OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

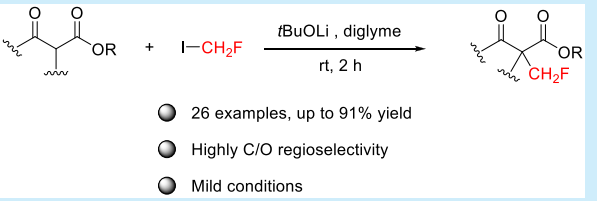
Highly Carbon-Selective Monofluoromethylation of β-Ketoesters with Fluoromethyl Iodide

Tianqi Ding, Lvqi Jiang,* Jie Yang, Yimin Xu, Guixiang Wang, and Wenbin Yi*

School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, P. R. China

Supporting Information

ABSTRACT: A highly carbon-selective monofluoromethylation of a broad range of β-ketoesters with fluoromethyl iodide under mild conditions is described. The uses of lithium *tert*-butoxide as the base and diglyme as the solvent made great contributions to the high C/O regioselectivity.



Over the past 20 years, fluorine-containing compounds have attracted increasing attention in pharmaceutical and agrochemical fields.[1] Nowadays, the strategic incorporation of a fluorine atom or a fluoroalkyl group (such as CF_3, CF_2H, and CH_2F) in different stages of drug development has become routine practice in drug discovery.[2] In this context, monofluoromethyl compounds are particularly valuable because the CH_2F functionality can mimic CH_3 and CH_2OH groups, which are often encountered in biologically active molecules.[3] But methods for the direct introduction of a monofluoromethyl group are far less developed in contrast.[4] Direct monofluoromethylation has been reported by using fluoromethanol[5] and its derivative fluoromethyl triflate[6] or fluoromethyl halides ($ClCH_2F$,[7] $BrCH_2F$,[8] or ICH_2F[9]) (**1a−e**, Figure 1). Recently, more shelf-stable yet highly reactive monofluoromethylating reagents (**1f−k**, Figure 1) have been developed.[10−15]

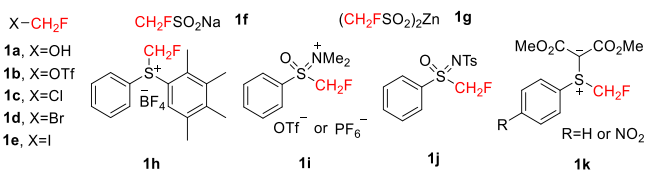
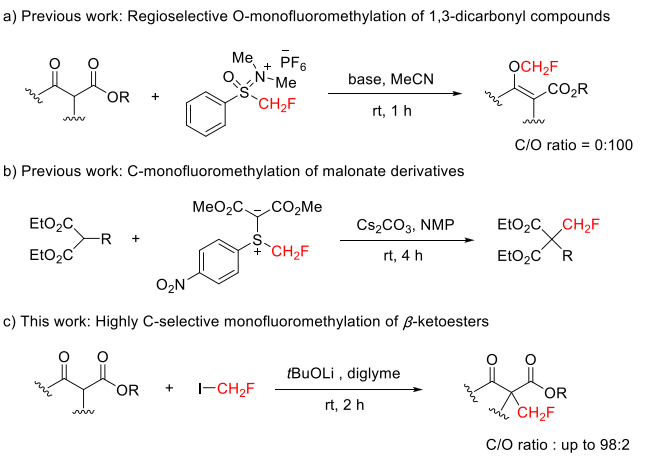


Figure 1. Direct monofluoromethylating reagents.

The control of carbon/oxygen (C/O) regioselectivity in the alkylation of enolates is one of the oldest research areas in organic chemistry.[16] The keto−enol tautomerism of substrates, alkylating agents, and reaction conditions, in particular, the base and solvents, play important roles in the C/O regioisomer ratio.[17] Although the control of C/O regioselectivity in the difluoromethylation of 1,3-dicarbonyl compounds has been widely researched in recent years,[18] the development of the control of C/O regioselectivity in the monofluoromethylation of 1,3-dicarbonyl compounds has been far less. In 2011, Shibata and coworkers discovered that an electrophilic monofluoromethylating reagent, *N*,*N*-dimethyl-*S*-monofluoromethyl-*S*-phenylsulfoximiniun hexafluorophosphate **1i**, was able to react with a variety of 1,3-dicarbonyl compounds. But only O-selective monofluoromethylation was observed (Scheme 1a).[13] Shortly after, Shen and coworkers developed another two electrophilic monofluoromethylating reagents **1k**, and both 2-aryl- and 2-alkyl-substituted malonates can react with monofluoromethyl(4-nitro-phenyl)sulfonium bis(carbomethoxy)methylide to generate the corresponding C-selective monofluoromethylated malonates (Scheme 1b).[15] However, the direct introduction of CH_2F to the Csp^3 center of general β-ketoesters remains challenging. Herein we report the first example of the highly carbon-selective monofluoromethylation of β-ketoesters with fluoromethyl iodide under mild conditions (Scheme 1c).

Scheme 1. Regioselective Electrophilic Monofluoromethylation of β-Ketoesters



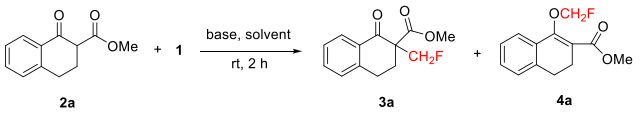
Initially, we chose the reaction of β-ketoester methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **2a** with fluoro-

Received: June 24, 2019

DOI: 10.1021/acs.orglett.9b02175
Org. Lett. XXXX, XXX, XXX−XXX

methyl iodide (reagent **1e**) as a model reaction to optimize the reaction conditions. To the best of our knowledge, the base and solvent play the most important roles of the C/O-alkylation ratio. After screening plenty of inorganic bases such as different barium salts, sodium salts, and potassium salts in DMF, we found that the reactions occurred smoothly to give the monofluoromethylated products (**3a** + **4a**) in good yields, but the C/O ratio was not satisfactory (Table 1, entries 1−7).

Table 1. Optimization of the Reaction Conditions[a]



entry	reagent	base	solvent	yield (%)[b]	C/O ratio[c]
1	**1e**	Cs_2CO_3	DMF	91	8:92
2	**1e**	CsF	DMF	57	12:88
3	**1e**	$CsOH·H_2O$	DMF	77	9:91
4	**1e**	NaOH	DMF	71	37:63
5	**1e**	$NaHCO_3$	DMF	trace	
6	**1e**	KOH	DMF	73	29:71
7	**1e**	K_2CO_3	DMF	69	15:85
8	**1e**	DBU	DMF	NR	
9	**1e**	DIPEA	DMF	NR	
10	**1e**	Et_3N	DMF	NR	
11	**1e**	LiOH	DMF	88	69:31
12	**1e**	Li_2CO_3	DMF	<5	
13	**1e**	LiOAc	DMF	<5	
14	**1e**	*t*BuOLi	DMF	86	76:24
15	**1e**	*t*BuOLi	toluene	trace	
16	**1e**	*t*BuOLi	DCM	trace	
17	**1e**	*t*BuOLi	dioxane	20	45:55
18	**1e**	*t*BuOLi	NMP	67	56:44
19	**1e**	*t*BuOLi	DMA	80	52:48
20	**1e**	*t*BuOLi	DME	52	81:19
21	**1e**	*t*BuOLi	THF	27	75:25
22	**1e**	***t*BuOLi**	**diglyme**	**87**	**90:10**
23	**1e**	*t*BuOLi	MeCN	48	68:32
24	**1c**	*t*BuOLi	diglyme	64	80:20
25	**1d**	*t*BuOLi	diglyme	70	85:15
26	**1k**	*t*BuOLi	diglyme	<10	

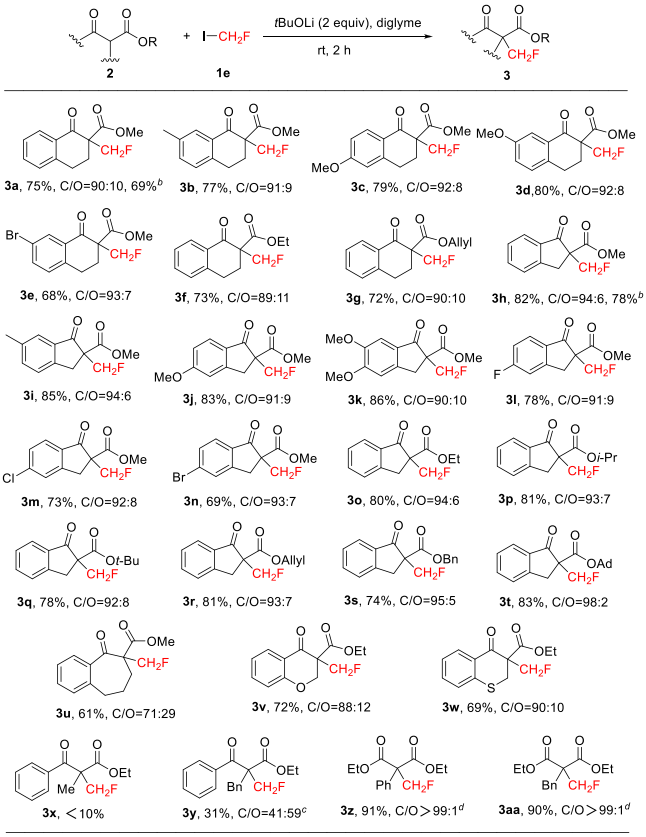
[a]Reaction conditions: **2a** (0.2 mmol), reagent **1** (0.5 mmol), base (0.4 mmol) in solvent (2 mL) at room temperature for 2 h. [b]Yields (**3a** + **4a**) were determined by GC. [c]Ratio of **3a**/**4a** was determined by ^{19}F NMR spectroscopy with fluorobenzene as the internal standard.

When an organic base such as DBU, DIPEA, or Et_3N was used, no corresponding monofluoromethylated products were observed (Table 1, entries 8−10). Considering that lithium salts made great contributions to the highly C-selective difluoromethylation of *β*-ketoesters,[18d,e] we then screened lithium salts as the base. To our delight, when a lithium salt LiOH was used, the C/O ratio was significantly improved to 69:31 (Table 1, entry 11). We then further investigated other lithium salts; the formation of monofluoromethylated products (**3a** + **4a**) was observed in <5% yield when Li_2CO_3 or LiOAc was used (Table 1, entries 12 and 13), but a slightly better result was observed when *t*BuOLi was used (Table 1, entry 14). Next, we studied the effect of the solvents on the yield and the regioselectivity of the reaction (Table 1, entries 15−23). It was found that diglyme gave the reaction satisfactory results in terms of both yield and regioselectivity (Table 1, entry 22).

The screening of other monofluoromethylating reagents **1c**, **1d**, and **1k** did not give better results (Table 1, entries 24−26). Furthermore, other reaction parameters such as time, temperature, and concentration were also screened. (For more details, see Table S1.) After screening the equivalent of ICH_2F, the equivalent of *t*BuOLi, the reaction temperature, the reaction time, and the reaction concentration, the combination of *β*-ketoesters **2**/ICH_2F (2.5 equiv)/*t*BuOLi (2.0 equiv) in diglyme (0.1 M) at room temperature for 2 h was selected as the optimized reaction condition.

With the optimized reaction conditions in hand, the scope of the monofluoromethylation of *β*-ketoesters **2** was explored (Scheme 2). A wide range of both tetralone carboxylates and

Scheme 2. Scope of C-Selective Monofluoromethylation of *β*-Ketoesters 2[a]



[a]Reaction conditions: **2** (0.2 mmol), reagent **1e** (0.5 mmol), *t*BuOLi (0.4 mmol) in diglyme (2 mL) at room temperature for 2 h. Isolated yields. The C/O ratio was determined by ^{19}F NMR spectroscopy with fluorobenzene as the internal standard. [b]Gram-scale synthesis. [c]DMF was used as solvent. [d]Cs_2CO_3 was used as base and DMF was used as solvent.

indanone carboxylates reacted with fluoromethyl iodide to afford the corresponding Csp^3-CH_2F products **3a**−**t** bearing a quaternary carbon center in good yield with high C/O regioselectivies. Tetralone carboxylates **2a** without a substituent afforded the corresponding product **3a** in 75% isolated yield with good C/O selectivity (90:10). Tetralone carboxylates with a methyl or methoxy group on the benzene ring provided the desired products **3b**−**d** with slightly improved yields and regioselectivities, whereas **2e** with a bromine atom on the benzene ring provided the product **3e** with slightly decreased yield. The ethyl tetralone carboxylates **2f** and the

DOI: 10.1021/acs.orglett.9b02175
Org. Lett. XXXX, XXX, XXX−XXX

allyl tetralone carboxylates **2g** were also adapted to this reaction system, affording desired products **3f,g** in good yield and with good regioselectivities. Moreover, indanone carboxylates **2h−t**, including electron-donating-group-substituted methyl indanone carboxylates **2i−k**, electron-withdrawing-group-substituted substrates **2l−n**, and alkyl, allyl, benzyl, and adamantyl indanone carboxylates **2o−t**, afforded the corresponding Csp^3-CH_2F products **3h−t** in high yield (69−86%) with high regioselectivities (C/O 90:10 to 98:2). Additionally, a decrease in yield (61%) and regioselectivity (71:29) was observed for the β-ketoester **2u** with a seven-membered ring. The heterocyclo-ketoesters **2v** and **2w** were also tolerated, providing **3v** in 72% yield with 88:12 C/O regioselectivity and **3w** in 69% yield with 90:10 C/O regioselectivity. The current process was scalable, as demonstrated by the gram-scale synthesis of **3a** (69% isolated yield) and **3h** (78% isolated yield). The less reactive acyclic aryl β-ketoesters **2x** and **2y** were not compatible, affording the corresponding C-selective monofluoromethylated products **3x** and **3y** in <10% yield. When changing the solvent from diglyme to DMF, **3y** was obtained in 31% yield with unsatisfactory C/O regioselectivity. Further applications of fluoromethyl iodide in the C-monofluoromethylation of malonates were also evaluated. **3z** and **3aa** were obtained in high yield with >99:1 C/O regioselectivities when using Cs_2CO_3 as the base and DMF as the solvent.

Mechanistically, the carbon-selective monofluoro-methylation of β-ketoester usually proceeds via a direct electrophilic substitution pathway. To gain more support for the high C/O regioselectivity, we studied the reaction of β-ketoester with fluoromethyl iodide by density functional theory calculations.[19] As shown in Figure 2, the relative free energy of the intermediate structure **In−C** for the electrophilic attack of the carbon atom is energetically lower by 11.8 kcal/mol than that of **In−O** for the electrophilic attack of the oxygen atom. The corresponding monofluoromethylated product **3a** is energetically lower by 24.0 kcal/mol than **4a**, leading to the ratio of C/O regioselectivity of 90:10.

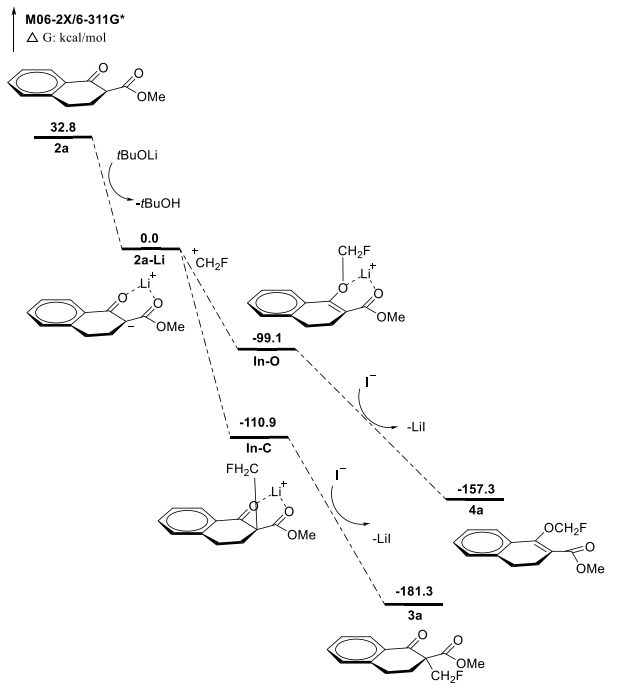
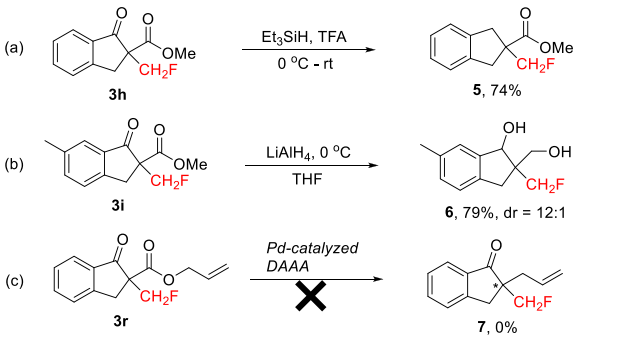


Figure 2. Energy profile (Δ*G* in kcal/mol) computed at the M06-2X/6-311G* level of theory for the formation of C- and O-monofluoromethylated products

Further synthetic applications of the C−CH_2F products were investigated. As is shown in Scheme 3, compound **5** was obtained via Et_3SiH/TFA reduction in 74% yield from **3h**, and compound **6** was obtained via $LiAlH_4$ reduction in 79% yield from **3i**. In addition, with the product **3r** in hand, a Pd-catalyzed Tsuji decarboxylative asymmetric allylic alkylation (DAAA)[20] was also surveyed, but no desired product **7** was obtained (Scheme 3c; for more details, see Table S2). Therefore, the synthesis of chiral monofluoromethylated compounds remains challenging.

Scheme 3. Synthetic Applications of C−CH_2F Products



In conclusion, we have developed the first protocol for highly carbon-selective monofluoromethylation of β-ketoesters with fluoromethyl iodide under mild conditions. A broad scope of β-ketoesters were converted into the corresponding C-selective CH_2F-products in good yield with high regioselectivities. The effect of the lithium ion had a great influence on the results. On the basis of the construction of chiral carbon, the development of the asymmetric monofluoromethylation is expected to make progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02175.

Experimental procedures, characterization data, and ^1H NMR, ^{13}C NMR, and ^{19}F NMR for products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: lvqi.jiang@njust.edu.cn (L.J.).
*E-mail: yiwb@njust.edu.cn (W.Y.).

ORCID

Wenbin Yi: 0000-0003-4606-7668

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21776138, 21476116), the Fundamental Research Funds for the Central Universities (30916011102,

DOI: 10.1021/acs.orglett.9b02175
Org. Lett. XXXX, XXX, XXX−XXX

30918011314), the Natural Science Foundation of Jiangsu (BK20180476), the Qing Lan and Six Talent Peaks in Jiangsu Province, the Priority Academic Program Development of Jiangsu Higher Education Institutions, and the Center for Advanced Materials and Technology in Nanjing University of Science and Technology for financial support.

REFERENCES

(1) (a) Bohm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (b) Sani, M.; Volonterio, A.; Zanda, M. *ChemMedChem* **2007**, *2*, 1693. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Fah, C.; Mathys, R.; Hardegger, L. A.; Meyer, S.; Bur, D.; Diederich, F. *Eur. J. Org. Chem.* **2010**, *2010*, 4617.

(2) (a) Wong, D. T.; Perry, K. W.; Bymaster, F. P. *Nat. Rev. Drug Discovery* **2005**, *4*, 764. (b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (c) Wang, J.; Sanchez-Rosello, M.; Acena, J.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(3) (a) Kollonitsch, J.; Patchett, A. A.; Marburg, S.; Maycock, A. L.; Perkins, L. M.; Doldouras, G. A.; Duggan, D. E.; Aster, S. D. *Nature* **1978**, *274*, 906. (b) Mckeage, K.; Keam, S. J. *Drugs* **2009**, *69*, 1799. (c) Rojas, R. A.; Paluga, I.; Goldfrad, C. H.; Duggan, M. T.; Barnes, N. *J. Asthma* **2007**, *44*, 437.

(4) A few examples: (a) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882. (b) Fukuzumi, T.; Shibata, N.; Sugiura, M.; Yasui, H.; Nakamura, S.; Toru, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4973. (c) Prakash, G. K. S.; Chacko, S.; Alconcel, S.; Stewart, T.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4933. (d) Su, Y.; Feng, G.; Wang, Z.; Lan, Q.; Wang, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 6003.

(5) (a) Olah, G. A.; Pavlath, A. *Acta Chim. Acad. Sci. Hung.* **1953**, *3*, 203. (b) Olah, G. A.; Pavlath, A. *Acta Chim. Acad. Sci. Hung.* **1953**, *3*, 425.

(6) Iwata, R.; Pascali, C.; Bogni, A.; Furumoto, S.; Terasaki, K.; Yanai, K. *Appl. Radiat. Isot.* **2002**, *57*, 347.

(7) (a) Rheude, U.; Sundermeyer, W. *Chem. Ber.* **1985**, *118*, 2208. (b) Grozinger, K. G.; Kriwacki, R. W.; Leonard, S. F.; Pitner, T. P. *J. Org. Chem.* **1993**, *58*, 709. (c) Gerus, I. I.; Kolomeitsev, A. A.; Kolycheva, M. I.; Kukhar, V. P. *J. Fluorine Chem.* **2000**, *105*, 31. (d) Gao, M.; Miller, M. A.; DeGrado, T. R.; Mock, B. H.; Lopshire, J. C.; Rosenberger, J. G.; Dusa, C.; Das, M. K.; Groh, W. J.; Zipes, D. P. *Bioorg. Med. Chem.* **2007**, *15*, 1289−1297. (e) Zhang, W.; Zhu, L. G.; Hu, J. *Tetrahedron* **2007**, *63*, 10569.

(8) (a) Lesuisse, D.; Gourvest, J. F.; Hartmann, C.; Tric, B.; Benslimane, O.; Philibert, D.; Vevert, J. P. *J. Med. Chem.* **1992**, *35*, 1588. (b) Kanai, T.; Kai, Y.; Sato, N.; Naito, T.; Kamiya, T.; Nakamura, T.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2335. (c) Hamill, T. G.; McCauley, J. A.; Burns, H. D. *J. Labelled Compd. Radiopharm.* **2005**, *48*, 1. (d) Donohue, S. R.; Halldin, C.; Pike, V. W. *Bioorg. Med. Chem.* **2006**, *14*, 3712. (e) Chin, F. T.; Morse, C. L.; Shetty, H. U.; Pike, V. W. *J. Labelled Compd. Radiopharm.* **2006**, *49*, 17. (f) An, L.; Xiao, Y.; Min, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 9079.

(9) (a) Zheng, L.; Berridge, M. S. *Appl. Radiat. Isot.* **2000**, *52*, 55. (b) Zhang, M.; Maeda, J.; Furutsuka, K.; Yoshida, Y.; Ogawa, M.; Suhara, T.; Suzuki, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 201. (c) Hamill, T. G.; Burns, H. D. *J. Labelled Compd. Radiopharm.* **2004**, *47*, 99. (d) Zhang, M.; Maeda, J.; Ito, T.; Okauchi, T.; Ogawa, M.; Noguchi, J.; Suhara, T.; Halldin, C.; Suzuki, K. *Bioorg. Med. Chem.* **2005**, *13*, 1811. (e) Zhang, M.; Ogawa, M.; Furutsuka, K.; Yoshida, Y.; Suzuki, K. *J. Fluorine Chem.* **2004**, *125*, 1879. (f) Doi, H.; Ban, I.; Nonoyama, A.; Sumi, K.; Kuang, C.; Hosoya, T.; Tsukada, H.; Suzuki, M. *Chem. - Eur. J.* **2009**, *15*, 4165. (g) Hu, J.; Gao, B.; Li, L.; Ni, C.; Hu, J. *Org. Lett.* **2015**, *17*, 3086.

(10) He, Z.; Tan, P.; Ni, C.; Hu, J. *Org. Lett.* **2015**, *17*, 1838.

(11) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95.

(12) Prakash, G. K. S.; Ledneczki, I.; Chacko, S.; Olah, G. A. *Org. Lett.* **2008**, *10*, 557.

(13) Nomura, Y.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 1885.

(14) Shen, X.; Zhou, M.; Ni, C.; Zhang, W.; Hu, J. *Chem. Sci.* **2014**, *5*, 117.

(15) Liu, Y.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 9930.

(16) (a) Eames, J. Acid−Base Properties of Enols and Enolates. In *Chemistry of Metal Enolates, Part 1*; Zabicky, J., Ed.; Wiley-VCH, 2009; pp 441−460. (b) Reutov, O. A.; Beletskaya, I. P.; Kurts, A. L. *Ambident Anions*; Michael, J. P., Ed.; Plenum: New York, 1983. (c) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (d) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913. (e) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.

(17) (a) Ho, T.-S. *Chem. Rev.* **1975**, *75*, 1. (b) Damoun, S.; Van de Woude, G.; Choho, K.; Geerlings, P. *J. Phys. Chem. A* **1999**, *103*, 7861 and references therein. .

(18) Selected examples: (a) Liu, G.; Wang, X.; Lu, X.; Xu, X.; Tokunaga, E.; Shibata, N. *ChemistryOpen* **2012**, *1*, 227. (b) Yang, Y.; Lu, X.; Liu, G.; Tokunaga, E.; Tsuzuki, S.; Shibata, N. *ChemistryOpen* **2012**, *1*, 221. (c) Pegot, B.; Urban, C.; Bourne, A.; Le, T. N.; Bouvet, S.; Marrot, J.; Diter, P.; Magnier, E. *Eur. J. Org. Chem.* **2015**, *2015*, 3069. (d) Wang, J.; Tokunaga, E.; Shibata, N. *Chem. Commun.* **2018**, *54*, 8881. (e) Zhu, J.; Zheng, H.; Xue, X.; Xiao, Y.; Liu, Y.; Shen, Q. *Chin. J. Chem.* **2018**, *36*, 1069. (f) Lu, S.; Li, X.; Qin, W.; Liu, J.; Huang, Y.; Wong, H. N. C.; Liu, G. *Org. Lett.* **2018**, *20*, 6925.

(19) All calculations were performed with: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2013. For more details, see the SI

(20) For selected reviews on the DAAA, see: (a) Mohr, J. T.; Stoltz, B. M. *Chem. - Asian J.* **2007**, *2*, 1476. (b) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (c) Trost, B. M. *Tetrahedron* **2015**, *71*, 5708. For selected examples of asymmetric synthesis of α-allyl-α-fluoroalkyl-ketones, see: (d) Shibata, N.; Suzuki, S.; Furukawa, T.; Kawai, H.; Tokunaga, E.; Yuan, Z.; Cahard, D. *Adv. Synth. Catal.* **2011**, *353*, 2037. (e) Kondo, H.; Maeno, M.; Hirano, K.; Shibata, N. *Chem. Commun.* **2018**, *54*, 5522. (f) Kondo, H.; Maeno, M.; Sasaki, K.; Guo, M.; Hashimoto, M.; Shiro, M.; Shibata, N. *Org. Lett.* **2018**, *20*, 7044.

DOI: 10.1021/acs.orglett.9b02175
Org. Lett. XXXX, XXX, XXX−XXX