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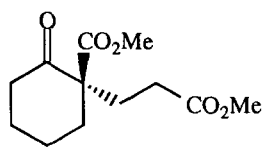
Highly Diastereoselective Addition of Methyl 2-(N-Benzylamino)-1-Cyclohexenecarboxylate to Chiral Acrylates

Katia Hervouet, André Guingant*

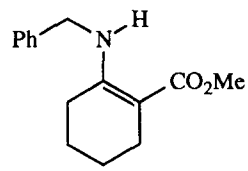
Laboratoire de Synthèse Organique, Faculté des Sciences et des Techniques, U.R.A au C.N.R.S N°475, 2 rue de la Houssinière, 44072 NANTES Cedex 03, France

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 synthons[1]. 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.



1



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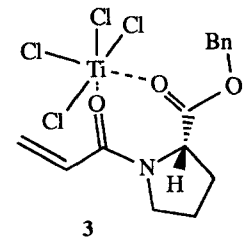
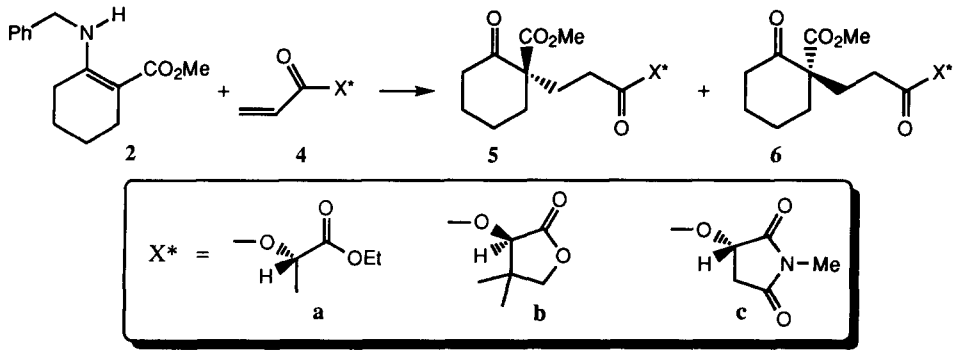


3

Scheme 1

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 diastereoselection[2]. 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, $TiCl_4$ 1 mol.eq., CH_2Cl_2, 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] $[\alpha]_D^{20}$	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]

[a]Diastereomeric ratios were estimated by ^1H NMR(400Mhz) in the presence of Eu(fod)3 [b]Determined in CCl_4 (c= 0.6 to 0.9) [c]4/96 after two recrystallizations from AcOEt - Petroleum Ether. [d] - 95.2 from the recrystallized primary adducts (see c). [e]Estimated by 1H NMR analysis in the presence of Eu (hfc)3. [f]Determined 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 methoxyde 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.

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