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Tandem Nucleophilic Addition−Intramolecular Aza-Michael Reaction: Facile Synthesis of Chiral Fluorinated Isoindolines

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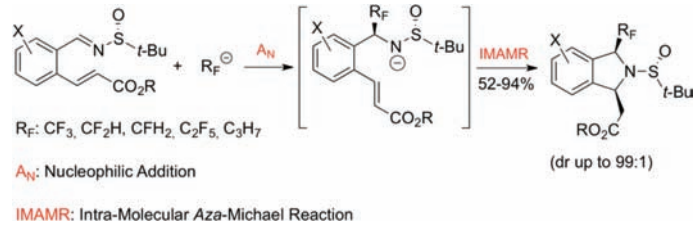
ABSTRACT



A highly stereoselective synthesis of fluorinated 1,3-disubstituted isoindolines is described. To this end, a tandem reaction consisting of a diastereoselective addition of fluorinated nucleophiles to Ellman's *N*-(*tert*-butanesulfinyl)imines followed by an intramolecular aza-Michael reaction has been developed. This strategy allows for the construction of isoindolines bearing several degrees of fluorination (mono-, di-, or trifluoromethyl as well as heavier fluorinated groups). In the majority of all cases, the products are formed as single isomers.

Selective incorporation of fluorine atom(s) into organic molecules has become a powerful strategy to modulate their biological properties. Specifically, the replacement of one or more hydrogen atoms by fluorine in the vicinity of an amine function results in a lower basicity. Thus, a decrease in acute toxicity and an increase in the metabolic stability of the target drug are usually observed.[1] On the other hand, although isoindolines are substructures present in a variety of natural products and pharmaceuticals,[2] they still lack general routes for their preparation in a stereoselective manner.[3] Furthermore, tandem reactions are very attractive since they increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of solvents and chemicals used, reducing cost and time and allowing for the creation of molecular complexity from simple substrates. Moreover, the synthesis of optically active compounds plays a pivotal role in medicinal chemistry.

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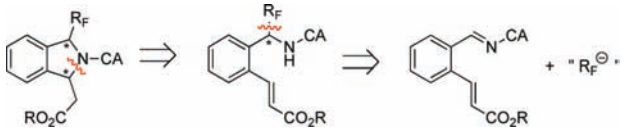
Therefore, the interest in combining asymmetric processes with tandem reactions is obvious since multiple stereogenic centers can be created in a single synthetic step.[4] Our group's interest in organofluorine chemistry[5] together with our ongoing efforts in tandem reactions including an intramolecular aza-Michael reaction as the last step[6] has led us to design the following cascade approach to α-fluoroalkylated 1,3-isoindolines (Scheme 1).[7] The isoindoline core would

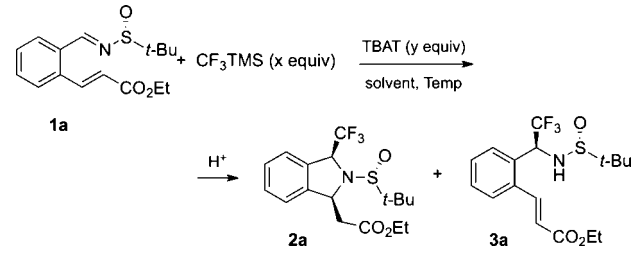
Scheme 1. Cascade Design



be formed through an intramolecular aza-Michael addition onto an α,β-unsaturated ester conveniently placed. The isoindoline structures thus obtained would constitute a new family of fluorinated β-amino acid derivatives.[5b] The required α-fluoroalkylated amine would arise from the diastereoselective addition of a fluorinated nucleophile to a suitable imine. Among the available chiral auxiliaries (CA), we chose Ellman's (*R*)-*N*-(*tert*-butanesulfinyl) imines[8] as they have been successfully used in this context.[9]

Given its wide use and availability, the Ruppert−Prakash reagent[10] (CF_3TMS) was regarded as the fluorinated nucleophile of choice in a first approach. TBAT has proved to be the appropriate activating agent for the addition of this nucleophile onto sulfinylimines.[11] When model substrate **1a** was reacted with CF_3TMS in the presence of TBAT in THF at −55 °C, we observed the formation of two products along with unreacted starting material. We were pleased to identify in the reaction mixture the target product **2a** resulting from the envisioned tandem reaction. Moreover, both **2a** and its noncyclized precursor **3a** were formed as single diastereoisomers.[12] This positive preliminary result prompted us to optimize this interesting transformation. Our initial screening for conditions is summarized in Table 1.

Table 1. Optimization of the Tandem Reaction Using CF_3TMS/TBAT as the Fluorinated Nucleophile



							2a + 3a[c]	
entry	x^a	y^b	solv	temp (°C)	t (h)	H^+	yield (%)	**2a:3a**
1	1	1	THF	−55	1	**A**	67	1:5
2	1	2	THF	−55	1	**A**	70	1:4
3	2	1	THF	−55	1	**A**	73	1:5
4	2	2	THF	−55	1	**A**	90	1:5
5	2	2	THF	−55 to rt	3	**A**	99	3:1
6	2	2	DMF	−55 to rt	3	**A**	40	5:1
7	2	2	Tol	−55 to rt	3	**A**	0	-
8	2	2	THF	−55 to rt	1	**B**	99	>20:1

[a] CF_3TMS equiv. [b] TBAT equiv. [c] **2a** and **3a** were formed as single diastereoisomers. **A**: NH_4Cl. **B**: 1 N HCl (2 drops)/SiO_2.

The addition of 2 equiv of both CF_3TMS and TBAT proved crucial for achieving good conversion (Table 1, entries 1−4). By allowing the reaction to reach room temperature, most of the product was obtained in the cyclized form **2a**, but a considerable proportion of the addition product **3a** was still observed (Table 1, entry 5).[13] THF was the best solvent, while the use of other solvents such as DMF or toluene led to unfavorable results (Table 1, entries 5−7). Finally, the quenching step was considered to obtain an optimum result. When using HCl/SiO_2 instead of NH_4Cl for the hydrolysis, only the desired tandem product was obtained (Table 1, entry 8). With these optimized conditions in hand, we turned to study the scope and limitations of this new transformation.[14] First, we explored the use of differently substituted arene rings (Table 2, entries 1−7). Electron-rich (Table 2, entries 2−4) as well as electron-poor (Table 2, entries 5−7) aromatic rings are suitable substrates for this transformation. We then turned our attention to the ester group, thus proving the expected lack of influence of the substitu-

(4) For a recent review of asymmetric tandem reactions, see: Pellissier, H. *Tetrahedron* **2006**, *62*, 1619.

(5) For recent reviews, see: (a) Fustero, S.; Sanz-Cervera, J. F.; Aceña, J. L.; Sánchez-Roselló, M. *Synlett* **2009**, 525. (b) Aceña, J. L.; Simón-Fuentes, A.; Fustero, S. *Curr. Org. Chem.* **2010**, *14*, 928.

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(7) For a recent approach to nonfluorinated 1,3-disubstituted isoindolines, see: Enders, D.; Narine, A. A.; Toulgoat, F.; Bisshops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 566, and references therein.

(8) The reaction was also performed with the (*S*)-*N*-(*p*-tolylsulfinyl)imine derivative; however, no product was formed, and mostly starting material was recovered from the reaction mixture.

(9) For a recent and exhaustive review about *tert*-butanesulfinamide and its use in synthesis, see: Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

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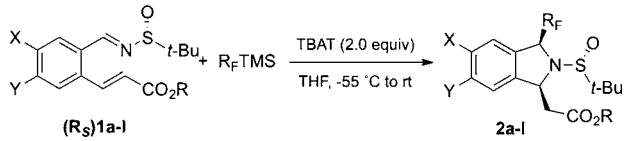
(11) For the diastereoselective addition of CF_3TMS to (*R*)-*N*-(*tert*-butanesulfinyl)imines, see: (a) Prakash, G. K. S.; Mandal., M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589. (b) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett* **2001**, 77.

(12) Diastereoselectivities were determined by integration of characteristic signals both in the ^1H and ^{19}F NMR on the crude NMR spectra. They were found inaltered after column chromatography. See: Soloshonok, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 766.

(13) In all cases, the intermediate product **3a**−**l** could be isolated. Treatment of the former with *t*-BuOK in THF at −40 °C gave the corresponding cyclized product **2a**−**l**.

(14) The required substrates (*R*,*S*)-**1a**−**l** are conveniently synthesized from commercially available starting materials in a two-step sequence (see Supporting Information).

Table 2. Scope of the New Tandem Reaction



entry	2	X	Y	R	R_F[a]	yield (%)[b]	dr
1	**2a**	H	H	Et	CF_3	94	99:1
2	**2b**	MeO	H	Et	CF_3	74	20:1
3	**2c**	O−CH_2−O		Et	CF_3	77[c]	99:1
4	**2d**	Me	H	Et	CF_3	84	35:1
5	**2e**	F	H	Et	CF_3	80	24:1
6	**2f**	CF_3	H	Et	CF_3	62	60:1
7	**2g**	NO_2	H	Et	CF_3	52	89:1
8	**2h**	H	H	^{i}Pr	CF_3	70	99:1
9	**2i**	H	H	^{t}Bu	CF_3	88[c]	99:1
10	**2j**	H	H	Et	C_2F_5	45	99:1
11	**2k**	H	H	^{t}Bu	C_2F_5	71	99:1
12	**2l**	H	H	^{t}Bu	C_3F_7	37	99:1

[a] R_FTMS (2.0 equiv), TBAT (2.0 equiv). [b] Isolated yields after flash column chromatography [c] Yields for the two-step procedure: the crude reaction was dissolved in THF and treated with *t*-BuOK at −40 °C for 0.5 h.

tion at this position (Table 2, entries 8 and 9). Finally, we decided to try some heavier analogues of the Ruppert−Prakash reagent. Both CF_3CF_2TMS and $CF_3CF_2CF_2TMS$ participate in this new tandem reaction, and the corresponding products were obtained in moderate to good yields (Table 2, entries 10−12).

The observed *syn* diastereoselectivity was determined by the cross peak observed between the CF_3 and the CH_2 α to the ester group in the 2D-NMR HOESY experiment carried out on product **2b** (Figure 1, left side).[15] The absolute

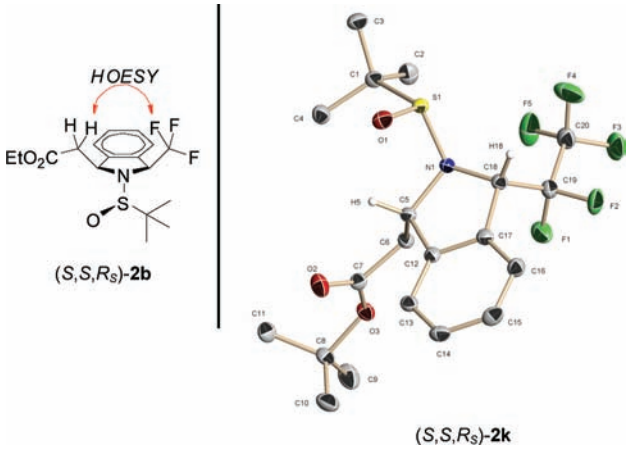
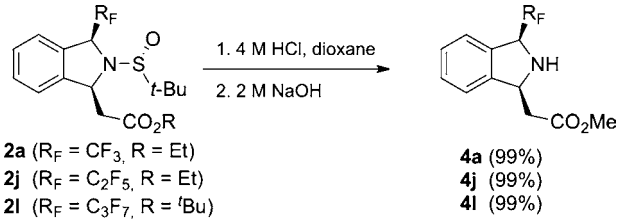


Figure 1. Determination of the relative and absolute stereochemistry by 2D-NMR and X-ray experiments.

stereochemistry was assigned related to the known (R_S) stereochemistry of the chiral auxiliary by analysis of the X-ray difraction pattern of a suitable crystal obtained by slow evaporation of a solution of **2k** in hexanes (Figure 1, right side). The stereochemical outcome is in accordance with the previous reports.[10a]

For one derivative of each class (bearing CF_3, C_2F_5, or C_3F_7), namely, **2a**, **2j**, and **2l**, the *tert*-butanesulfinyl group was removed with 4 M HCl in dioxane yielding the corresponding free amines after basification (Scheme 2).[16]

Scheme 2. Removal of the *tert*-Butanesulfinyl Group



To expand our methodology and make it synthetically more useful, we decided to use some partially fluorinated nucleophiles. The introduction of CF_2H and CFH_2 units, along with CF_3, in organic molecules is of major importance as the degree of fluorination plays a crucial role in the modification of their physical, chemical, and biological properties. Thus, for instance, α-monofluoromethylamines have been used as building blocks in the design of anticholinergic, antiemetic, and antispastic drugs and enzyme inhibitors since they were first reported as selective inhibitors of the biosynthesis of aminergic neurotransmitters more than 30 years ago.[17] Therefore, we used the nucleophilic fluoroalkylating agents $PhSO_2CFXH$ (**5**, X = H; **6**, X = F).[18]

When using the monofluorinated reagent **5**, product **7** (X = H) was obtained as a 1.5:1 mixture of two separable diastereoisomers, at the exocyclic stereocenter bearing the fluorine atom, in excellent yield by treating the crude addition product with *t*-BuOK in THF at −40 °C for 30 min (Scheme 3). The formation of the product **7** as a mixture of diastereoisomers is inconsequencial as this stereocenter is meant to be destroyed in a later step. On the other hand, the product **8** (X = F) arising from reagent **6** was formed in a tandem fashion just by allowing the reaction mixture to reach −20 °C during 3 h (Scheme 3).[19] For both substrates **7** and **8** the deprotection of the isoindoline nitrogen was carried

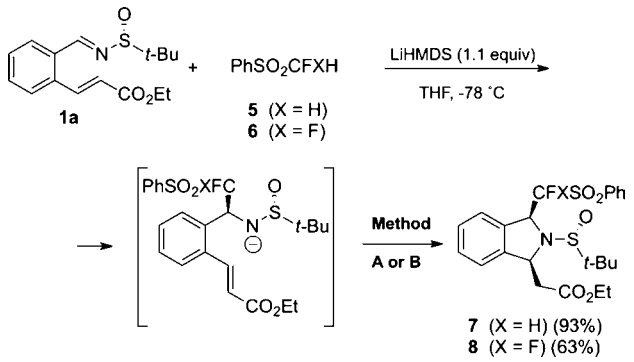
(15) Assuming the reversibility of the aza-Michael addition (see ref 6d) the formation of the thermodynamic product is expected. As can be inferred from the ORTEP diagram (Figure 1, right side), the substituents at the 1 and 3 positions are oriented *anti* to the bulky substituent on the nitrogen (thus *syn* to each other).

(16) During the deprotection step, a transesterification reaction with MeOH was observed.

(17) Kollonitsch, J.; Perkins, L. M.; Patchett, A. A.; Doldouras, G:A:; Marburg, S.; Duggen, D. E.; Maycock, A. L.; Aster, S. D. *Nature* **1978**, *274*, 906.

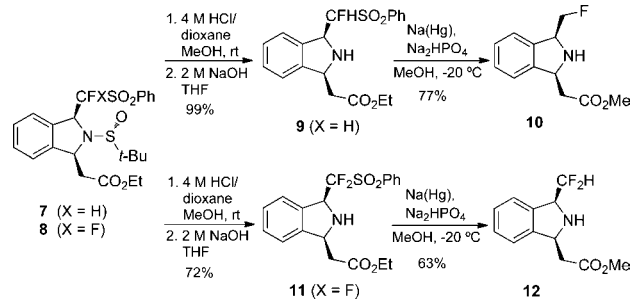
(18) (a) For the addition of **5** to *N*-(*tert*-butanesulfinyl)imines, see: Li, Y.; Ni, C.; Liu, J.; Zhang, L.; Zheng, J.; Zhu, L.; Hu, J. *Org. Lett.* **2006**, *8*, 1693. (b) For the addition of **6** to *N*-(*tert*-butanesulfinyl)aldimines, see: Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882. (c) For the addition of **6** to *N*-(*tert*-butanesulfinyl)ketimines, see: Liu, J.; Hu, J. *Chem.—Eur. J.* **2010**, *16*, 11443.

Scheme 3. Reaction with Mono- and Difluorinated Nucleophiles **5** and **6**[a]



[a] **Method A**: *t*-BuOK (0.5 equiv), THF, −40 °C, 0.5 h. **Method B**: −78 to −20 °C.

Scheme 4. Desulfonylation and Hydrolysis of **7** and **8**



out prior the desulfonylation step. The latter was achieved by treatment with Na(Hg) in MeOH (Scheme 4).[20]

In conclusion, a new tandem reaction consisting of the addition of fluorinated nucleophiles to (*R*)-*N*-(*tert*-butanesulfinyl)imines followed by an intramolecular aza-Michael addition has been described. This process has been applied to the diastereoselective synthesis of fluorinated 1,3-disubstituted isoindolines. Studies on the application of this strategy for the synthesis of other heteroaromatic motifs and the use of other nucleophiles (fluorinated and nonfluorinated) are currently ongoing in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds, as well as crystallographical data for compound **2k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Moreover, 28% of the noncyclized precursor **3m** was also obtained.

(20) (a) Other methods described for desulfonylation, such as Mg/MeOH, Mg/DMF, and Raney Ni proved ineffective for these systems. (b) In the desulfonylation step, a transesterification reaction with MeOH took place.