Asymmetric Aldol Reactions Using (*S*,*S*)-(+)-Pseudoephedrine-Based Amides: Stereoselective Synthesis of α-Methyl-*β*-hydroxy Acids, Esters, Ketones, and 1,3-Syn and 1,3-Anti Diols

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A very efficient method for performing stereoselective aldol reactions is reported. The reaction of (*S*,*S*)-(+)-pseudoephedrine-derived propionamide enolates with several aldehydes yielded exclusively one of the four possible diastereomers in good yields, although transmetalation of the firstly generated lithium enolate with a zirconium(II) salt, prior to the addition of the aldehyde, is necessary in order to achieve high syn selectivity. The so-formed *syn*-α-methyl-*β*-hydroxy amides were transformed into other valuable chiral nonracemic synthons such as α-methyl-*β*-hydroxyacids, esters, and ketones. Finally, a stereocontrolled reduction procedure starting from the so-obtained α-methyl-*β*-hydroxy ketones has been developed allowing the synthesis of either 1,3-*syn*- or 1,3-*anti*-α-methyl-1,3-diols in almost enantiopure form by choosing the appropriate reaction conditions.

Introduction

The aldol reaction is regarded as one of the most powerful tools in organic synthesis for the formation of carbon−carbon bonds. Consequently, over the past 20 years, an extensive number of methodologies for performing enantioselective aldol reactions of chiral enolates with achiral aldehydes 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 carbonyl compounds carrying chiral auxiliaries that can be easily removed from the final product,[2] (2) the use of metal enolates, typically B, Ti, Sn, or Li, with the presence of a chiral ligand bound covalently or not to the metal center,[3] and (3) performing the reaction in a catalytic fashion in the presence of a chiral catalyst.[4] Among the first ones, a vast array of compounds have been used as chiral inductors, such as Evans-type oxazolidinones,[1b,c,5] Meyers oxazolidines,[3a] bornane derivatives,[6] thiazolidinones, thiazolidinethiones or oxazolidinethiones,[7] imidazolidinones,[8] Oppolzer's sultams,[9] amino alcohols,[10] aziridines,[11] chiral sulfoxides,[12] ferrocenyliron complexes,[13] diols,[14] diamines,[15] benzoxazinones,[16] hydrazones,[17] atropisomeric amines,[18] menthone derivatives,[19] and so on.

If we assume that an enolate with one substituent at the α-possition and with a determined geometry (*E* or *Z*) undergoes an aldol reaction with an aldehyde, four possible diastereoisomers can be formed. Under kinetic conditions, the stereochemistry of the first chiral center would be controlled by the approach of the aldehyde from one of the two diastereotopic faces of the enolate (the so-called enantiofacial differentiation[1e] or diastereofacial selectivity[1a]) and therefore by the chiral information

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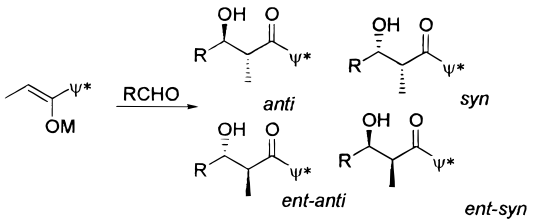
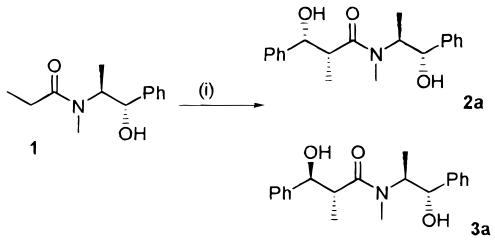


Figure 1.

attached to the enolate. The stereochemistry of the second chiral center would be controlled by the approach of the aldehyde from one of its two enantiotopic faces (named as simple diastereoselection[1a]) and therefore by the steric requirements derived from a cyclic transition state such as a Zimmermann−Traxler-like or related mechanism.[20] The main target when planning an aldol reaction is to achieve complete stereocontrol in both of the aforementioned aspects, thus allowing the preparation of a single isomer from the four possible ones (Figure 1).

In this context, in connection with our studies in the field of the asymmetric synthesis of natural products,[21] and continuing with our preliminary study on the stereocontrolled aldol reaction,[22] we wanted to develop an easy and cheap methodology to access to 1,3-dioxygenated

Scheme 1



Reagents and conditions (i) 1. LDA, THF, -78 °C. 2. MX_n THF, -78 °C. 3. PhCHO, THF, temperature.

chiral nonracemic building blocks. Taking into account the fact that (*S*,*S*)-(+)-pseudoephedrine, which is a commercially available reagent in both enantiomeric forms, has been recently used as a chiral auxiliary in asymmetric alkylation reactions with excellent results,[23] we decided to develop an extensive protocol for performing stereoselective aldol reactions employing this particular amino alcohol as the chirality source. Moreover, the obtained chiral nonracemic aldol products could be used as suitable starting materials for their conversion into useful chiral building blocks such as *β*-hydroxy acids, esters, and ketones and into 1,3-syn and 1,3-anti diols.

Results and Discussion

In a first test reaction, the amide **1** prepared by a reported procedure[23a] was deprotonated with 2 equiv of LDA at −78 °C and treated with benzaldehyde at 0 °C yielding a 1:1 mixture of **2a** and **3a** (Scheme 1), which could be easily separated by flash column chromatography. The presence of the corresponding diastereomers *ent*-**2a** or *ent*-**3a** could not be detected. Lowering the temperature to −78 °C increased the **2a**/**3a** ratio to 60:40 and to 65:35 at −105 °C. The absolute configuration of the two newly generated chiral centers of both products was established by hydrolysis and esterification to the corresponding methyl esters, whose coupling constants between H^1 and H^2 and $[\alpha]^{20}_D$ values were compared with those reported in the literature (see Experimental Section). In order to unambiguously assure that the products *ent*-**2a** and *ent*-**3a** were not present, the reaction mixture was subjected to HPLC analysis under previously optimized conditions with a mixture of the four products obtained by other procedures.[24] Although the syn/anti ratio (simple diastereoselection) was not good, the excellent results concerning to the face selection of the reaction indicated the utility of the chiral auxiliary (*S*,*S*)-(+)-pseudoephedrine in this reaction. It should also be pointed out that the reaction was clean and fast and did not require the aid of LiCl salts to accelerate it, as was previously reported in other reactions of pseudoephedrine amide lithium enolates.[25]

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(24) The isomers *ent*-**2a** and *ent*-**3a** were obtained as pure compounds by epimerizing the α-carbon of **3a** and **2a**, respectively, with LDA in refluxing THF followed by column chomatography separation of the two formed diastereoisomers (**3a** and *ent*-**2a** in the reaction of **3a** and **2a** and *ent*-**3a** in the reaction of **2a**).

Table 1. Transmetalation Assays in Order To Improve the Syn/Anti Ratio of the Aldol Reaction

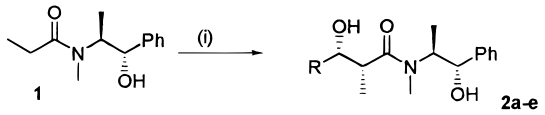
entry	metal salt	equiv	T^a (°C)	yield (%)	syn/anti[b]
1	$Ti(O^iPr)_4$	1	0	65	66/34
2	$Ti(O^iPr)_4$	1	−105	71	71/29
3	$Ti(O^iPr)_4$	2	−105	68	77/23
4	$TiCl(O^iPr)_3$	1	−105	73	64/36
5	$TiCl(O^iPr)_3$	2	−105	77	75/25
6	$SnCl_4$	1	0	75	53/47
7	$SnCl_4$	2	0	70	57/43
8	$CF_3SO_3B(^nBu)_2$	2	rt	38[c]	61/39
9	$CF_3SO_3B(^nBu)_2$	2	0	0	
10	$ZnCl_2$	2	0	81	60/40
11	$ZnCl_2$	2	−78	78	78/22
12	$MgCl_2$	1	−105	80	61/39
13	$MgCl_2$	2	−105	79	71/29
14	$ZrCp_2Cl_2$	2	0	75	80/20
15	$ZrCp_2Cl_2$	2	−78	79	89/11
16	$ZrCp_2Cl_2$	2	−105	90	94/6
17	$ZrCp_2Cl_2$	1	−105	87	83/17

[a] Temperature at which the PhCHO addition step was performed. [b] Determined by HPLC (Chiralcel OD column, UV detector, hexanes/^{i}PrOH 70:30, flow rate 1.00 mL/min). [c] Complete conversion was not achieved.

As it is known that the use of enolates of metals other than lithium with stronger chelation abilities improve the simple diastereoselection in aldol reactions,[26] several other metals in different proportions and temperatures were tested. In all cases, the lithium enolate was subjected to a transmetalation process, which was performed by adding the corresponding metal salt at −78 °C followed by stirring for 1h at this temperature (Table 1). In all trials, the use of 2 equiv of $ZrCpCl_2$ followed by addition of the aldehyde at −105 °C resulted in the best **2a**/**3a** ratio. This tendency for a high syn selection for zirconium enolates in aldol reaction has been previously reported.[10b,26a,h] As expected, the temperature of the addition step had a strong influence on the syn/anti selectivity. It should also be pointed out that the improvement observed with two equivalents of the metal salts instead of one turned out to be relevant to the mechanistic pathway of the reaction.

Once the methodology was optimized, it was extended to a full range of representative aldehydes, all of which reacted as expected to yield the aldols **2a**−**e** (Scheme 2, Table 2) in excellent yields and with high distereoface and syn selection, as HPLC analysis of the crude mixtures indicated. It could also be observed that the syn/anti selectivity improved when the bulkiness of the R chain in the aldehyde is increased.

Scheme 2



Reagents and conditions (i) 1. LDA, THF, -78 °C. 2. $ZrCp_2Cl_2$, THF, -78 °C. 3. RCHO, THF, -105 °C

Table 2. Yields and Stereoselectivities Obtained in the Asymmetric Aldol Reaction of Amide 1 with Several Representative Aldehydes

entry	product	R	syn/anti[a]	**2**/*ent*-**2**[a]	yield[b] (%)
1	**2a**	Ph	94/6	>99/<1	90
2	**2b**	Me	90/10	>99/<1	88
3	**2c**	Et	96/4	>99/<1	90
4	**2d**	^{i}Pr	>99/<1	>99/<1	94
5	**2e**	^{t}Bu	>99/<1	>99/<1	94

[a] Determined by HPLC (Chiralcel OD column, UV detector, hexanes/^{i}PrOH 70:30, flow rate 1.00 mL/min). [b] Yield of **2a**−**e** after flash column chromatography purification.

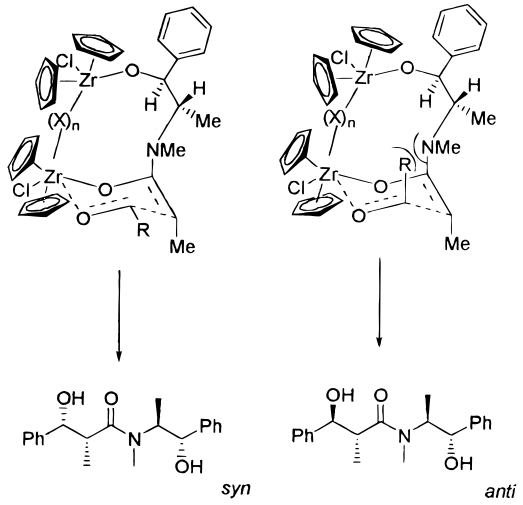


Figure 2.

These results are in accordance with a previously proposed mechanism[21b,23a] in which the adduct of the pseudoephedrine amide aldol reaction arises from attack of the preformed *Z* enolate of the less hindered *si* face of an intermediate in an opened staggered conformation, which remains rigid with the help of bridging solvent or ^{i}PrNH (from LDA) molecules (Figure 2). In this case, the fact that 2 equiv of metal salt was needed in order to improve the syn/anti diastereoselection overrides the possibility of an intermediate incorporating only one metal that could bind both alkoxide units via an O−M−O bond and supports the existence of the mentioned open intermediate. However, the possible formation of an internal chelate between the metal on the alkoxide oxygen of the chiral auxiliary and the amide nitrogen has been pointed out.[27]

Concerning simple diastereoselection, the use of enolates of transition metals allows the metal to employ its empty orbitals, exerting a strong influence on the angles between RCHO···M···$O_{enolate}$, as postulated in the Zim-

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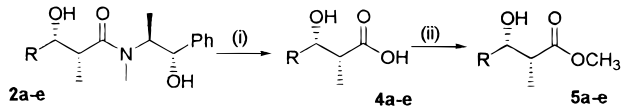
Scheme 3



Reagents and conditions (i) 4M H_2SO_4/Dioxane reflux. (ii) MeOH, HCl reflux.

Table 3. Yields and Stereoselectivities Obtained in the Asymmetric Synthesis of the α-Methyl-*β*-hydroxy Acids and Esters 4a−e and 5a−e

entry	product	R	yield[a] (%)	product	yield[b] (%)	ee[c] (%)
1	**4a**	Ph	90	**5a**	91	>99
2	**4b**	Me	93	**5b**	92	>99
3	**4c**	Et	85	**5c**	88	>99
4	**4d**	^{i}Pr	98	**5d**	86	>99
5	**4e**	^{t}Bu	96	**5e**	90	>99

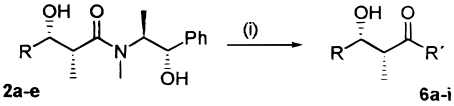
[a] Yield of pure product after acid−base standard workup. [b] Yield of pure product after flash column chromatography purification. [c] Determined by chiral HPLC (Chiracel OD, UV detector, hexanes/isopropyl alcohol 93:7 as eluent. Flow rate 0.75 mL/min.).

merman−Traxler transition state. This would result in a pseudo-chair[28] conformation for the transition state in which the bulky R substituent on the aldehyde would lie in an equatorial position in order to avoid steric repulsions with the chiral auxiliary and therefore afford the diastereoisomer of relative syn configuration (see Figure 2).

Transformation of the Aldol Products into Other Valuable Synthons. The α-methyl-*β*-hydroxy amides obtained from the aldol reaction were subjected to several derivatization processes in order to survey their possibilities in synthetic organic chemistry. In this way, α-methyl-*β*-hydroxy acids, esters, and ketones were obtained in nearly optically pure form. Also a protocol for reducing the latter to yield selectively chiral nonracemic 1,3-syn or 1,3-anti diols was investigated.

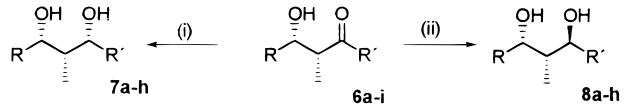
(a) Hydrolysis and Esterification. The amides **2a**−**e** were subjected to acid hydrolysis by refluxing them in a 1:1 mixture of 4 M H_2SO_4/dioxane, yielding the corresponding α-methyl-*β*-hydroxy acids in excellent yields (Scheme 3, Table 3). In none of the cases dehydration products from the possible action of sulfuric acid on the hydroxy functionality were observed. The acids were obtained as pure oils after standard acid−base workup, and upon treatment with refluxing methanol under acid catalysis, they yielded α-methyl-*β*-hydroxy esters in excellent yields after flash column chromatography purification. All the esters **5a**−**e** showed >99% ee as HPLC analysis in a chiral stationary phase indicated, showing that both processes procceded without racemization in any of the chiral centers of the starting molecule. Another remarkably feature on the synthetic scheme is the fact that the chiral auxiliary, (*S*,*S*)-(+)-pseudoephedrine, could be recovered from the extracts of the basic aqueous layer after workup of the hydrolysis mixture followed by crystallization in hexane/EtOAc 1:1 in ca. 80% yield and without racemization as the measurement of its $[\alpha]^{20}_D$ value indicated.

Scheme 4



Reagents and conditions (i) 1. R′Li, THF, -78 °C to rt. 2. AcOH, H_2O.

Scheme 5



Reagents and conditions (i) $BH_3(Me_2S)$, THF, rt. (ii) $LiBH_4$, MeOH, rt.

At this point, and as an example of useful products that can be obtained by this methodology, we were able to synthesize (2*S*,3*R*)-1-ethylpropyl-3-hydroxy-2-methylpentanoate **5f**, the enantiomer of the natural product (+)-sitophilate, which is the aggregation pheromone of the male granary weevil *Sitophilus granarius*.[29,30] The synthesis was posssible by performing the esterification reaction of the acid **4c** using 3-pentanol instead of methanol. The product was obtained in excellent yield (89%) and almost optically pure (ee >99%) according to chiral HPLC analysis.

(2) Synthesis of α-Methyl-*β*-hydroxy Ketones. It is known that reaction of organolithium reagents with tertiary amides yields the corresponding ketones in a single step.[31] In this case the key step is the formation of a stable tetrahedral intermediate after the addition of the organolithium reagent across the C═O double bond which, upon aqueous workup, affords the desired ketones. The stability of this intermediate avoids further attack by other molecules of organometallic reagent, which would result in the formation of a tertiary alcohol byproduct. In the particular case of the aldols **2a**−**e**, several other side reactions could occur as a consequence of the presence of a strongly basic medium. Thus, enolization would lead to epimerization at the α-carbon and thus to a mixture of *syn*- and *anti*-α-methyl-*β*-hydroxy ketones or amides, and *β*-elimination of the OH functionality would yield α,*β* unsaturated ketones or amides. However, by employing the conditions optimized by Myers et al. in the reaction of pseudoephedrine amides with organolithium reagents,[23a] and including an extra equivalent of organolithium reagent in order to deprotonate the extra hydroxy group present in the substrate, none of these side reactions were found to occcur and the desired ketones **6a**−**i** were obtained in excellent yields and as single diastereomers as the analysis of the ^{1}H NMR spectra of the crude reaction products indicated (Scheme 4). Also, in order to assure that no racemization had occurred during the process, the crude ketones were subjected to HPLC analysis on chiral column showing that all were nearly optically pure (ee >99%). It should

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Table 4. Yields and Stereoselectivities Obtained in the Asymmetric Synthesis of the α-Methyl-β-hydroxy Ketones 6a−i

entry	product	R	R′	yield[a] (%)	ee[c] (%)
1	**6a**	Ph	Ph	81	>99
2	**6b**	Ph	Me	79	>99
3	**6c**	Ph	^{n}Bu	72	>99
4	**6d**	Me	Ph	79	>99
5	**6e**	Et	Ph	79	>99
6	**6f**	Et	Me	88	>99
7	**6g**	Et	Et	75	>99
8	**6h**	^{i}Pr	Ph	69	>99
9	**6i**	^{t}Bu	Ph	89	>99

[a] Yield of pure product after flash column chromatography purification. [b] Determined by chiral HPLC (Chiracel OD, UV detector, hexanes/isopropyl alcohol 96:4 as eluent. Flow rate 0.75 mL/min).

Table 5. Yields and Stereoselectivities Obtained in the Asymmetric Synthesis of the 1,3-Syn and 1,3-Anti Diols 7a−h and 8a−h

entry	R	R′	product	yield[a] (%)	ee[c] (%)	product	yield[a] (%)	ee[c] (%)
1	Ph	Ph	**7a**	78		**8a**	95	>99
2	Ph	Me	**7b**	72	>99	**8b**	77	>99
3	Ph	^{n}Bu	**7c**	75	>99	**8c**	84	>99
4	Me	Ph	**7d**	79	>99	**8d**	89	>99
5	Et	Ph	**7e**	89	>99	**8e**	80	>99
6	Et	Me	**7f**	85	>99	**8f**	81	>99
8	^{i}Pr	Ph	**7g**	93	>99	**8g**	83	>99
9	^{t}Bu	Ph	**7h**	90	>99	**8h**	90	>99

[a] Yield of pure product after flash column chromatography purification. [b] Determined by chiral HPLC (Chiracel OD, UV detector, hexanes/isopropyl alcohol 93:7 as eluent. Flow rate 0.90 mL/min).

also be pointed out that even in the presence of the strongly basic *n*-BuLi reagent no enolization was observed and the desired ketone was obtained as a single isomer.

It should also be noted that the (4*R*,5*S*)-(−)-5-hydroxy-4-methyl-3-heptanone **6g** is the enantiomer of the natural product (+)-sitophilure, which is also a pheromone common to the rice weevil *Sitophilus oryzae* and the maize weevil *Sitophilus zeamais* (Table 4).[32]

(3) Synthesis of 1,3-Syn and 1,3-Anti Diols. The 1,3-diol framework is often found in compounds with interesting pharmacological properties. In particular, the propionate-based aldol products are important building blocks in the synthesis of natural products bearing 1,3-polyol moieties such as macrolide or ionophore antibiotics.[33] Among the different strategies for the access to this kind of compound,[34] the direct hydride reduction of β-hydroxy ketones is one of the most employed ones. In particular, when the chiral center that contains the hydroxy function has a fixed stereochemistry it can exert a very effective 1,3-chiral induction during the formation of the new stereogenic center in the reduction of the carbonyl group.[35] Besides, by careful choice of reaction conditions, the reduction can proceed with or without chelation control,[36] which would result in the selective formation of 1,3-syn or 1,3-anti diols, although the influence of the additional chiral center at the α-position in the starting ketone has to be taken into account in the stereochemical outcome of the reduction reaction.[37]

With these premises in mind, we chose the ketone (+)-(2*R*,3*R*)-3-hydroxy-2-methyl-1,3-diphenyl-1-propanone **6a** as a model compound to assay several reducing agents. We found that the use of an electrophilic hydride like $BH_3(Me_2S)$ in THF led to the final product preferentially with a 1,3-syn relative stereochemistry and the use of nucleophilic hydride sources such as metal borohydrides led to the preferential obtention of products with a 1,3-anti relationship. In the first case temperature control had a striking effect in the stereoselection of the process; thus, by refluxing the reaction mixture, fast conversion was observed to the final products but with low stereoselection (55/45). However, at room temperature, full stereochemical control of the reaction was achieved (only the 1,3-syn isomer could be detected), although longer reaction times were needed for achieving full conversion (12 h). In the case of the metal borohydride mediated reduction, the use of $NaBH_4$ in MeOH proceeded with low stereocontrol but by employing $LiBH_4$ in the same reaction the 1,3-anti isomer was cleanly obtained. The 1,3-syn/1,3-anti product distribution and the absolute configuration of the newly created chiral center were assigned by ^{1}H NMR spectroscopy by comparison of the coupling constants ($J_{1,2} = 2.8$ Hz for the syn isomer and $J_{1,2} = 6.8$ Hz and $J_{2,3} = 2.4$ Hz for the anti isomers, see Experimental Section) and also from the fact that in this particular case the 1,3-syn diol is a meso compound in which both carbon atoms C1 and C3 are equivalents.

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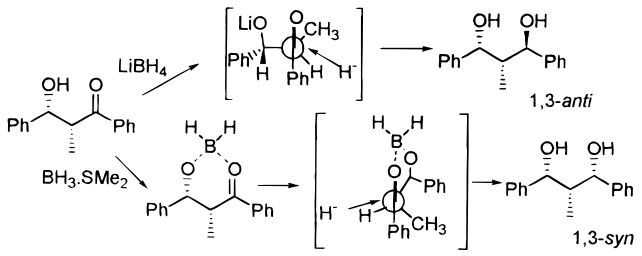

Figure 3.

These optimized conditions were further extended to the ketones **6a**−**i** yielding the diols **7a**−**i** and **8a**−**i** in good yields. Also this time, in order to assure that no racemization occurred during reduction of the ketones, the enantiomeric excesses of the final products were determined by chiral HPLC.

The stereochemical outcome of the reduction could be explained in terms of the Felkin model.[38] For $LiBH_4$, reduction in a very polar solvent like MeOH an open transition state can be proposed, followed by hydride attack from the less hindered face of the carbonyl group, as shown in Figure 3. In the BH_3·(Me_2S) reduction in THF, a closed Cram−Kopecki[39] transition state could be proposed in which the boron atom would remain intramolecularly coordinated to both oxygen atoms in the substrate resulting in the formation of the 1,3-syn isomer (Figure 3). This assumption was corroborated by reacting the ketone **6a** with $LiBH_4$ in THF in the presence of 1 eq of a Lewis acid like *n*-Bu_3B, yielding preferently the product with 1,3-syn relative stereochemistry (80:20).

Conclusions

A highly stereoselective protocol for performing aldol additions using (*S*,*S*)-(+)-pseudoephedrine as the chirality inductor has been developed through transmetalation of the starting lithium enolate with a zirconium salt prior to addition of the aldehyde. Also, the fact that 2 equiv of a metal salt were needed to achieve this high diastereocontrol provided further insight into the reaction mechanism. The aldol products were successfully converted into synthetically useful chiral nonracemic synthons such as α-methyl-*β*-hydroxy acids, esters, and ketones in ee's higher than 99%. Also, a procedure to selectively synthesize both 1,3-syn or 1,3-anti diols from the obtained α-methyl-*β*-hydroxy ketones has been optimized, with excellent diastereo- and enantioselectivities. In this context, the insect pheromones *ent*-sitophilure and *ent*-sitophilate were synthesized almost optically pure as a direct application. The main advantages of the methodology developed by us reside in the fact that the chirality source is cheap and commercially available in both enantiomeric forms. Clean and easy reactions convert the aldol products into other useful chiral synthons and no racemization during these conversions are observed. These reasons, together with the high stereoselectivities and yields, make this methodology an attractive tool for the synthetic organic chemist.

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Experimental Section[40]

General Procedure for the Aldol Reaction of (*S*,*S*)-(+)-Pseudoephedrine Propionamide. Synthesis of (2*R*,3*R*,1′*S*,2′*S*)-(+)-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-3-hydroxy-*N*,2-dimethyl-3-phenylpropanamide (2a). A solution of the propionamide **1** (1.00 g, 4.52 mmol) in dry THF (15 mL) was slowly added to a cooled (−78 °C) solution of LDA (9.04 mmol) in dry THF (20 mL). The mixture was stirred at this temperature for 1 h and allowed to reach to room temperature. The mixture was cooled again to −78 °C, at which temperature a THF (20 mL) solution of bis(cyclopentadienyl)zirconium dichloride (2.64 g, 9.04 mmol) was added at once and the resulting solution was stirred for 1 h at this temperature. The mixture was cooled to −105 °C, at which temperature a solution of benzaldehyde (0.51 mL, 4.52 mmol) in dry THF (10 mL) was dropwise added within 20 min. The mixture was stirred at −105 °C for 2 h and quenched with a saturated NH_4Cl solution (50 mL). The mixture was extracted with CH_2Cl_2, the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to yield a yellowish oil that was flash column chromatographed (hexanes/ethyl acetate 2:8) affording amide **2a**: yield 90%; mp 132−134 °C (Et_2O); $[\alpha]^{20}_D = +87.6$ (c = 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (3:2 rotamer ratio; *denotes minor rotamer peaks) δ 0.87−1.27 (m, 6H), 2.74 (s, 3H), 2.91* (s, 3H), 2.96 (m, 1H), 3.94 (m, 1H), 4.03* (m, 1H), 4.11 (bs, 2H), 4.46 (m, 1H), 4.90 (d, 1H, J = 3.3 Hz), 7.21−7.39 (m, 10H); ^{13}C NMR ($CDCl_3$) (3:2 rotamer ratio; *denotes minor rotamer peaks) δ 9.6*, 10.0, 13.9, 15.5*, 27.3, 31.5*, 41.0*, 42.6, 57.7, 72.7, 73.4*, 75.1, 75.6*, 125.9*, 126.2, 126.5, 126.6*, 127.0, 127.5*, 127.8, 127.9*, 128.0, 128.1*, 128.4, 128.5*, 141.6, 141.7, 178.3*, 178.8; IR (KBr) ν 3377, 1607 cm^{-1}; MS (EI) m/z (rel int) 327 (M^+, 1), 58 (100). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.28; H, 7.61; N, 4.20.

General Procedure for the Hydrolysis of the Amides 2a−e. Synthesis of (2*R*,3*R*)-(+)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (4a). A solution of the amide **2a** (0.50 g, 1.53 mmol) in dioxane (10 mL) was slowly added over a cooled (0 °C) 4 M H_2SO_4 solution (10 mL). When the addition was complete, the mixture was refluxed for 2 h. The reaction was quenched with water, carefully basified to pH = 12, and washed with EtOAc. The aqueous layer was carefully driven to pH = 3 and extracted with CH_2Cl_2. 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 in 80% yield. The collected organic acidic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo yielding the wanted acid as a yellowish oil: yield 90%; $[\alpha]^{20}_D = +29.3$ (c = 0.2, CH_2Cl_2) (lit.[26k] +28.5, c = 1.27, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3H, J = 7.1 Hz), 2.83 (m, 1H), 5.18 (d, 1H, J = 3.5 Hz), 5.18−5.58 (bs, 2H), 7.26−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.2, 46.2, 73.3, 125.9, 127.6, 128.3, 141.0, 180.2; IR ($CHCl_3$) ν 3401, 1707 cm^{-1}; MS (EI) m/z (rel int) 180 (M^+, 2), 107 (100). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.58; H, 6.62.

General Procedure for the Esterification of the Acids 4a−e. Synthesis of (2*R*,3*R*)-(+)-Methyl-3-hydroxy-2-methyl-3-phenylpropanoate (5a). A solution of the acid **4a** (0.29 g, 1.39 mmol) in MeOH (15 mL) was added concd HCl (5 mL) and the mixture was refluxed for 4 h. The reaction was quenched with water and extracted with CH_2Cl_2. After the solution was dried (Na_2SO_4) and filtered and the solvent removed from the collected organic fractions, the ester **5a** was isolated after purification by flash column chromatography (hexanes/EtOAc 1:1): yield 91%; $[\alpha]^{20}_D = +23.3$ (c = 0.2, CH_2Cl_2) (lit.[10c] +23.1, c = 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3H, J = 7.1 Hz), 2.72 (m, 1H), 3.61 (s, 3H), 4.77 (bs, 1H), 5.03 (d, 1H, J = 3.8 Hz), 7.18−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.6, 46.3, 51.9, 73.5, 125.9, 127.5, 128.2, 141.3, 176.4; IR ($CHCl_3$) ν 3462, 1722 cm^{-1}; MS (EI) m/z (rel int) 194 (M^+, 3),

(40) For general experimental procedures, see ref 21b.

88 (100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.10; H, 7.21.

General Procedure for the Synthesis of the Ketones 6a−i. Synthesis of (2*R*,3*R*)-(+)-3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (6a). Over a cooled (−78 °C) solution of the starting amide **2a** (0.92 g, 2.83 mmol) in dry THF was dropwise added a solution of PhLi (9.91 mmol). After the addition was complete, the mixture was allowed to warm to 0 °C, and after 25 min diisopropylamine (0.40 mL, 2.83 mmol) was added. The reaction was stirred for a further 15 min and quenched with a 10% solution of acetic acid in Et_2O (5 mL). Water (15 mL) was added, and the mixture was extracted with CH_2Cl_2. After drying (Na_2SO_4), filtering, and removing the solvent from the collected organic fractions, the ketone **6a** was isolated after purification by flash column chromatography (hexanes/EtOAc 7:3): yield 81%; $[\alpha]^{20}_D = +71.8$ ($c = 0.2$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 3H, $J = 7.2$ Hz), 3.72 (m, 1H), 5.23 (d, 1H, $J = 3.3$ Hz), 7.19−7.59 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 11.2, 47.0, 73.0, 125.9, 127.2, 127.2, 128.1, 128.3, 128.6, 133.4, 141.7, 205; MS (EI) *m*/*z* (rel int) 240 (M^+, 1), 146 (100). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.90; H, 6.68.

General Procedure for the Synthesis of 1,3-Syn Diols 7a−h. Synthesis of (1*R*,3*S*)-2-methyl-1,3-diphenyl-1,3-propanediol 7a. Over a cooled (0 °C) solution of the ketone **6a** (37 mg, 0.15 mmol) in dry THF (10 mL) was dropwise added a 1M solution of $BH_3{\cdot}(Me_2S)$ (0.33 mL, 0.33 mmol) in CH_2Cl_2 at 0 °C and then the resulting solution was allowed to reach to room temperature. The reaction was stirred at this temperature for 12 h after which it was quenched with saturated Na_2CO_3 (10 mL). The mixture was extracted with CH_2Cl_2, and the collected organic fractions were dried over Na_2SO_4, filtered and the solvent removed in vacuo affording pure diol **7a** after flash column chromatography (hexanes/EtOAc 7:3): yield 78%; ^{1}H NMR ($CDCl_3$) δ 0.68 (d, 3H, $J = 7.0$ Hz), 1.98 (m, 1H), 3.07 (s, 2H), 5.11 (s, 2H), 7.20−7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 4.1, 46.4, 77.6, 125.3, 126.9, 127.9, 142.9; IR ($CHCl_3$) ν 3366 cm^{-1}; MS (EI) *m*/*z* (rel int) 242 (M^+, 1), 118 (100). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.28; H, 7.53.

General Procedure for the Synthesis of 1,3-Anti Diols 8a−h. Synthesis of (1*R*,3*R*)-(+)-2-Methyl-1,3-diphenyl-1,3-propanediol 8a. Over a cooled (0 °C) solution of the ketone **6a** (17 mg, 0.07 mmol) in dry methanol (10 mL) was dropwise added a solution of $LiBH_4$ (7 mg, 0.15 mmol) in dry MeOH (5 mL) at 0 °C, and then the resulting solution was allowed to reach to room temperature. The reaction was stirred at this temperature for 7 h, after which it was quenched with saturated Na_2CO_3 (10 mL). The mixture was extracted with CH_2Cl_2, the collected organic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo affording pure diol **8a** after flash column chromatography (hexanes/EtOAc 7:3): yield 95%; $[\alpha]^{20}_D = +2.4$ ($c = 0.1$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.75 (d, 3H, $J = 7.1$ Hz), 2.19 (m, 1H), 3.13 (s, 1H), 3.19 (d, 1H, $J = 3.2$ Hz), 4.71 (d, 1H, $J = 6.7$ Hz), 5.03 (s, 1H), 7.24−7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 4.4, 46.6, 76.5, 125.3, 127.8, 127.9, 143.1; IR ($CHCl_3$) ν 3540 cm^{-1}; MS (EI) *m*/*z* (rel int) 242 (M^+, 1), 118 (100). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.33; H, 7.50.

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Supporting Information Available: Characterization of products **2b−e**, **4b−e**, **5b−f**, **6b−i**, **7b−h**, and **8b−h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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