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Studies of rhodium-catalyzed ring opening of vinyl epoxides

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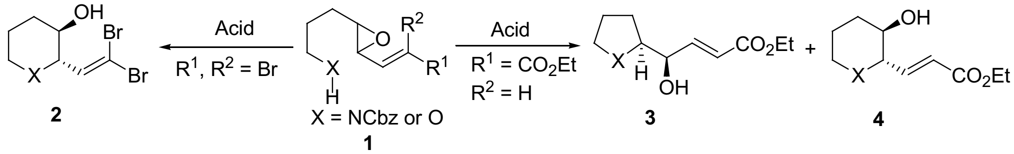
Abstract—The stereoselective 6-*endo* mode cyclization of vinyl epoxides has been achieved by the use of a catalytic amount of $[Rh(CO)_2Cl]_2$ affording six-membered heterocycle systems, such as piperidines and tetrahydropyrans. The scope and limitations of the reaction are discussed.

Functionalized six-membered heterocycles, such as piperidine and tetrahydropyran, have been found in many biologically active natural alkaloids or marine polycyclic ethers.[1] Thus, several successful synthetic strategies for constructing six-membered heterocycle systems have been devised. One of the most attractive methods would be ring opening of an epoxide by terminal heteroatoms (amine or hydroxy groups) in stereoselective 6-*endo* mode. Since ring closure of epoxides generally proceeds via the favored 5-*exo* mode rather than the 6-*endo* mode, introduction of π-orbital adjacent to the epoxide has been developed to override that tendency.[2,3] In the previous paper,[4] we developed the acid-catalyzed ring closure of vinyl epoxides bearing amino group for the construction of piperidine and pyrrolidine systems, and Nicolaou et al. also reported the ring closure of vinyl epoxides bearing hydroxy group for tetrahydropyran and tetrahydrofuran system.[2a,b] From both results, *trans*-epoxides with electron rich π-orbital always gave rise to the 6-*endo* mode products **2** over 5-*exo* mode products, while ring closure of electron deficient epoxides bearing the ester group at the vinyl terminus suffered from a poor regioselectivity to give a ca. 1:1 mixture of 6-*endo* **4** and 5-*exo* products **3**. Since suitably functionalized intermediate **4** can be used as a useful building block for the nucleus present in several major classes of alkaloids[2a] and marine polycyclic ethers, the regio- and stereoselective synthesis of **4**[5] has received much attention (Scheme 1).

Herein we wish to report a ring closure of various vinyl epoxides using $[Rh(CO)_2Cl]_2$, which takes place in a regio- and stereoselective manner. Although the general synthetic utility of the intermolecular rhodium-catalyzed ring opening of vinyl epoxides with alcohols and anilines has been well studied in a pioneering work by Lautens and co-workers,[6] the corresponding intramolecular version of this type has not yet been reported. To explore the scope of the intramolecular rhodium-catalyzed ring closure of vinyl epoxides, a variety of vinyl epoxides was prepared by following the literature procedures.[2a,4] As shown in Table 1, the vinyl epoxides were subjected to rhodium-catalyzed ring opening according to Lautens' condition.[6a] To a solution of vinyl epoxides **1a** (0.5 mmol) in THF (2 mL) was added $[Rh(CO)_2Cl]_2$ (0.01 mmol) at room temperature and the yellow solution was stirred for 10–30 min. After the solvent was removed, the residue was purified by column



Scheme 1.

Keywords: 6-*endo*; Vinyl epoxide; Rhodium-catalyzed.

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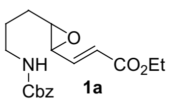
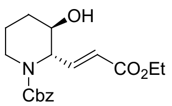
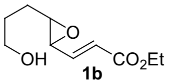
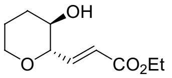
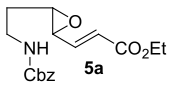
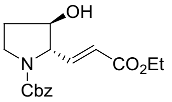
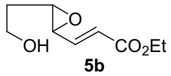
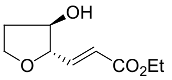
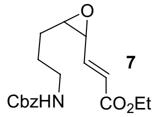
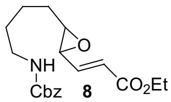
Table 1. $[Rh(CO)_2Cl]_2$-catalyzed ring closure of vinyl epoxides[a]

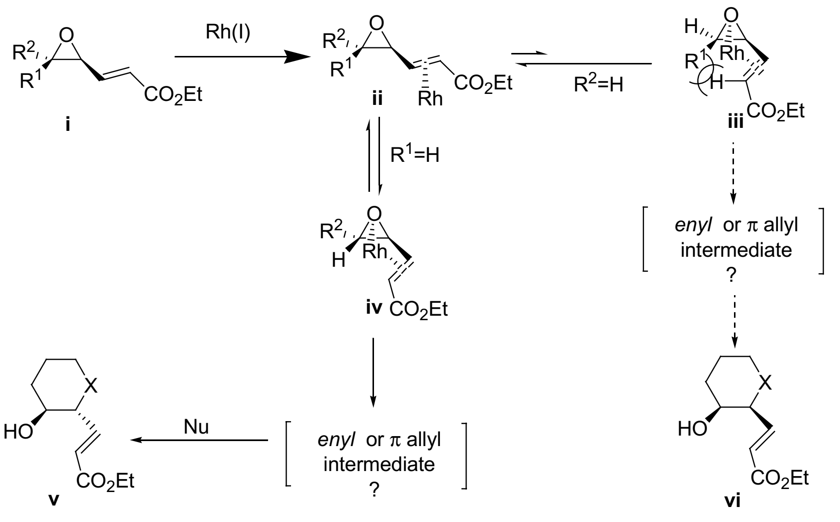
Entry		Product	Yield (%)
1	 **1a**	 **4a**	83
2	 **1b**	 **4b**	90
3	 **5a**	 **6a**	79
4	 **5b**	 **6b**	86
5	 **7**	NR[b]	
6	 **8**	NR[b]	

[a] Reaction condition: $[Rh(CO)_2Cl]_2$ (2 mol%), 25 °C, THF, 10–30 min.
[b] Starting material was recovered.

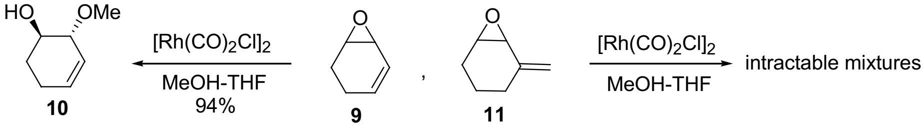
chromatography to give the piperidine derivative **4a** as a sole product in 83% yield.

The ring closure reaction was exclusively controlled in the regio- and stereoselective manner as expected. No trace of *exo* mode product, pyrrolidine derivative, was detected in the reaction mixture. When the Cbz protecting group of **1a** was changed to Boc group, the corresponding *N*-Boc piperidine derivative was also obtained in moderate yield (68%). Similar treatment of vinyl epoxide **1b** containing the terminal hydroxy group afforded the tetrahydropyran derivative **4b** exclusively in 90% yield. Ring closure of the lower homologous **5a** and **5b** furnished pyrrolidine **6a** (79%) and tetrahydrofuran **6b** (86%), respectively. In order to obtain the *cis*-substituted isomer of the corresponding *trans*-substituted piperidine **4**, the *cis*-vinyl epoxide **7** was also investigated. Unfortunately, the *cis*-vinyl epoxide **7** was found to be inert under the same condition for *trans*-vinyl epoxide, and both prolonged reaction time or increased reaction temperature resulted in the slow decomposition of starting material. Furthermore, intermolecular ring opening of **7** with methanol also failed. For the ring closure of the seven-membered ring precursor **8**, we were not able to detect any trace of 6-*exo* or 7-*endo* product and the starting material was recovered intact.

The mechanism for the rhodium-catalyzed substitution reaction has been discussed in a number of reports. Evans et al. reported the rhodium-catalyzed allylic alkylation of allyl carbonates, which proceeded with retention of absolute configuration by the S_N2' substitution,[7] whereas $[Rh(CO)_2Cl]_2$-catalyzed intermolecular ring opening of vinyl epoxides reported by Lautens coworkers proceeded with inversion of stereochemistry via a net S_N2 reaction.[6a,b] Although the reaction mechanism is not clearly explained so far, both reactions are considered to proceed through enyl or π-allyl intermediate. Since the α,β-saturated epoxide of the corresponding **1b** failed to give the cyclized product under the standard condition, the reaction is not likely proceeded by a normal S_N2 reaction, in which $[Rh(CO)_2Cl]_2$ is acting as a Lewis acid. The failure of the *cis*-vinyl epoxide **7** for both intra- and intermolecular reaction might provide evidence assuming the mechanism of these reactions. Scheme 2 summarizes our current mechanistic hypothesis. Probably rhodium (I) initially formed π-complex **ii** with vinyl group, followed by an oxidative addition resulting in the formation of enyl or π-allyl intermediate. During this process, when R^1 is H, the formation of the double coordinations **iv** of rhodium with both vinyl group and oxygen atom is likely crucial for an oxidative addition through C–O insertion of rhodium, ultimately affording to the *trans*-cyclized product **v**. On the other



Scheme 2.



Scheme 3.

hand, when R^1 substituent is alkyl group, the double coordinations **iii** should be difficult to form, due to a steric repulsion between the R^1 and vinyl moiety, thus not proceeding the C–O insertion and affording ring opening product through enyl or π-allyl intermediate, which is consistent with the experiment results.

As shown in Scheme 3, one final experiment presumably provides further evidence for this mechanism. The $[Rh(CO)_2Cl]_2$-catalyzed ring opening of cyclohexadiene oxide **9** with MeOH by Lautens,[5a] which is likely to form a double coordination intermediate readily due to the vinyl group fixed on the inside of ring, furnished the S_N2 substitution product in 94% yield. However, in the case of ring opening of *exo*-methylene cyclohexene oxide **11**[8] under the same condition, we found that the reaction was very sluggish, just affording intractable mixtures. Hence, this experiment clearly demonstrates that **11** having a vinyl group on the outside of ring may be difficult to form a double coordination system, not affording a ring opening product as appeared in the *cis*-vinyl epoxide **7**. In summary, we described the exploitation of the $[Rh(CO)_2Cl]_2$-catalyzed ring opening of vinyl epoxides with internal nucleophiles leading to heterocyclic systems.

The mechanism of this reaction involved in a double coordination system still need to be investigated. Nevertheless, this reaction proceeds in very mild condition and gives a cyclized product in high yield with excellent regio- and stereoselectivity. The *trans*-substituent heterocyclic systems possess useful functional groups for further elaboration toward several major classes of alkaloids and marine polycyclic ethers.

Acknowledgements

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References and notes

1. For reviews on piperidines, see: (a) Takahata, H.; Momose, T. *The Alkaloids* **1993**, *44*, 189; (b) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045; (c) Nishimura, Y. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 10, p 495;
(d) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619; (e) Nemr, A. E. *Tetrahedron* **2000**, *56*, 8579, and previous reference in this series; For reviews on tetrahydropyrans, see: (f) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1; (g) Moore, R. E. In *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic: New York, 1978; Vol. II; (h) Boiuin, T. L. B. *Tetrahedron* **1987**, *43*, 3309; (i) Rao, A. S.; Paknikar, S. K. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323.
2. For references on epoxy vinyl group, see: (a) Nicolaou, K. C.; Prasad, C. V. C.; Soners, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330; (b) Nicolaou, K. C.; Prasad, C. V. C.; Soners, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335; (c) Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545; (d) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927.
3. For references on alkyne-$Co_2(CO)_6$ complex, see: (a) Palazon, J. M.; Martin, V. S. *Tetrahedron Lett.* **1995**, *36*, 3549; (b) Mukai, C.; Sugimoto, Y.-i.; Ikeda, Y.; Hanaoka, M. *Tetrahedron* **1998**, *54*, 823; (c) Mukai, C.; Sugimoto, Y.-i.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281.
4. Ha, J. D.; Shin, E. Y.; Chung, Y.; Choi, J.-K. *Bull. Korean Chem. Soc.* **2003**, *24*, 1567.
5. For palladium catalyzed stereospecific cyclization of vinyl epoxides, see: (a) Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4747; (b) Oishi, T.; Maeda, K.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1997**, 1289.
6. (a) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319; (b) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650; (c) Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677; (d) Hogeveen, H.; Middelkoop, T. B. *Tetrahedron Lett.* **1973**, 3671; (e) Ashworth, R. W.; Berchtold, G. A. *Tetrahdron Lett.* **1977**, 339.
7. Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.
8. Abe, H.; Marino, J. P. *Synthesis* **1980**, 872.