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ENANTIOSELECTIVE SYNTHESIS OF 4-SUBSTITUTED γ-LACTONES

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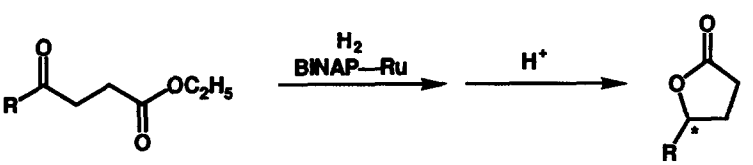
Summary: BINAP—Ru(II) catalyzed hydrogenation of prochiral 4-oxo carboxylic esters and *o*-acylbenzoates gives either enantiomer of the corresponding γ-lactones in >98% enantiomeric excesses.

We here describe a facile method for enantioselective preparation of 4-substituted γ-lactones which are ubiquitous units in insect pheromones, antifungal substances, flavor components, etc. This procedure is based on enantioselective hydrogenation of prochiral 4-oxo carboxylic esters followed by acid-catalyzed cyclization of the resulting hydroxy esters.

BINAP—Ru(II) complexes possess excellent ability to catalyze enantioselective hydrogenation of a range of functionalized olefins and ketones.[1] The rate and stereochemistry of the hydrogenation of ketones are both profoundly affected by the nature of the functional groups. Hydrogenation is considered to proceed via Ru—substrate chelate complexes where the carbonyl group and neighboring heteroatoms are coordinated to the Ru center.[2] Ketone substrates with heteroatoms at α and β positions to the carbonyl group are smoothly hydrogenated with RuX_2(binap)[3] and [$RuX(C_6H_6)$(binap)]X (X = Cl, Br, I)[5] as catalyst; however 4-oxo carboxylic esters of type **1** bearing the directing oxygen atom at the γ position are not hydrogenated under the standard conditions. We have found that a Ru catalyst formed *in situ* by addition of 2 equiv of HCl to $Ru(OCOCH_3)_2$(binap)[4] acts as more reactive catalytic species that allows for highly enantioselective hydrogenation of these substituted ketone substrates.



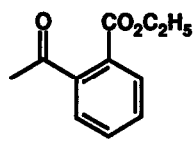
1 **2**

a: R = CH_3
b: R = C_2H_5
c: R = *n*-C_8H_{17}

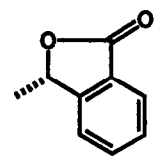
Thus hydrogenation of prochiral 4-oxo carboxylate **1** at 100 atm and 25—35 °C in ethanol solution containing 0.1—0.3 mol % of the BINAP—Ru catalyst, followed by heating of the products[6] with acetic acid in toluene gave optically active 4-substituted

4-butanolide **2** in high yield. The sense of asymmetric hydrogenation is identical with that observed with other functionalized ketones;[2] hydrogenation of **1** (R = methyl or primary alkyl) with the (*S*)-BINAP catalyst affords (*S*)-**2**, whereas the *R* catalyst produces the *R* enantiomer. The chemical yield and enantiomeric excess (ee) of **2** obtained were as follows: (*S*)-**2a**, 96% and 99.5% ee; (*R*)-**2b**, 90% and 98% ee; (*R*)-**2c**, 82% and 98% ee. (*R*)-**2b** and (*R*)-**2c** are sex pheromones of a female dermestid beetle[7] and rove beetle.[8] (*S*)-**2a** serves as a useful intermediate for synthesis of sulcatol (a beetle pheromone[9]) and geodiamolide A (a cyclodepsipeptide isolated from a sponge[10]). Ethyl 5-oxohexanoate, a homologue of **1**, was not hydrogenated under such reaction conditions.

The enantioselective hydrogenation can be extended to *o*-acylbenzoic esters, benzo analogues of simple 4-oxo carboxylates, giving a straightforward entry to optically active phthalides.[11] For example, hydrogenation of ethyl *o*-acetylbenzoate (**3**) in ethanol with 0.4 mol % of the (*S*)-BINAP—Ru catalyst at 100 atm and 35 °C for 165 h afforded directly the *S* phthalide **4** in 97% ee and in 97% yield.



3



4

This γ-lactone synthesis is most efficient relative to the various chemical[12] and biological[13] approaches so far repoted. Either enantiomer is provided in excellent enantioselectivity and high chemical yield. The operation is simple and adaptable to large scale production.

A typical procedure is illustrated by the synthesis of (*S*)-4-methyl-4-butanolide [(*S*)-**2a**]: An 80-mL Schlenk tube was charged with solid $Ru(OCOCH_3)_2$[(*S*)-binap][4] (57.6 mg, 68.4 μmol) and degassed ethanol (12 mL). To the resulting yellow solution was added 0.45 N HCl in ethanol (304 μL, 137 μmol) and the mixture was stirred under argon at 30 °C for 30 min to give an orange suspension. Another 80-mL Schlenk tube was charged with ethyl 4-oxopentanoate[14] (**1a**, 10.00 g, 69.4 mmol) and degassed ethanol (12 mL), and the solution was degassed by three freeze-thaw cycles and transferred via cannula to the Schlenk tube containing the Ru catalyst to give a clear orange solution. This solution was then transferred to a glass vessel in a 100-mL stainless steel autoclave. After pressurizing with hydrogen to 100 atm, the solution was stirred at 30 °C for 110 h. The hydrogen pressure was released, the solvent was removed under reduced pressure, and the residue was bulb-to-bulb distilled (90—100 °C, 25 mmHg) to give a 26:74 mixture of (*S*)-ethyl 4-hydroxypentanoate and (*S*)-**2a** (7.74 g, 98% yield). This mixture was heated with acetic acid (0.2 mL) in toluene (60

mL) at reflux for 4 h, then diluted with ether (100 mL), washed with saturated aqueous $NaHCO_3$ solution (50 mL), and dried over anhydrous Na_2SO_4. After evaporation of solvent, the crude product was purified by bulb-to-bulb distillation (90—100 °C, 25 mmHg) to give (*S*)-**2a** (6.68 g, 96% yield, 99.5% ee), $[\alpha]_D^{16}$ –36.8° (*c* 1.44, CH_2Cl_2) [lit.[12i] $[\alpha]_D^{20}$ –31.6° (*c* 0.86, CH_2Cl_2) for the *S* enantiomer of 95% ee]. Enantiomeric excess was determined by GC analysis (chiral capillary column, Lipodex^{R}B, 25 m fused silica; column temp, 150 °C; detection and injection temp, 190 °C; flow rate of He, 45 mL/min; split ratio, 40/1).

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3. BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. RuX_2(binap) (X = Cl, Br, I) is the empirical formula of the solid complex obtained by mixing $Ru(OCOCH_3)_2$(binap)[4] and HX or $(CH_3)_3SiI$ in a 1:2 ratio in CH_2Cl_2 followed by evaporation of the solvent.[2a,b]
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11. For reaction of *o*-acylbenzoic *acids*, see: ref 2b. Phenyl ketone **1** (R = C_6H_5) was much less reactive than **1a**—**1c**, and was hydrogenated with 0.3 mol % of the (*R*)-BINAP—Ru catalyst (100 atm, 35 °C, 258 h) to give (*S*)-**2** (R = C_6H_5) in 97% ee in only 30% yield.
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14. The keto ester purchased from Tokyo Chemical Co. was freshly distilled from Molecular Sieves 4A before use.

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