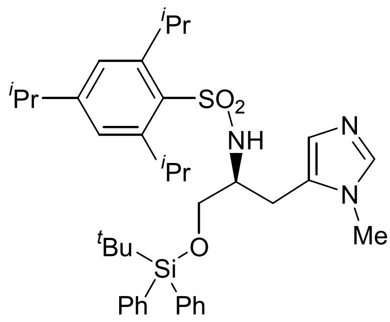
Minimal Artificial Acylase

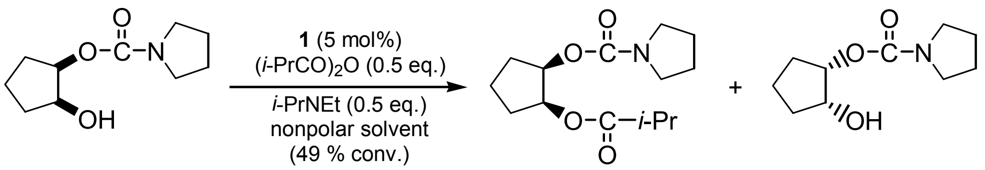
for the Kinetic Resolution of Racemic Alcohols



T2223 **1**

The development of environmentally friendly reaction processes for organic synthesis is currently a high priority goal in modern organic chemistry. One type of environmentally friendly reaction processes is based on enzymatic reactions for organic syntheses. However, the enzymatic reaction have problems of their own. For example, enzymatic reactions have low substrate generality, low rate of reaction, and a narrow range of reaction conditions. Moreover, since enzymes are large molecules, the reaction processes require relatively large amounts of enzymes.

Recently, Ishihara and co-workers have studied minimal artificial enzymes to overcome various problems of enzymatic reactions. One reagent that has been developed is a L-histidine-derived minimal artificial catalyst **1**. Ishihara and co-workers reported that **1** was a very effective catalyst for kinetic resolution of racemic alcohols by selective acylation. For example, kinetic resolution of (±)-*cis*-1-(*N*-pyrrolidinecarbonyloxy)-2-cyclopentanol **2** was achieved by selective acylation with isobutyric anhydride catalyzed by **1** to obtain (1*R*,2*S*)- **3** and (1*S*,2*R*)- **2** in high optical purity [$S(k_{fast}/k_{slow}) = 93$]. Moreover, the *S* value was increased to 132 when the reaction was done at –20ºC. Isobutyric anhydride is an effective acylating agent.



(±)-**2** $S\ (k_{fast} / k_{slow}) = 93$ (1*R*,2*S*)-**3** (94 %*ee*) (1*S*,2*R*)-**2** (90 %*ee*)

Hydrogen bonding between the sulfonamide proton of **1** and *N*-pyrrolidinecarbonyl group of alcohols plays an important role in the optical resolution. Interestingly, the catalytic activity of catalyst **1** is much higher than for the case of 1,5-dimethylimidazole. Acylation proceedes by adding 0.5 equivalent molar of isobutyric anhydride to racemic alcohols, and achieves conversion of nearly 50%. This is and extremely high, atom efficiency. Moreover, **1** can also be used as catalyst for the kinetic resolution of chain 1,2-diols, β-hydroxycarboxylic acids, and 2-amino alcohols after the suitable derivatization.

***Keyword** : kinetic resolution of racemic alcohols*

2007. Mar., R-5069E

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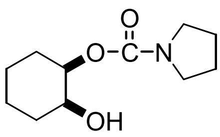
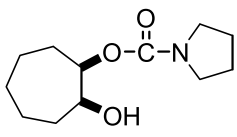
Other examples [reaction condition : **1** (5 mol%), (i-$PrCO)_2O$ (0.5 eq.), 0ºC]



S = 87



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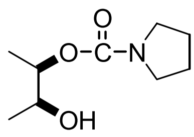

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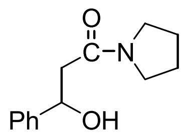

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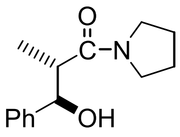

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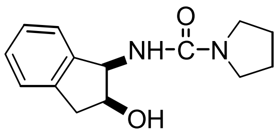

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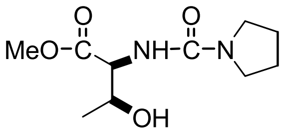

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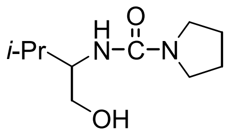
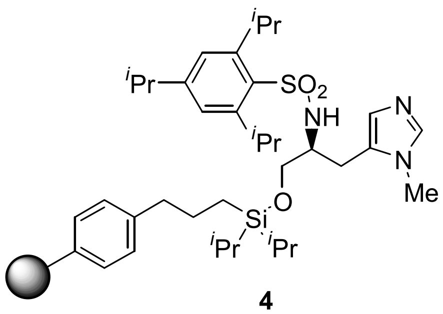


S = 39

The molecular weight of acylase is well over 10,000, while the molecular weight of **1** is much less, being only 660. Furthermore, catalyst **1** is so much more simple stereochemically, having only the one chiral center, which is derived from L-histidine. **1** has imidazole base of catalytic active center and sulfonamide proton which is required for the selective binding of the substrate through the chiral carbon atom in the molecule. With these two feature working together, the kinetic resolution is accomplished effectively. The quantity of catalyst **1** required is 5 mol% or less, and for the kinetic resolution of 1 mmol of racemic alcohol, 0.05 mmol (33 mg) or less of **1** is required.

In addition, Ishihara and co-workers have developed the polystyrene-bound catalyst **4** and have succeeded in recovering and reusing the catalyst **4**. Catalyst **4** can be easlily recovered from the reaction mixture by filtration, and it can be reused more than 10 times in acylation without loss of any activity or selectivity. Catalyst **4** is easily prepared from **1**.



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T2223 *N*$^{\alpha}$-(2,4,6-Triisopropylbenzenesulfonyl)-*O*-(*tert*-butyldiphenylsilyl)-π-methyl-L-histidinol (**1**) 100mg

Reference

K. Ishihara, Y. Kosugi, M. Akakura, *J. Am. Chem. Soc.*, **2004**, *126*, 12212.
Y. Kosugi, K. Ishihara, *Preprints of Chemical Society of Japan 85th Spring Meeting*, **1** C1-47, **2005**.
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