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Viable use of 2-substituted thiazolidine-4-methanol diastereoisomeric mixtures during asymmetric borane reduction of aromatic ketones

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Abstract: The reduction of aromatic ketones by borane in the presence of the inseparable diastereoisomeric mixture of 2-substituted thiazolidine-4-methanol has been investigated. Modest to high enantiomeric excesses were obtained increasing with thiazolidine steric hindrance. © 1997 Elsevier Science Ltd

Over recent years, a number of chiral 1,3,2-oxazaborolidines has been synthesized and applied in asymmetric synthesis,[1] particularly for the borane reduction of prochiral ketones.[1a,b] These chiral 1,3,2-oxazaborolidines are generated from chiral 1,2-amino alcohols and borane as first reported by Itsuno *et al.*[2]

(R)-Cysteine is a cheap commercially available chiral source which reacts readily with aldehydes or ketones to afford (R)-thiazolidine-4-carboxylic acids.[3] The corresponding sulfur-containing cyclic amino alcohols, obtained by reduction, have rigid structures close to that of prolinol widely used as a chiral catalyst precursor in the reactions mentioned above. Moreover, a wide range of 2-substituted thiazolidine-4-methanols can be easily prepared. Therefore, it seemed of interest to examine their use as chiral auxiliaries for asymmetric borane reduction of ketones. To our knowledge, the only previous report where unsubstituted (R)-thiazolidine-4-methanol has been used as catalyst during the borane reduction of acetophenone is in one recent paper[4] and moderate results were described (*e.e.*=45.3%). The aim of this work was to discover if employment of bulkier group in the 2-position of thiazolidine-4-methanol could give rise to better stereoselectivity. Unfortunately, it has been reported[5–7] that 2-substituted thiazolidines are generally obtained as inseparable diastereoisomer mixtures that could harm their efficiency as chiral auxiliary. Nevertheless, it has been noted that,[3c,7b,8] owing to facile ring opening-ring closure reactions,[5,6,9] N-formylation or N-acylation of the thiazolidine diastereoisomer mixture, gives rise to a single cis-isomer. In addition, action of phosgene on the diastereoisomer mixture of 2-t-butyl or 2-phenyl thiazolidine-4-(R)-methanol affords mainly (or totally for the t-butyl compound) the cis-substituted oxazolidinone-thiazolidine bicycle.[9] Finally, high enantiomeric excesses have been obtained during hydrosilylation of ketones with a thiazolidine diastereoisomeric mixture as cocatalysts.[6] Therefore, we hoped that the use of thiazolidino-oxazaborolidines formed by the action of borane on the 2-substituted thiazolidine-4-methanol diastereoisomer mixtures could give rise to a good stereoselectivity during reductions of ketones.

2-Substituted thiazolidine-4-methanol **2a–d** were synthesized by $NaBH_4$ reduction[10] of the corresponding 2-substituted thiazolidine-4-carboxylic esters **1a–d** which result from reaction of aldehydes and (R)-cysteine methyl ester hydrochloride according to established procedures.[3c] **1a–d** and **2a–d** were obtained as a mixture of two (2R,4R) and (2S,4R) diastereoisomers respectively in a ratio close to 65/35 and 55/45 as measured by ^1H NMR.[11]

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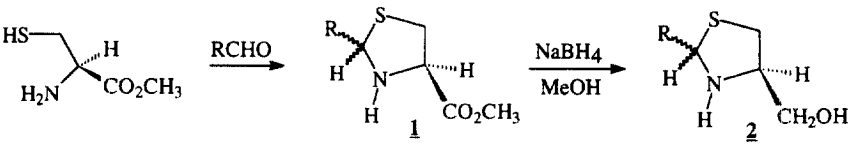
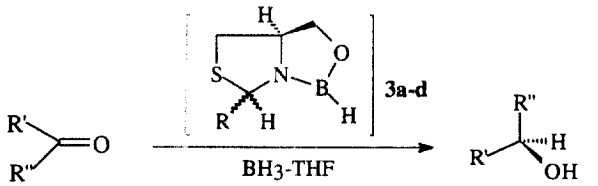
Table 1. Asymmetric reduction of acetophenone

entry	thiazolidine (equiv.)	T°C	yield%	ee %[12a]	config.[12b]
1	**2a** (1)	25°C	99	84	S
2	**2a** (0.2)	25°C	98	0	/
3	**2a** (0.1)	25°C	99	0	/
4	**2a** (1)	0°C	99	82	S
5	**2a** (1)	-20°C	15	80	S
6	**2b** (1)	25 °C	99	40	S
7	**2c** (1)	25° C	98	34	S
8	**2d** (1)	25°C	98	18	R
9	**2a** (2)[13c]	25°C	99	78	S



a : R = $C(CH_3)_3$, **b** : R = $CH(CH_3)_2$, **c** : R = CH_2CH_3, **d** : R = C_6H_5

Oxazaborolidines **3a–d** were prepared *in situ* by reacting the thiazolidines **2a–d** with 1.1 equivalents of borane in THF for 0.5 h at room temperature followed by 4 h reflux. These reactions were monitored by measuring the amount of H_2-gas evolved (2 equivalents). The solutions of **3a–d**, which were not stable enough for long storage, were then used without purification. The subsequent reduction of ketones was performed by slow addition of the ketone to a THF solution of BH_3 and 1,3,2-oxazaborolidine **3a–d**.



The effect of the experimental conditions and the C-2 thiazolidine substitution on the reaction development was first investigated in the case of the acetophenone reduction (Table 1). We observed (entries 1–3 and 9) that a stoichiometric amount of the asymmetric agent **2a**, with respect to the ketone, is necessary to observe a stereoselectivity effect (entries 1–3) independent of the temperature (entries 1, 4, 5). However, at −20°C the reduction is very slow and affords the alcohol in only 15% yield after 12 h. It is reasonable to speculate that the racemic alcohol obtained by using catalytic amount of **2a** (entries 2 and 3) might result from a competing free borane reduction pathway. The enantioselectivity increased with steric hindrance at C-2 (entries 1, 6–8) and the best result is achieved by using the bulkier compound **2a**. Moreover, the direction of the stereoselectivity is very dependent on the substitution at C-2. The reduction reaction affords mainly the (S)-1-phenylethanol when the thiazolidine ring is substituted by an alkyl group and these results are in agreement with those previously described by using the (R)-thiazolidine-4-methanol.[4] On the contrary, the (R) configuration is obtained when the substituent is a phenyl group (entry 8).

Next, the enantioselective reduction of some aromatic ketones has been considered under the same conditions (25°C, one equivalent of **2a**) (Table 2). The corresponding (S) alcohols are mainly produced except in the case of 2-chloroacetophenone (entry 12) where, as previously reported in the case of various chiral auxiliaries,[1b,4] the opposite configuration is obtained.

The high enantiomeric excess obtained when using **2a** is most probably the result of a predominant

Table 2. Enantioselective reduction at 25°C of aromatic ketones by using **2a**

entry	ketones	ee %[12a]	config.[12b]
1	$C_6H_5COCH_3$	84	S
10	4-$ClC_6H_4COCH_3$	68	S
11	$C_6H_5COCH_2CH_3$	78	S
12	$C_6H_5COCH_2Cl$	64	R
13	$C_6H_5COCH_2C_6H_5$	45	S
14	α-indanone	16	S
15	α-tetralone	35	S

formation of only one thiazolidino-oxazaborolidine diastereoisomer by a ring opening–ring closure reaction as in examples reported before. To check this hypothesis we have recorded the ^{11}B NMR decoupled spectrum and the ^1H NMR spectrum of **3a**. The ^{11}B NMR decoupled spectrum in THF showed two broadened peaks (downfield from BF_3–Et_2O) which might correspond to the two cis and trans thiazolidino-oxazaborolidine diastereoisomers: a major (approximately 90%) at 23.7 ppm and a minor at 29.5 ppm. Unfortunately, because of the complexity of the ^1H NMR spectrum in various solvents (THF-d_8 or $CDCl_3$) we could not assign the observed signals to the two diastereoisomers and obtain confirmation of the diastereoisomeric ratio. The two thiazolidino-oxazaborolidine–BH_3 complexes seem to have a similar conversion rate since identical enantiomeric excesses have been obtained by using either one or two thiazolidine **2a** equivalents (entries 1, 9).

In summary, a stereoselectivity effect is observed when using a diastereoisomeric mixture of 2-substituted thiazolidine-4-methanol for borane reduction of ketones. Enantiomeric excesses are both dependent on the bulkiness of the C-2 substitution of the thiazolidine **2** precursor and on the ketone structure. Work is now in progress to improve the enantioselectivity.

Experimental

Tetrahydrofuran (THF) was freshly distilled under argon from sodium and benzophenone; triethylamine (NEt_3) was distilled from KOH and ninhydrin. All other chemicals were commercially pure compounds and were used as received. Thin layer chromatography (tlc) was carried out on silica gel (60 F_{254}, Merck 5715) and spots located with UV light or iodine vapors. Melting points were determined with a Büchi apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AC 250 spectrometer. Data are reported as follows: chemical shifts (δ) in ppm with respect to TMS, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), coupling constants (J) in Hz. Enantiomeric excesses (*e.e.*) of alcohols were determined from crude products by HPLC (chiracel OD column (Daicel), 25 cm×4 mm, λ=254 nm, T=30°C, flow: 1 ml/min, hexane/*iso*-propanol: condition A: 97/3, condition B: 99/1).

General procedure for the preparation of methyl 2-substituted-1,3-thiazolidine-4-carboxylate ***1a–d***

A mixture of (R)-cysteine methyl ester hydrochloride (4.3 g, 25 mmol), aldehyde (50 mmol) and triethylamine (3.8 ml, 27.5 mmol) in pentane (40 ml) was refluxed for 24 h with continuous removal of water using a Dean–Stark trap. The resulting suspension was filtered, the residue was washed with ether and the filtrate was evaporated to give **1a–d** as a mixture of (2R,4R) and (2S,4R) diastereoisomers in a ratio close to 65/35 as measured by ^1H NMR.[11]

Methyl 2-tert-butyl-1,3-thiazolidine-4-carboxylate ***1a***

Following the general procedure from pivaldehyde (5.46 ml, 50 mmol), **1a** (4.8 g, 23.7 mmol, 95% yield) was obtained as a colourless oil; tlc (hexane/AcOEt 1/1) Rf=0.73; [FAB$^+$/NBA] $[M+H]^+$ 204; NMR data deduced from the data of the diastereoisomeric mixtures obtained above, major diastereoisomer: ^1H NMR ($CDCl_3$) δ=1.06 (s, 9H, $C(CH_3)_3$), 2.38 (br, 1H, N*H*), 2.67 (t, J=J′=10 Hz, 1H, 5-HC*H*), 3.25 (dd, J=6.7 Hz and J=10 Hz, 1H, 5-HC*H*), 3.76 (s, 3H, OCH_3), 3.80 (dd, J=6.7 Hz

and J=10 Hz, 1H, 4-C*H*), 4.45 (s, 1H, 2-C*H*); minor diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=0.96 (s, 9H, C(CH_3)$_3$), 2.38 (br, 1H, N*H*), 3.00 (dd, J=5.6 Hz and J=10.6 Hz, 1H, 5-HC*H*), 3.11 (dd, J=5.6 Hz and J=10.6 Hz, 1H, 5-HC*H*), 3.73 (s, 3H, OCH_3), 4.13 (t, J=J′=5.6 Hz, 1H, 4-C*H*), 4.52 (s, 1H, 2-C*H*). $C_9H_{17}NO_2S$ (203.29), calcd: C 53.2% H 8.4% N 6.9%. Found: C 53.3% H 8.3% N 6.9%.

Methyl 2-isopropyl-1,3-thiazolidine-4-carboxylate ***1b***

Following the general procedure from isobutylaldehyde (4.5 ml, 50 mmol), **1b** (4.3 g, 23 mmol, 92% yield) was obtained as a colourless oil; tlc (hexane/AcOEt 7/3) Rf=0.43; [FAB$^+$/NBA] [M+H]$^+$ 190; NMR data deduced from the data of the diastereoisomeric mixtures obtained above, major diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=1.02 (d, J=5.8 Hz, 3H, CHCH_3), 1.08 (d, J=5.6 Hz, 3H, CHCH_3), 1.96 (m, 1H, C*H*(CH_3)$_2$), 2.30 (br, 1H, N*H*), 2.73 (t, J=J′=9.8 Hz, 1H, 5-HC*H*), 3.25 (dd, J=7 Hz and J=9.8 Hz, 1H, 5-HC*H*), 3.74 (s, 3H, OCH_3), 3.80 (dd, J=7 Hz and J=9.8 Hz, 1H, 4-C*H*), 4.32 (d, J=7.2 Hz, 1H, 2-C*H*); minor diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=0.94 (d, J=5.2 Hz, 3H, CHCH_3), 0.98 (d, J=5.4 Hz, 3H, CHCH_3), 1.72 (m, 1H, C*H*(CH_3)$_2$), 2.30 (br, 1H, N*H*), 2.98 (dd, J=6.5 Hz and J=10.5 Hz, 1H, 5-HC*H*), 3.15 (dd, J=6.5 Hz and J=10.5 Hz, 1H, 5-HC*H*), 3.68 (s, 3H, OCH_3), 4.08 (t, J=J′=6.5 Hz, 1H, 4-C*H*), 4.42 (d, J=7.6 Hz, 1H, 2-C*H*). $C_8H_{15}NO_2S$ (189.27), calcd: C 50.8% H 8.0% N 7.4%. Found: C 50.7% H 7.9% N 7.5%.

Methyl 2-ethyl-1,3-thiazolidine-4-carboxylate ***1c***

Following the general procedure from propionaldehyde (3.6 ml, 50 mmol), **1c** (3.9 g, 22.5 mmol, 90% yield) was obtained as a colourless oil; tlc (hexane/AcOEt 1/1) Rf=0.52; [FAB$^+$/NBA] [M+H]$^+$ 176; NMR data deduced from the data of the diastereoisomeric mixtures obtained above, major diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=1.04 (t, J=7.4 Hz, 3H, CH_2CH_3), 1.80 (m, 2H, CH_2CH_3), 2.28 (br, 1H, N*H*), 2.79 (t, J=J′=9.6 Hz, 1H, 5-HC*H*), 3.24 (dd, J=6.4 Hz and J=9.6 Hz, 1H, 5-HC*H*), 3.74 (s, 3H, OCH_3), 3.78 (dd, J=6.4 Hz and J=9.6 Hz, 1H, 4-C*H*), 4.40 (dd, J=5.7 Hz and J=7 Hz, 1H, 2-C*H*); minor diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=0.96 (t, J=7.4 Hz, 3H, CH_2CH_3), 1.60 (m, 2H, CH_2CH_3), 2.28 (br, 1H, N*H*), 2.99 (dd, J=6.7 Hz and J=10.6 Hz, 1H, 5-HC*H*), 3.20 (dd, J=6.7 Hz and J=10.6 Hz, 1H, 5-HC*H*), 3.72 (s, 3H, OCH_3), 4.08 (t, J=J′=6.7 Hz, 1H, 4-C*H*), 4.54 (dd, J=6 Hz and J=7.6. Hz, 1H, 2-C*H*). $C_7H_{13}NO_2S$ (175.24), calcd: C 48.0% H 7.5% N 8.0%. Found: C 48.1% H 7.4% N 8.1%.

Methyl 2-phenyl-1,3-thiazolidine-4-carboxylate ***1d***

Following the general procedure from benzaldehyde (5.1 ml, 50 mmol), **1d** (5.28 g, 23.7 mmol, 95% yield) was obtained as a colourless oil; tlc (hexane/AcOEt 7/3) Rf=0.34; [FAB$^+$/NBA] [M+H]$^+$ 224; NMR data deduced from the data of the diastereoisomeric mixtures obtained above, major diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=3.13 (t, J=J′=10 Hz, 1H, 5-HC*H*), 3.48 (dd, J=7 Hz and J=10 Hz, 1H, 5-HC*H*), 3.78 (s, 3H, OCH_3), 4.02 (dd, J=7 Hz and J=10 Hz, 1H, 4-C*H*), 5.58 (s, 1H, 2-C*H*), 7.40 (m, 3H, *H*-arom.), 7.50 (m, 2H, *H*-arom.); minor diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=3.20 (dd, J=6 Hz and J=10.6 Hz, 1H, 5-HC*H*), 3.40 (dd, J=6 Hz and J=10.6 Hz, 1H, 5-HC*H*), 3.76 (s, 3H, OCH_3), 4.22 (t, J=J′=6 Hz, 1H, 4-C*H*), 5.83 (S, 1H, 2-C*H*), 7.40 (m, 3H, *H*-arom.), 7.50 (m, 2H, *H*-arom.). $C_{11}H_{13}NO_2S$ (223.28), calcd: C 59.2% H 5.9% N 6.3%. Found: C 59.3% H 5.8% N 6.2%.

General procedure for the preparation of 2-substituted 1,3-thiazolidine-4-methanol ***2a–d***

1 (10 mmol) Was dissolved in methanol (20 ml) and a solution of sodium borohydride (40 mmol) in methanol (40 ml) was added at room temperature under vigorous stirring. After the addition was complete, stirring was continued for 3 h. Then, a solution of hydrogen chloride in methanol (25%, 2 ml) was added. The solvent was removed and a concentrated aqueous ammonium hydroxide solution (80 ml) was added to the residue. The solution was then extracted with dichloromethane (3×40 ml) and the combined organic extracts were dried and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (1/1) as eluant. The thiazolidine **2** was

obtained as a mixture of (2R,4R) and (2S,4R) diastereoisomers in a ratio close to 55/45 as measured by ^{1}H NMR.[11]

2-tert-Butyl-1,3-thiazolidine-4-methanol 2a

Following the general procedure from **1a** (2 g, 10 mmol), **2a** (788 mg, 4.5 mmol, 45% yield) was obtained as a white solid; m.p. 69°C, tlc (hexane/AcOEt 1/1) Rf=0.16; [FAB$^+$/GT] [M+H]$^+$ 176; NMR data deduced from the data of the diastereoisomeric mixtures obtained above, major diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=1.03 (s, 9H, C(CH_3)$_3$), 2.56 (t, J=J′=10 Hz, 1H, 5-HC*H*), 2.93 (dd, J=6 Hz and J=10 Hz, 1H, 5-HC*H*), 3.29 (m, 1H, 4-C*H*), 3.72 (dd, J=5 Hz and J=11.2 Hz, 1H, *H*–CHOH), 3.95 (dd, J=3.7 Hz and J=11.2 Hz, 1H, H–CHOH), 4.47 (s, 1H, 2-C*H*); minor diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=1.03 (s, 9H, C(CH_3)$_3$), 2.64 (dd, J=2.9 Hz and J=10.5 Hz, 1H, 5-HC*H*), 2.90 (dd, J=7 Hz and J=10.5 Hz, 1H, 5-HC*H*), 3.40 (d, J=7.5 Hz, 2H, CH_2OH), 3.85 (m, 1H, 4-C*H*), 4.35 (s, 1H, 2-C*H*). $C_8H_{17}NOS$ (175.28), calcd: C 54.8% H 9.8% N 8.0%. Found: C 54.9% H 9.6% N 8.0%.

2-Isopropyl-1,3-thiazolidine-4-methanol 2b

Following the general procedure from **1b** (1.89 g, 10 mmol), **2b** (612 mg, 3.8 mmol, 38% yield) was obtained as a white solid; m.p. 60°C, tlc (hexane/AcOEt 3/7) Rf=0.22; [FAB$^+$/GT] [M+H]$^+$ 162; NMR data deduced from the data of the diastereoisomeric mixtures obtained above, major diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=1.03 (d, J=6.6 Hz, 6H, CH(CH_3)$_2$), 1.90 (m, 1H, C*H*(CH_3)$_2$), 2.62 (t, J=J′=10.2 Hz, 1H, 5-HC*H*), 2.96 (dd, J=6.4 Hz and J=10.2 Hz, 1H, 5-HC*H*), 3.30 (m, 1H, 4-C*H*), 3.72 (dd, J=5.2 Hz and J=11.1 Hz, 1H, *H*–CHOH), 3.94 (dd, J=3.8 Hz and J=11.1 Hz, 1H, *H*–CHOH), 4.37 (d, J=7.2 Hz, 1H, 2-C*H*); minor diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=1.06 (d, J=6.7 Hz, 3H, CHCH_3), 1.08 (d, J=6.7 Hz, 3H, CHCH_3), 1.90 (m, 1H, C*H*(CH_3)$_2$), 2.65 (dd, J=3.2 Hz and J=10.2 Hz, 1H, 5-HC*H*), 2.96 (dd, J=6.4 Hz and J=10.2 Hz, 1H, 5-HC*H*), 3.48 (m, 2H, CH_2OH), 4.08 (m, 1H, 4-C*H*), 4.25 (d, J=7.4 Hz, 1H, 2-C*H*). $C_7H_{15}NOS$ (161.26), calcd: C 52.1% H 9.4% N 8.7%. Found: C 52.3% H 9.3% N 8.6%.

2-Ethyl-1,3-thiazolidine-4-methanol 2c

Following the general procedure from **1c** (1.89 g, 10 mmol), **2c** (612 mg, 4.2 mmol, 42% yield) was obtained as a colourless oil; tlc (AcOEt) Rf=0.42; [FAB$^+$/NBA] [M+H]$^+$ 148; NMR data deduced from the data of the diastereoisomeric mixtures obtained above, major diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=1.04 (t, J=7.4 Hz, 3H, CH_2CH_3), 1.90 (m, 2H, CH_2CH$_3$), 2.70 (t, J=J′=6.3 Hz, 1H, 5-HC*H*), 2.97 (m, 1H, 5-HC*H*), 3.30 (m, 1H, 4-C*H*), 3.71 (dd, J=5.2 Hz and J=11.2 Hz, 1H, *H*–CHOH), 3.92 (dd, J=3.7 Hz and J=11.2 Hz, 1H, *H*–CHOH), 4.46 (dd, J=5.5 Hz and J=7.3 Hz, 1H, 2-C*H*); minor diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=1.02 (t, J=7.4 Hz, 3H, CH_2CH_3), 1.66 (m, 2H, CH_2CH$_3$), 2.68 (dd, J=6.3 Hz and J=10.4 Hz, 1H, 5-HC*H*), 2.97 (m, 1H, 5-HC*H*), 3.50 (m, 2H, CH_2OH), 3.76 (m, 1H, 4-C*H*), 4.39 (dd, J=5.7 Hz and J=7.5 Hz, 1H, 2-C*H*). $C_6H_{13}NOS$ (147.23), calcd: C 48.9% H 8.9% N 9.5%. Found: C 49.0% H 8.7% N 9.6%.

2-Phenyl-1,3-thiazolidine-4-methanol 2d

Following the general procedure from **1d** (2.23 g, 10 mmol), **2d** (902 mg, 4.6 mmol, 46% yield) was obtained as a colourless oil; tlc (hexane/AcOEt 3/7) Rf=0.25; [FAB$^+$/GT] [M+H]$^+$ 196; NMR data deduced from the data of the diastereoisomeric mixtures obtained above, major diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=2.95 (t, J=J′=9.8 Hz, 1H, 5-HC*H*), 3.14 (dd, J=6.2 Hz and J=9.8 Hz, 1H, 5-HC*H*), 3.46 (m, 1H, 4-C*H*), 3.75 (dd, J=5.2 Hz and J=11.2 Hz, 1H, *H*–CHOH), 3.97 (dd, J=3.8 Hz and J=11.2 Hz, 1H, *H*–CHOH), 5.58 (s, 1H, 2-C*H*) 7.33 (m, 3H, *H*-arom.), 7.45 (m, 2H, *H*-arom.); minor diastereoisomer: ^{1}H NMR ($CDCl_3$) δ=2.84 (dd, J=4.2 Hz and J=10.6 Hz, 1H, 5-HC*H*), 3.24 (dd, J=7 Hz and J=10.6 Hz, 1H, 5-HC*H*), 3.60 (d, J=6.5 Hz, CH_2OH), 3.86 (m, 1H, 4-C*H*), 5.52 (s,

1H, 2-C*H*), 7.33 (m, 3H, *H*-arom.), 7.45 (m, 2H, *H*-arom.). $C_{10}H_{13}NOS$ (195.27), calcd: C 61.5% H 6.7% N 7.2%. Found: C 61.5% H 6.6% N 7.1%.

General procedure for the reduction of ketones

To a solution at room temperature of 2 mmol of thiazolidine **2** dissolved in 2 ml of anhydrous THF was added, under argon, a BH_3–THF solution (2 ml, 1.0 M in hexane, 2 mmol). The resulting mixture was stirred at this temperature for 0.5 h followed by 4 h reflux. Then, at T°C and under a slight overpressure of argon, 1 more equivalent of BH_3–THF was added via a syringe pump over 1 h. After 0.5 h and at the same temperature, a solution of 2 mmol of ketone in 2 ml of anhydrous THF was added via a syringe pump over 1–2 h and the mixture was stirred for an additional 12 h at this temperature. The reaction mixture was then quenched with 2 M HCl followed by the addition of 20 ml of AcOEt.

Normal workup provided the crude product which was analysed by HPLC.

Condition A

Acetophenone r.t. 6.35 min, (R)-1-phenylethanol r.t. 11.85 min, (S)-1-phenylethanol r.t. 14.60 min; propiophenone r.t. 6.50 min, (R)-1-phenyl-1-propanol r.t. 10.48 min, (S)-1-phenyl-1-propanol r.t. 12.64 min; 2-chloroacetophenone r.t. 10.06 min, (S)-1-4-chlorophenyl ethanol r.t. 14.55 min, (R)-4-chlorophenylethanol r.t. 18.90 min; phenylacetophenone r.t. 11.43 min, (R)-1,2-diphenylethanol r.t. 15.65 min, (S)-1,2-diphenylethanol r.t. 19.83 min; indanone r.t. 8.72 min, (S)-indanol r.t. 12.81 min, (R)-indanol r.t. 14.50 min; tetralone r.t. 6.88 min, (R)-(1,2,3,4)-tetrahydronaphthol r.t. 11.09 min, (S)-(1,2,3,4)-tetrahydronaphthol r.t. 12.14 min.

Condition B

4-Chloroacetophenone r.t. 8.20 min, (S)-1-4-chlorophenyl ethanol r.t. 24.80 min, (R)-1-4-chlorophenyl ethanol r.t. 26.45 min.

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11. As the diastereoisomers exhibit different ^{1}H NMR spectra, the diastereoisomer ratio can be determined by the integration of the appropiate signal (H at C-2).
12. (a) *E.e.*s were determined by HPLC on a Chiracel OD column; mobile phase hexane/isopropanol (97/3); flow rate 1 mL/min; detector: UV 254 nm. (b) configurations were assigned by comparison with the sign of the optical rotation and known elution order from a chiracel OD column. (c) 3 equiv of BH_3–THF were used.

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