Allyltitanium Triphenoxide: Selective Cleavage of Oxiranes at the More Substituted Carbon Atom

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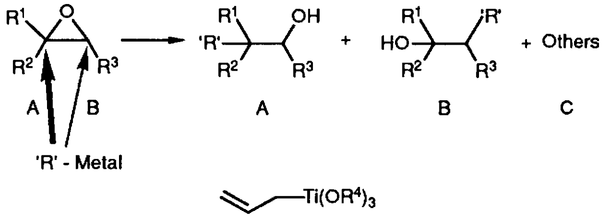
Allyltitanium triphenoxide was found to be an excellent reagent for regioselective allylation at the more substituted carbon atom of oxiranes.

Carbon–carbon bond formation *via* oxirane cleavage is an important weapon in the synthetic chemist's armoury.[1] Although there are numerous examples of attack at the less substituted carbon atom of epoxides with Grignard, organolithium, or organocopper reagents (type B), preferential alkylative opening of the epoxide at the more substituted carbon atom (type A) had not been reported until recently.[2] More recent examples are restricted to styrene oxide or vinylic epoxides.[3]† Alkylation at the more substituted oxirane carbon atom bearing alkyl substituents provides access to tertiary or quaternary carbon centres bearing a hydroxy function at the α-carbon, thereby giving a number of useful building blocks. We now report a highly regioselective allylation at the more substituted carbon atom of oxiranes by the reaction with allyltitanium triphenoxide (**II**) (type A reaction) (Scheme 1).

Reetz *et al.* described the reaction of styrene oxide at the benzylic carbon with the allylmagnesium bromide–titanium tetraisopropoxide complex or allyltitanium tri-isopropoxide (**I**) with > 99% selectivity.[3a] Seebach *et al.* reported similar high regioselectivity using acetylenic titanium reagents.[3c] However, these reagents exhibited low regioselectivity in reactions with alkyl substituted oxiranes. We needed to construct a quaternary carbon atom in a natural product synthesis, and so investigated the alkylative opening of several epoxides with alkyltitanium reagents. We found that the crude



(**I**) $R^4 = Pr^i$
(**II**) $R^4 = Ph$

Scheme 1

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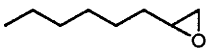
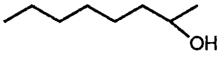
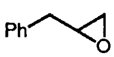
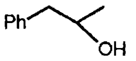
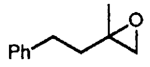
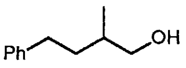
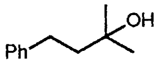
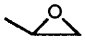
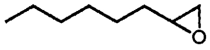
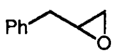
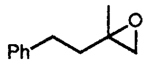
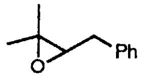
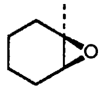
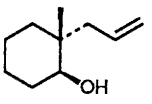
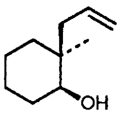
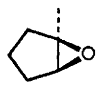
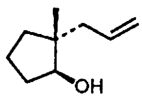
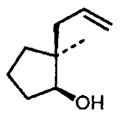
† These types of compound have an intrinsic tendency to be attacked at the more substituted carbon atom even by Grignard reagents.[3a,f]

Table 1. Oxirane cleavage with the allyltitanium reagents (**I**) and (**II**).[a]

Run	Substrate	Reagent	Product (% Yield)[b] ('R' = allyl in Scheme 1)				
1		(I)	A (14)	B (14)	C:		(29)
2		(I)	A[c]	B(15)	C:		(30)
3		(I)	A(47)	B[c]	C:		(15)
					C:		([c])
4		(II)	A(52[d])	B[c]	(A / B 12/1)		
5		(II)	A(77)	B[c]	(A / B 22/1)		
6		(II)	A(85)	B[c]	(A / B 49/2)		
7		(II)	A(90)				
8		(II)	A(83)				
9		(II)	A(85)				
10		(II)		(77)		(*trans* / *cis* 10/1)[c]	
11		(II)		(72)		(*trans* / *cis* 17/1)[c]	

[a] A typical procedure is as follows: a solution of $ClTi(OPh)_3$ in tetrahydrofuran (THF) (2.0 equiv.) was added dropwise to allylmagnesium chloride in THF (2.1 equiv.) at −78 °C. The mixture was stirred for 30 min, a solution of the oxirane (1 mmol) in tetrahydrofuran was added, and the mixture was gradually warmed to room temperature. Work-up similar to the procedure of Seebach *et al.*[3c] afforded the type A product selectively. All substrates are racemic. [b] Isolated yield. All isolated products were characterized by NMR and high resolution mass spectroscopy. [c] Detectable by GLC comparison with an authentic sample prepared alternatively, but not isolated in pure form. [d] The low yield is due to the volatility of the product.

product contained considerable amounts of reduction products (alcohols) when the titanium isopropoxide reagent (**I**) was used. We therefore used the titanium phenoxide reagent (**II**),‡ and investigated its reactions with mono-, 1,1-di-, and 1,1,2-trialkylsubstituted epoxides. The results are summarized in Table 1.

The allyltitanium triphenoxide (**II**) gave the type A product with high selectivity in ~80% yield, with no reduction product nor regioisomer (type B product) being isolated.§ Use of the

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‡ In the reaction of some aldehydes and but-2-enyltitanium trialkoxide, enhanced stereoselectivity was observed on changing the alkoxide into phenoxide: L. Widler and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 1085.

§ The reduction product or the regioisomer was prepared alternatively by $LiAlH_4$ reduction of the epoxide, hydroboration of the alkene, or reaction with Grignard reagent.

phenoxy instead of the isopropoxy substituent might avoid Meerwein–Pondorf–Verley-type reduction, and undoubtedly enhanced the regioselectivity dramatically. While the reagent **(I)** was ineffective for our purposes (runs 1—3), reagent **(II)** showed quite high regioselectivity (runs 4—9). Methyl- or vinyl-titanium triphenoxide did not afford alkylated products under the same conditions.

1-Methylcyclohexene oxide (run 10) afforded mainly the *trans*-opening product with high stereoselectivity (10 : 1). The stereochemistry of the product was determined by ^1H NMR analysis of the *p*-nitrobenzoate.¶ 1-Methylcyclopentene oxide (run 11) also exclusively gave the *trans*-opening product.||

Although a rationalisation of the reaction mechanism and extension to alkyl groups other than allyl depend on further work, it is clear that allyltitanium triphenoxide **(II)** is a good reagent for the regioselective allylative opening of epoxides at the more substituted carbon atom.

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¶ These alcohols could not be separated. After *p*-nitrobenzoylation followed by recrystallization, the pure ester of the main product was obtained. A nuclear Overhauser enhancement (NOE) was observed between 1-H (δ 4.92, dd, *J* 9.8 and 4.3 Hz) and the allylic methylene protons.

|| An NOE was observed between 1-H (δ 5.09, dd, *J* 6.7 and 4.9 Hz) and the allylic methylene protons of the *p*-nitrobenzoate.

References

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