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Synthesis of chiral 1,3-diols by radical-mediated regioselective opening of 2,3-epoxy alcohols using cp_2TiCl

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Abstract—Radical-mediated opening of chiral 2,3-epoxy alcohols **1a**–**e**, regioselectively at the 2-position, using cp_2TiCl in the absence of a hydrogen source leads to the formation of the 1,3-diols **2a**–**e**. © 2002 Published by Elsevier Science Ltd.

Although nucleophilic ring-opening reactions of epoxides are routinely used by synthetic organic chemists to construct a wide variety of structural moieties for use in the total synthesis of natural products, corresponding radical-mediated methods have found fewer applications.[1] A novel radical-mediated epoxide opening reaction using cp_2TiCl and cyclohexa-1,4-diene was developed by us[2] and successfully employed to construct 1,3-diols that are found in many polyketide natural products.[3–5] However, one hurdle that made its application in large-scale preparations somewhat problematic was the need for an excess of the hydrogen donor, cyclohexa-1,4-diene, a cancer suspect agent. In this communication, we now report that the same reaction can be performed with almost equal efficiency in the absence of any hydrogen source. This method is particularly valuable for the synthesis of 2-alkyl-1,3-diols.

While Ti(III) is known to open trisubstituted epoxides at the more substituted carbon in presence of cyclohexa-1,4-diene,[6] in the absence of any hydrogen donor it converts disubstituted 2,3-epoxy alcohols readily into their corresponding 3-hydroxy allylic alcohols.[7] In recent years, a Ti-catalytic version of the former reaction has been developed.[8,9] We observed that di- as well as trisubstituted 2,3-epoxy alcohols **1a**–**e** open regioselectively at the 2-position on treatment with cp_2TiCl, generated in situ from cp_2TiCl_2, to give the corresponding 1,3-diols as the only isolable products when the reactions were allowed to run for a longer period of time, typically 12–18 h. No 1,2-diol was formed in any of these reactions. The presence of cyclohexa-1,4-diene, previously used[2–5] as the hydrogen source for similar transformations, was found to be redundant. The results of our study are summarized in Table 1.

In THF–MeOH (2:1) cp_2TiCl opens α,β-epoxy ketones,[10] whereas under nonprotic conditions it often leads to β-hydride elimination to give olefins as the major products as observed by us earlier in certain substrates[11,12] and also by others.[13] In the present study where the reactions were carried out in THF alone, no β-hydride elimination was noticed. Although the isolated yields are somewhat lower as compared to our earlier results,[2] diastereoselectivities for the trisubstituted substrates **1c**–**e** were found to be excellent with no trace (**2c**) or very little of other isomers (**2d**, **2e**) seen in the ^{1}H NMR spectra of the products. The slight decrease in the yields can be attributed to the longer lifetime of the highly reactive radical intermediates in the reaction medium that probably leads to unidentified side-reactions. The six-membered cyclic Ti(IV) complex **II** (Scheme 1), with a stable carbon radical at the 2-position that was postulated by us[2,14] to be the intermediate in this epoxide opening reaction possibly remains intact due to the absence of any hydrogen source until the reaction was subjected to an aqueous work-up using dilute HCl.[15] Hydrogen abstraction by the carbon radical (**II**→**III**) is believed to be faster than the acid hydrolysis of Ti–O bonds and is consistent with the excellent diastereoselectivities observed in these reactions. This is further supported by the fact that the same reaction using a catalytic amount of the Ti-reagent according to the reported procedure[8,9] led to complete loss of diastereoselectivity, a fact that was observed by us earlier. As the cyclic Ti(IV)-intermediate

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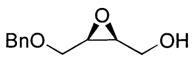
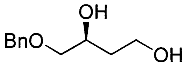
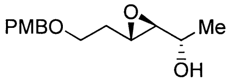
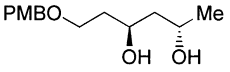
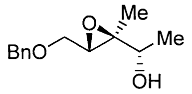
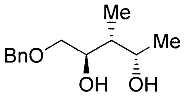
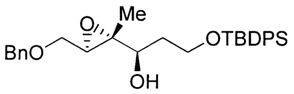
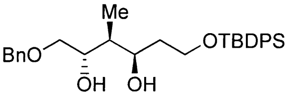
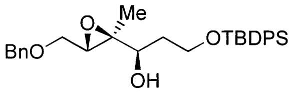
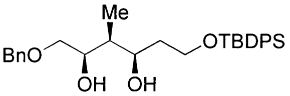
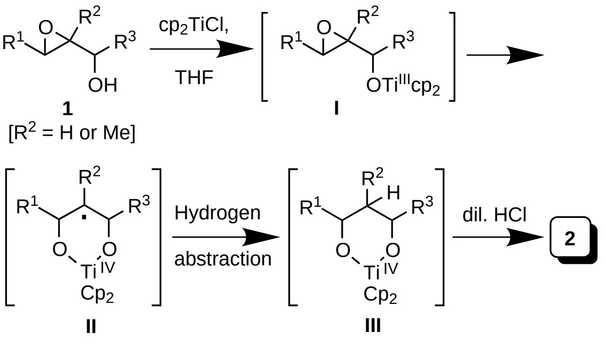
Table 1. Opening of 2,3-epoxy alcohols (**1**) using cp_2TiCl

Entry	2,3-Epoxy alcohols (**1**)	Products (**2**)	Reaction conditions[a] (time/h)	Yield (%) (ratio[b])
1.	 **1a**	 **2a**	B (18)	65
2.	 **1b**	 **2b**	A (14)	58
3.	 **1c**	 **2c**	A, B (15)	62 (>96%)[c]
4.	 **1d**	 **2d**	B (14)	62 (92:8)
5.	 **1e**	 **2e**	B (12)	66 (95:5)

[a] A: cp_2TiCl_2 (5 eq), Zn (10 eq), THF, 1 h at rt, then **1** added in THF at –20 °C, –20 °C to rt in 2 h, then stirred at rt for 10-16 h. B: cp_2TiCl_2 (3 eq), Zn (6 eq), $ZnCl_2$ (3 eq), THF, 1 h at rt, then **1** added in THF at –20 °C, –20 °C to rt in 2 h, then stirred at rt for 10-16 h. [b] Ratio of diastereomers with respect to the 2-methyl group (the major diastereomer is shown here). [c] The other diastereomer could not be detected by ^1H NMR analysis of the product.

was believed to be responsible for the observed diastereofacial selectivity during the hydrogen abstraction by the radical center at the 2-position, protonation of the Ti–O bonds as soon as they were formed by collidine. HCl in the catalytic version of the reaction[8,9] results in the loss of selectivity as it opens up the intermediate.

The starting materials listed in Table 1 were prepared according to reported procedures (**1a**,[16] **1b**,[17] **1c**[17] and **1d**[4]) from the corresponding allylic alcohols using Sharpless asymmetric epoxidation and kinetic resolution methods.[18,19] The chiral allylic alcohol (>96% e.e. by Mosher ester method), obtained during the preparation of **1d** by kinetic resolution, was subjected to *m*CPBA epoxidation to give a mixture of *syn* and *anti* epoxy alcohols (3:2 ratio) that could be easily separated by column chromatography to furnish pure **1e**. Reduction of cp_2TiCl_2 was carried out using dry activated Zn powder with or without $ZnCl_2$. The optimum ratios of the reagents in both methods are given in Table 1. In a typical experiment, cp_2TiCl_2 was added to a magnetically stirred suspension of dry activated Zn powder in dry THF (with, or without, freshly fused anhydrous $ZnCl_2$) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h while the color of the reaction mixture gradually changed from red to dark green. It was then cooled to −20°C and a solution of epoxy alcohol **1** in dry THF was added slowly with a syringe. The final volume of the reaction mixture was about 15 mL per mmol of **1**. The reaction mixture was allowed to warm to room temperature over a period of 2 h and stirring continued for an additional 12–16 h while the color of the reaction mixture changed from dark green to dark blue. The reaction was then quenched by slow addition of 1N HCl and extracted with EtOAc. Regular work-up was followed by purification of the crude product by stan-



Scheme 1.

dard silica gel column chromatography to furnish the diol **2**. The products were compared with known compounds prepared by us earlier[2–5,14,17] and confirmed further by ^{13}C NMR analysis of their acetonides.

The findings communicated here for the synthesis of chiral 1,3-diols from 2,3-epoxy alcohols using a Ti(III)-mediated ring opening reaction that can be carried out with excellent diastereoselectivity with trisubstituted substrates will find useful applications in the synthesis of many natural products that carry such structural moieties.

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