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The titanium-catalysed epoxidation of homoallylic α-amino alcohols

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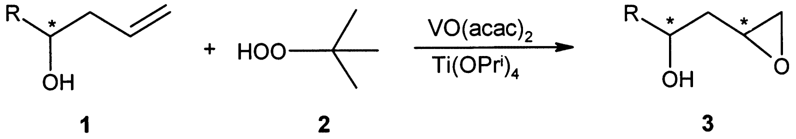
Abstract—Diastereoselective titanium-catalysed epoxidation reactions of acyclic homoallylic alcohols are presented. The results are compared to the stereochemical outcome obtained by the application of the commonly used vanadium catalyst, VO(acac)$_2$. The key role of the *syn*-bis-homoallylic carbamate group in obtaining high yields and reversed diastereoselectivities in the titanium-catalysed reactions is discussed. © 2002 Elsevier Science Ltd. All rights reserved.

The epoxidation reaction is of great importance in organic synthesis[1] as it usually allows the simultaneous introduction of two stereogenic centres. In addition, the wide range of highly regioselective ring-opening and other synthetically useful reactions of epoxides[2–4] afford access to a variety of functionalised products while maintaining full stereochemical control. However, the epoxidation reaction becomes a much more powerful synthetic tool when the configuration of the newly formed stereogenic centres can be predicted.[5–7]

Many research groups have been attracted to allylic alcohols as convenient substrates for metal-catalysed epoxidation reactions due to their high reactivity, which is caused by the directing influence of the hydroxy group.[7] Thus, allylic alcohols open the way to efficient and highly stereoselective syntheses of many natural products as well as enantiomerically pure building blocks such as 2,3-epoxy alcohols.[5,6] The systematic examination of potential catalysts has ranged from the role of various metals, such as vanadium(V),[8] titanium(IV),[9–11] zirconium(IV),[12] tungsten(VI),[13–15] arsenic(V),[16] aluminium(III),[17,18] tin(IV),[19] lanthanum(III), cerium(III), samarium(III), and ytterbium(III),[20] to the influence of ligands on the metal catalysts.[21–24] It was found that even zeolites alone catalyse diastereoselective epoxidations of allylic alcohols using *tert*-butyl hydroperoxide as the oxidant.[25]

A relatively small number of the above methods have been used in the stereoselective epoxidation of acyclic homoallylic alcohols. The enantioselective titanium-catalysed epoxidation reactions[26,27] afforded moderate yields and stereoselectivities in most cases. The diastereoselective processes employing the same catalyst seem to be more promising.[28] Vanadium(V) derivatives, typical catalysts for such diastereoselective processes, turned out to be a good choice for these oxidations in most cases, particularly after Mihelich et al. published their results,[29] which allowed the direction and degree of asymmetric induction to be predicted, depending on the olefin substitution pattern. Aluminium(III)[30] and tungsten(VI)[13,14] catalysts were also used.

Vanadyl bis-acetylacetonate combined with *tert*-butyl hydroperoxide **2** is the most commonly used catalytic system in the epoxidation of chiral homoallylic alcohols (Scheme 1). Usually, moderate *syn*-diastereoselectivities



Scheme 1.

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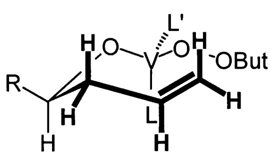
are obtained using the vanadium catalyst in the epoxidation reactions of unsubstituted terminal homoallylic alcohols of the type **1**.

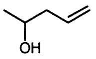
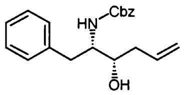
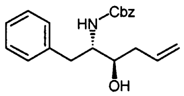
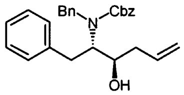
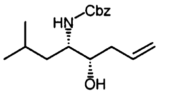
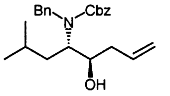
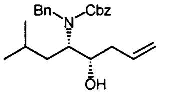
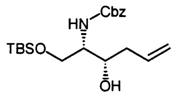
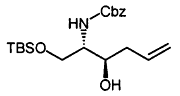
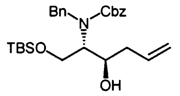
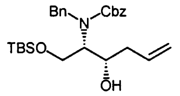
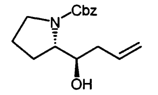
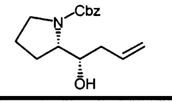
Mihelich et al.[29] proposed a chair-like transition state model **I** (Fig. 1) for this reaction, which explains the direction of diastereoselectivity by the pseudoequatorial position of the R group and suggests the best substitution pattern for obtaining the highest selectivities.



I

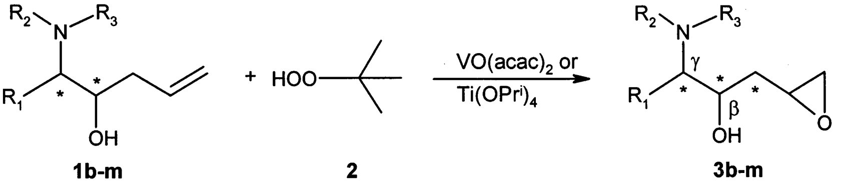
Figure 1.

Table 1. Comparison of vanadium- and titanium-catalysed epoxidations of olefins **1a**–**1m**

Substrate		Epoxidation method			
		VO(acac)$_2$/Bu^{t}OOH		Ti(OPr^i)$_4$/Bu^{t}OOH	
		Yield	*syn*:*anti*[a]	Yield	*syn*:*anti*[a]
	**1a**	70%	78:22	39%	53:47
	**1b**	87%	70:30	**78%**	**9:91**
	**1c**	61%	76:24	62%	49:51
	**1d**	85%	80:20	70%	35:65
	**1e**	83%	70:30	**88%**	**11:89**
	**1f**	81%	75:25[b]	64%	34:66[b]
	**1g**	77%	83:17	51%	47:53
	**1h**	65%	60:40	**81%**	**8:92**
	**1i**	53%	64:36	58%	45:55
	**1j**	79%	78:22	61%	39:61
	**1k**	67%	77:23	86%	35:65
	**1l**	55%	78:22	76%	37:63
	**1m**	46%	74:26[b]	50%	58:42

[a] All ratios were determined by ^{1}H NMR, except for [b]

[b] The ratios were weighted after cyclisation to corresponding pyrrolidines or pyrrolizidines and chromatographic separation



Scheme 2.

Our recent research into the asymmetric transformations of unsaturated amino alcohols to afford biologically active heterocycles has led us to unexpected discoveries. Indeed, the simple homoallylic alcohol **1a** (Scheme 1, $R=Pr^i$)[31] is epoxidised with *syn*-selectivity of 78:22 (Table 1).[34] Moreover, in structurally more complex compounds, such as the above-mentioned amino alcohols, substitution at the bis- and trishomoallylic position (substrates **1b**–**1m**, Scheme 2; R^1, R^2, R^3-see Table 1) has virtually no influence on the diastereoselectivity of the reaction.

On the other hand, olefin **1a** shows no diastereoselectivity in the titanium-catalysed epoxidation reaction.[35] The influence of other substituents present in compounds **1b**–**1m** is rather weak, except for compounds **1b**, **1e** and **1h**, possessing the *N*-unsubstituted carbamate functionality *syn* to the hydroxy group, where remarkably high reactivity was observed. These olefins furnish mixtures of epoxy alcohols with high diastereoselectivity, but of opposite configuration, as compared to the results of the vanadium-catalysed reactions. The exceptionally high rates of the epoxidation reactions of **1b**, **1e** and **1h** indicate that the process could be ligand-accelerated; in this case the reactant and the accelerating ligand would actually be the same molecule. The stereochemical course of these reactions can be explained by deprotonation of the carbamate functionality and the formation of titanium chelates of the type **II** (Fig. 2), in which the substituent is forced into a pseudoaxial position by the chelation process, thereby reversing the diastereoselectivity of the reaction. Compounds **1c** and **1i**, with an *anti* relationship between the carbamate and hydroxy groups, would form chelates of the type **III**, which are destabilised by 1,2-*cis* steric repulsion from the substituents of the five-membered ring. This results in loss of diastereoselectivity as well as lowering the rate of the reaction. Compounds **1d**, **1f**, **1g**, and **1j**–**1m** contain the *N*-benzyl carbamate group and therefore are unable to form the above-mentioned chelates, what explains the low reactivity and poor diastereoselectivity of these reactions.

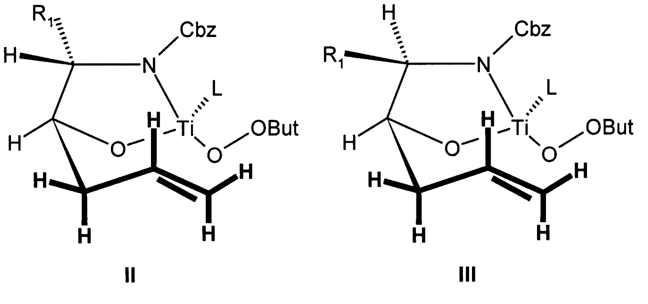


Figure 2.

The direction of asymmetric induction was assigned after reductive deprotection of the amino functionality and subsequent cyclisation of the obtained mixtures of *syn* and *anti* γ-amino epoxides **3b**–**3m** to the corresponding hydroxymethyl pyrrolidines. After chromatographic separation of the mixtures, relative configurations at the pyrrolidine rings were assigned using NOE techniques.

This is the first published example of significant assistance from a bis-homoallylic function in the titanium-catalysed epoxidation of homoallylic alcohols. It introduces a new method for efficient, highly diastereoselective epoxidation of γ-amino-β-hydroxy olefins, and presumably gives a new access to diols of specific relative configuration.

Compounds **1b** and **1j** have proven that the vanadium-catalysed epoxidation is a convenient reaction for introducing new stereogenic centres in total syntheses of (+)-preussin[32] and (−)-bulgecinine,[33] respectively. The reversed high diastereoselectivity in the titanium-catalysed epoxidation is therefore promising as a means to synthesise their diastereoisomers. Full results are to be published in the near future, including investigations into other metal catalysts in the epoxidation reaction, such as aluminium(III) derivatives, which allow other types of diastereocontrol.

Acknowledgements

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35. General procedure for titanium-catalysed epoxidation: CH_2Cl_2 with 1 equiv. of $Ti(OPr^i)_4$, 2 equiv. of Bu^tOOH and 3 Å molecular sieves at −15°C for 5 h (compounds **1b**, **1e** and **1h**) or 2–4 days (other olefins).