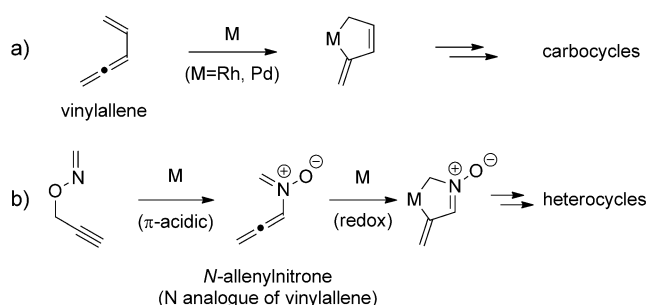


Synthesis of Azepine Derivatives by Rhodium-Catalyzed Tandem 2,3-Rearrangement/Heterocyclization**

Itaru Nakamura,* Masashi Okamoto, Yoshinori Sato, and Masahiro Terada

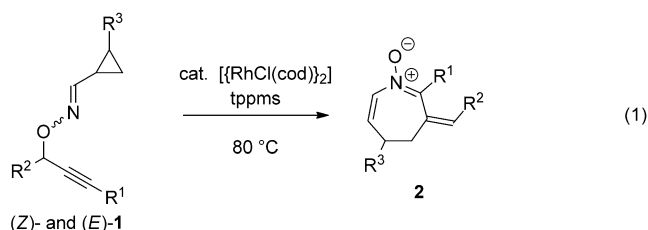
Catalytic carbocyclization through metallacyclic intermediates has served as one of the most powerful tools in the construction of highly elaborate cyclic compounds in organic synthesis.^[1] In particular, vinylallenes have been extensively utilized as the four-carbon unit in this method (Scheme 1 a).^[2]



Scheme 1. Cyclizations through metallacycle intermediates. a) From a vinylallene and b) from an *N*-allenyl nitrone intermediate (this work).

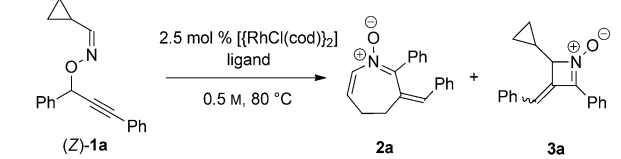
To the best of our knowledge, however, syntheses of heterocycles using *N*-allenylimine derivatives through the formation of aza-metallacycles have yet to be investigated, presumably because of the inherent instability of *N*-allenylimines.^[3–5] Recently, we demonstrated that *N*-allenyl nitrone species can be transiently generated during the metal-catalyzed 2,3-rearrangement of *O*-propargylic oximes.^[6] This may allow for tandem 2,3-rearrangement and aza-metallacyclization reactions in the construction of heterocyclic skeletons, as shown in Scheme 1 b. The use of rhodium complexes, which serve a dual role as both π -acidic and redox catalysts, is especially promising according to the recent reports by Tang et al.^[2g–i,7] Herein, we report on the reactions of *O*-propargylic cyclopropylcarbaldoximes **1** in the presence of rhodium catalysts,

which result in the corresponding azepine oxide derivatives **2** in good to high yields through a tandem 2,3-rearrangement/heterocyclization [Eq. (1)].^[8,9]



Initially, the reaction conditions were investigated using substrate (*Z*)-**1a**, as summarized in Table 1. Although the reaction involving $[\text{RhCl}(\text{cod})_2]$ and triphenylphosphine afforded **2a** in an excellent yield (entry 1), the product could not be separated from triphenylphosphine oxide that was formed during the work-up process.^[10–12] Consequently, we examined the use of polymer-bound and water-soluble

Table 1: Optimization of the reaction with (*Z*)-**1a**.^[a]



	Ligand (mol %) ^[b]	Solvent	<i>t</i> [h]	Yield of 2a [%] ^[c]	Yield of 3a [%] ^[c]
1	PPh ₃ (10)	toluene ^[d]	16	96	3
2	PPh ₃ ^[e] (15)	THF ^[d]	24	36	50
3	tppts (18)	DMF	16	59	18
4	tppms (18)	DMF	24	67	5
5	tppms (18)	DMF ^[f]	24	81	3
6	tppms (12)	DMF ^[f]	24	77	4
7	tppms (6)	DMF ^[f]	4	39	51
8	tppms (18)	DMSO ^[f]	24	76	10
9	tppms (18)	DMA ^[f]	8	60	23
10	tppms (18)	1,4-dioxane ^[f]	12	85	8
11	tppms (18)	1,4-dioxane	12	85	3
12	tppms (18)	1,4-dioxane ^[d]	16	(92)	5

[a] Reactions with (*Z*)-**1a** (0.4 mmol) were carried out at 80 °C in the presence of $[\text{RhCl}(\text{cod})_2]$ (2.5 mol %) and ligand in solvent (0.5 M). [b] Loading of phosphine ligand (mol %) shown in parentheses. [c] The yield was determined by ¹H NMR spectroscopy using 1,2-dichloroethane as an internal standard; yield of isolated product shown in parentheses. [d] 0.2 M. [e] Polymer-bound triphenylphosphine was used. [f] 4 Å molecular sieves (100 mg) were used. cod = 1,5-cyclooctadiene, DMA = dimethylacetamide, DMF = dimethylformamide, tppms = sodium diphenylphosphinobenzene-3-sulfonate, tppts = tris(3-sulfonatophenyl)phosphine.

[*] Prof. Dr. I. Nakamura, Prof. Dr. M. Terada
Research and Analytical Center for Giant Molecules
Graduate School of Science, Tohoku University
Sendai, 980-8578 (Japan)
E-mail: itaru-n@m.tohoku.ac.jp
Homepage: <http://www.orgreact.sakura.ne.jp/en-index.html>
M. Okamoto, Y. Sato
Department of Chemistry, Graduate School of Science
Tohoku University (Japan)

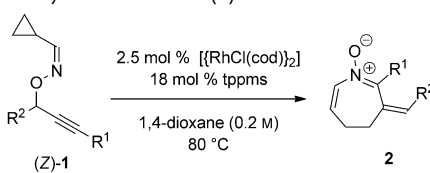
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phosphine ligands (entries 2–5), and decided on the use of tppms (sodium diphenylphosphinobenzene-3-sulfonate)^[13] for our reactions. When the loading of tppms was reduced to 6 mol %, the formation of a significant amount of **3a** was observed (entry 7). With regards to solvents, although DMF, DMSO, and DMA in the presence of 4 Å molecular sieves (MS) were effective, 1,4-dioxane gave the best result, even in the absence of 4 Å MS (entry 11). The yield was further improved by reducing the concentration (entry 12). It should be noted that, in the absence of Rh catalysts, the reaction at 80 °C afforded only a small amount of **3a** (11 %); the desired product, **2a**, was not detected.^[14]

Next, as summarized in Table 2, the reactions were carried out under the optimal reaction conditions (Table 1, entry 12) using various substrates to investigate the scope of (Z)-**1**.

Table 2: Rh-catalyzed reactions of (Z)-**1**.^[a]

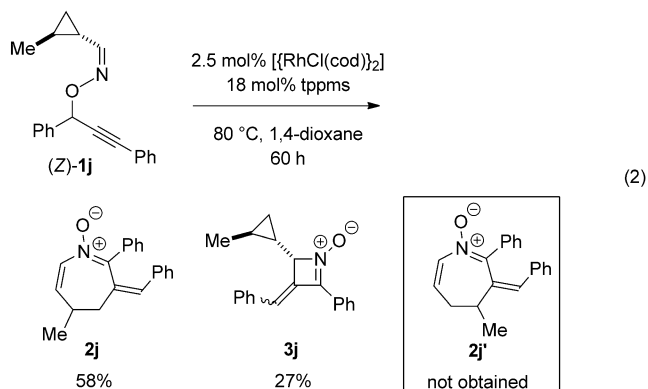
						
1	R ¹	R ²	t [h]	2	Yield [%] ^[b]	
1	1b	<i>p</i> -ClC ₆ H ₄	Ph	24	2b	84
2	1c	<i>p</i> -MeOC ₆ H ₄	Ph	12	2c	67 ^[c]
3	1d	<i>n</i> Pr	Ph	20	2d	36
4	1e	Cy	Ph	16	2e	67
5	1f	Ph	<i>p</i> -MeC ₆ H ₄	28	2f	79
6	1g	Ph	<i>p</i> -MeOC ₆ H ₄	36	2g	76
7	1h	Ph	<i>p</i> -F ₃ CC ₆ H ₄	12	2h	78
8	1i	Ph	<i>n</i> Pr	120	2i	45 ^[d]

[a] Reactions with (Z)-**1** (0.4 mmol) were carried out in the presence of [RhCl(cod)]₂ (2.5 mol %) and tppms (18 mol %) in 1,4-dioxane (2 mL) at 80 °C. [b] Yield of isolated product. [c] 20 % of the four-membered cyclic nitron **3c** was obtained. [d] A trace amount of the *E*-isomer of **2i** was detected using ¹H NMR spectroscopy. Cy = cyclohexyl, tppms = sodium diphenylphosphinobenzene-3-sulfonate.

Substrate (Z)-**1b**, which possesses an electron-deficient aromatic ring at the alkyne terminus, was successfully converted into product **2b** (Table 2, entry 1), whereas substrate (Z)-**1c**, which bears an electron-rich *p*-anisyl group, gave the product in a lower yield, along with a considerable amount (20 %) of the corresponding four-membered cyclic nitron **3c** as a by-product (entry 2). Substrate (Z)-**1e**, which possesses a cyclohexyl group at the alkyne terminus, was efficiently converted into the desired product, **2e**, in good yield (entry 4), whereas (Z)-**1d**, which bears an *n*-propyl group at the alkyne terminus, resulted in a low yield of **2d** owing to the instability of this product (entry 3). Substrates (Z)-**1f**, (Z)-**1g**, and (Z)-**1h**, all of which possess an aryl group at the propargyl position, were converted into products **2f**, **2g**, and **2h** (entries 5–7), respectively, in good yields, regardless of their electronic nature. In contrast, an alkyl substituent at the propargylic position (entry 8) decreased the efficiency of the reaction (longer reaction time and lower yield). It is

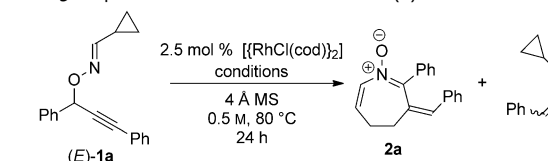
noteworthy that the reactions selectively afforded the product with a *Z* configuration at the alkylidene moiety.

Moreover, the reaction of (Z)-**1j**,^[15] which has a methyl group at the cyclopropane ring, afforded 2,3,5-trisubstituted azepine derivative **2j** in good yield, along with a considerable amount of the four-membered cyclic nitron **3j** [Eq. (2)]; the reaction did not afford the regioisomer **2j'**.^[2g,9c]



The *E* isomer of the substrate, (*E*)-**1a**, which results in the formation of the same product (**2a**), reacted under the same conditions (as the *Z* isomer) to give the product in poor yield (Table 3, entry 1). Therefore, the reaction conditions were

Table 3: Optimization of the reaction with (*E*)-**1a**.

					
tppts [mol %]	Solvent	2a [%] ^[a]	3a [%] ^[a]	1a [%] ^[a]	
1	18	1,4-dioxane ^[b]	16	8	54
2	18	DMSO	41	5	40
3	18	DMA	31	3	45
4	18	DMF	39	3	42
5	13	DMF	(73)	6	4
6	10	DMF ^[c]	40	43	0

[a] The yield was determined using ¹H NMR spectroscopy with 1,2-dichloroethane as an internal standard; yield of isolated product shown in parentheses. [b] 0.2 M, without 4 Å molecular sieves. [c] 12 h. cod = 1,5-cyclooctadiene.

reoptimized for (*E*)-**1a**, as summarized in Table 3. This time, the amount of tppms significantly affected the yield of **2a** (entries 4–6); the best result was obtained with tppms (13 mol %) in DMF in the presence of 4 Å MS (entry 5). The use of 10 mol % of tppms resulted in the unfavorable formation of the four-membered cyclic nitron **3a** (entry 6), whereas the use of 18 mol % of tppms resulted in a slow reaction (entry 4).

Substrates (*E*)-**1** were effectively converted into products **2** by carefully adjusting the amount of tppms, as summarized

Table 4: Rh-catalyzed reactions with the *E* isomer of **1**.^[a]

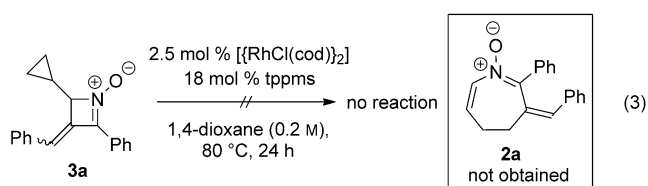
Reaction scheme showing the conversion of (*E*)-1 to 2. The starting material (*E*)-1 is a cyclopropylidene-alkyne ether. The reaction conditions are: 2.5 mol % $[(\text{RhCl}(\text{cod}))_2]$, tppms, 4 Å MS, DMF (0.5 M), 80 °C. The product 2 is a rhodium complex of a cyclopropylidene-alkyne ether, where the rhodium is coordinated to the cyclopropylidene group and the alkyne, and the alkyne is coordinated to the rhodium via its π-system.

	(<i>E</i>)-1	R ¹	R ²	tppms [mol %]	t [h]	2	Yield [%] ^[b]
1	1b	<i>p</i> -ClC ₆ H ₄	Ph	13	72	2b	62
2	1c	<i>p</i> -MeOC ₆ H ₄	Ph	17	24	2c	67 ^[c]
3	1e	Cy	Ph	15	120	2e	49 ^[d]
4	1f	Ph	<i>p</i> -MeC ₆ H ₄	16	48	2f	75 ^[e]
5	1h	Ph	<i>p</i> -F ₃ CC ₆ H ₄	9	28	2h	49
6	1i	Ph	<i>n</i> Pr	11	120	2i	20 ^[f]

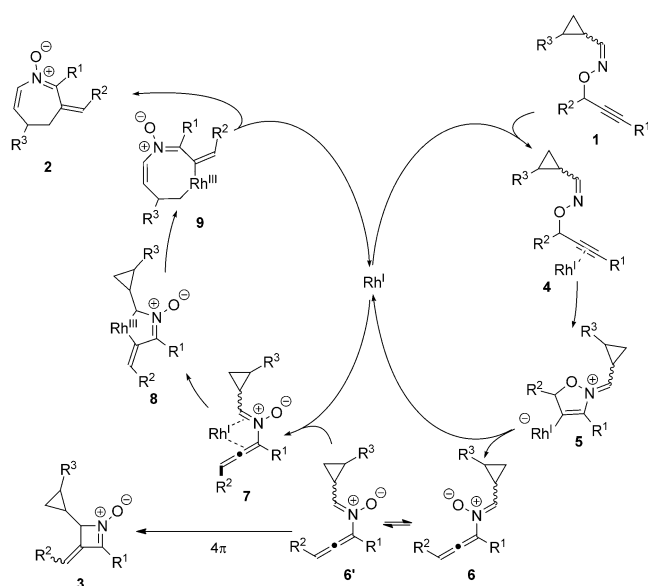
[a] Reactions with (*E*)-**1** (0.4 mmol) were carried out in the presence of [{RhCl(cod)}₂] (2.5 mol %), tppms (as indicated), and 4 Å MS (100 mg) in DMF (0.8 mL) at 80 °C. [b] Yield of isolated product. [c] **3c** was obtained in 22 % yield. [d] 6 % of **1e** was recovered. [e] **3f** was obtained in 12 % yield. [f] **3i** was obtained in 39 % yield. A trace amount of the *E* isomer of **2i** was observed in the ¹H NMR spectrum. cod = 1,5-cyclooctadiene, Cy = cyclohexyl, DMF = dimethylformamide, tppms = sodium diphenylphosphinobenzene-3-sulfonate.

in Table 4. The reactions of substrates (*E*)-**1c** and (*E*)-**1f**, which both have an electron-donating substituent, required higher amounts of tppms because of the competitive formation of four-membered cyclic nitron **3** (entries 2 and 4, respectively). In contrast, the reactions of (*E*)-**1b** and (*E*)-**1h**, which both bear an electron-deficient aromatic group, gave **2b** and **2h**, respectively, in good to moderate yields, (entries 1 and 5) because of the partial decomposition of the starting materials.

As **3a** was not converted to **2a** under the reaction conditions, the possibility of the presence of four-membered cyclic nitron **3** as a reactive intermediate, as shown in Equation (3), can be eliminated.^[8a,b]



A plausible mechanism for the reaction of **1** is shown in Scheme 2. First, the Rh catalyst coordinates to the alkyne moiety of **1** to form π -complex **4**. Nucleophilic attack by the oxime nitrogen atom at the electrophilically activated triple bond would lead to five-membered cyclic vinylrhodium intermediate **5**. Subsequent cleavage of the carbon–oxygen bond and elimination of the Rh catalyst gives *N*-allenylnitron intermediate **6**. The *s*-cis form of *N*-allenylnitron **6'** allows η^4 -coordination to the Rh catalyst from the opposite side of R², as shown in intermediate **7**. The formation of aza-rhodacycle **8** and ring expansion involving selective cleavage of the less-hindered carbon–carbon bond would lead to eight-membered aza-rhodacycle **9**. Finally, reductive elimination of



Scheme 2. Possible reaction mechanism.

the Rh catalyst produces **2**. It should be noted that the reactions of the *E* substrate were extremely sensitive to the amount of phosphine ligand present. For reactions involving 18 mol % of tppms (Table 3, entries 1–4), the high recovery of unreacted (*E*)-**1a** can be attributed to the decreased Lewis acidity of the Rh catalyst as well as competitive coordination between the substrate and tppms to the rhodium center, which would decelerate the cyclization process from **1** to **5**. In contrast, for the reaction involving 10 mol % of tppms (Table 3, entry 6), the increased formation of the four-membered cyclic nitron **3a** can be explained by the reduction of the electron-donating phosphine ligand, which would decelerate the formation of cyclic Rh-complexed intermediate **8** from intermediate **6**. Therefore, the amount of the phosphine ligand had to be adjusted for each substrate, according to its π -coordination ability, rate of metallacyclization, and rate of 4π -electrocyclization. Moreover, the mass balance for the reaction of (*E*)-**1** was lower than that of (*Z*)-**1**, which can be attributed to the decomposition of the substrate by coordination between the Rh catalyst and the oxime nitrogen atom followed by oxidative addition to the cyclopropane ring.^[4d,e] Further mechanistic studies are currently underway in our laboratory.

In conclusion, we have developed a new approach to the synthesis of seven-membered aza-heterocycles under mild reaction conditions. The present method can be employed to synthesize azepine derivatives, which are an important class of biologically active molecules, in an efficient manner.^[16,17]

Experimental Section

Standard reaction conditions: 1,4-dioxane (0.2 mL) was added to a mixture of [{RhCl(cod)}₂] (4.9 mg, 0.01 mmol) and tppms (26.2 mg, 0.072 mmol) in a vial under an argon atmosphere and then stirred at 100 °C for 1.5 h. (*Z*)-**1a** (0.4 mmol) in 1,4-dioxane (1.8 mL) was then added to this solution. The resulting mixture was stirred at 80 °C for

16 h, and then extracted using ether and water. The combined ether layers were evaporated in vacuo to afford the crude product, which was purified by flash column chromatography using hexane/ethyl acetate (5:1) and ethyl acetate/methanol (50:1) as eluents to give pure **2a** (101.1 mg, 92 %).

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