Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 761–764

# Convenient enantioselective synthesis of β-trifluoromethyl-β-aminoketones by organocatalytic asymmetric Mannich reaction of aryl trifluoromethyl ketimines with acetone

Volodymyr A. Sukach, Nataliya M. Golovach, Volodymyr V. Pirozhenko, Eduard B. Rusanov and Mykhaylo V. Vovk*

*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmans'ka 5, Kyiv 02094, Ukraine*

Received 7 February 2008; accepted 27 February 2008

**Abstract**—The L-proline-catalyzed asymmetric Mannich reaction has been performed between aryl trifluoromethyl ketimines and acetone to provide, for the first time, chiral β-aryl-β-trifluoromethyl-β-aminoketones in high yields and with 74–92% enantiomeric excesses.


## 1. Introduction

Modern organic chemistry calls for the development of efficient enantioselective synthetic routes to biologically active compounds. This challenge has arisen from the progressively higher requirements on the enantiomeric purity of the known and newly developed therapeutic agents, as well as the building blocks for preparing them.[1] Among the corresponding precursors, a prominent place is occupied by β-aminoketone derivatives, including some commonly used pharmaceuticals with a broad activity spectrum and the recently discovered biologically important species.[2,3]

In this context, there has been considerable recent interest in the preparation of enantiomerically pure β-aminoketone derivatives. Various synthetic routes to them have been found, the most widespread of which is based on the Mannich reaction between CH-acidic carbonyl compounds and imines or their precursors.[2,4] Catalytic enantioselective approaches to conversions of this kind are currently under active research.[5] It is notable that most of these recent papers address organocatalytic versions of the asymmetric Mannich reaction,[6] thus indicating the increasingly important role of this line of research.

Particularly promising are the new enantioselective synthetic strategies affording fluorine-substituted β-aminoketones, as fluorine atoms are known to substantially affect physical, chemical and biological properties of compounds.[7] β-Aminocarbonyl compounds containing the geminal amino and fluoroalkyl groups are scarcely described in the literature, and the reports on asymmetric access to them are scarce.[8,9] For instance, the groups of Kitazume et al. and Brigaut et al. succeeded in applying the auxiliary-based approach,[9a–c] whereas Fustero et al. and Funabiki et al.[9d,e] conducted the organocatalytic Mannich reaction of *N*-*p*-metoxyphenyl polyfluoroalkyl aldimines with aliphatic aldehydes or acetone used as nucleophilic components. As found, such conversions are efficiently catalyzed by L-proline but the yields of the target products are usually moderate (no more than 55%) due to side reactions. The above-mentioned studies involved thoroughly optimized reaction conditions; also, elimination of the protecting *N*-*p*-methoxyphenyl group was necessary in order to further react the resulting β-amino-substituted aldehydes and ketones.

To obtain new chiral fluorine-containing β-aminoketone derivatives, we have studied the reactions of aryl trifluoromethyl ketimines **1**[10] with acetone in the presence of L-proline. To the best of our knowledge, ketimines have not been hitherto applied in organocatalyst-mediated asymmetric Mannich reactions because of their low electrophilicity and increased steric hindrance to nucleophilic attack on the C=N bond. It is, therefore, intriguing theoretically to determine the ketimine behaviour in these conversions and to gain an insight into their stereochemistry. Compounds **1**

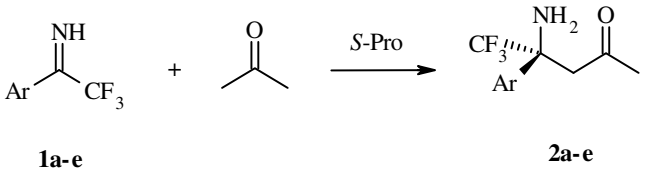
* Corresponding author. Fax: +380 44 5732643; e-mail: mvovk@i.com.ua

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.02.023

bear the imino group activated by the neighbouring trifluoromethyl substituent and thus are likely to react with acetone in the presence of the L-proline catalyst. The bare nitrogen atom in **1** may additionally influence the reaction course and stereoselectivity, and also dictate the configuration of the resulting stereogenic centre, as is typical in the reactions of this kind.[11]

## 2. Results and discussion

As found, ketimine **1a** reacts with 5 equiv excess of acetone in the presence of 10 mol % L-proline in DMSO at room temperature (18 °C) within 3 days to furnish 4-amino-5,5,5-trifluoro-4-phenylpentan-2-one **2a** with a 100% $^{19}F$ NMR-monitored conversion and in 81% isolated yield (see Scheme 1 and Table 1). An essentially quantitative yield of the reaction is somewhat reduced as a result of the separation of the raw product (by a simple non-chromatographic procedure) from the mesityl oxide impurity formed in the acetone self-condensation.




**1a-e** **2a-e**

**Scheme 1.** Preparation of β-aminoketones **2a–e**.

The enantiomeric purity of the synthesized aminoketone **2a** expressed as enantiomeric excess (ee) is equal to 80%; it has been determined by $^{19}F$ NMR spectroscopy using the chiral lanthanide shift reagent (LSR), *tris*(3-heptafluorobutyryl-*d*-camphorato)europium (III).[12] A complex of compound **2a** with the chiral LSR gives rise to a poorly diastereomerically resolved $^{1}H$ NMR spectrum, but its $^{19}F$ resonances from the trifluoromethyl group are clearly distinct for the two diastereomers thus allowing signal integration and hence straightforward and fairly accurate determination of the reaction enantioselectivity (see Fig. 1).

DMSO appears to be the optimal solvent for the reaction concerned, but similar results have also been obtained in DMF. If conducted in pure acetone at room temperature,

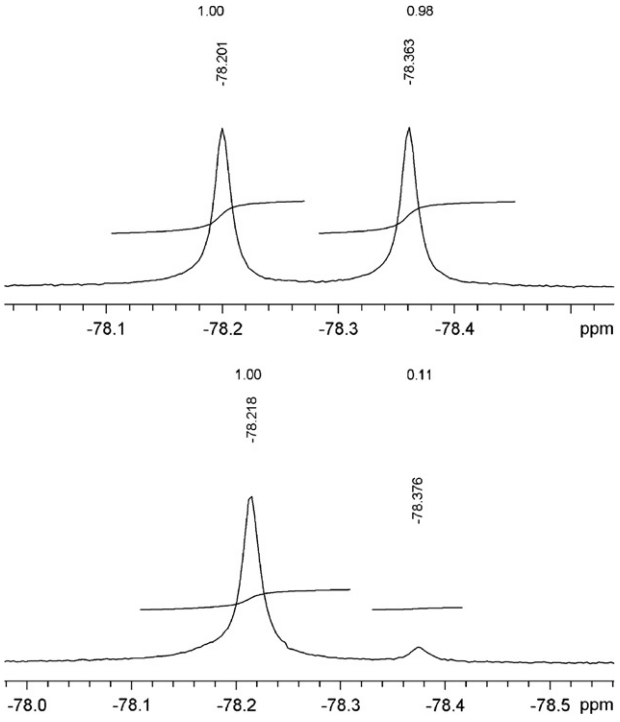



**Figure 1.** $^{19}F$ NMR spectra of the racemic (upper) and enantiomerically enriched (lower) compound **2a** in the presence of 100 mol % of *tris*(3-heptafluorobutyryl-*d*-camphorato)europium (III).

the addition reaction between imine **1a** and acetone is too slow being only 42% complete within 10 days; nevertheless, the resulting product has a high degree of enantiomeric purity (82%).

The reactions run in acetonitrile or dioxane under the same conditions yield only trace amounts of product **2a**. In boiling dichloromethane, the imine conversion does not exceed 44% but the enantioselectivity remains practically unchanged. Using more catalyst (20 mol % and over) had no significant effect on the reaction rate.

The same strategy extended to the reactions of other ketimines **1b–e** resulted in a number of chiral β-aminoketones **2b–e** prepared in excellent yields and with high ee values (see Table 1).[13] It has been found that the reaction rate and enantioselectivity are nearly insensitive to the nature

**Table 1.** Compound structures, reaction conditions, product yields and enantiomeric excesses for the **1→2** conversion

| Compounds **1**, **2** | Ar | Solvent | Time (h) | Temp (°C) | Conversion[a] (%) | Isolated yield (%) | ee[b] (%) |
|---|---|---|---|---|---|---|---|
| **a** | Ph | DMSO | 72 | 20 | 100 | 86 | 80 |
| **a** | Ph | DMF | 72 | 20 | 100 | 77 | 78 |
| **a** | Ph | $CH_2Cl_2$ | 48 | 40 | 44 | 25 | 82 |
| **a** | Ph | $CH_3CN$ or dioxane | 120 | 20 | <5 | — | — |
| **a** | Ph | Acetone | 240 | 20 | 42 | 23 | 82 |
| **b** | 3-$CH_3C_6H_4$ | DMSO | 72 | 20 | 100 | 80 | 92 |
| **c** | 4-$CH_3C_6H_4$ | DMSO | 72 | 20 | 100 | 82 | 74 |
| **d** | 4-$FC_6H_4$ | DMSO | 72 | 20 | 100 | 82 | 84 |
| **e** | 4-$CH_3OC_6H_4$ | DMSO | 72 | 20 | 100 | 75 | 78 |

[a] Determined by $^{19}F$ NMR spectroscopy.
[b] Determined by $^{19}F$ NMR spectroscopy using the chiral lanthanide shift reagent.

of substituents on the phenyl ring of ketimines except for the *m*-tolyl group, which provides the 92% enantiomeric purity of the corresponding product. Aminoketones **2** were isolated as stable colourless oils with the exception of compound **2c**, a solid (mp 67–68 °C) obtainable in an enantiomerically pure form by recrystallization from a 3:1 benzene–hexane mixture.

Although the trifluoromethyl substituent reduces the nucleophilicity of the geminal amino group, the latter can be acylated with acyl chlorides and carbamoylated with aryl isocyanates. Acylation of compound **2a** with *p*-bromobenzoyl chloride followed by recrystallization from a 3:1 benzene–hexane mixture afforded the corresponding optically pure *p*-bromobenzamide. Its absolute configuration was determined by X-ray structural analysis of a suitable single crystal (see Fig. 2).[14] As the nature of an aryl substituent in ketimines does not affect the direction of the nucleophilic attack on their C=N bond, one can assume that the *S*-configuration of the asymmetric centre is an inherent feature of all aminoketones **2**.

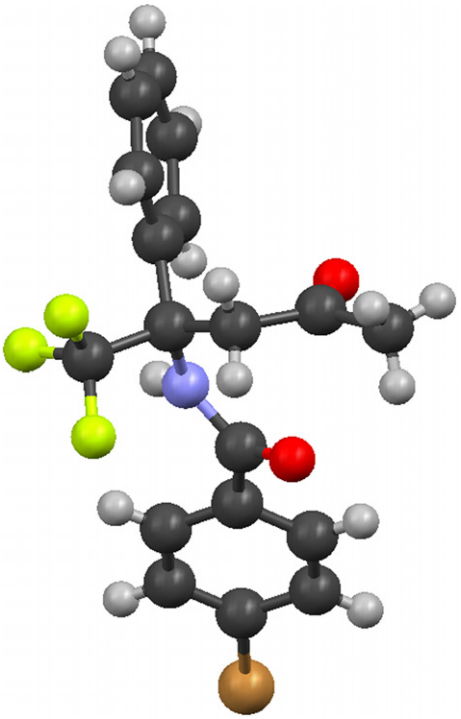


**Figure 2.** Molecular structure of 4-bromo-*N*-[3-oxo-1-phenyl-1-(trifluoromethyl)butyl] benzamide.

Since the literature lacks theoretically calculated transition state energies for L-proline-catalyzed asymmetric Mannich reactions of ketimines, we studied the data on absolute stereochemistry so as to suggest some plausible stereochemical patterns of the reaction between compounds **1** and acetone. According to the previously performed quantum chemical calculations for the related organocatalytic reactions between aldimines and ketones,[11] the most energetically favourable transition state model implies that the aldimine is in the more stable *E*-configuration, whereas the enamine formed from the acetone and the catalyst adopts the anti-conformation of the double bond relative to the carboxyl group of L-proline. With such relative positions of the molecular moieties involved in the reaction, the bulkiest substituent at the C=N bond (therefore this is an aryl substituent) is oriented pseudoaxially (see model A shown in Fig. 3).

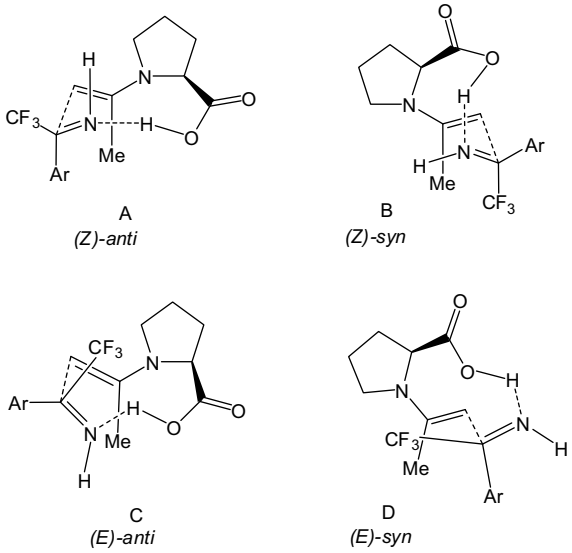
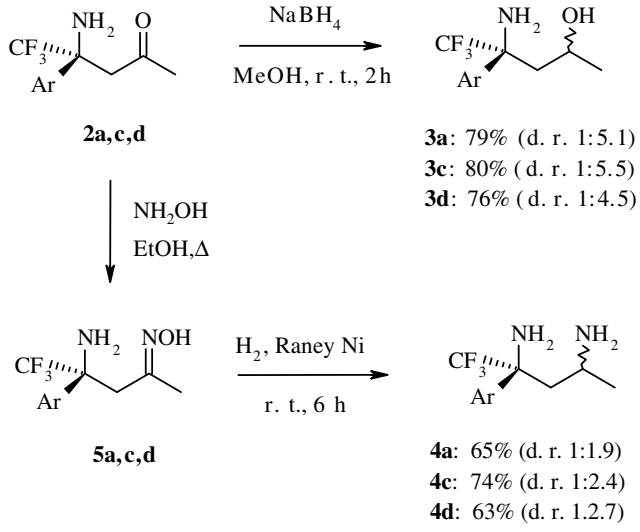



**Figure 3.** Possible stereochemical patterns of the L-proline-catalyzed reaction between ketimines **1** and acetone.

However, one cannot completely rule out transition state models B, C and D because, on the one hand, the *E*- and *Z*-forms of ketimines **1** are not significantly different in energy (as evidenced by their comparable contributions to the equilibrium mixture existing in a DMSO solution) while, on the other hand, the imino hydrogen atom is much less sterically demanding than either substituent at the carbon end of the double bond.

Taking advantage of the carbonyl group of compounds **2**, we have derivatized them to obtain chiral trifluoromethyl-substituted 1,3-aminoalcohols **3a**,**c**,**d** and 1,3-diamines




**Scheme 2.** Transformations of β-aminoketones **2a**,**c**,**d**.

**4a**,**c**,**d**. The former resulted from the reduction of aminoketones **2a**,**c**,**d** with sodium borohydride while the latter were produced by treating the aminoketones with hydroxylamine followed by hydrogenation of the corresponding oximes **5a**,**c**,**d** with hydrogen in the presence of Raney nickel (see Scheme 2). These reactions exhibited high yields but low diastereoselectivity, with a diastereomer ratio of 1:5.5 for compounds **3** and no more than 1:2.7 for compounds **4**.

## 3. Conclusion

Based on the L-proline-catalyzed asymmetric Mannich reaction between aryl trifluoromethyl ketimines and acetone, we have developed a facile and efficient synthetic access to chiral β-aryl-β-trifluoromethyl-β-aminoketones obtained in high yields and with 74–92% enantiomeric purity. The resulting aminoketones were derivatized to give trifluoromethyl-substituted 1,3-aminoalcohols and 1,3-diamines.

## References


1. Rouhi, A. M. *C&E News* **2004**, *82*, 47; Stinson, S. C. *C&E News* **2000**, *78*, 55.
2. (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044; (b) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102; (c) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895.
3. (a) Simplicio, A. L.; Clancy, J. M.; Gilmer, F. *Int. J. Pharm.* **2007**, *336*, 208; (b) Joshi, S.; Manikpuri, A. D.; Tiwary, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 645; (c) Dimmock, J. R.; Kandepu, N. M.; Das, U.; Zello, G. A.; Nienaber, K. H. *Pharmazie* **2004**, *59*, 502.
4. Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 647.
5. (a) Lou, S.; Dai, P.; Schaus, S. E. *J. Org. Chem.* **2007**, *72*, 9998; (b) Yang, J. W.; Stadler, M.; List, B. *Nat. Protoc.* **2007**, *2*, 1937; (c) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054; (d) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 9588; (e) Hayashi, Y.; Urushima, T.; Tsuboi, W.; Shoji, M. *Nat. Protoc.* **2007**, *2*, 113; (f) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900; (g) Cheng, L.; Wu, X.; Lu, Y. *Org. Biomol. Chem.* **2007**, *5*, 1018; (h) Guo, Q. X.; Liu, H.; Guo, C.; Luo, S. W.; Gu, Y.; Gong, L. Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790; (i) Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 1417; (j) Song, J.; Shih, H. W.; Deng, L. *Org. Lett.* **2007**, *9*, 603; (k) Ramasastry, S. S.; Zhang, H.; Tanaka, F.; Barbas, C. F. 3rd. *J. Am. Chem. Soc.* **2007**, *129*, 288; (l) Saruhashi, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11232; (m) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F. 3rd. *J. Am. Chem. Soc.* **2006**, *128*, 9630.
6. For a recent reviews on the organocatalytic asymmetric Mannich reaction, see: (a) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29; (b) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797.
7. (a) Hiyama, T. In Yamamoto, H., Ed.; Organofluorine Compounds, Chemistry and Applications; Springer: Berlin-Heidelberg, Germany, 2000; (b) Special issue on Fluorine in the Life Sciences, *ChemBioChem* **2004**, *5*, 557; (c) Seebach, D. *Angew. Chem., Int. Ed.* **1990**, *29*, 1320; (d) Duewel, H. S.; Daub, E.; Robinson, V.; Honek, J. F. *Biochemistry* **2001**, *40*, 13167.
8. For racemic fluorinated aminocarbonyl compounds, see: (a) Jeong, I. H.; Jeon, S. L.; Kim, M. S.; Kim, B. T. *J. Fluorine Chem.* **2004**, *125*, 1629; (b) Colantoni, D.; Fioravanti, S.; Pelacani, L.; Tardella, P. A. *J. Org. Chem.* **2005**, *70*, 9648; (c) Sosnovskikh, V. Y.; Barabanov, M. A.; Usachev, B. I. *J. Org. Chem.* **2004**, *69*, 8297; (d) Sergeeva, N. N.; Golubev, A. S.; Hennig, L.; Burger, K. *Synthesis* **2002**, *17*, 2579; (e) Blond, G.; Billard, T.; Langois, B. R. *J. Org. Chem.* **2001**, *66*, 4826; (f) Large, S.; Roques, N.; Langois, B. R. *J. Org. Chem.* **2000**, *65*, 8848; (g) Takaya, J.; Kagoshima, H.; Akiyama, T. *Org. Lett.* **2000**, *2*, 1577; (h) Cyrener, J.; Burger, K. *Monatsh. Chem.* **1994**, *125*, 1279; (i) Takana, K.; Ishiguro, Y.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 661; (j) Ogoshi, H.; Mizushima, H.; Toi, H.; Aogama, Y. *J. Org. Chem.* **1986**, *51*, 2366; (k) Matsumura, Y.; Tomita, T.; Sudoh, M.; Kise, N. *Tetrahedron Lett.* **1994**, *35*, 1271.
9. For chiral fluorinated aminocarbonyl compounds, see: (a) Kitazume, T.; Shibano, H. *J. Fluorine Chem.* **1997**, *82*, 185; (b) Kitazume, T.; Murata, K.; Okabe, A.; Takanashi, Y.; Yamazaki, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1029; (c) Huguenot, F.; Brigaud, T. J. *Org. Chem.* **2006**, *71*, 2159; (d) Fustero, S.; Jiminez, D.; Sanz-Cervera, J. F.; Sanchez-Rosello, M.; Esteban, E.; Simon-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433; (e) Funabiki, K.; Nagamori, M.; Goushi, S.; Matsui, M. *Chem. Commun.* **2004**, 1928.
10. (a) Fetyukhin, V. N.; Koretskii, A. S.; Gorbatenko, V. I.; Samarai, L. I. *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 244; (b) Koos, M.; Mosher, H. S. *Tetrahedron* **1993**, *49*, 1541.
11. Bahmaniar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249.
12. Talvitie, A.; Mannila, E.; Kral, A. *Acta Chem. Scand.* **1996**, *50*, 1143.
13. To a solution of aryl trifluoromethyl ketimine (0.036 mol) in DMSO (50 ml) and acetone (20 ml), L-proline (0.42 g, 10 mol %) was added. The reaction mixture was stirred for 72 h at room temperature and filtered, followed by dilution of the filtrate with water (50 ml) and extraction with dichloromethane (3 × 15 ml). After washing the organic layer with 15% hydrochloric acid (30 ml), the aqueous layer was separated and neutralized with a concentrated solution of potassium carbonate. The oily product was extracted with dichloromethane (2 × 15 ml), dried over $Na_2SO_4$, filtered, and evaporated. (*S*)-(+)-4-Amino-4-phenyl-5,5,5-trifluoro-2-pentanone **2a**. Yield 86%, oily substance, $n_D^{20} = 1.4848$. $^1$H NMR ($CDCl_3$/TMS), $\delta$ (ppm): 2.05 s (3H, $CH_3$), 2.33 s (2H, $NH_2$), 3.04 d (1H, $J = 27$ Hz, $CH_2$), 3.42 d (1H, $J = 27$ Hz, $CH_2$), 7.26–7.39 m (3H, Ar), 7.54 d (2H, $J = 15$ Hz, Ar). $^{19}$F NMR ($CDCl_3$/$CFCl_3$), $\delta$ (ppm): −80.29. $[\alpha]_D^{20} = +26.6$ (*c* 1.8, MeOH).
14. All crystallographic measurements were performed at room temperature on a Bruker Smart Apex II diffractometer operating in the $\omega$ and $\varphi$ scans mode. Flack parameter 0.050(19). Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the reference number CCDC 670156.