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Intramolecular Dearomatizing [3 + 2] Annulation of α-Imino Carbenoids with Aryl Rings Furnishing 3,4-Fused Indole Skeletons

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Supporting Information

ABSTRACT: The rhodium-catalyzed dearomatizing [3 + 2] annulation reaction of 4-(3-arylpropyl)-1,2,3-triazoles is described. It provides a straightforward synthetic pathway from simple 5-aryl-1-alkynes leading to tricyclic 3,4-fused dihydroindoles via the corresponding 1,2,3-triazoles.

A 3,4-fused indole skeleton presents a key structural motif of a number of natural products which exhibit a wide range of biological activities. These include dehydrobufotenine,[1] chuangxinmycin,[2] hapalindole U,[3] welwitindolinones,[4] and the *Ergot* family such as lysergic acid,[5] chanoclavine-I,[6] and rugulovasine A[7] (Figure 1).

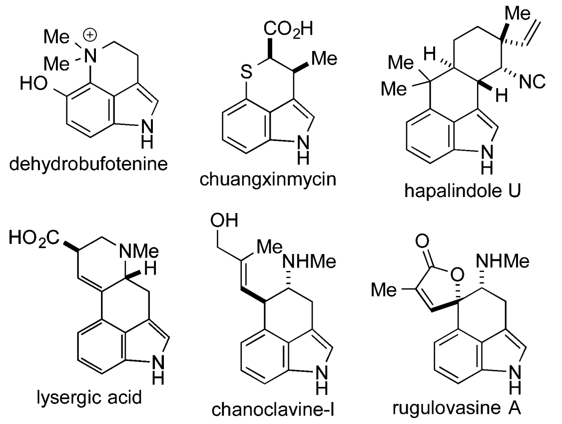


Figure 1. Natural products with 3,4-fused indole skeletons.

Thus, the development of efficient methods to create such a structural motif starting from readily available compounds has been highly desired.[8] Now, we report an intramolecular dearomatizing [3 + 2] annulation reaction[9] of 4-(3-arylpropyl)-1,2,3-triazoles. This new reaction constitutes a straightforward synthesis of 3,4-fused indoles starting from simple 5-aryl-1-alkynes in one pot (Figure 2).

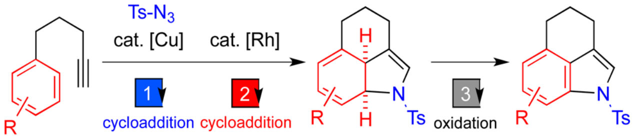
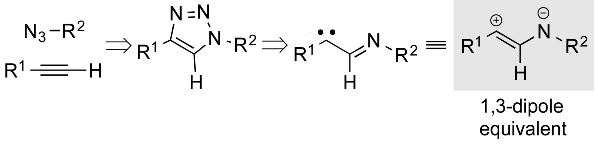


Figure 2. Construction of 3,4-fused indoles from 5-aryl-1-alkynes.

N-Sulfonyl-1,2,3-triazoles are readily prepared from 1-alkynes and act as the convenient precursor of α-imino metal carbene complexes.[10,11] The carbenoid carbon of the generated carbene complex is highly electrophilic, and the α-imino nitrogen is highly nucleophilic. Thus, the α-imino carbene complex behaves as a 1,3-dipole equivalent to participate in [3 + 2] annulation with unsaturated compounds of a nucleophilic character, forming five-membered heterocycles (eq 1).[12]



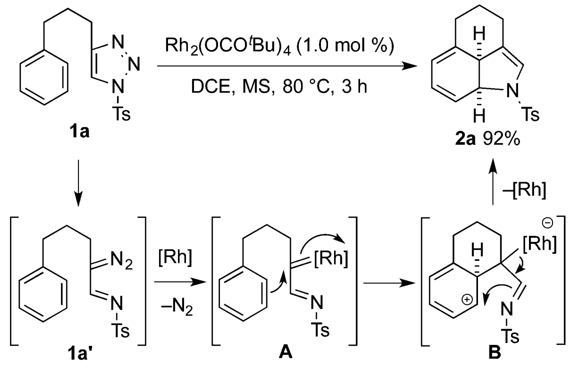
(1)

The reactions with nitriles,[10a] alkynes,[10b,13] allenes,[14] aldehydes,[15] isocyanates,[16] furans,[17] and indoles[18] afford the corresponding [3 + 2] cycloadducts. We have also disclosed[19] that the reaction with α,β-unsaturated aldehydes leads to the stereoselective production of 2,3-dihydropyrroles via the corresponding 4-oxazolines.[15] We were next interested in whether a benzene ring can act as the dipolarophile to construct a dihydroindole skeleton.[20] Thus, we first examined an intermolecular reaction of a triazole with various benzene substrates including 1,2-dimethoxybenzene in the presence of rhodium(II) catalysts. However, no formation of the corresponding [3 + 2] cycloadduct was observed even at 140 °C under microwave irradiation. Next, an intramolecular reaction was examined using the triazole **1a** possessing a 3-phenylpropyl side chain, which was readily prepared from 5-phenyl-1-pentyne and tosyl azide according to the procedure using copper(I) thiophene-2-carboxylate (CuTC).[21] When the triazole **1a** was treated with rhodium(II) pivalate dimer [$Rh_2(OCO^tBu)_4$, 1.0 mol %] and 4 Å molecular sieves (MS) in 1,2-dichloroethane (DCE) at 80 °C for 3 h, the 3,4-fused 3a,7a-dihydroindole **2a** was obtained in 92% isolated yield after chromatographic purification (Scheme 1).

The *cis* stereochemistry was determined by a single-crystal X-ray analysis. We assume the following mechanism for the production of **2a**: a reversible ring−chain tautomerization of the triazole moiety of **1a** generates α-diazo imine **1a′**, which immediately reacts with rhodium(II) to afford α-imino rhodium carbene **A** with release of molecular nitrogen. The carbenoid carbon of **A** is electrophilic enough to induce the intramolecular attack of the phenyl ring in a 6-exo mode to furnish the

Received: December 13, 2013

Scheme 1. Dearomatizing Annulation Reaction of 1a



zwitterionic intermediate **B**. The anionic rhodium releases bonding electrons, which cause cyclization at the imino nitrogen. It should be noted that the reactivity of α-imino rhodium carbene **A** markedly contrasts with that of α-oxo rhodium carbene complexes; whereas the intermediate **A** serves as an 1,3-dipole equivalent because of the nucleophilic character of the imino nitrogen, a similar rhodium carbene complex generated from α-diazo ester **3** undergoes an intramolecular Büchner reaction to produce bicyclo[5.3.0]-deca-1,3,5-triene **4** (eq 2).[22]

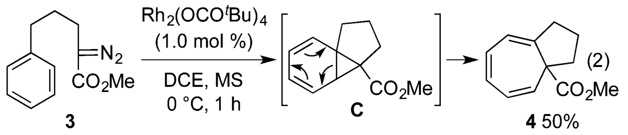
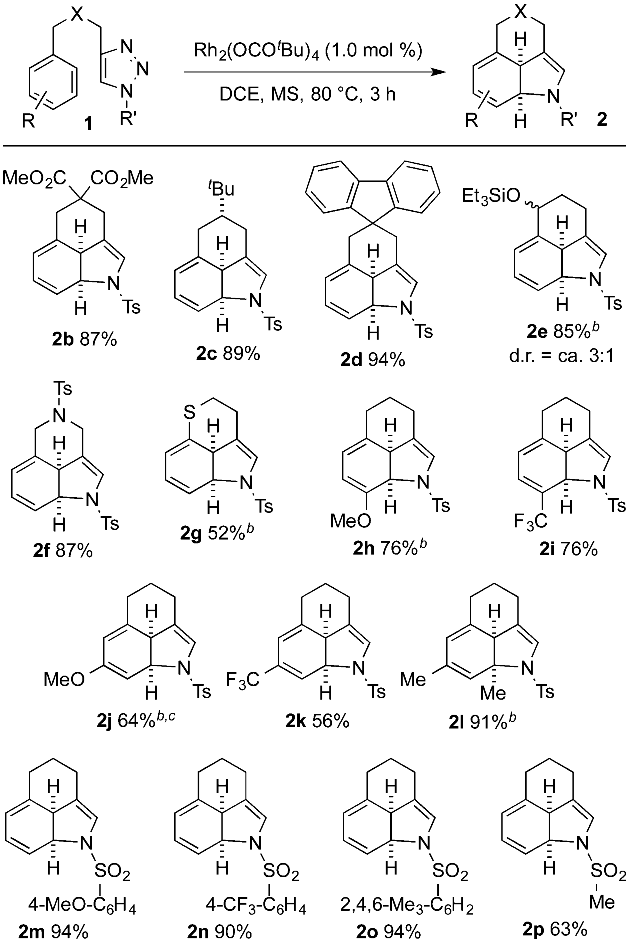


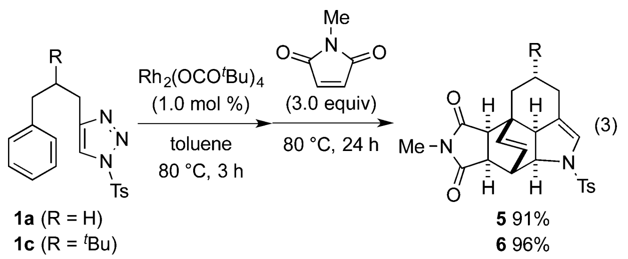
Table 1. Dearomatizing Annulation Reaction of 4-(3-Arylpropyl)-1,2,3-triazoles[a]



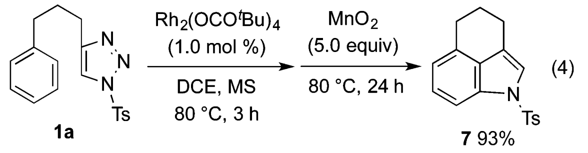
[a] Conditions: **1** (0.20 mmol), Rh$_2$(OCO^{t}Bu)$_4$ (2 μmol), and MS (40 mg) were heated in DCE (4 mL) at 80 °C for 3 h unless otherwise noted. Yield of isolated product after chromatography (average of two runs). [b] Using toluene (4 mL). [c] Purified by recrystallization.

The results shown in Table 1 delineate the scope of the [3 + 2] annulation reaction. Substrates possessing a three-carbon tether smoothly reacted, and the corresponding products **2b**–**2e** were isolated in yields ranging from 85% to 94%. The nitrogen- and sulfur-tethered substrates also underwent the [3 + 2] annulation reaction (**2f** and **2g**). Of note was that the electron-deficient benzene ring successfully participated in the transformation (**2i** and **2k**). With unsymmetrical *meta*-monosubstituted substrates, the annulation occurred regioselectively at the less-hindered side (**2j** and **2k**). It was possible, however, to install an angular methyl group at the bridgehead position of **2l** by using a 3,5-xylyl-substituted substrate. Various substituents including a methyl group were suitable for the sulfonyl substituent (**2m**–**2p**). On the other hand, substrates possessing a shorter or longer tether, i.e., two- or four-carbon tether failed to undergo a similar intramolecular [3 + 2] annulation reaction due to structural constrains, giving a complex mixture.

The resulting 3,4-fused dihydroindoles could act as the diene partner of a Diels–Alder reaction (eq 3). Endo cycloaddition selectively took place upon direct addition of *N*-methylmaleimide to the reaction mixtures containing **2a** and **2c** to afford the corresponding pentacyclic compounds **5** and **6**, respectively.

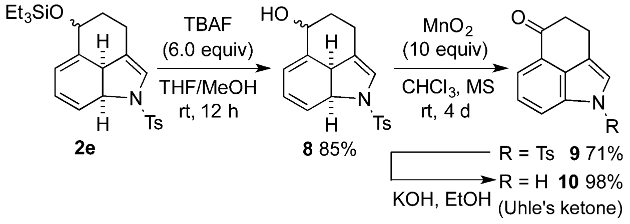


When manganese dioxide was directly added to the reaction mixture containing **2a**, oxidative aromatization[23] took place to produce 3,4-fused indole **7** in 93% yield (eq 4). Thus, the sequential procedure in one pot provides a facile synthetic pathway from simple 1-alkynes to 3,4-fused indoles.



The present [3 + 2] annulation reaction was successfully extended to the synthesis of Uhle's ketone **10**,[24] which have been often utilized in the synthesis of *Ergot* alkaloids[5a] (Scheme 2). Initially, the triethylsilyl group of the dihydroindole **2e** was deprotected by treatment with tetrabutylammonium fluoride (TBAF). The subsequent oxidation of alcohol **8** with manganese dioxide afforded *N*-tosylated Uhle's ketone **9**,[25]

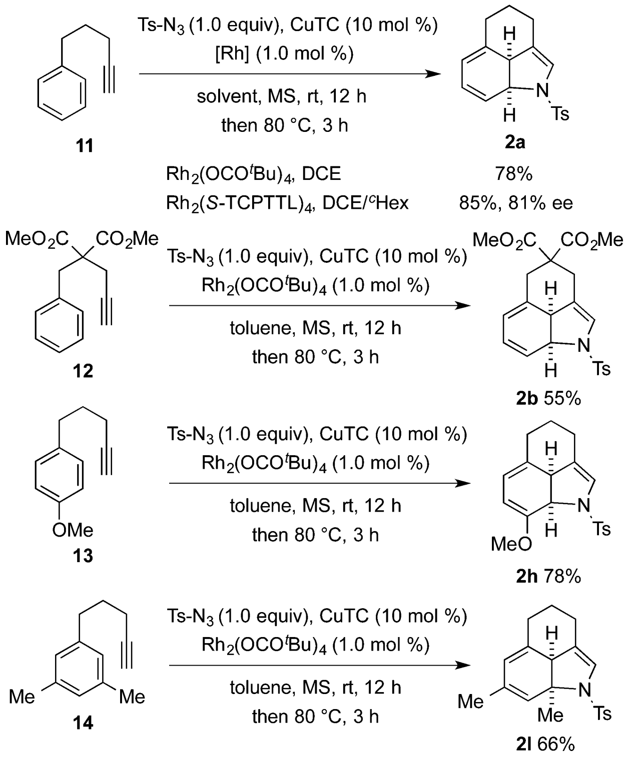
Scheme 2. Synthesis of Uhle's Ketone



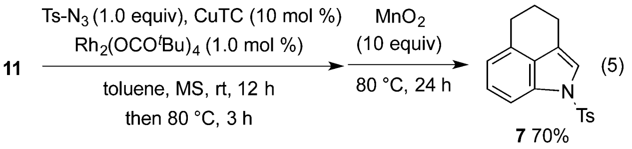
which was further converted into the Uhle's ketone **10** by detosylation with potassium hydroxide.[26]

The synthetic usefulness of the [3 + 2] annulation reaction was exemplified by its successful integration into a one-pot synthesis of 3,4-fused dihydroindoles **2** directly from 5-aryl-1-alkynes **11**−**14** (Scheme 3). For example, **11**, tosyl azide (1.0 equiv), CuTC (10 mol %), $Rh_2(OCO^tBu)_4$ (1.0 mol %), MS, and DCE were placed together in a reaction vessel. The reaction mixture was stirred at room temperature for 12 h, during which **11** was converted to the triazole **1a**. The reaction mixture was further stirred at 80 °C for additional 3 h. Finally, a single isolation procedure using preparative thin-layer chromatography furnished **2a** in 78% yield based on **11**. Interestingly, a good level of asymmetric induction (81% ee) was observed when chiral rhodium(II) complex, Rh_2(*S*-TCPTTL)$_4$,[27] was employed. The all-in-one-pot procedure shows that the reagents and catalysts requisite in each step hardly interfere with each other.

Scheme 3. One-pot Synthesis Starting from 5-Aryl-1-alkynes



Furthermore, the all-in-one-pot process could be even directly followed by oxidative aromatization using manganese dioxide to afford 3,4-fused indole **7** in 70% yield based on **11** (eq 5).



(5)

In summary, we have developed the intramolecular [3 + 2] annulation of the α-imino rhodium carbene complexes with aryl groups. Of note is that the annulation mode markedly contrasts with the addition mode of α-oxo rhodium carbene complex. It constitutes the key step of a unique method to synthesize 3,4-fused 3a,7a-dihydroindoles from 5-aryl-1-alkynes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and data. This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Prof. Teruaki Mukaiyama on the occasion of his 88th birthday (Beiju). We thank Dr. Y. Nagata (Kyoto University) for his kind help in an X-ray analysis. This work was supported by MEXT (Grant-in-Aid for Scientific Research on Innovative Areas nos. 22105005 and 24106718, Young Scientists (A) no. 23685019, Scientific Research (B) no. 23350041) and JST (ACT-C).

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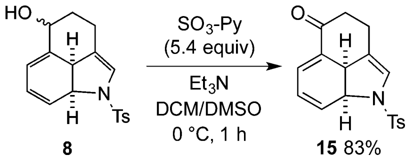

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