ORGANIC LETTERS

2005
Vol. 7, No. 16
3433−3436

Highly Enantioselective Synthesis of Fluorinated γ-Amino Alcohols through Proline-Catalyzed Cross-Mannich Reaction†

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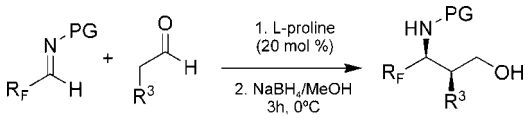
Received April 12, 2005

ABSTRACT



A new, simple route for the synthesis of fluorinated β-alkyl γ-amino alcohols in optically pure form in only two steps and featuring proline catalysis from inexpensive and readily available starting materials is described. The applied strategy allows for the introduction of diversity into both the β-fluoroalkyl and α-alkyl groups of these compounds.

One of the most important goals for organic chemists in the last few decades has been the development of new stereoselective methods for the synthesis of optically pure molecules that bear diversity in their structures. This search has been driven in part by the growing demand for chiral drugs due, in turn, to the increased control of the enantiopurity of drug candidates. In this context, enantiopure β-amino acids have received a great deal of attention because they are either present in or can be used as fundamental building blocks for a number of compounds with potential therapeutic properties.[1] In fact, many of these compounds have already been shown to display antifungal, antibiotic, and cytotoxic activity.[2]

Organocatalysis,[3] for its part, has become one of the key research areas in synthetic organic chemistry due to its unquestionable utility in asymmetric synthesis when applied to Mannich reactions,[4] among many others.[3] From a wide variety of known organocatalysts, perhaps the most remarkable is proline. Not only has this compound been studied more extensively than the others, as the first example of an organocatalyst,[5] but it is also an abundant and inexpensive chiral molecule available in both enantiomeric forms. Proline has thus become one of the most widely used organocatalysts today.

† Dedicated to Prof. José Barluenga on the occasion of his 65th birthday.

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(2) (a) Fernández, R.; Rodríguez, J.; Quiñoa, E.; Riguera, R.; Muñoz, L.; Fernández-Suarez, M.; Debitus, C. J. *J. Am. Chem. Soc.* **1996**, *118*, 11635−11643. (b) Hu, T.; Panek, J. J. *J. Org. Chem.* **1999**, *64*, 3000−3001.

(3) (a) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, 2005. Reviews: (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719−724. (c) Dalko, P. I.; Moisan, D. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175.

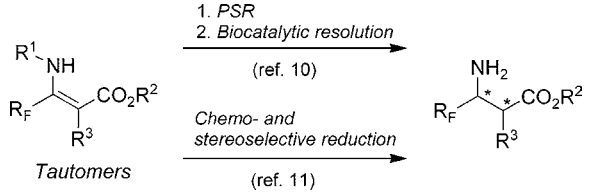
(4) For representative examples of organocatalyzed Mannich reactions, see: (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833. (c) Watanabe, S.; Córdova, A.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2002**, *4*, 4519−4522. (d) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866−1867. (e) Notz, W.; Tanaka, T.; Watanabe, S.; Chowdari, S. N.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624−9634. (f) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushihima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677−3680. (g) Notz, W.; Tanaka, T.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580−591. (h) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102−112. (i) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243−7246. (j) Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987−1997. (k) Zhuang, W.; Saaby, S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476−4478. (l) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84−96.

10.1021/ol050791f CCC: $30.25
Published on Web 07/14/2005

At the same time, organofluorine compounds have become increasingly more important in the past few years because the presence of fluorine atoms in a potentially bioactive molecule can dramatically change not only its physical but also its chemical properties.[6,7]

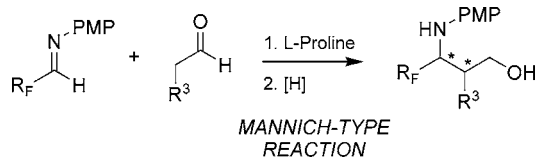
In recent years, several helpful approaches to α-alkyl *β*-amino acids[1e,8] have been reported, but surprisingly little work has been done on α-alkyl *β*-(fluoroalkyl) *β*-amino acids.[9] In fact, only two main strategies have been developed thus far for the synthesis of derivatives of these compounds in a chiral, nonracemic fashion (Scheme 1). Thus, Soloshonok[10] described in 1998 a chemoenzymatic two-step approach to α-alkyl *β*-fluoroalkyl *β*-amino acids that relies on a diastereoselective biomimetic transamination [proton shift reaction, or PSR] of fluorinated α-alkyl *β*-keto carboxylic esters followed by enantioselective biocatalytic resolution in the presence of *penicillin acylase*. More recently, our group published an effective and highly diastereoselective route to enantiopure syn-α-alkyl-*γ*-fluorinated *β*-amino acid derivatives based on a chemo- and diastereoselective reduction of chiral fluorinated *β*-enamino esters derived from (−)-8-phenylmenthol.[11]

Scheme 1



In connection with our ongoing investigations into the development of new routes to the synthesis of organofluorine nitrogen-containing compounds,[12] and on the basis of our previous experience in the synthesis of α-alkyl *β*-amino acid derivatives,[11] we report here a highly diastereo- and enantioselective approach to fluorinated *syn*-α-alkyl *γ*-amino alcohols by means of an indirect Mannich-type reaction of fluorinated aldimines and aliphatic aldehydes catalyzed by proline (Scheme 2).[13]

Scheme 2



We first decided to explore the feasibility of using fluorinated aldehydes as substrates for proline catalysis of three-component, one-pot asymmetric Mannich-type reactions. Since these compounds lack enolizable hydrogens, they do not undergo self-aldol condensations, making their behavior similar to that of aromatic aldehydes.[4] However, the results from our first reaction, which involved propanal, *p*-anisidine, and trifluoroacetaldehyde ethyl hemiacetal at −20 °C in *N*-methylpyrrolidone (NMP) as a solvent and in the presence of L-proline (20 mol %) as a catalyst, followed by $NaBH_4$ reduction of the initially formed *β*-amino aldehyde,[14] were disappointing, as the reaction did not afford the desired fluorinated *γ*-amino alcohol. Instead, we were only able to isolate byproducts corresponding to the self-Mannich reaction of propanal.[4e]

This negative result prompted us to modify our strategy. Since fluorinated aldehydes are stable as hydrates or hemiacetals, losing their characteristic reactivity in those forms, we decided to try an indirect version of the condensation described above, this time using a preformed fluorinated aldimine **1**. Indeed, when fluorinated aldimines **1** and propanal were initially reacted in the same conditions as those used by Hayashi and co-workers[4f] [NMP as a solvent at −20 °C in the presence of L-proline (20 mol %)], followed by the reduction of the amino aldehyde with $NaBH_4$ in MeOH at 0 °C, the desired *syn*-*γ*-amino alcohol **2** was obtained, albeit in only 17% yield, with a large quantity of starting material left unreacted.

We then attempted to optimize the reaction conditions in order to improve the chemical yield. Thus, when the reaction

(5) (a) Hajos, Z. G.; Parrish, D. R. *Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds*. German Patent DE 2102623, July 29, 1971. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497.

(6) (a) *Organo-Fluorine Compounds* in *Houben-Weyl Methods of Organic Chemistry*, Workbench Edition E10a−c; Georg Thieme Verlag: Sttutgart, 2000. (b) *Fluorine-Containing Amino Acids: Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, UK, 1995.

(7) The importance of organofluorinated compounds, and especially of their synthesis in chiral form, has been described in the very recent work of McMillan, Jørgensen, Barbas III, and Enders. See: (a) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826−8828. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjœrsgaard, A.; Jørgensen, R. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3707−3706. (c) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706−3710. (d) Enders, D.; Hüttl, M. R. *Synlett* **2005**, 991−993.

(8) Reviews: (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3−11.

(9) For the racemic synthesis of α-alkyl *β*-(fluoroalkyl) *β*-amino acids, see: (a) Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302−2312. (b) Takaya, J.; Kagoshima, H.; Akiyama, R. *Org. Lett.* **2000**, *2*, 1577−1579. (c) Sergeeva, N. N.; Golubev, A. S.; Burger, K. *Synthesis* **2001**, 281−285.

(10) Soloshonok, V.; Soloshonok, I.; Kukhar, V. P.; Svedas, V. K. *J. Org. Chem.* **1998**, *63*, 1878−1884.

(11) (a) Fustero, S.; Pina, B.; García de la Torre, M.; Navarro, A.; Arellano, C. R.; Simón, A. *Org. Lett.* **1999**, *1*, 977−980. (b) Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Arellano, C. R.; Simón, A. *J. Org. Chem.* **2002**, *67*, 4667−4679.

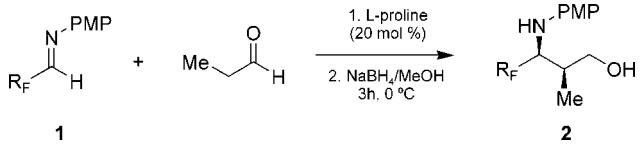
(12) (a) Fustero, S.; Piera, J.; Sanz-Cervera, J. F.; Catalan, S.; Ramirez de Arellano, C. *Org. Lett.* **2004**, *6*, 1417−1420. (b) Fustero, S.; Bartolome, A.; Sanz-Cervera, J. F.; Sanchez-Rosello, M.; Soler, J. G.; Ramirez de Arellano, C.; Fuentes, A. S. *Org. Lett.* **2003**, *5*, 2523−2526. (c) Fustero, S.; Salavert, E.; Sanz-Cervera, J. F.; Piera, J.; Asensio, A. *Chem. Commun.* **2003**, 844−845. (d) Fustero, S.; Soler, J. G.; Bartolome, A.; Rosello, M. S. *Org. Lett.* **2003**, *5*, 2707−2710. (e) Sani, M.; Bruché, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060−2063.

(13) Although proline has been recently shown to catalyze the addition of acetone to a few fluorinated aldimines, the yields obtained were generally low and the method was restricted to the use of acetone as both solvent and reagent; other ketones failed to react under these conditions. See: Funabiki, K.; Nagamori, M.; Goushi, S.; Matsui, M. *Chem. Commun.* **2004**, 1928−1929.

(14) Córdova, A. *Synlett* **2003**, 1651−1654. See also refs 4f and 4j.

temperature was allowed to increase stepwise from −20 to 0 °C, significantly better yields were obtained (entries 1−4, Table 1). On the other hand, when the reaction was performed at room temperature, only ill-defined products were formed and no defined compound could be isolated from the crude reaction mixture. Although other reaction conditions involving different times, amounts of aldehyde, solvents (DMF, DMSO, and DMPU), temperatures, and proportions of catalyst were tried, they did not provide better results.[15]

Table 1. Preparation of Fluorinated γ-Amino Alcohols **2** from Propanal and Aldimines **1**



1 **2**

entry[a]	R_F	time (days)	**2**	yield[b] (%)	syn/anti[c]	ee (%)
1[d]	CF_3	6.5	**2a**	45	96:4	99[e,f]
2	CF_3	3	**2a**	41	96:4	99[e,f]
3	CF_3	6.5	**2a**	50	96:4	99[e,f]
4[g]	CF_3	6.5	***ent*-2a**	48	96:4	99[e,f]
5[h]	CF_3	3	**2a**	12	96:4	99[e,f]
6	C_2F_5	3	**2b**	32	97:3	99[e]
7	$ClCF_2$	3	**2c**	35	96:4	99[e,f]
8	$PhCF_2$	3	**2d**	40	95:5	99[e]

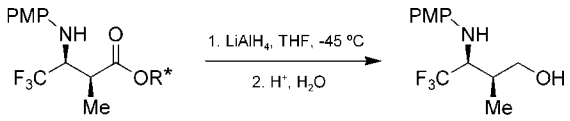
[a] Reaction conditions: 1 M solution of **1** in NMP, 2 equiv of propanal, 20 mol % L-proline, −20 to 0 °C. [b] Isolated yield. [c] Determined by means of ^{19}F NMR. [d] Performed with 5 equiv of propanal. [e] Determined by means of chiral HPLC (Chiracel OD column, hexane/2-propanol 95:5 eluent, flow rate 1 mL/min). [f] Determined by means of chiral GC-MS (Ciclodexβ column, 3 min at 130 °C, then 1 °C/min increase to 210 °C). [g] D-Proline instead of L-proline was used. [h] Performed with 100 mol % L-proline.

Interestingly, increasing the catalyst proportion to 100 mol % did not improve the yield, but actually produced lower yields compared to the same reaction in which only 20 mol % L-proline was used (entries 5 and 3, respectively, Table 1). Although we also tried three other proline-related organocatalysts under similar conditions,[16] they did not provide the desired fluorinated γ-amino alcohols; the only isolable reaction product was the amine derived from imine reduction.

Our next objective was to examine the scope of this methodology. We thus tried the reaction with several other fluorinated aldimines [R_F = C_2F_5 (**1b**), CF_2Cl (**1c**), $PhCF_2$ (**1d**)], successfully demonstrating its efficacy in indirect Mannich-type reactions. Although the reaction yields here were not substantially higher than in our earlier attempts, we found the selectivity in the formation of reaction products to be outstanding in all cases (syn/anti dr > 19:1, ee 99%, entries 6−8, Table 1). Additionally, between 10 and 20% of the amine derived from the reduction of unreacted imine was consistently isolated in all cases.

To determine the absolute configuration of the condensation products, γ-amino alcohols **2** were isolated and purified by means of flash chromatography. Their structures were corroborated through spectroscopic analyses (^1H, ^{19}F, ^{13}C NMR) and compared with previous results.[17] A suitable single crystal of **2c** was thus obtained, and its relative and absolute configuration was assigned as (2*S*,3*S*).[18] The absolute configuration of compounds **2** was confirmed by means of chemical correlation with the corresponding γ-fluorinated β-amino ester of (−)-8-phenylmenthol **3**,[11b] which was reduced with $LiAlH_4$ at low temperature (−45 °C) followed by aqueous treatment to yield a compound identical in all respects to (2*S*,3*S*)-**2a** (Scheme 3).

Scheme 3



3, R* = (-)-8-phenylmenthyl (2*S*, 3*S*)-**2a**

The stereochemical outcome of the reaction can be easily understood by taking into account the model proposed in the case of nonfluorinated aldimines (Figure 1).[4,19]

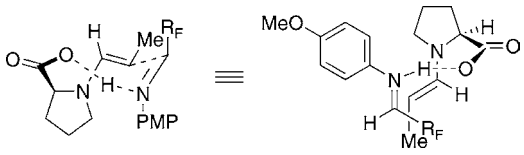
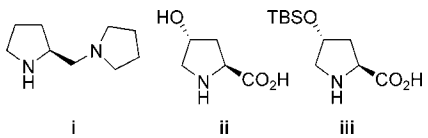


Figure 1.

Finally, to conclude our investigation of the scope of this reaction, we decided to introduce diversity into the α-alkyl chain through the reaction of trifluoroacetaldimine **1a** with different aldehydes. When the reaction was carried out under the same optimized conditions as for propanal (see Table 2) with other aldehydes such as butanal, 3-phenylbutanal, and 4-pentenal, the corresponding amino alcohols **2e**−**g** were successfully isolated with high diastereoselectivities (syn/

(15) It is worth noting that the alternative preparation of compounds **2** through a Mannich-type addition of lithium ester enolates to trifluoromethylimines **1** led only to a racemic mixture of β-amino esters in moderate yield (38%) and with low diastereoselectivity (de 28%). See ref 11b.

(16) Catalysts **i**, **ii** (both commercially available), and **iii** (Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435−1439) failed to catalyze the cross-Mannich reaction of **1a** with propanal.



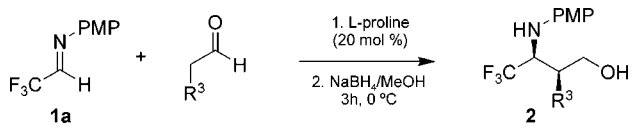
i ii iii

(17) All the new compounds that appear in Tables 1 and 2 were synthesized in racemic form as described in ref 11. For details, see Supporting Information.

(18) Full details of the X-ray structure of *syn*-(2*S*,3*S*)-**2c** will be published in a full account of this work.

(19) Houk, K. N.; Bahmanyar, S. *Org. Lett.* **2003**, *5*, 1249−1251.

Table 2. Preparation of Fluorinated γ-Amino Alcohols **2** from Aldimines **1** and Other Aldehydes



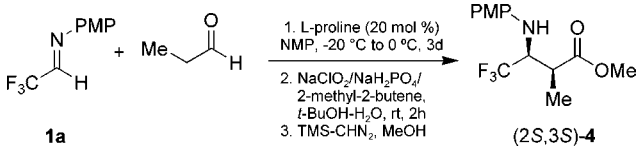
entry[a]	R^3	**2**	yield (%)[b]	syn/anti[c]	ee (%)
1	Me	**2a**	41	96:4	99[d,e]
2	Et	**2e**	31	>99:1	99[e]
3	$PhCH_2$	**2f**	35	>99:1	99[d]
4	$CH_2{=}CHCH_2$	**2g**	40	96:4	99[d]

[a] Reaction conditions: 1 M solution of **1a** in NMP, 2 equiv of propanal, 20 mol % L-proline, −20 °C for 1 day, −10 °C for 1 day, 0 °C for 1 day. [b] Isolated yield. [c] Determined by means of ^{19}F NMR. [d] Determined by means of chiral HPLC (Chiracel OD column, hexane/2-propanol 95:5 eluent, flow rate 1 mL/min). [e] Determined by means of chiral GC-MS (Ciclodexβ column, 3 min at 130 °C, then 1 °C/min increase to 210 °C).

anti dr > 24:1), excellent enantioselectivities (99% ee), and moderate yields after $NaBH_4$ reduction and flash chromatography purification of the crude reaction mixtures.[20]

We also decided to check how easy it would be to obtain a fluorinated β-amino acid derivative instead of the corresponding γ-amino alcohol. Thus, imine **1a** was condensed with propanal in the same conditions as in entry 1, Table 2, to yield a crude Mannich condensation product, which was first dissolved in aqueous *t*-BuOH and then treated with $NaClO_2$, 2-methyl-2-butene, and NaH_2PO_4 to yield the crude fluorinated β-amino acid after standard aqueous workup (Scheme 4).[21] This acid, in turn, was dissolved in MeOH

Scheme 4. Preparation of the Fluorinated β-Amino Ester *syn*-**4**



and treated with TMS-diazomethane to give crude ester **4**, which was present in a syn/anti dr 97:3. Flash chromatography purification allowed for the isolation of pure *syn*-**4** in 47% yield. This compound showed an ee of 98% in chiral HPLC analysis. In conclusion, our method can be used to obtain syn-γ-fluorinated, α-alkyl β-amino esters easily and with high diastereo- and enantioselectivities.

The results for our proline organocatalyzed cross-Mannich reactions between aliphatic aldehydes and fluorinated imines cannot be directly compared with those for nonfluorinated aliphatic imines, because they have not been described for the reasons discussed above. When compared with similar reactions in which imines from aromatic aldehydes were used, both higher diastereo- and enantioselectivities are observed in our case, albeit with lower yields.[22] Finally, the stereochemical outcome is the same: in both cases, the condensation is very predominantly syn, and the enantiomer with the same configuration is obtained when L-proline is used as a catalyst.

In summary, we have developed the most direct and convenient strategy to date for the synthesis of chiral, nonracemic acyclic fluorinated α-alkyl β-amino acid derivatives. Our approach involves a convenient Mannich condensation of fluorinated aldimines with aliphatic aldehydes in the presence of L- or D-proline, followed by reduction of the crude reaction mixture with $NaBH_4$. In this way, γ-fluorinated β-amino alcohols are obtained with high diastereo- and enantioselectivity. This synthetic approach greatly improves upon previous results[11] and allows for the introduction of diversity not only into the γ-fluoroalkyl chain but also into the β-alkyl group. Although the reaction yields are only moderate, we believe that the ease of preparation, along with the immediate availability and low cost of the starting products, makes this reaction the procedure of choice for the preparation of chiral, nonracemic fluorinated γ-amino alcohols.

Acknowledgment. We gratefully acknowledge financial support from the Ministerio de Educación y Ciencia of Spain (Proyecto BQU2003-01610) and the Generalitat Valenciana (GRUPOS03/193). D.J., M.S.-R., and E.E. thank the Generalitat Valenciana of Spain for FPI predoctoral fellowships.

Supporting Information Available: Spectroscopic and physical data and experimental procedure for the preparation of compounds **2a**−**g** and *syn*-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) To identify the secondary products formed, we analyzed by means of HPLC-MS methods the crude reaction mixture resulting from the condensation between aldimine **1a** and 3-butenal in the same conditions as described above. The results for this analysis appear in Supporting Information.

(21) Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507−2510.

(22) Tanaka, F.; Barbas, C. F., III. In *Enantioselective Synthesis of β-Amino Acids;* Juaristi, E., Soloshonok, V., Eds.; Wiley-Interscience: New York, 2005; Chapter 9, pp 195−214.