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Addition of Organozinc Species to Cyclic 1,3-Diene Monoepoxide

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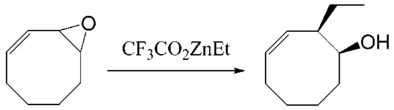
ABSTRACT



The reaction of organozinc reagents (ZnEt$_2$, ZnPh$_2$) with cyclic 1,3-diene monoepoxides in the presence of CF$_3$COOH gave the *cis*-addition products. Lewis acids such as (CF$_3$CO$_2$)$_2$Zn and ZnCl$_2$ mediated the nucleophilic addition of ZnEt$_2$ to cyclooctadiene monoepoxide with high stereoselectivity.

Vinylic epoxides are valuable synthetic building blocks, and their reactions have been extensively investigated.[1] The addition of organometallic reagents to vinylic epoxides is a fundamental preparation of allylic and homoallylic alcohols.[2] Grignard reagents,[3] allylstannanes,[4] and alkyllithiums[5] generally provide 1,2-addition products, and copper reagents[6] and copper-catalyzed organozinc reagents[7] yield 1,4-addition products. Mixtures of regio- and/or stereoisomers are often obtained in favor of a *trans* relationship between the hydroxy group and the substitutent. In contrast, the *syn* addition of carbon nucleophiles toward epoxide has received less attention.[8]

Recently, Zaidlewicz and Krzeminski reported that 1,2-*syn* addition was favored in the reaction of allyldiethylborane with six-, seven-, and eight-membered 1,3-diene monoepoxide.[9] The ratio of *cis/trans*-1,2-addition was up to 72/28 when 3,4-epoxycyclohexene reacted in ether at room temperature. α-*C*-Glycosides were also synthesized by the *syn* addition of aluminum or boron reagents to glycal epoxides.[10] We now wish to report a stereoselective addition of organozinc species to cyclic 1,3-diene monoepoxides.

Our investigation started with 1,3-cyclooctadiene monoepoxide **1c** as a substrate. The active organozinc species XZnR could be generated by reaction of ZnR$_2$ (R = Et, Ph) with acids (HX). When a solution of organozinc CF$_3$CO$_2$ZnEt and substrate **1c** in CH$_2$Cl$_2$ was stirred at 0 °C for 2 h,

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[9] They found a novel rearrangement reaction to occur in the reaction of allyldiethylborane with 5- membered rings. Zaidlewicz, M.; Krzeminski, M. P. *Org. Lett.* **2000**, *2*, 3897.

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[11] **Addition of CF$_3$COOZnEt to 1c.** To a solution of ZnEt$_2$ (1 M in *n*-hexane, 1.2 mL, 1.2 mmol) in 2 mL of CH$_2$Cl$_2$ at 0 °C was added CF$_3$COOH (92 μL, 1.2 mmol) very slowly via syringe under N$_2$. After 30 min of stirring, a solution of **1c** (124 mg, 1.0 mmol) in CH$_2$Cl$_2$ (1 mL) was added. The mixture was stirred for 2 h at 0 °C and then quenched with saturated aqueous NH$_4$Cl. The mixture was extracted with Et$_2$O (3 × 10 mL), washed with brine, dried (Na$_2$SO$_4$), and concentrated. Column chromatography afforded 102 mg (66%) of homoallylic alcohol *cis*-**2c**. GC−MS analysis of the crude reaction mixture revealed three peaks: **1c** (8%), 3-cycloocten-1-one of the rearrangement product from epoxide (19%), and *cis*-**2c** (73%).

[12] The stereochemistry of *cis*-**2c** was assigned from a similarity of its NMR spectrum to that of the known *cis*-2-allyl-3-cycloocten-1-ol in ref 9.

[13] Crystal data of *cis*-**2c**: C$_{10}$H$_{18}$O, crystal system, tetragonal; $a = 22.583(2)$ Å, $b = 22.583(2)$ Å, $c = 7.6273(9)$ Å, $V = 3889.9(7)$ Å^3; space group, I4(1)/*a*; $Z = 16$; $F(000) = 1376$; $\mu = 0.065$ mm^{-1}; full matrix least-squares refinement on F^2; residuals, R = 0.042, wR$_2$ = 0.0826.

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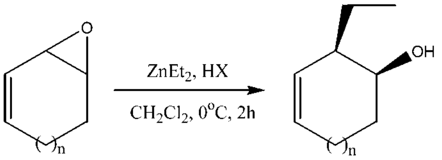
only 1,2-addition product *cis*-**2c** was obtained with 66% yield (Table 1).[11] The relative stereochemistry between the hydroxy group and the ethyl group was assigned on the basis of the proton NMR spectrum.[12] The relative configuration was further confirmed as *cis* by X-ray analysis of the crystal structure (Figure 1).[13] The *trans* isomer of the 1,2-addition product was not observed by ^{1}H NMR. The choice of the solvent was crucial to the success of the reaction. CH_2Cl_2 and toluene were suitable solvents. The use of a more nonpolar solvent such as hexane gave a 7% yield of *cis*-**2c**. However, Et_2O failed to result in the reaction as a result of coordination to Lewis acidic zinc species thereby attenuating its reactivity. The reactivity of the organozinc species XZnEt was highly dependent on the X group. The species CCl_3CO_2ZnEt, in place of CF_3CO_2ZnEt, only afforded a 20% yield using similar reaction conditions. In addition, when acid HX was anhydrous TsOH or CH_3COOH, no reaction occurred after stirring for 2 h at 0 °C.

Table 1. Addition of $ZnEt_2$ to Epoxides in the Presence of Acids



1a: n=0
1b: n=1
1c: n=3

***cis*-2a**
***cis*-2b**
***cis*-2c**

entry	epoxide	solvent	acid (HX)	yield[a] (%)
1	**1c**	CH_2Cl_2	CF_3CO_2H	66
2	**1c**	toluene	CF_3CO_2H	52
3	**1c**	*n*-hexane	CF_3CO_2H	7
4	**1c**	Et_2O	CF_3CO_2H	0
5	**1c**	CH_2Cl_2	CCl_3CO_2H	20
6	**1c**	CH_2Cl_2		0
7	**1a**	CH_2Cl_2	CF_3CO_2H	58
8	**1b**	CH_2Cl_2	CF_3CO_2H	63

[a] Isolated yields.

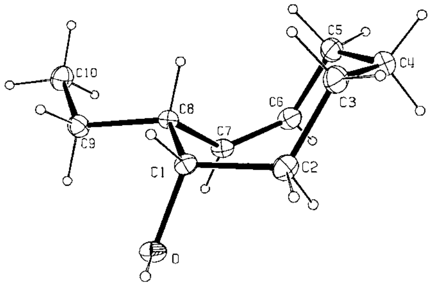
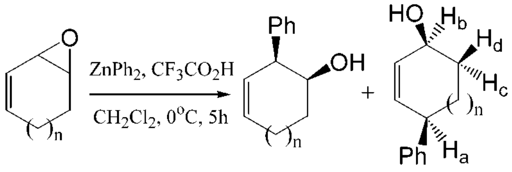


Figure 1. Crystal structure of *cis*-**2c**.

Similarly, the reaction of CF_3CO_2ZnEt with cyclopentadiene and 1,3-cyclohexadiene monoepoxides gave the same type of *cis*-1,2-addition with 56% and 63% yield, respectively. These results obtained show that $ZnEt_2$ is an effective nuclephile to cyclic 1,3-diene monoepoxide in the presence of CF_3COOH.[14] The byproducts of these reactions were the rearrangement products of monoepoxides of cyclic dienes, suggesting that organozinc species XZnEt have Lewis acid character in these reactions.

In addition to $ZnEt_2$, $ZnPh_2$ underwent the same reaction to give exclusively **3c** in 74% yield when CF_3CO_2ZnPh reacted with **1c** in CH_2Cl_2 at 0 °C for 5 h. However, cyclopentadiene and 1,3-cyclohexadiene monoepoxides gave both 1,2- and 1,4-regioisomers when reacting with CF_3CO_2ZnPh (Table 2). The 1,4-regioisomer was assigned from the chemical shift of the carbinol proton owing to its allylic character. On the other hand, the *cis* stereochemistry of **4a**, for example, is supported by the relative value of the chemical shifts of H_c (δ 2.87) and H_d (δ 1.58). The difference between H_c and H_d is larger than 1 ppm, demonstrating that the product is *cis*-1,4-disubstituted cyclopentene.[15]

Table 2. Addition of $ZnPh_2$ to Epoxides in the Presence of CF_3CO_2H



1a: n=0
1b: n=1
1c: n=3

3a
3b
3c

4a
4b
4c

entry	epoxide	**3**/**4**[a]	yield [b] (%)
1	**1a**	39/61	81
2	**1b**	25/75	79
3	**1c**	100	74

[a] Determined by GC−MS analysis. [b] Isolated yields.

Encouraged by this initial result, the reaction was investigated using Lewis acids in place of acid HX, since organozinc species XZnEt could be formed by the reaction of $ZnEt_2$ with ZnX_2. As shown in Table 3, 60% yield of **2c** could be obtained when $ZnEt_2$ reacts with $(CF_3CO_2)_2Zn$, which is formed in situ by the reaction of $ZnEt_2$ with CF_3COOH. Analysis of the crude reaction mixture using GC−MS shows that a small amount of 1,4-addition product is always obtained under the reaction conditions used. It is worth noting that $ZnCl_2$ was found to be reactive under these reaction conditions, affording good yield (78%) of **2c** but with a mixture of stereoisomer. The same reaction carried out with $ZnBr_2$ gave the homoallylic alcohol **2c** in a low yield (39%) with a decrease in both stereoselectivity and regioselectivity.

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(14) Shi reported that CF_3CO_2H accelerated the cyclopropanation of olefins. Yang, Z. Q.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621.

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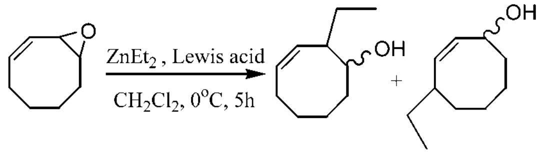
Table 3. Addition of $ZnEt_2$ to **1c** Mediated by Lewis Acids



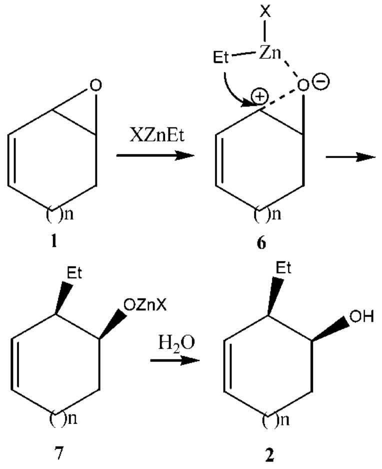
1c **2c** **5c**

entry	$ZnEt_2$ (equiv)	Lewis acid (equiv)	yield **2c**[a] (*cis*/*trans*)[b]	**2c**/**5c**[c]
1	0.6	$(CF_3CO_2)_2Zn$ (0.6)	60 (100)	99/1
2	0.6	$(CF_3CO_2)_2Zn$ (1.0)	53 (100)	98/2
3	1.2	$(CF_3CO_2)_2Zn$ (0.6)	36 (100)	98/2
4	1.2	$(CF_3CO_2)_2Zn$ (1.0)	52 (100)	98/2
5	0.6	$ZnCl_2$ (0.6)	26 (91/9)	97/3
6	1.2	$ZnCl_2$ (0.6)	52 (88/12)	94/6
7	1.2	$ZnCl_2$ (1.0)	78 (94/6)	94/6
8	1.2	$ZnBr_2$ (1.0)	39 (80/20)	89/11

[a] Isolated yields. [b] Determined by ^1H NMR [*cis* (δ 3.81), *trans* (δ 3.52), CH-OH]. [c] Determined by GC−MS analysis.

The *syn* addition appears to be occurring via the coordination of zinc to oxygen of the epoxide and intramolecular transfer of R group. The mechanism is closely related to that proposed by Rainier and Cox in their work[9] and outlined in Scheme 1. We considered the transfer of R group from XZnR occurred from the same face as the oxygen of epoxide and resulted in a *syn* addition, since organozinc reagents XZnR could act as a Lewis acid system as well as being nucleophilic in character.

Scheme 1



In conclusion, we have demonstrated a new nucleophilic ring-opening reaction of cyclo-1,3-diene monoepoxide using organozinc species. The *cis*-addition products were obtained when reacting with CF_3CO_2ZnEt, which is formed by mixture of $ZnEt_2$ with CF_3CO_2H or $(CF_3CO_2)_2Zn$. Additional studies of the scope are in progress.

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Supporting Information Available: Spectroscopic data for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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