Organic LETTERS
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

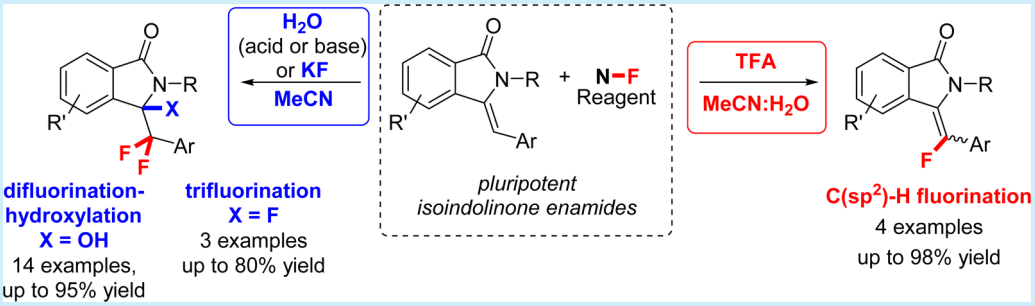
Direct Difluorination−Hydroxylation, Trifluorination, and C(sp^2)−H Fluorination of Enamides

Socrates B. Munoz,[†] Vinayak Krishnamurti,[†] Pablo Barrio,[‡] Thomas Mathew,[†] and G. K. Surya Prakash*[,†]

[†]Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089, United States

[‡]Departamento de Quimica Organica, Universidad de Valencia, E-46100 Burjassot, Spain

Supporting Information



ABSTRACT: A direct double functionalization involving both difluorination and hydroxylation of enamides is reported. With the appropriate combination of an electrophilic fluorinating reagent and H_2O, the most convenient and ecofriendly hydroxylating agent, the preparation of 3-(difluoroalkyl)-3-hydroxyisoindolin-1-ones was achieved under basic or Brønsted acidic conditions. Suitable conditions for trifluorination as well as C(sp^2)−H fluorination were also identified. Subsequent asymmetric functionalization of the obtained *gem*-difluorinated products has also been demonstrated.

Incorporation of fluorine into organic molecules imparts unique physicochemical and biological properties.[1] Hence, organofluorine compounds are of increasing interest in medicinal chemistry.[2] *gem*-Difluoromethylene[3] compounds have drawn increasing attention as the $-CF_2-$ unit can serve as a bioisostere to an oxygen atom in various functionalities such as alcohols,[4a] carbonyl groups,[4b] and phosphates.[5] The isoindolin-1-one scaffold is present in many naturally occurring products[6] as well as designed pharmaceuticals,[7] and it plays a key role in their specific biological properties (Figure 1). Surprisingly, methods for the preparation of fluorinated isoindolinones are scarce.[8,9]

Vicinal difunctionalization of unsaturated systems is one of the most direct, atom-economical, and synthetically important transformations.[10] Fluoro functionalization using pyridinium poly(hydrogen fluoride) (PPHF, Olah's reagent) in combination with several electrophilic reagents stands as a powerful strategy for the efficient preparation of fluorine-containing molecules.[11] The advent of electrophilic (or radical) fluorinating reagents[12] (primarily N−F reagents) has allowed for several alternative protocols.[13]

Because of our longstanding interest in organofluorine and heterocyclic chemistry,[14] we set out to develop a direct *gem*-difluorination−hydroxylation protocol for the preparation of CF_2-containing heterocycles. Inspired by an elegant work by Toste and co-workers[13d] on oxyfluorination of enamides **1**, we envisaged that the increased acidity of the α-proton (H_α) in the proposed α-fluoroiminium intermediate **A** would enable facile deprotonation, followed by subsequent oxyfluorination, resulting in the preparation of α,α-difluoro-*N*,*O*-aminal products **2** (Scheme 1).

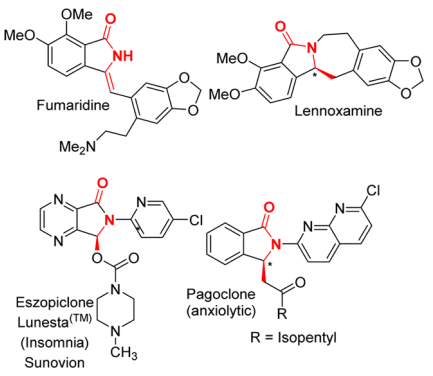


Figure 1. Naturally occurring and FDA-approved isoindolin-1-ones.

To validate this hypothesis, isoindolinone **1a** was selected as a model substrate and reacted with several electrophilic fluorine sources (N−F reagents) under varied reaction conditions (Table 1).

Received: December 22, 2017

DOI: 10.1021/acs.orglett.7b03994
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Working Hypothesis

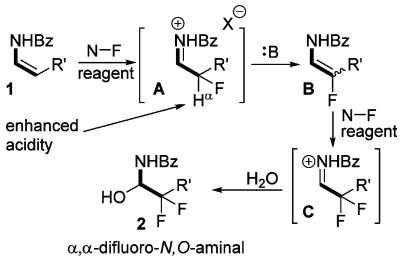
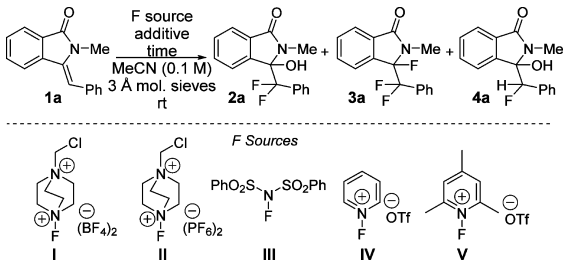


Table 1. Selected Optimization Studies[a]



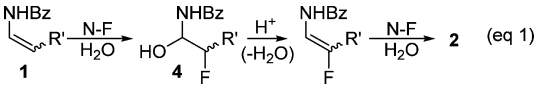
entry	F source (equiv)	additive (equiv)	time (h)	yield[b] (%) 2a	3a	4a
1[c,d]	I (2.0)	K_2CO_3 (1.2)	1	45	40	13
2	I (2.0)	K_2CO_3 (1.2)	1	24	63	3
3	I (3.2)	K_2CO_3 (1.2)	1	15	80	
4	I (2.0)	K_2CO_3 (1.2), KF (1.0)	1	14	80	
5	**II (2.2)**	**K_2CO_3 (1.2)**	**0.5**	**90**		
6	III (2.2)	K_2CO_3 (1.2)	12	trace		
7	IV (2.2)	K_2CO_3 (1.2)	12	dec		
8	V (2.2)	K_2CO_3 (1.2)	12	dec		
9[d]	I (2.2)	H_3PO_4 (10)	40	94		
10[d,e]	**I (2.2)**	**TFA (10)**	**4**	**95**		
11[d]	I (2.2)	BF_3/H_2O (10)	12	complex mixture		
12[d]	I (2.2)	TfOH (10)	12	complex mixure		

[a]Reactions were carried out with **1a** (0.25 mmol) and 3 Å molecular sieves (250 mg). [b]Determined by ^{19}F NMR using fluorobenzene internal standard. [c]MeCN (0.05 M) was used [d]Reaction performed in the absence of molecular sieves. [e]H_2O (100 μL was added after 1 h at 50 °C. See the Supporting Information for full details. TFA = trifluoroacetic acid, TfOH = trifluoromethanesulfonic acid.

Initials studies using Selectfluor, **I** (2.0 equiv), as the electrophilic fluorine source and K_2CO_3 (1.2 equiv) as the base in anhydrous MeCN afforded *α,α*-difluoro-*N,O*-aminal **2a** as the major product (Table 1, entry 1). However, the selectivity toward **2a** was rather poor, and varying quantities of monofluoro and trifluorinated derivatives (**4a** and **3a**, respectively) were also obtained.[15] Performing the reaction in the presence of 3 Å molecular sieves inhibited the formation of **4a** and afforded **2a** and **3a** in 24% and 63% yield, respectively (Table 1, entry 2).

The reaction using 3.2 equiv of **I** provided **3a** in 80% yield. A similar result was obtained when the reaction was conducted with **I** (2 equiv) in the presence of anhydrous KF (1 equiv) as an external fluoride source[16] (Table 1, entries 3 and 4). At this point, our attention shifted to alternative electrophilic fluorine sources, including F-TEDA-PF_6 (**II**), *N*-fluorobenzenesulfonimide (NFSI, **III**), and *N*-fluoropyridinium salts (**IV** and **V**) (Table 1, entries 5–8). From these reagents, **III** afforded traces of **2a**, while the use of pyridinium salts **IV** and **V** led to decomposition products. Notably, **II** emerged as the only reagent capable of promoting formation of the desired product **2a**, without the detection of trifluorinated derivative **3a**.[17] The optimized conditions were thus selected on the basis of this result (method A, Table 1, entry 5).

As a suitable alternative approach to this process, we envisioned that **1** could undergo a tandem hydroxyfluorination–dehydration–hydroxyfluorination sequence in the presence of Brønsted acids to afford the corresponding *α,α*-difluoro-*N,O*-aminal **2**, without requiring strictly anhydrous conditions. A practical, benchtop protocol can thus be developed via such a tandem sequence (eq 1).



Toward this end, several Brønsted acids were examined using commercially available Selectfluor (**I**) under benchtop conditions (Table 1, entries 9–12). To our delight, it was found that the use of trifluoroacetic acid (TFA) afforded **2a** with 95% yield in 4 h at 50 °C, whereas H_3PO_4 required 40 h at room temperature to provide a similar yield of **2a**. Stronger acids such as $BF_3{\cdot}H_2O$ or trifluoromethanesulfonic acid, provided complex reaction mixtures. Therefore, TFA was selected for further studies (method B, Table 1, entry 10).[15] Next, the reaction scope and limitations were examined using both methods A and B, and the results are shown in Scheme 2.

A variety of *N*-substituted-3-benzylideneisoindolinones were subjected to both optimized reaction conditions, and we found that, except for N-OMe isoindolinone **1e**, which failed to furnish the desired *gem*-difluorinated product, both methods were applicable to substrates bearing a variety of substituents on nitrogen including N-Me, N-Bn, and free N-H groups (Scheme 2, **2a–c**). In the case of N–Ph substituted isoindolinone **1d**, only method A under basic anhydrous conditions proved effective.

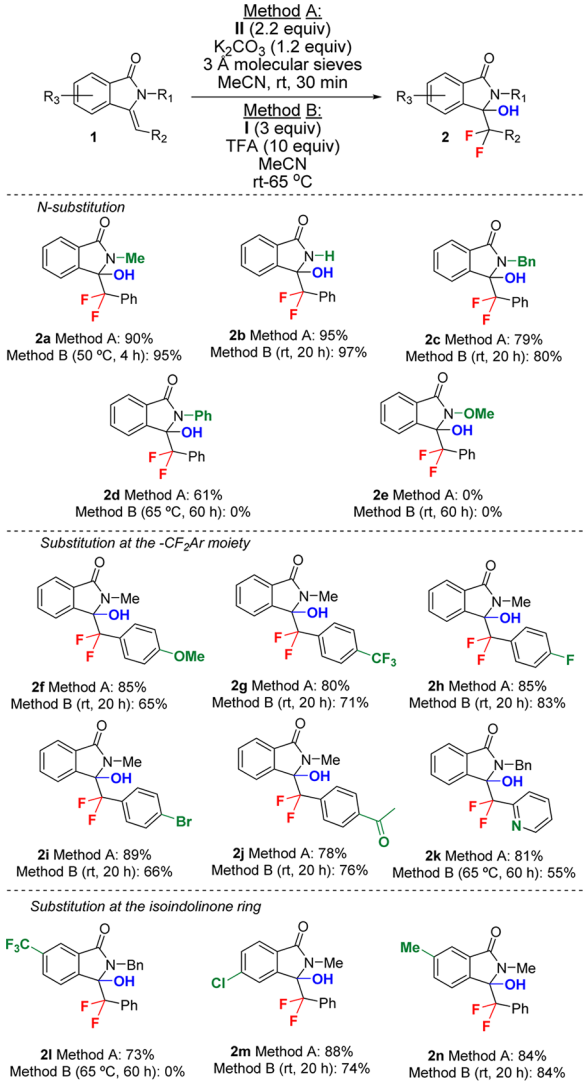
Substitution at the benzylidene moiety was next studied, and method A was found particularly effective for substrates bearing electron-donating as well as electron-withdrawing and heteroaryl functionalities. Accordingly, methoxy-, CF_3-, fluoro-, bromo-, acetyl-, and pyridyl-substituted isoindolinones **1f–k** smoothly reacted and afforded the desired *gem*-difluoro products **2f–k** after 30 min at room temperature (Scheme 2).

We next explored the effect of substituents on the isoindolinone ring and were pleased to find that the Cl-substituted substrate smoothly afforded the corresponding product **2m**. Similarly, both CF_3- and Me-substituted *gem*-difluoroisoindolinones **2l** and **2n**, respectively, could be easily obtained in high yields. The use of halo-substituted (Br and Cl) isoindolinones **1i** and **1m** is notable, as it allows for further product functionalization.

Next, parallel studies were performed using method B under Brønsted acidic conditions. In this case, the reactions are conveniently set up on the benchtop using commercially available **I**. Upon formation of derivatives **4** as detected by ^{19}F NMR (15 min), addition of TFA (10 equiv) to this reaction mixture effectively promotes a dehydration process, giving rise to difluorinated products **2**.[15] This approach was the method of choice for the substrates containing N-Me, N-Bn and N-H groups, affording the corresponding products **2a–c** in excellent yields, without any trace of monofluoro derivatives. Substrates bearing electron-donating (OMe) and electron-withdrawing groups (CF_3, F, Br, and acetyl) at the benzylidene ring also

DOI: 10.1021/acs.orglett.7b03994
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Tandem Difluorination–Hydroxylation of Isoindolin-1-ones[a]



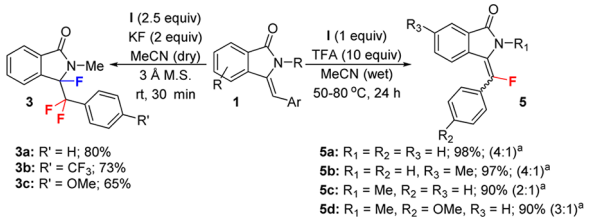
[a]Reactions performed using **1** (0.25 mmol, 1 equiv). See the Supporting Information for full details.

underwent the desired transformation after 20 h at room temperature leading to **2f–j** in good yields (65–83%). On the other hand, 2-pyridyl-substituted isoindolinone **1k** required prolonged heating (60 h at 65 °C) to furnish **2k** in 55% yield. In some cases, slightly inferior yields were obtained compared to method A (**2f–j** and **2m**), but the practicality, scalability,[18a] and ease of setup of method B make it an attractive approach. Importantly, controlling the initial amount of H_2O present in the system at the onset of the reaction is critical for the success of this method.[18b]

The results obtained from these parallel studies showed that both developed methods are complementary. In general, method A allows for a rapid synthesis (30 min) of *gem*-difluorinated products using **II** [F-TEDA-PF_6] under basic anhydrous conditions, and it is particularly effective in the cases where method B proved to be challenging (e.g., **2d**, **2k**, and **2l**). On the other hand, method B requires longer reaction times (4–60 h) and in some cases elevated temperatures were also necessary to afford products **2** in practical reaction times.

The utility of our approach was further demonstrated by the preparation of a series of hitherto unknown fluoroolefins **5** and trifluorinated products **3**. A C(sp^2)–H olefinic fluorination was successfully performed under conditions similar to those of method B, except that only 1 equiv of **I** was used. In addition, a trifluorination reaction of isoindolinones was achieved by the combination of **I** with KF as external fluoride source under basic, anhydrous conditions (Scheme 3).

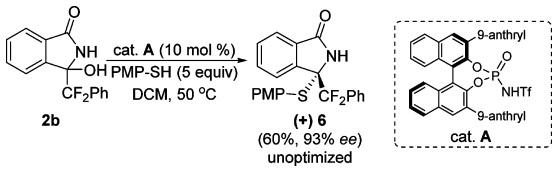
Scheme 3. C(sp^2)–H Olefinic Fluorination and Trifluorination of Isoindolinones



[a]See the Supporting Information for full details. *Z*/*E* ratio shown in parentheses.

Since iminium ion intermediates are prominent and well established versatile species,[19] accessing them from our products could greatly expand the utility of our method and enable molecular diversification by the addition of a variety of nucleophilic species. Accordingly, products **2** derived from this protocol are very well suited for this purpose.[20] To this end, **2b** was subjected to several chiral Brønsted acid-catalyzed nucleophilic addition reaction conditions.[21] An extensive experimental investigation showed that catalyst **A** promotes the enantioselective addition of *p*-methoxythiophenol (PMP-SH) in moderate yield and high enantiomeric excess (Scheme 4).[22] In

Scheme 4. Asymmetric Chemical Elaboration of 3-Hydroxy-3-difluoroalkylisoindolin-1-ones[a]



[a]See the Supporting Information. Tf = trifluoromethanesulfonyl; PMP = *p*-methoxyphenyl.

contrast to previously reported methodologies using 3-hydroxyisoindolin-1-one derivatives as substrates for chiral BINOL-derived phosphoric acid catalysis, **2b** required the use of more acidic triflimide derivative **A**.[23] This is not surprising given the deactivating effect of the *gem*-difluoro unit vicinal to the hemiaminal functionality.[24]

In conclusion, we have developed efficient methods for double functionalization (fluoro-functionalization) of enamides. Two complementary methods for difluorination–hydroxylation (under basic or Brønsted acidic conditions) were developed. Moreover, with appropriate selection of the reaction conditions, either an olefinic C(sp^2)–H fluorination or a trifluorination reaction can be accomplished. The utility of the obtained products was further demonstrated with the synthesis of enantioenriched *N,S*-aminal (+)-**6**.

DOI: 10.1021/acs.orglett.7b03994
Org. Lett. XXXX, XXX, XXX–XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03994.

Experimental procedures as well as NMR spectra and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gprakash@usc.edu.

ORCID

Thomas Mathew: 0000-0002-2896-1917

G. K. Surya Prakash: 0000-0002-6350-8325

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the Loker Hydrocarbon Research Institute is gratefully acknowledged. S.B.M. acknowledges financial support from a USC−CONACyT postdoctoral fellowship.

■ REFERENCES

(1) (a) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer-Verlag: Berlin, 2000. (b) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Weinheim, 2008. (c) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds In Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993.

(2) (a) Gouverneur, V.; Müller, K. *Fluorine in Pharmaceutical and Medicinal Chemistry: from biophysical aspects to clinical applications*; Imperial College Press: London, 2012. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (c) Catalán, S.; Munoz, S. B.; Fustero, S. *Chimia* **2014**, *68*, 382.

(3) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619.

(4) (a) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (b) Prakash, G. K.S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 3718. (c) O'Hagan, D.; Wang, Y.; Skibinski, M.; Slawin, A. M. Z. *Pure Appl. Chem.* **2012**, *84*, 1587.

(5) (a) Prakash, G. K. S.; Zibinsky, M.; Upton, T. G.; Kashemirov, B. A.; McKenna, C. E.; Oertell, K.; Goodman, M. F.; Batra, V. K.; Pedersen, L. C.; Beard, W. A.; Shock, D. D.; Wilson, S. H.; Olah, G. A. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 15693. (b) Upton, T. G.; Kashemirov, B. A.; McKenna, C. E.; Goodman, M. F.; Prakash, G. K. S.; Kultyshev, R.; Batra, V.; Shock, D. D.; Pedersen, L. C.; Beard, W. A.; Wilson, S. H. *Org. Lett.* **2009**, *11*, 1883.

(6) Blasko, G.; Gula, D. J.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 105.

(7) 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.

(8) (a) Bootwicha, T.; Panichakul, D.; Kuhakarn, C.; Prabpai, S.; Kongsaeree, P.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Org. Chem.* **2009**, *74*, 3798. (b) Pharikronburee, V.; Punirun, T.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Org. Biomol. Chem.* **2013**, *11*, 2022.

(9) Barrio, P.; Ibanez, I.; Herrera, L.; Roman, R.; Catalan, S.; Fustero, S. *Chem. - Eur. J.* **2015**, *21*, 11579.

(10) (a) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (c) Wolfe, J. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10224.

(11) (a) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, *1973*, 779. (b) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, *1973*, 780. (c) Olah, G. A.; Nojima, M. *Synthesis* **1973**, *1973*, 785. (d) York, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1994**, *59*, 6493.

(12) Baudoux, J.; Cahard, D. Electrophilic Fluorination with N−F Reagents. In *Organic Reactions*; John Wiley & Sons, Inc.: 2004; Vol. *69*, pp 347.

(13) (a) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. *Chem. Rev.* **2016**, *116*, 8912. (b) Miro, J.; del Pozo, C.; Toste, F. D.; Fustero, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 9045. (c) For a recent review, see: Chen, P.; Liu, G. *Eur. J. Org. Chem.* **2015**, *2015*, 4295. (d) Honjo, T.; Phipps, R. J.; Rauniyar, V.; Toste, F. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 9684. (e) For a related mono-fluorination of chiral enamides, see: Xu, Y.-S.; Tang, Y.; Feng, H.-J.; Liu, J.-T.; Hsung, R. P. *Org. Lett.* **2015**, *17*, 572.

(14) (a) Prakash, G. K. S.; Papp, A.; Munoz, S. B.; May, N.; Jones, J.-P.; Haiges, R.; Esteves, P. M.; Mathew, T. *Chem. - Eur. J.* **2015**, *21*, 10170. (b) Munoz, S. B.; Aloia, A. N.; Moore, A. K.; Papp, A.; Mathew, T.; Fustero, S.; Olah, G. A.; Surya Prakash, G. K. *Org. Biomol. Chem.* **2016**, *14*, 85. (c) Prakash, G. K. S.; Zhang, Z.; Wang, F.; Munoz, S.; Olah, G. A. *J. Org. Chem.* **2013**, *78*, 3300. (d) Surya Prakash, G. K.; Munoz, S. B.; Papp, A.; Mathew, T.; Olah, G. A. *Asian J. Org. Chem.* **2012**, *1*, 146. (e) Munoz, S. B.; Ni, C.; Zhang, Z.; Wang, F.; Shao, N.; Mathew, T.; Olah, G. A.; Prakash, G. K. S. *Eur. J. Org. Chem.* **2017**, *2017*, 2322. (f) Mathew, T.; Papp, A. Á.; Paknia, F.; Fustero, S.; Surya Prakash, G. K. *Chem. Soc. Rev.* **2017**, *46*, 3060.

(15) See the Supporting Information for full experimental details.

(16) These results suggest that the fluorine atom α to nitrogen originates from nucleophilic fluoride attack from BF_4^- (in the case of entry 3) or KF (entry 4) and not from the N−F unit.

(17) Though PF_6^- could release fluoride under certain conditions, the ability of **II** to selectively afford **2a** could be rationalized by the relative Lewis acidity strength of BF_3 vs PF_5 (fluoride ion affinity = 83.1 kcal/mol vs 94.9 kcal/mol, respectively). See: Christe, K. O.; Dixon, D. A.; McLemore, D.; Wilson, W. W.; Sheehy, J. A.; Boatz, J. A. J. *J. Fluorine Chem.* **2000**, *101*, 151.

(18) (a) Product **2b** was prepared successfully on a 1 g scale using method B. (b) As expected, large amounts of H_2O present at the onset of the reaction suppressed the dehydration of **4**. For a detailed study, see the Supporting Information.

(19) (a) List, B. *Chem. Commun.* **2006**, 819. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (d) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (e) Grondal, C.; Jeanty, V.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (f) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632.

(20) Huang, Y.-Y.; Cai, C.; Yang, X.; Lv, Z.-C.; Schneider, U. *ACS Catal.* **2016**, *6*, 5747.

(21) (a) Yu, X.; Wang, Y.; Wu, G.; Song, H.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2011**, *2011*, 3060. (b) Chen, M.-W.; Chen, Q.-A.; Duan, Y.; Ye, Z.-S.; Zhou, Y.-G. *Chem. Commun.* **2012**, *48*, 1698. (c) Suć, J.; Dokli, I.; Gredičak, M. *Chem. Commun.* **2016**, *52*, 2071. (d) Suneja, A.; Unhale, R. A.; Singh, V. K. *Org. Lett.* **2017**, *19*, 476.

(22) (a) We propose that the reaction proceeds through a TS analogous to the one reported in ref 21c, in agreement with Simon and Goodman's model; thus, we tentatively assign (+)-**6** as the *S* enantiomer. (b) Simón, L.; Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775. (c) The corresponding N-Me derivative **2a** gave rise to the addition product as a racemate, which lends support to the proposed transition state. See the Supporting Information.

(23) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.

(24) This deactivation could take place in two ways: (i) by decreasing the basicity of the hydroxyl group and (ii) by destabilizing the adjacent positive charge developed upon formation of the iminium ion.

DOI: 10.1021/acs.orglett.7b03994
Org. Lett. XXXX, XXX, XXX−XXX