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A PRACTICAL ASYMMETRIC SYNTHESIS OF CARNITINE

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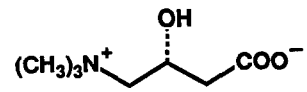
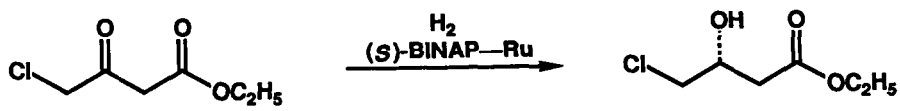
Summary: The first efficient chemical synthesis of (*R*)-carnitine has been accomplished on the basis of homogeneous enantioselective hydrogenation of ethyl 4-chloro-3-oxobutanoate.

We recently demonstrated that the BINAP-based Ru(II) catalysts have remarkable chiral recognition ability in hydrogenation of functionalized ketones.[1,2] Disclosed herein is the application of the enantioselective catalysis to chemical synthesis of (*R*)-carnitine (vitamin B_T) (**1**), a physiologically and pharmacologically significant agent, which is responsible for the human metabolism and transport of long-chain fatty acids through the mitochondrial membrane.[3]



1

The conditions effecting enantioselective hydrogenation of 3-oxobutanoate[1] failed to hydrogenate the chloro analogue **2** in a satisfactory manner. Thus the reaction of **2** catalyzed by $Ru(OCOCH_3)_2$[(*S*)-binap] or RuX_2[(*S*)-binap] (X = halogen)[4] under the standard conditions (ethanol as solvent, room temperature, 100 atm, 25–40 h) afforded the desired (*R*)-alcohol **3** in only <70% ee. The inefficient enantiofacial differentiation is perhaps due to the competitive directing effects of the ester group and halogen atom present in the same molecule.[2] Fortunately, however, a surprising chiral efficiency was obtained by the high-temperature, short-period reaction. Both $Ru(OCOCH_3)_2$(binap) and RuX_2(binap) (X = Cl, Br) were usable as the catalyst precursors. For example, when a 3.5 M ethanolic solution of **2** containing 0.05 mol % of $Ru(OCOCH_3)_2$[(*S*)-binap] was stirred under 100 atm of hydrogen at 100 °C, the hydrogenation was completed within 5 min, giving the (*R*)-alcohol **3** in 97% ee. The isolated yield of the 24-g scale reaction[6] was 97%, bp 74–75 °C/1 mmHg, $[\alpha]_D^{21}$ +20.9° (*c* 7.71, $CHCl_3$). In a similar manner, the *S* enantiomer[7] was prepared by the hydrogenation with the (*R*)-BINAP-based catalyst. The chloro alcohols can be converted to homochiral **1**, the *S* enantiomer,[9] or their salts by the standard functional group



2 **3**

transformation[8,10] followed by recrystallization. The chiral chloro alcohols also serve as intermediates for the synthesis of biologically interesting 4-amino-3-hydroxybutyric acid (GABOB),[13] 4-hydroxypyrrolidin-2-one,[10a,11] etc.

The (*R*)-alcohol, **3**, in high enantiomeric purity has been prepared by biological reductions of 4-chloro-3-oxobutanoates.[8,12] Syntheses of (*R*)-carnitine (**1**) from some naturally occurring chiral substances were also recorded.[13a-d] The present method, using the catalytic hydrogenation as the key step, is more convenient than such existing procedures in view of the excellent efficiency and simplicity.

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4. BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. RuX_2[(*S*)-binap] (X = Cl, Br, I) is the empirical formula of the complex formed by mixing $Ru(OCOCH_3)_2$[(*S*)-binap][5] and HX in a 1:2 ratio.
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6. The experimental procedure is analogous to that described in ref 1. The enantiomeric excess of **3** was determined by HPLC analysis after converting it to the corresponding (*R*)-MTPA ester (column, Develosil 100-5; eluent, 1:13 ether–hexane mixture; flow rate, 1 mL/min; detection, 254-nm light) The chromatogram showed two signals with t_R = 33.5 and 38.7 min in 1.4:98.6 ratio assignable to the (*R,S*)- and (*R,R*)-diastereomer, respectively.
7. Hydrogenation of **2** (24 g) with $Ru(OCOCH_3)_2$[(*R*)-binap] (62 mg) in ethanol (20 mL) at 100 °C for 5 min gave ethyl (*S*)-4-chloro-3-hydroxybutanoate, $[\alpha]_D^{20}$ -20.3° (*c* 8.11, $CHCl_3$); bp, 72–73 °C/0.9 mmHg. The reported rotation value of (*S*)-**3** in 55% ee is $[\alpha]_D^{23}$ -11.7° (*c* 5.75, $CHCl_3$).[8]
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