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

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Abstract

N-Sulfonyl 1,2,3-triazoles readily form rhodium(II) azavinyl carbenes, which react with olefins to produce cyclopropanes with excellent diastereo- and enantioselectivity and in high yield.

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 due to 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 wish to 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

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Supporting Information Available: Experimental details, characterization data and NMR spectral charts. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(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 the 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) complexes⁷ (Figure 1) in 1,2-dichloroethane at 80 °C (Table 1). The resulting sulfonyl imine **5** was smoothly converted into the corresponding aldehyde **6a** by treatment with K₂CO₃ in wet methanol.

First, we found that the use of 1-toluenesulfonyl derivative **4a** with Rh₂(*S*-DOSP)₄⁸ catalyst afforded cyclopropane-carboxaldehyde **6a** in high yield and excellent *trans*-diastereoselectivity. However, enantioselectivity of the reaction was low (Table 1, entry 1). Next, Rh₂(*S*-PTAD)₄⁹ and Rh₂(*S*-PTTL)₄¹⁰ 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 Rh₂(*S*-PTTL)₄ catalyst furnishing the cyclopropane product with 88% *ee* (entry 5). To our great delight, Rh₂(*S*-NTTL)₄¹¹ in combination with sulfonyl triazole **4b** allowed for excellent enantioselectivity (96% *ee*) and yield, 95% (entry 6). Remarkably, *n*-octylsulfonyl and isopropylsulfonyl triazoles **4c** and **4d** provided similar results with Rh₂(*S*-NTTL)₄ catalyst (entries 7 and 8). Interestingly, cyclopropanation of **4d** in the presence of Rh₂(*S*-DOSP)₄ complex provided the opposite enantiomer,^{9a} albeit with very low *ee* (entry 9).

Further optimization revealed that this cyclopropanation reaction performed well at lower temperature (65 °C) with reduced catalyst loading (entry 10). Notably, only slight excess of olefin (1.2 equiv) was required, and no slow addition techniques (*eg.* 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 cyclopropanecarbaldehydes¹³ **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* analog delivered almost racemic product **6i**. It is worth mentioning that in the last three cases, reaction proceeded with complete chemoselectivity, and the commonly observed insertion into allylic C-H bond^{8c,14} did not occur.

Examination of the scope of the process with respect to 1-sulfonyl 1,2,3-triazoles revealed (Scheme 2) that substrates possessing both electron-rich and electron-deficient aryl groups at C-4 reacted smoothly to produce cyclopropanes **6j-m** with excellent enantioselectivity. Moreover, heteroaryl- and alkenyl-substituted triazoles were competent substrates for this reaction (Scheme 2, **6n, 6o**), further demonstrating the utility of this methodology.

While the instability of sulfonyl imines **5** towards hydrolysis precluded their isolation in pure form, we recognized that a reduction of **5** immediately after they are synthesized could provide an easy access to chiral homo-aminocyclopropanes. Indeed, cyclopropanation of a series of styrenes, followed by the treatment of the crude imine product with LiAlH₄, furnished *N*-(cyclopropylmethyl) sulfonamides **7a-c** in good yields and excellent enantioselectivity (eq 2).

(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 cyclopropane carboxaldehydes and *N*-sulfonyl homo-amino cyclopropanes in generally excellent yields and with high enantioselectivity. Further studies on the scope, origins of high selectivity, and the mechanism of the reaction are underway in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. Generally, to avoid carbene dimerization side process a dilute solution of diazocompound is added over several hours to a mixture of rhodium catalyst and large excess (3–10 equiv) of olefin.
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Figure 1.
Rh(II) carboxylates for asymmetric cyclopropanation.

Scheme 1.

Enantioselective Cyclopropanation with 1,2,3-Triazoles: Scope of Olefins^a

^aUnless specified otherwise, all reactions were carried out on 0.5 mmol scale with 1.2 equiv of olefin and under ambient atmosphere; ^bdetermined by ¹H NMR of the crude reaction mixture; ^c2.0 equiv. of alkene were used.

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

^a All reactions were carried out in 0.5 mmol scale with 1.2 equiv of olefin, and under ambient atmosphere. ^b Determined by ¹H NMR of the crude reaction mixture.

Table 1Optimization of the Enantioselective Cyclopropanation of styrene with *N*-sulfonyl 1,2,3-triazoles^a $dr = >20:1^b$

entry	triazole	catalyst	yield, % ^c	ee, % ^d
1	4a (R = <i>p</i> -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 = <i>n</i> -C ₈ H ₁₇)	Rh ₂ (S-NTTL) ₄	99	96
8	4d (R = <i>i</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 Triazole **4** (0.2 mmol), styrene (1.0 mmol), Rh(II) catalyst (0.002 mmol), 1,2-dichloroethane (0.5 mL).^b Determined by ¹H NMR 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 1.2 equiv of styrene, 0.5 mol % of catalyst, 65 °C.