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Enzymatic Esterification of 1-Ferrocenylethanol: An Alternate Approach to Chiral Ferrocenyl Bis-phosphines

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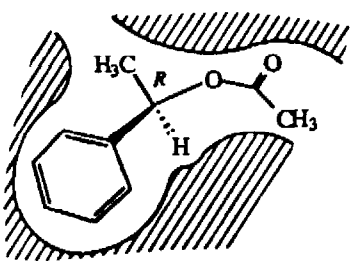
Summary: 1-Ferrocenylethanol was enzymatically esterified with high *R*-enantioselectivity by the lipase from *Pseudomonas fluorescens*, indicating that this organometallic compound behaves similarly to organic analogs within the enzyme active site (according to an active site model). Efficient separation of the enantiomers was effected by selective reaction of the ester with dimethylamine followed by simple aqueous acid extraction.

The largely unexplored marriage between organometallic and biocatalytic chemistry affords great potential, especially for the preparation of optically active catalysts and ligands. Though prior work has verified the ability of organometallic species to undergo both microbial[1] and cell-free enzyme[2,3,4] transformations,the behavior of organometallic species compared to organic materials within the enzyme active site has remained unexplored. The investigation of the applicability of known enzyme active site models to an organometallic substrate such as 1-ferrocenylethanol would provide much enlightenment. The recent report by Wong and coworkers on the enzymatic esterification of this compound[3] prompts us to report similar investigations based on active site considerations that afforded improved results.

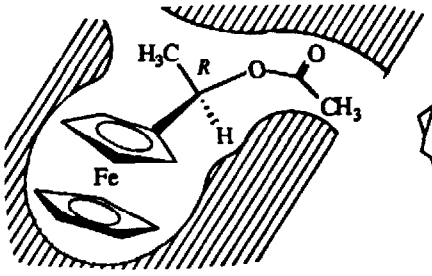
Reliable active-site models are available for several hydrolase enzymes.[5] The lipase from *Pseudomonas fluorescens*[5d,6] has a highly useful active-site working hypothesis.[5d,e] A schematic of this model that is effective for rationalizing both reactivity and enantioselectivity of acyclic compounds is shown below for phenethyl acetate (**1a**).[5d] This active site model contains, besides the catalytically active serine hydroxyl site, a hydrophobic pocket and a niche that will accept only an α-hydrogen, directing the *R*-enantioselectivity.

Our investigation sought to determine whether 1-ferrocenylethyl acetate would function as an organometallic analog of phenethyl acetate for biocatalytic scrutiny. As indicated by the reactivity and enantioselectivity described below, the ferrocenyl moiety performs similar to **1a** as an anchor in the hydrophobic pocket of the enzyme according to the active site model as depicted in **1b**, thus providing a useful positive probe for active site interactions with an organometallic compound. In addition, a highly enantioselective kinetic resolution of a 1-ferrocenylethanol derivative followed by an efficient separation would provide an alternative to classical resolution[7] or

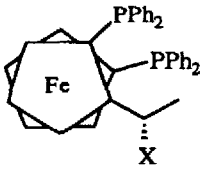
chromatographic separation[8] for the preparation of chiral ferrocenyl bis-phosphines such as BPPFA (**2a**) and BPPFOH (**2b**), highly useful ligands for homogeneous asymmetric catalysis.[9]



1a



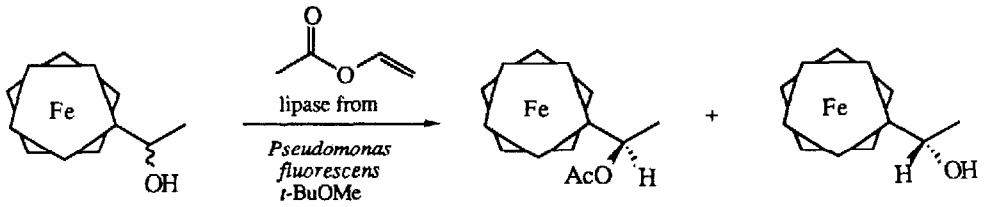
1b



2

a: X = NMe_2
b: X = OH

As reported by Wong et al.,[3] the documented lability of 1-ferrocenylethyl acetate to hydrolysis[10] rendered an enzymatic hydrolysis impossible. However, the reverse reaction, enzymatic esterification in organic solvents,[11] an area that has great potential due to the water-sensitivity of many organometallic materials, was still feasible. Therefore, racemic 1-ferrocenylethanol (**3**) was submitted to enzymatic esterification (lipase from *Pseudomonas fluorescens*, 3 equiv vinyl acetate,[12] organic solvent). The esterification reaction proceeded smoothly at room temperature and with high enantioselectivity, affording both the *R*-acetate *R*-(-)-**4** ($[\alpha]_D^{25}$ -25.5° (c. 1.755, ethanol), lit. for *R*-**4**,[9] $[\alpha]_D^{25}$ -30.5° (c. 1.3, ethanol)) and recovered *S*-alcohol *S*-(+)-**3** ($[\alpha]_D^{25}$ +28.8° (c. 1.165, benzene), lit. for *S*-**3**,[9] $[\alpha]_D^{25}$ +32.0° (c. 1.2, benzene)) in high optical purities (Table I),[13] indicating "normal" interactions of the ferrocenyl moiety within the active site.



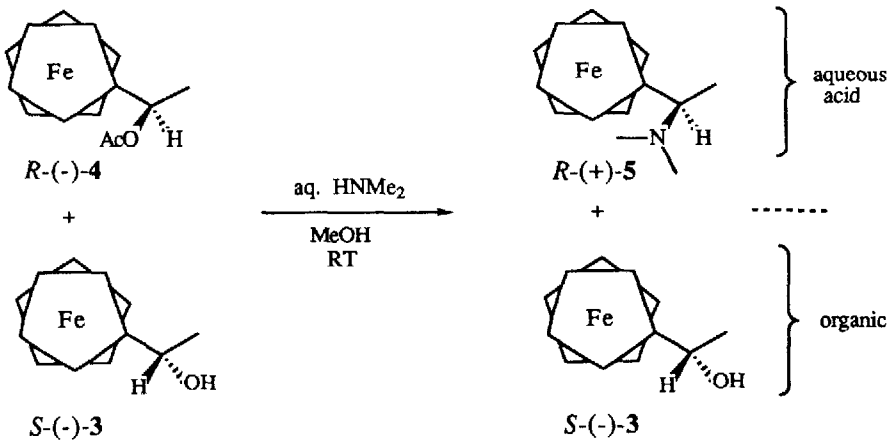
3 *R*-(-)-**4** *S*-(+)-**3**

Organic solvents reduce enzyme activity,[11] necessitating extended reaction time even in the optimal organic solvent (*t*-butyl methyl ether) to achieve 50% conversion to acetate at room temperature. However, organic solvents also increase enzyme rigidity,[11] allowing the use of elevated temperatures to increase the esterification rate with little erosion of enantioselectivity (Table I).[14]

Table I

Temperature	Time (h)	Percent Conversion	% e.e. *R*-**4**	% e.e. *S*-**3**
RT	294	50.0	96	92
40° C	144	49.5	92	90
60° C	96	50.5	92	90

A significant problem with enzymatic hydrolyses or esterifications of chiral alcohol derivatives is the separation of the differentiated enantiomers. When separation of the alcohol and ester by distillation is not possible, chromatography is often the only viable method. This becomes cumbersome as the scale of the reaction is increased, and other solutions are desirable. In this case the unusual configurational stability and facile formation of the 1-ferrocenylethyl carbonium ion[10,15] allowed selective reaction of the acetate **4** in the mixture of **3** and **4** with aqueous dimethylamine (methanol, room temperature).[10] This afforded the *R* -*N*,*N*-dimethylamino derivative *R*-(+)-**5** (90%) ($[\alpha]_D^{25}$ +12.8° (c. 1.21, ethanol), literature for *S*-(-)-**5**,[6a] $[\alpha]_D^{25}$ -14.1° (c. 1.6, ethanol)) and unreacted alcohol *S*-**3** (90%) without racemization of either species.[10,12] A simple acid extraction (10% aqueous citric acid) separated the amine from the alcohol, and the alcohol could then be recrystallized to optical purity.



Either the alcohol or amine can be elaborated to the optically active bis-phosphines mentioned above,[9,16] affording a unique method for the preparation of these chiral ligands while demonstrating the utility of the application of active-site considerations to the combination of biocatalytic and organometallic chemistry.

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(13) For *S*-**3**, the optical purity was determined by ^{1}H nmr analysis in the presence of the chiral shift reagent Eu(tfc)$_3$ after separation from the ester. The acetate *R*-**4** was hydrolyzed (1:1 acetone/water) to alcohol *R*-**3** with retention of configuration[9] and analyzed as above.

(14) A small amount of non-enzymatic esterification at the elevated temperatures as indicated by control reactions may account for part of the observed reduction in optical purities.

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