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Detrifluoroacetylative in Situ Generation of Free 3-Fluoroindolin-2-one-Derived Tertiary Enolates: Design, Synthesis, and Assessment of Reactivity toward Asymmetric Mannich Reactions

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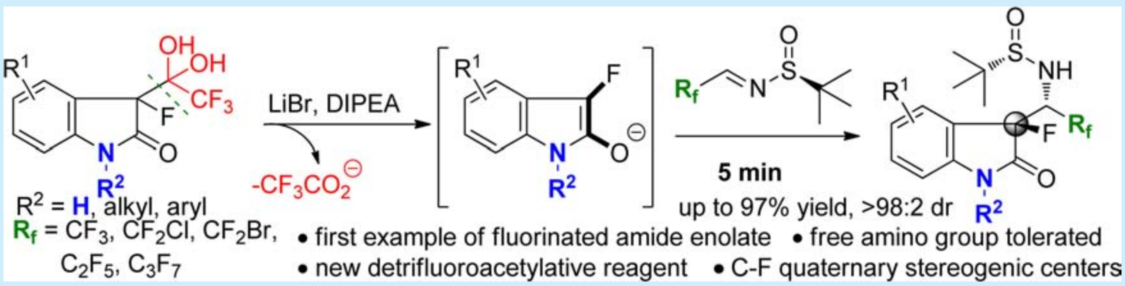
Supporting Information

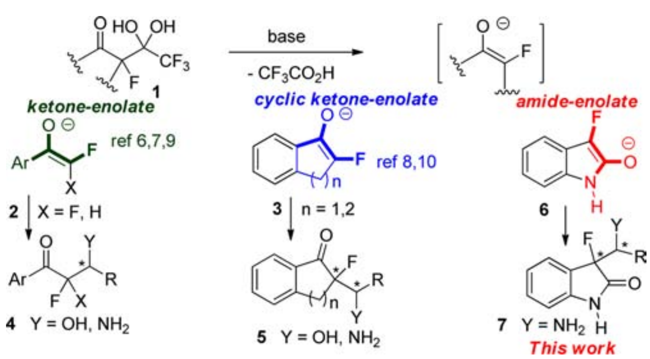


ABSTRACT: The discovery of detrifluoroacetylative in situ generation of a new type of fluorinated amide enolates derived from 3-fluoroindolin-2-one and their asymmetric Mannich additions with sulfinylaldimines bearing fluoroalkyl groups is reported, which afforded α-fluoro-β-(fluoroalkyl)-β-aminoindolin-2-ones containing C−F quaternary stereogenic centers with excellent yields and high diastereoselectivities.

Substitution of fluorine for hydrogen is currently a conventional strategy in the design of new pharmaceuticals[1] and other synthetic organic specialty products.[2] In particular, the remarkable therapeutic success of fluorine-containing healthcare products[1,3] calls for advances in the development of fluoro-organic chemistry to provide a wide range of molecules with the required structural and functional complexity for systematic biological studies. One of the most recent innovations in organofluorine methodology is the development of detrifluoroacetylative in situ generation of unprotected fluoro enolates[4] (Scheme 1).

Under mildly basic conditions, 1,3-diketo hydrates **1** readily undergo haloform-type C−C cleavage giving molecules of trifluoroacetic acid and the corresponding fluoro enolates. To date, only structurally simple linear **2**[5] and cyclic **3**[6] types of ketone enolates have been successfully developed. Early studies of their aldol[6−8] and Mannich[9,10] reactivity revealed their remarkable synthetic potential for practical preparation of fluorinated β-keto alcohols/amines.[4] Excellent chemical yields and diastereo-/enantioselectivity, normally observed in these reactions, indicate that innovative design of new and more structurally complex types of the detrifluoroacetylatively generated enolates might be of high synthetic value. To the best of our knowledge, the fluorinated amide enolate[11] has never been explored in the detrifluoroacetylative reaction.

Scheme 1. Detrifluoroacetylative Generation of Fluorinated Enolates



Furthermore, taking into account that the indolin-2-one (oxindole) frame is commonly found in naturally occurring bioactive compounds and synthetic drugs,[12] modification of this heterocyclic system with fluorine would be of general pharmaceutical potential. In this work, we disclose the successful design of novel detrifluoroacetylatively generated fluorinated amide enolate derived 3-fluoroindolin-2-ones and

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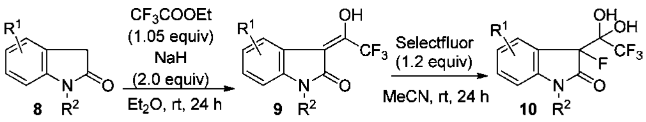
the assessment of their reactivity toward asymmetric Mannich additions. The reaction affords α-fluoro-β-amino-indolin-2-ones containing C−F quaternary stereogenic centers as products in excellent chemical yields and high diastereoselectivities.

β-Keto-amide hydrates **10** can be prepared by a two-step procedure as in Scheme 2. Starting oxindoles **8** were trifluoroacetylated using NaH/CF_3CO_2Et to afford compounds **9**, existing in enol form. The second step, fluorination of **9** with 20 mol % excess Selectfluor,[13] was performed in acetonitrile at ambient temperature to afford target β-keto-amide hydrates **10** in excellent yields (see the Supporting Information).

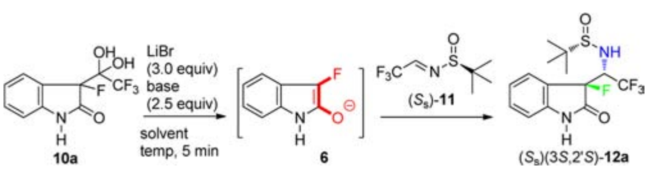
Scheme 2. Synthesis of β-Keto-amide Hydrates 10



R^1 = F, Cl, Br, CF_3, CO_2Me, Me, CF_3O; R^2 = H, Me, Et, Bn, allyl, Ph; 24 compounds

Having prepared the β-keto-amide hydrates **10**, we then studied their reactivity toward asymmetric Mannich addition reactions. Drawing from the literature data and our own experience in the chemistry of enolates **1** and **2**,[4−10] *N-tert*-butanesulfinyl-(3,3,3)-trifluoroacetaldimine **11** was selected as the Mannich acceptor.[14,15] To acquire the reactivity of keto-hydrates **10**, we conducted the reaction of **10a**, bearing a free *N*-H group, with imine **11** in THF using Et_3N as a base (entry 1, Table 1). The addition proceeded at very high rate, completing within just 5 min. The diastereoselectivity of the reaction was impressive, giving the corresponding products with 96% isolated yield. Although all four theoretically possible stereoisomers were detected by ^{19}F NMR of the crude reaction mixture, diastereomer **12a** was obtained with appreciable excess in a ratio of 2:2:3:93. We then examined the role of different organic bases. Application of Hünig's base (DIPEA),[16] instead of Et_3N, afforded the mixture of products with the same excellent yield but in a different proportion of stereoisomeric products (entry 2). The use of *N*-methylmorpholine as a base (entry 3) gave nearly the same diastereoselectivity but lower chemical yield (85%). The reactions conducted in the presence of *n*-Pr_3N (entry 4) and *n*-Bu_3N (entry 5) afforded very similar levels of diastereocontrol (∼90% de); however, the isolated yields were lower (entry 2 vs enries 4 and 5). Thus, selecting DIPEA as a base, we screened the role of the reaction solvent. Performing the addition in 2-Me-THF gave desirable results as major diastereomer **12a** was obtained in 96% yield and of markedly improved diastereomeric purity (96% de) (entry 6). Importantly, two minor diastereomers were not detectable at all in the reaction mixture. Application of other ethers such as 1,4-dioxane (entry 7) and Et_2O (entry 8) as the reaction solvents resulted in noticeably reduced stereochemical outcome. Further experiments demonstrated that increasing (entries 9 and 10) or decreasing (entries 11 and 12) the solvent polarity had a detrimental effect on the diastereomeric preferences. Clearly, the polar solvents, such as DMF (entry 9) and acetonitrile (entry 10), might compete for Li coordination, while the apolar and noncoordinating solvents such as DCM (entry 11) and toluene (entry 12) could not support highly organized, Li-chelated transition states. The final effort in optimizing the conditions was carried out on the reaction temperature. We conducted the experiments at 20, −20, and −40 °C (entries 13−15). Consistent with the previous observation made in the DIPEA/2-Me-THF addition (entry 6), only two diastereomeric products were detected in the reaction mixtures. However, the temperature effect was rather noticeable, affording major diastereomer **12a** with 95 (entry 13), 96.4 (entry 14), and 96.8% de (entry 15).

Table 1. Optimization of the Reaction Conditions[a]



entry	base	solvent	temp (°C)	yield[b] (%)	dr[c]
1	Et_3N	THF	0	96	2:2:3:93
2	DIPEA	THF	0	96	2:2:1:95
3	NMM[d]	THF	0	85	2:2:1:95
4	nPr_3N	THF	0	86	2:2:1:95
5	nBu_3N	THF	0	91	2/2/1/95
6	DIPEA	2-Me-THF	0	96	2/0/0/98
7	DIPEA	1,4-dioxane	20	94	2:0:6:92
8	DIPEA	Et_2O	0	94	2:7:9:82
9	DIPEA	DMF	0	93	32:0:0:68
10	DIPEA	CH_3CN	0	96	4:0:5:91
11	DIPEA	DCM	0	96	2:21:10:67
12	DIPEA	toluene	0	71	4:13:14:69
13	DIPEA	2-Me-THF	20	96	3:0:0:97
14	DIPEA	2-Me-THF	−20	96	1.8:0:0:98.2
15	DIPEA	2-Me-THF	−40	96	1.6:0:0:98.4

[a]Reaction conditions: **10a** (0.6 mmol), CF_3-sulfinylimine **11** (0.5 mmol), LiBr (156.3 mg, 1.8 mmol, 3.0 equiv), base (1.5 mmol, 2.5 equiv), 5 mL of solvent. [b]Isolated yields of mixture of isomers. [c]Determined by the ^{19}F NMR. [d]*N*-Methylmorpholine.

We then conducted substrate generality using keto-amide hydrates **10** (Scheme 3). As presented in Scheme 3, we assessed the effect of electron-withdrawing and -donating substituents in all positions on the aromatic ring: positions 4 (**12l**), 5 (**12b−e**, **m-q**), 6 (**12f−h**,**r**), and 7 (**12i**,**s**,**t**). We also included examples of disubstituted derivative **12j** as well as a series of compounds bearing free *N*-H function (**12a−j**), *N*-Me (**12k−t**), and examples of *N*-Et- (**12u**), *N*-Bn- (**12v**), *N*-allyl- (**12w**), and *N*-Ph-containing (**12x**) substrates. The major conclusion revealed by these experiments is the consistently excellent level of the diastereoselectivities, not noticeably influenced by the nature or by the position of the substituents on the phenyl ring. Thus, the chemical yields ranging from 83 to 97% and diastereomeric ratios from 92/8 to >98/2 were obtained. It should be emphasized that pure major diastereomers **12a−x** can be relatively easily obtained by using routine column chromatography.

To further investige the synthetic generalization of this method, the second substrate generality study using various fluoroalkyl-substituted imines (S_s)-**13a−d** was carried out (Scheme 4). For this substrate generality study, we selected two types of 3-fluoroindolin-2-one derived keto-amide hydrates **10**, containing free *N*-H and *N*-Me functions, along with imines bearing CF_2Cl, CF_2Br, C_2F_5, and C_3F_7 perfluoroalkyl groups (S_s)-**13a−d**. The examined fluorinated imines could work very well to give the desired product **14a−h** within 5 min. The reactions also showed excellent diastereoselectivity, as only one diastereomer was obtained for all of the cases. Most likely, the observed excellent diastereoselectivity is due to the greater

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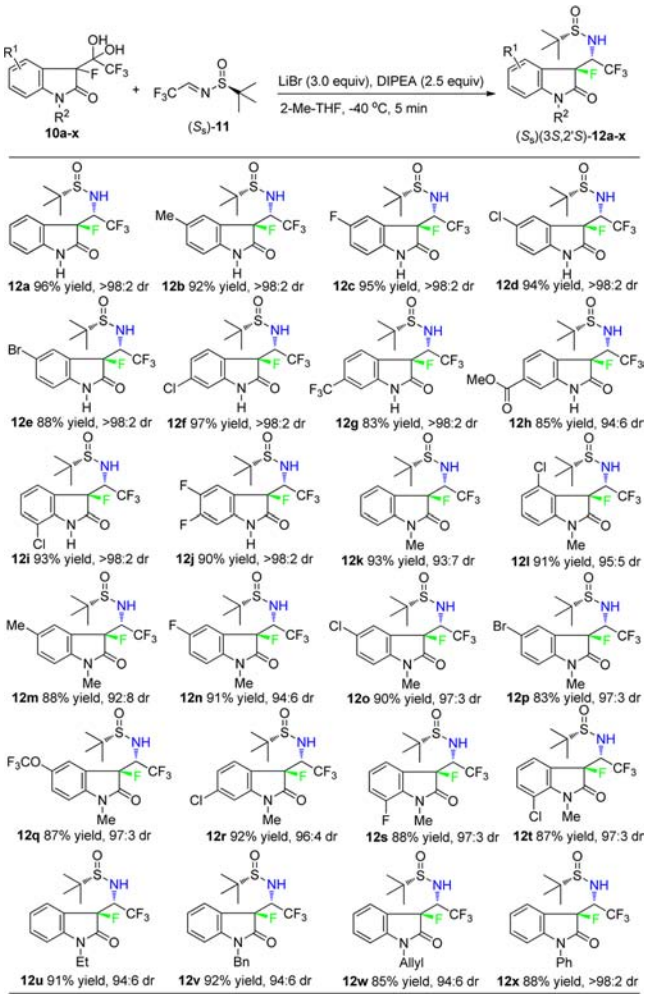
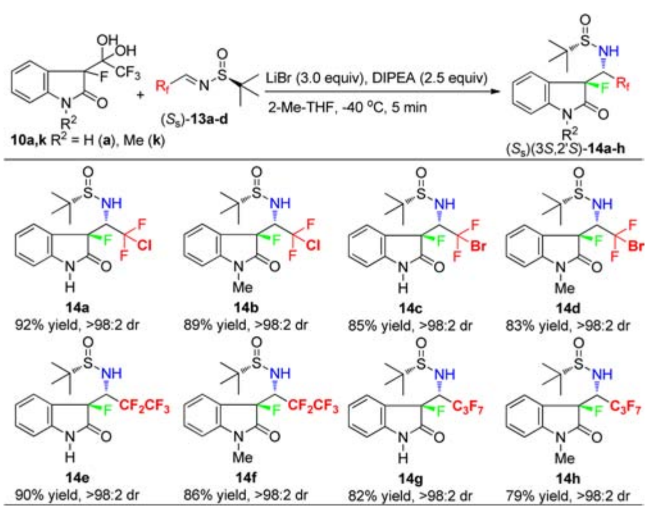
Scheme 3. Substrate Scope of Keto-amide Hydrates for the Detrifluoroacetylative Asymmetric Mannich Reactions



Scheme 4. Substrate Scope of R_f-Imines for the Detrifluoroacetylative Asymmetric Mannich Reactions



steric bulk[17] of the substituents R_f executing the complete control over the stereochemistry of two newly generated stereogenic centers. However, when these results were compared with the data obtained in the series of CF_3-imine (S_s)-**11** reactions (Scheme 3), slightly lower chemical yields were obtained for these imines.

The assignment of the absolute configuration of products **12** and **14** was established by crystallographic analysis of **12v**. The single-crystal X-ray analysis shows its (S_s)(3S,2′S) configuration (see the SI).

To account for the observed stereochemical outcome, the possible transition states (TSs) are presented in Figure 1. In

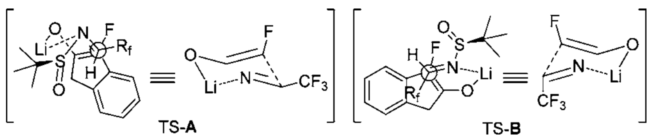
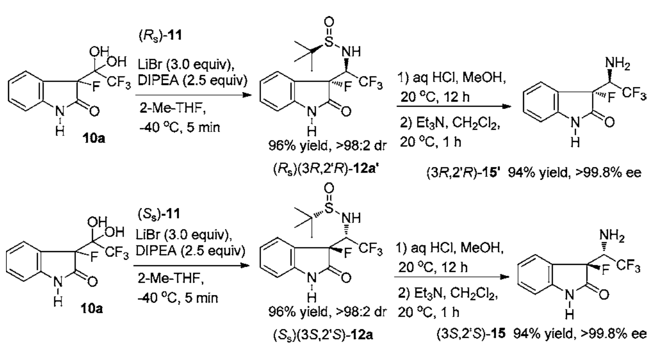


Figure 1. Plausible transition states (TS) **A** and **B** accounting for the observed stereochemical outcome.

TSs **A** and **B**, the enolate O−Li group and the imine nitrogen are located in close proximity to each other to comply with the principle of the minimum charge separation[18] allowing for the concerted oxygen−nitrogen charge transfer. In TS-**A**, leading to the products of the observed (Ss)(3S,2′S) absolute configuration, the stereocontrolling R_f group[19] is placed in the equatorial position, avoiding major unfavorable stereochemical interactions. On the other hand, in TS-**B**, the R_f group is axial and located over the 3-fluoroindolin-2-one derived enolate moiety. Consideration of these factors, the steric repulsion-free TS-**A** might be preferred over TS-**B**. Furthermore, this mechanistic rationale can also account for the higher level of diastereoselectivity observed in the reaction of imines **13** bearing bulkier R_f groups.

To demonstrate the deprotection of α-fluoro-β-(fluoroalkyl)-β-aminoindolin-2-ones products and preparation of target compounds containing free amino groups, we selected unsubstituted derivative **12a** for the deprotection reaction. Moreover, we decided to perform the reaction of (R_s)-**11** with 3-fluoroindolin-2-one derived keto-amide hydrate **10a** to show the synthesis of the enantiomeric products. As presented in Scheme 5, enolate precursor **10a** reacted with (R_s)-**11** to afford

Scheme 5. Deprotection of 12a



(R_s)(3R,2′R)-**12a′** with both excellent chemical yield and diastereoselectivity. Enantiomeric compounds (R_s)(3R,2′R)-**12a′** and (S_s)(3S,2′S)-**12a** were unprotected,[20] giving the enantiomers (3R,2′R)-**15′** and (3S,2′S)-**15** with 94% isolated yield and >99.8% ee. These compounds contain C−F and C−CF_3 SDE-phoric groups and present interesting models to study the self-disproportionation of enantiomers[21] via achiral chromatography and sublimation.[22]

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In summary, we developed the detrifluoroacetylative in situ generation of a new type of 3-fluoroindolin-2-one-derived fluorinated amide enolates and explored their asymmetric Mannich additions with sulfinylaldimines bearing CF_3, CF_2Cl, CF_2Br, C_2F_5, and C_3F_7 groups. This synthetic protocol is robust and displays broad substrate scope and functional group compatibility with excellent yield and high diastereoselectivity. The operational ease coupled with excellent stereochemical outcome bodes well for widespread application of this approach for preparation of α-fluoro-β-fluoroalkyl-β-amino-indolin-2-ones with C−F quaternary stereogenic centers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01516.

Experimental procedures; full spectroscopic data for compounds **10**, **12**, **14**, **15**; ^{1}H NMR and ^{13}C NMR spectra (PDF)
X-ray analysis of **12v** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422. (b) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37. (c) 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.

(2) (a) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16. (b) Zhang, W. *Chem. Rev.* **2009**, *109*, 749. (c) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496.

(3) (a) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (b) Begue, J. P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992. (c) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013. (d) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.

(4) Mei, H.; Xie, C.; Aceña, J. L.; Soloshonok, V. A.; Röschenthaler, G. V.; Han, J. *Eur. J. Org. Chem.* **2015**, *2015*, 6401.

(5) (a) Han, C.; Kim, E. H.; Colby, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 5802. (b) Saidalimu, I.; Fang, X.; Lv, W.; Yang, X.; He, X.; Zhang, J.; Wu, F. H. *Adv. Synth. Catal.* **2013**, *355*, 857. (c) John, J. P.; Colby, D. A. *J. Org. Chem.* **2011**, *76*, 9163. (d) Ding, R.; Wolf, C. *Chem. Commun.* **2016**, *52*, 3576.

(6) Xie, C.; Wu, L.; Han, J.; Soloshonok, V. A.; Pan, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 6019.

(7) (a) Zhang, P.; Wolf, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7869. (b) Zhang, P.; Wolf, C. *J. Org. Chem.* **2012**, *77*, 8840. (c) Saidalimu, I.; Fang, X.; He, X. P.; Liang, J.; Yang, X.; Wu, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5566.

(8) Zhang, L. J.; Xie, C.; Dai, Y. L.; Mei, H. B.; Han, J. L.; Soloshonok, V. A.; Pan, Y. *J. Fluorine Chem.* **2016**, *184*, 28.

(9) (a) Xie, C.; Wu, L.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2014**, *12*, 7836. (b) Xie, C.; Wu, L.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *Tetrahedron Lett.* **2014**, *55*, 5908. (c) Xie, C.; Wu, L.; Zhou, J.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *J. Fluorine Chem.* **2015**, *172*, 13.

(10) (a) Xie, C.; Dai, Y.; Mei, H.; Han, J.; Soloshonok, V. A.; Pan, Y. *Chem. Commun.* **2015**, *51*, 9149. (b) Liu, X.; Zhang, J.; Zhao, L.; Ma, S.; Yang, D.; Yan, W.; Wang, R. *J. Org. Chem.* **2015**, *80*, 12651.

(11) For examples on the reaction of amide enolates, see: (a) Manthorpe, J. M.; Gleason, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2091. (b) Manthorpe, J. M.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2338. (c) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (d) Lubin, H.; Tessier, A.; Chaume, G.; Pytkowicz, J.; Brigaud, T. *Org. Lett.* **2010**, *12*, 1496. (e) Datta, S.; Bayer, A.; Kazmaier, U. *Org. Biomol. Chem.* **2012**, *10*, 8268. (f) Tsukagoshi, S.; Ototake, N.; Ohnishi, Y.; Shimizu, M.; Kitagawa, O. *Chem. - Eur. J.* **2013**, *19*, 6845. (g) Lubin, H.; Dupuis, C.; Pytkowicz, J.; Brigaud, T. *J. Org. Chem.* **2013**, *78*, 3487. (h) Kim, G.; Sohn, T.; Kim, D.; Paton, R. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 272. (i) Latif, M.; Yun, J. I.; Seshadri, K.; Kim, H. R.; Park, C. H.; Park, H.; Kim, H.; Lee, J. *J. Org. Chem.* **2015**, *80*, 3315. (j) Sini, G.; Tessier, A.; Pytkowicz, J.; Brigaud, T. *Chem. - Eur. J.* **2008**, *14*, 3363.

(12) (a) Rudrangi, S. R. S.; Bontha, V. K.; Manda, V. R.; Bethi, S. *Asian J. Res. Chem.* **2011**, *4*, 335. (b) Shaveta; Singh, A.; Kaur, M.; Sharma, S.; Bhatti, R.; Singh, P. *Eur. J. Med. Chem.* **2014**, *77*, 185. (c) Brewer, M. R.; Pao, W. *Cancer Discovery* **2013**, *3*, 138. (d) Biersack, B.; Schobert, R. *Curr. Drug Targets* **2012**, *13*, 1705.

(13) Chatalova-Sazepin, C.; Hemelaere, R.; Paquin, J. F.; Sammis, G. *Synthesis* **2015**, *47*, 2554.

(14) (a) Shibata, N.; Nishimine, T.; Tokunaga, E.; Kawada, K.; Kagawa, T.; Sorochinsky, A. E.; Soloshonok, V. A. *Chem. Commun.* **2012**, *48*, 4124. (b) Röschenthaler, G. V.; Kukhar, V. P.; Kulik, I. B.; Belik, M. Y.; Sorochinsky, A. E.; Rusanov, E. B.; Soloshonok, V. A. *Tetrahedron Lett.* **2012**, *53*, 539. (c) Xie, C.; Mei, H.; Wu, L.; Soloshonok, V. A.; Han, J.; Pan, Y. *RSC Adv.* **2014**, *4*, 4763.

(15) (a) Turcheniuk, K. V.; Poliashko, K. O.; Kukhar, V. P.; Rozhenko, A. B.; Soloshonok, V. A.; Sorochinsky, A. E. *Chem. Commun.* **2012**, *48*, 11519. (b) Mei, H.; Xie, C.; Wu, L.; Soloshonok, V. A.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2013**, *11*, 8018. (c) Liu, Y.; Huang, Y.; Qing, F. L. *Tetrahedron* **2012**, *68*, 4955. (d) Liu, Y.; Yang, Y.; Huang, Y.; Xu, X. H.; Qing, F. L. *Synlett* **2014**, *26*, 67.

(16) Moore, J. L.; Taylor, S. M.; Soloshonok, V. A. *ARKIVOC* **2005**, 287.

(17) Dai, Y.; Xie, C.; Zhou, J.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *J. Asian J. Org. Chem.* **2015**, *4*, 1020.

(18) (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688. (b) Soloshonok, V. A.; Ohkura, H.; Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yamazaki, T. *Tetrahedron Lett.* **2002**, *43*, 5445.

(19) (a) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron* **1996**, *52*, 12433. (b) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 7845. (c) Soloshonok, V. A.; Yasumoto, M. *J. Fluorine Chem.* **2007**, *128*, 170.

(20) (a) Shevchuk, M. V.; Kukhar, V. P.; Roeschenthaler, G. V.; Bassil, B. S.; Kawada, K.; Soloshonok, V. A.; Sorochinsky, A. E. *RSC Adv.* **2013**, *3*, 6479. (b) Mei, H.; Xiong, Y.; Xie, C.; Soloshonok, V. A.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2014**, *12*, 2108. (c) Xie, C.; Mei, H.; Wu, L.; Soloshonok, V. A.; Han, J.; Pan, Y. *Eur. J. Org. Chem.* **2014**, *2014*, 1445.

(21) Soloshonok, V. A.; Roussel, C.; Kitagawa, O.; Sorochinsky, A. E. *Chem. Soc. Rev.* **2012**, *41*, 4180.

(22) (a) Soloshonok, V. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 766. (b) Ueki, H.; Yasumoto, M.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **2010**, *21*, 1396.

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Org. Lett. 2016, 18, 3270−3273