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Rhodium-Catalyzed Enantioselective Cyclopropanation of Olefins with *N*-Sulfonyl 1,2,3-Triazoles

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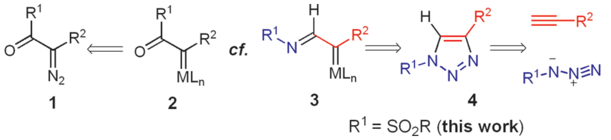
Diazocarbonyl compounds **1** are well-known precursors to metal carbenes **2** (eq 1).[1] The versatile reactivity of the latter is recognized by numerous synthetic applications.[2] In contrast, related azavinyl carbenes **3** have not been employed in synthesis,[3] primarily because of the limited availability of corresponding α-diazoimines.[4] These reactive intermediates can be viewed as synthetic equivalents of formyl carbenes, in which both amine and aldehyde functions can be revealed by simple transformations, thus significantly expanding the repertoire of chiral molecules that may be accessed via carbene-based synthetic methods. Herein we report a first example of highly diastereo- and enantioselective Rh(II)-catalyzed cyclopropanation employing azavinyl carbenes **3** derived from 1-sulfonyl 1,2,3-triazoles **4**. The latter can be obtained using the copper-catalyzed cycloaddition reaction of alkynes with sulfonyl azides.[5]



(1)

Our recent success in the Rh-catalyzed transannulation of *N*-sulfonyl 1,2,3-triazoles had proven that these easily available, reasonably stable, and seemingly unreactive compounds are reliable precursors of azavinyl carbenes.[6] Accordingly, we further explored Rh(II) catalysis with 1,2,3-triazoles, targeting enantioselective transformations. To this end, we examined the cyclopropanation of styrene with 1-sulfonyl-4-phenyl-1,2,3-triazoles **4** in the presence of various chiral Rh(II) complexes[7] (Figure 1) in 1,2-dichloroethane at 80 °C (Table 1). The resulting sulfonyl imines **5** were smoothly converted into the corresponding aldehyde **6a** by treatment with K_2CO_3 in wet methanol.

First, we found that the use of 1-toluenesulfonyl derivative **4a** with Rh_2(*S*-DOSP)$_4$[8] catalyst afforded cyclopropanecarboxaldehyde **6a** in high yield with excellent trans diastereoselectivity. However, the enantioselectivity of the reaction was low (Table 1, entry 1). Next, Rh_2(*S*-PTAD)$_4$[9] and Rh_2(*S*-PTTL)$_4$[10] catalysts were examined, providing **6a** with over 70% ee (entries 2 and 3). Increased steric demand of the ligands on rhodium resulted not only in very sluggish reaction but also in drastic erosion of the diastereoselectivity (entry 4). We hypothesized that switching to a less sterically encumbered carbene precursor might improve the overall performance of the reaction. Indeed, 1-mesyl triazole **4b** reacted smoothly in the presence of Rh_2(*S*-PTTL)$_4$ catalyst, furnishing the cyclopropane product with 88% ee (entry 5). To our great delight, Rh_2(*S*-NTTL)$_4$[11] in combination with **4b** (entry 6) allowed for excellent enantioselectivity (96% ee) and yield (95%). Remarkably, *n*-octylsulfonyl and isopropylsulfonyl triazoles **4c** and **4d**, respectively, provided similar results with Rh_2(*S*-NTTL)$_4$ catalyst (entries 7 and 8). Interestingly, cyclopropanation of **4d** in the presence of Rh_2(*S*-DOSP)$_4$ complex provided the opposite enantiomer,[9a] albeit with very low ee (entry 9).

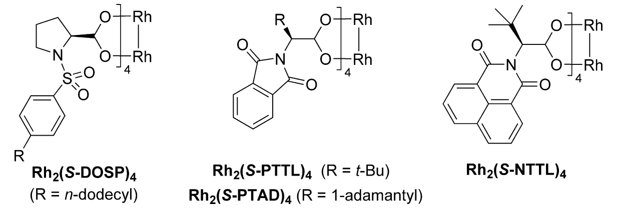
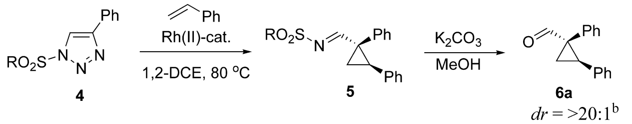


Figure 1. Rh(II) carboxylates for asymmetric cyclopropanation.

Table 1. Optimization of the Enantioselective Cyclopropanation of Styrene with *N*-Sulfonyl 1,2,3-Triazoles[a]



entry	triazole	catalyst	yield (%)[c]	ee (%)[d]
1	**4a** (R = *p*-Tol)	Rh_2(*S*-DOSP)$_4$	92	28
2	**4a**	Rh_2(*S*-PTAD)$_4$	91	74
3	**4a**	Rh_2(*S*-PTTL)$_4$	87	76
4	**4a**	Rh_2(*S*-NTTL)$_4$	42[e,f]	78
5	**4b** (R = Me)	Rh_2(*S*-PTTL)$_4$	91	88
6	**4b**	Rh_2(*S*-NTTL)$_4$	95	96
7	**4c** (R = *n*-C_8H_{17})	Rh_2(*S*-NTTL)$_4$	99	96
8	**4d** (R = *i*-Pr)	Rh_2(*S*-NTTL)$_4$	83	97
9	**4d**	Rh_2(*S*-DOSP)$_4$	75	−16
10[g]	**4c**	Rh_2(*S*-NTTL)$_4$	90	96

[a] Conditions: triazole **4** (0.2 mmol), styrene (1.0 mmol), Rh(II) catalyst (0.002 mmol), 1,2-dichloroethane (0.5 mL). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] NMR yield of **6a** after hydrolysis. [d] Determined by chiral HPLC. [e] Reaction did not proceed at temperatures below 100 °C. [f] dr = 3:1. [g] Using 1.2 equiv of styrene and 0.5 mol % catalyst at 65 °C.

Further optimization revealed that this cyclopropanation reaction performed well at lower temperature (65 °C) with reduced catalyst loading (entry 10). Notably, only a slight excess of olefin (1.2 equiv) was required, and no slow-addition techniques (e.g., a syringe pump) were needed.[12]

With the optimized conditions for the cyclopropanation with 1,2,3-triazoles in hand, we examined the scope with respect to the olefin (Scheme 1). As illustrated in Scheme 1, a broad range of substituted styrenes participated in the reaction, affording cyclopropanecarbaldehydes[13] **6b−f** in good to excellent yields and high enantioselectivity. Significantly less reactive 1-hexene afforded the corresponding *n*-butyl-substituted cyclopropane **6g** in 70% yield and 96% ee. Interestingly, *trans*-methylstyrene produced tetrasubstituted cyclopropane **6h** with excellent enantioselectivity, while the cyclopropanation of the cis analogue delivered almost racemic product **6i**. It is worth mentioning that in the last three cases, the

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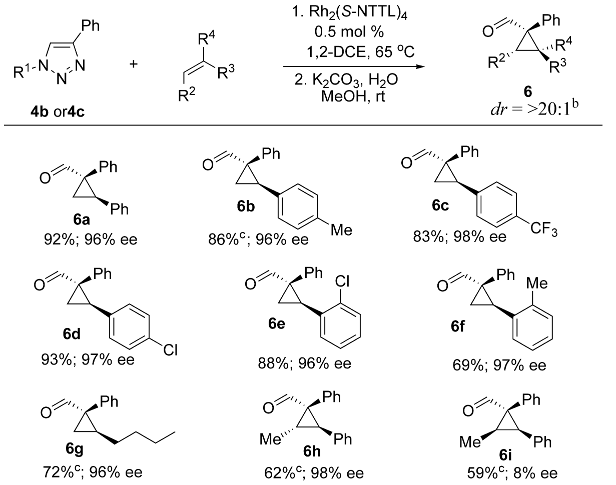
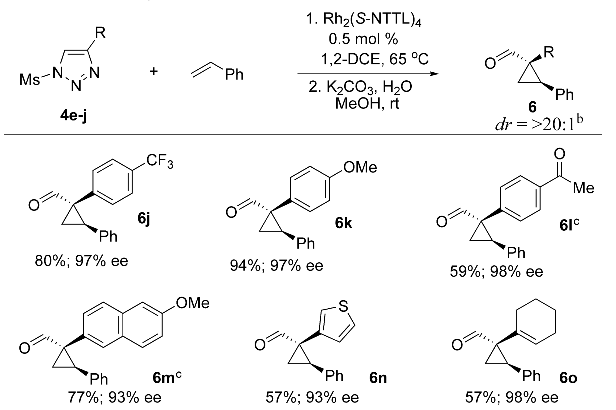
Scheme 1. Enantioselective Cyclopropanation with 1,2,3-Triazoles: Scope of Olefins[a]



[a] Unless specified otherwise, all reactions were carried out on a 0.5 mmol scale with 1.2 equiv of olefin under ambient atmosphere. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Using 2.0 equiv of alkene.

Scheme 2. Enantioselective Cyclopropanation of Styrene with *N*-Methanesulfonyl 1,2,3-Triazoles[a]



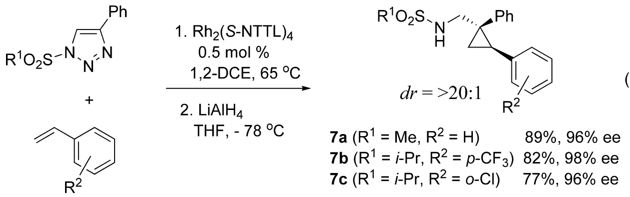
[a] All reactions were carried out on a 0.5 mmol scale with 1.2 equiv of olefin under ambient atmosphere. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Performed at 80 °C.

reaction proceeded with complete chemoselectivity, and the commonly observed insertion into the allylic C−H bond[8c,14] did not occur.

Examination of the scope of the process with respect to the 1-sulfonyl 1,2,3-triazoles (Scheme 2) revealed that substrates possessing both electron-rich and electron-deficient aryl groups at C4 reacted smoothly to produce cyclopropanes **6j**−**m** with excellent enantioselectivity. Moreover, heteroaryl- and alkenyl-substituted triazoles were competent substrates for this reaction (**6n**, **6o**; Scheme 2), further demonstrating the utility of this methodology.

While the instability of sulfonyl imines **5** toward hydrolysis precluded their isolation in pure form, we recognized that reduction of **5** immediately after their synthesis could provide an easy access to chiral homoaminocyclopropanes. Indeed, cyclopropanation of a series of styrenes followed by the treatment of the crude imine product with $LiAlH_4$ furnished *N*-(cyclopropylmethyl) sulfonamides **7a**−**c** in good yields with excellent enantioselectivity (eq 2).

In summary, a novel and very efficient Rh(II)-catalyzed asymmetric cyclopropanation methodology that utilizes stable and readily available *N*-sulfonyl 1,2,3-triazoles as azavinyl carbene precursors is now available. The azavinyl carbenes readily react with olefins under experimentally simple conditions, providing cyclopropanecarboxaldehydes and *N*-sulfonyl homoaminocyclopropanes in generally excellent yields with high enantioselectivity. Further studies of the scope, origin of high selectivity, and mechanism of the reaction are underway in our laboratories.



(2)

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Supporting Information Available: Experimental details, characterization data, NMR spectral charts, and crystallographic data for **7a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) 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.
(2) For recent reviews, see: (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (b) Doyle, M. P. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley: New York, 2005; pp 341−355. (c) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (d) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
(3) For related transformations involving (2-pyrydyl)carbenoids, see: (a) Davies, H. M. L.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595. (b) Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463.
(4) α-Diazoimines are known to exist in cyclic 1,2,3-triazole form, except for those bearing a strong electron-withdrawing group at N1. See: (a) Dimroth, O. *Ann.* **1909**, *364*, 183. (b) Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33.
(5) Raushel, J. *Diss. Abstr. Int., B* **2009**, *69*, 4763 (Ph.D. Dissertation, The Scripps Research Institute, La Jolla, CA, 2009). (b) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154. Also see ref 6a.
(6) (a) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972. For transannulation of related pyridotriazoles, see: (b) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757.
(7) Rh(II) carboxamidates were incompetent in this transformation. See the Supporting Information for the full catalyst screening data.
(8) For recent application examples, see: (a) Davies, H. M. L.; Nagashima, T.; Klino, J. L., III. *Org. Lett.* **2000**, *2*, 823. (b) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 1233. (c) Davies, H. M. L.; Coleman, M. G.; Ventura, D. L. *Org. Lett.* **2007**, *9*, 4971. Also see refs 3 and 6a.
(9) (a) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437. (b) Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625. (c) Denton, J. R.; Davies, H. M. L. *Org. Lett.* **2009**, *11*, 787.
(10) For cyclopropanation, see: (a) DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 7230. For C−H insertions, see: (b) Minami, K.; Saito, H.; Tsutsui, H.; Nambu, H.; Anada, M.; Hashimoto, S. *Adv. Synth. Catal.* **2005**, *347*, 1483. (c) Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2003**, *14*, 817. (d) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.
(11) (a) Müller, P.; Allenbach, Y. F.; Robert, E. *Tetrahedron: Asymmetry* **2003**, *14*, 779. (b) Müller, P.; Bernardinelli, G.; Allenbach, Y. F.; Ferry, M.; Flack, H. D. *Org. Lett.* **2004**, *6*, 1725. (c) Marcoux, D.; Charette, A. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 10155. (d) Marcoux, D.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 6970.
(12) Generally, to avoid the carbene dimerization side process, a dilute solution of diazo compound is added over several hours to a mixture of rhodium catalyst and a large excess (3−10 equiv) of olefin.
(13) For a recently reported synthesis of chiral cyclopropyl aldehydes via a highly efficient rhodium-catalyzed hydroformylation of cyclopropenes, see: Sherrill, W. M.; Rubin, M. *J. Am. Chem. Soc.* **2008**, *130*, 13804.
(14) Thompson, J. L.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090.

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