Ligand-accelerated vanadium-catalysed epoxidation in water†

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Vanadium-catalysed epoxidation of allylic alcohols, a classical example of ligand-decelerated catalysis, in water it turns into a ligand-accelerated process.

Asymmetric epoxidation of allylic alcohols is regarded as one of the major tools for introducing chirality into organic molecules.[1] Its wide recognition springs from the discovery by Sharpless and Katsuki of a very efficient process mediated by Ti-tartrate complexes.[2] Another useful methodology, pioneered by Sharpless,[3] is based on V-hydroxamate complexes. Attractive features of V catalysis,[4] in contrast to Ti, include low catalyst loading (1 mol% or less) and high tolerance of air and moisture. However, for more than two decades it remained in the shadow of Ti catalysis, until recently, when Yamamoto reported on a new family of hydroxamic acid ligands[5,6] which, in the latest development,[7] for the first time, surpassed the Ti(IV) systems in terms of enantioselectivity. However, there is a fundamental difference between the two methodologies: the Ti-mediated process is accelerated by ligands, while in the case of V, coordination of ligands results in a significant deactivation of the catalyst.[8] Despite a steady progress in tackling the ligand deceleration problem,[6,7,9] complexes of V with chiral ligands are still unable to match the rate of epoxidation exhibited by the non-coordinated vanadyl alkoxides.

Herein, we wish to report on our finding that in water, V catalysis turns into a ligand-accelerated process. Employing water as a solvent offers numerous advantages over traditional organic solvents.[10] Apart from the favourable environmental impact and low cost, it brings simplification to the synthetic protocols and the product isolation technique.

A selection of bidentate chiral hydroxamic acids **1–3** employed in this work are shown in Fig. 1. Compound **1** exhibited the best reactivity in the series of sulfonamide-derived hydroxamic acids,[9] ligand **3** represents a family of imido hydroxamic acids, introduced by Yamamoto, which were successfully employed in asymmetric epoxidation of allylic and homoallylic alcohols.[6] Hydroxamic acid **2** can be viewed as a hybrid of **1** and **3** sharing the sulfonamide functionality with **1** while the rest of the molecule duplicates **3**. Geraniol **4** and 2-methylcinnamyl alcohol **5** were chosen as the model substrates.

Asymmetric epoxidation catalysed by V complexes with ligands **1–3** in toluene was compared against the same reaction in water (Scheme 1, Table 1). In toluene, the standard conditions were employed[3,5,6,9] which included VO(*i*-PrO)$_3$ as a source of V (1 mol%) and anhydrous *t*-BuOOH as a stoichiometric oxidant. To take the full advantage of water as a solvent, alternative V sources and oxidants were assessed. Thus, $VOSO_4 \cdot H_2O$ was found to be as efficient as the more expensive, commonly employed VO(*i*-PrO)$_3$ or VO(acac)$_2$, while $(NH_4)VO_3$ proved less reactive. Furthermore, anhydrous *t*-BuOOH was replaced with a 70% aqueous solution.

Overall, the epoxidation in water proceeded at a lower rate than in toluene, however, the enantioselectivity was not affected. The sulfonamide-derived ligands **1** and **2** reacted faster and gave better conversions than their imido counterpart **3** boosting our earlier observations of the accelerating effect of the sulfonamide functionality.[9] Remarkably, ligands **2** and **3**, sharing the same *tert*-leucine framework, produced the opposite enantiomers of the products (compare entries 2 and 5 with entries 3 and 6) suggesting that the remote functional group plays a crucial role in shaping up the transition state which has still not been established in detail.[9,11]

Carrying out epoxidation in aqueous solution, particularly in the presence of a Lewis-acidic catalyst, can be complicated by a competing hydrolytic opening of the epoxide ring, thus affecting the yield of the target product.[12] In this regard, the rate of epoxidation in water represents an important factor in choosing a

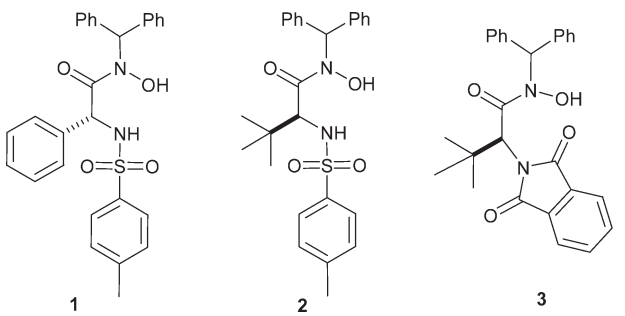
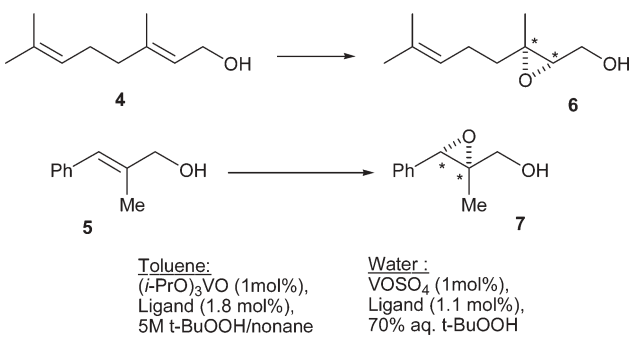


Fig. 1 Chiral hydroxamic acids.



Scheme 1 Asymmetric epoxidation in toluene and water.

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Table 1 Asymmetric epoxidation catalysed by V complexes of chiral hydroxamic acids **1–3** in toluene and water

		Toluene[a]		Water[b]	
Entry	Ligand	Yield (%)	ee (%), config.[c]	Yield (%)	ee (%), config.[c]
*Geraniol (**4**)*					
1	**1**	95	64 (*S*,*S*)	73	60 (*S*,*S*)
2	**2**	93	66 (*S*,*S*)	52[d]	32 (*S*,*S*)
3	**3**	97	54 (*R*,*R*)	22[d]	60 (*R*,*R*)
*2-Methylcinnamyl alcohol (**5**)*					
4	**1**	90	62 (*S*,*S*)	79	59 (*S*,*S*)
5	**2**	87	51 (*S*,*S*)	73	46 (*S*,*S*)
6	**3**	89	78 (*R*,*R*)	13[d]	78 (*R*,*R*)

[a] The reaction was carried out in toluene at −20 °C (ligand **1**, **2**) or at 0 °C (ligand **3**) for 20 h using 5–6 M solution of *tert*-butyl hydroperoxide in nonane (1.5 equiv.) as the oxidant, the catalyst was generated *in situ* from $VO(i\text{-}PrO)_3$ (1 mol%) and the ligand (1.8 mol%). [b] The reaction was carried out in water at 0 °C for 20 h using 70% aqueous solution of *tert*-butyl hydroperoxide (1.5 equiv.) as the oxidant, the catalyst was generated from vanadyl sulfate hydrate (1 mol%) and the ligand (1.1 mol%). [c] Determined by chiral GC. The absolute configuration of the products was deduced from their optical rotation and comparison with the literature data. [d] Conversion rather than yield, determined by GC and ^{1}H NMR.

suitable ligand, as the formation of epoxide should be significantly faster than its hydrolysis. Both sulfonamide ligands **1** and **2** provided good conversions while keeping hydrolysis to a minimum ($\leqslant$5%). Based on better overall performance, the subsequent experiments were carried out with ligand **1**.

Next, we investigated the effect of catalyst loading employing geraniol (**4**) as a model substrate. The results are summarised in Table 2. Surprisingly, conversion without a ligand turned out to be very low (18%) (entry 1) while the ligand alone did not promote any reaction at all (entry 2). On the other hand, addition of 1 equiv. of ligand **1** with respect to V resulted in a nearly complete conversion to the epoxide **5** (entry 4). Furthermore, even at 0.5 equiv. of the ligand content the catalytic system remained equally effective (entry 3) which represented a reverse trend compared to the reaction in organic solvents. The process in water turned into a ligand-accelerated catalysis. As expected, increasing the ligand/V ratio above 1.5 : 1 reduced the reaction rate as a result of the formation of VL_2 complexes that are known to be catalytically inactive (entries 8, 9).[3,8]

Table 2 Effect of ligand–V ratio and temperature on the asymmetric epoxidation of geraniol (**4**) in water[a]

Entry	Ligand **1**/mol%	V/mol%	*T*/°C	Conversion (%)	ee (%)
1	0	1	0	18	—
2	1	0	0	<1	—
3	0.5	1	0	84	57
4	1	1	0	93	60
5	1.1	1	0	73[b]	60
6	1.1	1	20	100[c]	—
7	1.1	1	−20	69[bd]	69
8	1.5	1	0	76	61
9	2.5	1	0	47	61

[a] The reactions were carried out for 20 h using 70% aqueous solution of *tert*-butyl hydroperoxide (1.5 equiv.) as the oxidant; the catalyst was generated from vanadyl sulfate hydrate and ligand **1**. [b] Isolated yield. [c] Opening of the epoxide took place (ref. 12). [d] The reaction was carried out in a 3 : 1 water–methanol mixture.

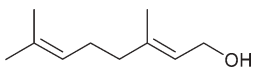
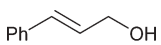
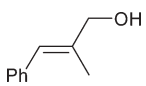
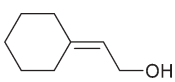
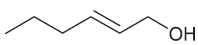
The epoxidation is likely to proceed in the organic phase, as water soluble V salts exhibited poor conversion. Hydroxamic acid, a well-known key structural fragment of natural siderophores,[13] coordinates to the V ion and transfers it to the organic phase where epoxidation is taking place. In these circumstances, the concentration of the catalytically active V complex will be controlled by the concentration of the ligand. Once extracted from water, V remains in the organic layer as a complex with hydroxamic acid; the aqueous phase turns out to be essentially free from the metal after the reaction is complete.

At room temperature, hydrolysis of the epoxide ring became the prevailing process leading to the corresponding triol in quantitative yield (entry 6). On the other hand, carrying out reaction at −20 °C, resulted not only in complete suppression of the undesired hydrolysis, but also led to increased enantioselectivity (entry 7). In order to prevent the reaction mixture from freezing at −20 °C, a 3 : 1 water–methanol mixture was employed. Note that in methanol alone the epoxidation is very sluggish,[9] while in aqueous solutions methanol content up to 25% is tolerated.

The efficacy of the protocol was assessed using the epoxidation of a range of allylic alcohols (Table 3).‡ The conditions in each case were optimised to maximise the yield of the target epoxides. Despite moderate selectivities, the results can be viewed as a step towards greener technologies.

In conclusion, we have developed a practical protocol for V-catalysed asymmetric epoxidation of allylic alcohols in water. We have demonstrated that in water the process becomes

Table 3 Asymmetric epoxidation of allylic alcohols in water using V complex with ligand **1**[a]

Entry	Substrate		*T*/°C	*t*/h	Yield (%)	ee (%)[b] (config.[c])
1		**4**	−20	20	69[d]	69 (*S*,*S*)
2		**8**	0	60	55[e]	57 (*R*,*R*)
3		**5**	0	60	79[e]	59 (*S*,*S*)
4		**9**	−20	60	92[de]	72 (+)
5		**10**	0	60	61	70 (*R*,*R*)
6		**11**	0	60	41[e]	63 (*S*,*R*)

[a] The reaction was carried out on 1 mmol scale. The catalyst was generated *in situ* from vanadyl sulfate hydrate (2 mol%) and ligand **1** (2.2 mol%), unless stated otherwise. [b] Determined by chiral GC and chiral HPLC. [c] The absolute configuration of the products was deduced from their optical rotation and comparison with the literature data. [d] The reaction was carried out in a 3 : 1 water–methanol mixture. [e] The catalyst was generated from vanadyl sulfate hydrate (3 mol%) and ligand **1** (3.3 mol%).

ligand-accelerated and an excess of the ligand is no longer required. A range of allylic alcohols were epoxidised with up to 72% ee.

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Notes and references

‡ General procedure for asymmetric epoxidation in water: Vanadyl sulfate hydrate (3.3 mg, 20 μmol or 5.0 mg, 30 μmol), ligand **1** (10.7 mg, 22 μmol or 16.0 mg, 33 μmol) and allylic alcohol (1 mmol) were added to distilled water (3 mL) for the reactions at 0 °C or a 3 : 1 water–methanol solution (3 mL) for the reactions at −20 °C. The mixture was stirred at room temperature for 30 min and then cooled to 0 °C or −20 °C. A 70% aqueous solution of *t*-BuOOH (0.2 mL, 1.5 mmol) was added and the mixture was stirred at the same temperature for the period of time indicated in Table 3. The reaction mixture was then quenched with a concentrated solution of Na_2SO_3 (10 mL) and after stirring for 1 h at 0 °C it was extracted with dichloromethane (2 × 20 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. Purification of the products was accomplished by column chromatography on silica gel (15 × 3 cm) with a 4 : 1 mixture of *n*-hexane–ethyl acetate. The absolute configuration of the epoxide products was assigned by comparison of their optical rotations with the literature data; the enantiomeric excess was determined using analysis by chiral GC or HPLC.

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