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Practical Asymmetric Oxidation of 3-[1-(2-Methylphenyl) imidazol-2-ylthio]propan-1-ol Based on a Titanium - Mandelic Acid Complex

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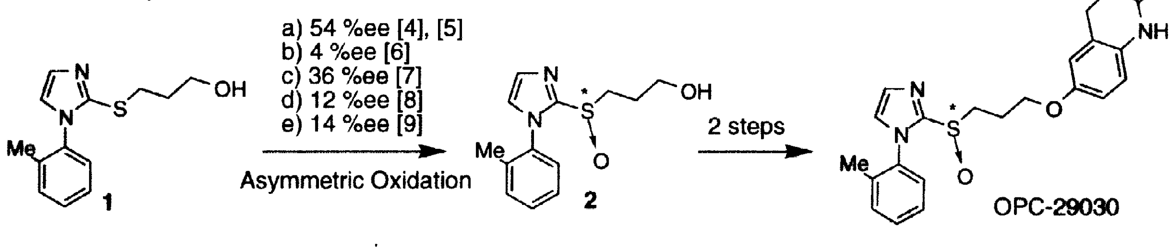
Abstract

A practical and effective asymmetric oxidation of prochiral sulfide **1** to (*S*)-**2** has been described. The enantioselectivity was not found to be influenced by moisture and moderate to high selectivity was obtained at room temperature (25 °C).

Keyword: Asymmetric induction; Ligands; Oxidation; Sulfides

OPC-29030, namely, (*S*)-(+)-3,4-dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)sulfinylpropoxy]-2(1*H*)-quinolinone is a sulfinyl derivative which exhibits a potent inhibition of the platelet adhesion by interfering with the release of 12(*S*)-hydroxyeicosatetraenoic acid (12-HETE) from platelets [1], and is now under clinical trial. To date, enantiomerically pure OPC-29030 has been synthesized with a modified Sharpless oxidation of 3-[1-(2-methylphenyl)imidazol-2-ylthio]propan-1-ol **1** [2] as a step introducing chirality of the molecule. However, the optical yield was low. Hence, a better stereoselective mono-oxidation of the sulfide was attempted (Scheme 1). Here, we report a practical and effective asymmetric oxidation of **1** to give (*S*)-**2** [3] which is a key compound for the synthesis of OPC-29030.

Scheme 1: Synthetic Route to OPC-29030



a) (+)-DET(2 eq.), CHP(1 eq.), $Ti(O^iPr)_4$(0.5 eq.), MS4A in CH_2Cl_2, -20 °C; b) (+)-DET(1 eq.), CHP(1 eq.), $Ti(O^iPr)_4$ (0.5 eq.), H_2O (0.5 eq.), MS4A in $C_2H_4Cl_2$, -30 °C; c) (+)-binaphthol(1eq.), CHP(1 eq.), $Ti(O^iPr)_4$ (0.5 eq.), MS4A in CH_2Cl_2, 25 °C; d) Davis reagent in CH_2Cl_2, 25 °C; e) Salen complex , H_2O_2 ^{t}BuOH soln. in MeCN, 25 °C .

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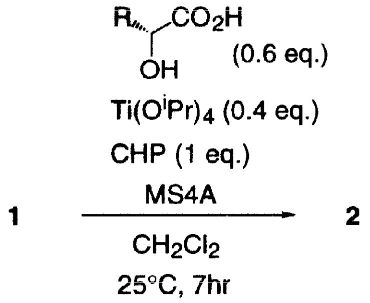
In order to achieve a high degree of enantioselectivity for the catalytic oxidation, a combination of chiral mandelic acid , titaniumtetraisopropoxide, cumene hydroperoxide (CHP)[1], molecular sieves 4A was found to be a good recipe(Table 1, Entry1). The optimized ratio of each reagent is shown in parentheses. The high enantiomeric excess (76 %ee)[2] obtained by this method is superior to the existing literature methods [4-9] .

Table 1: Oxidation Using Titanium-α-hydroxycarboxylic acids Complex



Entry	R	Yield of **2** (%)	Ee of **2** (%)*
1	Ph	89	76
2**	Ph	56	75
3	*p*-Methoxyphenyl	63	77
4	*p*-Chlorophenyl	70	51
5	Cyclohexyl	89	48
6	Isopropyl	69	31

* Enantiomeric excess was determined by HPLC (CHIRALCEL OJ®).
**In the presnce of H_2O of 1 equimolar instead of MS4A

Several beneficial aspects of the present oxidation may be summarized as below. (1) The reaction proceeds at ambient temperature (25°C)[3] affording products with moderate to high enantioselectivity. (2) The chiral ligand, mandelic acid, could be recovered readily by extracting with a weak base. (3) The presence of water in the reaction mixture has no significant influence on the stereoselectivity, although the reaction rate is slightly reduced (Table 1, Entry 2). This feature is particularly useful for a large scale synthesis. (4) The presence of the hydroxyl group in the substrate appears to be important for the high optical yield.[4]

The synthetic route involving a facile asymmetric oxidation step may be useful for the practical synthesis of OPC-29030 or similar compounds. Thus the application of this method to other substrates is currently under investigation.

[1] In the case of using ^{t}BuOOH, low selectivity (20 %ee) was obtained. [2] One recrystallization of the crude product improves the optical purity to more than 99.5 % ee. [3] While the rate of the reaction was found to be slow at 0 °C, the enantioselectivity was not at all affected. [4] In the case of using 2-methylthio-1-(2-methylphenyl)imidazole as the substrate, low selectivity (6 %ee) was obtained.

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