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# Rhodium(II)-catalyzed divergent intramolecular tandem cyclization of *N*- or *O*-tethered cyclohexa-2,5-dienones with 1-sulfonyl-1,2,3-triazole: synthesis of cyclopropa[cd]indole and benzofuran derivatives†

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A rhodium(II)-catalyzed divergent intramolecular tandem cyclization of *N*- or *O*-tethered cyclohexa-2,5-dienones with 1-sulfonyl-1,2,3-triazole has been disclosed in this paper. When the connecting atom between the cyclohexa-2,5-dienone unit and the 1-sulfonyl-1,2,3-triazole moiety was a *N*-sulfonated group, a cyclopropanation of the olefinic unit in the cyclohexa-2,5-dienone moiety could take place, affording cyclopropa[cd]indole derivatives in moderate to good yields. This is the first example of the cyclopropanation of  $\alpha$ -imino rhodium carbenes with electron-deficient intra-annular olefins. If the connecting linker was an oxygen atom, an oxy-Cope rearrangement could be triggered under similar reaction conditions, giving benzofuran derivatives. The reaction mechanisms have also been proposed along with a synthetic transformation.

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## Introduction

1-Sulfonyl-1,2,3-triazoles, easily prepared through copper(I)-catalyzed azide-alkyne cycloadditions (CuAAC),<sup>1</sup> have recently received much attention from synthetic organic chemists. Owing to the elegant work of Fokin, Gevorgyan, Davies, Murakami, Sarpong, our group<sup>2</sup> and others,<sup>3</sup> it has been well known that  $\alpha$ -imino rhodium carbenes generated from readily available 1-sulfonyl-1,2,3-triazoles could be easily utilized for a variety of novel carbene-induced transformations. For example, transannulations of 1-sulfonyl-1,2,3-triazoles with a variety of organic compounds containing unsaturated functional groups such as nitriles, alkynes, allenes, isocyanates, furans, aldehydes, and imines could provide a series of useful

heterocyclic compounds upon Rh(II) catalysis, which are privileged structural motifs in many biologically active and medicinally valuable molecules.<sup>4</sup> Besides,  $\alpha$ -imino rhodium carbenes could also undergo C–H, O–H or N–H insertion,<sup>5</sup> and arylation with boronic acids<sup>6</sup> or could be trapped by a heteroatom, such as sulfur, nitrogen, bromine or oxygen to realize further transformations.<sup>7</sup> The cyclopropanation of metal carbene complexes with olefins has been extensively researched in recent years.<sup>8</sup> More importantly, in 2009, Fokin and co-workers reported that  $\alpha$ -imino rhodium carbenes could undergo cyclopropanation with linear alkenes to afford cyclopropanecarbaldehydes in good yields (Scheme 1).<sup>9</sup> Furthermore, in recent years, Lee, Anbarasan, Li and co-workers successively disclosed that the reactions of  $\alpha$ -imino rhodium carbenes with electron-rich olefins could generate  $\alpha$ -imino cyclopropyl intermediates, which subsequently furnished dihydropyrroles through a Cloke–Wilson rearrangement (Scheme 1).<sup>10</sup> Inspired by these brilliant studies, we attempted to investigate the intramolecular tandem cyclization of intra-annular olefins with  $\alpha$ -imino rhodium carbenes to rapidly generate polycyclic or spirocyclic frameworks. Recently, we reported a Rh(II)-catalyzed intramolecular transannulation of 4-methoxycyclohexa-2,5-dienone tethered 1-sulfonyl-1,2,3-triazoles for the facile synthesis of azaspiro[5.5]undecane derivatives.<sup>11</sup> This interesting tandem cyclization reaction proceeded through an oxonium ylide generated from trapping a rhodium(II)-carbene by a methoxy group, a methoxy group migration, and C–N bond for-

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**Scheme 1** Previous work and our working hypothesis.

mation, providing a novel synthetic strategy for the construction of spirocyclic frameworks. We envisioned that *N*-tethered cyclohexa-2,5-dienones with 1-sulfonyl-1,2,3-triazole might yield an  $\alpha$ -imino rhodium carbene in the presence of rhodium(II) catalysts, which could undergo an intramolecular cyclopropanation with an electron-deficient intra-annular olefin in the cyclohexa-2,5-dienone moiety to deliver cyclopropa[*cd*]indole derivatives (Scheme 1). Herein, we wish to report our findings on this novel protocol to construct these *N*-heterocyclic compounds that may have potential applications in many biologically active and medicinally valuable molecules. Moreover, Rh(II)-catalyzed *O*-tethered cyclohexa-2,5-dienones with 1-sulfonyl-1,2,3-triazole to give benzofuran derivatives will also be disclosed (Scheme 1).

## Results and discussion

### Experimental investigations

Our studies were initiated by examining the reactivity of NBs (4-bromobenzene sulfonamide)-tethered cyclohexa-2,5-dienone with 1-sulfonyl-1,2,3-triazole **1a** in the presence of a variety of rhodium(II) catalysts, and the results are shown in Table 1. It was found that the desired cyclopropanation product **2a** could be obtained in 95% yield when **1a** was treated with 5 mol% Rh<sub>2</sub>(OAc)<sub>4</sub> in dry 1,2-DCE (1,2-dichloroethane) at 80 °C (Table 1, entry 1). The structure of **2a** has been unequivocally assigned by X-ray diffraction. The ORTEP drawing is shown in Table 1 and the CIF data are presented in the ESI.<sup>†</sup><sup>12</sup> By changing the Rh(II) catalyst to Rh<sub>2</sub>(Oct)<sub>4</sub> and Rh<sub>2</sub>(Piv)<sub>4</sub>, **2a** could be obtained in 94% yield, respectively (Table 1, entries 2 and 4). Using Rh<sub>2</sub>(esp)<sub>2</sub> as the catalyst gave **2a** in 56% yield, but the use of Rh<sub>2</sub>(tfa)<sub>4</sub> as the catalyst only afforded **2a** in lower yield (9%) (Table 1, entries 3 and 5). When the reaction was carried out in the absence of a rhodium catalyst, no reaction occurred and the starting material was recovered, indicating that a rhodium catalyst was essential in this reaction (Table 1, entry 6). The examination of solvent effects revealed that when the reaction was conducted in DCM (dichloromethane) or toluene, **2a** could be given in 94% and 87% yields, respectively (Table 1, entries 7 and 8). Using THF (tetrahydrofuran) and CH<sub>3</sub>CN (acetonitrile) as the solvents provided **2a** in 59% and 20% yields under otherwise identical conditions (Table 1, entries 9 and 10). Thus, Rh<sub>2</sub>(OAc)<sub>4</sub> was the best catalyst and DCE was the solvent of choice for this transformation to give **2a** in higher yield.

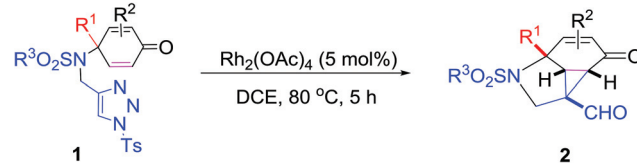
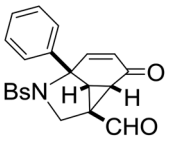
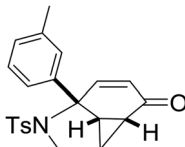
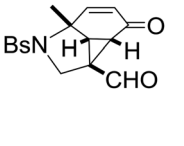
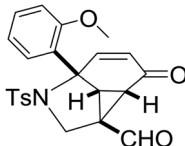
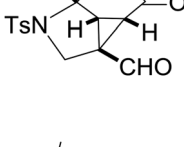
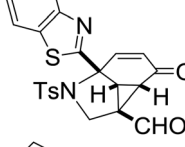
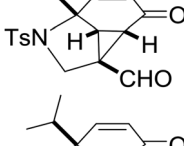
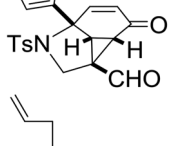
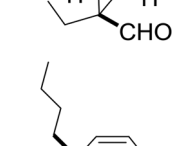
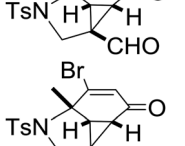
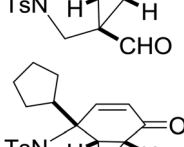
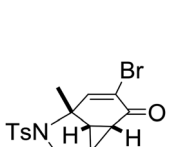
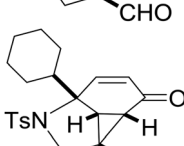
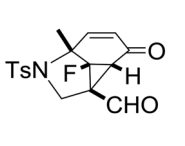
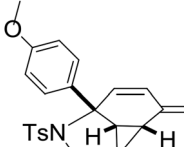
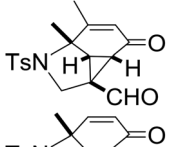
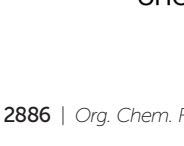
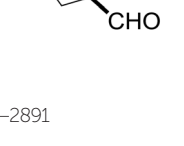
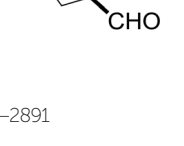
With the optimized reaction conditions in hand, we next examined the substrate scope of this reaction, and the results are summarized in Table 2. With NBs as the linker and the R<sup>1</sup> group being a methyl group, the desired product **2b** was

**Table 1** Optimization of the reaction conditions of rhodium(II)-catalyzed intramolecular tandem cyclization of **1a**<sup>a,b,c,d</sup>

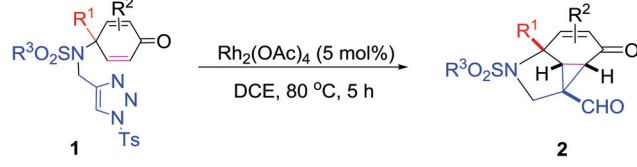
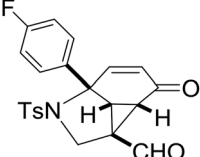
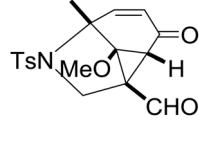
Entry <sup>a</sup>	Catalyst	Solvent	Additive	Temp. (°C)	Time (h)	Yield <sup>b</sup> (%)
1	Rh <sub>2</sub> (OAc) <sub>4</sub>	DCE	—	80	5	95
2	Rh <sub>2</sub> (Oct) <sub>4</sub>	DCE	—	80	5	94
3	Rh <sub>2</sub> (tfa) <sub>4</sub>	DCE	—	80	5	9 <sup>c</sup>
4	Rh <sub>2</sub> (Piv) <sub>4</sub>	DCE	—	80	5	94
5	Rh <sub>2</sub> (esp) <sub>2</sub>	DCE	—	80	5	56 <sup>c</sup>
6	—	DCE	—	80	5	— <sup>d</sup>
7	Rh <sub>2</sub> (OAc) <sub>4</sub>	DCM	—	80	5	94
8	Rh <sub>2</sub> (OAc) <sub>4</sub>	Toluene	—	80	5	87
9	Rh <sub>2</sub> (OAc) <sub>4</sub>	THF	—	80	5	59
10	Rh <sub>2</sub> (OAc) <sub>4</sub>	CH <sub>3</sub> CN	—	80	5	20 <sup>c</sup>

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), cat. (0.025 mmol), solvent (3 mL). <sup>b</sup> Yields of the isolated product. <sup>c</sup> NMR yield using 1,3,5-trimethoxybenzene as an internal standard. <sup>d</sup> No reaction and the starting material was recovered. Oct = octanoate, tfa = trifluoroacetic acid, Piv = pivalate, esp = a,a,a',a'-tetramethyl-1,3-benzenedipropionic acid.

**Table 2** Substrate scope of rhodium(ii)-catalyzed intramolecular tandem cyclization of **1**<sup>a,b</sup>

			
Product	No./yield (%)	Product	No./yield (%)
	<b>2a</b> , 95		<b>2k</b> , 94
	<b>2b</b> , 99		<b>2l</b> , —
	<b>2c</b> , 98		<b>2m</b> , 56
	<b>2d</b> , 86		<b>2n</b> , 75
	<b>2e</b> , 93		<b>2o</b> , 85
	<b>2f</b> , 85		<b>2p</b> , 55
	<b>2g</b> , 87		<b>2q</b> , 63
	<b>2h</b> , 86		<b>2r</b> , 67
	<b>2i</b> , 92		<b>2sa</b> , 36
			<b>2sb</b> , 34

**Table 2** (Contd.)

			
Product	No./yield (%)	Product	No./yield (%)
	<b>2j</b> , 98		<b>2t</b> , 54

<sup>a</sup> Reaction conditions: **1** (1.0 mmol), [Rh<sub>2</sub>(OAc)<sub>4</sub>] (0.05 mmol), DCE (5.0 mL). <sup>b</sup> Yields are those of the isolated products.

obtained in 99% yield. Then, we changed the linker to NTs-(4-toluene sulfonamide), a variety of R<sup>1</sup> groups have been investigated and the results are outlined in Table 2. In the cases of substrates **1c–1f**, in which R<sup>1</sup> was a methyl, ethyl, <sup>i</sup>Pr or <sup>n</sup>butyl group, the reactions proceeded efficiently to give the desired products **2c–2f** in 85–98% yields. Substrates **1g** and **1h** bearing a cyclopentyl group and a cyclohexyl group also gave the corresponding products **2g** and **2h** in 87% and 86% yields, respectively. These results suggested that a variety of aliphatic groups could be tolerated in this transformation without steric or electronic influence. Substrates **1i–1j**, in which R<sup>1</sup> was an aromatic group, were also prepared and used for this transformation. When a methoxyl group, a fluorine atom, or a methyl group was introduced at the 4- or 3-position of the benzene ring, the reactions still proceeded smoothly to afford the desired products **2i–2k** in 92–98% yields. Unfortunately, when a MeO group was introduced at the 2-position of the benzene ring, the desired product **2l** was not obtained and a complex mixture was formed, presumably due to which the increased steric bulkiness impaired the cyclopropanation process or the rhodium carbene could be captured by the adjacent MeO group to change the reaction pathway.<sup>13</sup> In addition, the heteroaromatic group was also compatible in this reaction. When R<sup>1</sup> was a benzothiazolyl or a furyl group, the desired products **2m** and **2n** could be afforded in 56% and 75% yields, respectively. Substrate **1o** containing a functionalized alkenyl group such as a 3-butenyl group was also suitable in this reaction, furnishing **2o** in 85% yield. To further evaluate the generality of this method, some substituents were introduced in the cyclohexa-2,5-dienone skeleton. When the α- or β-position of the carbonyl group was occupied by a bromine atom, the corresponding products **2p** and **2q** were produced in 55% and 63% yields, in which cyclopropanation exclusively took place at the non-substituted olefinic unit of cyclohexa-2,5-dienone. We assumed that the steric bulkiness of the bromine atom was a possible reason for this observation. Another reasonable

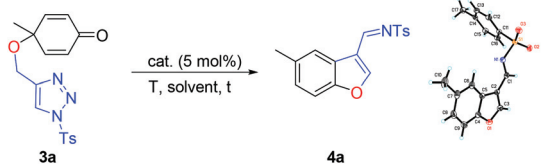
explanation was that the bromine atom could coordinate with the rhodium metal center, leading to the proposition that the non-substituted double bond could be closer to the carbon atom of the rhodium carbene center. As for substrates **1r** and **1t** bearing a fluorine atom or a methoxyl group at the  $\beta$ -position of the carbonyl group, cyclopropanation exclusively occurred at the substituted olefinic unit, giving the corresponding products **2r** and **2t** in 67% and 54% yields, respectively. In these cases, the steric influence did not have an impact on the proceeding reaction, but the electronic properties of the double bond may play a leading role. When an electron-neutral group such as a methyl group was introduced at the  $\beta$ -position of the carbonyl group, this cyclopropanation could occur on each side of the olefinic unit, affording the corresponding products **2sa** and **2sb** in 36% and 34% yields, respectively.

To further expand the substrate scope of this reaction, *O*-tethered cyclohexa-2,5-dienones with 1-sulfonyl-1,2,3-triazole **3a** were synthesized and utilized to process the reaction under similar conditions. An unexpected benzofuran derivative **4a** was isolated as a sole product in 48% yield upon treating **3a** with  $\text{Rh}_2(\text{OAc})_4$  in DCE at 70 °C for 5 h (Table 3, entry 1). The structure of **4a** has been unambiguously assigned by X-ray diffraction. The ORTEP drawing is shown in Table 3 and the CIF data are presented in the ESI.<sup>†</sup><sup>14</sup> Since benzofurans are important heterocyclic compounds occurring in a variety of natural products and synthetic pharmaceuticals, developing new methods for the preparation of these scaffolds is meaningful.<sup>15</sup> Next we optimized the cascade cyclization reaction conditions using a variety of rhodium(II) catalysts in various

solvents as well as examining the reaction temperatures (Table 3). Carrying out the reaction in toluene, THF,  $\text{CH}_3\text{CN}$  and DCM revealed that DCM was the best solvent in this transformation, affording **4a** in 75% yield and the desired product **4a** was not formed in THF (Table 3, entries 2–5). Next, we investigated rhodium(II) catalysts in DCM at 70 °C and identified that  $\text{Rh}_2(\text{Oct})_4$  gave a better result, affording **4a** in 86% yield (Table 3, entries 6–9). A quick solvent screening utilizing  $\text{Rh}_2(\text{Oct})_4$  as the catalyst demonstrated that DCM was still the solvent of choice (Table 3, entries 10–13). Moreover, when the reaction was conducted at 80 °C or at 90 °C in DCM in a sealed tube, **4a** was obtained in 89% or 83% yield, respectively (Table 3, entries 14 and 15). In the absence of the rhodium(II) catalyst, none of the desired products was obtained and the substrate **3a** was fully recovered (Table 3, entry 16).

Having the optimized reaction conditions in hand, we next investigated the generality of this reaction and the results are shown in Table 4. When  $\text{R}^1$  was an ethyl or isopropyl group ( $\text{R}^2 = \text{H}$ ), the corresponding products **4b** and **4c** could be obtained in 76% and 82% yields, respectively. We also investigated aromatic group substituted substrates in this reaction and found that when  $\text{R}^1$  was a phenyl group or a 3- $\text{MeC}_6\text{H}_4$  group, the corresponding products **4d** and **4e** could also be afforded in 81% or 76% yield, respectively. It is noteworthy that when  $\text{R}^1$  was a 2- $\text{MeC}_6\text{H}_4$  group (substrate **3f**), product **5f** could be obtained in only 11% yield as an imine-hydrolyzed product in the purification process. In this case, another cyclopropanation product **6f** was also isolated in 72% yield as the major product (Scheme 2). It was probably due to the fact that the steric bulkiness of substrate **3f** affected the 1,2-H shift and

**Table 3** Optimization of the reaction conditions of the rhodium(II)-catalyzed tandem intramolecular rearrangement of **3a**<sup>a,b,c</sup>

						
Entry <sup>a</sup>	Catalyst	Solvent	Additive	Temp (°C)	Time (h)	Yield <sup>b</sup> (%)
1	$\text{Rh}_2(\text{OAc})_4$	DCE	—	70	5	48
2	$\text{Rh}_2(\text{OAc})_4$	Toluene	—	70	5	36
3	$\text{Rh}_2(\text{OAc})_4$	THF	—	70	5	N.D
4	$\text{Rh}_2(\text{OAc})_4$	$\text{CH}_3\text{CN}$	—	70	5	21
5	$\text{Rh}_2(\text{OAc})_4$	DCM	—	70	5	75
6	$\text{Rh}_2(\text{Piv})_4$	DCM	—	70	5	67
7	$\text{Rh}_2(\text{tfa})_4$	DCM	—	70	5	13
8	$\text{Rh}_2(\text{Oct})_4$	DCM	—	70	5	86
9	$\text{Rh}_2(\text{esp})_2$	DCM	—	70	5	34
10	$\text{Rh}_2(\text{Oct})_4$	DCE	—	70	5	58
11	$\text{Rh}_2(\text{Oct})_4$	Toluene	—	70	5	46
12	$\text{Rh}_2(\text{Oct})_4$	THF	—	70	5	N.D
13	$\text{Rh}_2(\text{Oct})_4$	$\text{CH}_3\text{CN}$	—	70	5	24
14	$\text{Rh}_2(\text{Oct})_4$	DCM	—	80	3	89
15	$\text{Rh}_2(\text{Oct})_4$	DCM	—	90	3	83
16	—	DCM	—	90	3	— <sup>c</sup>

<sup>a</sup> Reaction conditions: **3a** (0.2 mmol) and Rh cat. (5 mol%) were stirred in 2 mL of solvent. <sup>b</sup> NMR yield using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> The starting material was recovered.

**Table 4** Substrate scope of the rhodium(II)-catalyzed tandem intramolecular rearrangement of **3**<sup>a,b</sup>

Product	No./yield (%)	Product	No./yield (%)
	<b>4b</b> , 76		<b>5f</b> , 11
	<b>4c</b> , 82		<b>4g</b> , 37
	<b>4d</b> , 81		<b>4h</b> , 86
	<b>4e</b> , 76		<b>4i</b> , 35
			<b>5i</b> , 27

<sup>a</sup> Unless otherwise stated, all reactions were carried out with **3** (0.5 mmol) and Rh<sub>2</sub>(Oct)<sub>4</sub> (0.025 mmol) in DCM (3 mL). <sup>b</sup> Yields are those of the isolated products.

**Scheme 2** Rhodium(II)-catalyzed intramolecular tandem cyclization reaction of **3f**.

intramolecular cyclopropanation became a prior process in this case (also see Scheme 3). When R<sup>1</sup> was a vinyl group, the corresponding product **4g** was obtained in 37% yield, probably due to the fact that the vinyl group influenced the oxy-Cope rearrangement. Then, we introduced two methyl groups at the two β-positions of the carbonyl group in the cyclohexa-2,5-dienone skeleton, and identified that the desired product **4h** could be obtained in 86% yield. When only one methyl group was introduced at the β-position, the products **4i** and **5i** were isolated in 35% and 27% yields, respectively. It should be noted that **5i** was also the hydrolyzed product of the imine during the purification process.

### Mechanistic proposal

**Proposed reaction pathways.** On the basis of the above results and the previously reported literature, the plausible mechanisms for these reactions are outlined in Scheme 3. Upon treatment with the rhodium(II) catalyst, the *N*-sulfonyl triazoles underwent a denitrogenation process to generate the corresponding α-imino rhodium carbene **A**. If the connector was a *N*-sulfonyl moiety, the rhodium carbene **A** underwent cyclopropanation to afford cyclopropa[*cd*]indole intermediate **B**, which could be hydrolyzed to give **2a** in the purification process. In fact, the formation of the by-product TsNH<sub>2</sub> could be actually identified during the purification process. On the other hand, when the connector was an oxygen atom, the corresponding α-imino rhodium carbene **A** could proceed through a release of the rhodium catalyst and a 1,2-H shift to give the intermediate **C**, which underwent an oxy-Cope rearrangement to deliver the intermediate **D**. After an isomerization, the subsequent intramolecular nucleophilic attack of the enolate to the carbonyl group generated intermediate **F**, which could afford the benzofuran product **4a** through the elimination of a H<sub>2</sub>O.

Further synthetic transformation of the polycyclic cyclopropa[*cd*]indole product **2k** was also conducted. Subjecting **2k** into DIBAL-H in THF at 0 °C afforded the corresponding reduction product **7k** in 64% yield. While treating **2k** with CeCl<sub>3</sub>·7H<sub>2</sub>O and NaBH<sub>4</sub> in MeOH, both the aldehyde unit and the α,β-unsaturated ketone moiety could be reduced to afford the corresponding products **8ka** and **8kb** in 42% and 46% yields, respectively (Scheme 4).

**Scheme 3** Proposed reaction mechanisms.**Scheme 4** Synthetic transformation.



## Conclusions

In conclusion, we have developed an unprecedented and highly efficient rhodium(II)-catalyzed divergent intramolecular tandem cyclization of *N*- or *O*-tethered cyclohexa-2,5-dienones with 1-sulfonyl-1,2,3-triazole bearing a variety of functional groups. This synthetic strategy provided a powerful and rapid access to polycyclic cyclopropa[*cd*]indole and benzofuran skeletons *via*  $\alpha$ -imino rhodium carbene and subsequently enriched the chemistry of 1-sulfonyl-1,2,3-triazoles. The substrate scope of this rhodium(II)-catalyzed intramolecular tandem cyclization is broad and diversified. The connecting atom (a linker such as the N or O atom) between the cyclohexa-2,5-dienone unit and the 1-sulfonyl-1,2,3-triazole moiety can significantly change the reaction pathway. These reaction mechanisms have also been proposed on the basis of the reaction outcomes and the previously reported literature. It should be emphasized here that we first disclosed in this paper that the cyclopropanation of  $\alpha$ -imino rhodium carbene derived from 1-sulfonyl-1,2,3-triazole with an electron-deficient intra-annular olefin could take place smoothly. Some useful synthetic transformations were also conducted to set up a stage for further synthetic applications. The utilization of this strategy for the synthesis of heterocycles existing in natural products or pharmaceutical molecules is currently under investigation.

## Experimental section

### General procedure for the synthesis of product 2

Under an argon atmosphere,  $\text{Rh}_2(\text{OAc})_4$  (0.05 mmol, 0.05 equiv.), dry 1,2-dichloroethane (5.0 mL), and substrate **1** (1.0 mmol, 1.0 equiv.) were added to a Schlenk tube. The reaction mixture was stirred for about 5 h at 80 °C until **1** was completely consumed by TLC monitoring. Then the solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc, 4/1–2/1) to give the product **2**.

**Compound 2a.** A white solid, 95% yield (435 mg). M.p.: 170–172 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  2.68 (d,  $J$  = 8.0 Hz, 1H), 2.91 (d,  $J$  = 8.0 Hz, 1H), 3.37 (d,  $J$  = 11.2 Hz, 1H), 4.49 (d,  $J$  = 11.2 Hz, 1H), 6.42 (d,  $J$  = 10.4 Hz, 1H), 7.39–7.51 (m, 8H), 7.61 (d,  $J$  = 8.4 Hz, 2H), 8.88 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  35.3, 44.8, 45.0, 46.8, 67.2, 125.6, 128.4, 128.6, 128.8, 128.9, 129.6, 132.2, 137.9, 139.9, 144.7, 188.8, 192.9. IR (neat)  $\nu$  3066, 2925, 1713, 1676, 1574, 1471, 1389, 1341, 1159, 1089, 1068, 1006, 964, 741, 700  $\text{cm}^{-1}$ . HRMS (ESI) Calcd for  $[\text{C}_{21}\text{H}_{16}\text{BrNO}_4\text{S} + \text{H}]$  requires 458.0056, found 458.0058  $[\text{M}^+ + \text{H}]$ .

## Conflicts of interest

There are no conflicts of interest to declare.

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