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Synthesis of Optically Active α,α-Disubstituted β-Keto Esters Via Chiral β-Enamino Esters

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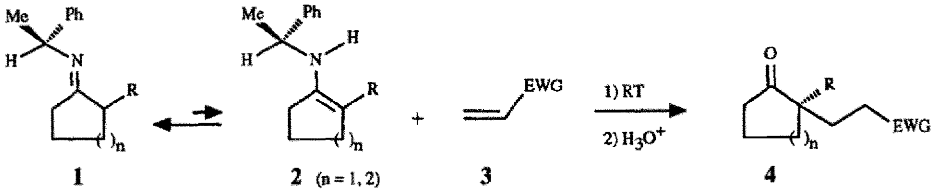
Abstract *: Michael addition of chiral β-enamino esters to MVK and acrylates promoted by Lewis acids ($ZnCl_2$, $MgBr_2$) or high pressure (11-14 Kbar) afforded, after hydrolytic work-up, α,α-disubstituted β-keto esters in good enantiomeric excesses.*

It has been recently reported [1] in our laboratory that chiral cyclic imines **1**, which are in equilibrium with their reactive enamine forms **2**, react regio- and stereoselectively with electrophilic alkenes **3** to give, after acid hydrolysis, chiral cyclanones **4** bearing an α quaternary carbon center.

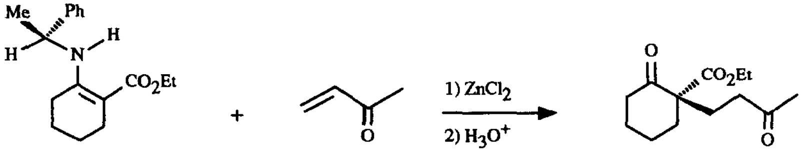


The chirality resident in substrate **1** is derived from commercially available (*R*) or (*S*) 1-phenylethylamine. The 1,4 asymmetric induction of this process is high, cyclanone **4** being isolated with enantiomeric excesses (ee) ≥ 90 %. Further works have established that the starting imine can accomodate an endo or exocyclic heteroatom [2]. Moreover intramolecular versions of this reaction have been described [3].

In connection with a synthetic program we became interested to determine whether or not cyclic β-enamino esters **2** (R = ester), notoriously poorer nucleophiles than enamines, could react, *in their neutral form,* with electrophilic alkenes **3** to give chiral α,α-disubstituted β-keto esters **4** (R = ester). Despite a great interest and activity in asymmetric synthesis of optically active compounds containing quaternary carbon centers, a few reports have appeared on the use of chiral β enaminoesters as precursors [4]. Recently, Brünner et al. have reported [4d] that cobalt chloride catalyzes the addition of β-enamino ester **5** with Michael acceptors. This study prompts us to disclose our results herein. In the present investigation, reaction of β-enamino esters **5** and **7** with methylvinylketone (MVK) and acrylates has been considered and two different modes of activation have been envisaged, e.g. : use of Lewis acids and application of high pressure conditions.

Reaction of 5 with M.V.K.

In the first set of experiments, reaction of (+)-**5** [5] with MVK was carried out in the presence of zinc chloride as the Lewis acid. After hydrolysis upon exposure to dilute AcOH, the known β-keto ester (*S*)-(–)-**6** [6] was obtained in good chemical and optical yields. The reaction conditions are summarized in Table 1.



(+)-5 (–)-6 (2)

Table 1 : Enantioselective alkylation of β- enaminoester (+)-5 with MVK

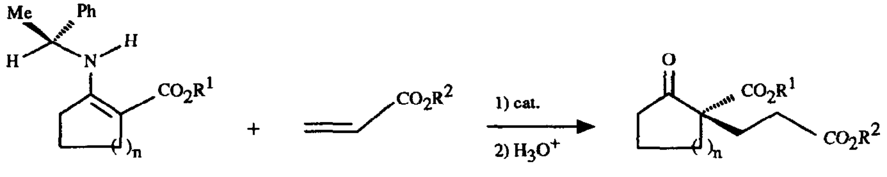
Entry	Reaction conditions [a]			% y [b]	$[\alpha]^{20}_{578}$ [c]	% ee [d]
	Solvent	temp. °C	time			
1	THF/ether 4/1	0	1,5 h	84	- 64	64 (*S*)
2	ether	0	2 h	90	- 71,7	72 (*S*)
3	ether	-78	1,5 h	80	- 76,2	79 (*S*)

[a] 5, MVK and $ZnCl_2$ were employed in the ratio 1:1,5:1. [b] isolated yield after purification by flash chromatography and bulb to bulb distillation. [c] measured in CCl_4 (c = 2,2). [d] determined by G.P.C. on a chiral column [7].

As can be seen from the data in Table 1, the reaction enantioselectivity is significantly temperature and solvent dependent. The % ee increased substantially upon lowering the temperature, the best result (~ 80 % ee) [8] being achieved at -78 °C [9].

Reaction of 5 and 7 with acrylates

In a second series of experiments, the reaction of β-enaminoesters **5** and **7** with several acrylates **8** was studied in the presence of a Lewis acid catalyst. The results are presented in Table 2.



(+)-**5** (n = 2, R^1 = Et)
(+)-**7** (n = 1, R^1 = Me)

8

(–)-**9** (n = 2, R^1 = Et)
(+)-**10** (n = 1, R^1 = Me)

Magnesium bromide was found very effective in mediating the Michael addition of (+)-**5** and (+)-**7** to methyl, ethyl and *tert*-butyl acrylates **8** to provide the β-keto esters (–)-**9** and (+)-**10** respectively. The reaction took place at RT and high asymmetric induction (up to 90 %, entry 3) was realized [11,12]. Ether is the solvent of choice (compare entries 6 and 7) although insolubility of complexed material can reduce the chemical yields.

In a final series of experiments we investigated the possibility of achieving this reaction under high pressure. Although the high pressure version of the Michael addition involving a β-enamino ester has not

Table 2 : Enantioselective alkylation of β-enamino esters **5** and **7** with acrylates

Entry	Substrate	R^2	Reaction conditions [a]			Product	% Y [b]	$[\alpha]_D$ [c]	% ee [d]
			cat.	temp. °C	solvent time				
1	**5**	Me	$MgBr_2$	20	ether, 2 h	**9a**	76	- 78.3	80 (*S*)
2	**5**	Et	$MgBr_2$	20	ether, 3 h	**9b**	80	- 72.3	79 (*S*)
3	**5**	*tert* Bu	$MgBr_2$	20	ether, 3 h	**9c**	60	- 71.6	90 (*S*)
4	**7**	Me	$MgBr_2$	20	ether, 1 h	**10a**	50	+ 12.6	70 (*S*)
5	**7**	Et	$MgBr_2$	20	ether, 1 h	**10b**	50	+ 10.2	65 (*S*)
6	**7**	*tert*-Bu	$MgBr_2$	20	ether, 1 h	**10c**	45	+ 18.5	85 (*S*)
7	**7**	*tert*-Bu	$MgBr_2$	65	THF, 72 h	**10c**	60	+ 15.9	73 (*S*)
8	**5**	Et	11 kbar	40	THF, 65 h	**9b**	63	- 79.2	88 (*S*) [10]
9	**5**	*tert*-Bu	14 kbar	45	THF, 72 h	**9c**	31	- 66.7	84 (*S*)
10	**7**	Et	14 kbar	20	THF, 67 h	**10b**	52	+ 13.2	84 (*S*)
11	**7**	*tert*-Bu	14 kbar	45	THF, 72 h	**10c**	45	+ 18.8	86 (*S*)

[a] Reactions were conducted with molar ratio of substrate : catalyst : acrylate = 1:1:1.5 ; Reactions under high pressure were conducted with molar ratio of substrate : catalyst = 1:1. [b] Yield is based on starting β-enamino ester and refers to material purified by flash chromatography and distillation. The recovered β-enamino ester (up to 50 %, entry 9) was not taken into account. [c] Measured in $CHCl_3$ (c = 1.4 to 1.8) for compounds **9a, 9b, 9c** and **10b** ; in CCl_4 (c = 2.8) for **10a** ; in EtOH (c = 2.4) for **10c**. [d] Determined by GPC on a chiral column [7] for compounds **9b, 10b, 10c** and by ^1H NMR analysis (250 MHz, C_6D_6) in the presence of $Eu(tfc)_3$ for **10a**. For compounds **9a** and **9c**, ee were evaluated by comparing the specific rotations with those obtained after chemical correlation with **9b**.

been previously reported, it is anticipated that the reaction will be accelerated by pressure. Indeed, (+)-**5** and (+)-**7** reacted with ethyl and *tert*-butyl acrylates under pressure ranging from 11 to 14 kbar. As can be seen from the data in Table 2 (see the last four entries) the ee are uniformly high in all cases examined. Thus the size of the ester function in **8** has only a subordinate effect on the enantioselectivity. This is in sharp contrast with the $MgBr_2$ catalyzed reaction in which the level of asymmetric induction is significantly enhanced on going from methyl or ethyl to *tert*-butyl acrylate (see entries 1 to 6). Finally it is worthy of note that, in close analogy with reaction involving imines **1**, the major enantiomer formed (*S* absolute configuration at the newly created quaternary center) is the one resulting from attack on the face opposite the phenyl group in (+)-**5** and (+)-**7**. Thus the steric course of the Michael process involving imines or β-enamino esters is quite similar [13] and is not greatly affected, in the latter case, by the presence of a Lewis acid or by the application of high pressure.

References and Notes

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5 β-Enamino ester (+)-**5** was prepared by the reaction of 2-(carboethoxy)-cyclohexanone with optically pure (*S*)-1-phenylethylamine (α_D = -40.6 neat) in toluene under reflux (a Dean-Stark apparatus was used as a water trap). It was isolated after flash chromatography on silica (eluant : Hexane-AcOEt 4-1) and bulb to bulb distillation as a colorless oil (77 % yield) ; $[\alpha]_D$ = + 544 (c = 1.0, EtOH) ;

β-Enamino ester (+)-**7** was prepared by the reaction of 2-(carbomethoxy)-cyclopentanone with optically pure (*S*)-1-phenylethylamine in CH_2Cl_2 (reflux for 24 h) containing 3 Å molecular sieves. It was isolated (same work-up as above) in 70 % yield as a colorless oil ; $[\alpha]_D$ = +480 (c = 2.2, EtOH) ;

6 Hermann, K. ; Wynberg, H. *J. Org. Chem.*, **1979**, *44*, 2238.

7 We thank Pr. Tabacchi, Université de Neuchâtel (Switzerland) for the measurements.

8 Comparison of the specific rotations measured for (–)-**6** (Table 1) with those given in the literature [4c,4d,6] showed the latter values to be greatly superevaluated.

9 *Experimental procedure* : $ZnCl_2$ (1 ml of 1 M solution in ether) was added dropwise to a solution of (+)-**5** (1 mmol) and MVK (1.5 mmol) in 5 mL of ether at -78 °C under nitrogen. Stirring was continued for 30 min at -78 °C during which time a white precipitate was formed. 3 cc of 10 % aqueous acetic acid solution and 7 cc of ether were then added. The temperature was raised to 20 °C and the heterogeneous solution stirred vigorously overnight. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (2:1 hexane : AcOEt) and bulb to bulb distillation to give the known (–)-**6** as a colorless oil.

10 Comparison of the specific rotation measured for (–)-**9b** with those given in the literature [4c,4d], showed the latter values to be superevaluated.

11 Absolute configurations of (–)-**9a** and (–)-**9c** were determined by chemical correlation with the known (*S*)-(–)-**9b**. Absolute configuration of (+)-**10c** was determined by chemical correlation with the known (*S*)-2-nonyl-2-(carbomethoxy) cyclopentanone (see accompanying communication). Absolute configurations of (+)-**10a** and (+)-**10b** were determined by chemical correlation with (+)-**10c**.

12 *Experimental procedure* (the preparation of (+)-**10c** is representative). To a stirred suspension of $MgBr_2$ (20 mmol) in ether (20 mL) was added dropwise an ethereal solution (20 mL) of (+)-**7** (20 mmol) and **8**, R^2 = *tert* Bu (30 mmol) at 20 °C under nitrogen. Vigorous stirring was continued for 1 h at 20 °C and 10mLof 10 % aqueous acetic acid solution added. Ether was distilled off and replaced by THF (30 mL). The resulting solution was heated at 60 °C for 12 h. After cooling at 20 °C, the solution was extracted with ether. The organic layer was then washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica gel (4:1 hexane : AcOEt) and bulb to bulb distillation to afford (+)-**10c** as a colorless oil.

13 d'Angelo, J. ; Revial, G. ; Guingant, A. ; Riche, C. ; Chiaroni, A. *Tetrahedron Letters*, **1989**, *30*, 2645.