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(*S*,*S*)-(+)-Pseudoephedrine as chiral auxiliary in asymmetric acetate aldol reactions

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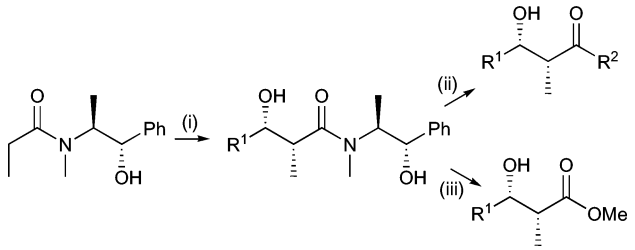
The asymmetric acetate-type aldol reaction using (*S*,*S*)-(+)-pseudoephedrine has been studied in detail. Experimental variables like the nature of the metal counterion of the enolate, the presence of additives and the structure of the aldehyde have been examined in order to reach to the highest possible yields and diastereoselectivities.

Introduction

The asymmetric aldol reaction is regarded as one of the most powerful tools in organic synthesis for the formation of new carbon–carbon bonds together with one or more new stereogenic centres. Consequently, over the last years an extensive number of methodologies for performing stereoselective aldol reactions have been reported in the literature.[1] The different strategies employed in order to achieve the desired high stereocontrol can be classified according to the position in which the chiral information is incorporated: (1) the use of metal enolates carrying chiral auxiliaries that can be easily removed from the final product, (2) the use of achiral metal enolates in the presence of a chiral ligand and (3) performing the reaction in the presence of a chiral catalyst. Related to the first strategy, a wide array of compounds have been used as chiral auxiliaries in asymmetric aldol reactions,[2] some of them still remaining as standards in total synthesis.[3]

In this context, we have made our own contribution to this field and quite recently we developed a protocol for performing highly stereocontrolled aldol reactions using the amino alcohol (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary (Scheme 1).[4] The main advantages of the use of this auxiliary rely upon the fact that it is a cheap reagent and commercially available in both enantiomeric forms. Furthermore, the auxiliary is very easy to attach to the starting carbonyl compound and to remove from the final aldol adduct and it can also be recovered in a very efficient way after it has been removed, which allows recycling for further uses. In addition, the pseudoephedrine amide moiety has shown an outstanding synthetic versatility in the sense that the aldol adducts could be easily transformed into many other interesting chiral building blocks, like β-hydroxy acids, esters and ketones.[5] We have also shown the applicability of this methodology in the total synthesis of isoflavanones.[6]



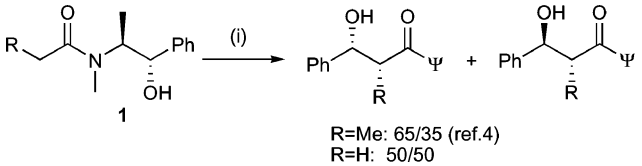
Scheme 1 *Reagents and conditions*: (i) 1) LDA, THF, −78 °C; 2) Cp_2ZrCl_2; 3) R^1CHO, −105 °C; (ii) R^2Li, THF, −78 to 0 °C; (iii) 1. 4 M H_2SO_4, dioxane, reflux; 2) MeOH, HCl (cat.), reflux.

However, there is still a long standing problem associated with the asymmetric aldol reaction in general and the chiral auxiliary-mediated methodologies in particular. While most of the auxiliaries developed behave well with reactions in which the enolate reagent bears an α-substituent (typically a methyl group; the so called "propionate-type" aldol reactions), most of them perform poorly when the enolate lacks of this α-substituent (the "acetate-type" aldol reaction). This situation, which is apparently simplified in the sense that only one stereogenic center is formed and therefore the *syn*/*anti* isomerism (simple selectivity) problem is no longer present, turns out to an unexpectedly problematic reaction that deserves special attention.[7] Related to this topic, some research groups worldwide have worked in the design of new chiral auxiliaries that specifically apply to the acetate aldol reaction.[8]

With these precedents in mind, we decided to explore the general applicability of our asymmetric aldol reaction methodology employing pseudoephedrine as chiral auxiliary to the stereoselective acetate-type aldol addition using simple achiral aldehydes.[9] We wish to report herein the more relevant results obtained in this context.

Results and discussion

We started our study using the reaction of (*S*,*S*)-(+)-pseudoephedrine acetamide **1** with benzaldehyde as shown in Scheme 2. Thus, when we performed this transformation under conditions typically employed by us in other propionate-type aldol reactions (LDA deprotonation followed by addition of the aldehyde at −105 °C) the analysis of the crude reaction mixture showed the presence of both possible diastereoisomers in almost 1 : 1 ratio (entry 1 in Table 1). This result is in contrast with the related aldol reaction of (*S*,*S*)-(+)-pseudoephedrine propionamide under the same conditions, which affords the corresponding aldol as a 65 : 35 mixture of *syn*/*anti* isomers but with complete facial stereoselection.[4]



Scheme 2 *Reagents and conditions*: (i) 1) LDA, THF, −78 °C; 2) PhCHO, −105 °C.

In a previous work we have noticed that the diastereoselectivity of the aldol reaction of pseudoephedrine amides could be substantially improved by using enolates of metals, other than lithium, with stronger chelation abilities. For that reason, we subjected the lithium enolate generated after the LDA deprotonation to a transmetalation process with 2 eq.

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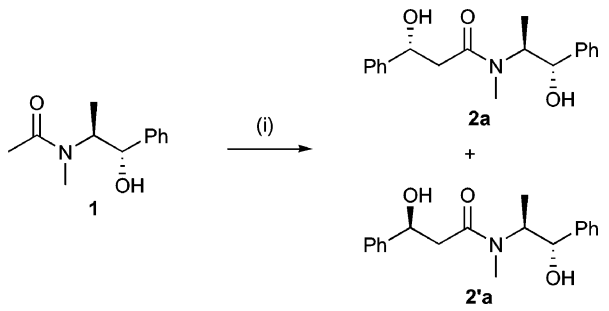
Table 1 Aldol reaction of **1** and benzaldehyde using different metal enolates

Entry	MX_n	Yield (%)[a]	Ratio **2a** : **2′a**[b]
1	—	58	54 : 46
2	$TiCl_4$	—[c]	—
3	$SnCl_4$	—[c]	—
4	$ZnCl_2$	15	67 : 33
5	Cp_2ZrCl_2	40	68 : 32
6	Cp_2TiCl_2	35	64 : 36
7	Me_2AlCl	34	61 : 39
8	Cp_2ZrCl_2[d]	65	61 : 39
9	Cp_2ZrCl_2[e]	77	61 : 39
10	Cp_2ZrCl_2[e,d]	77	63 : 37

[a] Global yield for the mixture of diastereoisomers. [b] Calculated by HPLC analysis of the crude reaction mixture (Chiralcel OD column, UV detector, hexanes–*i*-PrOH 95 : 5, 0.8 mL min^{-1}). [c] No reaction occurred. [d] Reaction was carried out in the presence of 5 eq. of LiCl. [e] Reaction was carried out using 2 eq. of PhCHO.

of different metal halides, which was performed by adding the corresponding metal salt to the lithium enolate at −78 °C, followed by stirring for 1 h at this temperature. Next, the mixture was cooled to −105 °C, at which temperature benzaldehyde was added at once (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) 1) LDA, THF, −78 °C; 2) MX_n; 3) PhCHO, −105 °C.

As we expected, the nature of the enolate counterion had an important influence both on the yield and the diastereoselectivity of the reaction. As it can be seen in Table 1, when $TiCl_4$ or $SnCl_4$ were used as a metal source in the transmetalation step, no reaction was observed and the starting material was recovered unchanged (entries 2 and 3). The use of $ZnCl_2$ gave low yield of the addition product and moderate diastereoselectivity (entry 4). Remarkably, the use of metals like Ti(IV) and Zr(IV) together with the presence of bulky ligands attached to the metal center resulted in better **2a** : **2′a** ratios, together with a moderate increase in the reaction yield (entries 5 and 6). We also surveyed the utility of aluminium enolates in this context but no better results were observed (entry 7). From all the trials performed, the best results concerning both the yield and diastereoselectivity arose from the experimental conditions shown in entry 5.

It is also known that the presence of lithium salts as additives has a striking influence on the yield and, in some cases, in the diastereoselectivity of the reactions in which pseudoephedrine amide enolates participate.[10] In our case, conducting the reaction with the zirconium enolate in the presence of 5 eq. of LiCl exerted a large influence on the yield, although the addition proceeded with a small decrease in the diastereoselectivity (Table 1, entry 8). We also tried the reaction using an excess of benzaldehyde, observing comparable results with yield improvement and a small decrease in the **2a** : **2′a** ratio (entry 9). Concurrent application of both modifications (presence of LiCl and 2 eq. of PhCHO) led to similar results (entry 10).

As has already been mentioned, pseudoephedrine propionamide enolates react with aldehydes with complete facial

Table 2 Aldol reaction of **1** and benzaldehyde–Lewis acid complex

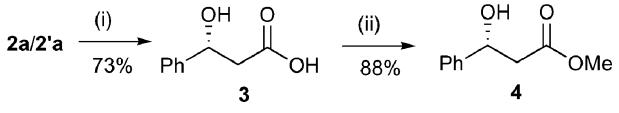
Entry	Lewis acid	Yield (%)[a]	Ratio **2a** : **2′a**[b]
1	—	58	54 : 46
2	$TiCl_4$	70	60 : 40
3	$SnCl_4$	61	59 : 41
4	$ZnCl_2$	72	59 : 41
5	$BF_3{\cdot}OEt_2$	45	58 : 42

[a] Global yield for the mixture of diastereoisomers. [b] Calculated by HPLC analysis of the crude reaction mixture (Chiralcel OD column, UV detector, hexanes–*i*-PrOH 95 : 5, 0.8 mL min^{-1}).

selectivity,[4] which implies that one of the diastereotopic faces of the enolate is effectively blocked to the incoming electrophile by the presence of the chiral auxiliary. Consequently, it is reasonable to assume that this behavior is still operating in the reaction of the parent acetamide enolate derived from **1** and, thus, the reason for the lower diastereoselectivity observed in this case should be attributed to the low degree of stereodifferentiation between the two enantiotopic faces of the aldehyde.

According to this hypothesis, we surveyed the possibility of performing the aldol addition using the aldehyde reagent previously complexed with a Lewis acid. This should introduce steric hindrance in the reaction intermediate and maybe better discrimination between both enantiotopic faces of the aldehyde could be achieved. Therefore, the lithium enolate of **1** was reacted with THF solutions of different benzaldehyde–Lewis acid complexes at −105 °C, with the results shown in Table 2. As can be seen in this table, this experimental protocol furnished the corresponding aldols in much better yields when compared with the reaction in the absence of any additive (entry 1), but the diastereoselectivity did not significantly improve and no significant dependence upon the nature of the Lewis acid employed was observed. This indicates that the Lewis acid is acting only as a simple carbonyl activating reagent but does not influence in the stereodiscrimination between its faces.

The absolute configuration of the stereogenic center created during the aldol addition was determined by chemical correlation, after conversion of the adduct into the known methyl 3-hydroxy-3-phenylpropanoate **4** (Scheme 4). Therefore, the mixture of aldols **2a** and **2′a** obtained under the best reaction conditions regarding to the diastereoselectivity of the process (entry 5 in Table 1) was subjected to hydrolysis by treatment with 4 M NaOH in refluxing THF–MeOH, leaving to the β-hydroxy acid **3**, which was obtained in good yield after standard acid–base work-up and the purity of which was assessed by NMR analysis. The chiral auxiliary (*S*,*S*)-(+)-pseudoephedrine could be recovered from the basic aqueous layer in 83% yield by simple acidification, followed by extraction and crystallization. It was isolated with no loss of optical purity as its $[\alpha]_D^{20}$ value indicated, which allowed us to recycle the auxiliary for further uses. Next, acid **3** was esterified with trimethylsilyldiazomethane, affording β-hydroxy ester **4** in excellent yield and in 37% ee as ^{1}H-NMR analysis of its Mosher ester indicated. As this ee is in full agreement with the **2a** : **2′a** ratio observed in the starting amide, it can be said that both hydrolysis and esterification steps proceeded with no racemization at the stereogenic center created in the aldol reaction. Comparison of the obtained $[\alpha]_D^{20}$ value (+3.6, c = 2.0, EtOH) with the reported one ($[\alpha]_D^{20}$ = +17.7, c = 2.05, EtOH for the *R* isomer)[11] allowed us to assign the *R* configuration for the β-hydroxy ester **4**.



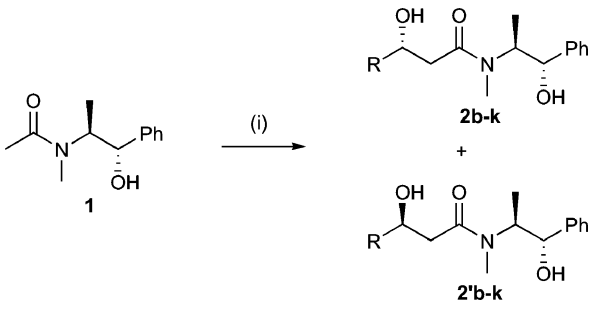
Scheme 4 *Reagents and conditions*: (i) 4 M NaOH, THF–MeOH, reflux; (ii) 1) $TMSCH_2N_2$, THF, 0 °C; 2) MeOH, rt.

Table 3 Aldol reaction of **1** and different aldehydes

Entry	Product	R	Yield (%)[a]	Ratio **2** : **2′**[b]
1	**2b**	*o*-$NO_2C_6H_4$	68	70 : 30
2	**2c**	*p*-$NO_2C_6H_4$	76	62 : 38
3	**2d**	*o*-FC_6H_4	72	71 : 29
4	**2e**	*p*-FC_6H_4	73	56 : 44
5	**2f**	*o*-$MeOC_6H_4$	33	64 : 36
6	**2g**	*p*-$MeOC_6H_4$	50	58 : 42
7	**2h**	*o*-MeC_6H_4	58	70 : 30
8	**2i**	3,5-$(MeO)_2C_6H_3$	32	60 : 40
9	**2j**	^{i}Pr	58	55 : 45
10	**2k**	^{t}Bu	54	63 : 37

[a] Global yield for the mixture of diastereoisomers. [b] Calculated by HPLC analysis of the crude reaction mixture (Chiralcel OD column, UV detector, hexanes–*i*-PrOH 95 : 5, 0.8 mL min^{-1}).

After all the experiments carried out, we proceeded to extend the best conditions obtained, concerning the diastereoselectivity in the aldol reaction, to a wide range of other aldehydes with different structures (Scheme 5). Therefore, acetamide **1** was deprotonated with LDA in THF at −78 °C, followed by transmetalation with 2 eq. of Cp_2ZrCl_2 and addition of the corresponding aldehyde at −105 °C, yielding β-hydroxy amides **2b–k** (Table 3).



Scheme 5 *Reagents and conditions*: (i) 1) LDA, THF, −78 °C; 2) Cp_2ZrCl_2; 3) RCHO, −105 °C.

As it can be seen in the data shown in Table 3, the structure of the aldehyde had a striking influence on the yield of the reaction, which goes from moderate to good when working with aromatic aldehydes with electron-withdrawing groups (entries 1–4), with respect to those containing electron-donating substituents (entries 5–8). It should also be noted that aromatic aldehydes with electron-withdrawing groups also give better yields than simple aliphatic aldehydes (entries 1–4 *vs.* 9–10). Concerning to the diastereoselectivity of the reaction, it was not so much dependent upon the structure of the aldehyde employed. However, significant differences were found when looking at the position of the substituents in the aromatic ring of the aldehyde, showing that substituents at the *ortho* position gave better **2a** : **2′** ratio than the same groups placed at the *para* position of the aryl moiety (entries 1 *vs.* 2, 3 *vs.* 4 and 5 *vs.* 6).

This should be interpreted in terms of steric bulk near the formyl group where the reaction is going to take place, in the sense that groups placed at the *ortho* position result in a more sterically demanding substituent in the aldehyde, which increases the degree of stereodiscrimination between its two enantiotopic faces. This dependence of the diastereoselectivity upon the steric bulk of the aldehyde substitution pattern is also observed in the aliphatic series, where pivalaldehyde reacts with improved diastereoselectivity than isobutyraldehyde (entries 9 *vs.* 10).

An explanation for the different degree of stereoselectivity attained in propionate and acetate aldol reactions using (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary can be envisaged in

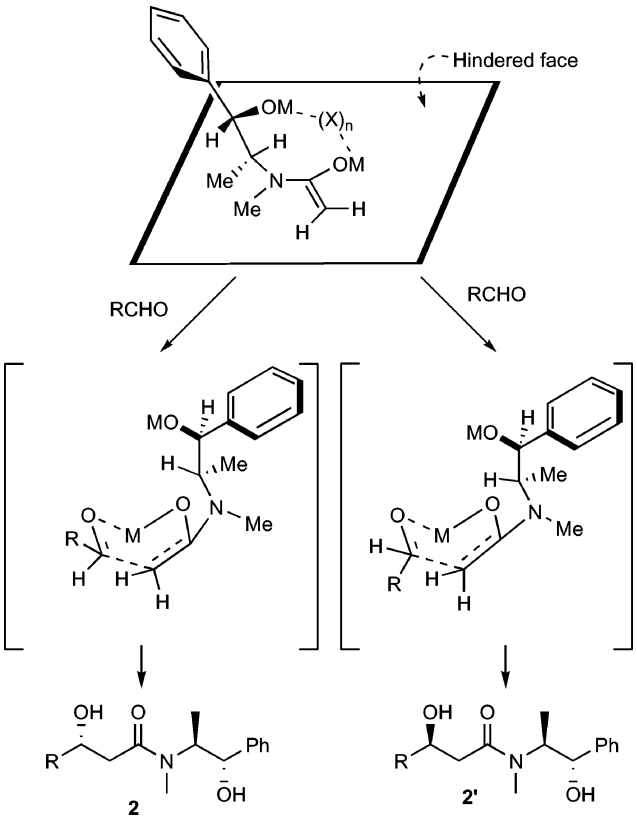


Fig. 1

mechanistic terms (Fig. 1). It has been previously proposed in other reactions between (*S*,*S*)-(+)-pseudoephedrine amide enolates and different electrophiles that the final product arises from the attack to the less hindered face of an intermediate in an opened staggered conformation, which remains rigid with the help of bridging solvent or ^{i}PrNH (from LDA) molecules.[5a,12] Therefore, as has been previously mentioned, we could assume that in this case one of the diastereotopic faces of the enolate reagent is effectively blocked by the chiral auxiliary. Concerning to the discrimination between the two enantiotopic faces of the aldehyde, in the propionate-type aldol reaction it is a Zimmerman–Traxler-type six membered chair-shaped transition state which accounts for the obtained high simple diastereoselection.[4] However, as other authors also point out,[13] when the enolate lacks of the α-substituent (as it is the case in the acetate aldol reaction), boat- or twist–boat-like transition states can compete with the chair model, which has been supported in some cases by computer modeling studies.[14] In our case, the possibility of such a boat-like transition state, as depicted in Fig. 1, could also account for the observed lower level of diastereoselection.

Conclusions

We have evaluated the asymmetric acetate-type aldol reaction using (*S*,*S*)-(+)-pseudoephedrine. A thoughtful study focused towards the optimization of different experimental variables like the nature of the enolate counterion, the presence of additives (LiCl or added Lewis acids) and the structure of the aldehyde, has been performed, concluding that the best conditions regarding the diastereoselectivity of the reaction involve the use of zirconium enolates, together with sterically demanding aldehydes. In addition, the yield of the reaction has shown to be highly dependent upon the nature of the aldehyde employed, showing that best yields are obtained with aromatic aldehydes containing electron-withdrawing substituents.

Experimental

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded at 20–25 °C, running at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CDCl_3$ solution and resonances are reported in ppm relative to tetramethylsilane unless otherwise stated. Assignment of individual ^{13}C resonances are supported by DEPT experiments. Mass spectra were recorded under electron impact at 70 eV. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kiesegel GF_{254}) and visualization was accomplished by UV light. Flash column chromatography on silica gel was performed with Merck Kiesegel 60 (230–400 mesh). All solvents used in reactions were dried and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon. The glassware was over dried (140 °C) overnight and purged with argon.

Typical procedure for the aldol reaction of (*S*,*S*)-(+)-pseudoephedrine acetamide

A solution of the acetamide **1** (1.0 mmol) in dry THF (15 mL) was slowly added to a cooled (−78 °C) solution of LDA (2.0 mmol) in dry THF (20 mL). The mixture was stirred at this temperature for 1 h and allowed to reach to rt. The mixture was cooled again to −78 °C, at which temperature a THF (20 mL) solution of bis(cyclopentadienyl)zirconium dichloride (2.0 mmol) was added at once and the resulting solution was stirred for 1 h at this temperature. The mixture was cooled down to −105 °C, at which temperature a solution of the corresponding aldehyde (1.0 mmol) in dry THF (10 mL) was added dropwise within 20 min. The mixture was stirred at −105 °C for 6 h and quenched with a saturated NH_4Cl solution (50 mL). The mixture was extracted with CH_2Cl_2 and the combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed under a reduced pressure. Pure aldols **2a–k** were isolated by flash column chromatography purification (hexanes–ethyl acetate 2 : 8).

[3*R*,1′*S*,2′*S*]- And [3*R*,1′*S*,2′*S*]-*N*-(2′-hydroxy-1′-methyl-2′-phenylethyl)-3-hydroxy-*N*-methyl-3-phenyl-propanamide (2a and 2′a). According to the general procedure, amide **1** (1.00 g, 4.83 mmol) was treated with LDA (prepared *in situ* by the addition of *n*-BuLi (1.5 M solution in hexanes, 6.40 mL, 9.66 mmol) to a THF (20 mL) solution of iPr_2NH (1.38 mL, 9.66 mmol) at −78 °C for 20 min), Cp_2ZrCl_2 (2.82 g, 9.66 mmol) and PhCHO (0.50 mL, 4.83 mmol). The mixture of amides **2a** and **2′a** (0.60 g, 1.93 mmol) was isolated after purification in 68 : 32 ratio as HPLC analysis indicated (see Table 1). Yield: 40%. δ_H(250 MHz, $CDCl_3$, Me_4Si) (3 : 2 rotamer ratio; * denotes minor rotamer resonances, resonances corresponding to the minor diastereosiomer are shown in italics) 0.85–0.92 (m, 3H), 2.49–2.60 (m, 2H), 2.72* (s, 3H), 2.87 (s, 3H), 3.81–3.87 (m, 1H), 3.99–4.05 (m, 1H), 4.40–4.49 (m, 2H), 4.69–4.78 (m, 2H), 4.97–5.16 (m, 2H), 7.23–7.35 (m, 10H). δ_C(67.8 MHz, $CDCl_3$, Me_4Si) 13.9, 14.9, 26.6, 26.8, 30.2*, 30.6*, 41.7*, 42.3*, 42.5, 42.8, 55.2*, 55.5*, 57.7, 58.2, 69.9, 71.0*, 74.7, 75.1, 125.4, 125.5, 126.5, 126.6, 126.9, 127.1, 127.5*, 127.7*, 128.0, 128.2*, 141.3, 141.4*, 141.5*, 142.8*, 142.9, 143.0, 172.4, 172.9, 173.0*, 173.2*. *m*/*z* (EI) 314 (M^+ + 1, 5), 207 (12), 206 (24), 107 (13), 105 (6), 79 (24), 77 (21), 58 (100).

Typical procedure for the hydrolysis of β-hydroxyamides 2a/2′a

A solution of the mixture of amides **2a/2′a** (0.60 g, 1.91 mmol) in THF (10 mL)–MeOH (5 mL) was slowly added over a cooled (0 °C) 4 M NaOH solution (10 mL). When the addition was complete, the mixture was refluxed for 4 h. The reaction was quenched with water, washed with EtOAc, the aqueous layer was carefully driven to pH = 3 and extracted with CH_2Cl_2. The collected organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under a reduced pressure yielding the wanted acid **3** as a white solid (0.23 g, 1.39 mmol). After drying (Na_2SO_4), filtering and removing the solvent from the basic organic extracts it was possible to recover, after crystallization (hexanes–EtOAc) pure (*S*,*S*)-(+)-pseudoephedrine (0.26 g, 1.58 mmol) in 83% yield.

[3*R*]-3-Hydroxy-3-phenylpropionic acid (3). Yield: 73%. Mp: 90–94 °C (hexanes–AcOEt). $\nu_{max}(CHCl_3)/cm^{-1}$ 3402 (OH); 1709 (C=O). δ_H(250 MHz, $CDCl_3$, Me_4Si) 2.71–2.78 (m, 2H); 5.13 (dd, J = 4.0, 8.7 Hz, 1H); 6.62 (bs, 1H); 7.23 (m, 5H). δ_C(67.8 MHz, $CDCl_3$, Me_4Si) 43.5; 70.3; 125.6, 127.7, 128.5; 142.3; 171.7. *m*/*z* (EI) 145 (4), 123 (18), 120 (17), 106 (16), 105 (85), 95 (10), 85 (55), 83 (100), 77 (63), 51 (18).

Typical procedure for the esterification of β-hydroxyacid 3

$TMSCHN_2$ (6.02 mL of a 2 M solution in Et_2O, 12.04 mmol) was added over a cooled (0 °C) solution of the acid **3** (0.50 g, 3.01 mmol) in dry THF (10 mL). After stirring for 2 h, MeOH (1 mL) was added at once and the mixture was stirred for further 45 min, after which it was quenched with water (15 mL). The mixture was extracted with CH_2Cl_2 and the combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to yield ester **4** (0.48 g, 2.65 mmol) as a colourless oil after flash column chromatography purification (hexanes–AcOEt 8 : 2). Ester **4** showed to be 36% ee by ^1H NMR analysis of its Mosher ester.

Methyl [3*R*]-3-hydroxy-3-phenylpropanoate (4). Yield: 88%. $[\alpha]_D^{20}$: +3.6 (*c* = 2.0, EtOH); lit.[9] +17.7, *c* = 2.05, EtOH). $\nu_{max}(CHCl_3)/cm^{-1}$ 3442 (OH); 1641 (C=O). δ_H(250 MHz, $CDCl_3$, Me_4Si) 2.74 (d, 1H, J = 4.3 Hz); 2.77 (d, 1H, J = 8.3 Hz); 3.43 (bs, 1H); 3.73 (s, 3H); 5.14 (dd, 1H, J = 4.3, 8.3 Hz); 7.29–7.38 (m, 5H). δ_C(67.8 MHz, $CDCl_3$, Me_4Si) 43.1, 51.9, 70.3, 125.6, 127.8, 128.5, 144.9, 172.8.

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