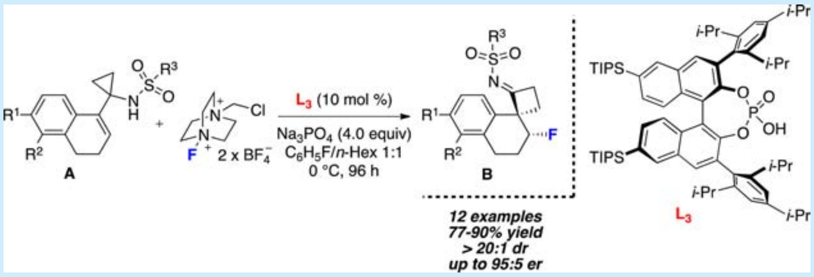
Organic Letters
Letter
pubs.acs.org/OrgLett

Enantioselective Catalytic Fluorinative Aza-semipinacol Rearrangement

Fedor Romanov-Michailidis,[†] Marion Pupier,[†] Céline Besnard,[‡] Thomas Bürgi,*[,§] and Alexandre Alexakis*[,†]

[†]Department of Organic Chemistry, [‡]Laboratory of Crystallography, and [§]Department of Physical Chemistry, University of Geneva, Quai Ernest Ansermet 30 CH-1211 Geneva 4, Switzerland

Supporting Information



ABSTRACT: An efficient and highly stereoselective fluorinative aza-semipinacol rearrangement is described. The catalytic reaction requires use of Selectfluor in combination with the chiral, enantiopure phosphate anion derived from acid **L3**. Under optimized conditions, cyclopropylamines **A** were transformed into β-fluoro cyclobutylimines **B** in good yields and high levels of diastereo- and enantiocontrol. Furthermore, the optically active cyclobutylimines were reduced diastereoselectively with L-Selectride in the corresponding fluorinated amines **C**, compounds of significant interest in the pharmacological industry.

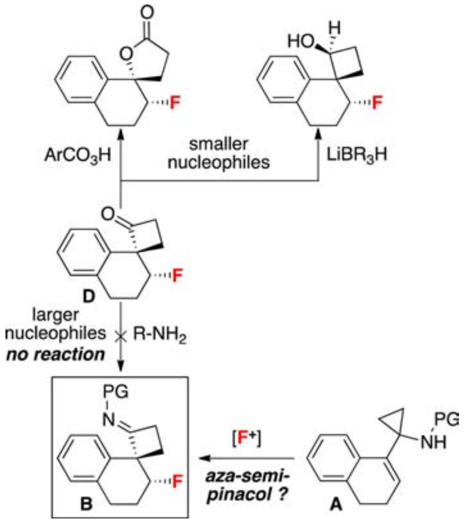
Medicinally relevant molecules overwhelmingly bear nitrogen functionality, with 179 of the top 200 brand name drugs containing at least one *N*-atom. Possible explanations for the prevalence of nitrogen in pharmaceuticals are diverse and include increased activity due to better interactions with the biological target as well as improved bioavailability.[1]

Furthermore, nitrogenous compounds that incorporate at least one fluorine atom are increasingly more valued as synthetic targets. The importance of fluorine is underlined by the fact that, despite its low abundance in biosynthetic routes, about 20−25% of all modern pharmaceuticals and agrochemicals incorporate at least one fluorine atom.[2] Consequently, the ability to access nitrogen- and fluorine-containing molecules bearing stereogenic carbon atoms is important due to their omnipresence in biologically active compounds.

Our group has recently applied the anionic phase-transfer fluorination protocol of Toste et al.[3] to perform the enantioselective fluorination-initiated semipinacol rearrangement of strained allylic alcohols.[4] When studying synthetic derivatizations of β-fluoro spiroketones (**D**) produced by our reaction, it was quickly noted that the reactivity of the carbonyl group in these molecules is significantly hampered, and synthetic manipulations were limited to the smallest of nucleophiles (such as the hydride anion for Red-Al reduction and the oxygen atom for Baeyer−Villiger oxidation). All attempts to condense the carbonyl function with a primary amine and carry out a reductive amination reaction were unsuccessful (Scheme 1). This synthetic limitation led us to consider the fluorination-initiated aza-semipinacol reaction as a means to access the imine products (**B**) directly.

To the best of our knowledge, the halogenation-initiated aza-semipinacol rearrangement of allylic amines was not reported in

Scheme 1. Motivation behind the Development of a Direct Fluorinative Aza-semipinacol Reaction



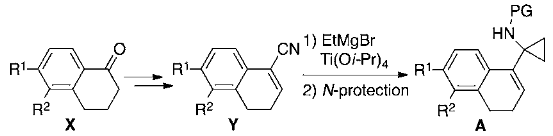
Received: July 30, 2014
Published: September 12, 2014

dx.doi.org/10.1021/ol5022355 | Org. Lett. 2014, 16, 4988−4991

scientific literature. In our opinion, this is due to the lower thermodynamic stability of the carbon−nitrogen double bond, as opposed to the carbon−oxygen double bond that is formed in the "normal" *oxa*-semipinacol transposition. Furthermore, if the aza-semipinacol rearrangement were to be initiated by exposing a strained allylic amine to an electrophilic halogen source, this last reagent would tend to react at the nitrogen atom rather than the carbon−carbon double bond. Nevertheless, we were motivated to probe the reactivity of various *N*-protected dihydronaphthalene-based cyclopropylamines of the type **A** with Selectfluor, under our previously established anionic phase-transfer conditions (Scheme 1).[4]

Before tackling any optimization studies, a reliable synthetic route to access compounds of the type **A** had to be established. First, dihydronaphthalenyl nitriles of the type **Y** were prepared from the commonly used α-tetralone scaffolds **X** (Scheme 2). These compounds were then subjected to a Kulinkovich−Szymoniak reaction with ethylmagnesium bromide and titanium(IV) isopropoxide.[5] Protection of the free amines furnished the desired allylic cyclopropylamines in moderate-to-good yields.[7]

Scheme 2. Preparation of the Substrate Allylic Cyclopropylamines (A)

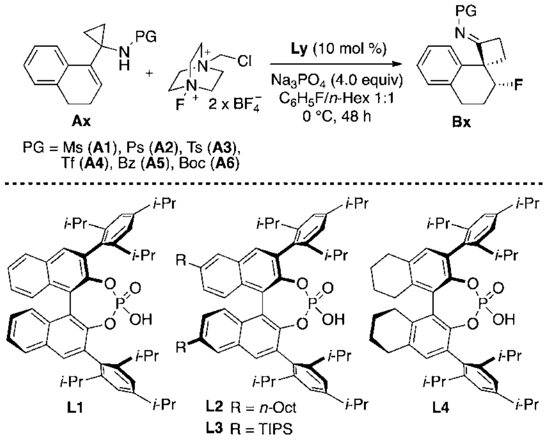


Optimization studies were carried out next on the dihydronaphthalene-based cyclopropylamines **Ax** with different protecting groups at the nitrogen atom: PG = Ms (**A1**), Ps (**A2**), Ts (**A3**), Tf (**A4**), Bz (**A5**), and Boc (**A6**). The initial trials were made with (*R*a)-TRIP phosphoric acid (**L1**), sodium phosphate as base, at 0 °C, in the binary mixture PhF/*n*-Hex 1:1 (v/v) as solvent (Table 1).

While no reaction took place with trifluoromethanesulfonyl- and *tert*-butoxycarbonyl-protected amines (**A4** and **A6**, respectively), substrates **A1** (PG = methanesulfonyl), **A2** (PG = phenylsulfonyl), **A3** (PG = *p*-tolylsulfonyl), and **A5** (PG = benzoyl) reacted to various extents to furnish diastereomerically pure material (>20:1 dr, according to ^{1}H NMR analysis of unpurified compounds). To our great delight, the sulfonylated products **B1**, **B2**, and **B3** structurally corresponded to the awaited β-fluoro cyclobutylimines (as evidenced from ^{1}H, ^{13}C, and ^{19}F NMR spectra) and were formed with decent levels of asymmetric induction (91:9, 88:12 and 89:11 er, respectively). On the other hand, the fluorinated product derived from the benzoylated substrate **A5** did not display a characteristic ^{13}C resonance at ca. 195 ppm (characteristic of an imine carbon), whereas its overall spectral properties were more consistent with a fluorocyclization-derived structure, similar to the ones reported by Toste et al.[3,7]

Moving to the more lipophilic variants of (*R*a)-TRIP, such as phosphoric acids **L2**, **L3**, and **L4**, led to an observable increase in yield of the β-fluoro cyclobutylimine product (**B1**). Moreover, the TIPS (triisopropylsilyl)-substituted phosphoric acid **L3** led to a slight increase in enantiomeric excess as well (up to 92:8 er, entry 8). Finally, the isolated yield of **B1** could be further improved by increasing the molar concentration to 0.08 M and extending the reaction time to 96 h (up to 85% yield, entry 10). Importantly, these changes did not affect the stereoselectivity of the fluorination-initiated aza-semipinacol reaction.

Table 1. Optimization of the Reaction Conditions



entry[a]	G_x	L_y	base	yield[b] (%)	dr[c]	er[d]
1	G_1	L_1	Na_3PO_4	67	>20:1	91:9
2	G_2	L_1	Na_3PO_4	48	>20:1	88:12
3	G_3	L_1	Na_3PO_4	73	>20:1	89:11
4	G_4	L_1	Na_3PO_4	0	n.d.	n.d.
5	G_5	L_1	Na_3PO_4	90[e]	>20:1	93:7
6	G_6	L_1	Na_3PO_4	0	n.d.	n.d.
7	G_1	L_2	Na_3PO_4	78	>20:1	91:9
8	G_1	L_3	Na_3PO_4	75	>20:1	92:8
9	G_1	L_4	Na_3PO_4	68	>20:1	91:9
10	G_1	L_3	Na_3PO_4	85[f]	>20:1	92:8
11	G_1	none	Na_3PO_4	trace	n.d.	n.d.
12	G_1	L_1	none	10[g]	10:1	59:41
13	G_1	none	Na_3PO_4	93[h]	4:1	50:50

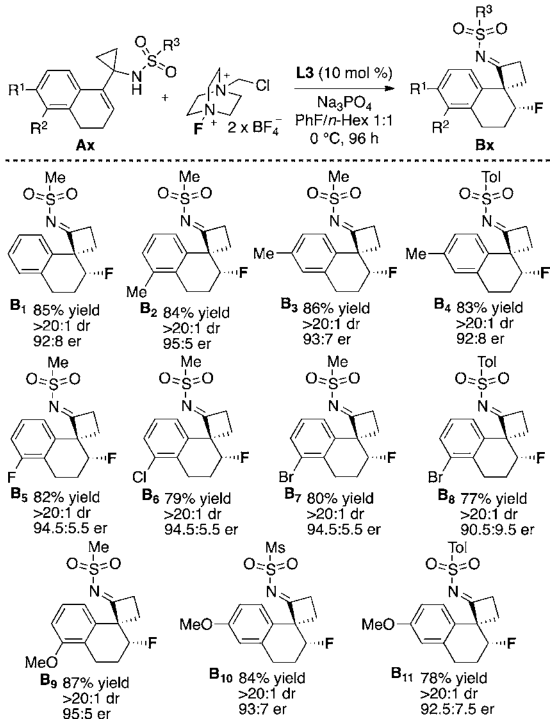
[a]Reaction conditions: see the Supporting Information. [b]Isolated yield after flash chromatography. [c]Determined by ^{1}H NMR analysis of unpurified mixtures. [d]Determined by chiral HPLC analysis of purified compounds. [e]Only the fluorocyclization product was isolated. [f]The reaction time was extended to 96 h, and the concentration was increased to 0.08 M. [g]^{1}H NMR conversion. [h]The reaction was performed in acetonitrile.

Racemic material was prepared by treating **A1** with Selectfluor in acetonitrile, under homogeneous reaction conditions (entry 13). Interestingly, in contrast to the "normal" oxa-semipinacol reaction for which the racemate was obtained as a ca. 1:1 mixture of diastereomers, the title aza-semipinacol rearrangement was moderately to-highly diastereoselective (depending on the substrate) even under these homogeneous reaction conditions.

Finally, omitting the phosphoric acid catalyst altogether led to no reaction in PhF/*n*-Hex (entry 11). Additionally, the addition of base turned out to be detrimental for the success of the fluorinative aza-semipinacol rearrangement, in terms of both the yield and enantioselectivity. Thus, when employing phosphoric acid **L1** in the absence of the sodium phosphate additive (entry 12), a significant drop in conversion and enantiomeric excess was noted. These observations support the assumption that the title process operates through anionic phase-transfer catalysis, where the chiral lipophilic phosphate anion is the catalytically active species in solution.[3,4]

Having established the optimal operational conditions, the generality of the fluorination-initiated aza-semipinacol reaction was probed next. To this end, methanesulfonyl- (x = 1−3, 5−7, 9, 10) and *p*-tolylsulfonyl- (x = 4, 8, 11) protected cyclopropylamines **Ax** were stirred with Selectfluor, sodium phosphate, and phosphoric acid **L3**, in PhF/*n*-Hex, at 0 °C, for 96 h (Scheme 3).

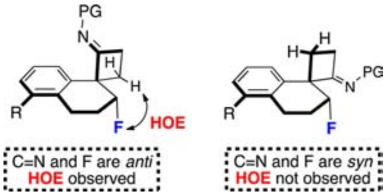
Scheme 3. Substrate Scope of the Fluorinative Aza-semipinacol Reaction



As can be seen from Scheme 3 above, the optimized aza-semipinacol reaction seems to tolerate both electron-releasing (MeO: products **B9**, **B10**, and **B11**) as well as electron-withdrawing (F, Cl, and Br: products **B5**, **B6**, **B7**, and **B8**) substituents at the C5 and C6 positions of the dihydronaphthalene ring. The enantiomer ratios of the product *β*-fluoro cyclobutylimines were generally high (up to 95:5 er for product **B9**). As already noted during optimization studies (vide supra), methanesulfonyl-protected substrates invariably led to more enantioselective reactions than their *p*-tolylsulfonyl-protected counterparts (for example, compare products **B7** and **B8**).

Initially, the relative configuration of the *β*-fluoro cyclobutylimine products in solution was tentatively assigned from heteronuclear Overhauser enhancement spectroscopy (HOESY, see Scheme 4).[6,7] This attribution was later confirmed by X-ray diffraction studies performed on the corresponding reduction products (vide infra).

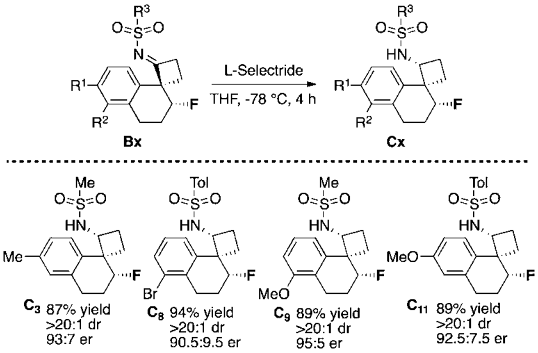
Scheme 4. Attribution of Relative Configuration of *β*-Fluoro cyclobutylimines in solution from ^{1}H−^{19}F NOE



As a next step, we were interested whether *β*-fluoro cyclobutylimines **Bx**, obtainable in high enantiomeric excesses following the title fluorination/aza-semipinacol reaction, could be reduced diastereselectively. If successful, the entire fluorination/aza-semipinacol/reduction sequence could provide a facile access to optically active fluorinated amines with three contiguous stereogenic centers, compounds of significant interest in the pharmacological industry.

After a collection of different reducing agents were screened, it was quickly established that L-Selectride in THF at −78 °C was optimal. With these conditions in hand, a representative panel of four *β*-fluoro cyclobutylimines **Bx** (*x* = 3, 8, 9 and 11) were successfully reduced to their corresponding fluorinated cyclobutylamines **Cx** (*x* = 3, 8, 9 and 11) (Scheme 5).

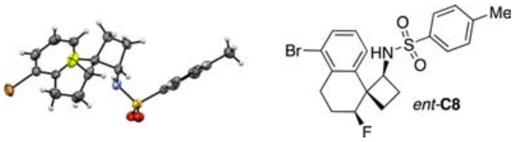
Scheme 5. Diastereoselective Reduction of *β*-fluoro Cyclobutylimines with L-Selectride



As can be seen from Scheme 5 above, the reduction took place smoothly for all four *β*-fluoro cyclobutylimines, affording the desired fluorinated amines in high isolated yields, high diastereoselectivity, and with complete retention of the chiral information.

Single crystals were grown from racemic *β*-fluoro cyclobutylamine **C8** for X-ray diffraction analysis.[8] The structure of *ent*-**C8** is given in Scheme 6 below. The high diastereoselectivity of L-Selectride reduction could be tentatively explained by the hydride ion attacking the imine C=N double bond from the face *anti* to the bulky edge of the phenyl ring.

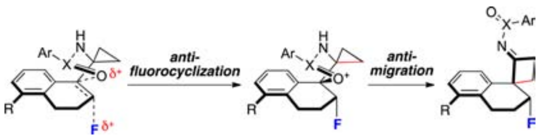
Scheme 6. X-ray Crystal Structure of *ent*-C8, Confirming the Relative Configuration



In accord with our previous assignment made from heteronuclear Overhauser enhancement spectroscopy, the X-ray crystal structure of racemic **C8** confirmed the *anti* orientation between the fluorine atom and the nitrogen-substituted terminus of the cyclobutane ring. Such a relative configuration is consistent with selective migration of the C−C bond that is *syn* to the fluoronium bridge in the parent allylic cyclopropylamine **A8**. This is rather unexpected because *anti* migration was observed previously for halogenation/semipinacol reactions of the related oxa substrates.[4,9] The dichotomy between the diastereoselectivities of aza and oxa rearrangements can be tentatively explained when considering the stronger electron-donating ability of nitrogen versus oxygen atoms. Consequently, the aza-semipinacol reaction presumably takes place via an open *β*-fluoro carbocation, as opposed to the oxa-semipinacol reaction that operates through a cyclic fluoronium bridge.

Alternatively, anchimeric assistance from the nitrogen protecting group might be operating as well (Scheme 7). In

Scheme 7. Tentative Stereochemical Model, Rationalizing the Observed *syn* C−C Migration

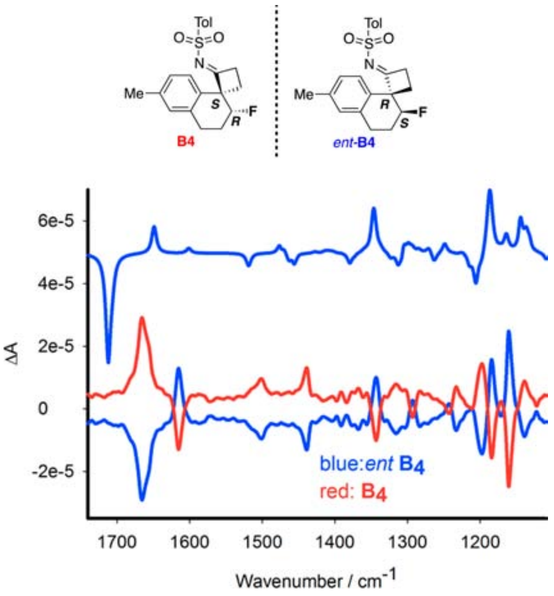


both cases, the outcome of reaction (cyclization versus C−C bond migration) becomes a function of the donor ability of the nitrogen atom (which itself depends on the nature of the protecting group).[10]

Depending on the chemical nature of the nitrogen protecting group, it may contribute to different extents to the stabilization of the intermediate β-fluoro carbocation. Thus, if fluorination occurs *anti* with respect to the protecting group (anchimeric assistance) and the subsequent C−C bond migration occurs *anti* with respect to the cyclic oxonium ion then an overall *syn* fluorination/C−C bond migration would result.

The absolute configuration of β-fluoro cyclobutylimine products was unequivocally established from vibrational circular dichroism (VCD) studies. To this end, calculations of several conformers of *ent*-**B4** were performed at the B3PW91/6-31G(d,p) level of theory. VCD spectra were then constructed for each conformer from the calculated rotational strengths.[7] For comparison with the experimental VCD spectra, a Boltzmann-weighted average of the calculated spectra of the conformers was used (Scheme 8).

Scheme 8. Experimental VCD Spectra for Both Enantiomers of B4 (Bottom), and Boltzmann-Weighted Average of Calculated VCD Spectra of *ent*-B4 (Top)



A good match between experimental and theoretical data is observed. By comparing the calculated spectrum for *ent*-**B4** with the experimental spectra for both enantiomers of **B4**, one can conclude that the absolute configuration is *S* and *R* for the spiro and the fluorinated carbons, respectively. This is consistent with *Re* face fluorination of the C−C double bond in the prochiral substrate.

In conclusion, we report here the first example of a highly enantioselective fluorinative aza-semipinacol rearrangement of strained allylic cyclopropylamines. The described reaction takes place under heterogeneous anionic phase-transfer conditions, and requires catalytic amounts of enantiopure phosphate anion derived from acid **L3** as the chirality inducer. The absolute configuration of product β-fluoro cyclobutylimines was assigned by VCD spectroscopy, while the relative configuration was determined by X-ray crystallography. Unexpectedly, a relative configuration consistent with *syn*-migration was observed. Most importantly, the product β-fluoro cyclobutylimines were reduced diastereoselectively into the corresponding chiral fluorinated amines, compounds of significant interest in the pharmacological industry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, NMR spectra, HPLC traces, computational details, IR and VCD spectra, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: Thomas.Buergi@unige.ch
*E-mail: Alexandre.Alexakis@unige.ch

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348. (b) Augner, D.; Gerbino, D. C.; Slavov, N.; Neudörfl, J.-M.; Schmalz, H. G. *Org. Lett.* **2011**, *13*, 5374. (c) Nozawa, Y.; Yamamoto, K.; Ito, M.; Sakai, N.; Mizoue, K.; Mizobe, F.; Hanada, K. *J. Antibiot.* **1997**, *50*, 635. (d) Comins, D.; Schilling, S.; Zhang, Y. *Org. Lett.* **2005**, *7*, 95. (e) Stuk, T. L.; Assink, B. K.; Bates, R. C.; Erdman, D. T.; Fedij, V.; Jennings, S. M.; Lassig, J. A.; Smith, R. J.; Smith, T. L. *Org. Process Res. Dev.* **2003**, *7*, 851. (f) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499.

(2) (a) Gribble, G. W. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer: New York, 1996; Vol. *68*, pp 1−498. (b) Gribble, G. W. In *Progress in the Chemistry of Organic Natural Products*; Kinghord, A. D., Falk, H., Kobayashi, J., Eds.; Springer: New York, 2009; Vol. *91*, pp 1−613. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (d) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645−652.

(3) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681−1684.

(4) Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9266−9270.

(5) Bertus, P.; Szymoniak, J. *Synlett* **2007**, *9*, 1346−1356.

(6) (a) Rinaldi, P. L. *J. Am. Chem. Soc.* **1983**, *105*, 5167−5168. (b) Yu, C.; Levy, G. C. *J. Am. Chem. Soc.* **1984**, *106*, 6533−6537.

(7) See the Supporting Information for details.

(8) The stereochemistry of *rac*-**C8** was confirmed by X-ray diffraction analysis. CCDC 1015431 contains all of the crystallographic data for this paper. This data is available free of charge from the Cambridge Crystallographic Data Centre under www.ccdc.cam.ac.uk/data_request/cif.

(9) Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. *Org. Lett.* **2013**, *15*, 5890−5893.

(10) As noted by one of the reviewers, depending on the chemical nature of the nitrogen protecting group, it may contribute at different extents to the stabilization of the intermediate β-fluoro carbocation.