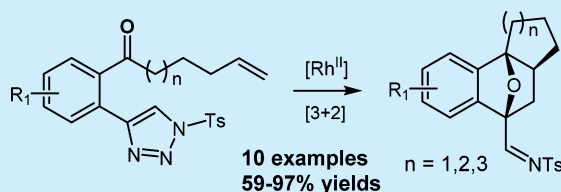


Stereoselective Synthesis of Oxabicyclo[2.2.1]heptenes via a Tandem Dirhodium(II)-Catalyzed Triazole Denitrogenation and [3 + 2] Cycloaddition

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S 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 metalcarbene followed by an inter- or intramolecular [3 + 2] dipolar cycloaddition with a range of alkynes and alkenes.



[3 + 2] cycloaddition reactions¹ 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 metalcarbene species³ 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 water⁷ to intermediate B results in the formation of dihydroisobenzofurans (C) and indanones (D), respectively. The indanones⁸ 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}

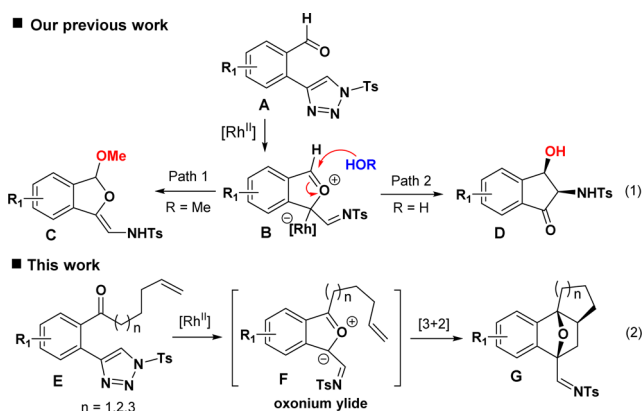


Figure 1. Rhodium(II)-catalyzed C–C bond-forming reactions of triazoles for the syntheses of dihydroisobenzofurans (C), indanones (D), and oxabicyclo[2.2.1]heptenes (G).

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 Rh₂(OAc)₄¹⁵ 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 $\text{NaBH}(\text{OAc})_3$. 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

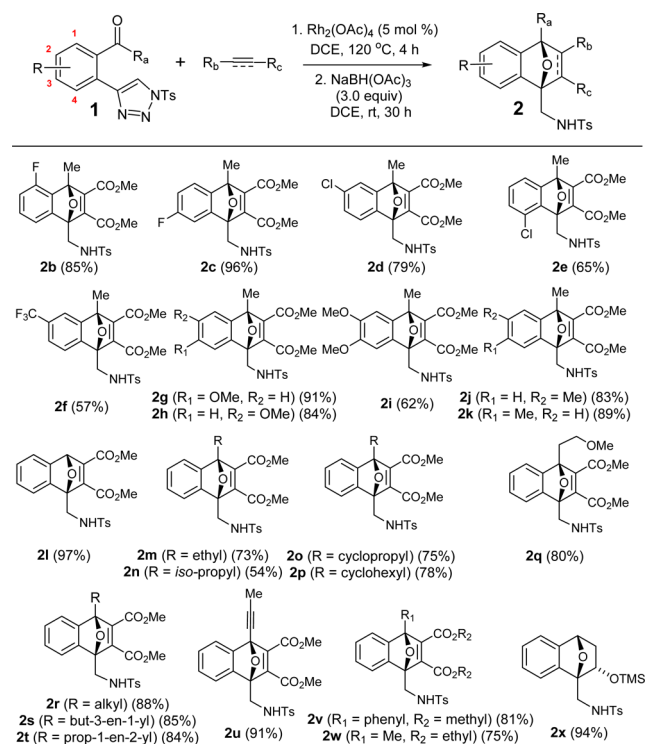
entry	catalyst	catalyst loading (mol %)	temp (°C)	solvent	time (h)	yield ^b (%)
1	$\text{Rh}_2(\text{OAc})_4$	5	reflux	DCE	8	74
2 ^c	$\text{Rh}_2(\text{OAc})_4$	5	120	DCE	4	95
3	$\text{Rh}_2(\text{OAc})_4$	5	reflux	DCE	8	74
4 ^c	$\text{Rh}_2(\text{OAc})_4$	5	120	DCE	4	81
5	$\text{Rh}_2(\text{OAc})_4$	5	reflux	toluene	8	63
6 ^c	$\text{Rh}_2(\text{OAc})_4$	5	120	toluene	4	74
7	$\text{Rh}_2(\text{OAc})_4$	1	120	DCE	4	78
8	$\text{Rh}_2(\text{OAc})_4$	2	120	DCE	4	83

^aReaction 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). ^bIsolated yield. ^cThe 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 $\text{Rh}_2(\text{OAc})_4$ 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 $\text{Rh}_2(\text{OAc})_4$ 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 $\text{Rh}_2(\text{OAc})_4$ 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}



^aReaction 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 sealed tube for 4 h. The crude product was treated with $\text{NaBH}(\text{OAc})_3$ at rt for 30 h. ^bYield of isolated product.

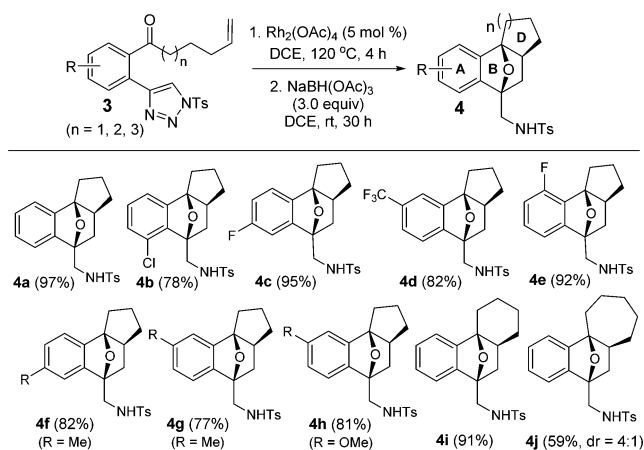
types of compounds can also be prepared via the reaction of substituted benzyne with substituted furans¹⁶ or through Diels–Alder reactions with α -thiocarbocations as dienes.¹⁷

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 $\text{Rh}(\text{II})$ -catalyzed [3 + 2] cycloaddition for the formation of oxabicyclo[2.2.1]heptene-based polycyclic compounds, we then explored an asymmetric synthesis.

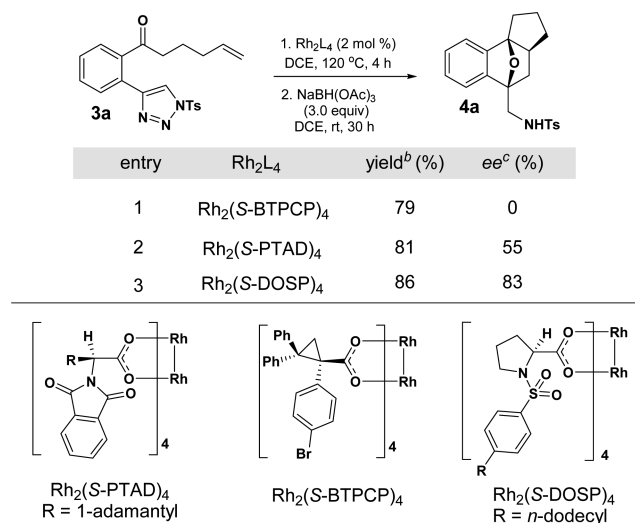
We profiled several commercially available catalysts (Scheme 3). The $\text{Rh}_2(\text{S-BTPCP})_4$ catalyst¹⁸ gave no asymmetric induction (entry 1), while $\text{Rh}_2(\text{S-PTAD})_4$ ¹⁹ could afford a moderate enantioselectivity (entry 2, 81% yield with 55% ee). This observation could be due to the more steric hindrance of adamantanyl group in $\text{Rh}_2(\text{S-PTAD})_4$ than that of the

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



^aReaction 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 sealed 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. ^bYield of isolated product.

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



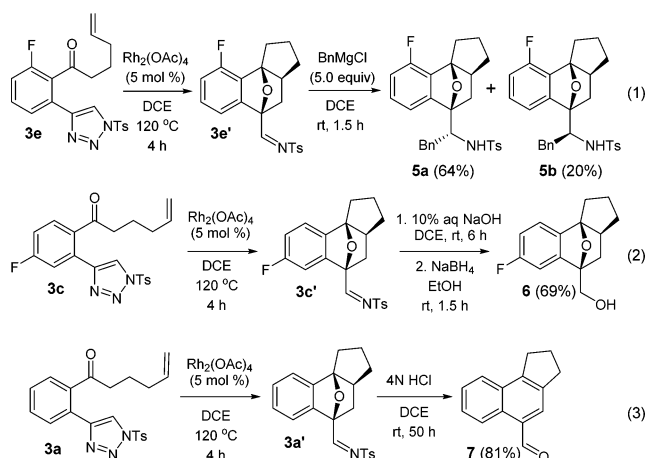
^aReaction conditions: 3a (0.2 mmol, 1.0 equiv), catalyst (0.004 mmol, 2 mol %), solvent (0.05 M for substrate), heating at 120 °C in a sealed tube for 4 h. The crude product was treated with NaBH(OAc)₃ at rt for 30 h. ^bYield of isolated product. ^cDetermined by chiral HPL analysis.

diphenylcyclopropyl group in Rh₂(S-BTPCP)₄. On the other hand, when Rh₂(S-DOSP)₄ 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 Rh₂(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 Rh₂(OAc)₄ under the optimized reaction conditions, and the resultant imine 3c' was hydrolyzed with a solution of NaOH (10% in H₂O) and then reduced with NaBH₄ 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 Rh₂(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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