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Development of Planar Chiral Iodoarenes Based on [2.2]Paracyclophane and Their Application in Catalytic Enantioselective Fluorination of β-Ketoesters

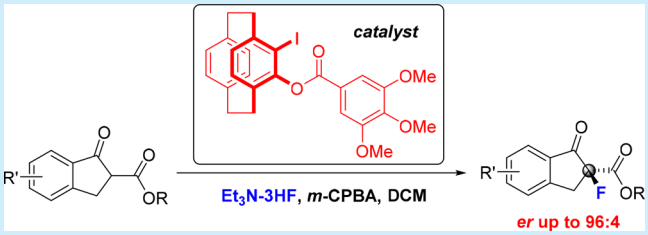
Yang Wang,[†,§] Hang Yuan,[‡,§] Hongfei Lu,[*,‡] and Wen-Hua Zheng[*,†]

[†]State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, 163 Xianlin Avenue, Nanjing 210023, Jiangsu, China

[‡]School of Environment and Chemical Engineering, Jiangsu University of Science and Technology, Zhenjiang 212003, Jiangsu, China

Supporting Information

ABSTRACT: The design and synthesis of novel planar chiral iodoarenes based on [2.2]paracyclophane is reported. A process of highly enantioselective oxidative fluorination of a β-ketoester with 3HF−Et_3N as a nucleophilic fluoride source mediated by these new hypervalent iodine catalysts has been developed. This represents the first highly enantioselective reaction catalyzed by planar chiral hypervalent iodine.



In recent decades, hypervalent iodine(III) reagents have been used in a wide range of synthetically important transformations,[1] even in a catalytic version.[2] Hypervalent iodine-catalyzed asymmetric organic transformations have received enormous attention in the past several years, and considerable efforts have been directed toward developing new asymmetric reactions.[3] Despite the significant progress made in this area, interest in developing new scaffold iodoarenes as catalyst is growing.

Early examples of chiral hypervalent iodine compounds are those bearing a chiral leaving group connected to iodine directly, but usually show low enantiocontrol in asymmetric catalysis (Figure 1).[4] Benchmarked by iodoarene with a chiral stereocenter *ortho* to the iodine atom on the aromatic ring developed by Wirth and co-workers, a variety of iodobenzenes with a chiral stereocenter on the side chain have been synthesized and then been applied in enantioselective oxidative reactions.[5] Notable among these seminal contributions are the development of conformationally flexible C_2-symmetric iodoarene catalysts by Ishihara's group,[6] which have been shown to be efficient in different kinds of reactions with high enantioselectivity. In addition, axially chiral or chiral spiro iodoarenes have been designed and synthesized.[7] Particularly, Kita[8] and co-workers discovered chiral iodides based on a spirobiindane backbone and applied it in asymmetric dearomatization of naphtholic substrates, affording the corresponding chiral products with excellent enantioselectivity. Despite these advances, the hypervalent iodine catalysts are still limited to containing chiral stereocenters or axially/spiro chiral elements. Therefore, it is still highly desirable to design a new hypervalent iodine catalyst based on a novel scaffold.

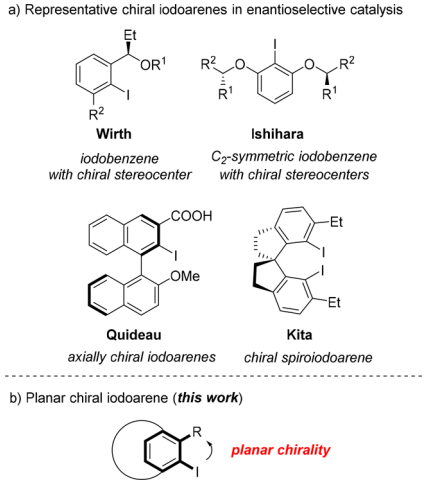


Figure 1. Chiral iodoarenes in enantioselective hypervalent iodine catalysis.

Planar chiral [2.2]paracyclophane[9] provides a unique framework with a conformationally stable chiral environment and has been widely used as chiral ligands in asymmetric catalysis and optical materials development. In this regard, we envisioned that planar chiral iodoarene-based [2.2]paracyclophane could potentially be an excellent catalyst in hypervalent iodine catalysis (Figure 1). Although iodoarene-based [2,2]-paracyclophanes are frequently used as intermediates in the synthesis of [2,2]paracyclophane derivatives, studies on hypervalent iodine bearing this framework are extremely limited.[10a] Moreover, to the best of our knowledge, only one study involving a chiral hypervalent iodine based on [2,2]-

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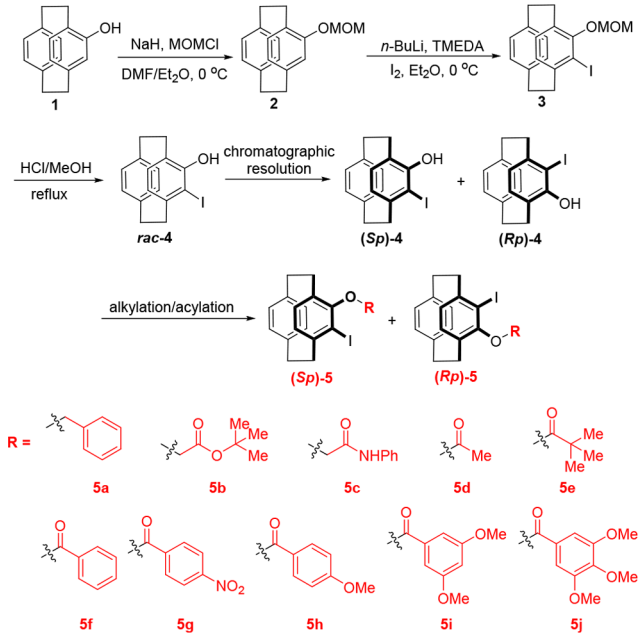
paracyclophane catalysis has been reported in the literature but afforded almost no enantioselectivity.[10b] Herein, we design and synthesize a new type of planar chiral iodoarene based on [2.2]paracyclophane.

Scheme 1 shows the syntheses of the target planar chiral iodoarenes we designed.[11] Starting from known racemic

Scheme 1. Preparation of Catalysts



[2.2]paracyclophane **1**, followed by protection with MOMCl, *ortho*-lithiation/quenched with I_2, and deprotection under acidic condition, iodo[2.2]paracyclophane **4** was obtained in high yield. Then optical resolution of ***rac*-4** was carried out on preparative HPLC using a chiral stationary phase column (see Supporting Information (SI)) to give both planar chiral iodoarenes **(*Sp*)-4** and **(*Rp*)-4**. With planar chiral **(*Sp*)-4** and **(*Rp*)-4** in hand, we next carried out an alkylation or acylation to obtain a series of planar chiral iodoarenes **5** with different functional groups on the hydroxyl group *ortho* to the iodine atom. The structure of **(*Rp*)-5i** was unambiguously determined by single crystal X-ray crystallography, as shown in Figure 2.

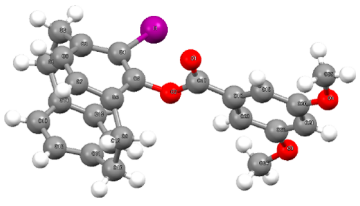
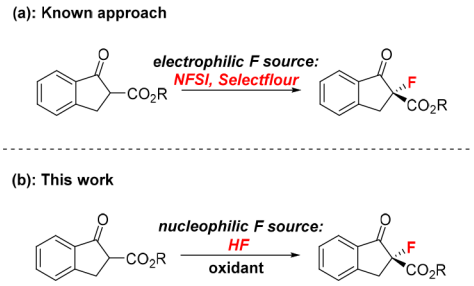


Figure 2. Ball-and-stick drawing of the single crystal X-ray of structure **(*Rp*)-5i**.

With these catalysts in hand, we next studied the catalytic ability. Enantioselective incorporation of fluoride into organic molecules is highly valuable in modern medicinal chemistry and material science.[12] Development of asymmetric fluorination involving electrophilic fluorinated[13] reagents has witnessed encouraging progress. However, enantioselective nucleophilic fluorination[14] is still in its infancy because of the low reactivity of the fluoride atom and few asymmetric inductive protocols available. In this regard, Jacobsen[15] and others have developed excellent processes in asymmetric difluorination/oxyfluorination reactions of alkenes with high enantioselectivity in the presence of chiral hypervalent iodine catalysts. In contrast, development of a highly enantioselective nucleophilic fluorination of α-carbonyl compounds catalyzed by hypervalent iodine remains a challenging task. Although the highly enantioselective electrophilic fluorination of α-carbonyl substrates is realized by transition-metal catalysts and organocatalysts,[13] the asymmetric nucleophilic α-fluorination of carbonyl compounds is less studied (Scheme 2). Very recently, Rueping and co-workers

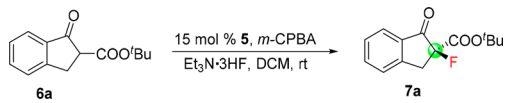
Scheme 2. Enantioselective Fluorination of β-Ketoester



reported the C_2 symmetric iodoarene catalyzed nucleophilic fluorination of β-ketoester with high enantioselectivity.[16] Herein, we report a highly enantioselective fluorination of a β-ketoester with a nucleophilic fluoride source in the presence of a new planar chiral iodoarene, as described above.

To test our hypothesis, we began with identification of the best catalyst using β-ketoester **6a** as a model substrate, hydrofluoride triethylamine as a nucleophilic fluoride source, and *m*-CPBA as the oxidant in the presence of a catalytic planar chiral iodoarene. As shown in Table 1, the transformation indeed took place, and the desired product **7a** was obtained in low yield and poor enantioselectivity with **4a**. It is worth mentioning that the major side product is α-hydroxyl β-ketoester, coming from oxidation of the substrate with *m*-CPBA

Table 1. Reaction Optimization[a]



entry	catalyst	yield (%)[b]	*er*[c]
1	**4a**	19	54:46
2	**5a**	24	61:39
3	**5b**	37	78:22
4	**5c**	24	59.5:40.5
5	**5d**	35	76.5:23.5
6	**5e**	37	78:22
7	**5f**	38	79:21
8	**5g**	31	85:15
9	**5h**	41	86:14
10	**5i**	39	89.5:10.5
11	**5j**	42	94:6
12[d]	**5j**	45	94.5:5.5

[a]Unless otherwise indicated, the reaction was carried out at the **6a** 0.1 mmol scale and catalyzed by 15 mol % (*Rp*)-**5** in DCM (1 mL) at rt for 24 h. The molar ratio of **6a**/*m*CPBA/Et_3N-3HF was 1:1.3:5. [b]Isolated yield. [c]The *er* value was determined by HPLC. [d]DCM (2 mL).

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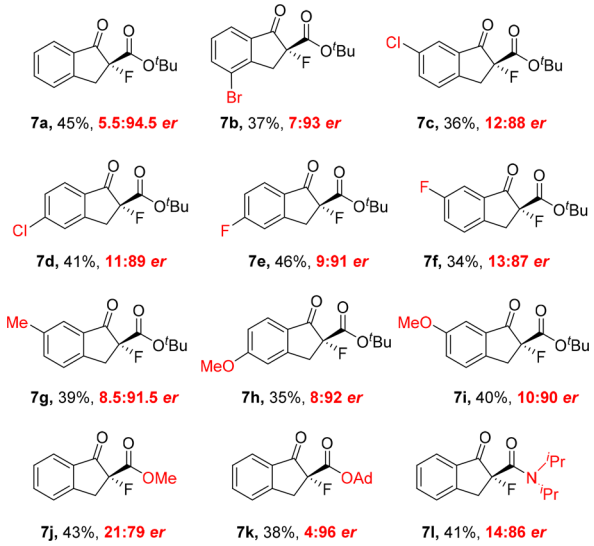
directly. After extensive screening of iodoarenes with different functional groups (Table 1, entries 2−7), benzoylated iodoarene was identified as the optimal catalyst, based on yield and *er* (38% yield and 79:21 *er*). Next, we examined iodoarenes **5g**−**5i** with different electronic effects on the phenyl ring. Although the enantioselectivity of **7a** with nitro-substituted **5g** is comparable to that with methoxyl-substituted **5h** (85:15 *er* to 86:14 *er*), the reaction activity of **5g** is much lower. In the search for additional improvement of the activity and enantioselectivity, we synthesized iodoarenes **5i**[17] (CCDC 1816180) and **5j** with more methoxyl groups on the phenyl ring. We were pleased that the *er* value of the product was further improved to 94:6 with **5j**, and a higher enantioselectivity was obtained at lower concentration (entry 12). Further attempts to improve the yield of the reaction by changing oxidants, solvents, and temperature proved to be unfruitful. The absolute configuration of **7a** was determined to be *S* by comparison of the sign of its optical rotation with that of the literature data.

Under the optimized conditions, a series of substrates were explored to prove the generality of this process. As shown in Scheme 3, *β*-ketoesters with a range of electron-withdrawing

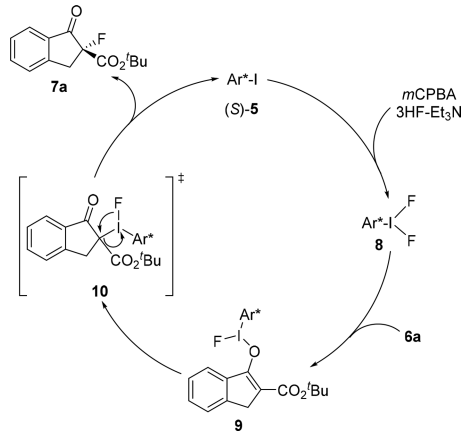
Scheme 3. Substrate Scope



and -donating groups were tolerated, affording corresponding products (**7a**−**7i**) with high enantioselectivity. The size of the ester group has an enormous impact on the enantioselectivity. For instance, **7j** with methyl ester was obtained with 21:79 *er*, lower than that of **7a**. In addition, **7k** with an ester, with a similar size to that of **7a**, was obtained with high enantioselectivity. Notably, *β*-ketoamide proceeded well under the above conditions, affording the product **7l** with excellent enantioselectivity. Further efforts toward extension to acyclic substrates proved to be unsuccessful.

Although the detailed mechanism for this transformation is unkown, a possible catalytic cycle is proposed based on literature.[17] As shown in Scheme 4, the catalytic cycle started with oxidation of iodoarene with *m*-CPBA and HF, affording fluoro-substituted tricoordinated intermediate **8**.[17a] Then, ligand exchange took place with the substrate *β*-ketoester **6a** to form O-bonded hypervalent iodine species **9**,[17b] which underwent 1,3-migration to afford intermediate **10**.[16,17b] This step is presumably the rate-determining and enantioselective

Scheme 4. Plausible Catalytic Cycle



step. Finally, reductive elimination of **10** occurred to regenerate the catalyst and deliver the desired product **7a**.

In summary, we have designed and synthesized a novel planar chiral iodoarene based on [2,2]paracyclophane. A process of highly enantioselective oxidative fluorination with a nucleophilic fluoride source mediated by hypervalent iodine has been developed. To the best of our knowledge, it represents the first hypervalent iodine catalysis with a planar chiral iodoarene. Detailed mechanism studies and further application of those chiral catalysts are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00711.

General Information, procedures of catalysts syntheses, spectral data and HPLC (PDF)

Accession Codes

CCDC 1816180 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: wzheng@nju.edu.cn.
*E-mail: zjluhf1979@just.edu.cn.

ORCID

Wen-Hua Zheng: 0000-0002-0299-3953

Author Contributions

§Y.W. and H.Y. contributed equally.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (c) Quideau, S.; Pouysegu, L.; Deffieux, D. *Synlett* **2008**, *2008*, 467. (d) Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (e) Silva, L. F., Jr.; Olofsson, B. *Nat. Prod. Rep.* **2011**, *28*, 1722. (f) *Iodine Chemistry and Applications*; Kaiho, T., Ed.; Wiley-VCH: Weinheim, 2015; pp 103. (g) Hypervalent Iodine Chemistry. In *Topics in Current Chemistry*; Wirth, T., Ed.; Springer: Switzerland, 2016. (h) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328.

(2) For recent reviews on hypervalent iodine-catalyzed reactions, see: (a) Parra, A.; Reboredo, S. *Chem. - Eur. J.* **2013**, *19*, 17244. (b) Zheng, Z.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Sci. China: Chem.* **2014**, *57*, 189. (c) Singh, F. V.; Wirth, T. *Chem. - Asian J.* **2014**, *9*, 950.

(3) For recent reviews on chiral hypervalent iodine chemistry, see: (a) Liang, H.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11849. (b) Parra, A.; Reboredo, S. *Chem. - Eur. J.* **2013**, *19*, 17244. (c) Harned, A. M. *Tetrahedron Lett.* **2014**, *55*, 4681. (d) Berthiol, F. *Synthesis* **2015**, *47*, 587.

(4) (a) Imamoto, T.; Koto, H. *Chem. Lett.* **1986**, *15*, 967. (b) Ray, D. G., III; Koser, G. F. *J. Am. Chem. Soc.* **1990**, *112*, 5672. (c) Ray, D. G., III; Koser, G. F. *J. Org. Chem.* **1992**, *57*, 1607. (d) Xia, M.; Chen, Z.-C. *Synth. Commun.* **1997**, *27*, 1315. (e) Tohma, H.; Takizawa, S.; Watanabe, H.; Fukuoka, Y.; Maegawa, T.; Kita, Y. *J. Org. Chem.* **1999**, *64*, 3519. (f) Tohma, H.; Takizawa, S.; Morioka, H.; Maegawa, T.; Kita, Y. *Chem. Pharm. Bull.* **2000**, *48*, 445.

(5) (a) Wirth, T.; Hirt, U. H. *Tetrahedron: Asymmetry* **1997**, *8*, 23. (b) Hirt, U. H.; Spingler, B.; Wirth, T. *J. Org. Chem.* **1998**, *63*, 7674. (c) Hirt, U. H.; Schuster, M. F. H.; French, A. N.; Wiest, O. G.; Wirth, T. *Eur. J. Org. Chem.* **2001**, *2001*, 1569.

(6) Recent examples of C_2-symmetric iodoarene catalyzed reactions: (a) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175. (b) Uyanik, M.; Yasui, T.; Ishihara, K. *Tetrahedron* **2010**, *66*, 5841. (c) Wu, H.; He, Y.-P.; Xu, L.; Zhang, D.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 3466. (d) Muñiz, K.; Barreiro, L.; Romero, R. M.; Martínez, C. *J. Am. Chem. Soc.* **2017**, *139*, 4354. (e) Uyanik, M.; Sasakura, N.; Mizuno, M.; Ishihara, K. *ACS Catal.* **2017**, *7*, 872. (f) Uyanik, M.; Yasui, T.; Ishihara, K. *J. Org. Chem.* **2017**, *82*, 11946.

(7) (a) Brown, K. J.; Berry, M. S.; Waterman, K. C.; Lingenfelter, D.; Murdoch, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 4717. (b) Ochiai, M.; Kitagawa, Y.; Takayama, N.; Takaoka, Y.; Shiro, M. *J. Am. Chem. Soc.* **1999**, *121*, 9233. (c) Richardson, R. D.; Desaize, M.; Wirth, T. *Chem. - Eur. J.* **2007**, *13*, 6745. (d) Yu, J.; Cui, J.; Hou, X.-S.; Liu, S.-S.; Gao, W.-C.; Jiang, S.; Tian, J.; Zhang, C. *Tetrahedron: Asymmetry* **2011**, *22*, 2039. (e) Ogasawara, M.; Sasa, H.; Hu, H.; Amano, Y.; Nakajima, H.; Takenaga, N.; Nakajima, K.; Kita, Y.; Takahashi, T.; Dohi, T. *Org. Lett.* **2017**, *19*, 4102.

(8) (a) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787. (b) Dohi, T.; Takenaga, N.; Nakae, T.; Toyoda, Y.; Yamasaki, M.; Shiro, M.; Fujioka, H.; Maruyama, A.; Kita, Y. *J. Am. Chem. Soc.* **2013**, *135*, 4558.

(9) Selected examples of planar chiral [2,2]paracyclophane chemistry: (a) Austeri, M.; Enders, M.; Nieger, M.; Braese, S. *Eur. J. Org. Chem.* **2013**, *2013*, 1667. (b) Heinz, C.; Cramer, N. *J. Am. Chem. Soc.* **2015**, *137*, 11278. (c) Braun, C.; Bräse, S.; Schafer, L. L. *Eur. J. Org. Chem.* **2017**, *2017*, 1760. (d) Wang, L.-Y.; Ye, M.; Wang, L.; Duan, W.-Z.; Song, C.; Ma, Y.-D. *Tetrahedron: Asymmetry* **2017**, *28*, 54. (e) An, P.; Huo, Y.-W.; Chen, Z.; Song, C.; Ma, Y.-D. *Org. Biomol. Chem.* **2017**, *15*, 3202.

(10) (a) Wang, B.-J.; Graskemper, J. W.; Qin, L.-L.; DiMagno, S. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4079. (b) Altermann, S. M.; Richardson, R. D.; Page, T. K.; Schmidt, R. K.; Holland, E.; Mohammed, U.; Paradine, S. M.; French, A. N.; Richter, C.; Bahar, A. M.; Witulski, B.; Wirth, T. *Eur. J. Org. Chem.* **2008**, *2008*, 5315.

(11) For details, see the Supporting Information.

(12) (a) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192. (b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (c) Campbell, M. G.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 474. (d) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(13) Selected examples of electrophilic fluorination of β-ketoesters: (a) Zheng, L.-S.; Wei, Y.-L.; Jiang, K.-Z.; Deng, Y.; Zheng, Z.-J.; Xu, L.-W. *Adv. Synth. Catal.* **2014**, *356*, 3769. (b) Gu, X.; Zhang, Y.; Xu, Z.-J.; Che, C.-M. *Chem. Commun.* **2014**, *50*, 7870. (c) Peng, J.; Du, D.-M. *RSC Adv.* **2014**, *4*, 2061. (d) Niu, T.; Han, X.-P.; Huang, D.-F.; Wang, K.-H.; Su, Y.; Hu, Y.; Fu, Y. *J. Fluorine Chem.* **2015**, *175*, 6. (e) Naganawa, Y.; Aoyama, T.; Kato, K.; Nishiyama, H. *ChemistrySelect.* **2016**, *1*, 1938.

(14) Suzuki, S.; Kamo, T.; Fukushi, K.; Hiramatsu, T.; Tokunaga, E.; Dohi, T.; Kita, Y.; Shibata, N. *Chem. Sci.* **2014**, *5*, 2754.

(15) (a) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 5000. (b) Woerly, E. M.; Banik, S. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 13858. (c) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *Science* **2016**, *353*, 51.

(16) While we were preparing the manuscript, Rueping and coworkers published a similar process mediated by C_2 symmetric iodobenzene; see: Pluta, R.; Krach, P. E.; Cavallo, L.; Falivene, L.; Rueping, M. *ACS Catal.* **2018**, *8*, 2582.

(17) (a) Suzuki, S.; Kamo, T.; Fukushi, K.; Hiramatsu, T.; Tokunaga, E.; Dohi, T.; Kita, Y.; Shibata, N. *Chem. Sci.* **2014**, *5*, 2754. (b) Sreenithya, A.; Patel, C.; Hadad, C. M.; Sunoj, R. B. *ACS Catal.* **2017**, *7*, 4189.

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Org. Lett. XXXX, XXX, XXX−XXX