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Stereoselective Synthesis of Oxabicyclo[2.2.1]heptenes via a Tandem Dirhodium(II)-Catalyzed Triazole Denitrogenation and [3 + 2] Cycloaddition

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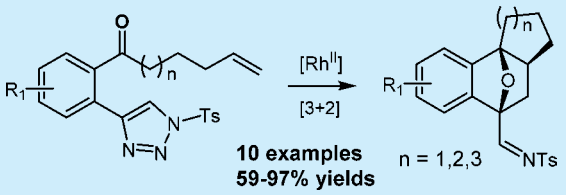
Supporting Information

ABSTRACT: A novel synthetic strategy for the diastereoselective synthesis of structurally diverse oxabicyclo[2.2.1]heptenes has been developed, featuring a tandem reaction combining a Rh-catalyzed triazole denitrogenation and a novel type of [3 + 2] cycloaddition reaction. This tandem reaction was thought to proceed via a five-membered oxonium ylide intermediate, which was formed by the intramolecular nucleophilic attack of the carbonyl group on the α-imino metallocarbene followed by an inter- or intramolecular [3 + 2] dipolar cycloaddition with a range of alkynes and alkenes.



[3 + 2] cycloaddition reactions[1] are important reactions in organic chemistry and have been used for the preparation of key intermediates in both academia and industry.[2] The development of novel [3 + 2] cycloaddition reactions is therefore important in organic synthesis.

N-Sulfonyl-1,2,3-triazoles are readily prepared from terminal alkynes and *N*-sulfonyl azides by copper-catalyzed 1,3-dipolar cycloaddition. The resultant intermediates can be converted to the corresponding α-imino metallocarbene species[3] upon treatment with rhodium(II) salts,[3] and the products can undergo a variety of useful transformations.[4]

In our previous communication, we reported the Rh(II)-catalyzed denitrogenation of *N*-sulfonyl-1,2,3-triazoles (**A**) for the syntheses of dihydroisobenzofurans (**C**) and indanones (**D**) in a chemoselective manner (eq 1 in Figure 1).[5] Mechanistically, these reactions occur via the key oxonium intermediate **B**.[6] The nucleophilic addition of MeOH and water[7] to intermediate **B** results in the formation of dihydroisobenzofurans (**C**) and indanones (**D**), respectively. The indanones[8] are important building blocks in medicinal chemistry.

The synthesis of polycyclic systems from readily available precursors in the minimum number of steps with regio- and stereochemical control constitutes an important synthetic challenge.[9] We envisaged that ketones bearing terminal olefins **E** might generate oxonium ylides **F** (eq 2 in Figure 1).[10] Potentially, these could undergo a subsequent [3 + 2] cycloaddition reaction to afford **G** bearing an oxabicyclo[2.2.1]-heptene core, which is a useful intermediate for the synthesis of more complex molecules.[11] Herein, we report our realization of the proposed chemistry, allowing for a concise synthesis of structurally diverse and unique polycyclic scaffolds bearing oxabicyclo[2.2.1]heptenes, which exist in many natural products with important biological activities.[12,13]

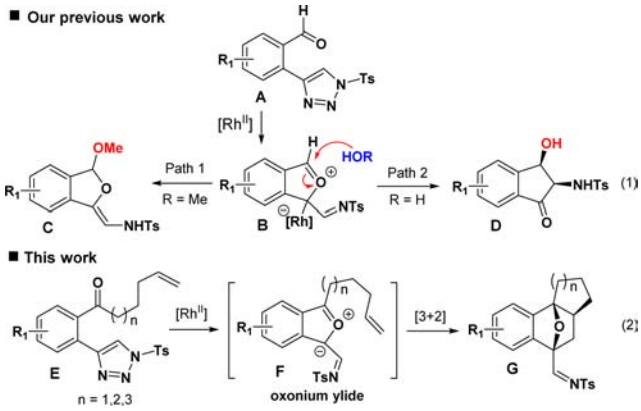


Figure 1. Rhodium(II)-catalyzed C−C bond-forming reactions of triazoles for the syntheses of dihydroisobenzofurans (**C**), indanones (**D**), and oxabicyclo[2.2.1]heptenes (**G**).

We initially investigated the Rh(II)-catalyzed intermolecular [3 + 2] cycloaddition reaction for the synthesis of **2a** using triazole **1a** and dimethyl but-2-ynedioate as the starting materials. Triazole **1a** was easily prepared using a Cu-catalyzed azide−alkyne cycloaddition reaction.[14]

When we treated triazole **1a** with 5 mol % of $Rh_2(OAc)_4$[15] in dichloroethane (DCE) in the presence of dimethyl but-2-ynedioate (3.0 equiv) at the desired temperature (ranging from 25 to 60 °C), none of the desired product **1a′** was observed. When the reaction was carried out at reflux for 8 h, the expected annulated product **1a′** was observed. However,

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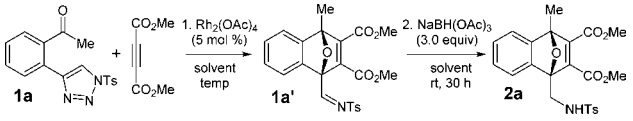
decomposition was observed upon chromatography on silica gel. We therefore decided to reduce the imine moiety in product **1a′** to the corresponding amine using $NaBH(OAc)_3$. As a result, product **2a** was obtained in 74% yield (entry 1 in Table 1). When the same reaction was run at 120 °C in DCE in a sealed tube (entry 2), to our delight, the reaction was complete within 4 h and afforded product **2a** in 95% yield.

Table 1. Optimization of the Reaction Conditions[a]



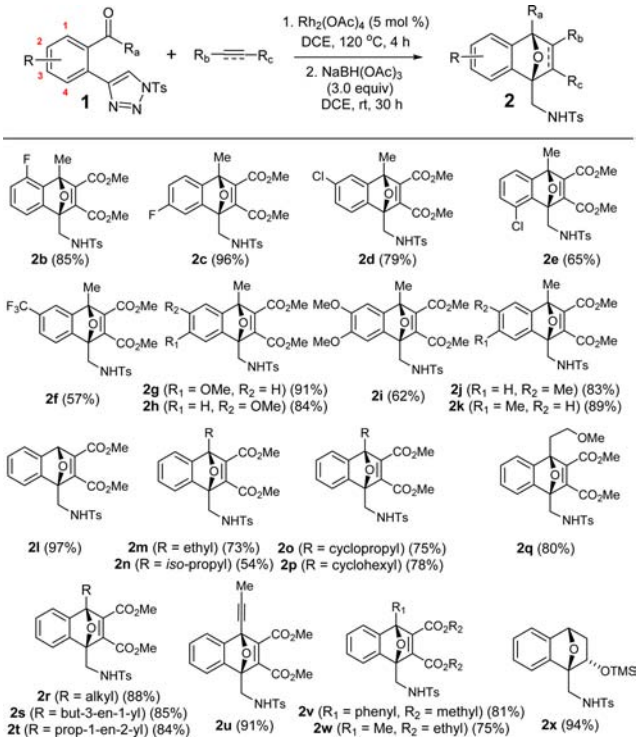
entry	catalyst	catalyst loading (mol %)	temp (°C)	solvent	time (h)	yield[b] (%)
1	$Rh_2(OAc)_4$	5	reflux	DCE	8	74
2[c]	**$Rh_2(OAc)_4$**	**5**	**120**	**DCE**	**4**	**95**
3	$Rh_2(OCt)_4$	5	reflux	DCE	8	74
4[c]	$Rh_2(OCt)_4$	5	120	DCE	4	81
5	$Rh_2(OAc)_4$	5	reflux	toluene	8	63
6[c]	$Rh_2(OAc)_4$	5	120	toluene	4	74
7	$Rh_2(OAc)_4$	1	120	DCE	4	78
8	$Rh_2(OAc)_4$	2	120	DCE	4	83

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), DMAD (0.6 mmol, 3.0 equiv), catalyst (0.01 mmol,5 mol %), solvent (0.05 M for substrate). [b]Isolated yield. [c]The reaction was run in a sealed tube.

To evaluate the effects of catalyst and solvent on the outcome of the annulation, following our previous observation,[5] we first tried to use $Rh_2(OCt)_4$ under the same conditions as entries 1 and 2, and product **2a** was obtained in 74% and 81% yield, respectively (entries 3 and 4).We then tried the tandem reaction using $Rh_2(OAc)_4$ as catalyst and toluene as solvent, but no improvement was observed (entries 5 and 6), presumably because toluene as a π-coordinating solvent could not stabilize the intermediates and/or the transition states of the reaction. Finally, when we ran the reaction with the $Rh_2(OAc)_4$ catalyst at lower loading levels (1 and 2 mol %), product **2a** was obtained in 78% and 83% yield, respectively (entries 7 and 8). The structure of product **2a** was confirmed by X-ray crystallographic analysis (see the SI for details).

The substrate scope of this reaction was then investigated under the optimal conditions. Selected substrates **1a−v** were prepared in good yields according to our optimized reaction conditions (see the SI for details). Substrates **1a−v** underwent annulation under the optimized tandem reaction conditions, and the results are shown in Scheme 1. Each of the substrates bearing either an electron-withdrawing group or an electron-donating group on the aromatic ring afforded the desired annulated products. However, it appeared that substrates bearing a substituent at C3 on the phenyl ring gave better yields (**2c**, **2g**, **2k**). The relatively low yields for the substrates bearing substituents on C2 and C4 of the phenyl ring could be due to the substituent effect on the resonance forms of intermediates **F** (Figure 1), especially those forms that extended the delocalization of the negative charge to the phenyl ring. Furthermore, a diverse range of alkyl, alkynyl, and aryl substituents were tolerated at the R_a substituent of the ketone. When R_a was a hydrogen atom (benzaldehyde-based triazole), the annulation proceeded in excellent yield to give 97% and 94% yield of **2l** and **2x**, respectively. The structure of **2p** was confirmed by X-ray crystallographic analysis. These

Scheme 1. Scope of the Intermolecular [3 + 2] Cycloaddition[a,b]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), alkene or alkyne (0.6 mmol), 3.0 equiv), catalyst (0.01 mmol, 5 mol %), solvent (0.05 M for substrate), heating at 120 °C in a sealted tube for 4 h. The crude product was treated with $NaBH(OAc)_3$ at rt for 30 h. [b]Yield of isolated product.

types of compounds can also be prepared via the reaction of substituted benzynes with substituted furans[16] or through Diels−Alder reactions with α-thiocarbocations as dienes.[17]

We then explored the proposed intramolecular [3 + 2] cycloaddition for construction of a polycyclic ring system bearing an oxabicyclo[2.2.1]heptene core. To this end, we first prepared substrates **3a−j** (see the SI for details) and then explored their tandem annulation reactions for the formation of products **4a−j**. To our delight, the substrates were subjected to the optimized conditions listed in Scheme 2 to give the expected annulated products **4a−j** in good to excellent yields (Scheme 2). Typically, substrates bearing a side chain with n = 1 or 2 afforded the annulated products **4a−i** with excellent diastereoselectivity. However, when n = 3, the product **4j** bearing a seven-membered ring was accessed in a relatively low yield and with poor diastereoselectivity, presumably because of its unfavorable entropic effect of the substrate. Interestingly, fluorinated compounds **3c** and **3e** afforded high yields of their annulated products.

Encouraged by the results of this intramolecular Rh(II)-catalyzed [3 + 2] cycloaddition for the formation of oxabicyclo[2.2.1]heptene-based polycyclic compounds, we then explored an asymmetric synthesis.

We profiled several commercially available catalysts (Scheme 3). The $Rh_2(S\text{-BTPCP})_4$ catalyst[18] gave no asymmetric induction (entry 1), while $Rh_2(S\text{-PTAD})_4$[19] could afford a moderate enantioselectivity (entry 2, 81% yield with 55% ee). This observation could be due to the more steric hindrance of adamantanyl group in $Rh_2(S\text{-PTAD})_4$ than that of the

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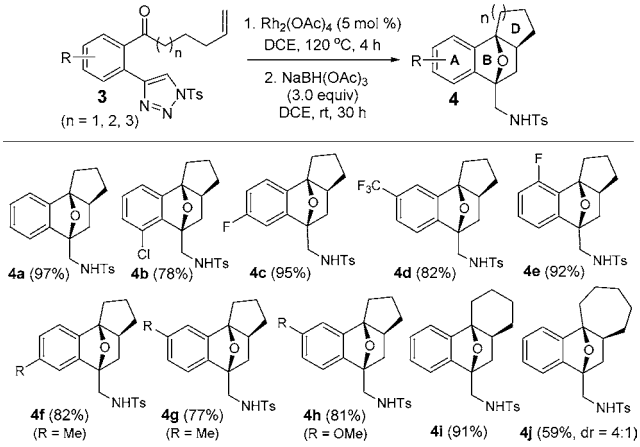
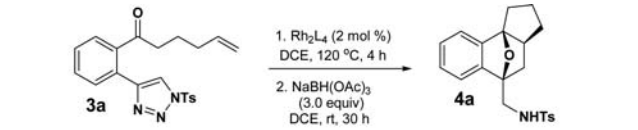
Scheme 2. Scope of the Intramolecular [3 + 2] Cycloaddition[a,b]

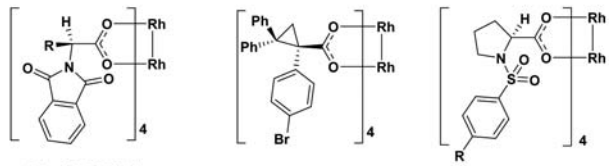


[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), catalyst (0.01 mmol, 5 mol %), solvent (0.05 M for substrate), heating at 120 °C in a sealted tube for 4 h (3 h for substrates **3b** and **3f**). The crude product was treated with $NaBH(OAc)_3$ at rt for 30 h. [b]Yield of isolated product.

Scheme 3. Asymmetric [3 + 2] Cycloaddition[a]



entry	Rh_2L_4	yield[b] (%)	ee[c] (%)
1	Rh_2(*S*-BTPCP)$_4$	79	0
2	Rh_2(*S*-PTAD)$_4$	81	55
3	Rh_2(*S*-DOSP)$_4$	86	83



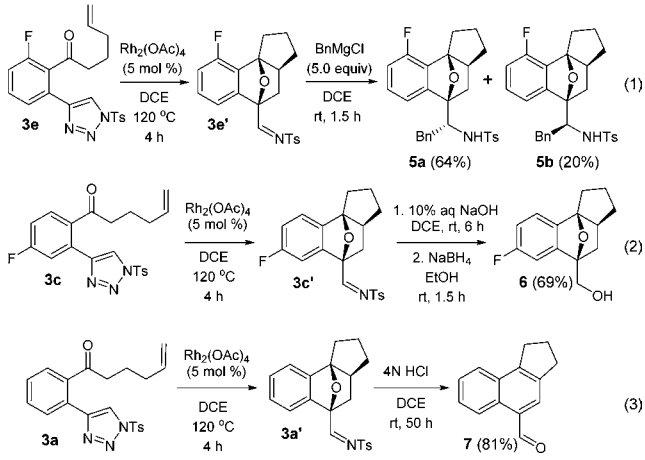
[a]Reaction conditions: **3a** (0.2 mmol, 1.0 equiv), catalyst (0.004 mmol, 2 mol %), solvent (0.05 M for substrate), heating at 120 °C in a sealted tube for 4 h. The crude product was treated with $NaBH(OAc)_3$ at rt for 30 h. [b]Yield of isolated product. [c]Determined by chiral HPL analysis.

diphenylcyclopropyl group in Rh_2(*S*-BTPCP)$_4$. On the other hand, when Rh_2(*S*-DOSP)$_4$[20] was used as the catalyst, a good yield and acceptable enantioselectivity (entry 3, 86% yield with 83% ee) were obtained.

We then explored the application of the Rh(II)-catalyzed [3 + 2] cycloaddition reaction to the synthesis of some synthetically useful intermediates. Compound **3e** was selected as the substrate and was first reacted with $Rh_2(OAc)_4$ under the optimized tandem reaction conditions. The resultant imine **3e′** was then treated with BnMgCl to afford the corresponding products **5a** and **5b** in 64% and 20% yield, respectively (eq 1 in Scheme 4).

We next investigated the transformation of the imine to the corresponding alcohol. To this end, substrate **3c** was treated

Scheme 4. Synthetic Transformations of the Imine Intermediates



with $Rh_2(OAc)_4$ under the optimized reaction conditions, and the resultant imine **3c′** was hydrolyzed with a solution of NaOH (10% in H_2O) and then reduced with $NaBH_4$ in EtOH to give product **6** in 69% overall yield (eq 2 in Scheme 4).

We also examined the treatment of the imine intermediate with an aqueous solution of HCl. Substrate **3a** was treated with $Rh_2(OAc)_4$ under the optimized reaction conditions, and the resultant imine **3a′** was hydrolyzed with HCl (4 N) at room temperature for 50 h to afford naphthalene-based aldehyde **7** in 81% overall yield (eq 3 in Scheme 4). The formation of **7** can be attributed to a cascade transformation including imine hydrolysis, nucleophilic oxygen-bridge opening, and elimination of water.

In summary, we have developed a tandem reaction that features a Rh(II)-catalyzed denitrogenation of *N*-sulfonyl-1,2,3-triazole and a [3 + 2] cycloaddition for the synthesis of structurally diverse of oxabicyclo[2.2.1]heptenes. In this reaction, two new carbon−carbon bonds, one carbon−oxygen bond, and two oxygenated quaternary centers are formed in a single step with excellent diastereoselectivity. Two types of polycyclic ring system have been constructed using this tandem reaction either through an intra- or an intermolecular process, both of which may find useful applications in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02703.

X-ray crystallographic data for **2a** (CIF)
X-ray crystallographic data for **2p** (CIF)
X-ray crystallographic data for **4a** (CIF)
Detailed experimental procedures, spectroscopic data, and characterization of products (PDF)

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Notes

The authors declare no competing financial interest.

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