

**Asymmetric Aldol Reactions with (+)-(*S,S*)-Pseudoephedrine.
Stereoselective Synthesis of α -Methyl β -Hydroxy Esters.**

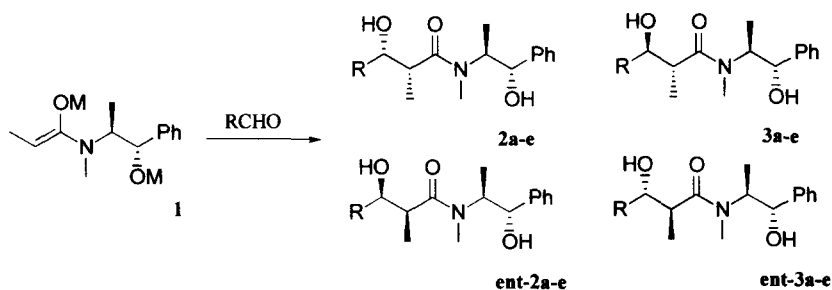
Jose L. Vicario, Dolores Badía,* Esther Domínguez[†] and Luisa Carrillo.

Departamento de Química Orgánica. Facultad de Ciencias. Universidad del País Vasco,
P.O. Box. 644, 48080 Bilbao, Spain.

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Abstract: A new methodology for performing aldol reactions with an excellent degree of enantio- and diastereoselectivity was developed employing (+)-(*S,S*)-pseudoephedrine as chiral auxiliary. © 1998 Elsevier Science Ltd. All rights reserved.

The asymmetric aldol reaction of pre-formed chiral enolates with achiral aldehydes is one of the fundamental carbon-carbon bond forming reactions of modern-day organic synthesis.¹ Among the numerous methodologies now available, the most successful process is probably using the Evans oxazolidine approach which often results in high levels of stereoselection.² On the other hand, pseudoephedrine which is a commercially available reagent in both enantiomeric forms has been recently used as chiral auxiliary in asymmetric alkylation reactions with good results.³ In this paper we report some preliminary results on the use of pseudoephedrine amides in asymmetric aldol reactions concerning both diastereo- and enantioselectivity.



Scheme 1

* e-mail: qopbaurm@lg.ehu.es

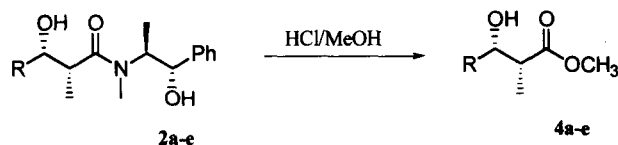
The acylation of (+)-(*S,S*)-pseudoephedrine with propionic anhydride as previously reported³ afforded the corresponding propionamide. This amide was deprotonated with lithium diisopropyl amide at low temperature (-78°C) yielding the enolate **1** which, in a test reaction reacted *in situ* with benzaldehyde at -105°C (Scheme 1) yielded the condensation product with excellent diastereofacial selectivity but as a mixture of both *syn/anti* diastereoisomers **2/3** (Table 1). The product distribution was determined by NMR spectroscopy by integration of the resonances due to the N-Me protons in the pseudoephedrine moiety. However, transmetallation of the lithium enolate with bis(cyclopentadienyl)zirconium dichloride prior to the condensation step afforded the wanted β -hydroxy amide with high *syn* selectivity (**2** vs **3**) and with excellent face stereoselection (**2** vs **ent-2**) (Table 1). The methodology was further extended to the use of other kind of aldehydes as electrophiles⁴ showing that the *anti/syn* selectivity is improved as the bulkiness of the R chain in the aldehyde is increased.

Table 1. Aldol reaction of pseudoephedrine propionamide enolate with aldehydes.

Entry	R	Metal	2(<i>syn</i>)/3(<i>anti</i>) ^a	2/ <i>ent-2</i> ^a	Yield (%) ^c
1	Ph	Li	65/35	>99/1	93
2	Ph	Zr	94/6	>99/1	90
3	CH ₃	Zr	90/10	>99/1	88
4	CH ₃ CH ₂	Zr	96/4	>99/1	90
5	(CH ₃) ₂ CH	Zr	>99/1	>99/1	94
6	(CH ₃) ₃ C	Zr	>99/1	>99/1	94

^a Determined by ¹H-NMR. ^b Isolated yield including all possible diastereoisomers.

Acid hydrolysis of the mixture and subsequent treatment with a refluxing 1:1 methanol/conc. HCl solution (Scheme 2) afforded, after flash column chromatography pure esters **4** in excellent yields and optical purity as confirmed by chiral HPLC (Table 2). It should also be pointed out that the *anti/syn* ratio remains unchanged after the hydrolytic treatment which was also confirmed by HPLC. The chiral auxiliary (+)-(*S,S*)-pseudoephedrine was recovered in ca. 83% yield without racemization after the hydrolysis/esterification process by a standard acid-base extraction procedure followed by crystallization and it can be reused.



Scheme 2

Table 2. Yields and optical purities of the esters 4a-e.

Entry	Product	R	e.e. (%) ^a	Yield (%)
1	4a	Ph	>99	91
2	4b	CH ₃	>99	92
3	4c	CH ₃ CH ₂	>99	88
4	4d	(CH ₃) ₂ CH	>99	86
4	4e	(CH ₃) ₃ C	>99	90

^a Determined by chiral HPLC (Chiralcel OD, Hexane/ iso-propanol 97:3 flow rate 0.75mL/min).

The relative configuration of the newly formed stereogenic centers during the aldol reaction was assigned according to the reported values of the coupling constants between the hydrogen atoms of both chiral centres for compound **4a** ($J=3.9\text{Hz}$ for the *syn* isomer and $J=9.0\text{Hz}$ for the *anti* one).⁵ The absolute configuration of the major products was established as (2*R*,3*S*) according to a previous report in which pseudoephedrine amides were alkylated with alkyl halides³ the final product arising from electrophilic attack on the (*Z*) enolate from the same face of the carbon-bound methyl group of the pseudoephedrine auxiliary (1,4-*syn* relationship). This is consistent with the obtained optical rotation value for compound **4a** ($[\alpha]_{\text{D}}^{20}=+23.7$) compared to the one reported in the literature ($[\alpha]_{\text{D}}^{20}=-23.1$ for the (2*S*,3*R*) isomer and +23.1 for the (2*R*,3*S*) isomer) for the same compound.⁵

In conclusion we have developed a new procedure for performing asymmetric aldol reactions with both high *syn*- and diastereofacial selectivity and starting from a cheap, commercially available chiral auxiliary which can be recovered and recycled.

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References and notes.

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2. Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, J.F. *J. Am. Chem. Soc.* **1990**, 108, 6395. And references cited therein.
3. Myers, A.G.; Yang, B.H.; Chen, H.; McKinstry, L. Kopecky, D.J.; Gleason, J.L. *J. Am. Chem. Soc.* **1997**, 119, 6496.
4. In a representative experimental procedure a solution of the propionamide (0.5mmol) in dry THF (5mL) was slowly added to a cooled (-78°C) solution of LDA (1mmol) in dry THF (10mL). The mixture was stirred at this temperature for 1h. and allowed to reach to room temperature. The mixture was cooled again to -78°C at which temperature a THF (5mL) solution of bis(cyclopentadienyl)zirconium dichloride (2mmol) was added at once and the resulting solution was stirred for 1h. at this temperature. The mixture was cooled down to -105°C at which temperature a solution of the aldehyde (0.5mmol) in dry THF (5mL) was dropwise added within 20min., the mixture was stirred at -78°C for 2h. and quenched with a saturated NH₄Cl solution (20mL). The mixture was extracted with CH₂Cl₂ (3x15mL) and the combined organic fractions were collected, dried over Na₂SO₄, filtered and the solvent was removed *in vacuo* to yield a yellowish oil which was flash column chromatographed (hexanes/ethyl acetate 2:8) affording separately the amides **2** and **3**.
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