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Conversion of Cyclic Ketones to 2,3-Fused Pyrroles and Substituted Indoles

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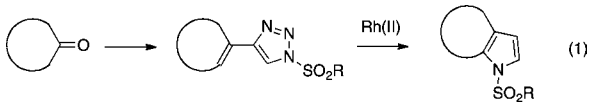
Supporting Information

ABSTRACT: A highly effective synthesis of 2,3-fused pyrroles from cyclic ketones has been achieved. The transformation includes a rhodium-catalyzed reaction of 4-alkenyl-1-sulfonyl-1,2,3-triazoles featuring an unusual 4π electrocyclization. The methodology was further extended to the synthesis of indoles using a one-pot reaction starting from 1-ethynylcyclohexenes.

Pyrroles are ubiquitous constituents in a wide variety of natural products, therapeutic agents, and high-value materials.[1] Consequently, the development of methods for the synthesis of pyrroles has been an active area of research. Traditional methods for pyrrole synthesis include the Knorr, Hantzsch, and Paal–Knorr syntheses.[2] Recently, many metal-catalyzed methods for the synthesis of pyrroles have been reported.[3] However, the synthesis of highly functionalized pyrroles remains challenging and often requires multiple steps or harsh reaction conditions. In this communication, we describe a novel approach to the synthesis of 2,3-fused pyrroles via an intramolecular rhodium(II)-catalyzed cyclization of 4-alkenyl-*N*-sulfonyltriazoles, which are readily derived from the corresponding ketones (eq 1). We further extend this methodology to the formation of substituted indoles from cyclohexanones.

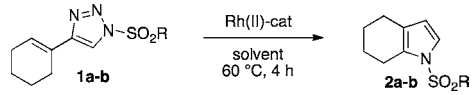


(1)

The Davies group has had a long-standing interest in the development of novel transformations of donor/acceptor carbenes derived from diazo compounds.[4] Fokin and Gevorgyan recently reported the use of 1,2,3-triazoles as alternative precursors for the formation of rhodium(II)-bound donor/acceptor carbenes.[5] The use of these iminocarbenes has enabled the development of novel transformations,[6] including direct heterocycle syntheses[7] and implementation of a heteroatom as the donor group[8] that otherwise could not be achieved with traditional donor/acceptor carbenes.

Among the most broadly used donor/acceptor carbenes are those in which the donor group is an alkenyl substituent.[9] Therefore, we have begun a program to examine the use of alkenyltriazoles as precursors to rhodium-bound alkenylcarbenes.[10] During the course of these studies, we discovered that rhodium-bound iminoalkenylcarbenes undergo facile cyclization to pyrroles in the absence of a trapping agent. Our preliminary reaction development was conducted with 4-cyclohexenyl-1-sulfonyl-1,2,3-triazoles[6a,11] **1** in the presence of 1.0 mol % Rh(II) catalyst (Table 1). The yield of the desired product was found to be dependent on both the nature of the sulfonyl group and the dirhodium catalyst. After exploring several achiral Rh(II) catalysts, $Rh_2(esp)_2$ was identified as the optimal catalyst for this transformation (entry 4). Increasing the steric bulk of the *N*-sulfonyl substituent provided improved yields of the desired product (compare entries 4 and 5). The effect of the solvent was less pronounced, which is in contrast to the solvent effect we had observed in our previous reports with *N*-sulfonyltriazoles.[7b,10a]

Table 1. Optimization Studies[a]



entry	substrate	$-SO_2R$	Rh(II) cat.	solvent	yield (%)[b]
1	**1a**	Ts	$Rh_2(OAc)_4$	1,2-DCE	47
2	**1a**	Ts	$Rh_2(TFA)_4$	1,2-DCE	0[c]
3	**1a**	Ts	$Rh_2(Oct)_4$	1,2-DCE	91
4	**1a**	**Ts**	**$Rh_2(esp)_2$**	**1,2-DCE**	**93 (94[d])**
5	**1b**	Ms	$Rh_2(esp)_2$	1,2-DCE	81
6	**1a**	Ts	$Rh_2(esp)_2$	EtOAc	53
7	**1a**	Ts	$Rh_2(esp)_2$	$PhCH_3$	91
8	**1a**	Ts	$Rh_2(esp)_2$	$CHCl_3$	92

[a]Triazole **1a** or **1b** (0.30 mmol, 1.0 equiv) and Rh_2L_n (0.0030 mmol, 0.01 equiv) were combined in solvent (2.0 mL) and heated at 60 °C for 4 h. [b]Isolated yields. [c]*N*-Sulfonyltriazole was recovered. [d]5.0 mmol scale (0.1 M).

Having developed optimized reaction conditions for the synthesis of **2**, we subsequently explored the scope of this transformation. The 4-alkenyl-1-tosyl-1,2,3-triazoles **1c–l** and **1n** were prepared from the cyclic ketones in three steps: vinyl triflate formation, Kumada-type coupling with ethynylmagnesium bromide in the presence of 3 mol % $Co(acac)_3$,[12] and copper(I) thiophene-2-carboxylate (CuTC)-catalyzed azide–alkyne cycloaddition (CuAAC) with TsN_3 (eq 2; see the Supporting Information for details).[11,13]

We were pleased to find that the reaction of a variety of 2- and 4-substituted cyclohexenyltriazole derivatives provided the desired tetrahydro-1*H*-indoles **2c–i** in excellent yields (86–92%; Table 2, entries 1–7). Heteroatoms in the ring were also

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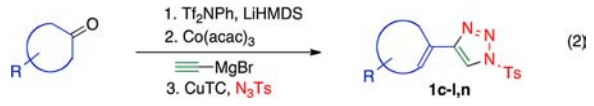
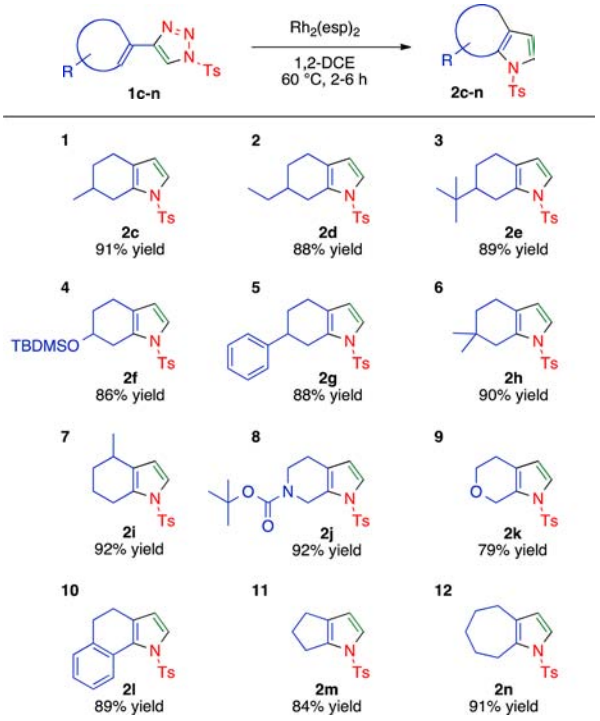


Table 2. Alkenyl-*N*-tosyltriazole Scope[a]



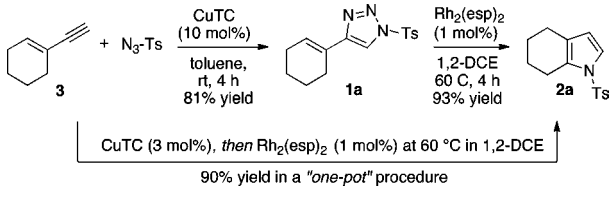
[a]**1** (0.26 mmol, 1.0 equiv) and $Rh_2(esp)_2$ (0.0026 mmol, 0.01 equiv) were combined in 1,2-DCE (2.0 mL) and heated at 60 °C for 2−6 h until consumption of **1** was apparent by thin-layer chromatography (TLC) analysis. Isolated yields of purified products are shown.

tolerated, as both the *N*-Boc-piperidinyl and pyranyl alkenyltriazoles **1j** and **1k** underwent the cyclization to provide pyrroles **2j** and **2k** in good yields (entries 8 and 9). The 1,2-dihydronaphthalen-2-yl derivative **1l** provided the dihydrobenzoindole product **2l** in excellent yield (89%; entry 10). The cyclopentenyl and cycloheptenyl triazole derivatives **1m** and **1n** also reacted to provide the fused pyrroles **2m** and **2n** in high yields (entries 11 and 12).

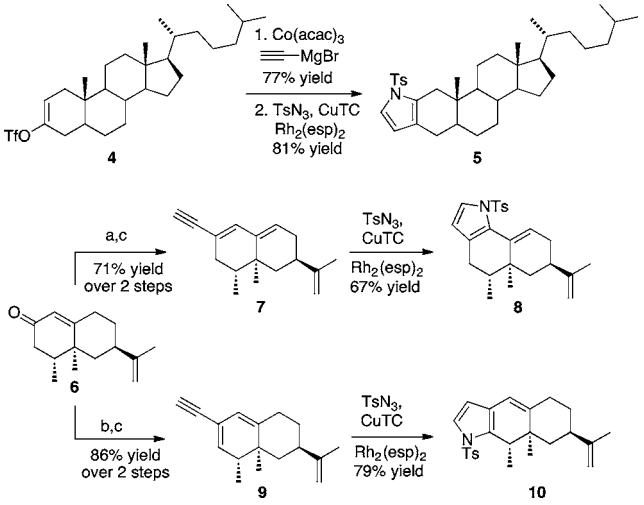
Since the CuAAC reaction can be performed in halogenated solvents,[6e,7b,8] it was feasible to perform the CuAAC reaction and the rhodium-catalyzed cyclization in the same reaction medium starting from enyne **3** (Scheme 1). The one-pot reaction gave the desired 2,3-fused pyrrole product **2a** in higher overall yield (90%) than in the sequence in which the triazole was isolated.

The utility of the one-pot 2,3-fused pyrrole synthesis was demonstrated using more complex frameworks, namely, the steroid skeletons of 5-cholestan-3-one and nootkatone (Scheme 2). For 5-cholestan-3-one, selective formation of vinyl triflate **4** and subsequent Co(III)-catalyzed coupling provided an enyne that was subsequently subjected to the one-pot CuAAC/rhodium-catalyzed cyclization sequence, furnishing pyrrole product **5** in good yield (81%). With nootkatone (**6**), both the kinetic and thermodynamic vinyl triflates could be formed regioselectively and then independently subjected to palladium-catalyzed coupling. The resulting enynes **7** and **9** were subjected to the one-pot protocol, providing pyrroles **8** (67% yield) and **10** (79% yield), respectively. Notably, electrocyclization to form the pyrrole was found to be preferred over a number of potential side reactions.

Scheme 1. One-Pot 2,3-Fused Pyrrole Synthesis



Scheme 2. Application to Complex Frameworks[a]



[a]Reagents and conditions: (a) Tf_2O, 2,6-lutidine, rt; (b) Tf_2NPh, LiHMDS, −78 °C; (c) $Pd(PPh_3)_4$, ethynylmagnesium bromide, rt.

Encouraged by the successful syntheses of 2,3-fused pyrroles, our attention turned to the possibility of synthesizing substituted indole derivatives by combining the electrocyclization with a 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation. To our delight, the reaction gave the desired indole products in good to excellent yields (Table 3). This one-pot reaction sequence can be extended to a variety of substituted cyclohexenyl derivatives to provide substituted indole products (entries 1−8). Notably, the siloxy derivative provided 6-siloxyindole **11e**, which may serve as a precursor for cross-coupling at the 6-position (entry 5). The *N*-Boc-protected piperidine derivative **3h** provided ready access to 6-azaindole **11h** (entry 8).

A proposed mechanistic rationale for the formation of the 2,3-fused pyrrole is provided in Scheme 3. The heating of triazole **I** in the presence of the dirhodium catalyst generates rhodium-stabilized iminocarbene intermediate **II** via ring−chain isomerization and nitrogen extrusion. The iminocarbene intermediate has to adopt an s-trans geometry, after which it participates in a 4π electrocyclization to form pyrrolylium cation **III**.[14] Proton elimination with aromatization gives pyrrole **IV**. Termination by a unique protonation of the vinylrhodium species would give the product, **V**, and complete the catalytic cycle. An alternative possible mechanism for the conversion of **III** to **V** would be two sequential 1,5-H shifts followed by Rh release.

In summary, we have developed a highly effective synthesis of 2,3-fused pyrroles from readily available starting materials via

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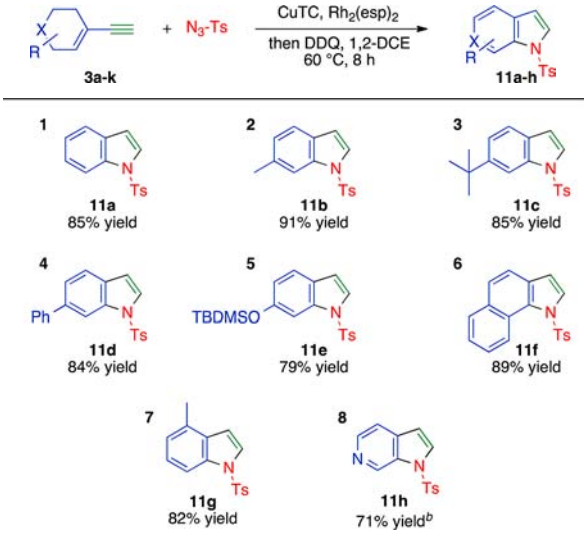
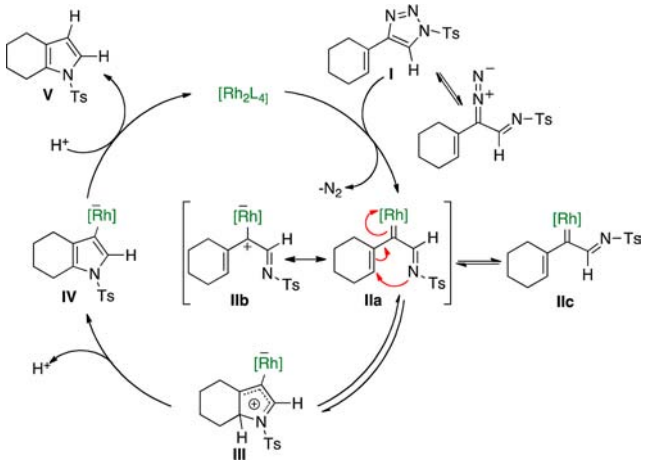
Table 3. One-Pot Indole Synthesis from Cyclohexenyl Derivatives[a]



[a] **3** (1.00 mmol, 1.0 equiv), TsN_3 (1.00 mmol, 1.0 equiv), and CuTC (0.05 mmol, 0.05 equiv) were combined in 1,2-DCE (2.0 mL) for 3−4 h followed by $Rh_2(esp)_2$ (0.01 mmol, 0.01 equiv) in 1,2-DCE (1 mL) with heating at 60 °C for 2−4 h until consumption of **1** was apparent by TLC analysis. Then DDQ (2.00 mmol, 2.0 equiv) suspended in 1,2-DCE (3 mL) was added, and the mixture was heated at 60 °C for 1 h. Isolated yields of purified products are shown. [b] 4 h at 40 °C after the addition of DDQ (2.0 equiv).

Scheme 3. Proposed Mechanism for Pyrrole Formation



an intramolecular rhodium-catalyzed cyclization of 4-alkenyl-1-sulfonyl-1,2,3-triazoles. This reaction was further extended to a one-pot synthesis of indoles starting from cyclic enynes. The substrate scope of this transformation is broad and the products are formed under mild reaction conditions, enabling the extension of this methodology to more complex frameworks. This novel transformation contrasts with the vast majority of reactions of *N*-sulfonyltriazoles, which involve intermolecular reactions of the iminocarbene intermediates.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic details and spectral data. 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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