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Formation of Cyclopropyl Carbinols Through a Highly Diastereoselective Hydrozirconation of Vinyloxirane Derivatives

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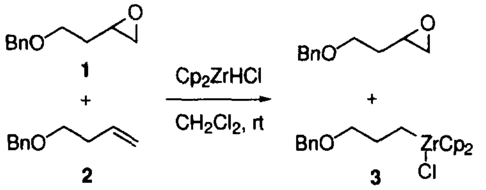
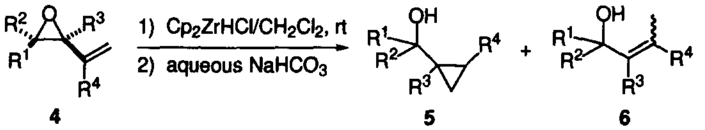
Abstract: *Cyclopropyl carbinol derivatives were efficiently prepared through a highly diastereoselctive hydrozirconation of vinyloxiranes and the intramolecular nucleophilic attack of the generated alkylzirconocene with the inversion of the configuration at the reacting oxirane carbon.*

Hydrozirconation of alkenes or alkynes with zirconocenehydrochloride (Cp_2ZrHCl, Schwartz reagent) is one of the most convenient procedures to generate organozirconocene compounds, which can be easily converted to other organometallic compounds by transmetalation, and a number of examples of their synthetic use have been reported.[1] The reactions of Cp_2ZrHCl with oxirane derivatives have been reported to reduce an oxirane ring in a regioselective manner to give alcohol derivatives.[2] However, the treatment of an equimolar mixture of oxirane **1** and alkene **2** compounds with 1 equivalent of Cp_2ZrHCl yielded an exclusive hydrozirconation product from the alkene **2** and no trace of the oxirane ring-reduced alcohol or the alcohol derived from the intermolecular nucleophilic attack of alkylzirconocene **3** on the oxirane **1** was observed in the reaction mixture. This observation implies the faster hydrozirconation of the alkene than the reduction of oxirane and the poor nucleophilicity of alkylzirconocene as have been reported.[3]



We report herein the diastereoselective formation of cyclopropyl carbinol derivatives **5** from vinyloxirane derivatives **4** by the reaction with Cp_2ZrHCl. The reactions of Cp_2ZrHCl with vinyloxirane derivatives **4** in CH_2Cl_2 at ambient temperature turned out to be an alternative possibility to prepare the optically active cyclopropyl carbinols **5**, which are normally prepared by the diastereo- or enantioselective Simmons-Smith cyclopropanation of allylic alcohols,[4] since the vinyloxirane derivatives **4** can be easily derived from optically active epoxy alcohols.[5] The results of the reactions of **4** with Cp_2ZrHCl are listed in Table 1. In all cases examined, the yields of the cyclopropyl carbinols **5** were good to excellent. In the reactions of vinyloxiranes **4a-e** (R^4 = H) Z-allylic alcohols **6a-e** (R^4 = H) were isolated as a side product. It has been reported that the hydrozirconation of alkenes is influenced by steric hindrance and the presence of chelating heteroatoms and aryl rings.[1a] Thus, in the reactions of **4a-e** which possess an oxygen functionality at the allylic position, the hydrozirconation is considered to proceed with lowered regioselectivity to give a regioisomeric product which gives **6** through a facile β-elimination of the carbon-oxygen bond of the oxirane ring.[6] The nonexistence of allylic alcohol as a side product in the reaction mixture of **4f** indicates that the hydrozirconation proceeds with complete regioselectivity to avoid the steric repulsion between the methyl and cyclopentadienyl groups to give the terminal zirconocene product.[1,7] Thus, the formation of the allylic alcohol **6** indicates the regioselectivity of the hydrozirconation of vinyloxiranes.

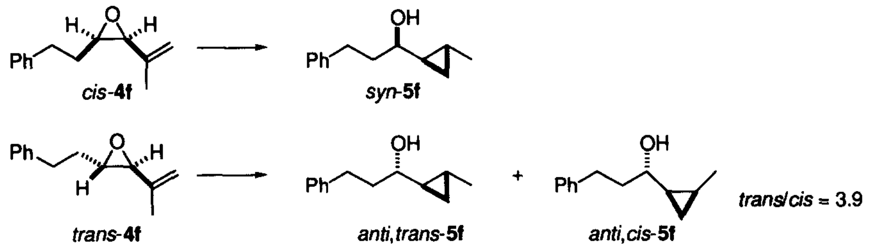
Table 1. Reaction of vinyloxirane derivatives with Cp_2ZrHCl



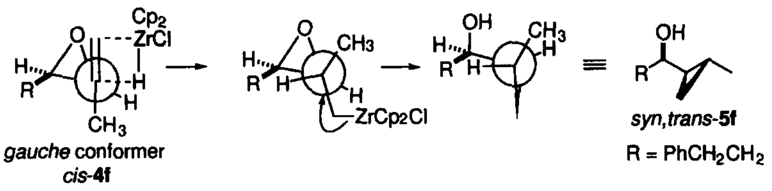
Substrates	R^1	R^2	R^3	R^4	Yields (%) 5	Yields (%) 6	
cis-**4a**	$Ph(CH_2)_2$	H	H	H	72	18	(*Z* only)
trans-**4a**	H	$Ph(CH_2)_2$	H	H	59	15	(*Z* only)
4b	$BnOCH_2$	H	H	H	52	22	*E*/*Z* = 1/7.3
4c	H	$Ph(CH_2)_2$	CH_3	H	76	2	*E*/*Z* = 1/1.9
4d	Ph	H	H	H	75	11	*E*/*Z* = 1/2.0
4e	H	Ph	CH_3	H	70	5	*E*/*Z* = 1/5.1
cis-**4f**	$Ph(CH_2)_2$	H	H	CH_3	98	—	
trans-**4f**	H	$Ph(CH_2)_2$	H	CH_3	75	—	

The results for the reactions of *cis*-**4f** and *trans*-**4f** are very significant for discussion of the reaction mechanisms. The exclusive formations of *syn*-**5f** from *cis*-oxirane **4f** and the *anti*-**5f** from *trans*-oxirane **4f** imply that the stereospecific formation of the cyclopropyl ring is a result of the intramolecular nucleophilic attack of the alkyl zirconocene,[8] which is derived from the first stage of the hydrozirconation reaction of **4f**, to the oxirane carbon with *the inversion of the configuration at the oxirane carbon.* More importantly, the exclusive formation of the *trans* cyclopropane unit of *syn*-**5f** from *cis*-**4f** and the poorly selective formation (*trans*/*cis* = 3.9) of the cyclopropyl unit of *anti*-**5f** from *trans*-**4f** suggest that the completely diastereoselective hydrozirconation to the double bond of *cis*-**4f** and the poorly diastereoselective hydrozirconation for *trans*-**4f** took place, respectively (Scheme 1).[9] The structure of *syn*-**5f** was confirmed by an alternative synthesis through the *syn*-selective cyclopropanation of *E*-allylic alcohol **7** according to the procedure developed by Charrette.[10] Similarly, the structures of *anti,trans*-**5f** and *anti,cis*-**5f** from *trans*-**4f** were determined by the *anti*-selective cyclopropanations of the benzyl ethers **8** and **9** of the *E*- or Z-allylic alcohol derivatives and the subsequent debenzylation.[10]

Scheme 1



Scheme 2



The transition state of the hydrozirconation with Cp_2ZrHCl to an olefin is theoretically concluded to be a very early transition state (reactant-like transition state) with a very small activation energy (0–15 kcal/mol).[11] Taking into consideration the inversion of the configuration at the reacting site of the oxirane ring in the present cases, the exclusive formation of *syn*-**5f** from *cis*-**4f** might be explained by the approach of Cp_2ZrHCl from the sterically less crowded *Si*-face of the most stable *gauche* conformer[12] of *cis*-**4f** and the subsequent cyclopropane ring formation as shown in Scheme 2. Applicability of the present distereoselective preparations of cyclopropyl carbinols to the synthesis of biologically attractive cyclopropyl compound is now under investigation.

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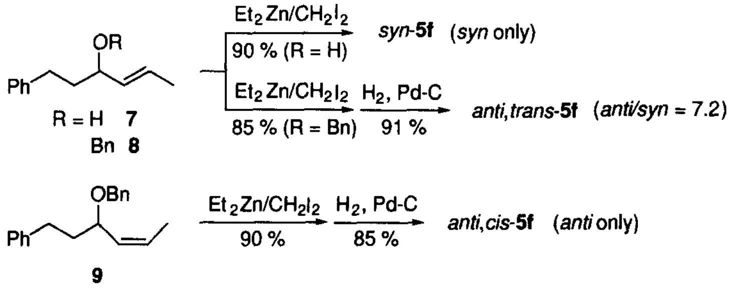

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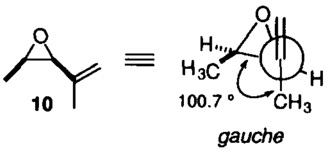

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