

S0957-4166(96)00024-9

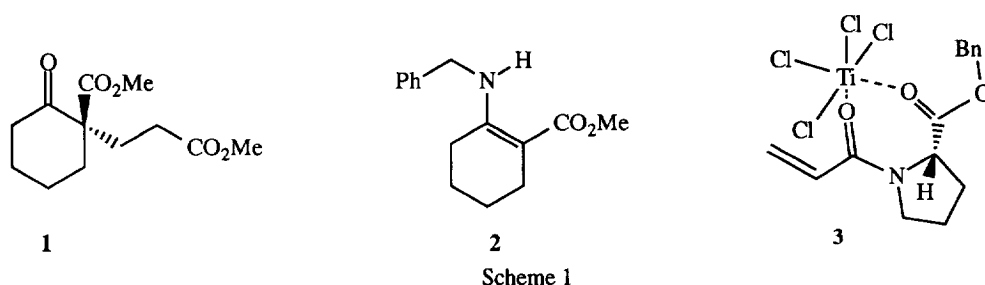
Highly Diastereoselective Addition of Methyl 2-(N-Benzylamino)-1-Cyclohexenecarboxylate to Chiral Acrylates

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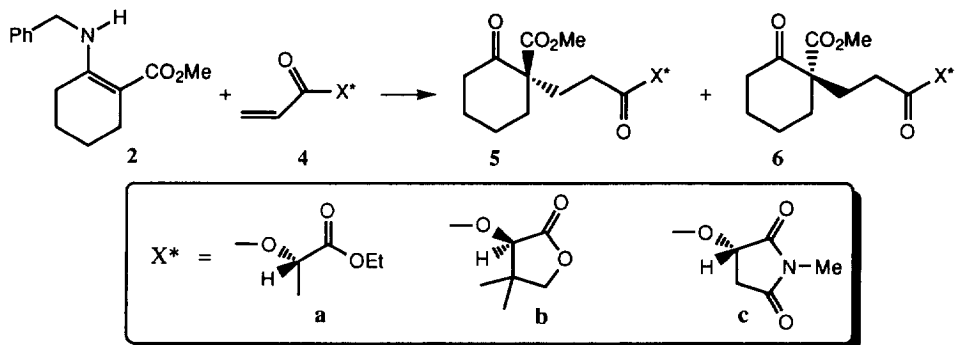
Abstract: Conjugate addition reaction of achiral Methyl 2-(N-benzylamino)-1-cyclohexenecarboxylate **2** to chiral acrylates **4a**, **4b**, **4c** led, after treatment of the primary adducts with sodium methoxyde, to α,α -disubstituted β -keto ester **1** with high enantiomeric excesses.

Chiral α,α -disubstituted β -keto esters are versatile building-blocks for the synthesis of many natural compounds containing stereogenic quaternary carbon centres. In spite of their significant synthetic importance there are few reported asymmetric syntheses of these valuable synthons¹. In the preceding communication we disclosed a novel two-step methodology to prepare the functionalized β -keto ester **1** and its five membered-ring analogue in up to 96% ee. Our methodology involved the addition of β -enamino ester **2** to the TiCl_4 -chelated N-acryloyl-(*S*)-proline benzylester **3** (Scheme 1) followed by treatment of the primary adduct with an excess of Meerwein reagent in order to remove the chiral auxiliary.



Not unexpectedly, the latter step that required the cleavage of an amide bond proved to be a rather difficult and poor-yielding process. In order to circumvent the aforementioned limitation and broaden the synthetic utility of our method we have now considered the possibility of adding β -enamino ester **2** to a set of three chiral acrylates, namely **4(a,b,c)** derived from (*S*)-ethyl lactate, (*R*)-pantolactone and (*S*)-*N*-methyl-2-hydroxysuccinimide, respectively (Scheme 2). These acrylates share in common with **3** the possibility of forming a seven membered-ring chelate with TiCl_4 , a structural key feature for achieving a high level of diastereoselection². Moreover, recovery of the chiral auxiliaries would be greatly facilitated by comparison with **3** as it requires the cleavage of an ester bond.

Reactions were performed using the optimized experimental conditions established for olefin **3** (i.e **2**:**4** = 1:1, TiCl₄ 1 mol.eq., CH₂Cl₂, 20°C, 3h) and the results so obtained are summarized in the Table.



Scheme 2

Table : Reaction of β -enamino ester **2** with chiral acrylates **4a**, **4b** and **4c**.

Entry	acrylate	5 : 6 ^a	Yield %	1 ^b [α] _D ²⁰	1 % ee
1	4a	94/6	70	+ 90.5	87 (R) ^e
2	4b	8/92 ^c	76	- 81 ^d	82 (S) ^e
3	4c	97/3	75	+ 97.1	95 (R) ^f

^aDiastereomeric ratios were estimated by ¹H NMR(400Mhz) in the presence of Eu(fod)₃

^bDetermined in CCl₄ (c= 0.6 to 0.9) ^c4/96 after two recrystallizations from AcOEt - Petroleum Ether. ^d - 95.2 from the recrystallized primary adducts (see c). ^eEstimated by ¹H NMR analysis in the presence of Eu (hfc)₃. ^fDetermined by HPLC analysis with a Daicel Chiralcel OD column using 5% iPrOH in hexane.

The important observation to be made is that acrylates **4** behaved similarly to acrylamide **3** leading to adducts **5** and **6** with a high level of diastereoselection. The best result was achieved with acrylate **4c**. In that case adduct **5c** was isolated with a 97/3 diastereomeric ratio. In a synthetic point of view it is worthy of note that **4(a,c)** and **4b** yielded products of opposite configuration at the quaternary carbon centre and that, as expected, removal of the chiral auxiliaries to give (*R*) or (*S*) **1** was easily accomplished (up to 88% yield) by treatment of adducts **5** and **6** with an excess of freshly prepared sodium methoxide in dry methanol.

In summary, we have developed a new method for the preparation of α,α -disubstituted β -keto esters of high enantiomeric purity. Its convenience, the ease of preparation of the starting materials and the facility with which the chiral auxiliaries can be removed make this method a very attractive one and suggest its further application in natural product chemistry.

References

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