Enantioselective Reformatsky Reaction with Ketones. Asymmetric Synthesis of β-(*tert*-Hydroxy)esters

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Optically active β-(*tert*-hydroxy)esters with good enantiomeric excesses (up to 75% e.e.) are synthesised *via* enantioselective Reformatsky reaction with ketones in the presence of chiral *N,N*-dialkylnorephedrine.

The enantioselectivities of the addition of metal enolates to prochiral *ketones* are usually lower than those to prochiral *aldehydes*.[1] This tendency can be attributed to the greater difficulty in differentiating between the two carbon-containing substituents in ketones than in differentiating one carbon-containing substituent from hydrogen in aldehydes.

Chiral β-(*tert*-hydroxy)esters **4** are important units which are involved in some naturally occurring compounds such as (*R*)-mevalonolactone[2] and in an intermediate in a synthesis of colchicine.[3] Although some diastereoselective syntheses of β-(*tert*-hydroxy)esters have been reported,[4] enantioselective synthesis of **4** by the Reformatsky reaction[5] with ketones using chiral ligands, if it were possible, would become a more direct and convenient method than the diastereoselective methods. To the best of our knowledge, no good method has been reported for the enantioselective Reformatsky reaction with ketones leading to optically active **4**. β-(*tert*-Hydroxy)-esters **4** with only 7–39% enantiomeric excess (e.e.) have been reported in the enantioselective Reformatsky reaction with ketones in the presence of (−)-sparteine.[6a] Thus, the enantioselective synthesis of **4** with higher e.e.s is a challenging problem. We have reported the enantioselective alkylation of aldehydes (and not ketones) with dialkylzinc reagents using *N,N*-dialkylnorephedrines as chiral catalysts.[7]

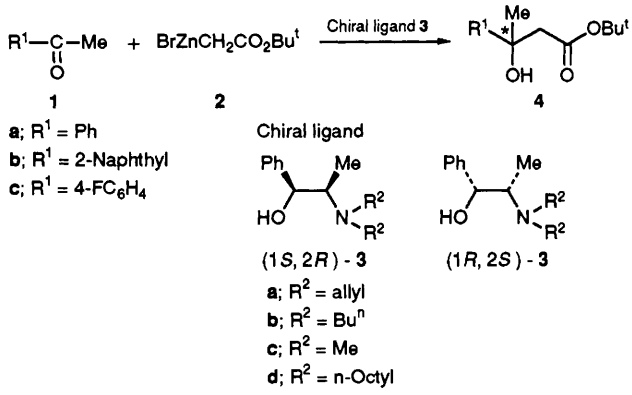
Table 1 Enantioselective Reformatsky reaction with ketones

					β-(*tert*-Hydroxy)ester **4**			
Entry[a]	Ketone **1**	Chiral ligand **3**	*T*/°C	*t*/h		Yield (%)	E.e. (%)[b]	Config.[c]
1	**1a**	(1*S*,2*R*)-**3a**	−13	25	**4a**[d]	65	74	*S*
2	**1a**	(1*R*,2*S*)-**3a**	0	21	**4a**	47	74	*R*
3	**1a**	(1*R*,2*S*)-**3a**	0	21	**4a**	21	73	*R*
4	**1b**	(1*S*,2*R*)-**3a**	−13	45	**4b**[e]	38	75	
5	**1c**	(1*S*,2*R*)-**3a**	−13	24	**4c**[f]	57	73	
6	**1a**	(1*S*,2*R*)-**3b**	0	18	**4a**	35	65	*S*
7	**1a**	(1*S*,2*R*)-**3c**	0	23	**4a**	17	61	*S*
8	**1a**	(1*S*,2*R*)-**3d**	0	21	**4a**	36	50	*S*

[a] Solvent was THF–toluene, 5:3 (v/v). Molar ratio for entries 3, 6, 7 and 8, **1**:**3**:**2** = 1:1:5. For other entries, **1**:**3**:**2** = 1:2:10. [b] Determined by HPLC analyses using a chiral column (0.46 × 25 cm). Eluent: 1% propan-2-ol in hexane; column temperature 40 °C; 254 nm UV detector. For (*S*)-**4a**, chiral column: Chiralcel OD; flow rate: 0.3 ml min^{-1}; retention time (*t*/min): 17.29 (*S*)-minor, 18.78 (*R*)-major. For **4b**, chiral column: Chiralpak AD; flow rate 1.0 ml min^{-1}; retention time (*t*/min): 14.19 minor, 17.87 major. For **4c**, chiral column: Chiralcel OD; flow rate: 0.3 ml min^{-1}; retention time (*t*/min): 17.63 minor, 19.49 major. [c] Configuration was determined as follows: reduction of (+)-**4a** (41% e.e.) $[\alpha]_D^{24}$ + 4.41° (*c* 4.63, C_6H_6) with lithium aluminium hydride afforded (*S*)-(−)-3-phenylbutane-1,3-diol **5** $[\alpha]_D^{24}$ −11.30 (*c* 3.67, EtOH) in 44% yield. Literature value for (*S*)-**5**, $[\alpha]_D^{25}$ −32.2 (*c* 10, EtOH) (S. L. Abidi and J. L. Wolfhagen, *J. Org. Chem.*, 1979, **44**, 433). [d] $[\alpha]_D^{28}$ + 8.20 (*c* 3.1, C_6H_6). [e] $[\alpha]_D^{25}$ −8.86 (*c* 2.3, MeOH). [f] $[\alpha]_D^{24}$ + 9.57 (*c* 1.9, C_6H_6).

We report now the enantioselective addition of the Reformatsky reagent **2** to prochiral ketones using *N,N*-dialkylnorephedrines **3** as chiral ligands. When **1a** was treated with the reagent **2** (prepared from *tert*-butyl bromoacetate and zinc) in a mixed solvent of tetrahydrofuran (THF) and toluene at 0 °C in the presence of (1*R*,2*S*)-*N,N*-diallylnorephedrine **3a**[8] (1 equiv.), (*R*)-**4a** with 73% e.e (determined by HPLC analysis using a chiral column) was obtained in 21% yield (entry 3). When 2 equiv. of (1*R*,2*S*)-**3a** were employed, (*R*)-**4a** with 74% e.e. was obtained in 47% yield (entry 2). The amount of the chiral ligand **3a** thus affected the synthetic yield of **4a** but not the enantioselectivities. When the reaction temperature was lowered to −13 °C using (1*S*,2*R*)-**3a**, (*S*)-**4a** with 74% e.e. was obtained in 65% yield.†‡ In a similar manner, the reaction with methyl 2-naphthyl ketone **1b** afforded **4b** with 75% e.e. (entry 4). It should be noted that the same **4a** with only 7% e.e. was previously obtained from the Reformatsky reaction in the presence of (−)-sparteine.[6a]

Among the chiral ligands **3** examined, **3a** was the most enantioselective. Under the reaction conditions in which the enantioselectivity of **3a** was 73% e.e. (entry 3), the enantioselectivities with *N,N*-dimethyl-**3c**, *N,N*-dibutyl-**3b** and



N,N-dioctyl-norephedrine **3d** were 61, 65 and 50% e.e., respectively (entries 6–8).

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† Typical procedure is as follows. (*i*) Preparation of Reformatsky reagent **2**: *tert*-butyl bromoacetate (11.2 mmol) was added to a suspension of zinc–copper couple (0.791 g, zinc content 11 mmol) in 11 ml of THF. The mixture was refluxed for 1 h, and then the dark green mixture was cooled to room temperature. (*ii*) Enantioselective Reformatsky reaction with **1a**: ketone **1a** (0.120 g, 1 mmol) in 2 ml of toluene was added to a toluene (4 ml) solution of (1*S*,2*R*)-**3a** (0.464 g, 2 mmol). The solution was cooled to −13 °C and **2** was added to the solution. The mixture was stirred for 25 h at −13 °C, and the reaction was quenched with water (5 ml). The precipitate was filtered off. The filtrate was extracted with dichloromethane (10 ml × 4) and dried (Na_2SO_4). The organic layer was evaporated, and the residue was purified on preparative silica gel TLC. (*S*)-**4a** (0.156 g) was obtained in 65% yield.

‡ Compounds **4a–c** showed ^{1}H NMR, IR, and high resolution mass spectra consistent with the structures shown.

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