

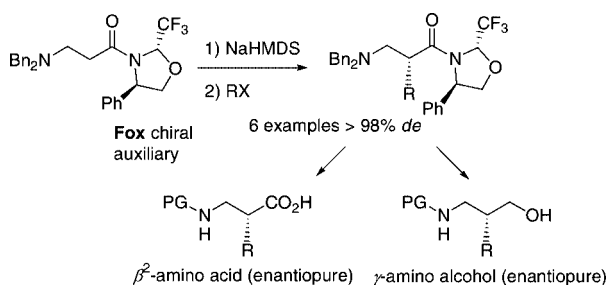
Highly Diastereoselective Synthetic Route to Enantiopure β^2 -Amino Acids and γ -Amino Alcohols Using a Fluorinated Oxazolidine (Fox) as Chiral Auxiliary

Arnaud Tessier, Nour Lahmar, Julien Pytkowicz, and Thierry Brigaud*

Laboratoire "Synthèse Organique Sélective et Chimie Organométallique" (SOSCO), UMR CNRS 8123, Université de Cergy-Pontoise, 5, Mail Gay Lussac Neuville sur Oise 95031, Cergy-Pontoise Cedex, France

thierry.brigaud@u-cergy.fr

Received March 12, 2008



The alkylation reactions of an amide enolate derived from a trifluoromethylated oxazolidine (Fox) chiral auxiliary occur with a complete diastereoselectivity and in good yields with various electrophiles. This reaction provides a versatile and straightforward strategy for the synthesis of β^2 -amino acids and γ -amino alcohols in enantiopure form.

β^2 -Amino acids are finding an increasing interest because of their biological properties.¹ Moreover, their incorporation into a peptide chain gives rise to the formation of well-defined β -peptide secondary structures² associated with specific biological activities. For these reasons, several chiral auxiliary-based³ or catalytic asymmetric methods⁴ have recently been reported for their preparation. From all of these strategies, it appears that the stereoselective alkylation of a homoglycine-type precursor would be one of the more versatile methods for the synthesis of enantiomerically pure compounds, provided that the control of the stereoselectivity is total to avoid tedious separations and that the reaction is general. However, until now there has been

a challenge to find a suitable chiral auxiliary which would combine complete diastereoselectivity and good reactivity with hindered halogenated compounds such as isobutyl and isopropyl iodides. We recently reported the highly diastereoselective alkylation of amides enolates using a trifluoromethylated oxazolidine (Fox) as the chiral auxiliary.⁵ In the present paper, we report now a new facet of the use of the Fox chiral auxiliary for a straightforward synthetic route to various enantiopure β^2 -amino acids and γ -amino alcohols through diastereoselective alkylation of a unique chiral homoglycine precursor.

The starting *N*- β -aminopropanoyloxazolidine **3a** was conveniently prepared from (*R*)-phenylglycinol and fluoral based oxazolidines **1a,b**⁶ in a two-step procedure. The one-pot *N*-acylation/dehydrochlorination reaction of the **1a,b** diastereomeric mixture with 3-chloropropanoylchloride in triethylamine gave the corresponding *trans*- and *cis*-*N*-propanoyloxazolidines **2a** and **2b** in very good isolated yield after an easy silica gel

(3) (a) Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 2812–2825. (b) Beddow, J. E.; Davies, S. G.; Smith, A. D.; Russell, A. J. *Chem. Commun.* **2004**, 2778–2779. (c) Moumne, R.; Denise, B.; Guitot, K.; Rudler, H.; Lavielle, S.; Karoyan, P. *Eur. J. Org. Chem.* **2007**, 1912–1920. (d) Moumne, R.; Lavielle, S.; Karoyan, P. *J. Org. Chem.* **2006**, *71*, 3332–3334. (e) Ponsinet, R.; Chassaing, G.; Vaissermann, J.; Lavielle, S. *Eur. J. Org. Chem.* **2000**, 83–90. (f) Seebach, D.; Schaeffer, L.; Gessier, F.; Bindtschadler, P.; Jaeger, C.; Josien, D.; Kopp, S.; Lelais, G.; Mahajan, Y. R.; Micuch, P.; Sebesta, R.; Schweizer, B. W. *Helv. Chim. Acta* **2003**, *86*, 1852–1861. (g) Lelais, G.; Campo, M. A.; Kopp, S.; Seebach, D. *Helv. Chim. Acta* **2004**, *87*, 1545–1560. (h) Sebesta, R.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 4061–4072. (i) Guichard, G.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 187–206. (j) Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A. *Org. Lett.* **2000**, *2*, 3527–3529. (k) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553–2557. (l) Juaristi, E.; Quintana, D.; Balderas, M.; Garcia-Perez, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233–2246. (m) Gutiérrez-García, M. M.; López-Ruiz, H.; Reyes-Rangel, G.; Juaristi, E. *Tetrahedron* **2001**, *57*, 6487–6496. (n) Juaristi, E.; Balderas, M.; López-Ruiz, H.; Jiménez-Pérez, V. M.; Kaiser-Carril, M. L.; Ramírez-Quirós, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 3493–3505. (o) Lee, H.-S.; Park, J.-S.; Kim, B. M.; Gellman, S. J. *J. Org. Chem.* **2003**, *68*, 1575–1578. (p) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216. (q) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K. I. *J. Org. Chem.* **1997**, *62*, 5830–5837. (r) Eilitz, U.; Lessmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 189–191. (s) Eilitz, U.; Lessmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 3095–3097. (t) Sibi, M. P.; Patil, K. *Tetrahedron: Asymmetry* **2006**, *17*, 516–519. (u) Stoncius, A.; Nahrwald, M.; Sewald, N. *Synthesis* **2005**, 1829–1837. (v) Barnish, I. T.; Corless, M.; Dunn, P. J.; Ellis, D.; Finn, P. W.; Hardstone, J. D.; James, K. *Tetrahedron Lett.* **1993**, *34*, 1323–1326.

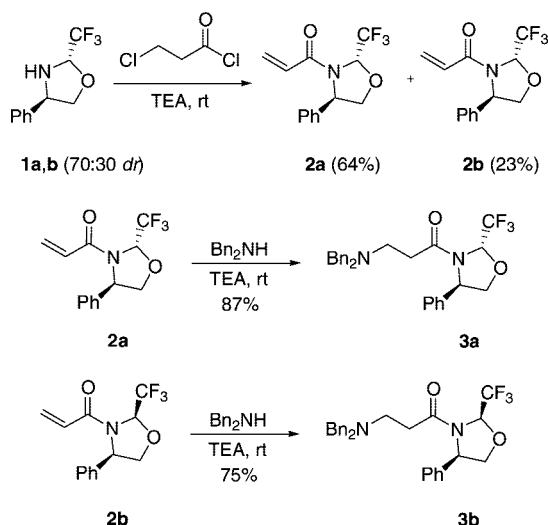
(4) (a) Chi, Y.; English, E. P.; Pomerantz, W. C.; Horne, W. S.; Joyce, L. A.; Alexander, L. R.; Fleming, W. S.; Hopkins, E. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 6050–6055. (b) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804–6805. (c) Sibi, M. P.; Tatamidani, H.; Patil, K. *Org. Lett.* **2005**, *7*, 2571–2573. (d) Sibi, M. P.; Patil, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1235–1238. (e) Sibi, M. P.; Prabakaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796–11797. (f) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442–4443. (g) Sewald, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5794–5795. (h) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197–2199. (i) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701. (j) Hoen, R.; Timmersma-Wegman, T.; Procuranti, B.; Lefort, L.; De Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2007**, *2*, 267–275. (k) Swiderska, M. A.; Stewart, J. D. *Org. Lett.* **2006**, *8*, 6131–6133. (l) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359–3362. (m) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2001**, *12*, 657–667. (n) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79–80. (o) Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1309–1319.

(5) (a) Tessier, A.; Pytkowicz, J.; Brigaud, T. *Angew. Chem.* **2006**, *118*, 3759–3763. (b) *Angew. Chem., Int. Ed.* **2006**, *45*, 3677–3681.

(6) Oxazolidines **1a,b** were prepared according to the procedure reported by Mikami et al.: Ishii, A.; Higashiyama, K.; Mikami, K. *Synlett* **1997**, 1381–1382.

(1) (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035. (b) Aguilar, M.-I.; Purcell, A.; Devi, R.; Lew, R.; Rossjohn, J.; Smith, A. I.; Perlmutter, P. *Org. Biomol. Chem.* **2007**, *5*, 2884–2890. (c) Pratt, L. M.; Beckett, R. P.; Davies, S. J.; Launchbury, S. B.; Miller, A.; Spavold, Z. M.; Todd, R. S.; Whittaker, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2585–2588.

(2) (a) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111–1239. (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232. (c) Norgren, A. S.; Buttner, F.; Prabpai, S.; Kongsaree, P.; Arvidsson, P. *J. Org. Chem.* **2006**, *71*, 6814–6821.

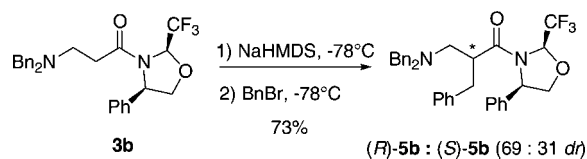
SCHEME 1. Synthesis of *N*- β -Aminopropanoyloxazolidines **3a,b**

TABLE 1. Alkylation of **3a**

entry	RX	product	yield ^a (%)	de ^b (%)
1	MeI ^c	(<i>R</i>)- 4a	84	>98
2	BnBr ^c	(<i>R</i>)- 5a	86	>98
3	allylBr ^c	(<i>R</i>)- 6a	82	>98
4	EtI ^c	(<i>R</i>)- 7a	80	>98
5	<i>i</i> BuI ^d	(<i>R</i>)- 8a	51	>98
6	<i>i</i> PrI ^e	(<i>R</i>)- 9a	51	>98

^a Yield of pure isolated product. ^b One single diastereomer was detected by ¹⁹F and ¹H NMR spectroscopy analysis of the crude reaction mixture. ^c Reactions conditions: 1.9 equiv of halogenated compound, 3 h, -78 °C. ^d Reaction conditions: 4 equiv of halogenated compound, 24 h, -50 °C. ^e Reaction conditions: 8 equiv of halogenated compound, 36 h, -50 °C.

separation⁷ (Scheme 1). This procedure proved to be much more efficient than the direct *N*-propenoylation of **1a,b** with acryloyl chloride leading mainly to polymerization. Both isolated *trans*- and *cis*-oxazolidines **2a** and **2b** were then submitted to a Michael addition of dibenzylamine to give the corresponding *N*- β -aminopropanoyloxazolidine **3a** and **3b** in 87% and 75% yield, respectively. Hence, the performance of both *trans*- and *cis*-Fox chiral auxiliary will be compared for the diastereoselective alkylation reaction.

As we anticipated that the highest diastereoselectivity would be achieved with the substrate **3a** bearing a *trans*-Fox chiral auxiliary,⁵ the NaHMDS-promoted alkylation reaction of **3a** was performed using various halogenated electrophiles (Table 1). Using this *trans* chiral auxiliary, all of the alkylation reactions occurred with excellent diastereoselectivity. In all cases, only one single diastereomer was detected by ¹⁹F or ¹H NMR spectroscopy or GC analysis of the crude reaction mixtures. The complete diastereoselectivity of the methylation of **3a** (Table 1, entry 1) was confirmed by epimerization of (*R*)-**4a** into (*S*)-**4a** with sodium methylate proving that no measurable amount

SCHEME 2. Benzylation Reaction with the *cis*-Fox Chiral Auxiliary


of (*S*)-**4a** was present in the crude reaction mixture. The alkylation with benzyl bromide, allyl bromide, and ethyl iodide was also performed in good yield and with complete diastereoselectivity (Table 1, entries 2–4). Interestingly, the reaction with more hindered halogenated compounds such as isobutyl iodide and isopropyl iodide giving rise to β^2 -homoleucine and β^2 -homovaline precursors were also completely diastereoselective (Table 1, entries 5 and 6). However, longer reaction times, higher temperature (-50 °C), and 4–8 equiv of electrophiles were necessary for these reactions. To our knowledge, the direct introduction of an isopropyl group has only previously been reported by Davies et al. to occur in a very low yield (8%) using the SuperQuat chiral auxiliary.^{3a,b} Moreover, Lavielle et al.^{3c} reported that the enolate alkylation reaction with isobutyl iodide failed using Oppolzer's sultam chiral auxiliary, and these authors had to use the more reactive triflate to succeed in introducing the isobutyl side chain. Very recently, Davies et al.^{3a} and Karoyan et al.^{3c} circumvented this difficulty by diastereoselective conjugate addition of lithium amide or Mannich-type reaction. Therefore, the completely diastereoselective direct introduction of isopropyl and isobutyl groups that we are reporting now can be considered as a significant improvement for the general synthesis of β^2 -amino acids.

As we had the *cis*-Fox precursor **3b** in hand, we then decided to investigate the performance of the *cis* chiral auxiliary in the stereoselective benzylation reaction (Scheme 2). Using this chiral auxiliary, the stereoselectivity of the benzylation was very low. As we have previously reported,⁵ this is probably due to the absence of pseudo-*C*₂ symmetry of this chiral auxiliary.

Using the benzylated diastereomerically pure amide (*R*)-**5a** as a representative substrate, we then performed the removal of the Fox chiral auxiliary in order to obtain enantiopure β^2 -homophenylalanine (*R*)-**10** and the corresponding γ -amino alcohol (*R*)-**11**. In both cases, these transformations were conveniently achieved in a two-step procedure involving a LiAlH₄ reduction of (*R*)-**5a** followed by the oxidation or the NaBH₄ reduction of the intermediate amino aldehyde (Scheme 3). As the *trans*-Fox chiral auxiliary proved to be stable in oxidation and NaBH₄ reduction conditions, the mixture of amino aldehyde and oxazolidine **1a** was engaged in the next step without purification. The β^2 -homophenylalanine (*R*)-**10** and the amino alcohol (*R*)-**11** were then obtained in good isolated yield after silica gel separation with a satisfactory recovery of the *trans*-Fox chiral auxiliary.

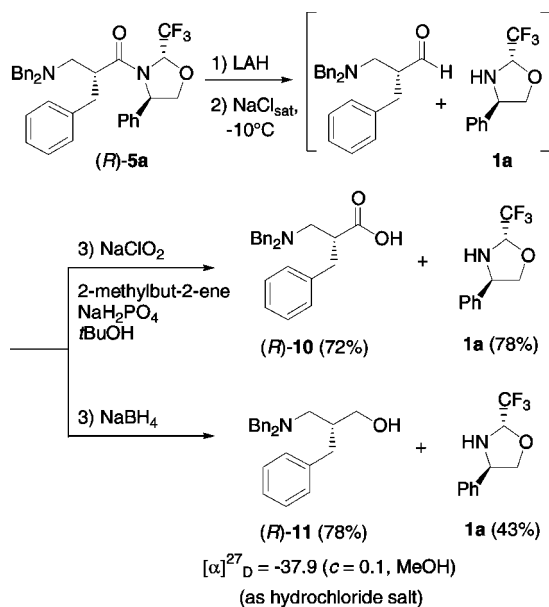
The (*R*) configuration of **11** was assigned by the comparison of its optical rotatory value with literature data.⁸ In order to confirm the *R* configuration of **10** and to have a β^2 -amino acid ready to use in peptide synthesis, (*R*)-**10** was hydrogenolized using Pearlman's catalyst and protected with a Boc group to afford the known *N*-Boc- β^2 -homophenylalanine (*R*)-**12**.⁹ The comparison of its optical rotatory value with literature data

(7) The silica gel separation of *trans*- and *cis*-oxazolidines **2a** and **2b** was very efficiently achieved because of a large *R_f* difference between the two diastereomers ($\Delta R_f = 0.17$, cyclohexane/ethyl acetate: 80/20).

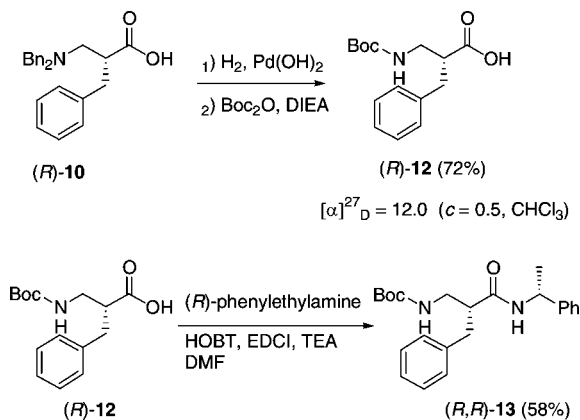
(8) (a) Reference 4b. (b) Ibrahim, I.; Zhao, G.-L.; Córdova, A. *Chem. Eur. J.* **2007**, *13*, 683–688.

(9) For the (*R*)-enantiomer, see ref 3c, e. For the (*S*)-enantiomer, see ref 4a.

SCHEME 3. Transformation of (*R*)-5a into β^2 -Amino Acid and γ -Amino Alcohol with Recovery of the Chiral Auxiliary



SCHEME 4. Derivatization of the Amino Acid (*R*)-10



confirmed its (*R*) configuration (Scheme 4). Finally, the enantiopurity of (*R*)-12 was confirmed by formation of the (*R*)-phenylethylamide derivative (*R,R*)-13, which was obtained as a single diastereomer.¹⁰

The (*R*) configuration of the unique diastereomer is in good agreement with a favored *re* face alkylation of the *Z* amide enolate. To explain the excellent diastereoselectivity, we propose the coexistence of two transition states presenting F...Na or π ...Na interactions (Figure 1).¹¹ Due to the pseudo-*C*₂ symmetry of the *trans*-Fox chiral auxiliary, both transition states will give the same (*R*) diastereomer through *re* face alkylation of the enolate.

In conclusion, we have developed a useful and straightforward route to enantiopure β^2 -amino acids and γ -amino alcohols using the *trans*-Fox chiral auxiliary. A key feature of this strategy is that the diastereoselective alkylation step can even be efficiently

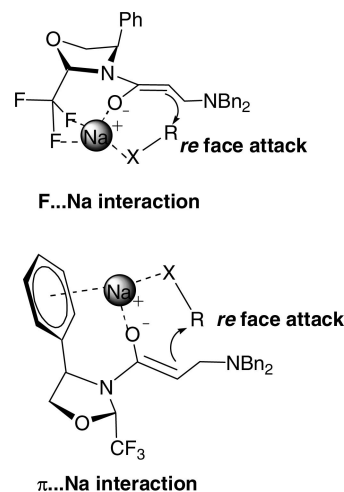


FIGURE 1. Postulated transition states, both leading to *re* face attack of the enolate.

performed with hindered isobutyl and isopropyl iodides. Further synthetic applications toward the synthesis of unnatural amino acids synthesis are ongoing.

Experimental Section

Typical Procedure for Alkylation Reactions: Synthesis of (2*S*,4*R*)-2-Trifluoromethyl-4-phenyl-3-((2*R*)-3-*N,N*-dibenzyl-2-methylaminopropanoyl)oxazolidine ((*R*)-4a). To a solution of the amide 3a (0.532 g, 1.14 mmol) in THF (10 mL) was added dropwise a NaHMDS (1.4 mL of 2 M solution in THF, 2.79 mmol) at -78 °C under argon atmosphere. The resulting yellow solution was stirred for 1.5 h, and the methyl iodide (396 mg, 2.79 mmol) was added at this temperature. The mixture was stirred for 3 h at -78 °C and hydrolyzed with a saturated solution of NH₄Cl (15 mL). The aqueous layer was extracted successively with diethyl ether (2 × 30 mL) and dichloromethane (30 mL). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The crude mixture was purified by silica gel chromatography (cyclohexane/ethyl acetate: 96/4) to give (*R*)-4a (460 mg, 84%) as a white solid: [α]_D²⁵ +19.8 (*c* 2.75, CHCl₃); mp = 103 °C; *R*_f = 0.35 (cyclohexane/ethyl acetate: 90/10); ¹H NMR (400 MHz, CDCl₃) δ 1.13 (d, 3H, ³*J* = 6.4 Hz), 1.92 (d, 1H, ²*J* = 10.1 Hz), 2.45 (m, 2H), 2.72 (d, 2H, ²*J* = 14.2 Hz), 3.09 (d, 2H, ²*J* = 14.2 Hz), 4.05 (d, 1H, ²*J* = 8.7 Hz), 4.68 (dd, 1H, ²*J* = 8.7 Hz, ³*J* = 6.4 Hz), 4.99 (d, 1H, ³*J* = 6.4 Hz), 6.13 (q, 1H, ³*J*_{H-F} = 5.0 Hz), 7.12–7.30 (m, 15H); ¹⁹F NMR (376.2 MHz, CDCl₃) δ -80.67 (d, 3 F, ³*J*_{H-F} = 5.0 Hz); ¹³C NMR (100.5 MHz, CDCl₃) δ 16.8, 37.9, 54.6, 57.9, 60.4, 76.5, 85.1 (q, CH, ²*J*_{C-F} = 38.3 Hz), 123.4 (q, C, ¹*J*_{C-F} = 288.5 Hz), 125.5, 126.7, 128.1, 128.7, 129.6, 139.2, 141.9, 176.4; IR ν 3034, 2980–2798, 1661, 1281, 1227, 1178, 1147, 745, 700 cm⁻¹; MS (EI) 481 (1), 405 (1), 391 (59), 286 (2), 210 (77), 174 (6), 118 (7), 91 (100). Anal. Calcd for C₂₈H₂₉F₃N₂O₂: C, 69.69; H, 6.06; N, 5.81. Found: C, 69.39; H, 6.10; N, 5.59.

(2*R*)-2-Benzyl-3-(*N,N*-dibenzylamino)propanoic Acid ((*R*)-10). LAH (0.135 g, 3.8 mmol) was added portionwise to a solution of the amide (*R*)-5a (0.384 g, 0.68 mmol) in anhydrous diethyl ether (8 mL) at -10 °C. The reaction was stirred for 2.5 h at this temperature and was smoothly hydrolyzed at -10 °C with a saturated NaCl solution. The mixture was extracted with diethyl ether (2 × 20 mL) and dichloromethane (20 mL). The combined organic layers were washed by a saturated ammonium chloride solution and dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. At this stage, the intermediate aldehyde was characterized by ¹H NMR and engaged in the next step without further purification. To a solution of the

(10) In order to confirm the diastereomeric purity of (*R,R*)-13, the same 5 to 13 reaction sequence was performed from the (*R*)- and (*S*)-5b mixture giving a (*R,R*)- and (*S,R*)-13 mixture. Comparison of the ¹H and ¹³C NMR spectra clearly established the complete diastereomeric purity of (*R,R*)-13.

(11) Sini, G.; Tessier, A.; Pytkowicz, J.; Brigaud, T. *Chem. Eur. J.* **2008**, *14*, 3363–3370.

(12) Litt value: [α]_D -44.1 (*c* 0.14; MeOH, as hydrochloride salt). Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804–6805.

crude material in *tert*butyl alcohol (16 mL) at room temperature was added a 2 M solution of 2-methylbut-2-ene in tetrahydrofuran (110 mL, 220 mmol), and a solution of sodium chlorite (NaClO_2 , 0.860 g, 9.5 mmol) and sodium dihydrogenophosphate monohydrate (NaH_2PO_4 , 1.18 g, 7.5 mmol) in water (10 mL). The yellow biphasic mixture was vigorously stirred 1 h at room temperature and water was added (50 mL). The mixture was extracted with a cyclohexane/ethyl acetate mixture (9/1), dried over magnesium sulfate, and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (cyclohexane/ethyl acetate: 4.5/5.5) to yield oxazolidine **1a** as a colorless oil (120 mg; 78%) and amino acid (*R*)-**10** as a colorless oil (180 mg, 72%): $[\alpha]_D^{25} -56.4$ (*c* 1; MeOH); ^1H NMR (400 MHz, CDCl_3) δ 2.53–2.56 (m, 2H), 2.71–2.73 (m, 2H), 3.21 (dd, 1H, $^2J = 14.2$ Hz, $^3J = 3.6$ Hz), 3.43 (d, 2H, $^2J = 13.2$ Hz), 3.72 (d, 2H, $^2J = 13.2$ Hz), 7.15–7.26 (m, 15H); ^{13}C NMR (100.5 MHz, CDCl_3) δ 26.7, 34.8, 41.9, 53.5, 57.2, 125.7, 126.2, 127.8, 128.3, 128.7, 129.3, 134.9, 139.0, 175.6; IR ν 3027, 1708, 1602, 1494, 1453, 908, 732 cm^{-1} . Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{NO}_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 79.85; H, 6.97; N, 4.05.

(*2R*)-3-(*N,N*-Dibenzylamino-2-benzylpropan-1-ol) (*R*)-**11**). To 535 mg of a crude mixture of (*2R*)-2-benzyl-3-(*N,N*-dibenzylamino)propanal and (*2S,4R*)-2-trifluoromethyl-4-phenyloxazolidine **1a** in methanol (5 mL) was added sodium borohydride (41.6 mg, 1.1 mmol) at ambient temperature. The solution was stirred for 2 h at ambient temperature and quenched by slow addition of water (5

mL). The organic layer was extracted with dichloromethane (10 mL), dried over magnesium sulfate, and evaporated under reduced pressure to give 616 mg of crude material which was purified by flash chromatography (cyclohexane/ethyl acetate 9/1) to afford **1a** as a colorless oil (102 mg, 43%) and (*R*)-**11** as a colorless oil (214 mg, 78%): $[\alpha]_D^{25} -37.9$ (*c* 0.1; MeOH, as hydrochloride salt¹); ^1H NMR (400 MHz, CDCl_3) δ 2.24–2.37 (m, 3H), 2.44 (ddd, 1H, $^2J = 11.2$ Hz, $^3J = 2.2$ Hz), 2.56 (dd, 1H, $^2J = 12.3$ Hz, $^3J = 10.5$ Hz), 3.15 (d, 2H, $^2J = 13.2$ Hz), 3.30 (dd, 1H, $^2J = 10.5$ Hz, $^3J = 8.2$ Hz), 3.66 (ddd, 1H, $^2J = 10.5$ Hz, $^3J = 2.2$ Hz), 3.93 (d, 2H, $^2J = 13.2$ Hz), 5.41 (broadband, 1H), 7.06–7.29 (m, 15H); ^{13}C NMR (100.5 MHz, CDCl_3) δ 27.0, 36.5, 38.5, 58.9, 59.0, 68.4, 127.5, 128.5, 128.6, 129.0, 129.4, 137.8, 140.0; IR ν 2922, 1653, 1494, 1452, 1364, 1280 cm^{-1} .

Acknowledgment. We thank the French ministry of research for awarding a research fellowship to A.T. and Central Glass Company for financial support and the generous gift of trifluoroacetaldehyde hemiacetal.

Supporting Information Available: General experimental methods, complete experimental procedures, and characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO800562X