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Stereoselective Synthesis of 2,3-Dihydropyrroles from Terminal Alkynes, Azides, and *α,β*-Unsaturated Aldehydes via *N*-Sulfonyl-1,2,3-triazoles

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Supporting Information

ABSTRACT: A stereoselective method for synthesis of *trans*-2,3-disubstituted 2,3-dihydropyrroles is reported. *N*-Sulfonyl-1,2,3-triazoles prepared from terminal alkynes generate *α*-imino rhodium carbene complexes, which when combined with *α,β*-unsaturated aldehydes produce *trans*-2,3-disubstituted dihydropyrroles. The method can be successfully applied to a one-pot process starting from terminal alkynes.

The 2,3-dihydropyrrole ring system is a valuable structural motif found in a number of biologically active compounds.[1] In addition, 2,3-dihydropyrroles have been widely employed as important intermediates in the synthesis of natural products[2] and other complex molecules.[3] Thus, the development of efficient methods for their synthesis from readily accessible starting materials is highly desired.[4] Now, we report a sequential procedure for the diastereoselective synthesis of *trans*-2,3-disubstituted 2,3-dihydropyrroles from terminal alkynes, *N*-sulfonyl azides, and *α,β*-unsaturated aldehydes (Figure 1).

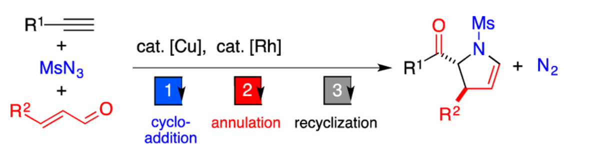
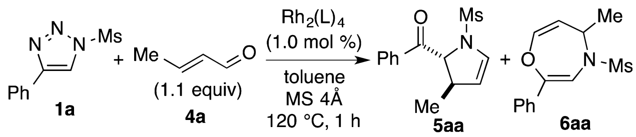


Figure 1. Construction of 2,3-dihydropyrroles starting from terminal alkynes, *N*-sulfonyl azides, and *α,β*-unsaturated aldehydes.

N-Sulfonyl-1,2,3-triazoles, which can be easily prepared from terminal alkynes by copper-catalyzed 1,3-dipolar cycloaddition with *N*-sulfonyl azides,[5] have recently received much attention as precursors of *α*-imino metal carbenes.[6] The generated metal carbene species are electrophilic in nature to accept various nucleophiles, including those having acidic protons like water[7] and allylic alcohols.[8] In our previous report, the addition of allylic alcohols was immediately followed by a Claisen rearrangement to afford *α*-allyl-*α*-amino-ketones. On the other hand, the nitrogen atom of the *α*-imino group exhibits a higher nucleophilic character than the related *α*-oxo metal carbenes. This nucleophilicity, when combined with the electrophilic character of the carbene carbon, enables the compound to incorporate unsaturated compounds such as nitriles, alkynes, allenes, isocyanates, furans, and indoles to produce the corresponding *N*-heterocycles.[9] For example, the reaction with aldehydes leads

Table 1. Denitrogenative Reaction of Triazole 1a with (*E*)-Crotonaldehyde (4a): Screening of Rhodium(II) Catalysts[a]



entry	$Rh_2(L)_4$	yield (%)[b] 5aa	6aa
1	$Rh_2(OCOC_7H_{15})_4$	32	34
2	$Rh_2(OCO^tBu)_4$	49	18
3	Rh_2(OCO-1-Ad)$_4$	67	19
4	Rh_2[(*S*)-DOSP]$_4$	46	48
5	Rh_2[(*S*)-PTPA]$_4$	40	16
6	Rh_2[(*S*)-NTTL]$_4$	74 (80)	3

[a]Conditions: **1a** (0.20 mmol), **4a** (0.22 mmol), and 4 Å MS (40 mg) were heated in toluene (1 mL) at 120 °C for 1 h in the presence of $Rh_2(L)_4$ (2.0 μmol). [b]^{1}H NMR yield using $CHBr_2CHBr_2$ as an internal standard, with isolated yield in parentheses.

to the production of 4-oxazolines, as recently reported by Fokin et al.[10] As a continuation of our previous studies on the utilization of *N*-sulfonyl-1,2,3-triazoles for synthetic purposes, we next examined the use of *α,β*-unsaturated aldehydes as the reaction partner. Thus, we initially prepared 1-methanesulfonyl-4-phenyl-1,2,3-triazole (**1a**) from phenylacetylene (**2a**) and methanesulfonyl azide (**3a**) according to the procedure using copper(I) thiophene-2-carboxylate (CuTC).[5b] Triazole **1a** (0.20 mmol) was reacted with (*E*)-crotonaldehyde (**4a**, 0.22 mmol) in the presence of $Rh_2(OCOC_7H_{15})_4$ (1.0 mol %) and 4 Å molecular sieves (MS) in refluxing toluene (Table 1, entry 1). Triazole **1a** was completely consumed in 1 h, giving a mixture of 2,3-dihydropyrrole (**5aa**, 32% NMR yield) and 4,5-dihydro-1,4-oxazepine (**6aa**, 34% NMR yield). The relative stereochemistry at the 2,3-positions of **5aa** was unambiguously assigned as *trans* by a single-crystal X-ray analysis. Next, a variety of ligands on rhodium(II) (Figure 2) were examined in terms of product selectivity, which showed a significant dependence on the ligands (entries 2−6). In particular, when the sterically bulky chiral ligand (*S*)-NTTL[11] was employed, formation of **6aa** was suppressed (3% NMR yield) and *trans*-**5aa** was obtained in 80% isolated yield as a racemic mixture. Production of the five-membered-ring compound **5aa** is in sharp contrast to the

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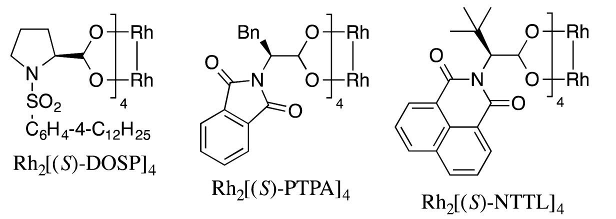
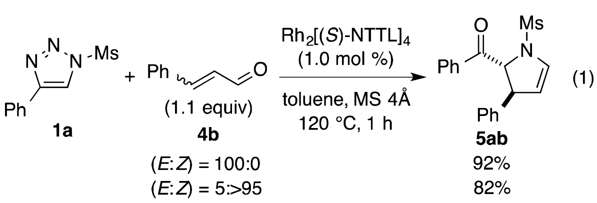


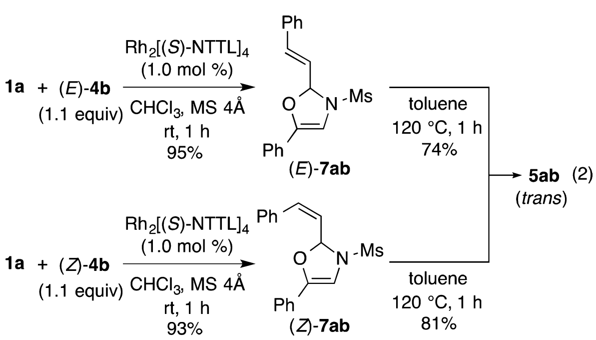
Figure 2. Chiral Rh(II) catalysts examined in the optimization studies.

reaction of rhodium α-oxo-carbene intermediates with α,β-unsaturated aldehydes, which furnished alkenyl-substituted epoxides without participation of the α-oxo moieties.[12]

A pair of (E)- and (Z)-isomers of cinnamaldehyde (**4b**) was then used to compare the stereochemical outcomes. The two isomers were independently subjected to the reaction conditions (Rh$_2$[(S)-NTTL]$_4$, 120 °C, 1 h), and both isomers furnished exclusively the *trans*-2,3-disubstituted dihydropyrrole **5ab** in high yield as a racemic mixture (eq 1).



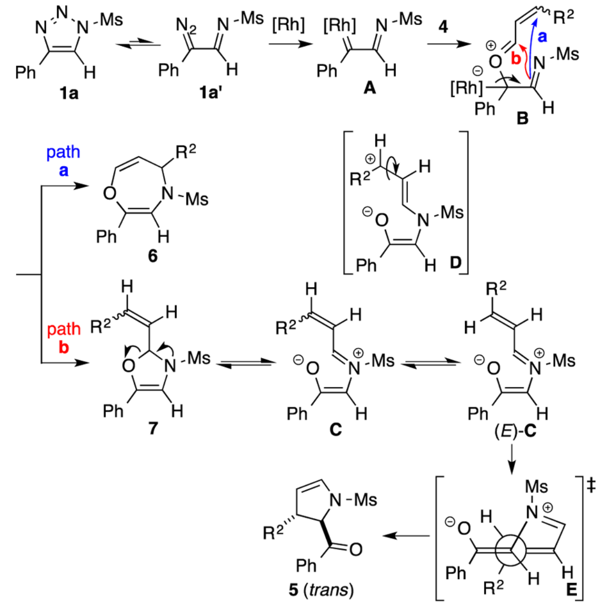
When the reaction of triazole **1a** with (E)- and (Z)-**4b** was carried out for 1 h at room temperature in chloroform, the corresponding (E)- and (Z)-2-styryl-4-oxazolines **7ab**, which retained their original double-bond geometries, were isolated respectively.[13] When each isolated **7ab** was independently heated in refluxing toluene for 1 h, both isomers exclusively afforded the *trans*-isomer of 2,3-dihydropyrrole **5ab** (eq 2).[10]



The rearrangement reaction of the 4-oxazolines **7ab** was monitored at 50 °C by ^{1}H NMR. When starting from (E)-**7ab**, only the remaining (E)-**7ab** and the *trans*-product **5ab** were detected throughout the reaction course. On the other hand, when starting from (Z)-**7ab**, the (E)-**7ab** was detected in addition to the (Z)-**7ab** and the *trans*-product **5ab**. These results suggested that the (Z)-**7ab** isomerized to (E)-**7ab** prior to the rearrangement process.

On the basis of these results and the previous study on the formation of 4-oxazolines from aldehydes,[10] we propose a mechanism for the formation of products **5** and **6** from triazole **1a** and the α,β-unsaturated aldehyde **4** as depicted in Scheme 1. Initially, a reversible ring−chain tautomerization of the triazole **1a** generates α-diazo imine **1a′**,[14] which reacts with rhodium(II) in an irreversible manner to afford an α-imino rhodium carbene **A** with extrusion of molecular nitrogen. Nucleophilic addition of the α,β-unsaturated aldehyde **4** to the electrophilic carbene center of **A** occurs to furnish the zwitterionic intermediate **B**. The anionic rhodium releases an electron pair, which induces the imino nitrogen to attack on either the α- or γ-carbon of the oxonium ion. Attack on the γ-carbon forms 4,5-dihydro-1,4-oxazepine **6** (path a), whereas attack on the α-carbon forms the 4-oxazoline intermediate **7** (path b). The C−O bond of the *N,O*-aminal moiety of **7** is selectively cleaved, probably due to the higher electronegativity of oxygen and the higher electron-donating ability of nitrogen,[15] giving the zwitterionic intermediate **C**. Double bond isomerization occurs readily with the delocalized conjugate cation moiety of **C**, which converges into a form of the more stable (E)-isomer. Finally, the enolate moiety of (E)-**C** intramolecularly couples with the delocalized conjugate cation moiety through conformation **E**, which experiences less gauche interactions along the axis of the developing carbon−carbon bond, to give the *trans*-configured 2,3-dihydropyrrole **5**. Although a [3,3] sigmatropic rearrangement presents an alternative option for the mechanistic pathway, the ionic mechanism mentioned above is favored on the basis of the non-stereospecificity between the isolated enantiomerically enriched 4-oxazoline intermediate and the product *trans*-**5aa**,[13] and the production of the racemic dihydropyrroles in the other cases (vide infra).

Scheme 1. Proposed Mechanism for the Formation of Products 5 and 6 from Triazole 1a and α,β-Unsaturated Aldehyde 4



The scope of α,β-unsaturated aldehydes **4** was examined using Rh$_2$[(S)-NTTL]$_4$ as the catalyst (Table 2). (E)-β-Monosubstituted substrates **4c−g**, possessing a wide variety of alkyl and aryl groups, reacted cleanly with triazole **1a** to afford products **5ac−ag** in yields ranging from 71% to 90% (entries 1−5). In addition, the mono(dimethyl acetal) of fumaraldehyde (**4h**) and fumaraldehydic acid methyl ester (**4i**) successfully participated in the annulation reaction (entries 6 and 7). As in the case of (E)- and (Z)-cinnamaldehyde (**4b**) (eq 1), both (E)- and (Z)-isomers of hex-2-enal (**4c**) selectively gave the *trans* isomer of the product **5ac** (entries 1 and 8). The reaction of (Z)-3-bromoacrylaldehyde (**4j**) was followed by the subsequent E1cB process, resulting in the formation of 2-benzoylpyrrole **8** (entry 9). Acyclic α,β-disubstituted substrates **4k−n** were also effectively converted

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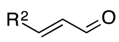
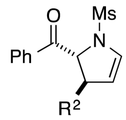
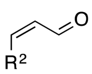
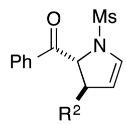
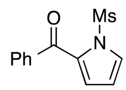
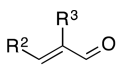
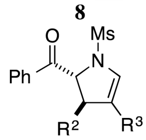
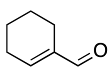
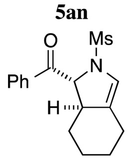
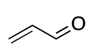
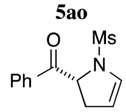
Table 2. Rh(II)-Catalyzed Denitrogenative Annulation of Triazole 1a with Various α,β-Unsaturated Aldehydes 4c–p[a]

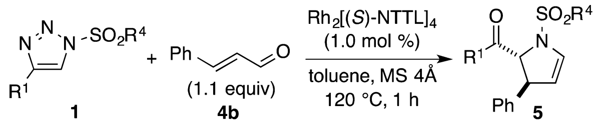
entry	α,β-unsaturated aldehyde **4**		product **5**	yield (%)[b]
				
1	R^2 = ⁿPr	**4c**	**5ac**	75
2	R^2 = Cy	**4d**	**5ad**	78
3	R^2 = ᵗBu	**4e**	**5ae**	71
4	R^2 = 4-MeO-C_6H_4	**4f**	**5af**	90
5	R^2 = 4-NO_2-C_6H_4	**4g**	**5ag**	85
6	R^2 = $CH(OMe)_2$	**4h**	**5ah**	73
7	R^2 = CO_2Me	**4i**	**5ai**	85
				
8	R^2 = ⁿPr	**4c**[c]	**5ac**	74
9	R^2 = Br	**4j**[d]	 **8**	65[e]
				
10	R^2 = Me, R^3 = Me	**4k**	**5ak**	70[e]
11	R^2 = Ph, R^3 = Me	**4l**	**5al**	88
12	R^2 = OEt, R^3 = Me	**4m**	**5am**	91
13	R^2 = Ph, R^3 = Br	**4n**	**5an**	56
14	 **4o**		 **5ao**	35
15	 **4p**		 **5ap**	73[e]

[a]Conditions: **1a** (0.20 mmol), **4** (0.22 mmol), and 4 Å MS (40 mg) were heated in toluene (1 mL) at 120 °C for 1 h in the presence of $Rh_2[(S)\text{-NTTL}]_4$ (2.0 μmol). [b]Isolated yield (average of two runs). [c]*E*:*Z* = 9:91. [d]*E*:*Z* = 5:>95. [e]Using **4** (0.40 mmol).

into the products **5ak–an** (entries 10–13). 1-Cyclohexene-1-carbaldehyde (**4o**) gave the bicyclic compound **5ao** in only 35% yield due to low product selectivity **5**/**6** (entry 14).[16] Acrolein (**4p**) was also a suitable substrate, furnishing the product **5ap** in 73% yield (entry 15). The products **5ad**, **5ae**, **5af**, **5ag**, and **5ap** were analyzed by chiral HPLC and determined to be racemic.

Variation of triazoles **1** was also examined in the reaction with (*E*)-cinnamaldehyde (**4b**) (Table 3). Triazoles **1b–d**, possessing aryl groups at the 4-position, afforded the corresponding products **5bb–db** in yields ranging from 73% to 91% (entries 1–3). The reaction of the alkyl-substituted triazole **1e** gave the product **5eb** in moderate yield, due to 1,2-hydride migration occurring with the rhodium carbene intermediate to form *N*-mesyl-pent-2-en-1-imine (entry 4).[17] The annulation reaction was amenable with respect to the R^4 substituent on the sulfonyl group to give the products **5fb–ib** in high yields (entries 5–8).

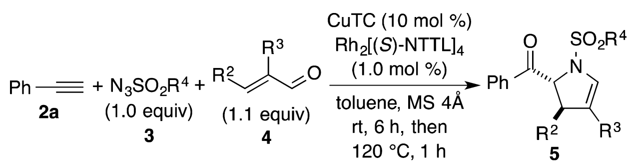
Table 3. Rh(II)-Catalyzed Denitrogenative Annulation of Various Triazoles 1b–i with (*E*)-Cinnamaldehyde (4b)[a]



entry	triazole **1** R^1	R^4		product **5**	yield (%)[b]
1	4-MeO-C_6H_4	Me	**1b**	**5bb**	91
2	4-CF_3-C_6H_4	Me	**1c**	**5cb**	87
3	3-thienyl	Me	**1d**	**5db**	73
4	ⁿPr	Me	**1e**	**5eb**	48[c]
5	Ph	$(CH_2)_2TMS$	**1f**	**5fb**	89
6	Ph	4-Tol	**1g**	**5gb**	83
7	Ph	4-MeO-C_6H_4	**1h**	**5hb**	88
8	Ph	4-Br-C_6H_4	**1i**	**5ib**	77

[a]Conditions: **1a** (0.20 mmol), **4b** (0.22 mmol), and 4 Å MS (40 mg) were heated in toluene (1 mL) at 120 °C for 1 h in the presence of $Rh_2[(S)\text{-NTTL}]_4$ (2.0 μmol). [b]Isolated yield (average of two runs). [c]Using **4b** (0.60 mmol), $Rh_2[(S)\text{-NTTL}]_4$ (5.0 μmol), and 4 Å MS (10 mg) in toluene (0.2 mL) for 2 h.

Table 4. One-Pot Synthesis of 2,3-Dihydropyrroles 5 Starting from Phenylacetylene (2a)[a]



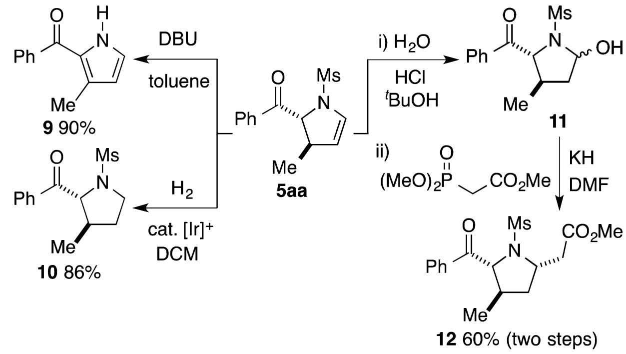
entry	azide **3** R^4		α,β-unsaturated aldehyde **4** R^2	R^3		product **5**	yield (%)[b]
1	Me	**3a**	Me	H	**4a**	**5aa**	68
2	Me	**3a**	Ph	H	**4b**	**5ab**	70
3	4-Tol	**3g**	Ph	H	**4b**	**5gb**	74
4	Me	**3a**	Ph	Me	**4l**	**5al**	69
5	Me	**3a**	Me	H	**4a**	**5aa**	68[c]

[a]Conditions: **2a** (0.20 mmol), **3** (0.20 mmol), **4** (0.22 mmol), CuTC (20 μmol), $Rh_2[(S)\text{-NTTL}]_4$ (2.0 μmol), and 4 Å MS (40 mg) in toluene (1 mL) were stirred at rt for 6 h, then heated at 120 °C for 1 h. [b]Isolated yield (average of two runs). [c]On a 10 mmol scale using **4a** (15 mmol).

With the detailed study on the transformation of the triazoles **1** into the 2,3-dihydropyrroles **5** finalized, we next carried out a one-pot synthesis of compounds **5** from terminal alkyne **2** in order to demonstrate the practical convenience of the present transformation (Table 4). Phenylacetylene (**2a**, 0.20 mmol), *N*-sulfonyl azides **3** (0.20 mmol), α,β-unsaturated aldehydes **4** (0.22 mmol), CuTC (10 mol %), $Rh_2[(S)\text{-NTTL}]_4$ (1.0 mol %), 4 Å MS, and toluene (1 mL) were placed in a reaction vessel, and the reaction mixture was simply stirred at room temperature. Both **2a** and **3** were consumed after 6 h. The reaction mixture was subsequently stirred at 120 °C for an additional 1 h. After chromatographic separation, the compounds **5** were isolated in overall yields ranging from 68% to 74% (entries 1–4). An experiment using 1.0 g of **2a** (10 mmol) also gave a comparable result (entry 5).

The synthetic utility of the dihydropyrrole products was exemplified by further transformations. Deprotective aromatiza-

Scheme 2. Synthetic Derivatization of 2,3-Dihydropyrroles



tion took place on treatment with 1,8-diazabicycloundec-7-ene (DBU) through an E1cB/prototropy sequence (Scheme 2).[10] Tetrahydropyrrole (2,3-disubstituted pyrrolidine) **10** was obtained when **5aa** was hydrogenated using Crabtree's catalyst. Furthermore, 2,3,5-trisubstituted pyrrolidine **12** was diastereoselectively synthesized through a sequence of hydration under acidic conditions, Horner–Wadsworth–Emmons olefination, and an aza-Michael reaction.[18]

In summary, we have disclosed an interesting and useful reactivity of α-imino rhodium carbenes toward α,β-unsaturated aldehydes, providing an efficient method for the diastereoselective synthesis of *trans*-2,3-disubstituted 2,3-dihydropyrroles from terminal alkynes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectral data for the new compounds, and details of the X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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