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Reactivity of *N*-(1,2,4-Triazolyl)-Substituted 1,2,3-Triazoles

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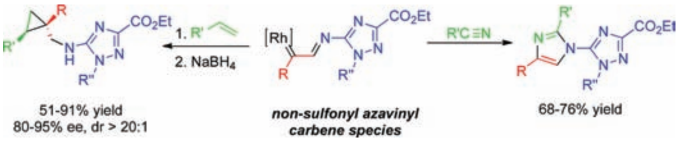
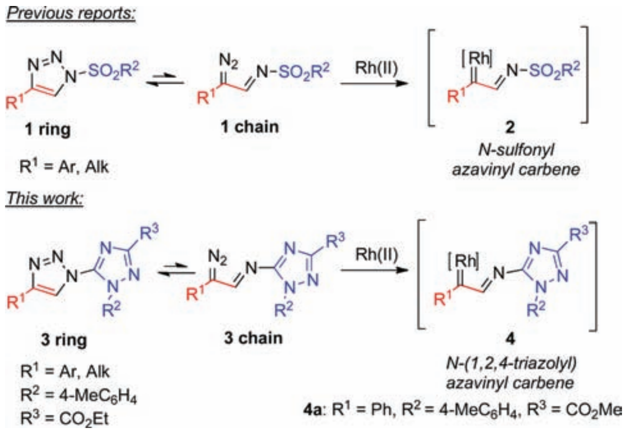
ABSTRACT



Synthetically useful rhodium(II) carbenes were obtained from *N*-(1,2,4-triazolyl)-substituted 1,2,3-triazoles and Rh(II) carboxylates. The electron-withdrawing 1,2,4-triazolyl group reveals the heretofore unknown reactivity of nonsulfonyl 1,2,3-triazoles, which exhibit the reactivity of diazo compounds. The resulting carbenes provide ready asymmetric access to secondary homoaminocyclopropanes (80–95% *ee*, dr >20:1) via reactions with olefins and also engage in efficient transannulation reactions with nitriles.

The intrinsic ability of certain electron-deficient triazoles to undergo ring-chain isomerism[1] opens the possibility of using them as latent diazo compounds. We have recently demonstrated that 1-sulfonyl-1,2,3-triazoles **1** can indeed serve as stable and readily available progenitors of *N*-sulfonyl azavinyl carbenes **2** (Scheme 1, top).[2] Similarly to transition metal carbenes obtained from diazocarbonyl compounds,[3] azavinyl carbenes are useful and versatile reactive intermediates. Their generation does not require preparation and handling of diazo compounds, and their electronic and steric properties, and hence reactivity, can be finely tuned by varying the imine functionality at the vicinal carbon atom.

Scheme 1. Azavinyl Carbenes from 1,2,3-Triazoles



Reactions of carbenes generated from 1,2,3-triazoles are experimentally convenient and, because the concentration of the reactive carbene is low, do not require special precautions in order to avoid side reactions.

Until now, only sulfonyl triazoles have been shown to produce transition metal azavinyl carbenes. We report here a first example of 1,2,3-triazoles **3** designed to undergo Rh(II)-catalyzed transformations, and we demonstrate that an electron-deficient heterocycle at the *N*-1 position

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(1) α-Diazoimines are known to exist in cyclic 1,2,3-triazole form, except for those bearing a strong electron-withdrawing group at N-1: (a) Dimroth, O. *Ann.* **1909**, *364*, 183. (b) Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33.

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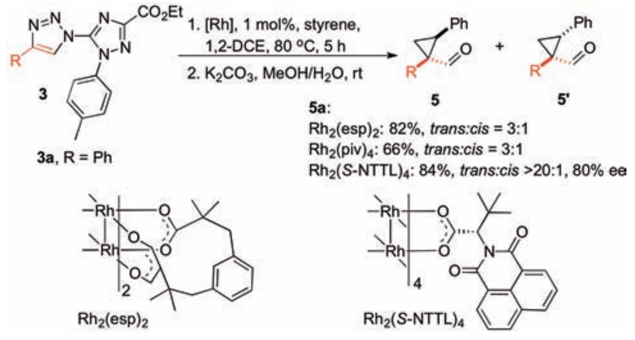
of the 1,2,3-triazole ring can facilitate its conversion to the carbene species **4** (Scheme 1). This route significantly expands the repertoire of accessible azavinyl carbenes and allows practical access to synthetically useful secondary amines, which are difficult to obtain by other methods.

Ethyl 1,2,4-triazolyl-1,2,3-triazoles **3**[4] (see Supporting Information for the preparation procedure) were found to readily produce azavinyl carbenes **4** that reacted with olefins. Thus, in the presence of the $Rh_2(esp)_2$ complex,[5] styrene was converted to cyclopropane carboxaldehyde **5a** in 82% isolated yield (*trans*/*cis* ratio 3:1; Scheme 2). The $Rh_2(piv)_4$ catalyst provided the product aldehyde with similarly low diastereoselectivity as well as a somewhat lower yield (66%). In contrast, the same reaction carried out with the Rh_2(*S*-NTTL)$_4$ catalyst gave **5a** in 84% yield and 80% ee with a significantly improved *trans*/*cis* ratio (**5**:**5′** > 20:1). The low diastereoselectivity observed in reactions catalyzed by $Rh_2(piv)_4$ and $Rh(esp)_2$ suggests that it is determined not only by the donor–acceptor electronic properties of these carbenes but also by the steric demands of the imine group, as compared to the sulfonyl azavinyl carbenes[2d] and those derived from diazoacetates.

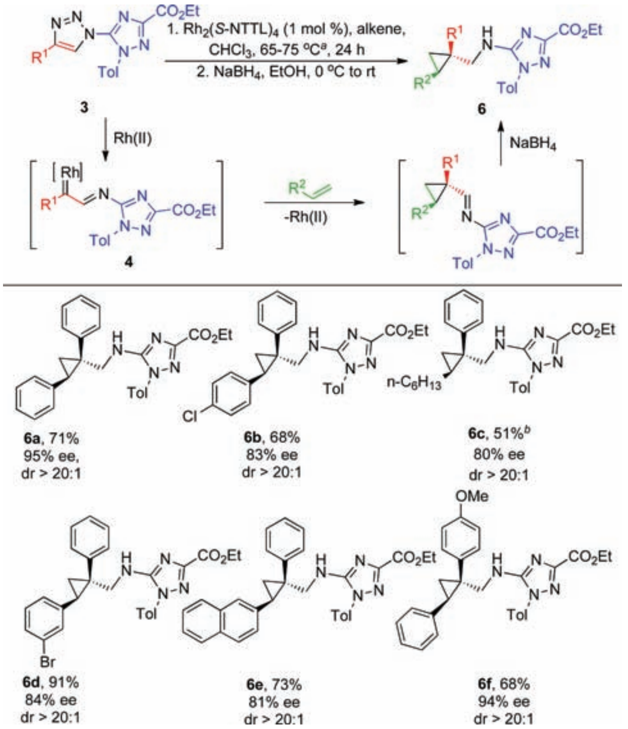
Scheme 2. Cyclopropanation of Styrene with Triazole **3a** Catalyzed by Rh(II) Carboxylates



Other chiral Rh(II) carboxylates were then evaluated in the cyclopropanation reaction (cf. Table S2 of the Supporting Information). However, instead of removing the 5-amino-1,2,4-triazolyl group, we carried out the one-pot reduction of the intermediate imine in order to access valuable heterocyclic secondary amine **6a**. Most chiral catalysts showed excellent diastereoselectivity (dr > 20:1) compared to 3:1 obtained for $Rh_2(esp)_2$. As for the enantioselectivity, Rh_2(*S*-NTTL)$_4$[6] and Rh_2(*S*-PTAD)$_4$ emerged as the most promising catalysts after the initial screening, which was performed in 1,2-DCE at 80 °C. Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-NTV)$_4$ provided **6a** as an opposite enantiomer with 38% and 66% *ee*, respectively. Optimization of the reaction conditions revealed that Rh_2(*S*-NTTL)$_4$ performed better than other catalysts, giving cyclopropane products with a high 95% *ee* (dr > 20:1; 65 °C in $CHCl_3$).

Hydrolysis of the intermediate imine confirmed both the relative and absolute stereochemistry of the cyclopropane products. These results correlate well with our prior findings for reactions of 1-sulfonyl-1,2,3-triazoles, in which Rh_2(*S*-NTTL)$_4$ also gave excellent asymmetric induction in chloroform and 1,2-DCE.[2b,c] It is worth mentioning that performing the reaction at an elevated temperature did not affect its enantio- and diastereoselectivity.

Scheme 3. Rh_2(*S*-NTTL)$_4$-Catalyzed Enantio- and Diastereoselective Cyclopropanation of Alkenes with Triazoles **3**[a]



[a] All reactions were performed at 75 °C except for compounds **6a** and **6b**, which were obtained at 65 °C. [b] At 40% conversion.

When other alkenes and triazoles **3** were examined in the reaction with Rh_2(*S*-NTTL)$_4$, excellent diastereoselectivity and good enantioselectivity were a general trend for this type of carbene (Scheme 3).

The only downside of using the Rh_2(*S*-NTTL)$_4$ catalyst was the increased reaction time (24 h). Electron-rich olefins (4-methoxystyrene and 1,1-diphenylethylene) produced substituted 2-pyrrolines instead of cyclopropanes in good yields.[2b] Reactions of triazoles **3** with aromatic and aliphatic nitriles provide substituted triazolylimidazoles **7**. These compounds are likely formed via the initial attack of the nitrile nitrogen at the electrophilic carbene center. Screening of several readily available achiral Rh(II) carboxylates and solvents in the reaction of **3a** with benzonitrile revealed that $Rh_2(esp)_2$ was the most effective catalyst for this transannulation reaction. Although the imidazole

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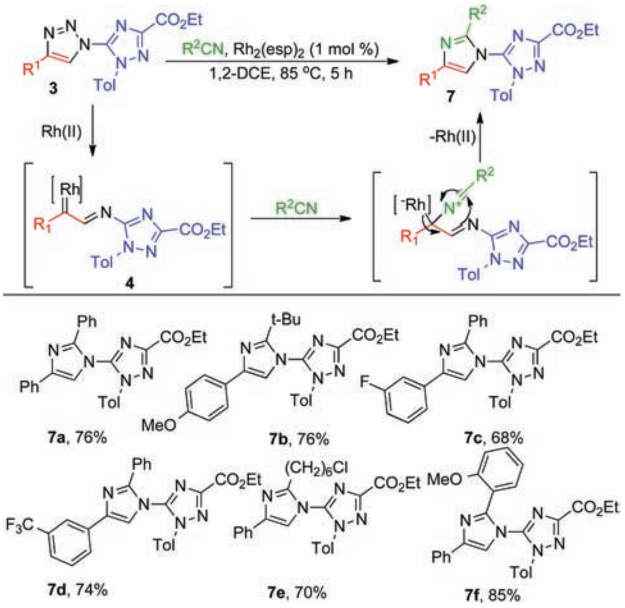
product was formed in all of the tested solvents, 1,2-dichloroethane (1,2-DCE) and chloroform (Table S1 of Supporting Information) gave consistently high yields. Interestingly, the lowest temperature at which the reaction occurs is 65 °C. However, it is unclear which particular step requires an elevated temperature: 1,2,3-triazole ring opening, the formation of the Rh-carbene complex, or the addition of a nitrile. Slightly higher temperatures resulted in shorter reaction times and comparable yields.

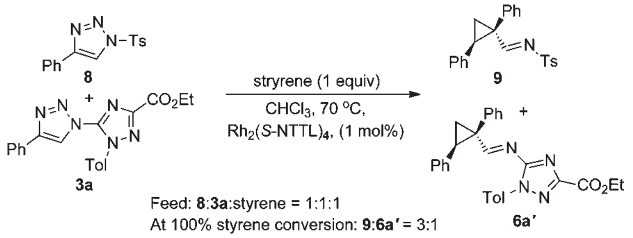
Scheme 4. $Rh_2(esp)_2$-Catalyzed Transannulation of Triazoles **3** with Nitriles



At 85 °C, both aliphatic and aromatic nitriles produced imidazoles **7** in good yield (Scheme 4). Despite the multiple attempts to react 4-alkyl (R^1 = *t*-Bu, *n*-C_6H_{13}, CH_3OCH_2–) substituted 1,2,3-triazoles with nitriles, we were unable to isolate the corresponding imidazoles in synthetically useful yields. The failure of this reaction is most likely due to the β-hydride shift of the carbene intermediate. Rather surprisingly, the adduct of *p*-trifluoromethyl phenylacetylene was also found to be a poor carbene precursor for the transannulation reaction.

The relative reactivity of new triazolyl-triazoles **3** was compared with 1-sulfonyl-1,2,3-triazoles in a competition experiment, wherein sulfonyl triazole **8** (1 equiv), triazole **3a** (1equiv), and styrene (1 equiv) were reacted in chloroform in the presence of 1 mol % of Rh_2(*S*-NTTL)$_4$ at 70 °C (Scheme 5). After 90 min, full consumption of styrene was observed, and the ratio of the corresponding cyclopropanes **9** and **6a′** was 3:1, indicating that the *N*-sulfonyl triazole **8** reacted with styrene more readily than triazole **3a**. An identical experiment performed at ambient temperature exhibited a similar trend (after 24 h, 10% of styrene was consumed, and **9**:**6a′** ratio was 3:1). Another control reaction of sulfonyl triazole with 1 equiv of styrene at ambient temperature demonstrated a slightly faster consumption of styrene (15% after 24 h). These results point to the generally lower reactivity of triazolyl triazoles **3a** compared to *N*-sulfonyl triazoles such as **8** and do not support the notion of possible catalyst deactivation by **3a** via the coordination of the nitrogen atoms to the Rh center.[7]

Scheme 5. Relative Reactivity of **3a** and *N*-Sulfonyl Triazole **8**



In summary, a new family of azavinyl carbenes obtained form 1,2,3-triazoles containing a carbon substituent at the *N*-1 position is now available. These species display high thermal stability, excellent reactivity, and high chemo- and stereoselectivity in reactions with olefins and nitriles. These *N*-(1,2,4-triazolyl) azavinyl carbenes are versatile reactive intermediates that provide access to highly substituted imidazoles and chiral cyclopropanes containing complex heterocyclic secondary amines.

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Supporting Information Available. Experimental conditions, optimization procedures, NMR and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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