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Stereoselective Mannich Reaction of *N*-(*tert*-Butylsulfinyl)imines with 3-Fluorooxindoles and Fluoroacetamides

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Abstract. A diastereoselective Mannich reaction has been developed for the construction of stereogenic C–F units by the reaction of α-fluoro-substituted amides, including highly activated 3-fluoro-oxindoles, and simple linear fluoroacetamides with N-*tert*-butylsulfinylimines. This method provides a concise route to a variety of structurally diverse α-fluoro-β-amino amides containing stereogenic fluorinated carbon centers. This protocol has the benefit of using readily accessible starting materials and is operationally simple. The Mannich reactions of cyclic and linear α-fluoro-substituted amides resulted in different stereochemical outcomes, suggesting that these substrates reacted via closed and open transition states, respectively.

Keywords: fluorine; asymmetric synthesis; amides; amines; chiral auxiliaries

Fluorine is highly regarded in medicinal chemistry, where the replacement of a hydrogen atom or a hydroxyl group with a fluorine atom can lead to improved binding affinity, metabolic stability and bioavailability.[1] It is therefore not surprising that there has been a resurgence in synthetic organofluorine chemistry during the past decade, which has led to considerable progress in this area.[2] In this context, research efforts towards the synthesis of stereogenic C–F units has attracted considerable attention because these units occur in many pharmaceuticals and bioactive molecules,[1c] including sofosbuvir (Figure 1), which is used in clinical practice to treat patients infected with the hepatitis C virus.

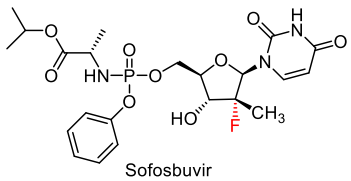
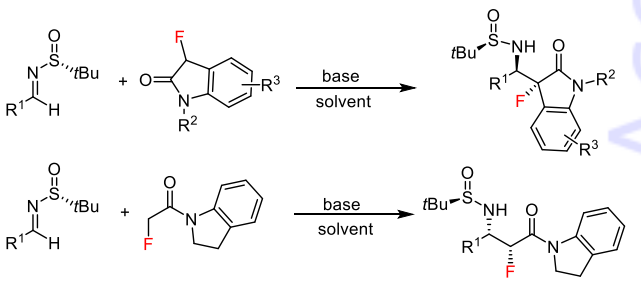


Figure 1. Sofosbuvir

α-Fluorocarbonyl compounds are important fluorocarbon nucleophiles[3-7] that have been widely used in the synthesis of stereogenic C–F units. The best results reported in this area to date have been achieved using α-fluoro-β-ketoesters,[4] 2-fluoro-1,3-diketo hydrates,[5] fluoromalonic acid halfthioesters,[6] and relatively reactive cyclic α-fluoroketones.[7] α-fluoro-substituted amides are also regarded as readily accessible fluorocarbon nucleophiles. However, the use of α-fluoro-substituted amides for the asymmetric construction of C–F motifs has been limited by the reluctance of these systems to enolize.[8-10] In this respect, highly activated 3-fluorooxindoles have often been used as surrogates for these systems and several reports have recently been published in the literature pertaining to the conjugate addition and asymmetric allylic alkylation reactions of these systems.[8] The use of simple α-fluoro-substituted amides in the asymmetric synthesis of C–F units is even less common. Very recently, Shibasaki, Kumagai and co-workers reported the first enantioselective addition of N-(fluoroacetyl)-7-azaindoline to N-Cbz-imines.[9] The diastereoselective aldol reactions of chiral fluoroacetyl-ephedrine-oxazolidinone with α-amino aldehydes have also been documented.[10]



Scheme 1. Mannich Reactions of α-Fluoro Amides with Ellman's Imines

We have an ongoing interest in the use of simple α-carbonyl compounds to synthesize stereogenic C–F centers.[11] Very recently, we showed that weakly

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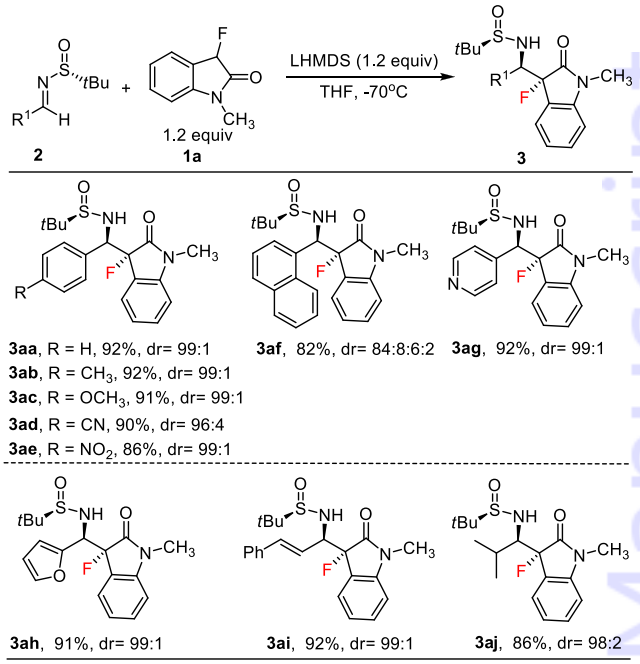
acidic α-fluoro carboxylate esters are competent fluorocarbon reagents that can be converted to α-fluoro-β-amino acid derivatives through a highly diastereoselective Mannich reaction.[11b,11c] Herein, we disclose an efficient Mannich reaction between 3-fluorooxindoles and Ellman's imines[12] to provide access to a wide variety of β-amino amides containing α-fluorinated stereogenic carbon centers (Scheme 1). This method was also extended to N-(fluoroacetyl)-indoline.

We initially evaluated 3-fluorooxindole **1a** as a model substrate because this structural motif can be found in a wide range of important pharmaceutical agents.[13] This substrate was also selected as a model system because it would react via a stereodefined enolate intermediate. After a quick survey of the reaction parameters, we identified an optimized reaction system consisting of **1a** (1.2 mmol), imine **2a** (1.0 mmol) and LiHMDS (1.2 mmol) in THF at −70 °C, which afforded **3aa** in 92% yield with excellent diastereoselectivity up to 99:1 (Table 1). The current reaction can be scaled to 5 mmol (for **1a**), yielding compound **3aa** in a slightly higher yield (1.74 g, 93% yield, 99:1 dr).

We then checked the substrate scope of the reaction with regard to the imines. As shown, aromatic (**3aa**–**3af**), heteroaromatic (**3ag** and **3ah**) and aliphatic imines (**3ai** and **3aj**) all reacted as anticipated to afforded the desired products in satisfactory yields with good to excellent diastereoselectivities. The introduction of a substituent at the para-position of the aromatic rings had a considerable impact on the yield of reaction. For example, substrates bearing an electron-donating group afforded the desired products in excellent yields with excellent diastereoselectivities (**3ab** and **3ac**), whereas those bearing an electron-withdrawing group at the same position gave lower yields and diastereoselectivities (**3ad**–**3ae**). Importantly, 4-pyridinyl and 2-furanyl imines also reacted smoothly under the standard reaction conditions to afford the corresponding addition products **3ag** and **3ah** with excellent diastereoselectivities. Aliphatic α,β-unsaturated imine **2i** also reacted as expected to afford the desired product **3ai** in 92% yield with 99:1 diastereoselectivity. Even the aliphatic isovaleraldehyde sulfinyl imine **2j**, which has a tendency to undergo enolization under strongly basic conditions, was well tolerated, affording the corresponding products **3aj** in very good yield (86%).

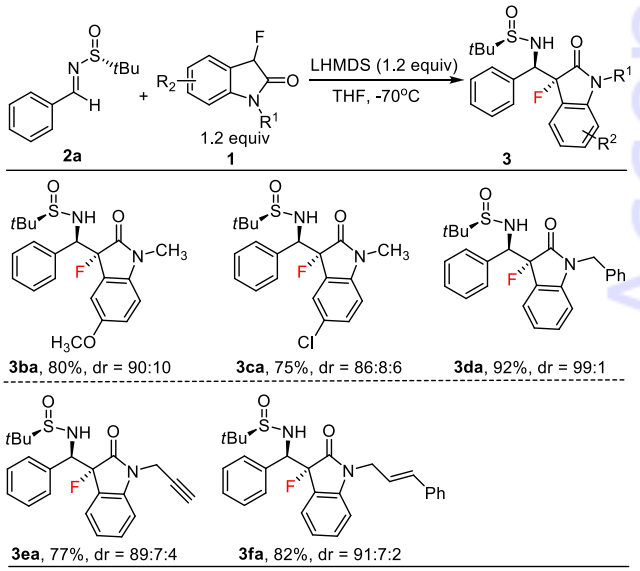
We subsequently proceeded to investigate the generality of this reaction using a variety of different 3-fluorooxindole derivatives. As shown (Table 2), the introduction of an electron-donating methoxy (**3ba** *vs* **3aa**) or electron-withdrawing chloro (**3ca** *vs* **3aa**) substituent led to decreases in the diastereoselectivity, indicating that steric interactions between the reactants may play an important role in determining the stereochemical outcome of the reaction. The influence of the N-substituent on the outcome of reaction was also evaluated. The N-benzyl substituted substrate **1d** gave the expected product in excellent yield and diastereoselectivity (**3da**, 92% yield, 99:1 dr). Last, the N-allyl and N-propargyl substituted substrates **1e** and **1f** also reacted smoothly to afford the corresponding products **3ea** and **3fa** in 77% and 82% yields with diastereoselectivities of 89:7:4 and 91:7:2, respectively. It is noteworthy that the double and triple bonds in these products could be used as handles for further functionalization.[14]

Table 1. The Mannich Reaction of 3-Fluoro-oxindoles **1a** with Ellman's Imines[a,b]



[a] The yields refer to isolated yields of the major stereoisomers. [b] dr determined by ^{19}F NMR spectroscopy on the crude products.

Table 2. The Mannich Reaction of 3-Fluoro-oxindoles **1b**–**1f** with Ellman's Imine **2a**[a,b]



[a] The yields refer to the isolated yields of the major stereoisomers. [b] dr determined by ^{19}F NMR spectroscopy on the crude products.

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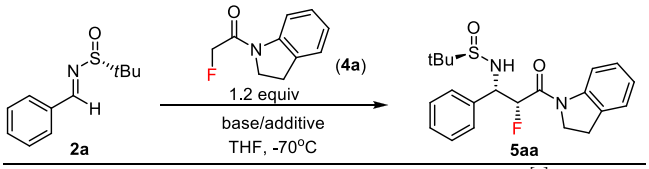
Linear α-fluoro-substituted amides, especially fluoroacetamides, are challenging substrates for the asymmetric synthesis of stereogenic C–F units, because they do not tend to form stereodefined enolate intermediates. To determine whether this new Mannich process was amenable to the reaction of linear α-fluoro-substituted amides with N-sulfinyl imines, we investigated the reaction of the readily accessible substrate **4a** with N-sulfinylimine **2a** under the reaction conditions used in Table 2. Disappointingly, however, this reaction resulted in a low diastereoselectivity (dr = 55:24:17:4) (Table 3, entry 1). Furthermore, changing the solvent to toluene or the base to NaHMDS had no discernible impact on the outcome of the reaction (Table 3, entries 2 and 3). Further optimization revealed that the use of KHMDS as a base afforded the desired product **5aa** with a diastereoselectivity of 93:7 (Table 3, entry 5). However, the conversion ratio of **4a** was low, with 35% of the material being recovered unchanged. We also investigated the effect of adding an additive to the reaction (Table 3, entry 6–8) or a large amount of base (Table 3, entry 9), but all of these changes failed to produce an increase in the yield. With the optimum conditions (Table 3, entry 5), the current reaction can be performed on a 5 mmol scale, furnishing the product **5aa** in a comparable yield (1.32 g, 68% yield, 94:6 dr).

Table 3. Survey of Reaction Conditions for the Addition of Fluoromethyl Amide **4a** to Imine **2a**[a]



Entry	base	Solvent /additive	Yield (%)	dr[g]
1[b]	LHMDS	THF	92[e]	55:24:17:4
2[b]	LHMDS	PhMe	85[e]	82:18
3[b]	NaHMDS	THF	90[e]	82:16:2
4[b]	KHMDS	THF	58[f]	94:6
5[c]	KHMDS	THF	70[f]	93:7
6[c]	KHMDS	THF/HMPA	67[f]	89:6:5
7[c]	KHMDS	THF/LiBr	57[f]	92:8
8[c]	KHMDS	THF/ $MgBr_2$	60[f]	90:10
9[d]	KHMDS	THF	66[f]	90:10

[a] A combination of 1.5 mL of THF and/or 0.15 mL of HMPA (or 0.1 mmol metal additive) was used on a 0.5 mmol scale (for **2a**). [b] The ratio of **2a**/**4a**/base is 1.0/1.2/1.2. [c] The ratio of **2a**/**4a**/base is 1.0/1.2/1.4. [d] The ratio of **2a**/**4a**/base is 1.0/1.5/1.7. [e] The yields refer to the combined yields of the stereoisomers. [f] The yields refer to the isolated yields of the major stereoisomers. [g] dr determined by ^{19}F NMR spectroscopy on the crude products.

Using KHMDS as the base (Table 3, entry 5), we evaluated the substrate scope of the imine moiety. As shown in Table 4, aromatic (**5aa**–**5aj**), heteroaromatic (**5ak** and **5al**) and α,β-unsaturated aliphatic imines (**5am**) were all found to be suitable substrates for this reaction, generally affording the corresponding products with diastereoselectivities (around 90:10) in moderate to good yields. The results revealed that the position of the substituent on the aromatic ring had very little impact on the outcome of the reaction, as exemplified by the ortho-, meta- and para-methyl substituted substrates **5ab**, **5ad** and **5af**, which gave comparable yields and diastereoselectivities. However, the electronic properties of the substituent had a noticeable effect on the reaction. For example, substrates bearing an electron-donating substituent (**5ac**, **5ad**, **5af** and **5ag**) gave higher yields than those bearing an electron-withdrawing substrate (**5ae**, **5ah** and **5ai**). 2-Furanyl imines were also found to be good substrates, although the inclusion of a methyl group at the 2-position led to a slight decrease in the yield and diastereoselectivity (**5ak** *vs* **5al**). The α,β-unsaturated aliphatic imine substrate **2m** also reacted smoothly under the standard conditions to afford the desired product **5am** with a diastereoselectivity of 92:5:3. However, aliphatic imines bearing an α-hydrogen such as the butylaldehyde imine **2n** failed to react as expected because of their tendency to enolize under the strongly basic reaction conditions, with compound **4a** being recovered almost quantitatively.

We also evaluated the performance of several other fluoromethyl amides in the Mannich reaction, including amides derived from the reaction of methyl fluoroacetate with various amines, including N,N-diethyl amine (**4b**), N,N-dibutyl amine (**4c**), morphine (**4d**) and piperidine (**4e**). The results revealed that these reaction generally proceeded well, albeit with low diastereoselectivities (see the Supporting Information), which indicated that the structure of the amide had a considerable impact on the diastereoselectivity of the reaction. Fluoroacetamide **4f** derived from indole was not a competent substrate; complex reaction mixtures were afforded.

The absolute configurations of **3ag** and **5ah** were determined by single-crystal X-ray analysis.[15] Notably, the fluoro and amino substituents in compound **3ag** adopted a *anti* configuration, whereas the same substituents adopted a *syn* configuration in compound **5ah**. This result indicated that different transition states were involved in the reactions of the 3-fluoro-oxindoles **1** and fluoromethyl amides **4** with Ellman's imines. A chair-like transition state was proposed to explain the stereochemical outcome of compound **3**, where the Z-fluoroenolate of the α-fluoro-substituted amide would approach the less hindered Si face of the (R)-sulfinylimine substrate (Figure 2a). Similar transition states have been suggested by Davis, Ellman and several other researchers to rationalize the condensation reactions of metal enolates with sulfinylimines.[12] It is

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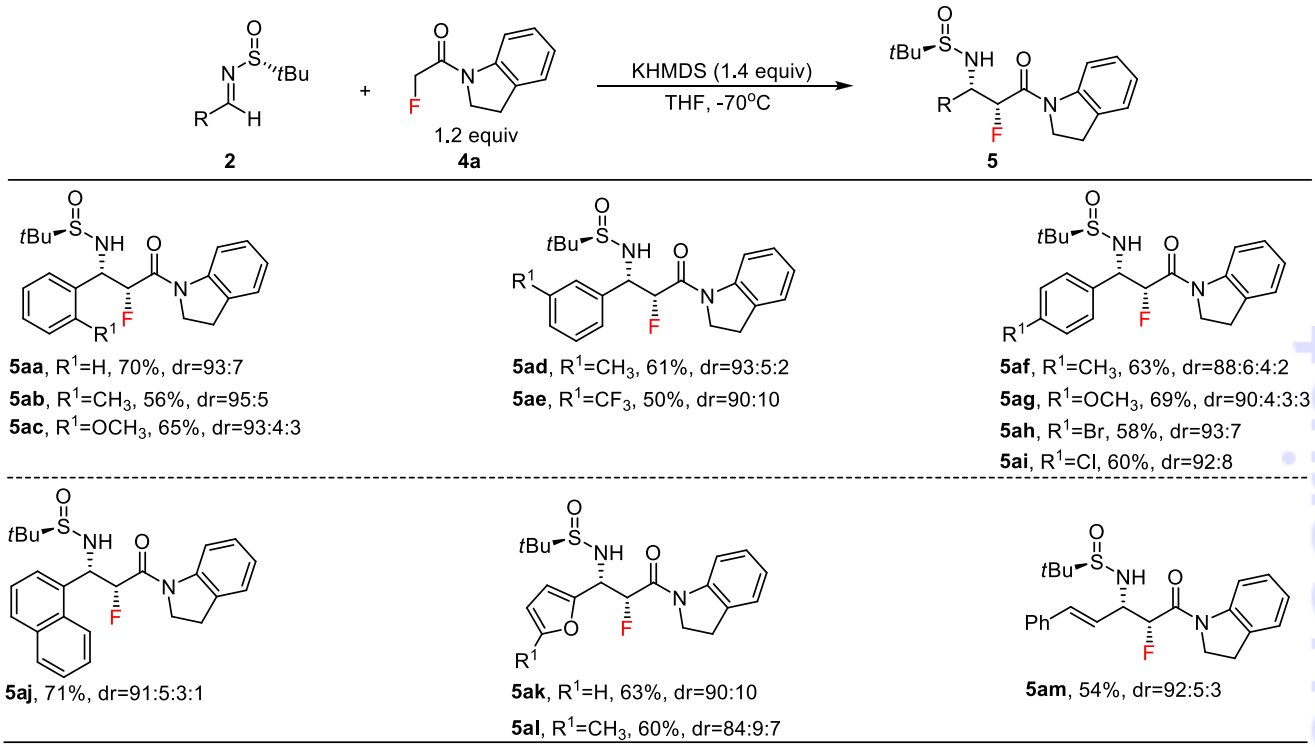
Table 4. The Mannich Reaction of Fluoromethyl Amide **4a** with Ellman's Imine **2**[a,b,c]



[a] The yields refer to isolated yields of the major stereoisomers. [b] dr determined by ^{19}F NMR spectroscopy on the crude product. [c] For **5ae**, **5ah** and **5ai**, a combination of KHMDS (1.0 equiv) and NaHMDS (0.4 equiv) was used (to increase the yield).

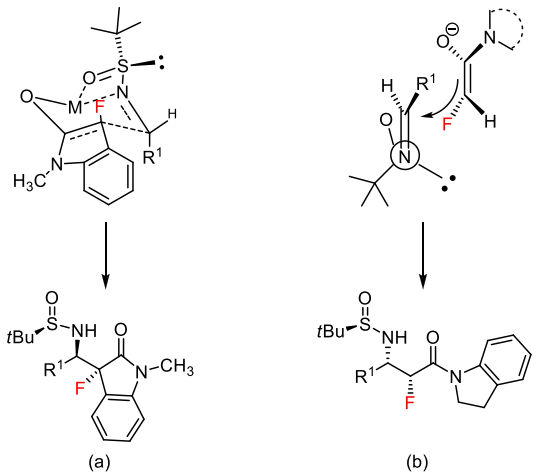


Figure 2. (a) Closed transition-state mode proposed for the addition of 3-fluoro-oxindole **1** to Ellman's imine. (b) Open transition-state mode proposed for the addition of fluoromethyl amide **4a** to Ellman's imine.

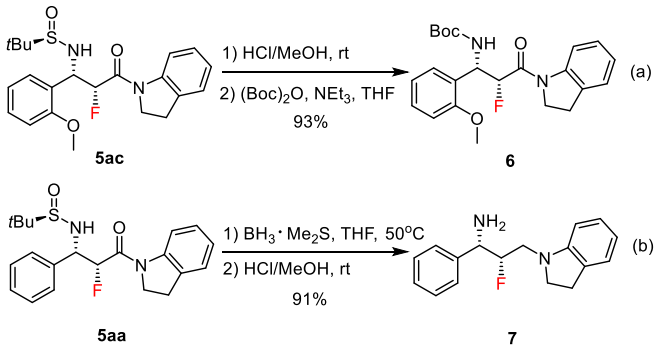
noteworthy that the addition of the fluoroenolate of 3-fluoro-oxindole (derived from the β-keto-amide hydrate via an in situ detrifluoroacetylation) to N-sulfinyl imine afforded the *syn*-configured product, with the Z-fluoroenolate attacking the Si face of the (S)-sulfinylimine substrate. [5d]

The diastereoselectivity observed for compound **5** was explained based on an open transition state (Figure 2b). As shown, the Z-enolate of fluoromethyl amide **4** would adopt an antiperiplanar orientation and attack the sterically less hindered *Si* face of (R)-sulfinylimine to afford the observed stereoselectivity.[16] We previously reported a comparable transition state to explain the stereochemical outcome of the reaction of methyl fluoroacetate with N-sulfinyl imines. [11b]

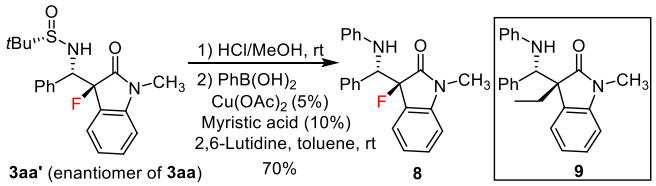
To demonstrate the utility of our method for preparing useful organofluorine compounds, we selected compound **5** as a representative substrate for further elaborations. As shown in Scheme 2a, compound **5ac** was initially treated with HCl/MeOH to remove its *t*BuS(O) group. The resulting ammonium salt was then treated with Boc_2O to give the N-Boc product **6** as a single diastereomer in 93% yield (Scheme 2a). This highlights the robust nature of this newly formed fluorinated α-carbon center to mildly acidic or basic conditions. Moreover, the amide moiety in compound **5aa** can be reduced efficiently with borane-SMe_2 complex giving the 3-indolinyl intermediate which, without purification, further underwent the removal of the *t*BuS(O) group with HCl/MeOH to afford the free amine **7** in 91% yield over the two steps (Scheme 2b).

The synthetic utility of our protocol was further demonstrated by the synthesis of compound **8** containing the 3-aminomethyl-oxindole scaffold. The *t*BuS(O) group was readily cleaved with HCl/MeOH affording the corresponding intermediate which,

without purification, was subjected to copper-catalyzed couping with $PhB(OH)_2$[17] to give compound **8**, and its 3-ethyl analogue **9** has been reported to be bioactive against human breast cancer MCF-7 cells (Scheme 3).[18]



Scheme 2. Transformation of the Mannich Product **5**



Scheme 3. Synthesis of the NH-Ph Compound **8**

In summary, we have developed a highly diastereoselective Mannich reaction of α-fluoro-substituted amides. 3-Fluoro-oxindoles and fluoromethyl amides behaved as competent substrates for this reaction, affording the corresponding α-fluoro-β-amino amides in a concise and efficient manner. The differences observed in the stereoselectivities of these two different types of substrate were attributed to them progressing via closed and open transition states. This new process represents a robust approach for the syntheses of diverse α-fluoro-β-amino carbonyl compounds bearing a stereogenic C–F unit.

Experimental Section

Typical Procedure for the Diastereoselective Addition of *N*-Methyl 3-Fluoro-oxindoles (1a) to N-*tert*-Butylsulfinyl Imine (2).

Under a N_2 atmosphere, LHMDS (1.2 equiv, 0.6 mL, 1.0 mol/L in THF) was added slowly to a mixture of **1a** (0.6 mmol, 1.2 equiv), imine **2** (0.5 mmol, 1.0 equiv), and THF (1.5 mL) at −70 °C. Reaction mixtures were stirred at this temperature for 30 min. Then, 1 N TFA/THF (2 mL) was added, and the quenched reaction mixture was extracted three times with ethyl acetate (20 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum, followed by flash column chromatography on silica gel, gave the corresponding product **3**.

Acknowledgements

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References

[1] a) *Fluorine in Medicinal Chemistry and Chemical Biology*; I. Ojima, Ed.; Wiley-Blackwell: Chichester, U.K., **2009**; b) J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Hoboken, NJ, **2008**; c) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.

[2] For selected reviews, see: a) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem., Int. Ed.* **2013**, *52*, 8214–8264; b) J. R. Wolstenhulme, V. Gouverneur, *Acc. Chem. Res.* **2014**, *47*, 3560–3570; c) P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, J.-F. Paquin, *Chem. Rev.* **2015**, *115*, 9073–9174; d) X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev.* **2015**, *115*, 826–870; e) J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455–529; f) C. Ni, M. Hu, J. Hu, *Chem. Rev.* **2015**, *115*, 765–825.

[3] α-Haloimines have often been used as masked α-haloketones in organic synthesis, see; a) G. Verniest , E. Van Hende , R. Surmont , N. De Kimpe, *Org. Lett.* **2006**, *8*, 4767–4770; b) S. Mangelinckx, N. Giubellina, N. De Kimpe, *Chem. Rev.* **2004**, *104*, 2353–2399; c) N. Giubellina, W. Aelterman, N. De Kimpe, *Pure Appl. Chem.* **2003**, *75*, 1433–1442; d) J. T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry; John Wiley & Sons: New York, **1991**; e) N. De Kimpe, P. Sulmon, N. Schamp, *Angew. Chem., Int Ed.* **1985**, *24*, 881–882; f) J. T. Welch, K. W. Seper, *J. Org. Chem.* **1988**, *53*, 2991–2999.

[4] a) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem., Int. Ed.* **2009**, *48*, 7604–7607; b) W.-B. Liu, C. M. Reeves, B. M. Stoltz, *J. Am. Chem. Soc.* **2013**, *135*, 17298–17301; c) Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang, C.-H. Tan, *Chem. -Eur. J.* **2010**, *16*, 779–782; d) H.-F. Cui, Y.-Q. Yang, Z. Chai, P. Li, C.-W. Zheng, S.-Z. Zhu, G. Zhao, *J. Org. Chem.* **2010**, *75*, 117–122; e) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. W. Wong, C.-H. Tan, *Angew. Chem., Int. Ed.* **2009**, *48*, 3627–3631; f) X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.* **2009**, 2044–2046; g) X. Han, F. Zhong, Y, Lu, *Adv. Synth. Catal.* 2010, *352*, 2778–2782.

[5]a) H. Mei, C. Xie, J. L. Aceña, V. A. Soloshonok, G. V. Röschenthaler, J. Han, *Eur. J. Org. Chem.*, **2015**, 6401–6412; b) I. Saidalimu, X. Fang, X. P. He, J. Liang, X. Yang, F.-H. Wu, *Angew. Chem., Int. Ed.* **2013**, *52*, 5566–5570; c) C. Xie, L. Wu, J. Han, V. A. Soloshonok, Y. Pan, *Angew. Chem., Int. Ed.* **2015**, *54*, 6019–6023; d) C. Xie, L. Zhang, W. Sha, V. A. Soloshonok, J. Han, Y. Pan, *Org. Lett.* **2016**, *18*, 3270–

3273; e) X. Liu, J. Zhang, L. Zhao, S. Ma, D. Yang, W. Yan, W. Wang, *J. Org. Chem.* **2015**, *80*, 12651–12658.

[6] a) J. Saadi, H. Wennemers, *Nat. Chem.* **2016**, *8*, 276–280; b) E. Cosimi, O. D. Engl, J. Saadi, M.-O. Ebert, H. Wennemers, *Angew. Chem., Int. Ed.* **2016**, *55*, 13127–13131.

[7] a) B. M. Trost, T. Saget, A. Lerchen, C.-I. Hung, *Angew. Chem., Int. Ed.* **2016**, *55*, 781–784; b) V. Vaithiyanathan, M. J. Kim, Y. Liu, H. Yan, C. E. Song, *Chem. Eur. J.* **2017**, *23*, 1268–1272; c) Y. Zhao, Y. Pan, H. Liu, Y. Yang, Z. Jiang, C.-H. Tan, *Chem. Eur. J.* **2011**, *17*, 3571–3574; d) S. Arai, M. Oku, T. Ishida, T. Shioiri, *Tetrahedron Lett.* **1999**, *40*, 6785–6789; e) B. Thierry, T. Perrard, C. Audouard, J.-C. Plaquevent, D. Cahard, *Synthesis* **2001**, 1742–1746.

[8] a) K. Balaraman, C. Wolf, *Angew. Chem., Int. Ed.* **2017**, *56*, 1390–1395; b) X. Dou, Y. Lu, *Org. Biomol. Chem.* **2013**, *11*, 5217–5221; c) T. Wang, D. L. Hoon, Y. Lu, *Chem. Commun.* **2015**, *51*, 10186–10189; d) Y. Jin, M. Chen, S. Ge, J. F. Hartwig, *Org. Lett.* **2017**, *19*, 1390–1393.

[9] L. Brewitz, F. A. Arteaga, L. Yin, K. Alagiri, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2015**, *137*, 15929–15939.

[10] a) C. Albler, W. Schmid, *Eur. J. Org. Chem.* **2014**, 2451–2459; b) C. Albler, W. Schmid, *Eur. J. Org. Chem.* **2015**, 1314–1319.

[11] a) Y. Li, X. Li, H. Shang, X. Chen, X. Ren, *J. Org. Chem.* **2016**, *81*, 9858–9866; b) H. Shang, Y. Li, X. Li, X. Ren, *J. Org. Chem.* **2015**, *80*, 8739–8747; c) X. Li, Y. Li, H. Shang, *Org. Biomol. Chem.* **2016**, *14*, 6457–6461.

[12] For the application of N-sulfinyl imines in synthesis, see: a) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600–3740; b) F. A. Davis, *J. Org. Chem.* **2006**, *71*, 8993–9003; c) D. Morton, R. A. Stockman, *Tetrahedron* **2006**, *62*, 8869–8905.

[13] a) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.* **2005**, *127*, 10164–10165; b) P. Hewawasam, V. K. Gribkoff, Y. Pendri, S. I. Dworetzky, N. A. Meanwell, E. Martinez, C. G. Boissard, D. J. Post-Munson, J. T. Trojnacki, K. Yeleswaram, L. M. Pajor, J. Knipe, Q. Gao, R. Perrone, J. E. Starrett, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1023–1026.

[14] a) R. Lázaro, R. Román, D. M. Sedgwick, G. Haufe, P. Barrio, S. Fustero, *Org. Lett.* **2016**, *18*, 948–951; b) P. Barrio, I. Ibáñez, L. Herrera, R. Román, S. Catalán, S. Fustero, *Chem. -Eur. J.* **2015**, *21*, 11579–11584; c) S. Fustero, R. Lázaro, N. Aiguabella, A. Riera, A. Simón-Fuentes, P. Barrio, *Org. Lett.* **2014**, *16*, 1224–1227; d) S. Fustero, R. Lázaro, L. Herrera, E. Rodríguez, N. Mateu, P. Barrio, *Org. Lett.* **2013**, *15*, 3770–3773.

[15] CCDC 1537505 (**3ag**) and CCDC 1537519 (**5ah**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] a) M. Hennum, H. Fliegl, L.-L. Gundersen, O. Eisenstein, *J. Org. Chem.* **2014**, *79*, 2514–2521; b) Y. Arroyo, A. Meana, J. F. Rodriguez, M. A. Sanz-Tejedor, I. Aloson, J. L. Garcia Ruano, *J. Org. Chem.* **2009**, *74*, 4217–4224.

[17] a) J. C. Antilla, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 2077–2079; b) D. M. T. Chan, K. L. Monaca, R.-P. Wanag, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933–2936; c) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941–2944.

[18] a) W.-H. Hu, M. Li, L. Zan, J. Zhou, X. Zhang, L.Yang, *patent* CN 102491931, **2012**; b) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle, W.-H. Hu, *Nature Chem.* **2012**, *4*, 733–738.

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