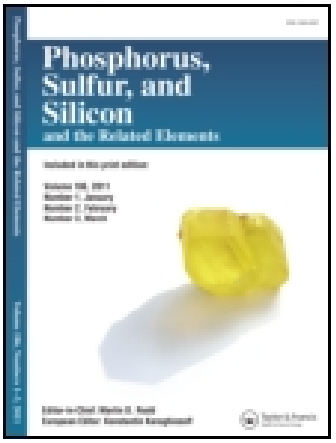

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ASYMMETRIC TANDEM REACTIONS: NEW STRATEGIES AND APPLICATIONS

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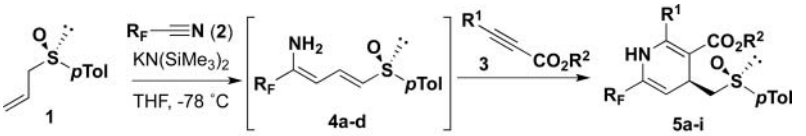
GRAPHICAL ABSTRACT



R_F = $PhCF_2$, $allylCF_2$, 2-naphtylCF_2, 1-naphtylCF_2
R^1 = H, CO_2Et, Ph
R^2 = Me, Et

Abstract *The application of allylic sulphoxides and, particularly, the chiral amine reagent tert-butanesulphinamide has been extended to three different tandem processes. The condensation of (R)-(+)-allyl p-tolyl sulphoxide, fluorinated nitriles and alkyl propiolates led to a new family of enantiomerically pure fluorine-containing 1,4- dihydropyridines. A diastereoselective nucleophilic addition of fluorinated nucleophiles onto (R)-(tert-butanesulphinyl) imines, followed by an intramolecular aza-Michael reaction gave rise to either fluorinated isoindolines or 3-substituted indanones in a stereoselective manner.*

Keywords Tandem reaction; aza-Michael addition; chiral sulphoxides; sulphinamide; fluorinated dihydropyridine; fluorinated isoindoline; indanone

SYNTHESIS OF ENANTIOMERICALLY PURE FLUORINE-CONTAINING 1,4-DHPS

Introduction

Dihydropyridines (DHPs) constitute an important class of biologically active heterocycles. They can be considered "privileged structures" in medicinal chemistry exhibiting a

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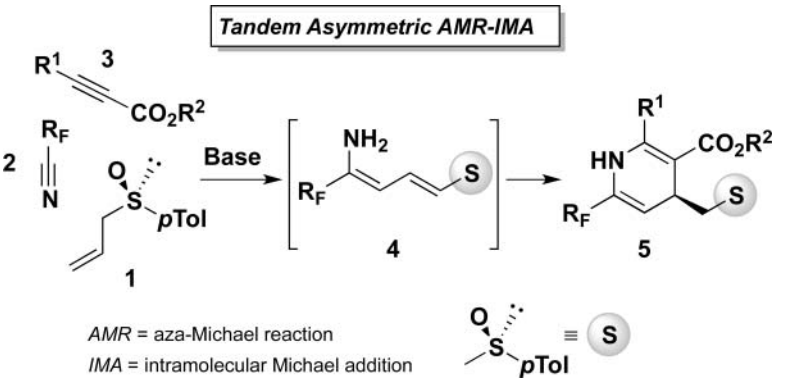
wide range of pharmacological and biological activities.[1] One of the most straightforward routes to the synthesis of 1,4-DHPs is the Hantzsch condensation, which was first developed in 1882.[2] Despite the biological importance of enantiomerically pure DHPs, a general method for their asymmetric synthesis still remains an important challenge. Traditional strategies make use of either enzymatic[3] or chemical[4] resolutions of racemates or, alternatively, chiral auxiliaries.[5] In this context, chiral sulphoxides are reliable chiral synthons able to bring about important asymmetric transformations.[6] As part of our continued interest in the preparation of new fluorinated building blocks,[7] we envisioned a closely related asymmetric Hantzsch transformation by using allylic sulphoxides, fluorinated nitriles, and alkyl propiolates as the three components of the novel one-pot tandem *Michael reaction-Intramolecular Michael addition* (IMA),[8] summarized in Scheme 1. This methodology allows for the preparation of a new family of enantiomerically pure fluorinated 1,4-DHPs.

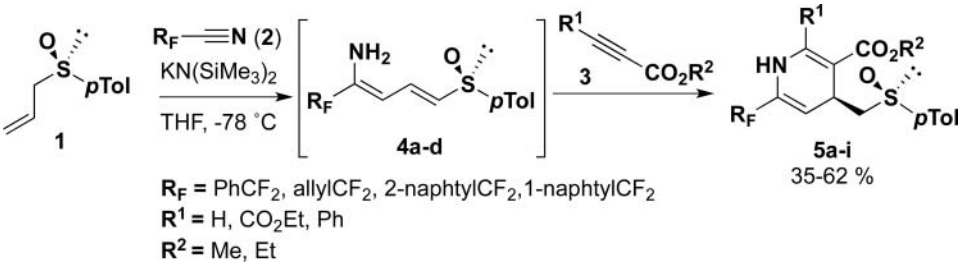


Scheme 1

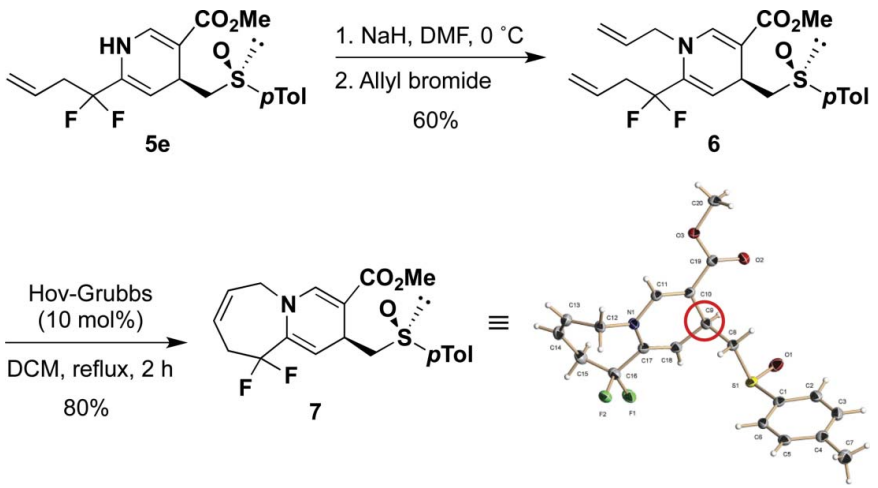
Results and Discussion

Our synthetic strategy starts with the regioselective preparation of enamino sulphoxide **4**, the key intermediate of the synthetic pathway. After testing several bases and temperatures, we found that optimal reaction conditions involved the treatment of (*R*)-(+)-allyl *p*-tolyl sulphoxide **1** with $KN(SiMe_3)_2$ at $-78^{\circ}C$ in THF, followed by addition of fluorinated nitriles **2**. The reaction took place exclusively over the γ-carbon of **1** giving rise to dienic sulfoxides **4** after tautomerization of the iminic double bond to the more conjugated enamine tautomer. The one-pot sequence was then followed by a double tandem Michael addition, initiated by reaction of sulfoxides **4** with newly added alkyl propiolates **3**. Thus, the final step led to the formation of the corresponding fluorinated 1,4-DHPs **5** in moderate isolated yields, in most cases, as a single diastereoisomer (Scheme 2).

The absolute stereochemistry of the newly created stereocenter was determined by means of X-ray analysis of derivative **7** (Scheme 3). Thus, *N*-allylation of **5e** generated diene **6**, which smoothly cyclized in the presence of second generation Hoveyda–Grubbs catalyst [Cl_2(IMes)Ru=CH(*o*-*i*-PrOC_6H_4)]. The absolute configuration of the chiral center was found to be *S* (Scheme 3), and an identical stereochemical outcome was assumed for all examples in Scheme 2.

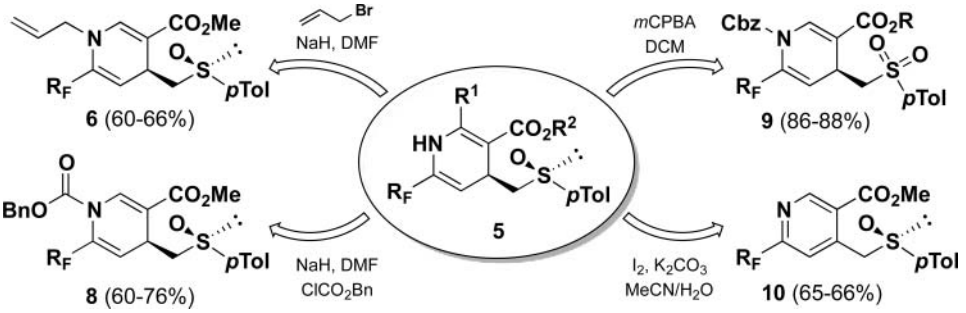


Scheme 2



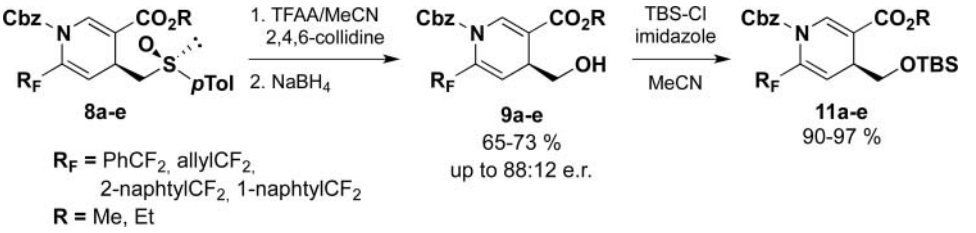
Scheme 3

Further functionalizations of DHPs **5** are possible besides the *N*-allylation (**6**) or *N*-acylation (**8**) reaction (Scheme 4). The oxidation to the corresponding sulphones **9** took place under standard conditions. Finally, the aromatization to fluoropyridines **10** was accomplished under mild conditions using iodine as oxidant in the presence of K_2CO_3 in good yields.



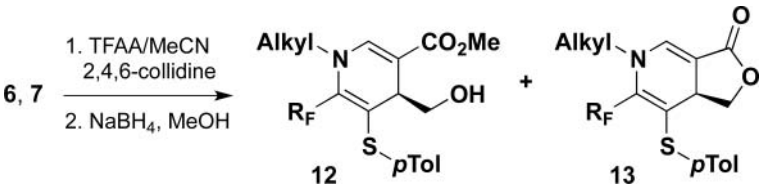
Scheme 4

The last step in our study was the removal of the chiral auxiliary from the final products. To this end, Pummerer-type reactions are extensively used in organic synthesis. The nonoxidative variant of the Pummerer reaction (NOPR) enables the conversion of different sulphoxides into the corresponding alcohols by reaction with TFAA and *sym*-collidine followed by $NaBH_4$ reduction.[9] In this context, when several *N*-Cbz-protected DHPs **8** were subjected to NOPR conditions, alcohols **9** were isolated in reasonable yields (Scheme 5).[10] However, a partial erosion of the ee was observed during the sulphoxide cleavage, as determined by chiral HPLC analysis of the alcohols **9**. This was probably due to the acidity of the hydrogen present in the stereocenter, since it is located in a double allylic position, and therefore susceptible to racemization under NOPR conditions. Although several attempts directed toward avoiding the erosive process of the ee in the NOPR reaction were unsuccessful, we found that the protection of the hydroxyl group of **9** as *tert*-butyl dimethylsilyl ether rendered DHPs **11**, which were susceptible to separation by means of semipreparative chiral HPLC. In this way, it was finally possible to access DHPs **11** in enantiomerically pure form.



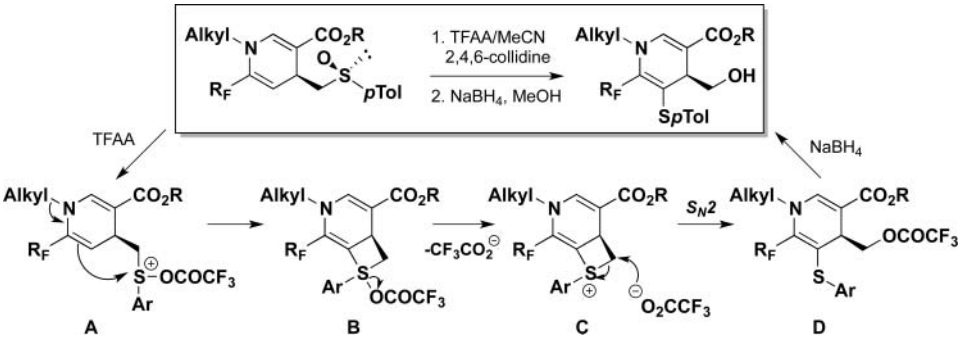
Scheme 5

A different behavior was observed for compounds **6** and **7** under NOPR conditions since sulphides **12** and **13** were obtained instead (Scheme 6). Their formation would involve the migration of the sulfur atom to the C-3 position of the ring, which occurred under the reaction conditions. The higher nucleophilicity of the nitrogen atom in *N*-alkyl substituted derivatives by comparison with the *N*-acyl ones is likely to explain this different reactivity.



Scheme 6

These results can be rationalized assuming the formation of the sulphonium ion intermediate **A** (commonly accepted in a Pummerer-type process). Then, an intramolecular nucleophilic attack of the enamine functionality would afford intermediate **B**. The elimination of a trifluoroacetate anion would generate a new sulphoxonium cation **C**, which would undergo an S_N2-type displacement with the previously liberated trifluoroacetate to give intermediate **D**. Reduction with $NaBH_4$ would result in the corresponding alcohols **12**, which partly lactonize to derivatives **13** (Scheme 7).



Scheme 7

Thus, we have outlined a new strategy for the preparation of optically pure fluorinated 1,4-DHPs involving a one-pot tandem *Michael reaction-IMA*, with excellent diastereoselectivity.

TANDEM NUCLEOPHILIC ADDITION/INTRAMOLECULAR AZA-MICHAEL REACTION

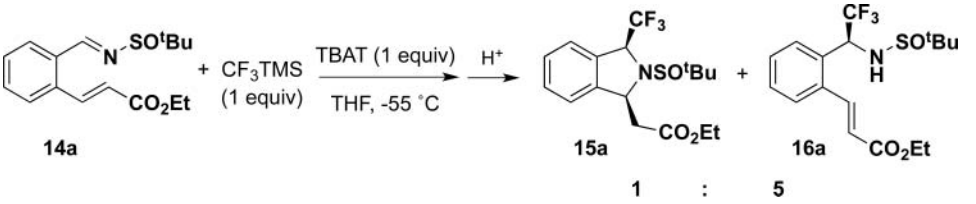
Introduction

Additionally, a new strategy for the asymmetric synthesis of isoindoline derivatives with different degrees of fluorination through a new tandem *nucleophilic addition-intramolecular aza-Michael reaction* (AMR), starting from α,β-unsaturated esters bearing an imino moiety has been developed. This strategy allows for the preparation of new enantiomerically pure beta-amino acid derivatives. Recently, our group reported a tandem process CM-IMAMR leading to pyrrolidines and piperidines in good chemical yields.[11] Moreover, the aza-Michael step may lead to the formation of a stereogenic center. Our research group has also developed two approaches for achieving optically active products by coupling an asymmetric intramolecular AMR with a CM process.[12] A second strategy involves the nucleophilic addition to a substrate, which already contains both the Michael acceptor and an electrophilic imino grouping.[13] Given our experience with *tert*-butylsulphinamines as nitrogen nucleophiles in IMAMR[13a] and also the wide use and availability of the Rupert–Prakash reagent,[14] we decided to explore their joint use in our tandem nucleophilic addition/IMAMR process.

Results and Discussion

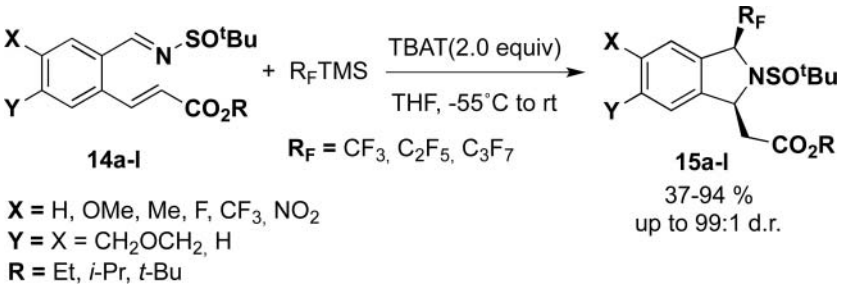
The initial reaction of model substrate **14a** with CF_3TMS in the presence of tetrabuty lammonium difluorotriphenylsilicate (TBAT), THF as solvent and at $-55^{\circ}C$ provided product **15a** resulting from the tandem process along with its noncyclized precursor **16a** (both as single diastereoisomers) and unreacted starting material (Scheme 8).[15] The optimization process enable us to find some crucial experimental details, namely: the addition of 2 equiv of both CF_3TMS and TBAT appear to be crucial for achieving a good conversion; by allowing the reaction to reach room temperature, most of the product was obtained in the cyclized form; THF was the best solvent and, finally, the hydrolysis step proved crucial for the completion of the cyclization step. Thus, the use of SiO_2 along with two drops of

HCl provided the tandem isoindoline in very good yield and as a single diastereoisomer by NMR.[16]



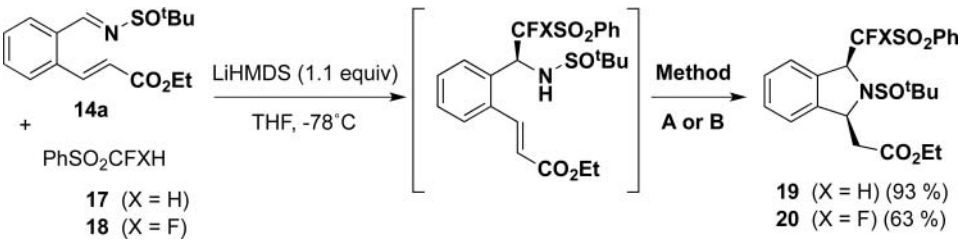
Scheme 8

Under optimized conditions, we prepared a small library of optically pure fluorinated isoindolines containing two stereogenic centers with different substitution patterns in the aromatic ring, the ester group and fluorinated nucleophile were obtained, in general, in good yields and excellent diastereoselectivity[17] in a simple and selective manner (Scheme 9).



Scheme 9

Then, we decided to use some partially fluorinated nucleophiles,[18,19] namely, the nucleophilic mono- and difluoroalkylating agents **17** and **18** (Scheme 10).

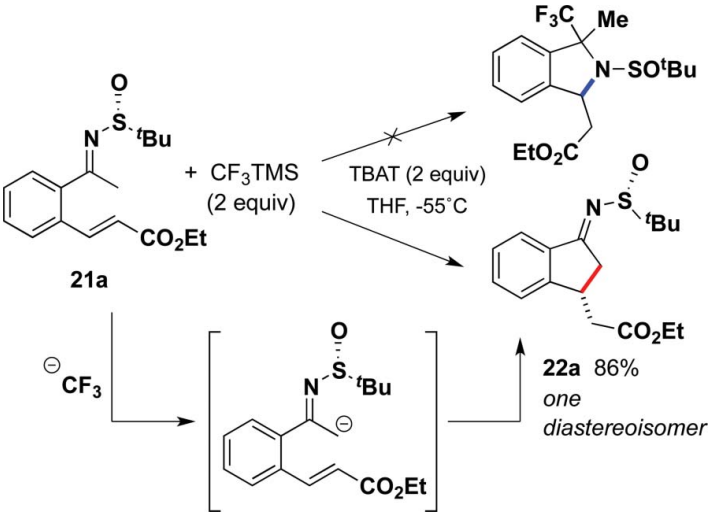


Scheme 10

Thus, the corresponding isoindoline products were obtained in good yields as single diastereoisomers.[20] The phenylsulphone moiety was then removed by treatment with sodium amalgam giving rise to the corresponding fluoro- or difluoromethyl groups.

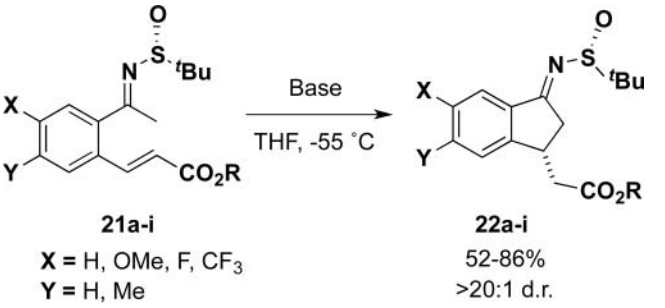
We then decided to explore the use of *ketimines* instead of aldimines that would lead to isoindolines bearing a quaternary stereocenter. Unexpectedly, when ketimine **21a** was

treated with the Ruppert–Prakash reagent, under conditions optimized for the aldimines, the indane imine derivative **22a** was obtained in good yield and selectivity (Scheme 11).[21]



Scheme 11

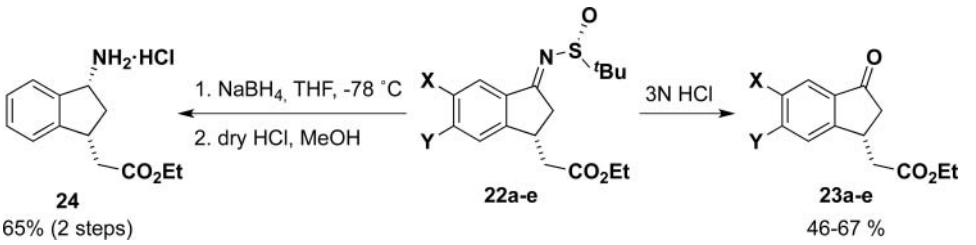
This different reactivity can be rationalized by the inherent lower reactivity of ketimines toward nucleophiles and the presence of acidic protons at the α-position, which provides an alternative reaction pathway. Thus, the "CF_3^-" anion formed upon mixing the Ruppert–Prakash reagent with a fluorine source acts as a base, while in the case of the aldimines it behaves as a nucleophile. Surprisingly, bases more commonly used in enolate chemistry such as LDA or LiHMDS lead to less favorable results, TBAF being the only base that affords the indanone derivative in comparable yield to the initial conditions. The scope of this new methodology was then studied (Scheme 12).



Scheme 12

A small library of indanone imines with different substitution patterns both at the aromatic ring and the ester functionality were prepared in good chemical yields and excellent diastereoselectivities in all cases. The reactivity of these imines was studied next and we found that hydrolysis provided indanones **23** in moderate chemical yields and the reduction

with $NaBH_4$ in THF at -78^oC afforded exclusively enantiomerically pure *syn* δ-amino ester derivative **24** also in good chemical yields (Scheme 13).



Scheme 13

CONCLUSIONS

In conclusion, a novel asymmetric one-pot domino Hantzsch-type process by reaction of (*R*)-(+)-allyl *p*-tolyl sulphoxide, fluorinated nitriles and alkyl propiolates has been described. Moreover, the process involved a tandem AMR- IMA, which took place with complete selectivity, leading to a new family of fluorinated 1,4-DHPs in enantiomerically pure form and moderate yields. Furthermore, different reactivity patterns were also observed during the NOPR process depending on the nucleophilicity of the 1,4-DHP nitrogen.

On the other hand, the differential reactivity of Ellman's aldmines and ketimines led to the development of two new diastereoselective processes: a tandem nucleophilic addition/intramolecular AMR affording *cis*-1,3-disubstituted isoindolines bearing several degrees of fluorination, and an IMA leading to indanone derivatives.

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17. The *tert*-butanesulfinyl group was removed with 4 M HCl in dioxane yielding the corresponding free amines after basification.
18. Hu has reported very useful asymmetric syntheses of fluorinated amines with different degrees of fluorination starting from aldimines or ketimines and several fluorinated nucleophiles, see: (a) Li, Y.; Ni, C.; Liu, J.; Zhang, L.; Zheng, J.; Zhu, L.; Hu, J. *Org. Lett.* **2006,** 8, 1693-1696. (b) Li, Y.; Hu, J. *Angew. Chem. Int. Ed.* **2005,** 44, 5882-5886. (c) Liu, J.; Hu, J. *Chem. Eur. J.* **2010,** 16, 11443-11454.
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