

# Dr. Richard Fish

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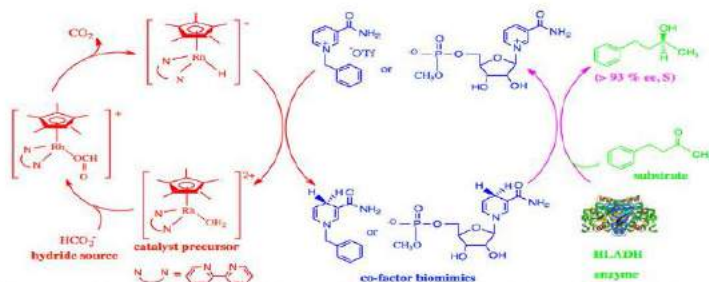
“LaTandem Catalyzed, Regioselective Formation of 1, 4-NADH Biomimetic Analogs, N-Substituted-1,4-Dihydronicotinamides, with  $[\text{Cp}^*\text{Rh}(\text{bpy})\text{H}]^+$ , Coupled to Enantioselective Reductions of Prochiral Ketones to Chiral S-Alcohols with Horse Liver Alcohol Dehydrogenase, and to Engineered Cytochrome P450s for Selective C-H Oxidation Reactions”

## Abstract



We present two novel tandem catalysis approaches for the chiral synthesis of S-alcohols from reduction of their prochiral ketones with Horse Liver Alcohol Dehydrogenase (HLADH), and selective C-H oxidation reactions with protein engineered Cytochrome P450s. We utilized a co-factor regeneration procedure with three biomimetic NAD<sup>+</sup> models that do not contain the pyrophosphate, nor the adenosine group, and either/or a ribose, N-

1-benzylnicotinamide triflate, **1**, N-4-methoxybenzylnicotinamide triflate, **2**, and -nicotinamide-5'-ribose methyl phosphate, **3**, in conjunction with in situ formed  $[\text{Cp}^*\text{Rh}(\text{bpy})\text{H}]^+$  from  $[\text{Cp}^*\text{Rh}(\text{bpy})(\text{H}_2\text{O})]^{2+}$  ( $\text{Cp}^* = 5\text{-C}_5\text{Me}_5$ , bpy = 2,2'-bipyridyl) and the hydride source, sodium formate, to regioselectively provide their 1,4-NADH analogs, N-benzyl-1,4-dihydronicotinamide, **4**, N-4-methoxybenzyl-1,4-dihydronicotinamide, **5**, and 1,4-dihydronicotinamide-5'-ribose methyl phosphate, **6**. Surprisingly, the 1,4-NADH biomimics, **4** and **6**, were recognized, in the second tandem catalysis approach, by the natural 1,4-NADH dependent enzyme, HLADH, for catalyzed, highly enantioselective conversions of prochiral ketones to chiral S-alcohols (Scheme). Furthermore, the use of protein engineered cytochrome P450 enzymes provided improved molecular recognition of the above mentioned 1,4-NADH biomimetic co-factors, **4** and **5**, for selective C-H oxidation reactions. For example, 1,4-NADH dependent mutants of natural 1,4-NAD(P)H dependent P450 BM-3 and 1,4-NADH dependent P450 CAM, with biomimetic co-factors **4** and **5**, provided selective oxidation of *p*-nitrophenoxydecanoic acid to  $\omega$ -oxydecanocarboxylic acid and *p*-nitrophenol, via C-H hydroxylation and  $\beta$ -hydrogen elimination, while oxidation of camphor provided hydroxycamphor, respectively.



**Scheme.** Tandem catalysis: biomimetic co-factor regeneration, followed by reduction of prochiral ketones to chiral S-alcohols, with horse liver alcohol dehydrogenase (HLADH).

FRIDAY

April

20

4:00 p.m.

Jones Physical  
Science Center  
(JONES) 006

Refreshments will be  
served at 3:45 p.m.

