Published in final edited form as:
Angew Chem Int Ed Engl. 2014 March 24; 53(13): 3452–3456. doi:10.1002/anie.201306706.

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

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Keywords

rhodium; azavinyl carbene; NH triazoles; dihydropyrrole; enamide

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 manufacturing of computer chips[2] to the synthesis of pharmaceuticals[3] and production of insecticides.[4] In contrast to α-diazo-carbonyl compounds, the reactivity and synthetic potential of the related α-diazo-imines has remained relatively unexplored, in large part due to 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 due to the ring-chain tautomerism of the latter.[9] Among the reactive triazoles are 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*-triflyl triazoles formed in this way are readily converted to azavinyl carbenes that readily react with a variety of olefins, **2**, yielding highly enantioenriched cyclopropane carboxaldehydes, **3**.

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

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). Similarly to the trends observed in the Rh(II)-catalyzed cyclopropanations,[6c, d]

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increasing the steric volume of the dirhodium catalysts improved the enantiomeric excess of product **4aa** (Entry **1** to **5**), with Rh_2(*S*-NTTL)$_4$ catalyst providing the highest enantioselectivity (72% *ee*, entry **5**).[6d] Intriguingly, increasing steric demands further via the introduction of a 4-bromo-substituent into the naphthalene ring (entry **6**) did not significantly affect the enantioselectivity. Furthermore, 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 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 triazole ring, e.g. 4-trifluoromethyl, **4ab**, and 4-cyanophenyl group, **4ac**, reduced the *ee* of the products by ~10%, while introduction of a less electronegative group, such as 3-chlorophenyl, returned the *ee* 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-methoxy-phenyl group, at the C4-position drastically reduced the enantiomeric excess of the product, **4ae** (15% *ee*). The strong dependence of the enantioselectivity on the electronics of the substrates was further illustrated by the reaction of 4-ethyl-carboxy N*H*-triazole with 4-methoxy styrene, which delivered a racemic mixture of **4af** in 38% yield. These results indicated that *NH*-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-methoxy styrene was replaced with the bulkier, but still electron-rich, 2-methoxy styrene. Reaction between 4-phenyl-N*H*-triazole and 2-methoxy styrene led to a ~10% reduction in *ee* (**4ag** *cf.* **4aa)**. The steric and electronic effects on the *ee* were also shown to be cumulative: reaction of 4-cyano-phenyl-*NH*-triazole with 2-methoxy reduced the *ee* of the product to 49% (**4ah** *cf.* **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 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 on 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 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 via the reaction of the more stable 4-phenyl-octylsulfonyltriazole (**5**) and 4-methoxystyrene. The Rh_2(*S*-NTTL)$_4$-catalyzed reaction was performed in $CDCl_3$ at 60 °C, and was monitored by ^{1}H-NMR (Scheme 4). These experiments demonstrated that 2,3-dihyrdopyrroles were formed in two consecutive steps: initially, triazole **5** was converted to cyclopropyl imine **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 via lithium aluminum hydride reduction of **6** (Scheme 4). Importantly, in these ^{1}H-NMR studies the presence of **7** was not detected prior to the complete conversion of **5** to **6**. These results suggest that an analogous cyclopropane intermediate may exist in 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-dihydropyrroles products were formed when **9** was heated in $CDCl_3$ at 60°C for 12 hr, whether in the presence 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 cyclopropyl imines rearrange to 2,3-dihydropyrroles under acidic conditions. In addition, related acid-mediated ring expansions of cyclopropyl aldehydes and ketones, yielding 2,3-dihydrofurans, are also well documented.[15] We therefore suspected that trace amount of a sulfonic acid, generated via the hydrolysis of the starting material, sulfonyl triazole, might be responsible for the observed rearrangement. To test this hypothesis, methanesulfonic acid, MsOH, (0.01 equiv) was added to a solution of racemic mixture of **9** in $CDCl_3$, resulting in the rapid (< 5 min) formation of racemic $\mathbf{10_{rac}}$ at room temperature (Scheme 5). This result establishes the kinetic competency of alkylsuflonic 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 enantio-enriched 2,3-dihyrdopyrroles, **10** (58% *ee*) (Scheme 6).

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 cyclopropyl imine, due to the increased electron-withdrawing power of trifluoromethanesulfonyl group, when 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 **12** by ^{1}H-NMR and chiral HPLC indicated the presence of *cis* and *trans* stereoisomers, implicating the rotation around the C_α–C_β as the cause. This bond rotation limits the transfer of chirality from the presumably highly enantio-enriched cyclopropane to the 2,3-dihydropyrrole.[16] The apparent upper limit of ee (~70%) observed in the chiral catalyst screen (Table 1) is likely a result of erosion of enantioselectivity due to 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 cyclopropyl imines into enantioenriched 2,3-dihydropyrroles. Manipulation of the products should enable asymmetric synthesis of cyclic amines, amino acid analogs,[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*-NTTL)$_4$ (2.5 mg, 0.0017 mmol, 0.5 mol%), 2,6-di-*t*-butyl-4-methylpyridine (DTBMP) (84 mg, 0.41 mmol, 1.2 equiv), phenyl-*NH*-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 the 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 minutes, neat triflic anhydride (102 mg, 60 μL, 0.36 mmol, 1.05 equiv) was added in one portion via 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 sat. aq. $NaHCO_3$ (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 eluting solvent to recover 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 colorless oil (120 mg, 92%).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

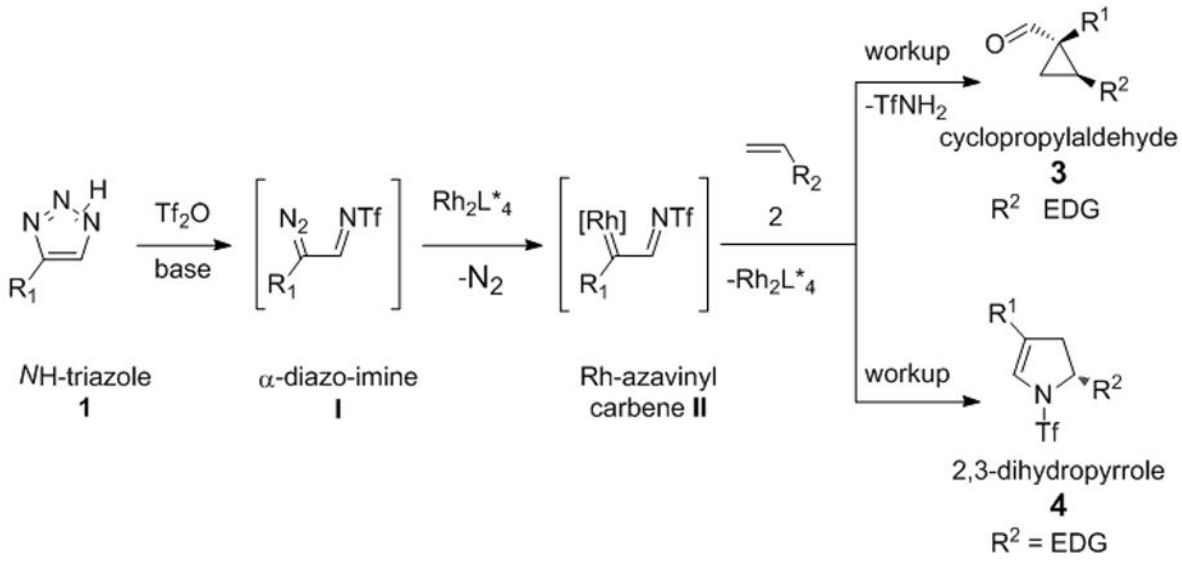
This work was supported by the National Institute of General Medical Sciences, National Institutes of Health (GM087620). We thank Prof. Hisashi Yamamoto (Univ. Chicago) for his kind gift of chiral phosphoric acids.

References

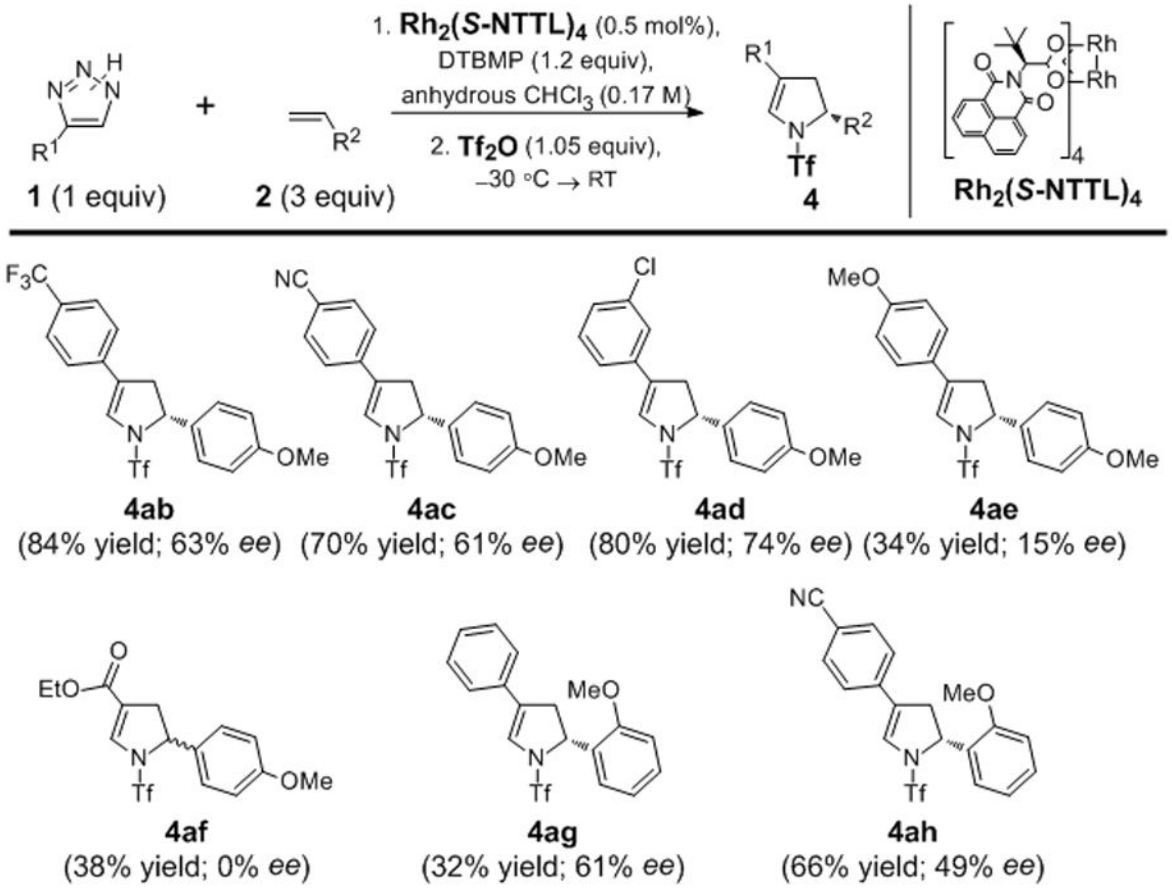
1. Doyle, MP.; McKervey, MA.; Ye, T. Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides. Wiley; New York: 1998.
2. Reiser A, Shih HY, Yeh TF, Huang JP. Angew Chem Int Ed. 1996; 35:2428.
3. Salzmann TN, Ratcliffe RW, Christensen BG, Bouffard FA. J Am Chem Soc. 1980; 102:6161.
4. a) Aratani T, Yoneyoshi Y, Nagase T. Tetrahedron Lett. 1975; 16:1707.b) Aratani T, Yoneyoshi Y, Nagase T. Tetrahedron Lett. 1977; 18:2599.c) Aratani T. Pure Appl Chem. 1985; 57:1839.
5. a) Hermes ME, Marsh FD. J Am Chem Soc. 1967; 89:4760.b) Harmon RE, Stanley FJ, Gupta SK, ohnson JJ. J Org Chem. 1970; 35:3444.
6. a) Chuprakov S, Hwang FW, Gevorgyan V. Angew Chem Int Ed. 2007; 46:4757.b) Horneff T, Chuprakov S, Chernyak N, Gevorgyan V, Fokin VV. J Am Chem Soc. 2008; 130:14972. [PubMed: 18855475] c) Chuprakov S, Kwok SW, Zhang L, Lercher L, Fokin VV. J Am Chem Soc. 2009; 131:18034. [PubMed: 19928917] d) Grimster N, Zhang L, Fokin VV. J Am Chem Soc. 2010; 132:2510. [PubMed: 20131915] e) Chuprakov S, Malik JA, Zibinsky M, Fokin VV. J Am Chem Soc. 2011; 133:10352. [PubMed: 21619004] f) Selander N, Worrell BT, Chuprakov S, Velaparthi S, Fokin VV. J Am Chem Soc. 2012; 134:14670. [PubMed: 22913576] g) Zibinsky M, Fokin VV. Angew Chem Int Ed. 2013; 52:1507.h) Chuprakov S, Kwok SW, Fokin VV. J Am Chem Soc. 2013; 135:4652. [PubMed: 23477345]
7. a) Miura T, Yamauchi M, Murakami M. Chem Commun. 2009:1470.b) Miura T, Biyajima T, Fujii T, Murakami M. J Am Chem Soc. 2012; 134:194. [PubMed: 22129424] c) Miura T, Tanaka T, Biyajima T, Yada A, Murakami M. Angew Chem, Int Ed. 2013; 52:3883.d) Miura T, Hiraga K, Biyajima T, Nakamuro T, Murakami M. Org Lett. 2013; 15:3298. [PubMed: 23777199] e) Miura T, Tanaka T, Biyajima T, Yada A, Murakami M. Angew Chem Int Ed. 2013; 135:3975.f) Liu R, Zhang M, Winston-McPherson G, Tang W. Chem Commun. 2013; 49:4376.g) Meza-Aviña ME, Patel MK, Croatt MP. Tetrahedron. 2013; 69:7840.h) Schultz EE, Sarpong R. J Am Chem Soc. 2013; 135:4696. [PubMed: 23477843] i) Parr BT, Green SA, Davies HML. J Am Chem Soc. 2013; 135:4716. [PubMed: 23477809] j) Spangler JE, Davies HML. J Am Chem Soc. 2013; 135:6802. [PubMed: 23607705] k) Alford JS, Spangler JE, Davies HML. J Am Chem Soc. 2013; 135:11712. [PubMed: 23915171]
8. a) Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. Angew Chem Int Ed. 2002; 41:2596.b) Tornøe CW, Christensen C, Meldal M. J Org Chem. 2002; 67:3057. [PubMed: 11975567] c) Yoo EJ, Ahlquist Må, Kim SH, Bae I, Fokin VV, Sharpless KB, Chang S. Angew Chem Int Ed. 2007; 46:1730.d) Wang F, Fu H, Jiang Y, Zhao Y. Adv Synth Catal. 2008; 350:1830.e) Raushel J, Fokin VV. Org Lett. 2010; 12:4952. [PubMed: 20931987]
9. Fabian WMF, Bakulev VA, Kappe CO. J Org Chem. 1998; 63:5801. [PubMed: 11672180]
10. a) Wenkert E, Alonso ME, Buckwalter BL, Chou KJ. J Am Chem Soc. 1977; 99:4778.b) Alonso ME, Morales A, Chitty AW. J Org Chem. 1982; 47:3747.c) Wenkert E, Alonso ME, Buckwalter BL, Sanchez EL. J Am Chem Soc. 1983; 105:2021.
11. a) Doyle MP, Griffin JH, Bagheri V, Dorow RL. Organometallics. 1984; 3:53.b) Davies HML, Ahmed G, Calvo RL, Churchill MR, Churchill DG. J Org Chem. 1998; 63:2641. [PubMed: 11672131]
12. Stevens RV. Acc Chem Res. 1977; 10:193.
13. Anada M, Tanaka M, Washio T, Yamawaki M, Abe T, Hashimoto S. Org Lett. 2007; 9:4559. [PubMed: 17894504]
14. Cloke JB. J Am Chem Soc. 1929; 51:1174.
15. a) Alonso ME, Morales A. J Org Chem. 1980; 45:4530.b) Nakajima T, Segi M, Mituoka T, Fukute Y, Honda M, Naitou K. Tetrahedron Lett. 1995; 36:1667.c) Yadav VK, Balamurugan R. Org Lett. 2001; 3:2717. [PubMed: 11506617] d) Zhang Z, Zhang Q, Sun S, Xiong T, Liu Q. Angew Chem

Int Ed. 2007; 46:1726.e) Zhang R, Liang Y, Zhou G, Wang K, Dong D. J Org Chem. 2008; 73:8089. [PubMed: 18798678] f) Huang P, Zhang N, Zhang R, Dong D. Org Lett. 2012; 14:370. [PubMed: 22168361]

16. The enantiomeric excess of the proposed cyclopropylaldimine intermediate can be determined from the percentage ratio of the diastereomers 12 (see SI).
17. Garcia ALL, Correia CRD. Tetrahedron Lett. 2003; 44:1553.
18. Evans P, McCabe T, Morgan BS, Reau S. Org Lett. 2005; 7:43. [PubMed: 15624973]

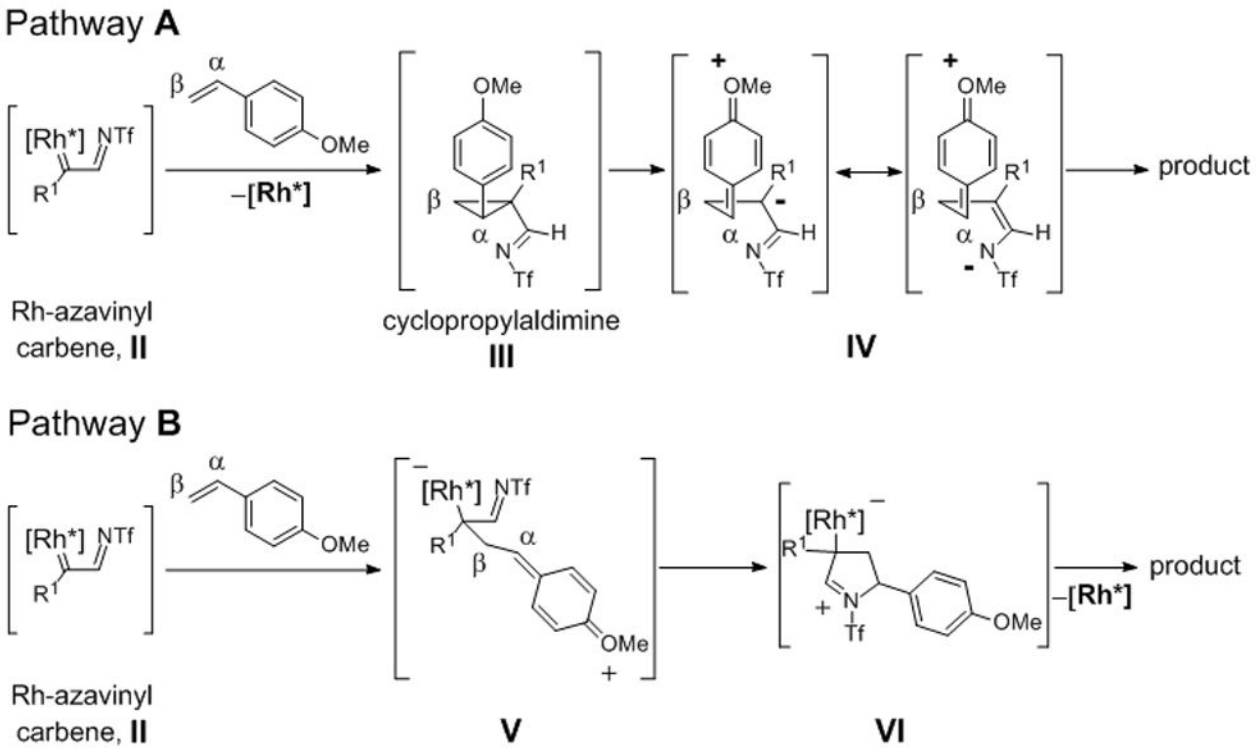


Scheme 1.
Reactions of *N*-triflyl-Rh-azavinyl carbenes with olefins.

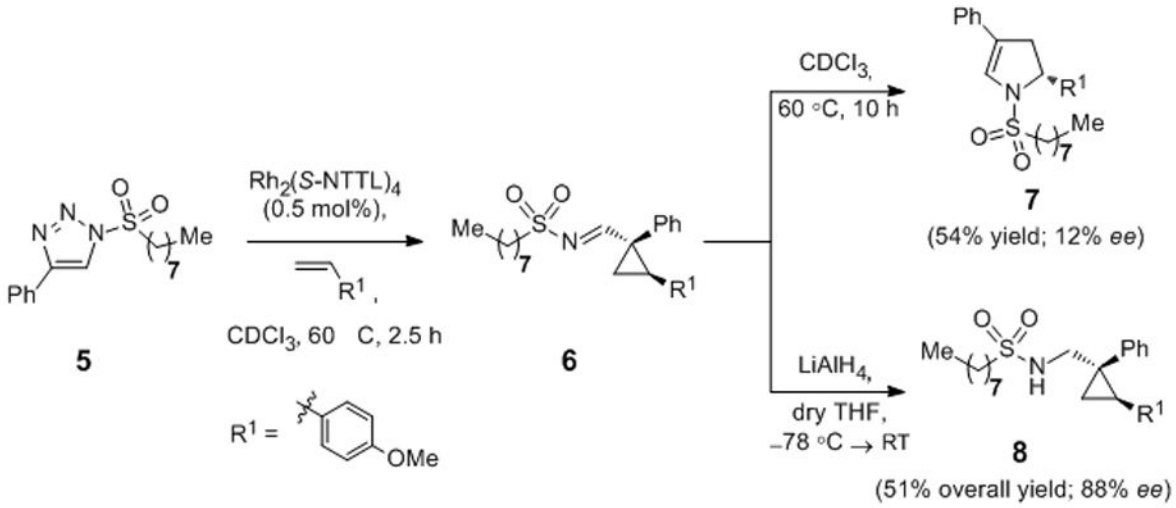


Scheme 2.

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

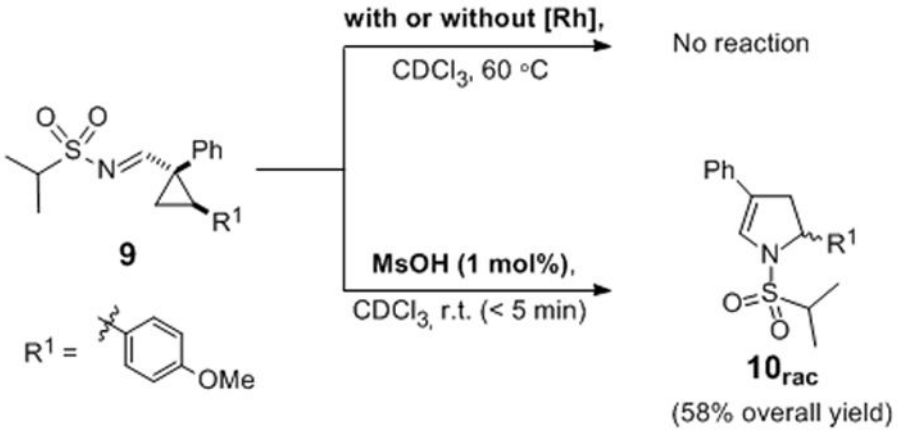


Scheme 3.
Proposed pathways for the formation of 2,3-dihydropyrroles.

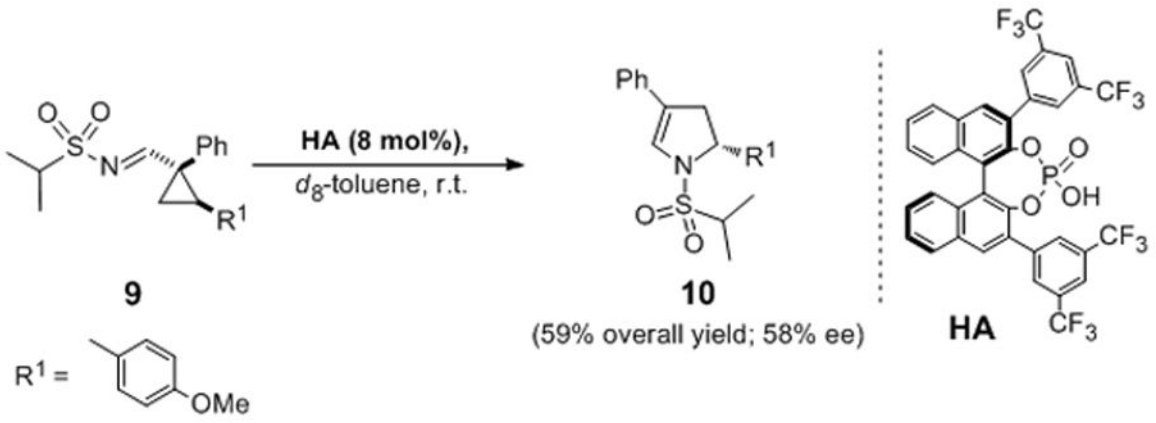


Scheme 4.

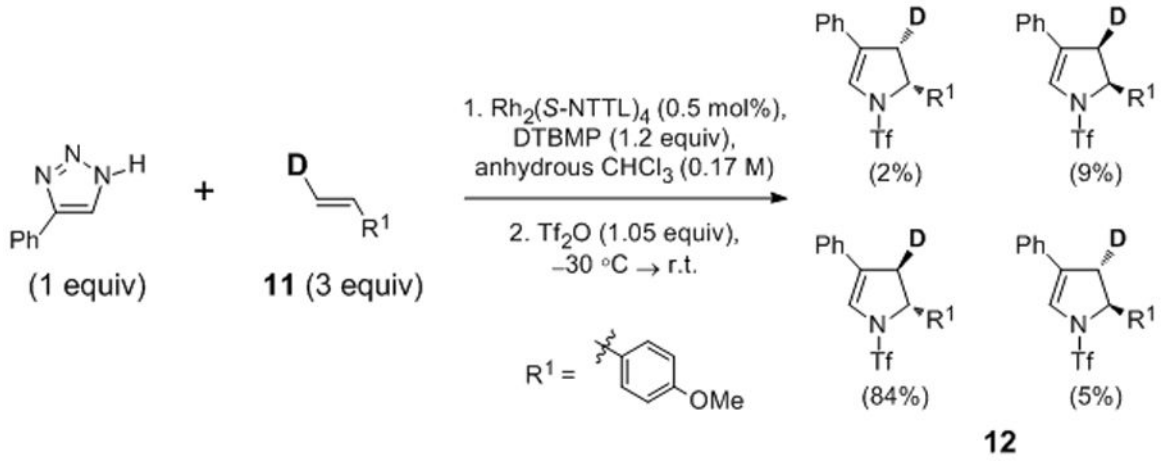
Rearrangement of cyclopropyl *N*-octylsulfonylimine **6** into 2,3-dihydropyrrole **7**.



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



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

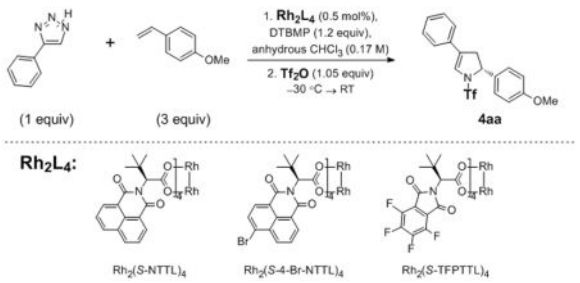


Scheme 7.

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

Table 1

Screening of chiral catalysts.[a]



Entry	Chiral Catalyst	Yield, (%)	*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; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine; all yields are isolated.