

The authors declare no competing financial interest.