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Synthesis of Chiral, Non-racemic Aldols from Chiral β-Hydroxy-Weinreb Amides Prepared by Enantioselective Reformatsky-like Reaction Induced by Chiral β-Aminoalcohols

José M. Andrés, Rafael Pedrosa* and Alfonso Pérez-Encabo

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Doctor Mergelina s/n, 47011-Valladolid, Spain

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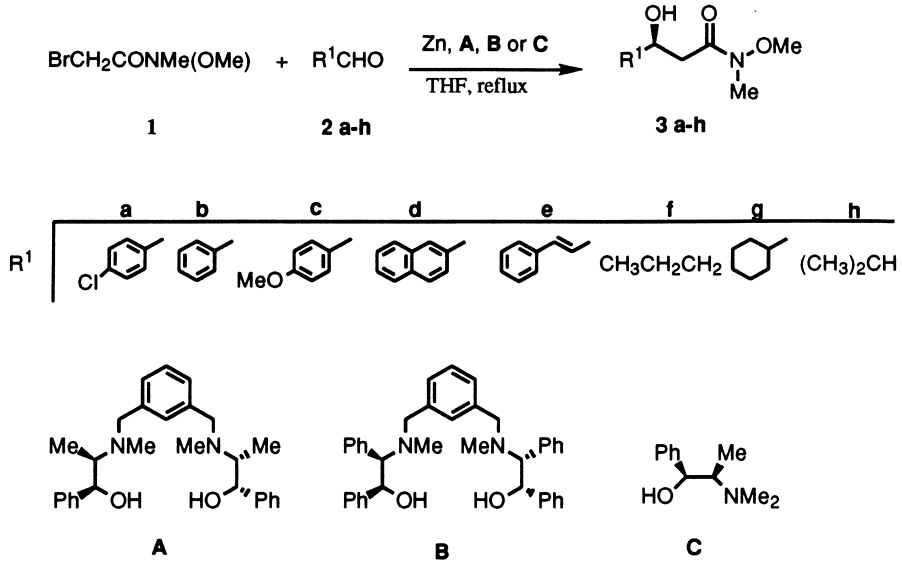
Abstract—Chiral 1,2-aminoalcohols catalyze enantioselective Reformatsky addition of zinc derivatives of α-bromo Weinreb amides. Reaction of Grignard reagents with the resulting β-hydroxy *N*-methoxy-*N*-methyl amides allowed the preparation of β-hydroxy ketones regio- and enantioselectively.

The aldol condensation is one of the most important methods of forming carbon–carbon bonds leading to structures with 1,3-oxygen functionalities. One of the most important problems with this reaction is the formation of by-products resulting from cross condensation when two different enolizable carbonyl compounds are used, and a variety of solutions have been proposed.[1] On the other hand, the formation of at least one stereocenter is a problem to solve when non-racemic β-hydroxy carbonyl compounds are desired, and a lot of stereoselective variants have been developed,[2] such as the use of chiral bases,[3] chiral auxiliaries[4,5] or novel versions of the reaction.[6]

Some time ago, Palomo[7] developed a regioselective entry to β-hydroxy ketones based on the Reformatsky-type reaction of α-bromo Weinreb amides followed by the straightforward transformation of *N*-methoxy-*N*-methylamides into carbonyl compounds.[8]

As part of our ongoing project for enantioselective synthesis



Scheme 1.

Keywords: chiral aminoalcohols; enantioselective synthesis; Reformatsky reaction; stereoselective aldol reaction.
* Corresponding author. Tel.: +983-423211; fax: +983-423013; e-mail: pedrosa@qo.uva.es

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Table 1. Enantioselective addition of **1** to aldehydes **2a**–**f** in the presence of aminoalcohols **A**–**C**

Entry	Aldehyde (**2**)	Aminoalcohol	Molar ratio **2**:**1**:**L***	*t* (h)	Yield (%)[a]	e.e. (%)[b]	(Config.)
1	**2a**	**A**	1:3:0.5	24	**3a** (68)	46	(*S*)
2	**2a**	**B**	1:3:0.5	24	**3a** (59)	15	(*S*)
3	**2a**	**C**	1:3:1	24	**3a** (75)	43	(*S*)
4	**2b**	**A**	1:3:0.5	24	**3b** (65)	46	(*S*)
5	**2b**	**A**	1:4:0.5	24	**3b** (75)	47	(*S*)
6	**2c**	**A**	1:3:0.5	39	**3c** (26)	23	(*S*)
7	**2c**	**A**	1:4:0.5	23	**3c** (54)	24	(*S*)
8	**2d**	**A**	1:3:0.5	42	**3d** (38)	33	(*S*)
9	**2d**	**A**	1:4:0.5	29	**3d** (65)	35	(*S*)
10	**2e**	**A**	1:4:0.5	16	**3e** (51)	24	(*S*)
11	**2f**	**A**	1:4:0.5	22	**3f** (21)	23	(*R*)
12	**2g**	**A**	1:4:0.5	21	**3g** (50)	37	(*S*)
13	**2h**	**A**	1:4:0.5	22	**3h** (54)	47	(*S*)

[a] Yields refer to isolated and purified products.
[b] Determined by integration of the signals of ^{1}H and ^{19}F NMR of the Mosher derivatives.

promoted by chiral β-aminoalcohols,[9] we now report the results obtained in the enantioselective Reformatsky-type reaction of α-bromo *N*-methoxy-*N*-methylacetamide **1** and the subsequent transformation of the resulting β-hydroxy amides into chiral non-racemic aldols. Starting α-bromo *N*-methoxy-*N*-methylacetamide **1** was prepared in 65% yield by reaction of α-bromoacetyl bromide with *N*,*O*-dimethylhydroxylamine hydrochloride in CH_2Cl_2 and triethylamine at low temperature.[8,10]

The enantioselective Reformatsky reactions were carried out by heating in THF at reflux a mixture of previously activated[11] zinc dust and excess of **1** (4 equiv.), the chiral aminoalcohols **A**–**C** (0.5 equiv.) and the corresponding aldehydes **2a**–**h**. Under these conditions, β-hydroxy amides **3a**–**h** were obtained in good yields and in low to moderate enantioselection (Scheme 1).

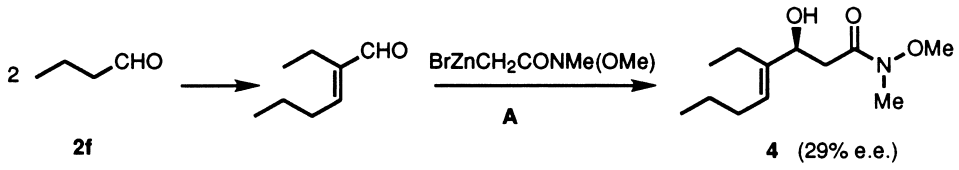
It is noteworthy that, contrary to that described for α-bromoesters,[9b] it was not possible to perform the reaction in two steps because it was not possible to prepare the zinc derivatives of α-bromoesters of acetamide **1**.

Table 1 summarizes the results obtained for the reactions with different conditions. Initially, the enantioselection ability of the chiral bis-aminoalcohols derived from (1*S*,2*R*)-ephedrine (**A**), and from (1*S*,2*R*)-1,2-diphenyl-aminoethanol (**B**) and (1*S*,2*R*)-*N*,*N*-dimethylnorephedrine (**C**) was tested taking 4-chlorobenzaldehyde as model aldehyde (entries 1–3 in Table 1).

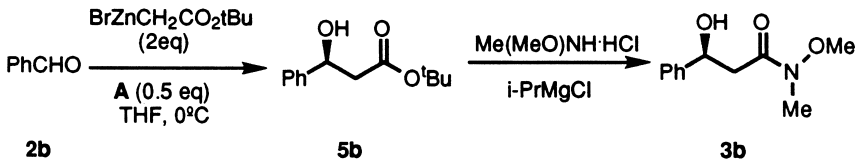
The results indicated that the best enantiomeric excess was obtained when the ephedrine derivative **A** was used as chiral inductor, and they are coincident with those reported for the enantioselective Reformatsky addition of α-bromoesters[9b] although the e.e.'s are lower for amides. The best yields were obtained when a four-fold excess of the zinc derivative with respect to aldehyde was used, and the enantiomeric excesses were only dependent on the structure of the carbonyl compound, and were unaffected by the amount of the organometallic. The enantioface discrimination was better for aromatic than for aliphatic aldehydes, although 4-methoxybenzaldehyde and 2-naphthaldehyde lead to β-hydroxy amides with very modest e.e.

It is interesting to note the behavior of butyraldehyde: in the described reactions conditions, **3f** was isolated in only 21% yield, whereas the major product of reaction was β-hydroxy-amide **4** (28%). The formation of this compound is explained as a consequence of a fast formation of *E*-2-ethyl-2-hexenal by autocondensation of butyraldehyde due to the enolizable character of **2f**, followed by the Reformatsky reaction on the unsaturated aldehyde (Scheme 2).

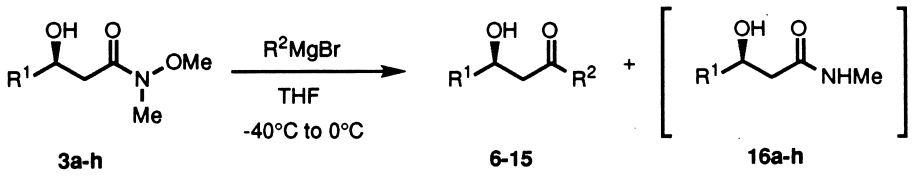
The absolute stereochemistry for β-hydroxy amides **3a**–**h**



Scheme 2.



Scheme 3.



Scheme 4.

was initially assigned on the basis of the stereochemical outcome of α-bromoesters catalyzed by chiral amino-alcohols[9a,b] and confirmed for **3b** as outlined in Scheme 3. To this end, (*R*)-*t*-butyl-3-hydroxy-3-phenyl propionate **5b** was prepared by enantioselective addition of *tert*-butoxy carbonylmethylzinc bromide to benzaldehyde in the presence of ephedrine-derived aminoalcohol **A**. The transformation of **5b** into **3b** (50% yield) was carried out by treatment with a mixture of isopropyl magnesium bromide (4 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.5 equiv.) in THF at −20°C.[12] Attempts to improve the yield by increasing both the reaction temperature or the amount of the reactants failed because dehydration of the resulting amide took place. The conversion of **5b** into **3b** by reaction with *N*-methoxy-*N*-methyl dimethyl aluminum amide generated from trimethylaluminum and *N*,*O*-dimethylhydroxylamine hydrochloride[13] also failed in our case.

The final β-hydroxy ketones were prepared by reaction of β-hydroxy amides **3a**–**h** with different Grignard derivatives (Scheme 4).

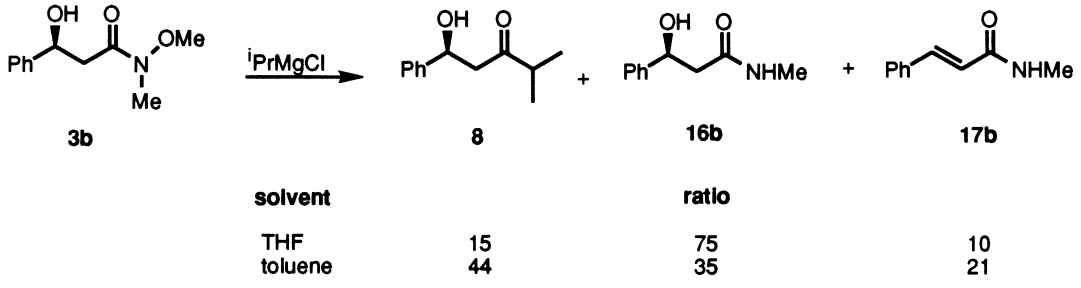
Compounds **3a**–**h** were treated with an excess (4.5 equiv.) of the corresponding Grignard reagent in THF at −40°C and the results are collected in Table 2. The stereochemical integrity of the starting compounds was unaffected in this transformation, and β-hydroxy ketones **6**–**15** were obtained in moderate chemical yields, accompanied by variable amounts (5–17%) of β-hydroxy amides **16a**–**h** derived from demethoxylation of **3a**–**h**. The only exception is referred to the reaction of **3b** with isopropylmagnesium chloride (Scheme 5). In this case, a mixture of β-hydroxy ketone **8**, demethoxylated β-hydroxy amide **16b** and α,β-unsaturated amide **17b** were formed in a ratio which depends on the solvent: in THF, the major product obtained was **16b**, and **8** was isolated in only 10% yield, whereas in toluene the yield of isolated β-hydroxy ketone increased to 26%.

The proposed sequence of enantioselective Reformatsky reaction of Weinreb amides catalyzed by chiral amino-alcohols, followed by reaction with magnesium derivatives of the resulting β-hydroxy *N*-methoxy-*N*-methylamides allows the preparation of enantioenriched aldols starting from both enolizable and non-enolizable aldehydes regio-specifically as demonstrated in the synthesis of **8** and **15** (entries 3 and 10 in Table 2) by simply changing the structure of the starting aldehyde and the nature of the Grignard reagent (Scheme 6).

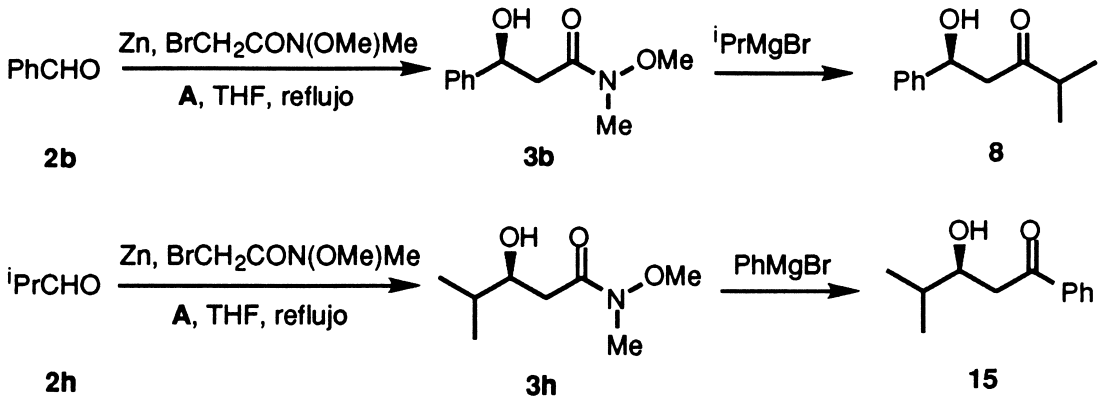
Table 2. Synthesis of chiral β-hydroxy ketones **6**–**15** by reaction of **3a**–**h** with Grignard derivatives

Entry	β-Hydroxy amide	R^2	β-Hydroxy ketone	Yield (%)[a]	o.p. (%)[b]	(Config.)
1	**3a**	Et	**6**	51	46	(*S*)[c]
2	**3b**	Me	**7**	57	45	(*S*)
3	**3b**	*i*-Pr	**8**	24	45	(*S*)
4	**3b**	*n*-Bu	**9**	49	46	(*S*)
5	**3b**	Ph	**10**	52	49	(*S*)
6	**3c**	Ph	**11**	50	24	(*S*)[c]
7	**3d**	Ph	**12**	64	34	(*S*)
8	**3e**	Ph	**13**	66	26	(*S*)
9	**3g**	Ph	**14**	63	37	(*S*)
10	**3h**	Ph	**15**	54	47	(*S*)

[a] Yields refer to pure and isolated compounds and they are not optimized.
[b] The optical purity (o.p.) and the configuration were determined by comparison of the sign and the optical rotation previously described.
[c] The configuration was tentatively assigned by analogy to the other compounds.



Scheme 5.



Scheme 6.

Experimental

General

The ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and ^{19}F NMR (282 MHz) spectra were recorded on a Bruker AC 300. The chemical shifts are given in ppm using TMS (^{1}H and ^{13}C NMR) as internal standard. IR spectra were recorded on a Philips PU 9706 Spectrometer as film or KBr dispersion. Mass spectra were recorded on a Hewlett-Packard 5988-A mass spectrometer by electronic impact at 70 eV. Optical rotations were measured on a Perkin–Elmer 241 Polarimeter in a 1 dm cell, and concentrations are given in g/100 mL.

(1*R*,2*S*)-Bis-[*N*-methyl-*N*-(2-hydroxy-1-methyl-2-phenyl)-ethyl]-*m*-xylylenediamine (**A**), (1*R*,2*S*)-bis[*N*-methyl-*N*-(2-hydroxy-1,2-diphenyl)-ethyl]-*m*-xylylenediamine (**B**) and (1*S*,2*R*)-*N*,*N*-dimethyl norephedrine (**C**) were prepared as previously described in the literature.[9c] All the reactions were carried out in anhydrous solvents, in oven-dried glassware and under argon atmosphere. Column flash chromatography was performed on silica gel 60 (Merck).

Enantioselective Reformatsky reaction using chiral aminoalcohols

Chlorotrimethylsilane (0.09 mL) was added to a suspension of 654 mg Zn dust (10 mmol, 5 equiv.) in anhydrous THF (1 mL). The mixture was refluxed for 20 min, the heating was stopped, and a solution of aldehyde (2 mmol, 1 equiv.), the corresponding aminoalcohol (1 mmol, 0.5 equiv.), and 1.45 g (8 mmol, 4 equiv.) α-bromo *N*-methoxy-*N*-methyl-acetamide in anhydrous THF (11 mL) was added. The mixture was stirred and refluxed until the reaction was finished (TLC) and then quenched at 0°C with 16 mL of a 10% solution of hydrochloric acid. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were eliminated on Rotavapor and the residue purified by flash column chromatography (silica gel, hexane–ethyl acetate). The e.e. for *N*-methoxy-*N*-methyl-β-hydroxyamides was determined by integration of the OCH_3 signals in ^{1}H NMR spectra or CF_3 signals in ^{19}F NMR spectra of the diastereomeric mixtures of ester derived from *R*-(+)-MTPA.[14] The following compounds were prepared in this way.

(*S*)-3-(4-Chlorophenyl)-3-hydroxy-*N*-methoxy-*N*-methyl-propanamide (3a). 68% yield, white solid, mp 77–78°C (from hexane–ethyl acetate); e.e.=46%; $[\alpha]_D^{23}=-30.6$ (c=0.7, $CHCl_3$). IR (film): 3380; 1630 cm^{-1}. ^{1}H NMR ($CDCl_3$): 2.73 (dd, 1H, J=16.9, 9.4 Hz, C*H*HCON); 2.85 (dd, 1H, J=16.9, 2.8 Hz, CH*H*CON); 3.20 (s, 3H, CH_3N); 3.63 (s, 3H, CH_3O); 4.38 (br s, 1H, O*H*); 5.12 (dd, 1H, J=9.3, 2.8 Hz, C*H*OH); 7.30–7.40 (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$): 31.7 (N*C*H$_3$); 40.3 (*C*H$_2$); 61.2 (O*C*H$_3$); 69.4 (*C*HOH); 127.1, 128.5 (*C*H$_{arom}$); 133.0, 141.5 (C_{arom}); 172.8 (*C*=O). MS-EI, *m*/*z* (%): 243 (M$^+$, 3); 212 (13); 141 (83); 77 (100). Calcd for $C_{11}H_{14}ClNO_3$: C, 54.22; H, 5.79; N, 5.75. Found: C, 54.19; H, 5.64; N, 5.79.

(*S*)-3-Hydroxy-*N*-methoxy-*N*-methyl-3-phenylpropanamide (3b). 75% yield, colorless oil; e.e.=47%; $[\alpha]_D^{23}=-36.6$ (c=1, $CHCl_3$). IR (film): 3400; 1630 cm^{-1}. ^{1}H NMR ($CDCl_3$): 2.83 (m, 2H, CH_2); 3.20 (s, 3H, CH_3N); 3.62 (s, 3H, CH_3O); 4.29 (br s, 1H, O*H*); 5.15 (dd, 1H, J=9.0, 3.5 Hz, C*H*OH); 7.25–7.45 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$): 31.6 (*C*H$_3$N); 40.3 (*C*H$_2$); 61.0 (*C*H$_3$O); 69.8 (*C*HOH); 125.5, 127.2, 128.1 (*C*H$_{arom}$); 142.9 (C_{arom}); 172.8 (*C*=O). MS-EI, *m*/*z* (%): 209 (M$^+$, 2); 178 (14); 131 (18); 107 (100); 61 (93). Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.02; H, 7.12; N, 6.72.

(*S*)-3-Hydroxy-*N*-methyl-*N*-methoxy-3-(4-methoxyphenyl)-propanamide (3c). 54% yield, colorless oil; e.e.=24%; $[\alpha]_D^{23}=-18.2$ (c=1.1, $CHCl_3$). IR (film): 3420; 1630 cm^{-1}. ^{1}H NMR ($CDCl_3$): 2.80 (m, 2H, CH_2CO); 3.19 (s, 3H, CH_3N); 3.62 (s, 3H, CH_3O); 3.79 (s, 3H, CH_3O); 4.28 (br s, 1H, O*H*); 5.10 (dd, 1H, J=8.0, 4.5 Hz, C*H*OH); 6.82 (d, 2H, J=8.7 Hz, H_{arom}). ^{13}C NMR ($CDCl_3$): 31.7 (*C*H$_3$N); 40.3 (*C*H$_2$); 55.1 (*C*H$_3$O); 61.1 (O*C*H$_3$); 69.6 (*C*HOH); 113.6, 126.8 (*C*H$_{arom}$); 135.1, 158.8 (C_{arom}); 173.1 (*C*=O). MS-EI, *m*/*z* (%): 239 (M$^+$, 3); 208 (27); 161 (8); 137 (100). Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.07; H, 7.25; N, 5.89.

(*S*)-3-Hydroxy-*N*-methoxy-*N*-methyl-3-(2-naphthyl)propanamide (3d). 65% yield, white solid, mp 73–74°C (from hexane–ethyl acetate); e.e.=35%; $[\alpha]_D^{23}=-23.8$ (c=1,

$CHCl_3$). IR (film): 3400; 1630 cm^{-1}. ^1H NMR ($CDCl_3$): 2.86 (dd, 1H, *J*=16.9, 9.4 Hz, C*H*HCON); 2.97 (dd, 1H, *J*=16.9, 2.9 Hz, CH*H*CON); 3.22 (s, 3H, CH_3N); 3.63 (s, 3H, CH_3O); 4.40 (br s, 1H, O*H*); 5.32 (dd, 1H, *J*=9.4, 2.9 Hz, C*H*OH); 7.40–7.55 (m, 3H, H_{arom}); 7.80–7.90 (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$): 31.7 (*C*H_3N); 40.3 (*C*H_2); 61.1 (*C*H_3O); 70.1 (*C*HOH); 123.8, 124.2, 125.6, 126.0, 127.5, 127.8, 128.0 (*C*H_{arom}); 132.7, 133.1, 140.4 (C_{arom}); 172.9 (*C*=O). MS-EI, *m*/*z* (%): 259 (M^+, 10); 228 (9); 157 (56); 129 (85); 61 (100). Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.19; H, 6.53; N, 5.43.

(3*S*,4*E*)-3-Hydroxy-*N*-methoxy-*N*-methyl-5-phenyl-4-pentenamide (3e). 51% yield, colorless oil; e.e.=24%; $[\alpha]_D^{23}=-1.7$ (*c*=0.9, MeOH). IR (film): 3400; 1630 cm^{-1}. ^1H NMR ($CDCl_3$): 2.69 (dd, 1H, *J*=16.7, 8.9 Hz, C*H*HCON); 2.81 (d, 1H, *J*=16.7 Hz, CHHCON); 3.22 (s, 3H, CH_3N); 3.70 (s, 3H, CH_3O); 4.05 (br s, 1H, O*H*); 4.76 (m, 1H, C*H*OH); 6.26 (dd, 1H, *J*=15.9, 6.0 Hz, C*H*=CHPh); 6.68 (d, 1H, *J*=15.9 Hz, PhC*H*); 7.20–7.45 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$): 31.7 (*C*H_3N); 38.3 (*C*H_2); 61.1 (*C*H_3O); 68.5 (*C*HOH); 126.3, 127.4, 128.4 (*C*H_{arom}); 130.0 (CH=*C*H); 130.4 (*C*H=CH); 136.5 (C_{arom}); 172.9 (*C*=O). Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.08; H, 6.97; N, 5.90.

(*R*)-3-Hydroxy-*N*-methoxy-*N*-methylhexanamide (3f). 21% yield, colorless oil; e.e.=23%; $[\alpha]_D^{23}=-2.7$ (*c*=0.8, $CHCl_3$). IR (film): 3400; 1630 cm^{-1}. ^1H NMR ($CDCl_3$): 0.94 (t, 3H, *J*=7.0 Hz, CH_3CH$_2$); 1.40–1.60 (m, 4H, CH_2CH_2); 2.45 (dd, 1H, *J*=16.8, 9.6 Hz, C*H*HCON); 2.67 (d, 1H, *J*=16.8 Hz, CH*H*CON); 3.20 (s, 3H, CH_3N); 3.69 (s, 3H, CH_3O); 3.80 (br s, 1H, OH); 4.04 (m, 1H, CHOH). ^{13}C NMR ($CDCl_3$): 14.0 (*C*H_3CH$_2$); 18.7 (*C*H_2CH$_3$); 31.8 (*C*H_3N); 38.1 (*C*H_2); 38.6 (*C*H_2CO); 61.2 (*C*H_3O); 67.6 (*C*HOH); 174.0 (*C*=O). Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 54.68; H, 9.86; N, 8.06.

(*S*)-3-Cyclohexyl-3-hydroxy-*N*-methoxy-*N*-methylpropanamide (3g). 50% yield, colorless oil; e.e.=37%; $[\alpha]_D^{23}=-18.3$ (*c*=0.9, $CHCl_3$). IR (film): 3420; 1630 cm^{-1}. ^1H NMR ($CDCl_3$): 1.05 (m, 2H, CH_2); 1.25 (m, 3H); 1.41 (m, 1H, C*H*CHOH); 1.70 (m, 4H, *C*H_2); 1.90 (m, 1H); 2.46 (dd, 1H, *J*=16.6, 9.9 Hz, C*H*HCON); 2.68 (d, 1H, *J*=16.6 Hz, CH*H*CON); 3.20 (s, 3H, CH_3N); 3.70 (s, 3H, CH_3O); 3.76 (m, 2H, C*H*OH and O*H*). ^{13}C NMR ($CDCl_3$): 25.9, 26.0, 26.3, 28.2, 28.7 (*C*H_2); 31.7 (*C*H_3N); 35.1 (*C*H_2CO); 42.9 (*C*H); 61.0 (*C*H_3O); 71.8 (*C*HOH); 174.1 (*C*=O). Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. MS-EI, *m*/*z* (%): 215 (M^+, 0.1); 132 (33); 95 (50); 61 (100). Found: C, 61.21; H, 9.61; N, 6.59.

(*S*)-3-Hydroxy-*N*-methoxy-*N*-methyl-4-methylpentanamide (3h). 54% yield, colorless oil; e.e.=47%; $[\alpha]_D^{23}=-27.8$ (*c*=0.8, $CHCl_3$). IR (film): 3460; 1640 cm^{-1}. ^1H NMR ($CDCl_3$): 0.95 (d, 3H, *J*=6.8 Hz (CH_3(CH$_3$)CH)); 0.98 (d, 3H, *J*=6.8 Hz (CH$_3$(CH_3)CH)); 1.74 (m, 1H, C*H*(CH_3)$_2$); 2.45 (dd, 1H, *J*=16.5, 10.0 Hz, C*H*HCON); 2.67 (d, 1H, *J*=16.5 Hz, CH*H*CON); 3.21 (s, 3H, CH_3N); 3.71 (s, 3H, CH_3O); 3.79 (m, 2H, C*H*OH and O*H*). ^{13}C NMR ($CDCl_3$): 17.9, 18.4 ((*C*H$_3$)$_2$CH); 3.18 (*C*H_3N); 33.0 (*C*H(CH$_3$)$_2$); 35.0 (*C*H_2); 61.1 (*C*H_3O); 72.5 (*C*HOH); 174.2 (*C*=O). Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 54.60; H, 9.66; N, 8.09.

(*S*)-4-Ethyl-3-hydroxy-*N*-methoxy-*N*-methyl-4-octenamide (4). Colorless oil; e.e.=29%; $[\alpha]_D^{23}=-14.6$ (*c*=0.95, $CHCl_3$). IR (film): 3420; 1630 cm^{-1}. ^1H NMR ($CDCl_3$): 0.92 (t, 3H, *J*=7.4 Hz, CH_3CH$_2$); 1.03 (t, 3H, *J*=7.5 Hz, CH_3CH$_2$); 1.40 (m, 2H, CH_2); 2.04 (m, 3H, CH_2 and C*H*HCH$_3$); 2.16 (m, 1H, CH*H*CH$_3$); 2.59 (dd, 1H, *J*=16.6, 9.7 Hz, C*H*HCON); 2.70 (d, 1H, *J*=16.6 Hz, CH*H*CON); 3.20 (s, 3H, CH_3N); 3.70 (s, 3H, CH_3O); 3.78 (br s, 1H, O*H*); 4.42 (d, 1H, *J*=9.6 Hz, C*H*OH); 5.49 (t, 1H, *J*=7.2 Hz, C*H*=C). ^{13}C NMR ($CDCl_3$): 13.9, 14.1 (*C*H$_3$CH$_2$); 20.8 (CH$_2$*C*H$_2$CH$_2$); 22.8 (*C*H$_2$C=C); 29.4 (*C*H$_2$C=C); 31.8 (*C*H$_3$N); 37.7 (*C*H$_2$CO); 61.2 (*C*H$_3$O); 71.3 (*C*HOH); 126.0 (*C*H=); 141.5 (*C*=); 173.8 (*C*=O). Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.68; H, 10.20; N, 6.17.

Transformation of β-hydroxyester (5b) into *N*-methoxy-*N*-methyl-β-hydroxyamide (3b)

A 2 M ethereal solution of isopropylmagnesium bromide (2 mL, 4 mmol) was added at −20°C to a suspension of **5b** (222 mg, 1 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (146 mg, 1.5 mmol, 1.5 equiv.) in anhydrous THF (9 mL). The mixture was stirred at rt until the reaction was finished (TLC) and then quenched with saturated NH_4Cl and extracted with ether (3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvents were eliminated on Rotavapor. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate).

Reaction of *N*-methoxy-*N*-methyl-β-hydroxyamides (3) with Grignard reagents

To a solution of the corresponding β-hydroxyamide (1 mmol, 1 equiv.) in 2 mL of anhydrous THF was added, via syringe, the corresponding organomagnesium reagent (4.5 mmol, 4.5 equiv.) at −40°C. The mixture was allowed to rise to 0°C and then stirred at this temperature until the reaction was finished (TLC) and quenched with 8 mL of saturated NH_4Cl and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate). The e.e. were determined by comparison of the specific rotations with the maximum values previously described: **7**: $[\alpha]_D^{23}=+56.7$ (*c*=1, $CHCl_3$) for 78% e.e. (*R*).[6b] **8**: $[\alpha]_D^{23}=-56.6$ (*c*=3.64, $CHCl_3$) for 82% e.e. (*S*).[5h] **9**: $[\alpha]_D^{23}=+59.8$ (*c*=0.5, $CHCl_3$) for 90% e.e. (*R*).[5b] **10**: $[\alpha]_D^{23}=+32.7$ (*c*=0.5, $CHCl_3$) for 89% e.e. (*R*).[5b] **12**: $[\alpha]_D^{23}=+32.6$ (MeOH) for 85% e.e.[3] **13**: $[\alpha]_D^{23}=+31.1$ (*c*=1, C_6H_6) for 83% e.e.[5c] **14**: $[\alpha]_D^{23}=+40.4$ ($CHCl_3$) for 65% e.e. (*R*).[3] **15**: $[\alpha]_D^{23}=+64.9$ (*c*=1, $CHCl_3$) for 86% e.e.[6b] The following β-hydroxy ketones were prepared in this way.

(*S*)-1-(4-Chlorophenyl)-1-hydroxy-3-pentanone (6). 51% yield, white solid, mp 63–64°C (from hexane); e.e.=46%; $[\alpha]_D^{23}=-15.7$ (*c*=0.6, $CHCl_3$). IR (KBr): 3450; 1705 cm^{-1}.

^{1}H NMR ($CDCl_3$): 1.07 (t, 3H, J=7.3 Hz, CH_3); 2.46 (q, 2H, J=7.3 Hz, CH_2CH$_3$); 2.75 (dd, 1H, J=4.4, 17.4 Hz, CHHCON); 2.83 (dd, 1H, J=8.0, 17.4 Hz, CHHCON); 3.56 (br s, 1H, OH); 5.13 (dd, 1H, J=8.0, 4.4 Hz, CHOH); 7.27–7.34 (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$): 7.4 (CH_3); 36.8 (CH_2CH_3); 50.5 (CH_2CH); 69.2 ($CHOH$); 126.9, 128.6 (CH_{arom}); 133.2, 141.3 (C_{arom}); 211.7 (C=O). MS-EI, m/z (%): 212 (M^+, 15); 183 (24); 141 (65); 77 (91); 43 (100). Calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16. Found: C, 61.96; H, 5.97.

(*S*)-4-Hydroxy-4-phenyl-2-butanone (7). 57% yield, white solid, mp 34–35°C (from CCl_4), e.e.=45%; $[\alpha]_D^{23}$=−32.3 (c=0.6, $CHCl_3$). IR (film): 3420; 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$): 2.19 (s, 3H, CH_3CO); 2.81 (dd, 1H, J=17.6, 3.6 Hz, CHHCO); 2.90 (dd, 1H, J=17.6, 8.8 Hz, CHHCO); 3.34 (br s, 1H, OH); 5.15 (dd, 1H, J=8.8, 3.6 Hz, CHOH); 7.25–7.40 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$): 30.6 (CH_3); 51.9 (CH_2); 69.7 ($CHOH$); 125.5, 127.5, 128.4 (CH_{arom}); 142.7 (C_{arom}); 209.0 (C=O). MS-EI, m/z (%): 164 (M^+, 3); 146 (2); 77 (28); 43 (100).

(*S*)-1-Hydroxy-4-methyl-1-phenyl-3-pentanone (8). 26% yield, colorless oil; e.e.=45%; $[\alpha]_D^{23}$=−31.0 (c=0.84, $CHCl_3$). IR (film): 3420; 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.10 (d, 6H, J=6.9 Hz, (CH_3)$_2$CH); 2.59 (m, 1H, CH(CH$_3$)$_2$); 2.83 (dd, 1H, J=17.6, 7.9 Hz, CHHCO); 2.90 (dd, 1H, J=17.6, 4.4 Hz, CHHCO); 3.49 (br s, 1H, OH); 5.15 (dd, 1H, J=7.9, 4.4 Hz, CHOH); 7.25–7.40 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$): 17.9 ((CH_3)$_2$CH); 41.5 ($CH(CH_3)_2$); 48.7 (CH_2); 69.9 ($CHOH$); 125.6, 127.6, 128.5 (CH_{atom}); 142.8 (C_{arom}); 215.3 (C=O). MS-EI, m/z (%): 192 (M^+, 2); 149 (11); 107 (31); 71 (50); 43 (100).

(*S*)-1-Hydroxy-1-phenyl-3-heptanone (9). 49% yield, colorless oil; e.e.=46%; $[\alpha]_D^{23}$=−30.8 (c=0.6, $CHCl_3$). IR (film): 3440; 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.89 (t, 3H, J=7.3 Hz, CH_3CH$_2$); 1.29 (m, 2H, CH_2CH$_3$); 1.55 (m, 2H, CH_2CH$_2$CO); 2.42 (t, 2H, J=7.4 Hz, CH$_2$CH_2CO); 2.76 (dd, 1H, J=17.4, 3.8 Hz, CHHCHOH); 2.85 (dd, 1H, J=17.4, 8.6 Hz, CHHCHOH); 3.47 (d, 1H, J=2.7 Hz, OH); 5.14 (m, 1H, CHOH); 7.25–7.40 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$): 13.7 (CH_3); 22.1, 25.5 (CH_2); 43.3 (CH_2CH_2CO); 50.9 ($CHOHCH_2CO$); 69.8 ($CHOH$); 125.5, 127.5, 128.4 (CH_{arom}); 142.8 (C_{arom}); 211.5 (C=O). MS-EI, m/z (%): 206 (M^+, 8); 188 (2); 149 (31); 107 (80); 77 (100).

(*S*)-3-Hydroxy-1,3-diphenyl-3-propanone (10). 52% yield, colorless oil; e.e.=49%; $[\alpha]_D^{23}$=−18.2 (c=0.8, MeOH). IR (film): 3420; 1660 cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.37 (d, 2H, J=6.0 Hz, CH_2); 3.60 (d, 1H, J=2.8 Hz, OH); 5.35 (dt, 1H, J=6.0, 2.8 Hz, CHOH); 7.15–1.65 (m, 8H, H_{arom}); 7.90–8.00 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$): 47.4 (CH_2); 70.0 ($CHOH$); 125.7, 127.6, 128.1, 128.5, 128.7, 133.6 (CH_{arom}); 136.5, 142.9 (C_{arom}); 200.1 (C=O). MS-EI, m/z (%): 226 (M^+, 2); 208 (4); 105 (58); 77 (100).

(*S*)-3-Hydroxy-3-(4-methoxyphenyl)-1-phenyl-1-propanone (11). 50% yield, colorless oil; e.e.=24%; $[\alpha]_D^{23}$=−12.3 (c=1, $CHCl_3$). IR (film): 3460; 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.60 (br s, 1H, OH); 3.80 (s, 3H, CH_3O); 5.28 (m, 1H, CHOH); 6.90 (d, 2H, J=8.7 Hz, H_{arom}); 7.35 (d, 2H, J=8.7 Hz, H_{arom}); 7.30–7.60 (m, 3H, H_{arom}); 7.90–8.00 (m, 3H, H_{arom}). ^{13}C NMR ($CDCl_3$): 47.2 (CH_2); 55.1 (CH_3O); 69.5 ($CHOH$); 113.7, 126.9, 128.0, 128.5, 133.4 (CH_{arom}); 135.1, 136.4, 158.9 (C_{arom}); 200.0 (C=O). MS-EI, m/z (%): 256 (M^+, 6); 237 (3); 135 (55); 105 (55); 77 (100). Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.75; H, 6.35.

(*S*)-3-Hydroxy-3-(2-naphthyl)-1-phenyl-1-propanone (12). 64% yield, white solid, mp 76–77°C (from hexane–ethyl acetate); e.e.=34%; $[\alpha]_D^{23}$=−13.1 (c=1.2, $CHCl_3$). IR (film): 3460; 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.43 (m, 2H, CH_2); 3.89 (br s, 1H, OH); 5.51 (dd, 1H, J=7.5, 4.5 Hz, CHOH); 7.40–7.60 (m, 6H, H_{arom}); 7.80–8.00 (m, 6H, H_{arom}). ^{13}C NMR ($CDCl_3$): 47.2 (CH_2); 70.0 ($CHOH$); 123.8, 124.4, 125.8, 126.1, 127.6, 127.9, 128.1, 128.2, 128.6, 133.6 (CH_{arom}); 132.8, 133.2, 136.4, 140.3 (C_{arom}); 200.0 (C=O). MS-EI, m/z (%): 276 (M^+, 5); 156 (29); 127 (40); 105 (46); 77 (100).

(3*S*,4*E*)-3-Hydroxy-1,5-diphenyl-4-penten-1-one (13). 66% yield, colorless oil; e.e.=26%; $[\alpha]_D^{23}$=−9.8 (c=1, C_6H_6). IR (film): 3400; 1670; 750; 690 cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.26 (d, 2H, J=5.9 Hz, CH_2); 3.55 (br s, 1H, OH); 4.94 (m, 1H, CHOH); 6.30 (dd, 1H, J=16.0, 6.0 Hz, CH=CHPh); 6.70 (d, 1H, J=16.0 Hz, PhCH); 7.20–7.60 (m, 8H, H_{arom}); 7.90–8.00 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$): 4.51 (CH_2); 68.5 ($CHOH$); 126.4, 127.6, 128.0, 128.5, 128.6 (CH_{arom}); 130.2, 133.5, (CH=); 136.5 (C_{arom}); 199.9 (C=O). MS-EI, m/z (%): 252 (M^+, 2); 131 (14); 105 (61); 77 (100).

(*S*)-3-Cyclohexyl-3-hydroxy-1-phenyl-1-propanone (14). 63% yield, colorless oil; e.e.=37%; $[\alpha]_D^{23}$=−23.2 (c=1.0, $CHCl_3$). IR (film): 3360; 1675 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.18 (m, 5H); 1.47 (m, 1H, CHCHOH); 1.74 (m, 4H); 1.93 (m, 1H); 3.05 (dd, 1H, J=17.5, 9.2 Hz, CHHCOPh); 3.18 (dd, 1H, J=17.5, 2.6 Hz, CHHCOPh); 3.26 (br s, 1H, OH); 3.99 (m, 1H, CHOH); 7.45–7.65 (m, 3H, H_{arom}); 7.90–8.00 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$): 26.0, 26.2, 26.4, 28.3, 28.9 (CH_2); 42.0 (CH_2CO); 43.0 ($CHCHOH$); 71.7 ($CHOH$); 128.0, 128.6, 133.4 (CH_{arom}); 136.8 (C_{arom}); 20.13 (C=O). MS-EI, m/z (%): 232 (M^+, 1); 214 (1); 149 (22); 105 (100); 77 (51).

(*S*)-3-Hydroxy-4-methyl-1-phenyl-1-pentanone (15). 54% yield, colorless oil; e.e.=47%; $[\alpha]_D^{23}$=−35.7 (c=0.9, $CHCl_3$). IR (film): 3480; 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.99 (d, 3H, J=6.7 Hz, (CH_3(CH$_3$)CH)); 1.01 (d, 3H, J=6.7 Hz, (CH$_3$(CH_3)CH)); 1.82 (m, 1H, CH(CH$_3$)$_2$); 3.04 (dd, 1H, J=17.5, 9.3 Hz, CHHCON); 3.19 (dd, 1H, J=17.5, 2.3 Hz, CHHCON); 3.23 (br s, 1H, OH); 4.01 (m, 1H, CHOH); 7.40–7.60 (m, 3H, H_{arom}); 7.90–8.00 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$): 17.8, 18.5 ((CH_3)$_2$CH); 33.0 ($CH(CH_3)_2$); 41.9 (CH_2); 72.3 ($CHOH$); 128.0, 128.5, 133.3 (CH_{arom}); 136.9 (C_{arom}); 201.2 (C=O). MS-EI, m/z (%): 193 (M+1, 5); 175 (9); 105 (51); 47 (100).

(*S*)-3-Hydroxy-*N*-methyl-3-phenylpropanamide (16b). 20% yield, colorless solid, mp 101–102°C (from hexane–ethyl acetate). $[\alpha]_D^{23}$=−27.3 (c=0.5, $CHCl_3$). IR (KBr): 3300; 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$): 2.50 (m, 2H, CH_2); 2.73 (d, 3H, J=4.8 Hz, (CH_3NH)); 4.60 (br s, 1H, OH); 5.02 (dd, 1H, J=8.4, 4.1 Hz, CHOH); 6.35 (br s, 1H, NH);

7.20–7.40 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$): 26.1 (CH_3); 44.4 (CH_2); 70.8 (*C*HOH); 125.5, 127.6, 128.4 (CH_{arom}); 143.1 (C_{arom}); 172.5 (*C*=O). MS-EI, *m*/*z* (%): 179 (M^+, 11); 160 (2); 105 (21); 77 (100); 58 (95). Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 66.72; H, 7.08; N, 7.73.

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