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Rh-Catalyzed Transannulation of *N*-Tosyl-1,2,3-Triazoles with Terminal Alkynes

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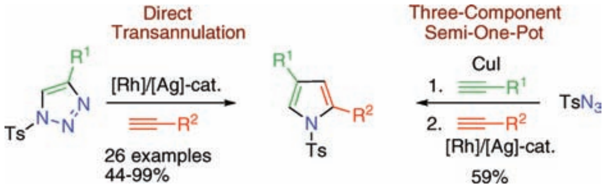
ABSTRACT



The first transannulation of 1,2,3-triazoles with *terminal* alkynes into pyrroles is reported. The reaction proceeds in the presence of a $Rh_2(oct)_4$/$AgOCOCF_3$ binary catalyst system providing a straightforward approach to 1,2,4-trisubstituted pyrroles in good to excellent yields.

Transition-metal-catalyzed transannulation is an emerging tool for the interconversion of various heterocyclic cores. Thus, triazoles can be exploited as a convenient precursory platform for the formation of diverse heterocyclic systems. We found that N-fused pyridotriazoles[1] can undergo the Rh-catalyzed transannulation with alkynes[2] and nitriles[3] to produce indolizines and imidazopyridines, respectively.[4] Likewise, it has been also shown that the Rh-catalyzed transannulation of N-tosyltriazoles **1** with nitriles, proceeding via intermediacy of **2** (a), can be used for the construction of imidazoles (eq 1).[5] Further developments of the transannulation concept include recently reported Rh-[6] as well as Pd-[7] and Ni[8]-catalyzed transformations.

Thus, Murakami has recently disclosed[8c] the Ni/$AlPh_3$-catalyzed transannulation of **1** with *internal* alkynes into the tetrasubstituted pyrroles (b). The reaction was proposed to proceed via azanickelacycle **5**.[9] Importantly, attempted by both groups (a, b) transannulation of triazoles **1** with *terminal* alkynes was unsuccessful.[5,8c] Herein, we report the first transannulation of *N*-tosyltriazoles **1** with *terminal* alkynes in the presence of a $Rh_2(oct)_4$/$AgOCOCF_3$ binary catalyst system (c). This reaction is efficient with electron-rich arylacetylenes and tolerates a

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[1] Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757.

[2] For representative examples on the Rh-catalyzed reactions of diazocarbonyl compounds with alkynes, see: (a) Davies, H. M. L.; Romines, K. R. *Tetrahedron* **1988**, *44*, 3343. (b) Kinder, F. R.; Padwa, A. *Tetrahedron Lett.* **1990**, *31*, 6835. (c) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1991**, *56*, 6971. (d) Davies, H. M. L.; Cantrell, W. R.; Romines, K. R., Jr.; Baum, J. S. *Org. Synth.* **1992**, *70*, 93. (e) Doyle, M. P.; Winchester, W. P.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968. (f) Padwa, A.; Kinder, F. R. *J. Org. Chem.* **1993**, *58*, 21. (g) Doyle, M. P.; Protopopova, M.; Müller, P.; Ene, D.; Shapiro, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 8492.

[3] For Rh-catalyzed cycloaddition of diazocarbonyl compounds with nitriles, see: Connell, R.; Scavo, F.; Helquist, P. *Tetrahedron Lett.* **1986**, *27*, 5559.

[4] For cyclopropanation of alkenes with 2-pyridyl diazo compounds, see: Davies, H. M. L.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595.

[5] Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972.

[6] For Rh-catalyzed transannulation of triazoles with alkenes, see: (a) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034. (b) Grimster, N.; Zhang, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2010**, *132*, 2510.

[7] Transannulation of triazoles with Pd-catalyst, see: (a) Nakamura, I.; Nemoto, T.; Shiraiwa, N.; Terada, M. *Org. Lett.* **2009**, *11*, 1055. (b) Miura, T.; Nishida, Y.; Morimoto, M.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2011**, *13*, 1429.

[8] Transannulation of triazoles with Ni-catalyst, see: (a) Miura, T.; Yamauchi, M.; Kosaka, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4955. (b) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085. (c) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, 1470.

[9] For involvement of analogous azametallocycle intermediate in the Pd-catalyzed transannulation of benzotriazoles with internal alkynes, see ref 7a.

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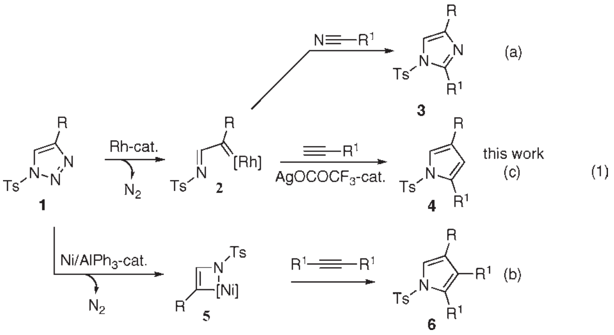
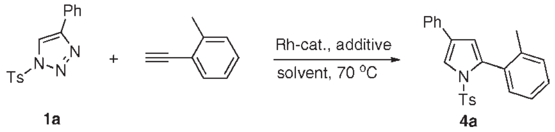
wide range of substituents R at the triazole ring to produce trisubstituted pyrroles **4** (eq 1).



(1)

First, we attempted the transannulation of triazole **1a** with *o*-tolylacetylene in the presence of several Rh catalysts and various additives (Table 1). Thus, attempted reactions in the presence of $Rh_2(OAc)_4$/$AgOCOCF_3$ and $Rh_2(pfb)_4$/$AgOCOCF_3$ combinations were unsuccessful (Table 1, entries 1, 2).

Table 1. Optimization of the Transannulation Reaction of Triazole **1a**[a]



no.	catalyst (2.5 mol %)	Lewis acid (5.0 mol %)	solvent 0.06 M	yield[b] (%)
1	$Rh_2(OAc)_4$	$AgOCOCF_3$	toluene	NR
2	$Rh_2(pfb)_4$	$AgOCOCF_3$	toluene	NR
3	$Rh_2(dosp)_4$	$Al(OTf)_3$	toluene	63
4	$Rh_2(oct)_4$	$AgOCOCF_3$	toluene	53
5	$Rh_2(oct)_4$	$AgOCOCF_3$	hexane	67
6	$Rh_2(oct)_4$	-	hexane	NR[c]
7	$Rh_2(oct)_4$	AgOTf	hexane	NR
8	$Rh_2(oct)_4$	CsF	hexane	NR
9	$Rh_2(oct)_4$	$Zn(OTf)_2$	hexane	NR
10	$Rh_2(oct)_4$	$Y(OTf)_3$	hexane	NR
11	$Rh_2(oct)_4$	$AgOCOCF_3$	DCM	NR
12	$Rh_2(oct)_4$	$AgOCOCF_3$	DCE	NR
13	$Rh_2(oct)_4$	$AgOCOCF_3$	THF	NR
14	$Rh_2(oct)_4$	CF_3SO_3H	hexane	Dec.[d]
15	$Rh_2(oct)_4$	CF_3CO_2H	hexane	Dec.

[a] All reactions were performed at 70 °C for 12 h with 0.2 mmol of **1a** and 0.3 mmol of alkyne. [b] Isolated yield. [c] NR = No Reaction. [d] Dec. = Decomposition.

Gratifyingly, it was found that employment of the $Rh_2(dosp)_4$/$Al(OTf)_3$ combination afforded the desired product **4a** in 63% yield (entry 3). Use of $Rh_2(oct)_4$ gave a slightly lower yield (53%) of the product (entry 4). Further improvement of the yield (67%) was achieved in the presence of $Rh_2(oct)_4$ and $AgOCOCF_3$ in hexane (entry 5). The reaction did not proceed without a Lewis acid additive at all (entry 6). Further screening of Lewis (Brønsted) acid additives and solvents did not reveal more efficient conditions for this reaction (entries 7–15).

With the optimized conditions in hand, the generality of the transannulation reaction of triazoles **1** with terminal alkynes was examined (Table 2). It was found that these conditions were very efficient for a transannulation of a wide range of *N*-tosyl-1,2,3-triazoles with electron-rich alkynes. Thus, reaction of 4-phenyltriazole **1a** with a number of terminal arylalkynes (and alkenylalkyne) proceeded smoothly to give the trisubstituted pyrrole derivatives **4a–h** in good to excellent yields (entries 1–8). Triazole **1b**, possessing an electron-deficient aryl ring (entries 9–15), and the *p*-tolyl containing triazole **1c** (entries 16–20) were equally efficient in this reaction. Bromophenyl derivative **1d** proved to be an excellent substrate for the transannulation reaction, producing pyrroles **4u**,**v** in 99 and 86% yields (entries 21–22). It was also found that triazoles, possessing alkyl (**1e**) and ester (**1f**) groups at the C-4 position of the ring, as well as C-4 unsubstituted triazole **1g**, could also participate in the transannulation reaction with alkynes, though the yields of pyrrole were moderate (entries 23–26).

It deserves mentioning that this transannulation reaction was efficient with various electron-rich arylalkynes, possessing alkyl, methoxy, phenoxy, and isopropyl groups. Cyclohexenylacetylene was also competent in this reaction.[10]

The synthetic utility of this transannulation approach was further highlighted by a three-component *semi-one-pot* synthesis of pyrrole **4p** from tosylazide and two different terminal alkynes. First, tosyl azide was allowed to react with *p*-tolylacetylene in the presence of 10% CuI and 1.2 equiv of 2,6-lutidine in 0.5 M $CHCl_3$ at 0 °C for 12 h.[11] The reaction mixture, containing a newly formed *N*-tosyltriazole, was filtered through a short pad of silica, evaporated, and used as crude in the subsequent Rh-catalyzed transannulation reaction with 1-ethynyl-2-methyl-4-methoxybenzene to produce pyrrole **4p** in 59% overall yield (eq 2).

We propose the following plausible mechanism for this transannulation reaction (Scheme 1). Upon treatment with $Rh_2(oct)_4$, triazole **1**,[12] generates the Rh-iminocarbene **7**.[5] A direct nucleophilic attack of the terminal alkyne at the latter produces ylide **8** (**path a**),[13] which upon cyclization forms a cyclic zwitterionic species **9**. Elimination of the Rh catalyst from **9** forms the reaction product **4**. On the other hand, the in situ generated silver acetylide may attack **7** to form a Rh-containing propargylimine species **10** (**path b**). Alternatively, **10** may arise via a proton loss from **8** (**path b′**).

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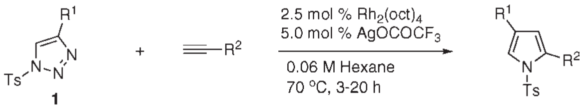
[10] Simple aliphatic alkynes, as well as electron-deficient arylalkynes were not effective in this transformation.

[11] For Cu-catalyzed synthesis of *N*-tosyl-1,2,3-triazoles from tosylazide and terminal alkynes, see: 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.

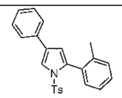
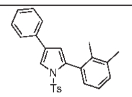
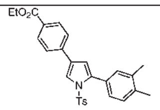
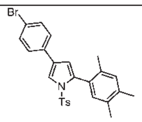
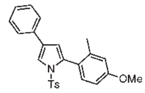
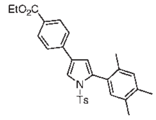
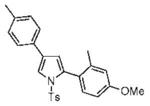
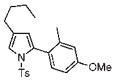
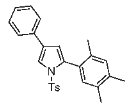
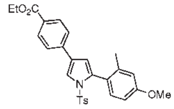
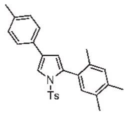
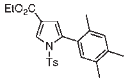
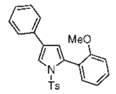
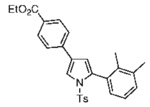
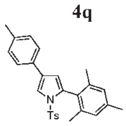
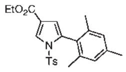
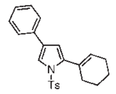
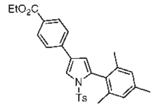
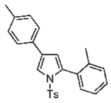
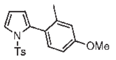
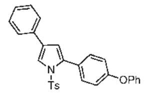
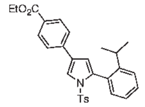
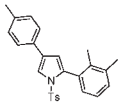
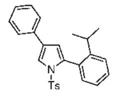
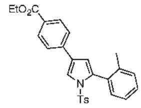
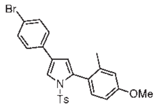
[12] Doyle, K. J.; Moody, C. J. *Tetrahedron* **1994**, *50*, 3761.

[13] For involvement of ylide intermediates in the Rh-catalyzed reactions of diazocarbonyl compounds with nitriles, see: Connell, R.; Scavo, F.; Helquist, P.; Akermark, B. *Tetrahedron Lett.* **1986**, *27*, 5559. See also ref 5.

Table 2. Synthesis of Pyrroles via Rh-Catalyzed Transannulation of *N*-Tosyltriazoles with Terminal Alkynes[a]

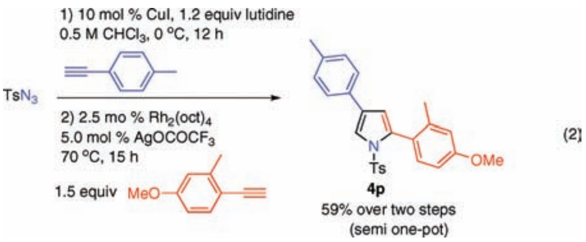


1a, $R^1 = C_6H_5$ **1d**, $R^1 = C_6H_4$(4-Br) **1g**, R^1 = H
1b, $R^1 = C_6H_4(4\text{-}CO_2Et)$ **1e**, R^1 = *n*-Bu
1c, $R^1 = C_6H_4(4\text{-}CH_3)$ **1f**, $R^1 = CO_2Et$

no.	product	yield (%)[b]	no.	product	yield (%)[b]	no.	product	yield (%)[b]	no.	product	yield (%)[b]
1	 **4a**	67	8	 **4h**	66	15	 **4o**	60	22	 **4v**	86
2	 **4b**	97	9	 **4i**	74	16	 **4p**	81	23	 **4w**	44
3	 **4c**	79	10	 **4j**	94	17	 **4q**	77	24	 **4x**	57
4	 **4d**	51	11	 **4k**	58	18	 **4r**	87	25	 **4y**	46
5	 **4e**	52	12	 **4l**	72	19	 **4s**	54	26	 **4z**	54
6	 **4f**	52	13	 **4m**	46	20	 **4t**	70			
7	 **4g**	54	14	 **4n**	65	21	 **4u**	99			

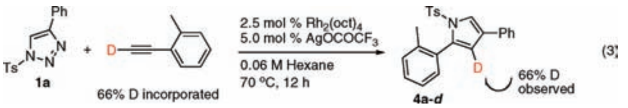
[a] All reactions were performed on 0.2 mmol scale. [b] Isolated yield; for more information see Supporting Information (SI).

Proton-assisted 5-*endo*-*trig* cyclization of **10** would afford the cyclic intermediate **9**.

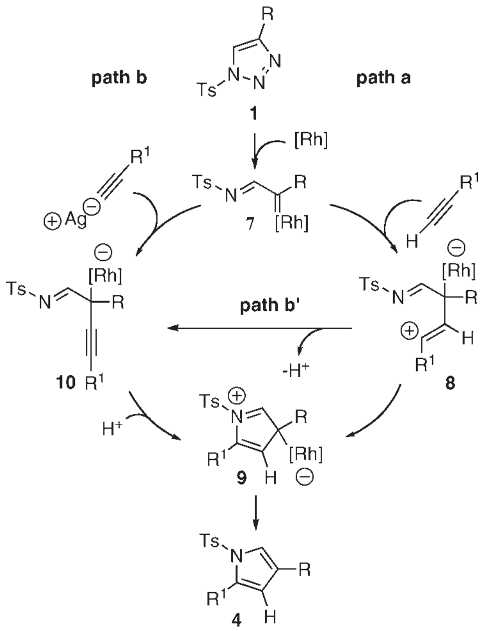


In order to gain further insight into the mechanism of this transannulation reaction, the following deuterium labeling experiment was performed (eq 3).

A deuterated *o*-tolylacetylene was subjected to the standard transannulation reaction with **1a** to produce **4a-*d*** with complete preservation of the deuterium label. This result undoubtedly rules out possible involvement of the **paths b** and **b′**, which would result in partial or complete deuterium scrambling. Althoug, the crucial role of silver trifluoroacetate in **path a** is not clear, it possibly acts as a Lewis acid which, via a coordination to the imine, activates the electrophilic Rh carbene



Scheme 1. Proposed Mechanism for the Transannulation of *N*-Tosyltriazoles with Terminal Alkynes



moiety toward the nucleophilic attack by an alkyne. The higher reactivity of electron-rich alkynes in this transformation reasonably fits into the most plausible reaction **path a**.

In conclusion, we have developed the transannulation reaction of *N*-tosyltriazoles with terminal alkynes in the presence of a $Rh_2(oct)_4/AgOCOCF_3$ binary catalyst system. This new protocol is highly efficient for the synthesis of 1,2,4-trisubstituted pyrroles from diversely C-4-substituted triazoles and eletron-rich terminal alkynes. Furthermore, it has been also shown that trisubstituted pyrroles **4** can also be synthesized in a three-component semi-one-pot fashion from two different terminal alkynes and tosylazide. A mechanistic rationale, involving a direct nucleophilic attack of an electron-rich alkyne at the Rh-iminocarbene intermediate, followed by cyclization step was proposed for this new transannulation reaction.

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Supporting Information Available. Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.