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New “Cp_2Zr”-Mediated Ring Transformations of 2-Vinylheterocycles to Carbocycles

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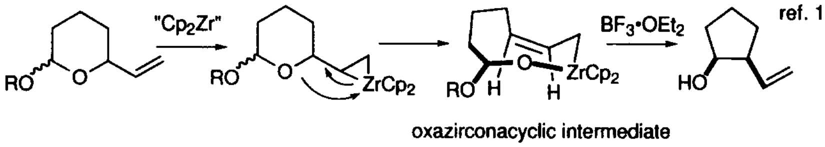
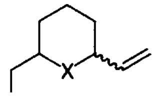
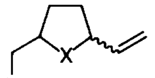
***Abstract**: Novel “Cp_2Zr”-mediated ring transformations of 2-vinylheterocycles (1, 2) to carbocycles (3, 4, 5) were shown to proceed through an intramolecular allylation of Z-allylic zirconocene species to the epoxide or aziridine intermediate.*

Highly diastereoselective ring-contraction reactions[1] of 2-vinyl cyclic acetal derivatives to *cis* 2-vinylcycloalkanols through zirconocene-(1-butene) complex (“Cp_2Zr”)[2] have previously been reported by us. This ring contraction process is brought about by the facile formation of the oxazirconacyclic intermediate containing a Z-allylzirconocene species in its framework and subsequent intramolecular allylation to the oxocarbenium ion to give ring contracted products.




cis- or *trans-***1**


cis- or *trans-***2**

a X = O, Y = Br

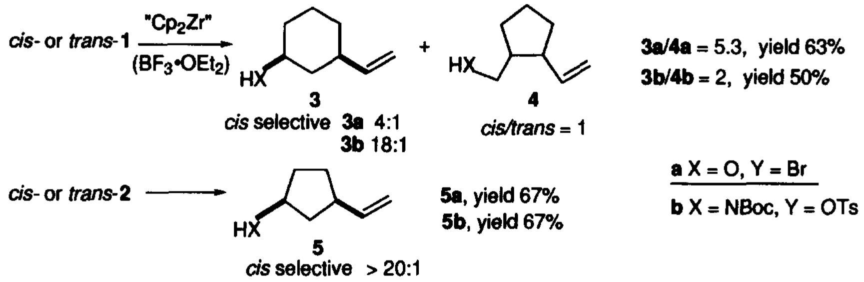
b X = *N*-Boc, Y = OTs

In our continuous effort to search for new reactions using “Cp_2Zr”, this ring contraction hinted to us that we should examine the reaction of 2-vinylheterocycles (**1**, **2**)[3] which have a leaving group (Y = Br or OTs) at a distinct position. We report herein new “Cp_2Zr”-mediated ring transformations of **1** and **2** to carbocycles and the stereoselectivity of the present ring transformation reactions.

The reaction of *cis*-**1a** with “Cp_2Zr” yielded a mixture of **3a** (*cis/trans* = 4:1) and **4a** (*cis/trans* = 1) in 5.3 : 1 ratio (63% yield) (Scheme 1). Almost identical results [**3a** (*cis/trans* = 3.5 : 1) : **4a** (*cis/trans* = 1) = 5 : 1 (61% yield)] were obtained by treating *trans*-**1a** with “Cp_2Zr”. In the reactions of *cis*- and *trans*-starting materials (**1**, **2**), no significant differences were observed in product ratio, yield and stereoselectivity shown in Scheme 1. Thus, the stereochemistry of **1** and **2** would be negligible in the present reactions.[4] Unlike the reaction of **1**, the reaction of **2** with “Cp_2Zr” gave **5** (*cis/trans* = >20:1) as the sole isolated product (67% yield). It is worth mentioning that the combination of dimethoxyethane (DME) as the solvent and bromide as the leaving group is preferable for the oxygen heterocycles **1a**, **2a**. While, in the reactions of nitrogen heterocycles **1b**, **2b**, the combination of tetrahydrofuran (THF) as the solvent and p-toluenesulfonyl ester as the leaving group along with the addition of Lewis acid (BF_3•OEt_2)

are necessary to obtain good results.

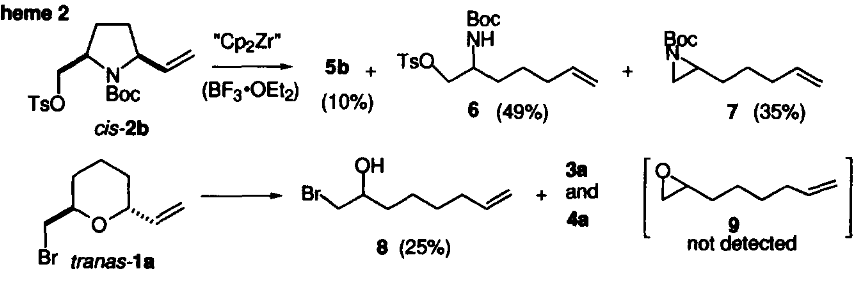
Scheme 1



In all cases examined, the existence of intermediates was confirmed by silica gel thin layer chromatography (TLC) in the early stages of the reaction. For example, in the reaction of *cis*-**2b**, *N*-Boc *cis* 3-vinylcyclopentyl amine **5b** (10%), *N*-Boc amino alcohol tosylate **6** (49%) and *N*-Boc aziridine **7** (35%) were isolated by quenching the reaction mixture after the disappearance of the starting material **2b** (Scheme 2). Tracing of the reaction of *cis*-**2b** by TLC revealed the first appearance of **6** at around 0°C – ambient. Stirring of the reaction mixture at the ambient temperature indicated gradual increases in **5b** and **7** with a decrease in **6**. Addition of BF_3•OEt_2 to the reaction mixture of *cis*-**2b** is required for the exclusive formation of **5b** (vide infla). In the reaction of *trans*-**1a**, bromohydrine **8** (25%) was isolated in addition to **3a** and **4a** but oxirane intermediate **9** was not isolated at the stage of complete consumption of starting material *trans*-**1a**.[5]

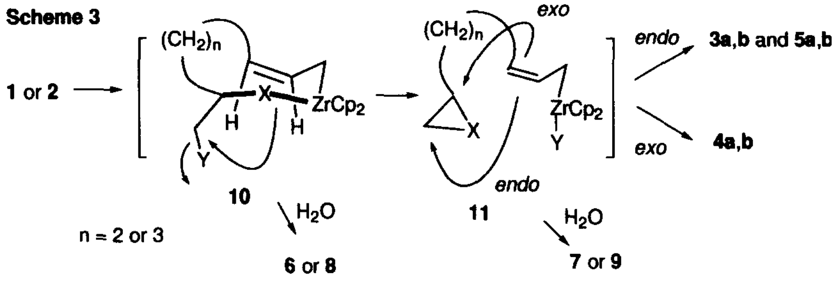
The general reaction procedure is as follows: A solution of Cp_2ZrCl_2 (0.68 mmol) in DME or THF (10 ml) was treated with 2 equivalent of n-BuLi at -78°C under an argon atmosphere and the resulting mixture was stirred at the same temperature for 1 hr. The 2-vinylheterocycle **1** or **2** (0.52 mmol) was added at -78°C and the mixture was gradually heated to room temperature or 60°C and then treated with BF_3•OEt_2, when necessary. After adding an 1N HCl, the mixture was extracted with ether. Purification of the crude product was carried out by silica gel column chromatography with pentane-ether or hexane-ethyl acetate as eluting solvents. Final purification of the product was carried out by converting the product to benzoate (PhCOCl/Py, 0°C) and the subsequent purification with medium pressure column chromatography (silica gel).

Scheme 2



Our previous reports about ring contractions of 2-vinyl cyclic acetal derivatives,[1] and the isolation of intermediate products (**6**, **7** and **8**) in the present reactions suggest the first intervention of cyclic *Z*-allylic zirconocene intermediate **10**[6] and the following conversion to oxirane **11** (X = O) or aziridine intermediate **11** (X = *N*Boc) (Scheme 3). Intramolecular allylation to the oxirane or aziridine carbon in **11** with inversion of the configuration gives the products (**3**, **4** and **5**).[7] Thus, the required addition of $BF_3 \cdot OEt_2$ to the reaction mixture of **1b** and **2b** plays a role to activate the less reactive aziridine intermediate **11** (X = *N*-Boc). The 1,3-*cis* selectivity of **3** and/or **5** can be explained by comparing the two possible transition states **A** and **B** for 5-*endo* and/or 6-*endo* cyclizations (Figure 1). The transition state **A** is sterically preferred over **B** owing to the unfavorable steric interaction between the Z-allylic zirconocene species and the oxirane or aziridine hydrogen in the transition state **B**. The poor stereoselectivity in the formation of **4** is not surprising since transition states C and D leading to *cis*- and *trans*-**4** suffer similar steric crowding as shown in Figure 1.

Scheme 3



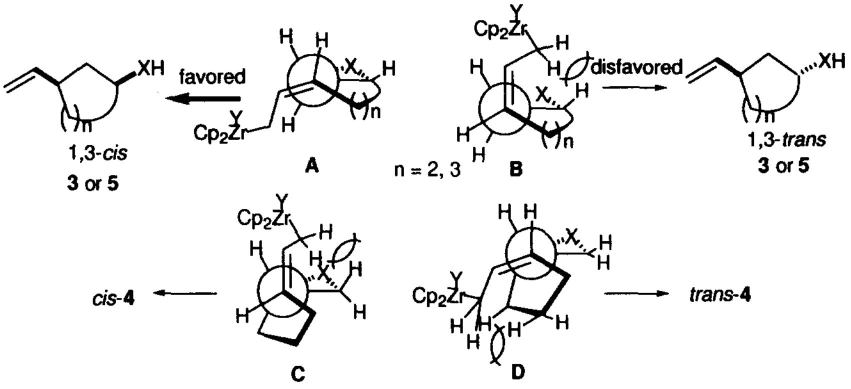
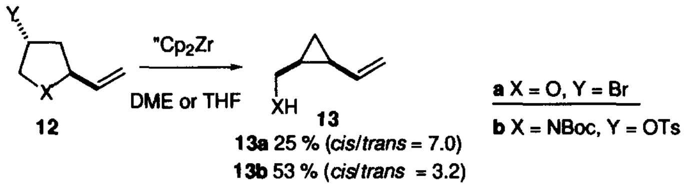


Figure 1.Transition state models **A/B** for 5-*endo* and 6-*endo* cyclizations and **C/D** for 5-*exo* cyclization

Scheme 4

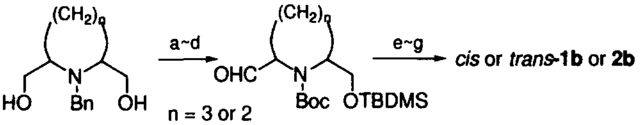


The present concept for the "Cp_2Zr"-mediated ring transformation can be applied to compounds **12a,b**. Thus, the reaction of **12** gives the vinylcyclopropane derivative **13** in moderate *cis*-selectivity (Scheme 4). For the purpose of finding further utility for the present ring transformations we are now examining the rections using highly functionalized 2-vinylheterocycles.

References and Notes

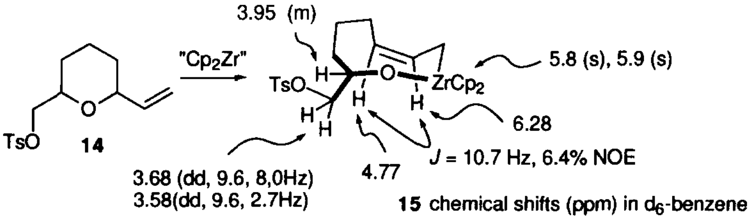
1. a) Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299. b) Ito, H.; Motoki, T.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835. c) Ito, H.; Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y.; Shiro, M. *J. Am. Chem. Soc.* **1994**, *116*, 5469. d) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1993**, *34*, 7639.
2. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
3. a) Preparations of *cis*- or *trans*-**1a** or **2a** were carried out by the bromination (CBr_4–Ph_3P) of the corresponding alcohols. Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927.

   b) Compounds **1b** and **2b** were prepared as follows:



reagents
a TBDMSCl/ NaH/THF, b H_2/10% Pd-C, c $(Boc)_2O/NaHCO_3$,
d $DMSO/(COCl)_2/Et_3N/CH_2Cl_2$ e Ph_3PCH_2/THF, f TBAF, g TsCl/Py

   See also: a) Couper, L.; Robins, D. J. *Tetrahedron Lett.* **1992**, *33*, 2717. b) Koh, K.; Ben, R. N.; Durst, T.; *Tetrahedron Lett.* **1994**, *35*, 375
4. All reactions were carried out using the purely isolated *cis*- and *trans*-starting compounds. Structures of the products were confirmed by comparing to the authentic samples and spectral data. a) Procter, G.; Russell, A. T.; Murphy, P. J.; Tan, T. S.; Mather, A. N.; *Tetrahedron* **1988**, *44*, 3953. b) Schaefer, J. P.; Higgins, J.; *J. Org. Chem.* **1974**, *39*, 248. c) Crandall, J. K.; Mayer, C. F.; Arrington, J. P. *J. Org. Chem.* **1974**, *39*, 248. d) Apparu, M.; Barrelle, M. *Tetrahedron* **1978**, *34*, 1691. e) Gajewski, J. G.; Hawkins, C. M.; Jimenez, J. L.; *J. Org. Chem.* **1990**, *55*, 674. f) Viani, R.; Bricout, J.; Marion, J. P.; Reymond, D. *Helv. Chim. Acta* **1969**, *52*, 887. g) Bergmeier, S. C.; Steh, P. P. *Tetrahedron Lett.* **1995**, *36*, 3793.
5. The difference between these two observations might be ascribable to the poor nucleophilicity of the *O*–*Zr* species compared to the *N*–*Zr* species and the higher reactivity of the oxirane ring in **11** (X = O) than the aziridine ring in **11** (X = *N*Boc) toward the nuclophile.
6. The assumption is supported by the generation of cyclic Z-allylzirconocene **15** from **14**. Conversion of **15** to **3a** and **4a** was unsuccessful, probably due to the reason described in ref. 5. This observation further indicates the requirement of bromide as a leaving group for oxygen heterocycles.



15 chemical shifts (ppm) in d_6-benzene

7. The 5-*endo* and/or 6-*endo* cyclizations of epoxy-allylic stannane have been reported to give cyclized products with the inversion of the configuration at the epoxide carbon. a) Yoshitake, M.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2157. b) Yoshitake, M.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2161.

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