Chiral Auxiliaries with a Switching Center: New Tools in Asymmetric Synthesis. Application to the Synthesis of Enantiomerically Pure (*R*)- and (*S*)-α-Amino Acids

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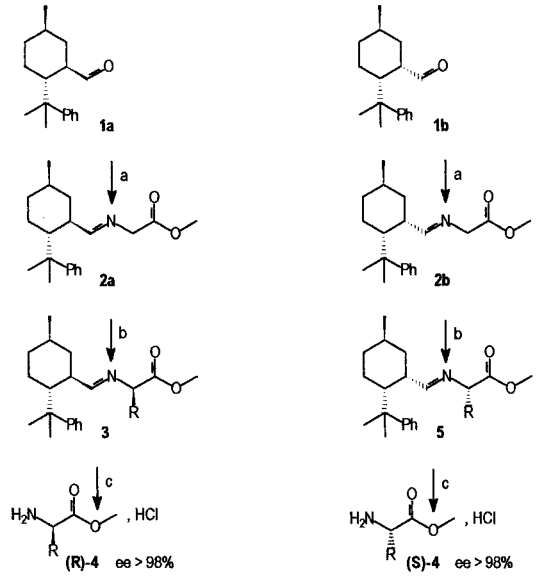
Chiral auxiliaries are common construction elements in asymmetric synthesis.[1ab] Typically, when a final product of opposite configuration is desired, it is common to use the enantiomeric auxiliary. However, we show that in some cases with auxiliaries containing multiple stereogenic centers, it is possible to use an auxiliary in which only a single center has been inverted: in this communication, a new type of chiral auxiliary, containing such a "switching center", is introduced. The principle is illustrated by use of the new chiral auxiliaries, epimeric aldehydes **1a** and **1b**, precursors of iminoesters **2a** and **2b**. Alkylation of **2a** gave α-amino acids of (*R*)-configuration (ee > 98%) while alkylation of **2b** yielded the enantiomeric product, also in high stereochemical yield (ee > 98%).

Iminoester **2a** was obtained in quantitative yield by condensation of **1a** with methyl glycinate in CH_2Cl_2 at ambient temperature in the presence of molecular sieves. Deprotonation with LDA followed by alkylation led to products **3**.[2] Compounds **3** (single diastereomer) were separated from unreacted starting material by chromatography on silica gel. Mild hydrolysis with dilute hydrochloric acid at room temperature yielded hydrochlorides of methyl aminoesters **4** of (*R*)-configuration in ee > 98% (Scheme 1, Table 1). The alkylation was perfomed using either benzyl or allyl bromides or phenethyl or butyl iodides (for these two last cases, the presence of HMPA (1.5 equiv) was needed). The same reactions starting from epimeric aldehyde **1b** led via the iminoesters **2b** and **5** to hydrochlorides **4** of (*S*)-methyl aminoesters in ee > 98% (Scheme 1, Table 1).

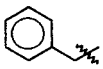
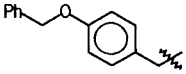
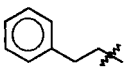
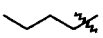
The chiral induction can be explained by assuming that the starting aldimines **2a** and **2b** (single geometrical isomer) are in the anti form and that one face of their lithium enolates **6a** and **6b** is shielded by the phenyl group of the chiral auxiliary,[5] forcing the electrophilic approach from the *Re* face of the nucleophilic C_2 of **6a** and the *Si* face of **6b** (Scheme 2).

Scheme 1[a]



[a] (a) Freshly liberated methyl glycinate, CH_2Cl_2, 4 Å sieves, rt, 12 h; (b) (i) LDA, THF, −78 °C; (ii) RX, HMPA used for less reactive alkyl halides (see text), THF, −78 °C; (c) 1 N HCl, Et_2O, rt.

Table 1. (*R*)- and (*S*)-α-Amino Acids Hydrochlorides 4 from Alkylation of Iminoesters 2a and 2b

Entry	R	2	3 / 5	4	
			yd%[a]	yd%[b]	ee% (conf)[c]
1		**2a**	77	74	> 99 (R)
2		**2b**	85	80	98 (S)
3		**2a**	90	96	> 98.5[d] (R)
4		**2a**	95	93	> 99 (R)
5		**2a**	80	59	> 99 (R)
6		**2b**	90	80	> 99 (S)
7		**2a**	96	93	> 99 (R)

[a] Isolated by chromatography on silica gel. [b] calculated from **1a** or **1b**. [c] Determined by HPLC on Crownpack CR (+). [d] Determined after hydrolysis.

† Deceased on May 7, 1997.

(1) (a) *Stereochemistry of Organic Compounds*; Eliel, E. L., Wilen, S. H., Eds.; Wiley and Sons, Inc.: New York, 1994. (b) *Houben-Weyl, Methods of Organic Chemistry*; Thieme G. Verlag: Stuttgart, 1995; vol. E 21 a. (c) First alkylation of Schiff bases of methyl glycinate: Stork, G.; Leong, A. Y. W.; Touzin, A.-M. *J. Org. Chem.* **1976**, *41*, 3491−3493 (racemic series). Reviews: (d) Williams, R. M. *Synthesis of Optically Active* α-Amino Acids; Pergamon: Oxford, 1989. (e) Williams, R. M. *Aldrichimica Acta* **1992**, *25*, 11−25. (f) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539−1550. (g) Seebach, D.; Sting, A. R.; Hoffmann, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2709−2748.

(2) Enantioselective alkylations of noncyclic amino acid derivatives (recent references): (a) Duhamel, P.; Eddine, J. J.; Valnot, J. Y. *Tetrahedron Lett.* **1987**, *28*, 3801−3804. (b) Duhamel, P.; Duhamel, L.; Fouquay, S.; Eddine, J. J.; Peschard, O.; Plaquevent, J. C.; Ravard, A.; Solliard, R.; Valnot, J. Y.; Vincens, H. *Tetrahedron* **1988**, *44*, 5495−5506. (c) Genêt, J. P.; Ferroud, D.; Jugé, S.; Ruiz-Montes, J.; Gaudin, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, *11*, 718−719. (d) Genêt, J. P.; Jugé, S.; Achi, S.; Mallart, S.; Ruiz-Montes, J.; Levif, G. *Tetrahedron* **1988**, *44*, 5263−5272. (e) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353−2355. (f) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507−4518. (g) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (h) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595−8598.

(3) Diastereoselective alkylations of noncyclic amino acid derivatives (recent references): (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 6009−6010. (b) Zhong, J. Y.; Guilan, L.; Changyou, Z.; Huri, P.; Lanjun, W.; Aiqiao, M. *Synth. Commun.* **1991**, *21*, 1087−1090. (c) Genêt, J. P.; Kopola, N.; Jugé, S.; Ruiz-Montes, J.; Antunes, O. A. C.; Tanier, S. *Tetrahedron Lett.* **1990**, *31*, 3133−3136. (d) El Adrami, M.; Lavergne, J. P.; Viallefont, Ph.; Ait Itto, M. Y.; Hasnaoui, A. *Tetrahedron Lett.* **1991**, *32*, 3985−3988. (e) Zhong, J. Y.; Changyou, Z.; Huri, P. *Synth. Commun.* **1989**, *19*, 881−888. (f) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *Tetrahedron* **1992**, *48*, 5163−5178. (g) Sanchez-Obregon, R.; Fallis, A. G. *Can. J. Chem.* **1992**, *70*, 1531−1536. (h) Alvarez-Ibarra, C.; Csàky, A. G.; Maroto, R.; Luz Quiroga, M. *J. Org. Chem.* **1995**, *60*, 7934−7940. (i) Voigt, K.; Stolle, A.; Salaün, J.; De Meijere, A. *Synlett* **1995**, *3*, 226−228. (j) Ferey, V.; Toupet, L.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 430−432. (k) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am.Chem. Soc.* **1997**, *119*, 656−673.

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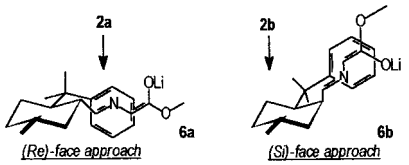
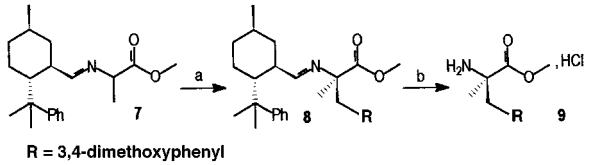
Scheme 2



Scheme 3[a]



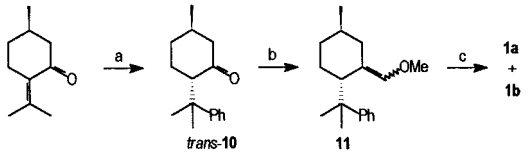
[a] (a) (i) LDA, THF, −78 °C; (ii) 3,4-dimethoxybenzyl bromide, THF, −78 °C; (b) 1 N HCl, Et_2O, rt.

This methodology also provides access to a nonproteinogenic α-amino acid with a quaternary chiral center: a derivative of (*R*)-methyl dopa **9**,[6] by alkylation of iminoester **7** (prepared from aldehyde **1a** and racemic methyl alaninate) followed by hydrolysis of **8**. The ee of **9** (>98%) was determined by ^{1}H NMR of the free aminoester, using a chiral europium chelate [Eu(tfc)$_3$],[7] and the absolute configuration was determined by the sign of rotation.[8]

Aldehydes **1a** and **1b** were prepared from (*R*)-pulegone. Conjugate addition of PhMgBr and epimerization according to Corey and Ensley[5a,9] led to a mixture of ketones **10** (trans/cis = 85/15) which were separated by chromatography on silica gel. Condensation of *trans*-**10** with the anion of Ph_2POCH_2OMe[10] gave enol ethers **11** (*Z* and *E* isomers) that were hydrolyzed to aldehydes **1a** and **1b** (isolated by chromatography in 80% and 10% yields, respectively) (Scheme 4).

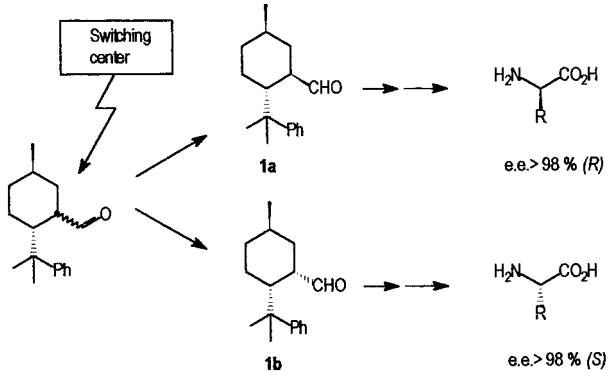
In asymmetric synthesis, chiral auxiliaries are typically obtained from the chiral pool and consequently are inexpensive and available in large amounts. Often, however, only one enantiomer is available, the other being rare and expensive (for example, (*S*)-pulegone) or difficult to synthesize.[11] To avoid using the rare and expensive enantiomer,[12,13] we have used epimeric aldehydes **1a** and **1b** that are obtained from the inexpensive (*R*)-pulegone. This represents the first use of this new tool in asymmetric

Scheme 4[a]



(a) (i) PhMgBr, CuI, Me_2S, Et_2O; (ii) 6 N HCl; (iii) KOH, EtOH, 50 °C (*trans*-**10**: 70%); (b) $Ph_2P(O)CH_2OCH_3$, HMPA, THF; (c) (i) CF_3CO_2H, H_2O, THF, reflux; (ii) sat. $NaHCO_3$.

Scheme 5



synthesis: chiral auxiliaries with a switching center (Scheme 5). Two conditions are required for a switching center: (i) the inversion of configuration of only one of its stereogenic centers must lead to reaction products of opposite configuration; (ii) the inversion of configuration of this strategic switching center must be easy. These two conditions are fulfilled with aldehydes **1**.[14]

In summary, we have shown that using aldehydes **1a** and **1b** (chiral auxiliaries with a switching center) lead to monoalkylated or dialkylated α-amino acids of (*R*)- or (*S*)-configuration in good to excellent yields with high stereoselectivity.[15]

Acknowledgment. We are grateful to the ORIL Company and the Région Haute-Normandie for financial support. We also thank Doctor Loïc Toupet for the X-ray analysis of **1a** and Doctor Bernard Elissondo for his support.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**−**5**, **7**−**11**; ORTEP representation of the X-ray structure of aldehyde **1a** (21 pages).

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(4) Asymmetric alkylation of cyclic amino acids derivatives (recent references): (a) Williams, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 9276. (b) Schöllkopf, U. *Liebigs Ann. Chem.* **1993**, 321−323. (c) Williams, R. M. *Advances in Asymmetric Synthesis*, JAI Press Inc.: Greenwich, CT, 1995; vol. 1, pp 45−94. (d) Seebach, D.; Sting, A. R.; Hoffmann, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2709−2748. (e) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nàjera, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 995−997.

(5) In the following examples using phenylmenthol derivatives, the efficiency of the shielding has been attributed to π-stacking: (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908−6909. (b) Oppolzer, W.; Robbiani, C.; Bättig, K. *Helv. Chim. Acta* **1980**, *63*, 2015−2018. (c) Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, M.; Moffatt, F. *Helv. Chim. Acta* **1981**, *64*, 2802−2811. (d) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112. (e) Whitesell, J. K.; Lawrence, R. M.; Chen, H. H. *J. Org. Chem.* **1986**, *51*, 4479−4484. (f) Ort, O.; Jayasingh, R.; White, J. D. *Org. Synth.* **1987**, *65*, 203-214. (g) Barluenga, J.; Bernard, P. L., Jr.; Concellon, J. M.; Pineras-Nicolas, A.; Garcia-Granda, S. *J. Org. Chem.* **1997**, *62*, 6870−6875.

(6) For the pharmacological properties of α-alkylated alanines see ref 4c and references therein.

(7) Eu(tfc)$_3$: [3-((trifluoromethyl)hydroxymethylene)-(+)-camphorato]-europium(III). In $CDCl_3$, the racemic aminoester showed four signals of equal intensity for the two methoxy groups of the aromatic substituent (δ 4.15; 4.02; 3.96; 3.84) whereas the corresponding aminoester synthezised from **7** presented only two (δ 3.95 and 3.83).

(8) $[\alpha]_D$ reported for **9** ((*S*) isomer): + 0.7 (*c* 1.1; EtOH; 20 °C) Schöllkopf, U.; Groth, U.; Westphalen, K. O.; Deng, C. *Synthesis* **1981**, *12*, 969−971; our result: $[\alpha]_D$−0.6 (same conditions).

(9) Ort, O.; Jayasingh, R.; White, J. D. *Org. Synth.* **1987**, *65*, 203−214.

(10) (a) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans 1* **1979**, 3099−3106. (b) Jefford, C. W.; Velard, J. A.; Bernardelli, G.; Bray, D. H.; Warhust, D. C.; Milhous, W. K. *Helv. Chim. Acta* **1993**, *76*, 2775−2788.

(11) (−)-Phenylmenthol is easily prepared from (*R*)-pulegone (three steps) ref 5a. For a synthesis of (+)-phenylmenthol from (*R*)-pulegone (ten steps) see: Ensley, H. E.; Parnel, C. A.; Corey, E. J. *J. Org. Chem.* **1978**, *43*, 1610−1612. For a synthesis of (*S*)-pulegone from citronellol (four steps), see: Buschmann, H.; Scharf, H. D. *Synthesis* **1988**, 827−829.

(12) If only one epimer of the chiral auxiliairy is available, it is possible to prepare the reaction product of opposite configuration by changing the configuration (*Z*-*E*) of the prochiral intermediate (ref 3h) or by introducing the substituents in the reverse order (for example, Kawatanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857−860). These two routes are not general. For a discussion of convergent reactions, see: Duhamel, P.; Duhamel, L. *C. R. Acad. Sci. Paris* **1995**, *t. 320*, *IIb*, 689−694; Duhamel, P. *Bull. Soc. Chim. Fr.* **1996**, *133*, 457−459; and 13b.

(13) A simplified version of the rare and expensive enantiomer has been realized: (a) Chaumette, J. L. These of the University of Rouen, 1996. (b) Duhamel, P. Diastereoselective halogenations. In *Roots of Organic Development*; Desmurs, J. R., Ratton, S., Eds.; Industrial chemistry library, Elsevier: New York, 1996; vol. 8, pp 176−188.

(14) Starting from a mixture **1a**/**1b** = 60/40, a new mixture, 90/10, was quantitatively obtained by treating with KOH (1.5 equiv) in EtOH at ambient temperature for 2 h.

(15) Obviously, if the methyl substituent of the cyclohexane ring of aldehydes **1a** and **1b** was omitted, the same results would be obtained. Using (*R*)-pulegone as starting material avoids a resolution step.