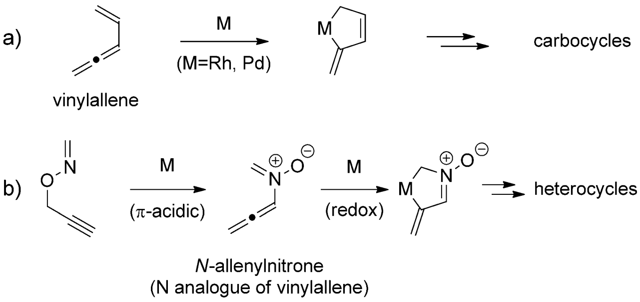
DOI: 10.1002/ange.201205285

VIP **Heterocycles**

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

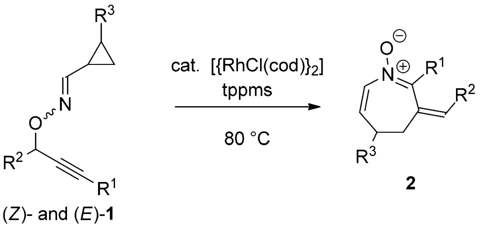
Itaru Nakamura, Masashi Okamoto, Yoshinori Sato, and Masahiro Terada*

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 1a).[2]



Scheme 1. Cyclizations through metallacycle intermediates. a) From a vinylallene and b) from an *N*-allenylnitrone 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*-allenylnitrone 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 1b. 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]



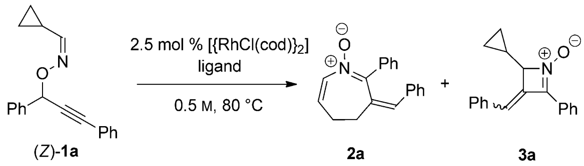
(*Z*)- and (*E*)-**1**

2

(1)

Initially, the reaction conditions were investigated using substrate (*Z*)-**1a**, as summarized in Table 1. Although the reaction involving [{RhCl(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	*t* [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 [{RhCl(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 ^{1}H 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)

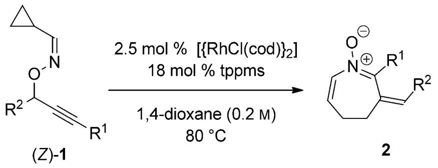
[**] This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from the Ministry of Education, Culture, Sports, Science and Technology (Japan).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201205285.

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**. 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 nitrone **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.

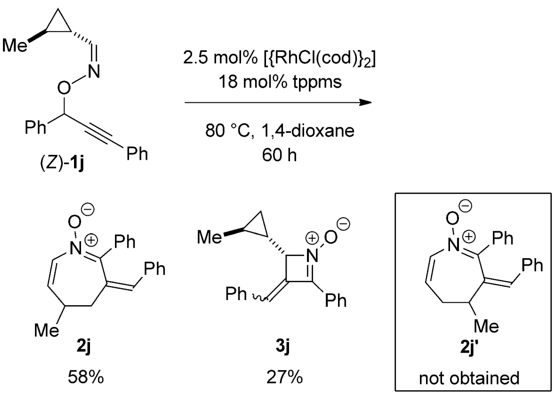
Table 2: Rh-catalyzed reactions of (*Z*)-**1**.[a]



	1	R1	R2	*t* [h]	2	Yield [%][b]
1	**1b**	*p*-ClC$_6$H$_4$	Ph	24	**2b**	84
2	**1c**	*p*-MeOC$_6$H$_4$	Ph	12	**2c**	67[c]
3	**1d**	*n*Pr	Ph	20	**2d**	36
4	**1e**	Cy	Ph	16	**2e**	67
5	**1f**	Ph	*p*-MeC$_6$H$_4$	28	**2f**	79
6	**1g**	Ph	*p*-MeOC$_6$H$_4$	36	**2g**	76
7	**1h**	Ph	*p*-F$_3$CC$_6$H$_4$	12	**2h**	78
8	**1i**	Ph	*n*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 nitrone **3c** was obtained. [d] A trace amount of the *E*-isomer of **2i** was detected using ^{1}H NMR spectroscopy. Cy = cyclohexyl, tppms = sodium diphenylphosphinobenzene-3-sulfonate.

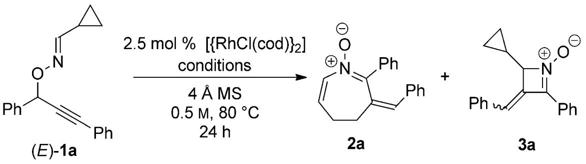
Moreover, the reaction of (*Z*)-**1j**,[15] which has a methyl group at the cyclopropane ring, afforded 2,3,5-trisubstituted azepine derivative **2j** in good yield, along with a considerable amount of the four-membered cyclic nitrone **3j** [Eq. (2)]; the reaction did not afford the regioisomer **2j′**.[2g,9e]



(2)

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 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 nitrone **3a** (entry 6), whereas the use of 18 mol% of tppms resulted in a slow reaction (entry 4).

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

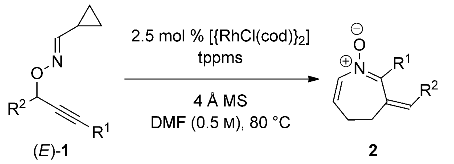


	tppms [mol%]	Solvent	**2a** [%][a]	**3a** [%][a]	**1a** [%][a]
1	18	1,4-dioxane[b]	16	8	54
2	18	DMSO	41	5	40
3	18	DMA	31	3	45
4	18	DMF	39	3	42
5	13	DMF	(73)	6	4
6	10	DMF[c]	40	43	0

[a] The yield was determined using ^{1}H 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.

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]

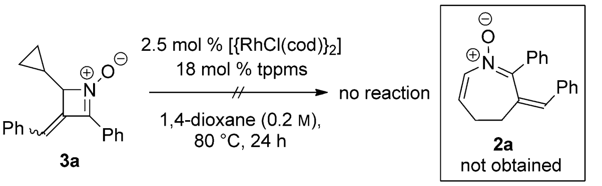


	(*E*)-**1**	R^1	R^2	tppms [mol %]	*t* [h]	**2**	Yield [%][b]
1	**1b**	*p*-ClC$_6$H$_4$	Ph	13	72	**2b**	62
2	**1c**	*p*-MeOC$_6$H$_4$	Ph	17	24	**2c**	67[c]
3	**1e**	Cy	Ph	15	120	**2e**	49[d]
4	**1f**	Ph	*p*-MeC$_6$H$_4$	16	48	**2f**	75[e]
5	**1h**	Ph	*p*-F$_3$CC$_6$H$_4$	9	28	**2h**	49
6	**1i**	Ph	*n*Pr	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 ^{1}H NMR spectrum. cod = 1,5-cyclooctadiene, Cy = cyclohexyl, DMF = dimethylformamide, tppms = sodium diphenylphosphinobenzene-3-sulfonate.

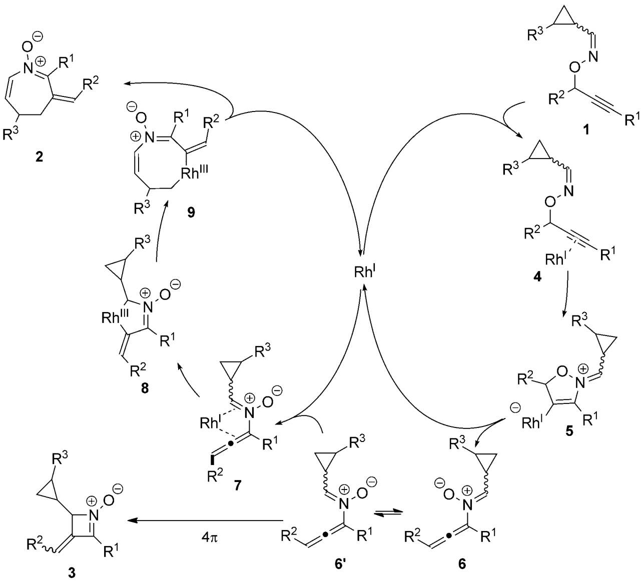
in Table 4. The reactions of substrates (*E*)-**1c** and (*E*)-**1f**, which both have an electron-donating substituent, required higher amounts of tppms because of the competitive formation of four-membered cyclic nitrone **3** (entries 2 and 4, respectively). In contrast, the reactions of (*E*)-**1b** 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 nitrone **3** as a reactive intermediate, as shown in Equation (3), can be eliminated.[8a,b]



(3)

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*-allenylnitrone intermediate **6**. The *s*-cis form of *N*-allenylnitrone **6'** allows η^4-coordination to the Rh catalyst from the opposite side of R^2, 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 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 nitrone **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.



Scheme 2. Possible reaction mechanism.

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%).

Received: July 5, 2012

Keywords: alkynes · nitrogen heterocycles · rearrangement · rhodium · ring expansion

---

[1] a) P. A. Wender, F. C. Bi, G. G. Gamber, F. Gosselin, R. D. Hubbard, M. J. C. Scanio, R. Sun, T. J. Williams, L. Zhang, *Pure Appl. Chem.* **2002**, *74*, 25–31; b) M. Fujiwara, I. Ojima in *Modern Rhodium-Catalyzed Organic Reaction* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, pp. 129–148; c) N. Jeong in *Modern Rhodium-Catalyzed Organic Reaction* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, pp. 215–239; d) J. E. Robinson in *Modern Rhodium-Catalyzed Organic Reaction* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, pp. 241–262; e) P. A. Wender, G. G. Gamber, T. J. Williams in *Modern Rhodium-Catalyzed Organic Reaction* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, pp. 263–299.

[2] a) M. Murakami, K. Itami, Y. Ito, *Angew. Chem.* **1995**, *107*, 2943–2946; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2691–2694; b) M. Murakami, M. Ubukata, K. Itami, Y. Ito, *Angew. Chem.* **1998**, *110*, 2362–2364; *Angew. Chem. Int. Ed.* **1998**, *37*, 2248–2250; c) M. Murakami, K. Itami, Y. Ito, *J. Am. Chem. Soc.* **1997**, *119*, 7163–7164; d) M. Murakami, K. Itami, Y. Ito, *Angew. Chem.* **1998**, *110*, 3616–3619; *Angew. Chem. Int. Ed.* **1998**, *37*, 3418–3420; e) M. Murakami, R. Minamida, K. Itami, M. Sawamura, Y. Ito, *Chem. Commun.* **2000**, 2293; f) P. H. Lee, K. Lee, Y. Kang, *J. Am. Chem. Soc.* **2006**, *128*, 1139; g) X. Li, M. Zhang, D. Shu, P. J. Robichaux, S. Huang, W. Tang, *Angew. Chem.* **2011**, *123*, 10605–10608; *Angew. Chem. Int. Ed.* **2011**, *50*, 10421–10424; h) X. Li, S. Huang, C. M. Schienebeck, D. Shu, W. Tang, *Org. Lett.* **2012**, *14*, 1584–1587; i) S. Huang, X. Li, C. L. Lin, I. A. Guzei, W. Tang, *Chem. Commun.* **2012**, *48*, 2204–2206.

[3] a) J.-C. Guillemin, J.-M. Denis, *Tetrahedron* **1988**, *44*, 4431–4446; b) S.-F. Chen, E. Ho, P. S. Mariano, *Tetrahedron* **1988**, *44*, 7013–7026.

[4] For representative reports on catalytic heterocyclization through oxidative cyclization with carbon–carbon and carbon–nitrogen multiple bonds by an aza-metallacyclic intermediate, see: a) M. S. Sigman, B. E. Eaton, *J. Org. Chem.* **1994**, *59*, 7488; b) T. Morimoto, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **1999**, *121*, 1758–1759; c) N. Chatani, T. Morimoto, A. Kamitani, Y. Fukumoto, S. Murai, *J. Organomet. Chem.* **1999**, *579*, 177; d) A. Kamitani, N. Chatani, T. Morimoto, S. Murai, *J. Org. Chem.* **2000**, *65*, 9230–9233; e) P. A. Wender, T. M. Pedersen, M. J. C. Scanio, *J. Am. Chem. Soc.* **2002**, *124*, 15154–15155; f) C. Mukai, T. Yoshida, M. Sorimachi, A. Odani, *Org. Lett.* **2006**, *8*, 83–86; g) R. T. Yu, R. K. Friedman, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13250–13251.

[5] For azarhodacycles, see: a) V. M. Williams, J. R. Kong, B. J. Ko, Y. Mantri, J. S. Brodbelt, M.-H. Baik, M. J. Krische, *J. Am. Chem. Soc.* **2009**, *131*, 16054–16062; b) A. Dauth, J. A. Love, *Angew. Chem.* **2012**, *124*, 3694–3697; *Angew. Chem. Int. Ed.* **2012**, *51*, 3634–3637.

[6] a) I. Nakamura, D. Zhang, M. Terada, *J. Am. Chem. Soc.* **2010**, *132*, 7884–7886; b) I. Nakamura, D. Zhang, M. Terada, *J. Am. Chem. Soc.* **2011**, *133*, 6862; c) I. Nakamura, T. Araki, D. Zhang, Y. Kudo, E. Kwon, M. Terada, *Org. Lett.* **2011**, *13*, 3616–3619; d) I. Nakamura, D. Zhang, M. Terada, *Tetrahedron Lett.* **2011**, *52*, 6470–6472; e) I. Nakamura, Y. Kudo, T. Araki, D. Zhang, E. Kwon, M. Terada, *Synthesis* **2012**, 1542–1550.

[7] a) D. Shu, X. Li, M. Zhang, P. J. Robichaux, W. Tang, *Angew. Chem.* **2011**, *123*, 1382–1385; *Angew. Chem. Int. Ed.* **2011**, *50*, 1346–1349; b) H. Gao, J. Zhang, *Chem. Eur. J.* **2012**, *18*, 2777–2782.

[8] For representative reports on rhodium-catalyzed reactions through the ring-expansion of a metal–carbinyl cyclopropane intermediate, see: a) M. A. Huffman, L. S. Liebeskind, *J. Am. Chem. Soc.* **1991**, *113*, 2771–2772; b) M. A. Huffman, L. S. Liebeskind, *J. Am. Chem. Soc.* **1993**, *115*, 4895–4896; c) P. A. Wender, H. Takahashi, B. Witulski, *J. Am. Chem. Soc.* **1995**, *117*, 4720–4721; d) P. A. Wender, C. O. Husfeld, E. Langkopf, J. A. Love, *J. Am. Chem. Soc.* **1998**, *120*, 1940–1941; e) P. A. Wender, A. J. Dyckman, C. O. Husfeld, D. Kadereit, J. A. Love, H. Rieck, *J. Am. Chem. Soc.* **1999**, *121*, 10442–10443.

[9] Preparation of **1**: Condensation of propargyloxyamine and cyclopropanecarbaldehyde afforded a roughly 1:1 mixture of *E*/*Z* isomers, which were readily separated by silica gel column chromatography (see the Supporting Information for details).

[10] B. Richter, A. L. Spek, G. von Koten, B.-J. Deelman, *J. Am. Chem. Soc.* **2000**, *122*, 3945–3951.

[11] Attempts to separate **2a** from triphenylphosphine oxide using flash silica gel column chromatography, GPC, or HPLC were unsuccessful.

[12] CCDC 890237 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] S. Ahrland, J. Chatt, N. R. Davies, A. A. Williams, *J. Chem. Soc.* **1958**, 276–288.

[14] The reaction of (*Z*)-**1a** in toluene at 80 °C for 24 h, in the absence of Rh catalysts, afforded **3a** (11%) along with the recovery of 83% of unreacted (*Z*)-**1a**.

[15] A 1:1 mixture of the diastereomers (at the propargylic moiety) of (*Z*)-**1j** was used. Moreover, a trace amount of the *cis* diastereomer (of the cyclopropane ring) was obtained in (*Z*)-**1j**. See the Supporting Information.

[16] a) M. D. Surman, R. H. Hutchings in *Science of Synthesis, Vol. 17* (Ed.: S. M. Weinreb), Thieme, Stuttgart, **2004**, pp. 749–823; b) "Monocyclic Azepines": G. R. Proctor, J. Redpath in *The Chemistry of Heterocyclic Compounds* (Ed.: E. C. Taylor), Wiley, Chichester, **1996**.

[17] For π-acidic metal-catalyzed reactions synthesizing azepine derivatives, see: a) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 9244–9245; b) H. Liu, X. Li, Z. Chen, W.-X. Hu, *J. Org. Chem.* **2012**, *77*, 5184–5190; c) Y. Karibe, H. Kusama, N. Iwasawa, *Angew. Chem.* **2012**, *124*, 6318–6322; *Angew. Chem. Int. Ed.* **2012**, *51*, 6214–6218.