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Highly Diastereoselective Addition of Cyclic β-Enamino Esters to N-Acryloyl-(*S*)-Proline Derivatives

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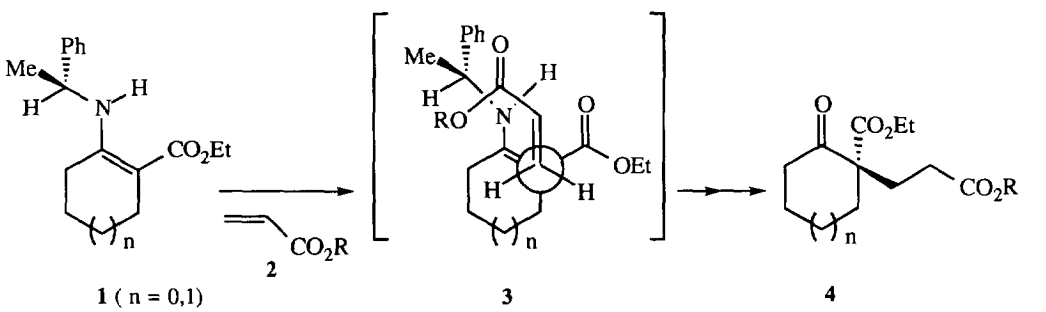
Abstract: Considerable asymmetric induction can be obtained by reacting cyclic β-enamino esters with chiral acrylamides derived from (*S*)-proline in the presence of Lewis acids.

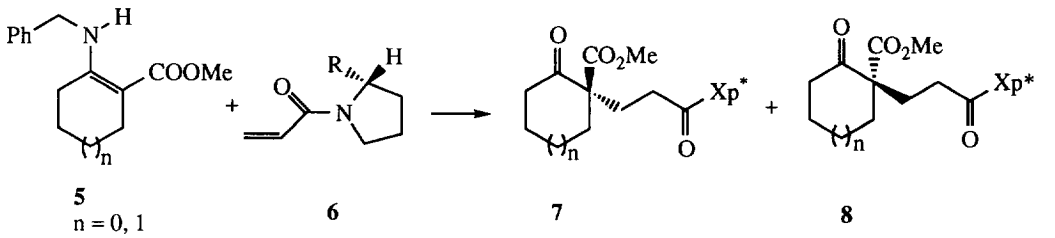
α,α-Disubstituted β-keto esters (e.g., **4**) bearing a functional chain at the quaternary carbon centre are potential intermediates for the synthesis of many naturally occurring compounds[1]. We previously reported[2] that they could be prepared by the reaction of chiral β-enamino esters **1** derived from (*S*)-1-phenylethylamine with acrylates **2**, followed by acidic hydrolysis. Enantiomeric excesses ranged from 65% to 90% depending both on the nature of the R substituent in **2** and on the activation mode utilized (Lewis acid or high pressure)[3]. A working model[4] has been proposed to rationalize the stereochemical outcome of the reaction. It is assumed that the reaction proceeds through a compact activated complex with a gauche-relationship of the donor and the acceptor Π systems[5] as depicted in the Newman-projection **3**. This reactive complex is stabilized by secondary orbital attractive interactions developing mainly between the N atom in **1** and the C-atom of the carbonyl in **2** which are situated close to each other (quasi-chair topology). The β-enamino ester **1** adopts the conformation as shown to minimize both A1,3 and A1,2 allylic strains and the steric screening provided by the phenyl substituent leads to significant discrimination of the two Π-faces by the incoming **2**[6].



Scheme 1

In an extension of this work and in the hope of improving upon our previous results we have now considered the unprecedented asymmetric conjugate addition of *achiral* β-enamino esters to *chiral* electrophilic olefins and disclose herein our first results.

We first elected to investigate the reaction of cyclic β-enamino esters **5** (n = 0, 1) with the acrylamide derivative **6a**, a compound easily prepared from (*S*)-proline in two simple steps[7,8]. β-Enamino esters **5** are not sufficiently reactive to add to **6a** and the presence of a Lewis acid promotor[9] was required. Some selected results are reported hereafter.



5
n = 0, 1

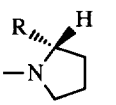
6

7

8

a : R = $COOCH_2Ph$
b : R = COOH
c : R = CH_2OCH_3

Xp* =



Scheme 2

Table : Reaction of β-enamino esters **5** with chiral acrylamides **6a**, **6b** and **6c**.

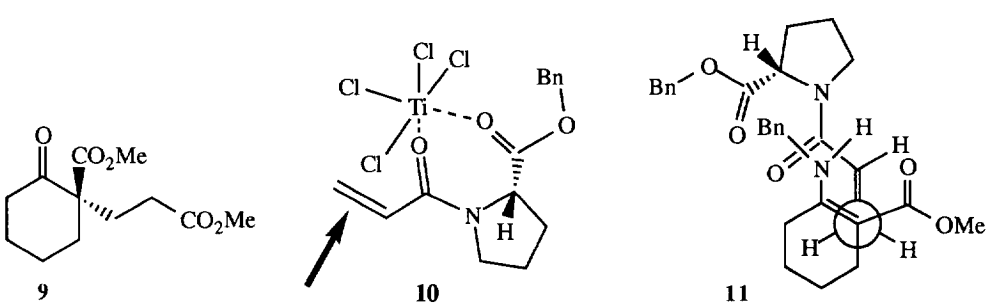
Entry	Enamino-ester	Proline derivative	Experimental Conditions[a]				Yield %	Ratio of Diastereomers[b]
			Lewis acid(eq)		temp.(°C)	time (h)		**7/8**
1	**5** (n=1)	**6a**	$TiCl_4$	(1)	20	5	85	**98/2**
2	**5** (n=1)	**6a**	$TiCl_4$	(1)	0	5	68	93/7
3	**5** (n=1)	**6a**	$TiCl_4$	(1)	- 40	5	17	72/28
4	**5** (n=1)	**6a**	$TiCl_4$	(0.5)	20	5	21	82/18
5	**5** (n=1)	**6a**	$TiCl_4$	(0.25)	20	5	12	80/20
6	**5** (n=1)	**6a**	Et_2AlCl	(1)	20	5	93	75/25
7	**5** (n=1)	**6a**	Et_2AlCl	(0.5)	20	5	35	66/34
8	**5** (n=1)	**6a**	$EtAlCl_2$	(1)	20	5	80	75/25
9	**5** (n=0)	**6a**	$TiCl_4$	(1)	20	5	70	**95/5**
10	**5** (n=1)	**6b**	$TiCl_4$	(1)	20	5	57	**98/2**
11	**5** (n=1)	**6c**	$TiCl_4$	(1)	20	3	37	69/31[c]

[a]Lewis acid-promoted reactions were conducted in CH_2Cl_2 with molar ratio of β-enamino ester:chiral acrylamide = 1:1. b see ref.10
[c]The absolute configuration of the major diastereomer is unknown.

As can be seen in the Table (entries 1,5), both yields and selectivity were greatly dependent upon the stoichiometry of the Lewis acid promotors, the most remarkable result being obtained by using one equivalent amount of $TiCl_4$ at 20°C in CH_2Cl_2. *Under these preferred experimental conditions the reaction of* **5** *(n=1) with* **6a** *proceeded with very high selectivity yielding the adduct* **7a** *(n=1, oil) with a 98/2 diastereomeric ratio*[10]. The five membered-ring analogue **5** (n=0) behaved similarly giving **7a** (n=0) with a comparable selectivity (entry 9). In contrast to the preceding results, aluminum derivatives proved to be less effective promotors than $TiCl_4$ leading to **7a** (n=1) in modest selectivity (entries 6,8). We have also observed a significant and rather unexpected inverse temperature effect on diastereoselectivity (entries 1,3)[11].

Two other chiral acrylamides derived from (*S*)-proline, namely **6b** and **6c**, have been also tested. Reaction of β-enamino ester **5** (n=1) with **6b**, prepared in one step from (*S*)-proline[12], gave **7b** (n=1, white solid) with a selectivity comparable to that observed for **6a** (entry 10). It is worthy of note that **7b** (n=1) could be obtained in virtually pure form after one crystallization (mp: 135°C), although in modest overall yield. Finally, chiral acrylamide **6c**[13], though having two oxygen atoms capable of anchoring $TiCl_4$ (vide infra) led to disappointing results (entry 11) suggesting the presence of two carbonyl groups, as in **6a** and **6b**, to be a prerequisite for obtaining good selectivity.

The absolute configuration at the newly created quaternary carbon centre of **7a** (n=1) could be easily established by its transformation into the β-keto diester (*R*)-**9**[14,15] by treatment with an excess of Meerwein reagent ($Me_3O^+BF_4^-$, 3eq., CH_2Cl_2, reflux for 24h) and subsequent hydrolysis of the O-methylated intermediate (50-60% yield). The diastereoselectivity can be accounted for by assuming that the chiral acrylamide **6a** in an s-cis conformation, forms a seven-membered ring chelate **10** in which the *Re* face of the reacting double bond is masked by one Ti-Cl bond[16,8b]. The β-enamino ester is then directed to the less-hindered *Si* face to provide adduct **7a**,via a compact quasi-chair transition state[17]**11** (the Lewis acid has been omitted for clarity) similar to **3**.



9 **10** **11**

Scheme 3

The accompanying communication provides with additional results that establish the potential of this new reaction for synthetic applications.

Notes and references

1 For a recent review on the preparation of quaternary carbon centres, see: Fuji, K. *Chem. Rev.*; **1993**, *93*, 2037-2066.

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3 For other examples of acid-promoted conjugate addition reactions of chiral β-enaminoesters to electrophilic olefins, see: Bohlmann, C.; Bohlmann, R.; Rivera, E.G.; Vogel, C.; Manandhar, M.D.; Winterfeldt, E. *Liebigs Ann. Chem.* **1985**, 1752-1763. Brunner, H.; Kraus, J.; Lautenschlager, H-J. *Monatshefte für Chemie*, **1988**, *119*, 1161-1167.

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6 For reviews, see: d'Angelo, J.; Desmaele, D.; Dumas, F.; Guingant, A. Tetrahedron *Asymmetry*, **1992**, *3*, 459-505 . d'Angelo, J.; Cavé, C.; Desmaele, D.; Dumas, F. Trends in Org. Chem. **1993**, *4*, 555-616.

7 (a) Ramachandran, J.; Li, C.H. *J. Org. Chem.* **1963**, *28*, 173-177. (b) Waldmann, H. *J. Org. Chem.* **1988**, *53*, 6133-6136. (c) Effenberger, F.; Isak, H. *Chem. Ber.* **1989**, *122*, 545-551.

8 This compound was previously shown to react with cyclopentadiene and other dienes to give the corresponding Diels Alder cycloadducts in good to excellent stereoselectivities. See ref. 7b and the following ones : (a) Waldmann, H. *Liebigs Ann. Chem.* **1990**, 671-680. (b) Waldmann, H.; Dräger, M. *Liebigs Ann. Chem.* **1990**, 681-685. See also, for a recent example of asymmetric 1,3-dipolar cycloaddition involving acrylamide **6a** : Waldmann, H.; Bläser, E.; Jansen, M.; Letschert, H.P. *Angew. Chem. Int. Ed. Engl.* **1993**, *115*, 683-685.

9 Attempts to conduct the reaction in the absence of a Lewis acid or under high pressure activation (up to 12 kbar) failed to provide any evidence of adducts **7** and **8**.

10 Either diastereomer **7** and **8** exists as a mixture of two rotamers in a ratio of ca. 6.5 to 1 in $CDCl_3$. The diastereomeric ratios were best determined by 400 MHz ^1H NMR in the presence of $Eu(fod)_3$.

11 Some rare examples of reactions showing this behaviour were previously reported. See, Markó, I.E; Chesney, A; Hollinshead, D.M.*Tetrahedron: Asymmetry*, **1994**,*5*, 569-572 and references cited therein.

12 Bueno, M.P.; Cativiela, C.A.; Mayoral, J.A.; Avenoza, A. *J. Org. Chem.* **1991**, *56*, 6550-6555.

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14 $[\alpha]_D^{20}$ = + 99.8 (c = 1.0, CCl_4). The enantiomeric excess was determined to be 98% by HPLC analysis using a Daicel Chiralcel OD column with 5% *i*-PrOH in hexane for elution (1mL/min; t_R 4.4 min for *R* enantiomer and 6.4 min for *S* enantiomer). This result is in disagreement with a recent report [15] in which compound (*R*)-**9** $[\alpha]_D^{20}$ = +79 (c = 2.8, CCl_4), prepared under similar conditions reported in ref. 2, was described as having an ee-value > 95%. In our hands, a sample of (*S*)- **9**, $[\alpha]_D^{20}$ = -78.3 (c = 2.8, CCl_4)[2], was determined to possess an ee value of 75% both by chiral HPLC (see above) and careful NMR analysis in the presence of $Eu(hfc)_3$.

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17 It is worth noting that the alternative compact quasi-boat transition state would have led to the opposite (*S*) configuration at the quaternary carbon centre of **9**.

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