Pure Appl. Chem., Vol. 82, No. 3, pp. 669–677, 2010.
doi:10.1351/PAC-CON-09-09-07

Asymmetric tandem reactions: New synthetic strategies*

Santos Fustero[1,2,‡], María Sánchez-Roselló[2], and Carlos del Pozo[1]

[1]Department of Organic Chemistry, University of Valencia, E-46100 Burjassot, Spain; [2]Laboratory of Organic Molecules, Research Center "Principe Felipe", E-46012 Valencia, Spain

Abstract: The use of domino and multicomponent reactions in asymmetric synthesis is constantly increasing nowadays. This allows for the synthesis of complex molecules in a single synthetic sequence, usually with high atom economy. Herein, we report three examples of new asymmetric tandem reactions recently developed in our laboratories, giving rise to new families of enantiomerically enriched fluorinated and nonfluorinated heterocycles. Thus, 1,4-dihydropyridines (1,4-DHPs) bearing fluorinated substituents at C6 were assembled by means of a Hantzsch-type reaction; cyclic β-amino carbonyl derivatives were prepared using a cross-metathesis (CM)–intramolecular aza-Michael sequence; while fluorinated indolines were obtained, for the first time, in a tandem nucleophilic addition–intramolecular aromatic substitution.

Keywords: cyclic β-amino carbonyl compound; fluorinated β-amino acids; fluorinated dihydropyridine; fluorinated indolines; tandem reactions.

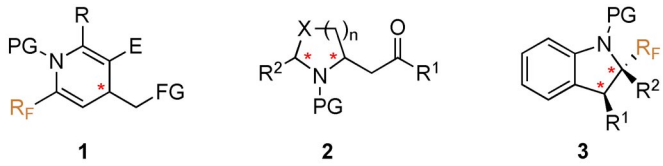
INTRODUCTION

The pursuit of new chemical transformations that provide shorter, less expensive and environmentally friendly synthetic routes is one of the main goals in modern organic chemistry. These requirements may be fulfilled by tandem processes, in which multiple reactions take place sequentially in one synthetic operation. On the other hand, the synthesis of optically active compounds plays a pivotal role in medicinal chemistry. Therefore, the interest in combining asymmetric processes with tandem reactions is obvious, since multiple stereogenic centers could be created in a single synthetic step [1].

In this paper, we present three asymmetric tandem processes that led to the formation of the different nitrogen heterocycles depicted in Fig. 1. The first one is related to the synthesis of enantiomerically pure fluorinated 1,4-dihydropyridines **1** through a *tandem intermolecular aza-Michael reaction-intramolecular Michael addition*. The second one deals with the preparation of cyclic β-amino carbonyl derivatives **2** through a *new tandem cross-metathesis (CM)–intramolecular aza-Michael process.* Finally, the last reaction involves a *nucleophilic addition followed by an aromatic nucleophilic substitution* which provides enantiomerically pure fluorinated indolines **3**. In addition, this strategy allowed for the preparation of new enantiomerically pure β-amino acid derivatives.

*Paper based on a presentation at the 9th International Conference on Heteroatom Chemistry (ICHAC-9), 30 June–4 July 2009, Oviedo, Spain. Other presentations are published in this issue, pp. 505–677.

‡Corresponding author



1 2 3

Fig. 1 Nitrogen heterocycles: 1,4-DHPs, cyclic β-amino carbonyl derivatives, and indolines.

ASYMMETRIC SYNTHESIS OF FLUORINATED 1,4-DIHYDROPYRIDINES 1

1,4-Dihydropyridines (1,4-DHPs) are privileged structures in medicinal chemistry displaying a wide range of biological activities, therefore constituting an important class of biologically active heterocycles [2]. Probably, the best known family of 1,4-DHPs are *calcium channel blockers*, compounds routinely used in the treatment of a variety of vascular disorders. The biological activity of these molecules depends, among other factors, on the absolute configuration of the C4-stereogenic center of chiral DHPs [3]. A classical example is shown in Fig. 2. Thus, whereas the *R*-enantiomer of Bay K 8644 behaves as calcium antagonist, the *S*-enantiomer induces the opposite effect. Despite the biological importance of these derivatives, a general method for their asymmetric synthesis still remains an important challenge.

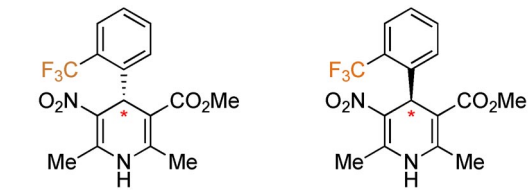
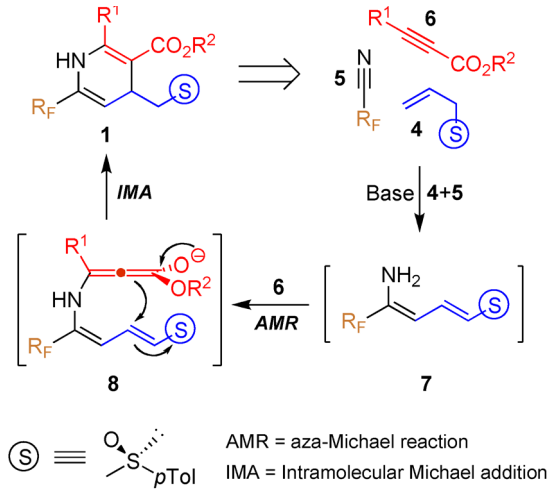


Fig. 2 Biologically active 1,4-DHPs.

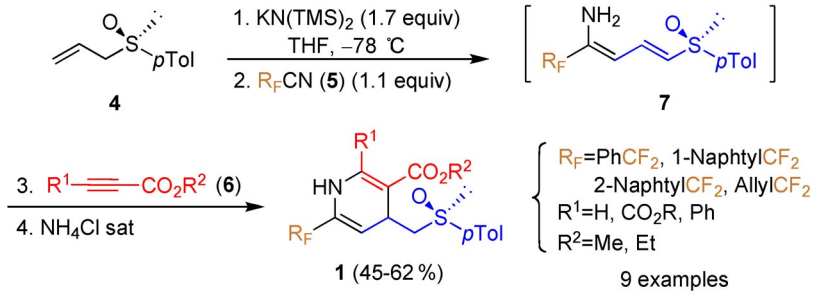
It is known that one of the most straightforward routes to the synthesis of 1,4-DHPs is the Hantzsch condensation, which was first developed in 1882 [4]. This process constitutes an emblematic example of a multicomponent reaction, allowing for the creation of the DHP-ring between an aldehyde, 2 equiv of β-keto esters, and a nitrogen donor such as ammonia or ammonium acetate. Herein, we report a closely related asymmetric Hantzsch transformation, using allylic sulfoxides **4**, fluorinated nitriles **5**, and alkyl propiolates **6** as the three components of the novel one-pot domino reaction outlined in Scheme 1. This methodology allowed for the preparation of a new family of enantiomerically pure fluorinated 1,4-DHPs **1**.

In an optimized procedure, the slow addition of fluorinated nitriles **5** to a solution of metalated (*R*)-allyl *p*-tolyl sulfoxide **4** in tetrahydrofuran (THF) at −78 °C generated β-enamino sulfoxides **7** in almost quantitative yields. This reaction took place in a complete regioselective fashion, affording exclusively the product arising from the reaction through the γ-position of the sulfoxide **4**. The subsequent addition of alkyl propiolates **6**, either in the same flask or after isolation of dienes **7**, triggered a tandem process involving an intermolecular aza-Michael reaction followed by an intramolecular Michael addition, which gave rise to DHPs **1** in moderate to good yields as single diastereoisomers (Scheme 2) [5].

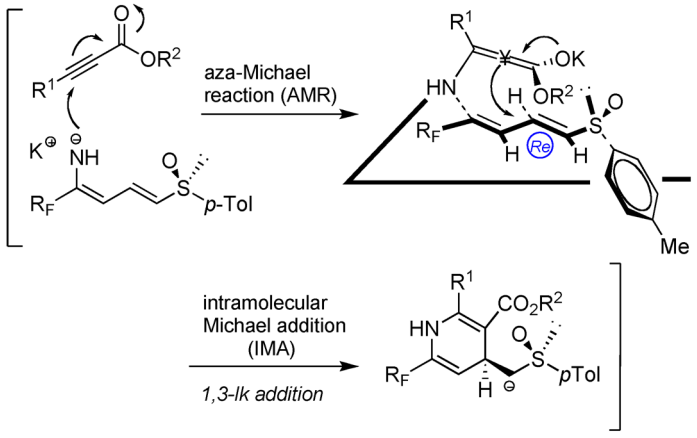
The stereochemical outcome of the overall process could be rationalized as depicted in Scheme 3. After the initial aza-Michael addition of the enaminic nitrogen to the propiolate, a potassium enolate



Scheme 1 Synthetic strategy for the preparation of fluorinated 1,4-DHPs.



Scheme 2 One-pot asymmetric synthesis of fluorinated 1,4-DHPs.



Scheme 3 Mechanism for the synthesis of fluorinated 1,4-DHPs.

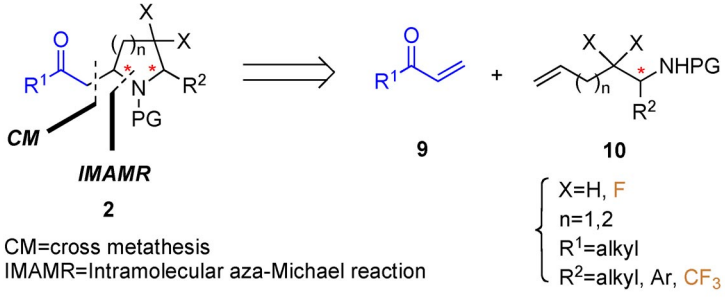
bearing an allene functionality would be formed. Assuming that the S-lone pair should be coplanar to the C=C bond, the most favored approach would be to the *Re* face in a 1,3-like-type addition, since the *p*-tolyl substituent would block the *Si* face.

PREPARATION OF CYCLIC β-AMINOCARBONYL DERIVATIVES 2

Conjugate addition of amines or their synthetic equivalents to α,β-unsaturated compounds, the so-called aza-Michael reaction, constitutes one of the most interesting methods for C–N bond formation. The resulting β-amino carbonyl derivatives are very important structures present in a large number of natural products and pharmaceutical ingredients [6]. The intramolecular version of this transformation is particularly relevant, since it allows for the direct generation of nitrogen-containing heterocycles.

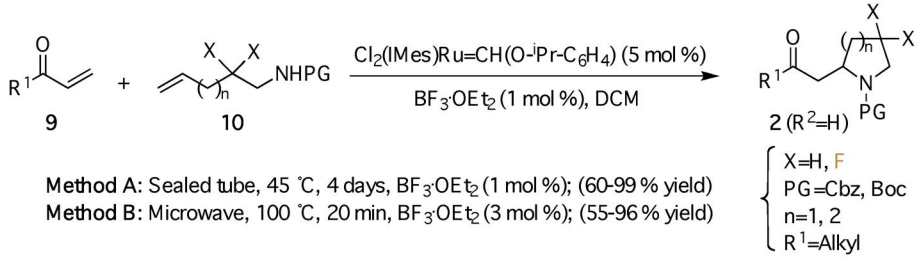
On the other hand, olefin metathesis is widely considered one of the most powerful synthetic tools in organic chemistry for the creation of C–C double bonds [7]. The development of robust ruthenium catalysts has had a tremendous impact on the use of the CM reaction, improving both the chemo- and stereoselectivity of this process. Additionally, the use of these ruthenium alkylidene complexes in tandem reactions has found a wide range of synthetic applications, thus extending their usefulness beyond olefin metathesis [8].

Herein, we discuss a new strategy for preparing different families of cyclic β-amino carbonyl derivatives. It involves the combination of a CM and an aza-Michael reaction in a tandem process, starting from carbamates **10** bearing a remote olefin functionality and α,β-unsaturated ketones **9** (Scheme 4). This tandem protocol might provide rapid access to nitrogen-protected β-homoproline and β-pipecolic acid derivatives in only one step.



Scheme 4 Tandem CM–intramolecular aza-Michael reaction.

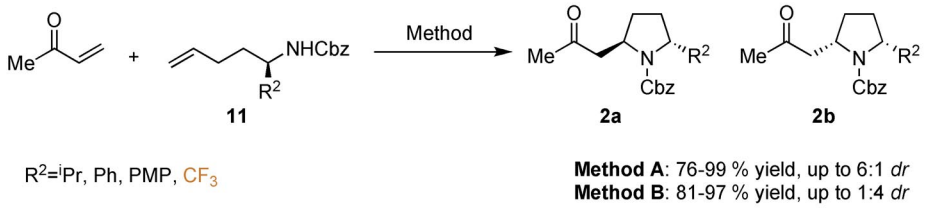
The synergistic effect of Hoveyda–Grubbs second-generation catalyst with boron trifluoride led us to identify suitable conditions to carry out the tandem transformation. Thus, the heating of a dichloromethane solution of α,β-unsaturaded ketones **9** and carbamates **10** in a sealed tube in the presence of 5 mol % of the ruthenium catalyst and 1 mol % of BF_3 for 4 days led to the formation of heterocycles **2** in good to excellent yields (Scheme 5, **Method A**). In order to reduce the reaction times needed for the tandem process, microwave irradiation was employed. To our delight, heating the previously described solution at 100 °C under microwave irradiation and increasing the load of the co-cata-



Scheme 5 Synthesis of cyclic β-amino carbonyl derivatives.

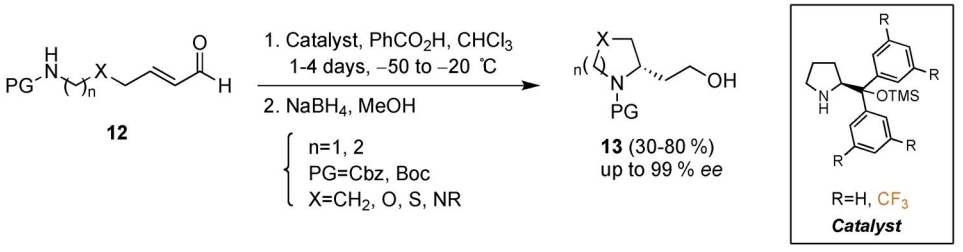
lyst to 3 mol % afforded, in only 20 min, comparable yields of compounds **2** to those obtained by regular heating (Scheme 5, **Method B**) [9].

After determining the optimum conditions for the tandem protocol, we directed our efforts toward the asymmetric version of the process. With this purpose, we prepared a set of chiral branched Cbz-protected amines **11** following known protocols. These were subjected to the optimized tandem conditions, using methyl vinyl ketone as the enone component. Both conventional and microwave heating gave the desired products **2** with comparable yields but a different stereochemical outcome. Whereas thermal conditions (45 °C; Method A) favored the *trans*-isomer **2a** (thermodynamic product), under microwave irradiation (100 °C; Method B) the *cis*-isomer **2b** (kinetic product) was the major product (Scheme 6) [9].



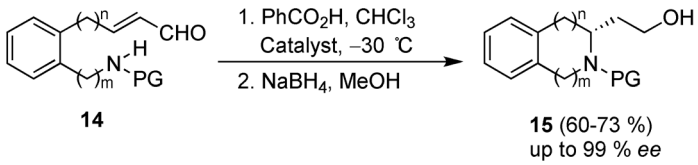
Scheme 6 Tandem protocol with enantioenriched amines.

All attempts performed to develop the catalytic enantioselective version of this tandem protocol were unsuccessful. However, in the last few years, several groups have developed catalytic enantioselective aza-Michael reactions, both under metal catalysis or by using the emerging technique of organocatalysis [10]. However, most of the examples reported in this field are intermolecular reactions, while the intramolecular version has remained almost unexplored. We decided to fill this gap and, in a stepwise procedure, we performed the enantioselective organocatalytic intramolecular aza-Michael reaction of compounds **12** (previously prepared by CM reaction of the corresponding carbamates with acrolein) by using Jørgensen catalysts. After reduction of the resulting cyclic aldehydes, amino alcohols **13** were isolated in good yields and excellent ee's. In this manner, we achieved the enantioselective formation of several five- and six-membered heterocycles with different heteroatoms and protecting groups (Scheme 7) [11].



Scheme 7 Enantioselective organocatalytic intramolecular aza-Michael reaction: synthesis of five- and six-membered heterocycles.

Finally, we extended this study to the preparation of benzofused nitrogen-containing heterocycles, such as tetrahydroquinolines, tetrahydroisoquinolines, indolines, and isoindolines using the aforementioned prolinol catalysts. The reaction proceeded with good yields and high enantioselectivities (Scheme 8) [12].

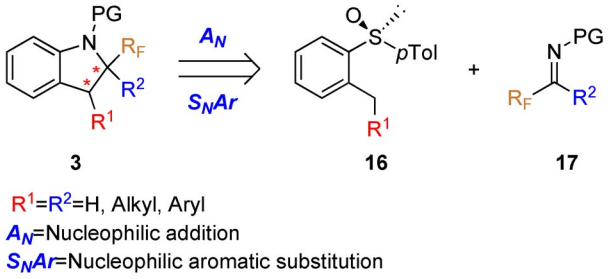


Scheme 8 Synthesis of benzofused nitrogen-containing heterocycles.

ASYMMETRIC SYNTHESIS OF FLUORINATED INDOLINES 3

The indoline substructure is a recurring structural feature within heterocyclic alkaloid natural products with diverse biological activity [13]. Additionally, this framework has also been successfully employed as chiral auxiliary in asymmetric synthesis [14]. Accordingly, this structural motif has stimulated the development of a wide range of methods aimed at the stereoselective construction or functionalization of indoline rings [15]. Surprisingly, no examples of fluorinated indolines have been reported despite the fact that the inclusion of fluorinated fragments, such as the trifluoromethyl group in organic molecules, has significantly contributed to the development of new pharmaceuticals.

Herein, we report, in collaboration with García-Ruano's group, a simple methodology for preparing enantiomerically pure fluorinated indolines **3** starting from diaryl-substituted sulfoxides **16** and fluorinated aldimines or ketimines **17**. The process represents a new asymmetric tandem reaction involving a nucleophilic addition (A_N) followed by an intramolecular nucleophilic aromatic substitution (S_NAr) (Scheme 9).

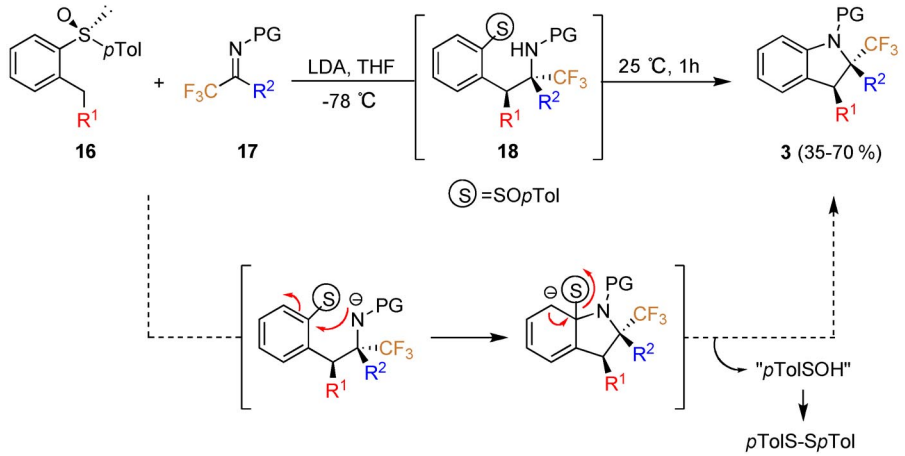


Scheme 9 Synthetic strategy for the preparation of fluorinated indolines.

Once we tested the feasibility of the process in a stepwise manner, we found that the reaction of benzyl carbanions derived from sulfoxides **16** at –78 °C with fluorinated imines **17** provided the addition products **18**, which smoothly cyclisized to give indolines **3** in moderate to good yields when the reaction mixture was allowed to reach room temperature within 1 h (Scheme 10) [16].

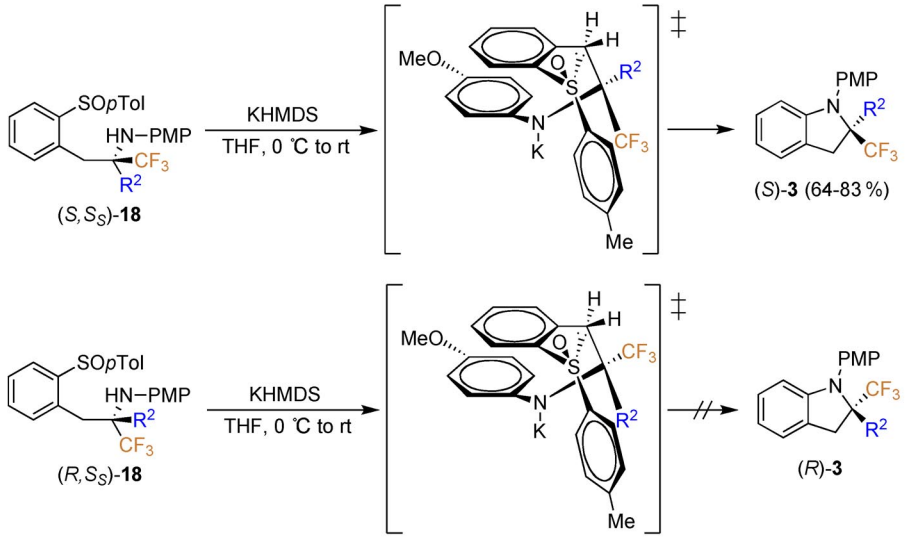
The formation of the target indolines **3** can be explained by an initial nucleophilic addition with C–C bond formation to give compounds **18**, followed by an unusual intramolecular nucleophilic aromatic substitution with C–N bond formation.

It is worth mentioning that when $R^1 \neq H$, the formation of intermediates **18** took place with complete selectivity, affording final indolines **3** as single diastereoisomers after the intramolecular cyclization. Therefore, two vicinal chiral centers were created simultaneously, one of them being quaternary when the reaction was carried out with ketimines **17** ($R^2 \neq H$).



Scheme 10 Tandem nucleophilic addition-intramolecular S_NAr: asymmetric synthesis of fluorinated indolines.

When sulfoxide **16** with R^1 = H was used, the selectivity in the addition to imines **17** dropped (from 69:31 to 96:4, depending on the nature of R^2), yielding the corresponding amines **18** as a mixture of diastereoisomers. In this case, in order to obtain enantiomerically pure indolines **3**, it was necessary to employ a stepwise process, performing the separation of the diastereoisomers formed during the addition process prior to the cyclization step. To our surprise, while compounds (*S*,*Ss*)-**18** cyclisized efficiently in the presence of $KN(TMS)_2$ to afford indolines (*S*)-**3**, their diastereoisomers (*R*,*Ss*)-**18** were unreactive under these conditions (Scheme 11).



Scheme 11 Rationale for the different behavior of diastereoisomeric amines **18**.

The ready cyclization observed in the first case suggests that the CF_3 group is able to interact favorably with the *p*-methylphenyl group attached to the sulfur. Taking into account the electronic deficiency of this ring and the electron-rich nature of the CF_3 group, a donor–acceptor interaction between both (similar to a π,π-stacking interaction) could explain the experimental results. Thus, this different

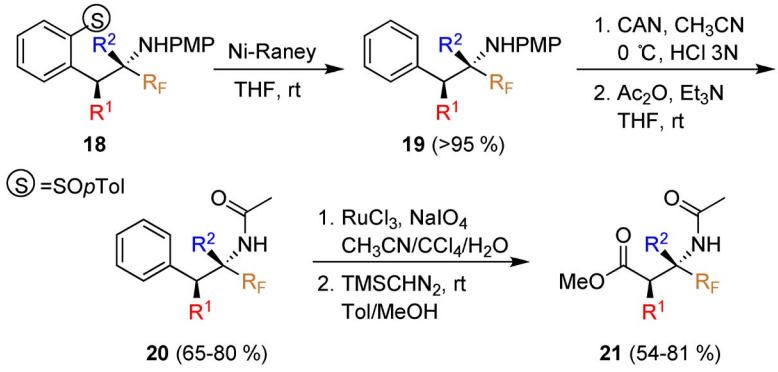
behavior can be attributed to the CF_3/*p*-tolyl interaction, which stabilizes the transition state (TS) from (*S*,*Ss*)-**18**, while it is absent in the TS from (*R*,*Ss*)-**18** (Scheme 11) [17].

Considering the lack of reactivity observed for diastereoisomers (*R*,*Ss*)-**19** in the cyclization step, it can be concluded that it is also possible to carry out the tandem process with the unsubstituted starting sulfoxides **16** (R^1 = H), since only the addition diastereoisomers (*S*,*Ss*) will cyclisize to the corresponding indolines.

This process was also extended to nonfluorinated aromatic aldimines and ketimines, showing an analog behavior. In these cases, a double π,π-stacking interaction was invoked to explain the experimental results [17].

Finally, compounds **18** were used as synthetic intermediates for the preparation of fluorinated β-amino acid derivatives **21**. This implied the use of the phenyl-*p*-tolylsulfoxide group both as chiral inducer in its reaction with fluorinated aldimines and ketimines and as a precursor of the carboxylic moiety by a two-step desulfinylation–phenyl ring oxidation sequence.

Thus, removal of the sulfoxide group was achieved by treatment with Ni-Raney, which afforded the desulfurated products **19** in almost quantitative yields after several hours at room temperature. The transformation of the phenyl ring into the carboxylic acid required the previous conversion of the PMP group into another protecting group compatible with the oxidation step. For this purpose, amines **19** were first treated with CAN (cerium ammonium nitrate) and then acylated under standard conditions to afford compounds **20**. Final oxidation with "ruthenium oxide", followed by esterification of the carboxylic acid with trimethylsilyl diazomethane provided the targeted amino acids **21** in good yields (Scheme 12). It is noteworthy that this is one of the first methods described in the literature for the stereoselective preparation of enantiomerically pure *anti*-β-fluoroalkyl-α-alkyl β-amino esters and the first one for compounds containing quaternary centers [18].



Scheme 12 Synthesis of enantiomerically pure *anti*-β-fluoroalkyl-β-amino acid derivatives.

CONCLUSIONS

In summary, we have developed three different asymmetric tandem reactions that allow for the preparation of 1,4-dihydropyridines (in an aza-Michael reaction–intramolecular Michael addition process), β-amino carbonyl derivatives (obtained by a CM–intramolecular aza-Michael reaction) and, for the first time, fluorinated indolines (through a nucleophilic addition-S_NAr). Additionally, a new family of fluorinated β-amino acids was also prepared.

ACKNOWLEDGMENTS

Financial support of this work by the Ministerio de Educación y Ciencia (grants CTQ2006-06741/BQU and CTQ2007-61462) is gratefully acknowledged. M. S.-R. and C. P. express their thanks to the same Institution for a Juan de la Cierva and a Ramón y Cajal contract, respectively. We also thank Prof. García-Ruano for his collaboration in the synthesis of indolines.

REFERENCES

1. For recent reviews of asymmetric multicomponent and tandem reactions, see: (a) H. Pellisier. *Tetrahedron* **62**, 1619 (2006); (b) H. Pellisier. *Tetrahedron* **62**, 2143 (2006); (c) D. J. Ramón, M. Yus. *Angew. Chem., Int. Ed.* **44**, 1602 (2005).
2. (a) D. A. Horton, G. T. Bourne, M. L. Smythe. *Chem. Rev.* **103**, 893 (2003); (b) C. O. Kappe. *Eur. J. Med. Chem.* **35**, 1043 (2000).
3. For a review, see: S. Goldmann, J. Stoltefuss. *Angew. Chem., Int. Ed. Engl.* **30**, 1559 (1991).
4. A. Hantzsch. *Justus Liebigs Ann. Chem.* **215**, 1 (1882).
5. S. Fustero, S. Catalán, M. Sánchez-Roselló, V. Rodrigo, C. del Pozo. Unpublished results.
6. E. C. Juaristi, V. A. Soloshonok (Eds.), *Enantioselective Synthesis of β-Amino Acids*, 2nd ed., Wiley-VCH, New York (2005).
7. R. H. Grubbs. In *Handbook of Metathesis*, Vols. 1–3, Wiley-VCH, Weinheim (2003).
8. B. Alcaide, P. Almendros, A. Luna. *Chem. Rev.* **109**, 3817 (2009).
9. S. Fustero, D. Jiménez, M. Sánchez-Roselló, C. del Pozo. *J. Am. Chem. Soc.* **129**, 6700 (2007).
10. For two representative examples, see: (a) Y. K. Chen, M. Yoshida, D. W. C. MacMillan. *J. Am. Chem. Soc.* **128**, 9328 (2006); (b) C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengoa, J. M. García. *J. Am. Chem. Soc.* **126**, 9188 (2004).
11. S. Fustero, D. Jiménez, J. Moscardó, S. Catalán, C. del Pozo. *Org. Lett.* **9**, 5283 (2007).
12. S. Fustero, J. Moscardó, D. Jiménez, M. D. Pérez-Carrión, M. Sánchez-Roselló, C. del Pozo. *Chem.—Eur. J.* **14**, 9868 (2008).
13. P. M. Dewick. *Medicinal Natural Products-A Biosynthetic Approach*, 2nd ed., John Wiley, New York (2002).
14. F. Andersson, E. Hedenström. *Tetrahedron: Asymmetry* **17**, 1952 (2006) and refs. therein.
15. For recent examples of synthesis of indolines, see: (a) A. Minatti, S. L. Buchwald. *Org. Lett.* **10**, 2721 (2008) and refs. therein; (b) R. Viswanathan, C. R. Smith, E. N. Prabhakaran, J. N. Johnston. *J. Org. Chem.* **73**, 3040 (2008) and refs. therein.
16. J. L. García-Ruano, J. Alemán, S. Catalán, V. Marcos, S. Monteagudo, A. Parra, C. del Pozo, S. Fustero. *Angew. Chem., Int. Ed.* **47**, 7941 (2008).
17. J. L. García-Ruano, A. Parra, V. Marcos, C. del Pozo, S. Catalán, S. Monteagudo, S. Fustero, A. Poveda. *J. Am. Chem. Soc.* **131**, 9432 (2009).
18. S. Fustero, C. del Pozo, S. Catalán, J. Alemán, A. Parra, V. Marcos, J. L. García-Ruano. *Org. Lett.* **11**, 641 (2009).

