Heterocycles

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Sulfonyl-1,2,3-Triazoles: Convenient Synthones for Heterocyclic Compounds**

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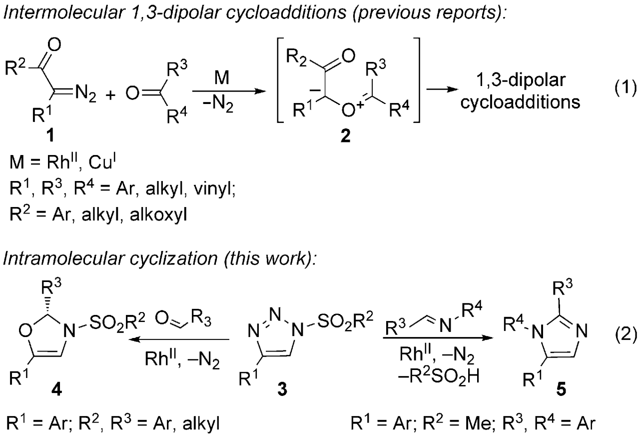
1-Sulfonyl-1,2,3-triazoles, which are readily available through copper-catalyzed azide-alkyne cycloaddition,[1] are stable precursors to Rh^{II}–azavinyl carbenes,[2] as well as carbene complexes of other metals.[3] Among other transformations, these reactive intermediates can be used for the introduction of a nitrogen atom into various heterocycles[2b,4] that are important in both synthetic and medicinal chemistry.

Carbenes generated from diazocarbonyl compounds **1** are known to react with carbonyl groups to produce ylides **2**, which usually react in subsequent 1,3-dipolar cycloadditions to access complex structures [Eq. (1)].[5] Herein, we report that Rh^{II}–azavinyl carbenes react with aldehydes to give adducts that undergo an intramolecular cyclization instead of a 1,3-dipolar cycloaddition. This transformation results in homochiral 3-sulfonyl-4-oxazolines **4** [Eq. (2), left], which are produced in excellent yield and with high enantioselectivity. These sparsely studied compounds[5] contain an easily installed stereocenter and a synthetically useful electron-rich double bond.

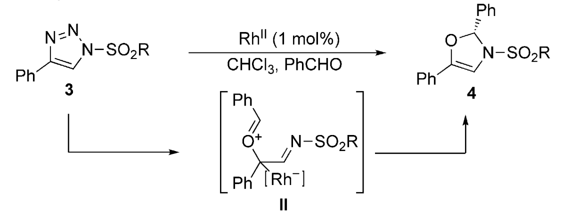


Oxazolines have been exploited in organic synthesis as protecting groups[6] and chiral auxiliaries,[7] in asymmetric catalysis as chiral ligands,[8] as well as in medicinal chemistry[9] and drug delivery applications.[10] Although methods for the synthesis of 3-sulfonyl-4-oxazolines are scarce,[11] 3-acyl-4-oxazolines, their close analogs, have been used in organic synthesis.[12]

In addition to aldehydes, triazoles **3** react with aldimines through a cyclization–elimination sequence, leading directly to 1,2,5-trisubstituted imidazoles **5** [Eq. (2), right].

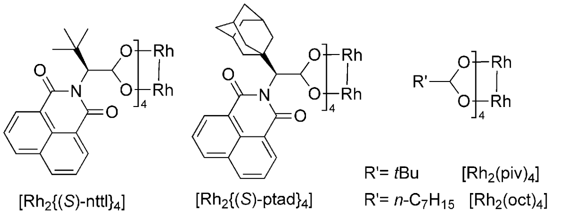
An initial examination of Rh^{II}-catalysts (Table 1) revealed that [$Rh_2(piv)_4$] and [$Rh_2(oct)_4$] (piv = pivalate, oct = octanoate) catalyzed the formation of oxazolines **4** from triazole **3** and benzaldehyde (3 equiv) at 100 °C (Table 1, entries 1 and 2). Attempts to trap the ylide intermediate **II** with reactive dipolarophiles were unsuccessful.

Table 1: Optimization of the reaction conditions.[a]



Entry	R	Catalyst	Temp.	Time	Yield [%][b]	*ee* [%][c]
1	Me	[$Rh_2(oct)_4$]	100 °C[d]	15 min	61	–
2	Me	[$Rh_2(piv)_4$]	100 °C[d]	15 min	83	–
3	Me	[$Rh_2(piv)_4$]	RT	12 h	82	–
4	Me	[$Rh_2\{(S)\text{-nttl}\}_4$]	RT	12 h	75	88
5	Me	[$Rh_2\{(S)\text{-nttl}\}_4$]	40 °C	9 h	80	73
6	Me	[$Rh_2\{(S)\text{-ptad}\}_4$]	RT	12 h	70	45
7	C_6H_4Me	[$Rh_2\{(S)\text{-nttl}\}_4$]	RT	48 h	–[e]	–
8	C_6H_4Me	[$Rh_2\{(S)\text{-ptad}\}_4$]	RT	12 h	82	55

[a] For the full table, see the Supporting Information. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Microwave irradiation was used. [e] Less than 50% conversion of **3**.



Further investigation of the reaction conditions revealed that lowering the temperature from 100 °C to ambient resulted in longer reaction times without significantly affecting the yield of oxazolines **4** (Table 1, entry 3). Several chiral catalysts were also examined at various temperatures (Table 1, entries 4–8) and in combination with various

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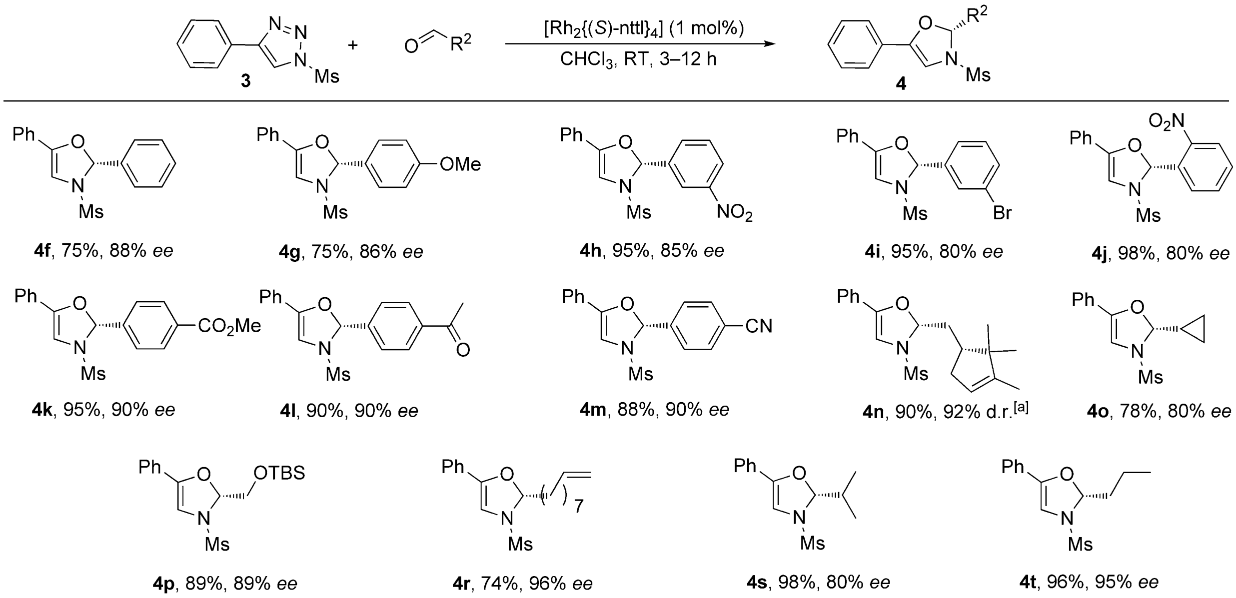
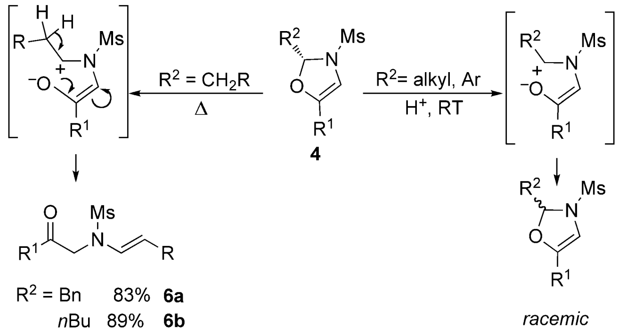


Scheme 1. Asymmetric synthesis of 4-oxazolines **4** from various aldehydes. All yields are of isolated products. Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [a] Enantiomeric composition of the starting aldehyde was retained in the product; the *ee* remained at 98%. Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl.

sulfonyl groups at N1 of triazole **3**, resulting in the enantioselective version of the reaction. Optimal enantioselectivity was obtained in reactions of 1-mesyl-1,2,3-triazoles performed at ambient temperature with of $[Rh_2\{(S)\text{-nttl}\}_4]$ (1 mol%; see Table 1 for structure) catalyst (Table 1, entry 4). Among the solvents tested, chloroform provided oxazoline products with consistently high yield and enantioselectivity.

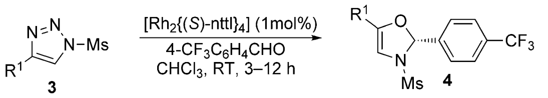
Variously substituted aryl and alkyl aldehydes readily participated in the reaction (Scheme 1). Ketones, esters, terminal and endocyclic olefins, nitriles, and silyl ethers were all compatible with the reaction. Prolonged reaction times significantly lowered the enantiomeric purity of most products. The reversible ring opening of N,O-aminals (**4**) because of the lability of the C–O bond (Scheme 2, right) could explain this observation. It may also account for the slightly lower enantioselectivity of this reaction compared to other transformations of azavinyl carbenes, such as cyclopropanations and C–H insertions.[2d–f] Acidity of the C2 hydrogen is an unlikely cause of racemization: when **4a** was treated with various bases (1,8-diazabicyloundec-7-ene, triethylamine, and potassium carbonate), the enantioselectivity did not deteriorate. Hemiaminals arising from aliphatic aldehydes underwent irreversible ring opening at elevated temperature at the C–O bond of the aminal, followed by β-proton elimination (Scheme 2, left side).



Scheme 2. Isomerization of 4-oxazolines **4**.

Examination of the reaction scope with respect to the C4 substituent of the triazole (Table 2) revealed that aryl-substituted triazoles provided oxazolines in excellent yield and enantioselectivity; both were largely unaffected by the electronic properties of this substituent. Alkyl-substituted triazoles failed to provide oxazoline products in synthetically useful yields, likely owing to the facile 1,2-hydride shift of the carbene intermediate.[2b,c,e]

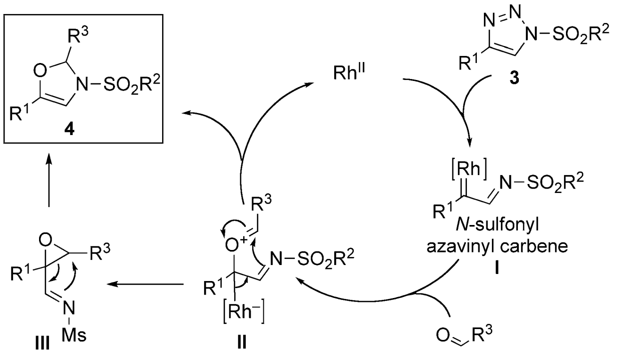
Table 2: Reaction scope with respect to the substitution at C4 of the triazole.



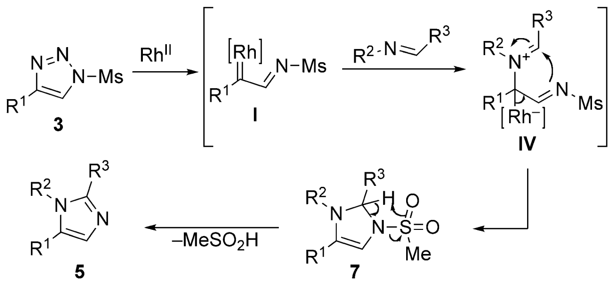
Entry	R^1	Yield [%][a]	*ee* [%][b]	Compound
1	Ph	85	92	**4a**
2	$4\text{-}CF_3C_6H_4$	86	92	**4b**
3	$4\text{-}MeC_6H_4$	97	94	**4c**
4	$4\text{-}MeOC_6H_4$	93	88	**4d**
5	3-thiophenyl	91	80	**4e**
6	$n\text{-}C_5H_{11}$	trace	–	–

[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase.

The key steps of the proposed mechanism of this reaction are shown in Scheme 3. Triazole **3**, upon reaction with



Scheme 3. Proposed mechanism for the formation of 4-oxazolines.



Scheme 4. Proposed pathway for the formation of imidazoles **5**.

a catalyst, extrudes dinitrogen and forms Rh^{II}–azavinyl carbene species **I**. Interaction of the carbonyl group with the carbene center leads to the formation of ylide **II**, which undergoes cyclization, leading to the formation of oxazoline **4**. An alternative pathway, through the formation of epoxide **III**, cannot be ruled out at this time, however, we have no evidence supporting the intermediacy of these species.

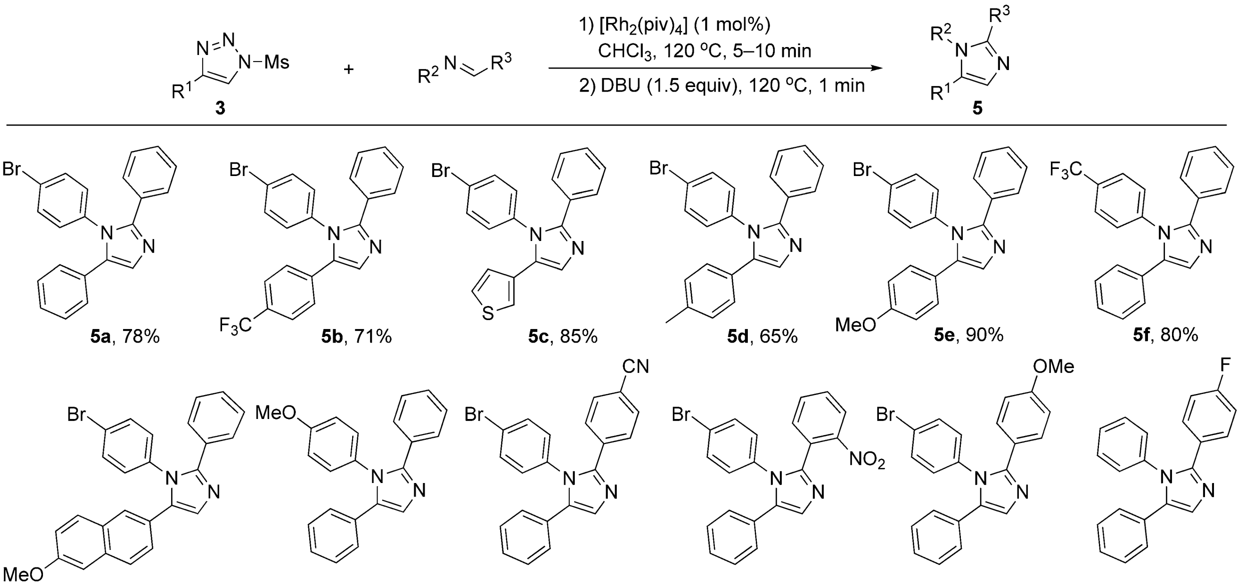
Similar to aldehydes, aldimines react with rhodium(II) azavinyl carbenes to produce imidazoles. Thus, triazole **3** reacted with benzylidene-4-bromo-benzenamine within 30 min at 100 °C in the presence of [Rh$_2$(piv)$_4$] to produce imidazole **5**. Lowering the temperature to 40 °C allowed the isolation of intermediate imidazoline **7**, which was thermally unstable and underwent elimination of sulfinic acid (Scheme 4). The bulky substitutents at the 1-, 2-, 3-, and 5-positions of imidazoline **7** impose considerable steric demands on this intermediate, which explains the facility of aromatization.

The optimized conditions for the preparation of imidazoles **5** required the heating of a chloroform solution of triazole **3** (0.2 M) and an aldimine (1.5 equiv) for 5–10 min at 120 °C in the presence of [Rh$_2$(piv)$_4$] (1 mol %). After the triazole was consumed, 1,8-diazabicyloundec-7-ene (DBU; 2 equiv) was added and heating continued for one more minute. The addition of DBU was necessary to achieve full conversion to **5**. The reaction proceeds well with different 4-aryl-substituted triazoles and aldimines prepared from a variety of aromatic aldehydes and anilines (Scheme 5).

In summary, the reactions of azavinyl carbenes with aldehydes and aldimines described herein exhibit excellent functional group tolerance and proceed under simple experimental conditions, thus underscoring the unique reactivity of azavinyl carbenes and expanding the repertoire of the useful transformations of these reactive intermediates.

Experimental Section

Typical procedure for the [Rh$_2${(*S*)-nttl}$_4$]-catalyzed reaction of 1-sulfonyl-1,2,3-triazoles with aldehydes: 1-methanesulfonyl-4-aryl-1,2,3-triazole (**3**; 0.36 mmol) and [Rh$_2${(*S*)-nttl}$_4$] (5.2 mg, 1 mol %, 0.0036 mmol) were added under inert atmosphere to an oven-dried 5 mL vial equipped with a stir bar. The vial was sealed and a mixture of aldehyde (1.08 mmol, 3.0 equiv) in dry chloroform (1.5 mL) was added via syringe. The reaction was stirred at room temperature for 3–12 h until complete conversion was observed. The content was then



Scheme 5. Preparation of 1,2,5-trisubstituted imidazoles **5** from aldimines. All yields are of isolated products.

transferred directly onto silica and purified by eluting with hexanes/ethyl acetate (8:2). Removal of the solvent followed by drying under vacuum afforded 4-oxazoline **4** in high purity.

Typical procedure for the [$Rh_2(piv)_4$]-catalyzed reaction of 1-sulfonyl-1,2,3-triazoles with aldimines: 1-methanesulfonyl-4-aryl-1,2,3-triazole (**3**; 0.3 mmol), [$Rh_2(piv)_4$] (1.8 mg, 1 mol%, 0.003 mmol), and an aldimine (1.5 equiv, 0.45 mmol) were added under inert atmosphere to an oven-dried 5 mL vial equipped with a stir bar. The vial was sealed and dry chloroform (1.5 mL) was added via syringe. The vial was placed in an oil bath, which was heated to 120°C. After 5–10 min, DBU (2.0 equiv, 0.6 mmol) was added via syringe and the reaction mixture was heated for an additional minute. Then, the vial was cooled down to room temperature and its content was transferred directly onto silica and purified by eluting with hexanes/ethyl acetate (7:3). Removal of the solvent followed by drying under vacuum afforded imidazole **5** in high purity.

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[1] a) J. Raushel, V. V. Fokin, *Org. Lett.* **2010**, *12*, 4952–4955; b) Y. Liu, X. Wang, J. Xu, Q. Zhang, Y. Zhao, Y. Hu, *Tetrahedron* **2011**, *67*, 6294–6299.

[2] a) S. Chuprakov, F. W. Hwang, V. Gevorgyan, *Angew. Chem.* **2007**, *119*, 4841–4843; *Angew. Chem. Int. Ed.* **2007**, *46*, 4757–4759; b) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 14972–14974; c) M. Zibinsky, V. V. Fokin, *Org. Lett.* **2011**, *13*, 4870–4872; d) S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher, V. V. Fokin, *J. Am. Chem. Soc.* **2009**, *131*, 18034–18035; e) N. Grimster, L. Zhang, V. V. Fokin, *J. Am. Chem. Soc.* **2010**, *132*, 2510–2511; f) S. Chuprakov, J. A. Malik, M. Zibinsky, V. V. Fokin, *J. Am. Chem. Soc.* **2011**, *133*, 10352–10355; g) B. Chattopadhyay, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2012**, *51*, 862–872; h) T. Miura, T. Biyajima, T. Fujii, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 194–196.

[3] T. Miura, M. Yamauchi, M. Murakami, *Chem. Commun.* **2009**, 1470–1471.

[4] B. Chattopadhyay, V. Gevorgyan, *Org. Lett.* **2011**, *13*, 3746–3749.

[5] a) A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263–309; b) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley & Sons, New York, **1998**; c) A. DeAngelis, M. T. Taylor, J. M. Fox, *J. Am. Chem. Soc.* **2009**, *131*, 1101–1105.

[6] A. I. Meyers, D. L. Temple, D. Haidukewych, E. D. Mihelich, *J. Org. Chem.* **1974**, *39*, 2787–2793.

[7] a) D. J. Rawson, A. I. Meyers, *J. Org. Chem.* **1991**, *56*, 2292–2294; b) T. G. Gant, A. I. Meyers, *Tetrahedron* **1994**, *50*, 2297–2360.

[8] a) H. Brunner, U. Obermann, P. Wimmer, *Organometallics* **1989**, *8*, 821–826; b) G. Balavoine, J. C. Clinet, I. Lellouche, *Tetrahedron Lett.* **1989**, *30*, 5141–5144; c) H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, K. Itoh, *Organometallics* **1989**, *8*, 846–848; d) R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005–6008; e) D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726–728; f) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651.

[9] a) P. N. Yadav, R. E. Beveridge, J. Blay, A. R. Boyd, M. W. Chojnacka, A. Decken, A. A. Deshpande, M. G. Gardiner, T. W. Hambley, M. J. Hughes, L. Jolly, J. A. Lavangie, T. D. MacInnis, S. A. McFarland, E. J. New, R. A. Gossage, *MedChemComm* **2011**, *2*, 274–277; b) C. Liu, M. Tamm, M. W. Nötzel, K. Rauch, A. de Meijere, J. K. Schilling, A. Lakdawala, J. P. Snyder, S. L. Bane, N. Shanker, R. Ravindra, D. G. I. Kingston, *Eur. J. Org. Chem.* **2005**, 3962–3972.

[10] N. Adams, U. S. Schubert, *Adv. Drug Delivery Rev.* **2007**, *59*, 1504–1520.

[11] E. Gayon, O. Debleds, M. Nicouleau, F. Lamaty, A. van der Lee, E. Vrancken, J.-M. Campagne, *J. Org. Chem.* **2010**, *75*, 6050–6053.

[12] a) E. Hunt, I. I. Zomaya, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1509–1517; b) S. Suga, D. Yamada, J.-i. Yoshida, *Chem. Lett.* **2010**, *39*, 404–406; c) L. Ghosez, G. Yang, J. R. Cagnon, F. L. Bideau, J. Marchand-Brynaert, *Tetrahedron* **2004**, *60*, 7591–7606; d) J. Cagnon, F. L. Bideau, J. Marchand-Brynaert, L. Ghosez, *Tetrahedron Lett.* **1997**, *38*, 2291–2294.