Azavinyl Carbenes

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Catalytic Asymmetric Transannulation of N*H*-1,2,3-Triazoles with Olefins**

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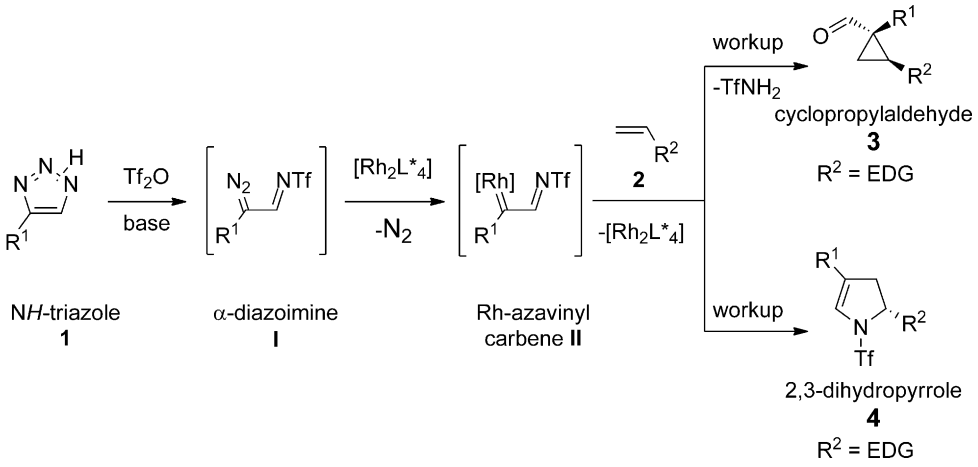
Abstract: *A convenient one-pot asymmetric synthesis of 2,3-dihydropyrroles from in situ generated triflated triazoles and olefins is described that further expands the utility of azavinyl carbene chemistry and provides access to an important class of cyclic enamides. Mechanistic investigations support the involvement of triflated cyclopropylaldimine intermediates in the formation of 2,3-dihydropyrrole. To the best of our knowledge, this is the first example of a chiral Brønsted acid catalyzed rearrangement of cyclopropylimines into enantioenriched 2,3-dihydropyrroles.*

The multifaceted reactivity of diazo carbonyl compounds[1] is illustrated by their many uses in both research and industrial laboratories, ranging from photolithography in the manufacture of computer chips[2] to the synthesis of pharmaceuticals[3] and production of insecticides.[4] In contrast to α-diazocarbonyl compounds, the reactivity and synthetic potential of the related α-diazoimines has remained relatively unexplored, in large part because of the dearth of safe and convenient routes to access this class of compounds.[5] Recently, we[6] and others[7] have demonstrated that transition-metal/azavinyl carbenes can be accessed directly from certain electron-deficient 1,2,3-triazoles,[8] likely as a result of the ring-chain tautomerism of the latter.[9] The reactive triazoles include 1-sulfonylated derivatives, which can be synthesized in multigram amounts, isolated, and safely stored,[8e] or can be generated in situ from stable N*H*-triazoles **1** with triflic anhydride under mild conditions (Scheme 1).[6d] In the presence of Rh^{II} catalysts, *N*-triflyltriazoles formed in this way are readily converted into azavinyl carbenes, which readily react with a variety of olefins **2** to yield highly enantioenriched cyclopropane carboxaldehydes **3**.

However, when 4-methoxystyrene was subjected to the reaction, only 2,3-dihydropyrroles **4** were obtained in excellent yield and moderate enantioselectivity. While formation of 2,3-dihydrofurans by the reaction of α-diazocarbonyl compounds with electron-rich olefins is known,[10,11] the analogous transformation of α-diazoimines[6d,7j] had not been reported prior to our recent disclosure.[6d]



Scheme 1. Reactions of *N*-triflyl-Rh-azavinyl carbenes with olefins. Tf = triflate, EDG = electron-donating group.

Here, we describe our studies of this novel transformation and results of a mechanistic investigation of possible pathways that give rise to this useful class of heterocycles.[12] To improve the enantioselectivity of this transformation, a panel of chiral dirhodium catalysts was evaluated in the reaction of 4-phenyl-N*H*-1,2,3-triazole and 4-methoxystyrene (Table 1). Similar to the trends observed in the Rh^{II}-catalyzed cyclopropanations,[6c,d] increasing the steric volume of the dirhodium catalysts improved the enantiomeric excess of product **4aa** (entries 1–5), with the $[Rh_2(S\text{-NTTL})_4]$ catalyst providing the highest enantioselectivity (72% *ee*, entry 5).[6d] Intriguingly, increasing steric demands further through the introduction of a 4-bromo substituent into the naphthalene ring (entry 6) did not significantly affect the enantioselectivity.

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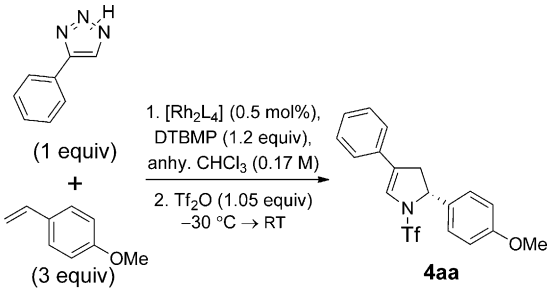
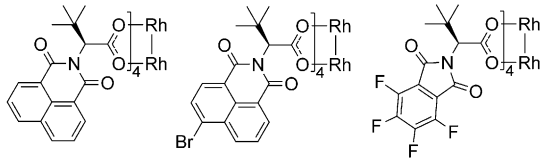
Table 1: Screening of chiral catalysts.[a]



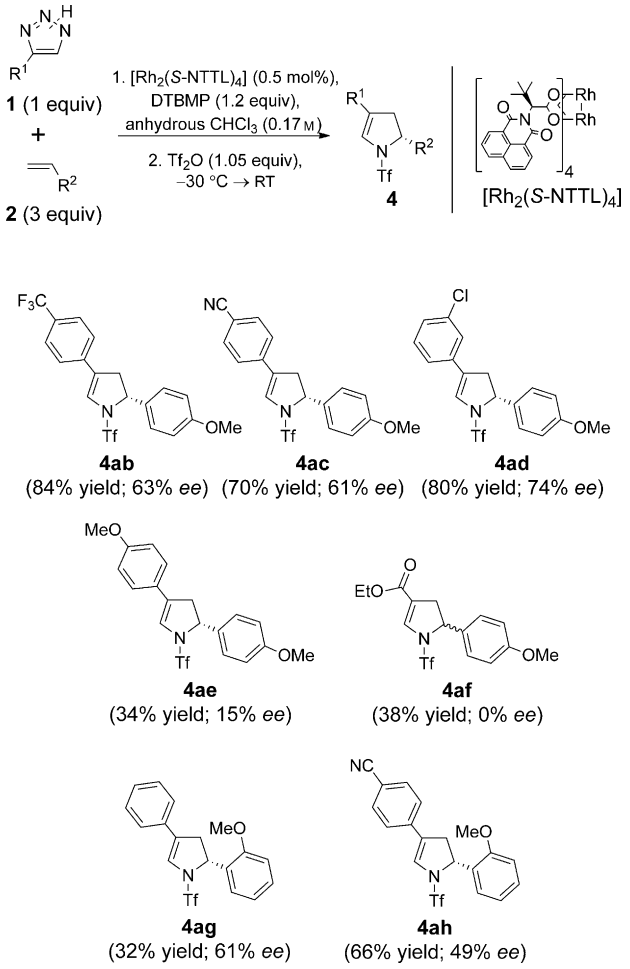
[Rh_2L_4]:



[Rh_2(*S*-NTTL)$_4$] [Rh_2(*S*-4-Br-NTTL)$_4$] [Rh_2(*S*-TFPTTL)$_4$]

Entry	Chiral catalyst	Yield [%][b]	*ee* [%]
1	[Rh_2(*S*-NTA)$_4$]	68	23
2	[Rh_2(*S*-NTL)$_4$]	74	20
3	[Rh_2(*S*-NTPA)$_4$]	67	44
4	[Rh_2(*S*-NTV)$_4$]	61	55
5	[Rh_2(*S*-NTTL)$_4$]	92	72
6	[Rh_2(*S*-4-Br-NTTL)$_4$]	40	70
7	[Rh_2(*S*-PTTL)$_4$]	15	46
8	[Rh_2(*S*-TFPTTL)$_4$]	56	70
9	[Rh_2(*S*-4-Me-PTTL)$_4$]	34	66
10	[Rh_2(*S*-BPTTL)$_4$]	33	64

[a] Unless otherwise specified, all reactions were performed initially at −30 °C and were then allowed to warm up to room temperature.
[b] Yields of isolated product. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

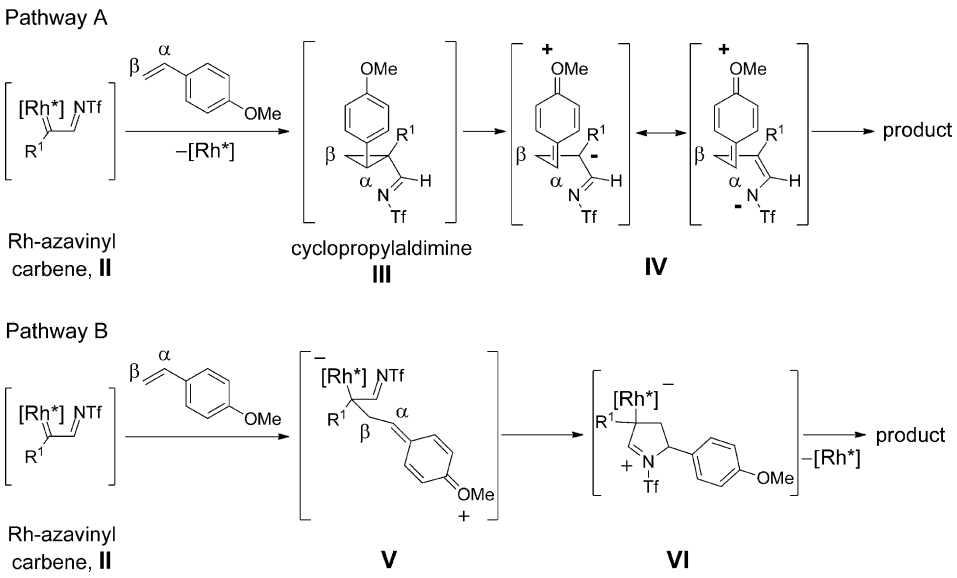


Scheme 2. Substrate scope of [Rh_2(*S*-NTTL)$_4$]-mediated synthesis of 2,3-dihydropyrroles.

Furthermore, the enantioselectivity remained essentially unchanged with [Rh_2(*S*-TFPTTL)$_4$], a catalyst that Hashimoto and co-workers used to significantly improve the enantioselectivity of Rh^{II}-catalyzed nitrene transfers[13] (entry 8). These observations suggested that the enantioselectivity of the reaction was only partially determined by the catalyst.

Intrigued by the apparent limit of enantioselectivity, we examined the electronic and steric effects of substrates on the process. To this end, substituents on both the 1,2,3-triazole ring and the olefin partner were varied (Scheme 2). Interestingly, incorporation of an electron-withdrawing substituent at the C4-position of the triazole ring, for example, 4-trifluoromethyl (**4ab**) and 4-cyanophenyl (**4ac**), reduced the *ee* value of the products by about 10%, while introduction of a less electronegative group, such as 3-chlorophenyl, returned the *ee* value to approximately the same level as seen for the parent reaction (**4ad**, 74% *ee*). In contrast, the presence of an electron-donating substituent, such as 4-methoxyphenyl, at the C4-position drastically reduced the enantiomeric excess of the product (**4ae**; 15% *ee*). The strong dependence of the enantioselectivity on the electronic properties of the substrates was further illustrated by the reaction of 4-ethylcarboxy-N*H*-triazole with 4-methoxystyrene, which delivered a racemic mixture of **4af** in 38% yield. These results indicated that N*H*-triazoles containing either strongly electron-donating or strongly electron-deficient substituents at the C4-position were less efficient reaction partners with electron-rich olefins under the current set of experimental conditions. To examine steric effects, 4-methoxystyrene was replaced with the bulkier, but still electron-rich, 2-methoxystyrene. Reaction between 4-phenyl-N*H*-triazole and 2-methoxystyrene led to a reduction in the *ee* value by approximately 10% (**4ag** versus **4aa**). The steric and electronic effects on the enantioselectivity were also shown to be cumulative: the reaction of 4-cyanophenyl-N*H*-triazole with 2-methoxystyrene reduced the *ee* value of the product to 49% (**4ah** versus **4ac**).

To gain insight into the mechanism of the reaction and to improve both the enantioselectivity and yield of this process, we carried out a series of experiments aimed at establishing the role that the rhodium catalyst plays in the formation of the 2,3-dihyrdopyrroles. Subsequent to the generation of the rhodium carbene **II**, two pathways can account for the formation of the observed product (Scheme 3). In pathway A, the carbene reacts with the electron-rich olefin to yield

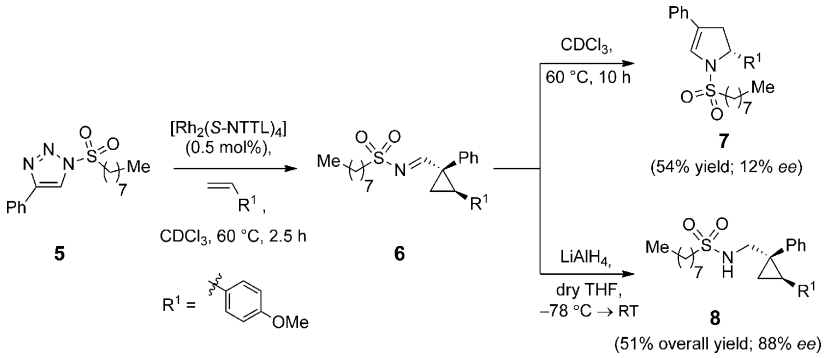


Scheme 3. Proposed pathways for the formation of 2,3-dihydropyrroles.

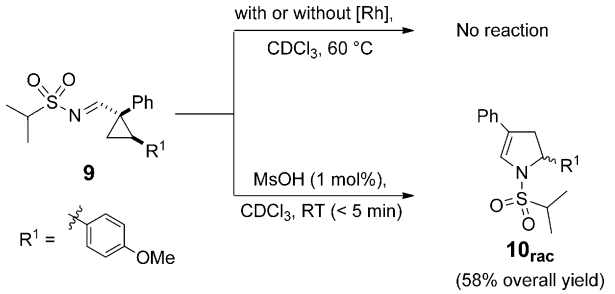
cyclopropylaldimine **III**. The presence of the strongly electron-withdrawing triflate combined with the electron-donating methoxy group facilitates the cleavage of the cyclopropane ring, and generates a stabilized zwitterionic intermediate **IV**, which collapses into the corresponding 2,3-dihyrdopyrrole. In this mechanism, the chiral rhodium catalyst exerts stereocontrol over the final product by determining the enantioselectivity of the intermediate cyclopropane. The subsequent rearrangement leads to the erosion of enantiomeric excess of the final product, the extent of which is dependent on the relative rate of rotation about the C_α–C_β bond versus the rate of ring closure of the open-chain intermediate **IV**. In pathway B, the electron-rich alkene reacts with the Rh-carbene species to form the rhodium-bound zwitterionic intermediate **V**. Cyclization of **V** and release of the Rh catalyst from **VI** affords the desired product. The chiral rhodium catalyst would thus be expected to directly control the final stereoselectivity of this reaction.

The general instability of cyclopropyl-*N*-triflylimine intermediates, combined with the heterogeneity of the reaction mixture, complicated NMR studies. To circumnavigate these problems, we focused on detecting the formation of 2,3-dihydropyrroles prepared by the reaction of the more stable 4-phenyloctylsulfonyltriazole (**5**) and 4-methoxystyrene. The $[Rh_2(S\text{-NTTL})_4]$-catalyzed reaction was performed in $CDCl_3$ at 60 °C, and was monitored by ^{1}H NMR spectroscopy (Scheme 4). These experiments demonstrated that 2,3-dihydropyrroles were formed in two consecutive steps: initially, triazole **5** was converted into cyclopropylimine **6**, which subsequently rearranged to 2,3-dihydropyrrole **7**. The intermediacy of **6** was further confirmed by isolation and spectroscopic characterization of its derivative **8** (88 % *ee*), which was obtained by reduction of **6** with lithium aluminum hydride (Scheme 4). Importantly, in these ^{1}H NMR studies, the presence of **7** was not detected prior to the complete conversion of **5** into **6**. These results suggest that an analogous cyclopropane intermediate may exist during the formation of the triflated 2,3-dihydropyrroles (Pathway A, Scheme 3).

The ring expansion of the cyclopropane intermediate was examined using cyclopropylaldimine **9**, which was synthesized, isolated, and characterized. We were pleased to observe that no 2,3-dihydropyrrole products were formed when **9** was heated in $CDCl_3$ at 60 °C for 12 h, either in the presence



Scheme 4. Rearrangement of cyclopropyl-*N*-octylsulfonylimine **6** into 2,3-dihydropyrrole **7**.

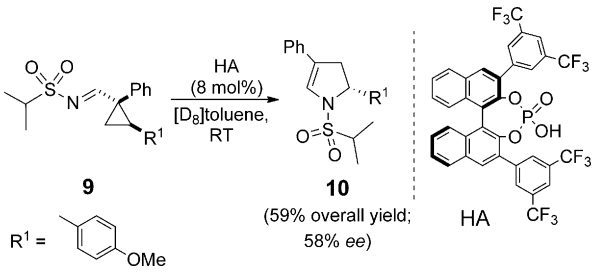


Scheme 5. Acid-catalyzed ring expansion of cyclopropylaldimine **9**.

or absence of a dirhodium catalyst (Scheme 5), thus eliminating the possibility that either the catalyst or heat is responsible for the rearrangement of cyclopropylaldimine. Pioneering studies by Cloke[14] and further investigations by Stevens[12] established that cyclopropylimines rearrange to 2,3-dihydropyrroles under acidic conditions. In addition, related acid-mediated ring expansions of cyclopropyl aldehydes and ketones to yield 2,3-dihydrofurans are also well documented.[15] We, therefore, suspected that trace amounts of

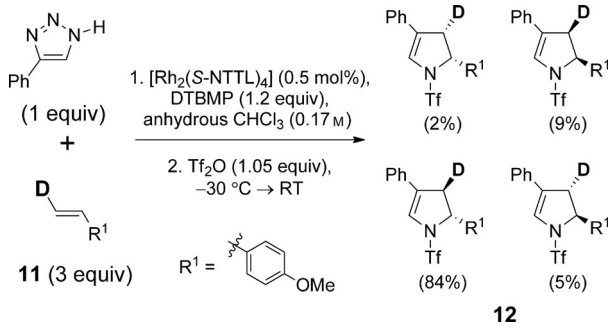
a sulfonic acid, generated by hydrolysis of the starting material, sulfonyltriazole, might be responsible for the observed rearrangement. To test this hypothesis, methanesulfonic acid (MsOH, 0.01 equiv) was added to a solution of a racemic mixture of **9** in $CDCl_3$, which resulted in the rapid (< 5 min) formation of racemic $\mathbf{10}_{rac}$ at room temperature (Scheme 5). This result establishes the kinetic competency of alkylsulfonic acids in catalyzing the ring expansion of cyclopropylaldimine **9** to 2,3-dihydropyrroles $\mathbf{10}_{rac}$.

We further hypothesized that the introduction of a chiral Brønsted acid may induce an enantioselective rearrangment. Indeed, subjecting a racemic mixture of **9** to a catalytic amount of chiral phosphoric acid (HA) generated enantioenriched 2,3-dihyrdopyrroles **10** (58% *ee*; Scheme 6).



Scheme 6. Chiral Brønsted acid catalyzed ring expansion of cyclopropylaldimine **9**.

The results of these mechanistic investigations are consistent with the involvement of a cyclopropylaldimine intermediate in the reaction, with the resultant 2,6-di-*tert*-butyl-4-methylpyridinium triflate acting as the possible source of the Brønsted acid. Proton activation, however, may have limited importance in the rearrangement of triflated cyclopropylimines, because of the increased electron-withdrawing power of the trifluoromethanesulfonyl group compared with alkylsulfonyl groups. While we could not obtain spectroscopic data to unambiguously identify triflated cyclopropylimines in the reaction mixtures, we were able to probe this intermediate by replacing 4-methoxystyrene with deutero-4-methoxystyrene **11** and generating the corresponding deutero-2,3-dihydropyrroles **12** under standard reaction conditions (Scheme 7). Characterization of the isolated deuterium-labeled products



Scheme 7. Reaction with (*E*)-1-methoxy-4-(2-^{2}H-vinyl)benzene (**11**) generates a mixture of deuterium-labeled *cis* and *trans* diastereomers of **12**; the value in parentheses indicates product distribution.

12 by ^{1}H NMR spectroscopy and chiral HPLC indicated the presence of *cis* and *trans* stereoisomers, thus implicating the rotation around the C_α–C_β bond as the cause. This bond rotation limits the transfer of chirality from the presumably highly enantioenriched cyclopropane to the 2,3-dihydropyrrole.[16] The apparent upper limit of the enantioselectivity (ca. 70% *ee*) observed in the chiral catalyst screen (Table 1) is likely a result of the erosion of the enantioselectivity through rapid bond rotation during the rearrangement.

The convenient one-pot asymmetric synthesis of 2,3-dihydropyrroles from in situ generated triflated triazoles and olefins described here further expands the utility of azavinyl carbene chemistry and provides access to an important class of cyclic enamides. Mechanistic investigations support the involvement of triflated cyclopropylaldimine intermediates in the formation of 2,3-dihydropyrrole. To the best of our knowledge, this is the first example of a chiral Brønsted acid catalyzed rearrangement of cyclopropylimines into enantioenriched 2,3-dihydropyrroles. Manipulation of the products should enable asymmetric synthesis of cyclic amines, amino acid analogues,[17] and complex polycyclic architectures[18] found in natural products and pharmaceutically useful compounds. These studies, along with computational investigations, are currently underway.

Experimental Section

Typical procedure for the synthesis of 2,3-dihydropyrroles as exemplified by the synthesis of **4aa**: $[Rh_2(S\text{-NTTL})_4]$ (2.5 mg, 0.0017 mmol, 0.5 mol%), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (84 mg, 0.41 mmol, 1.2 equiv), phenyl-N*H*-1,2,3-triazole (50 mg, 0.34 mmol, 1.0 equiv), and anhydrous chloroform (2 mL) were added to an oven-dried reaction vessel fitted with a magnetic stirrer bar, and sealed with a septum under a dry nitrogen atmosphere. 4-Methoxystyrene (138 mg, 137 μL, 1.03 mmol, 3.0 equiv) was then added, and the resulting purple suspension was cooled to −30 °C while stirring. After 2–3 min, neat triflic anhydride (102 mg, 60 μL, 0.36 mmol, 1.05 equiv) was added in one portion with a glass syringe. The color of the reaction mixture changed immediately from purple to green. The reaction mixture was allowed to warm from −30 °C to room temperature overnight, then quenched with saturated aqueous $NaHCO_3$ (4 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel with 2% EtOAc in hexanes as the eluting solvent to recover the DTBMP (83 mg, 99%). The solvent gradient was gradually raised to 10% EtOAc in hexanes to elute the product. Concentrating the desired fractions under reduced pressure afforded **4aa** as a colorless oil (120 mg, 92%).

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