

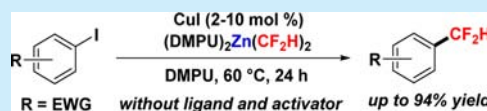
Copper-Catalyzed Difluoromethylation of Aryl Iodides with (Difluoromethyl)zinc Reagent

Hiroki Serizawa, Koki Ishii, Kohsuke Aikawa, and Koichi Mikami*

Department of Chemical Science and Engineering, School of Materials and Chemical Technology, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8552, Japan

Supporting Information

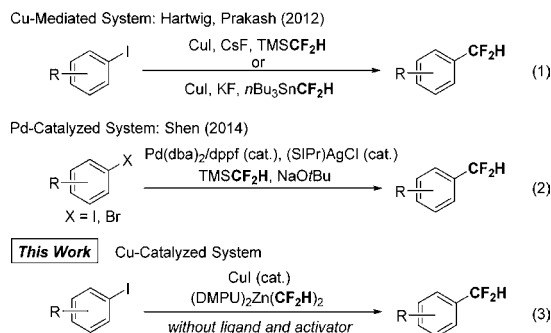
ABSTRACT: The combination of difluoroiodomethane and zinc dust or diethylzinc can readily lead to (difluoromethyl)zinc reagents. Therefore, the first copper-catalyzed difluoromethylation of aryl iodides with the zinc reagents is accomplished to afford the difluoromethylated arenes. The reaction proceeds efficiently through the ligand/activator-free operation without addition of ligands for copper catalyst (e.g., phen and bpy) and activators for zinc reagent (e.g., KF, CsF, and NaO-*t*-Bu). Moreover, transmetalation of the CF₂H group from zinc reagent to copper catalyst proceeds even at room temperature to form the cuprate [Cu(CF₂H)₂][−].



Organic compounds possessing fluorinated functional groups are of great interest in the field of pharmaceuticals and agrochemicals.¹ In particular, trifluoromethylated arenes have attracted much attention, and therefore, a variety of trifluoromethylations to aromatic rings have been actively explored.² Interest in a difluoromethyl (−CF₂H) group, which is considered a lipophilic hydrogen-bonding donor with unique characteristics in pharmaceutical and agrochemical applications, is rapidly increasing.³ Difluoromethylated arenes can be conventionally synthesized via the deoxofluorination reaction of aldehydes with harsh reagents such as *N,N*-diethylaminosulfur trifluoride (DAST) and its derivatives.⁴

Recently, direct and regiospecific difluoromethylations of aryl halides have been desired as practical and reliable synthetic methods for difluoromethylated arenes. However, reports have so far been quite limited,⁵ while synthetic methods for arenes with functionalized difluoromethyl (−CF₂R) groups are quickly progressing.^{6,7} In 2012, Hartwig reported the first example of difluoromethylation of aryl iodides employing an organosilicon reagent, Me₃SiCF₂H (5 equiv), and a stoichiometric amount of CuI along with CsF (3 equiv) at 120 °C and detected the cuprate, [Cu(CF₂H)₂][−], in equilibrium with neutral and active CuCF₂H (Scheme 1, eq 1).⁸ This method is effective in aryl iodides with electron-donating substituents but ineffective with electron-withdrawing ones, giving the protonated arenes as the major product. In contrast, Prakash has reported an alternative difluoromethylation of aryl iodides with an organotin reagent, *n*-Bu₃SnCF₂H (2–3 equiv) prepared from Me₃SiCF₃, with a slight excess (1.3 equiv) of CuI and KF (3 equiv) at 100–120 °C.⁹ Interestingly, the same neutral and active CuCF₂H species, proposed independently, exhibited contrasting reactivity with electron-withdrawing substituents to give high yields but with electron-donating substituents in lower yields. Then Shen succeeded in the first catalytic difluoromethylation of aryl iodides and bromides by originally developing the cooperative dual palladium/silver catalyst system with Me₃SiCF₂H (2 equiv) (Scheme 1, eq 2).¹⁰ The drawback of this catalytic system is that

Scheme 1. Metal-Mediated and -Catalyzed Difluoromethylations



(1) (SIPr)AgCl is required as a mediator because the direct transmetalation of the CF₂H group to palladium from the silicon reagent cannot take place and (2) NaO-*t*-Bu (2 equiv) possessing a high nucleophilicity is also needed. Therefore, the development of practical and reliable catalytic difluoromethylation of aryl halides is still challenging.

As part of our research project based on (trifluoromethyl)- and (perfluoroalkyl)zinc as organozinc reagents,¹¹ we focused on the preparation of (difluoromethyl)zinc reagent and its application to catalytic aromatic difluoromethylation. Herein, we report the first copper-catalyzed difluoromethylation of aryl iodides with (difluoromethyl)zinc reagent through the ligand/activator-free operation (eq 3).¹² While this research was being finalized, Vici reported the nickel-catalyzed difluoromethylation of aryl halides with a similar (difluoromethyl)zinc reagent.¹³

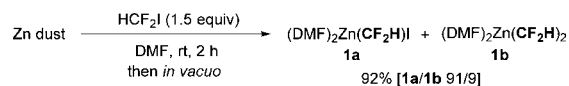
As described above, our laboratory has previously reported synthetic protocols involving (trifluoromethyl)- and (perfluoroalkyl)zinc with DMPU or diamine as ligands.^{11,14} In these

Received: June 15, 2016

Published: July 21, 2016

studies, the synthetic utility of the zinc reagents was improved on the basis of original reports in which $L_2Zn(CF_3)Br$ and $L_2Zn(R_F)_2$ were prepared from CF_3Br /zinc dust¹⁵ and R_FI /dialkylzinc in solvent (L),¹⁶ respectively. Thus, in the preparation of difluoroiodomethylzinc reagents, we decided to employ difluoroiodomethane (HCF_2I) as a difluoromethyl source. As a result, it was found that the combination of zinc dust and difluoroiodomethane in DMF readily led to $(DMF)_2Zn(CF_2H)I$ (**1a**) as a major product, along with $(DMF)_2Zn(CF_2H)_2$ (**1b**) as a minor product (Scheme 2).¹⁷

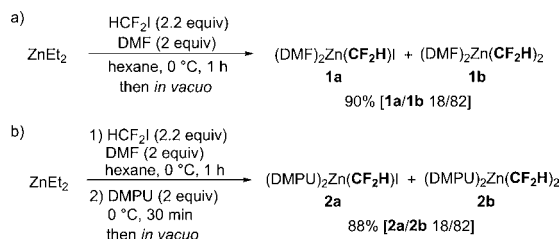
Scheme 2. Preparation of Mono(difluoromethyl)zinc Reagent^a



^aYield was determined by ¹⁹F NMR spectroscopy.

Moreover, we gained the best protocols by various investigations¹⁸ to obtain bis(difluoromethyl)zinc reagents with $L_2Zn(CF_2H)_2$ (**b**) as a major product.¹⁹ Consequently, treatment of diethylzinc, difluoroiodomethane, and DMF (2 equiv) in hexane underwent the reaction to provide $(DMF)_2Zn(CF_2H)I$ (**1a**) and $(DMF)_2Zn(CF_2H)_2$ (**1b**) in a 18:82 ratio in 90% yield (Scheme 3a). Subsequently, the ligand exchange between DMF

Scheme 3. Preparation of Bis(difluoromethyl)zinc Reagents^a



^aYield and ratio of a/b were determined by ¹⁹F NMR spectroscopy.

and DMPU took place smoothly to produce $(DMPU)_2Zn(CF_2H)_2$ (**2b**) as a major product (Scheme 3b). We also observed a Schlenk equilibrium between $(DMPU)_2Zn(CF_2H)_2$ (**2b**) and $(DMPU)_2Zn(CF_2H)I$ (**2a**) by addition of 1 equiv of ZnI_2 at 60 °C.¹⁷

The thermal stability of (difluoromethyl)zinc reagents was examined in DMF solution (0.1 M) at 60 °C by ¹⁹F NMR spectroscopy, and **1** and **2** were found to almost decompose at 60 °C after 24 h (Table 1a and 1b). In the decomposition process, we

Table 1. Thermal Stability of Zinc Reagents at 60 °C^a

(a) Zn reagent 1 in DMF		(b) Zn reagent 2 in DMF		(c) Zn reagent 2 in DMPU	
time (h)	$ZnCF_2H$ (%) [1a:1b]	time (h)	$ZnCF_2H$ (%) [2a:2b]	time (h)	$ZnCF_2H$ (%) [2a:2b]
1	12:75	1	12:77	1	11:81
6	12:31	6	8:40	6	10:75
12	7:5	12	4:8	12	7:71
24	3:<1	24	1:<1	24	7:61

^aConditions: zinc reagents (0.1 mmol, a/b 18%/82%) in DMF or DMPU (1 mL) at 60 °C for 24 h. Remaining zinc reagents a/b (%) were determined by ¹⁹F NMR analysis using BTF (benzotrifluoride) as an internal standard.

did not observe HF_2C-CF_2H and $HFC=CFH$ formed via generation of difluoromethyl radical and monofluorocarbene species, only difluoromethane (CF_2H_2) via protonation of zinc reagents by adventitious water in DMF. In sharp contrast, the zinc reagent **2** in DMPU, which can serve as a stronger coordinating solvent, was demonstrated to be more stable at 60 °C, and thus, 68% of **2** remained even after 24 h (Table 1c). Based on these results, we expected that the zinc reagents prepared can be adequately employed for the difluoromethylation which requires heating, while the decomposition proceeds during the reaction at 60 °C.

The copper-catalyzed difluoromethylation of aryl iodides was executed with the (difluoromethyl)zinc reagents (Table 2). A

Table 2. Copper-Catalyzed Difluoromethylation of Aryl Iodide^a

entry	Zn reagent ^b	solvent	X (mol %)	t (°C)	yield ^c (%)
1	$(DMPU)_2Zn(CF_2H)_2$ (2b)	DMPU	100	60	75
2	$(DMPU)_2Zn(CF_2H)_2$ (2b)	DMPU	10	60	90 (85) ^d
3 ^e	$(DMF)_2Zn(CF_2H)_2$ (1b)	DMF	10	60	57
4 ^e	$(DMF)_2Zn(CF_2H)I$ (1a)	DMF	10	60	7
5	$(DMPU)_2Zn(CF_2H)_2$ (2b)	DMPU	10	50	81
6	$(DMPU)_2Zn(CF_2H)_2$ (2b)	DMPU	10	70	86
7	$(DMPU)_2Zn(CF_2H)_2$ (2b)	DMPU	5	60	85
8 ^f	$(DMPU)_2Zn(CF_2H)_2$ (2b)	DMPU	2	60	80
9	$(DMPU)_2Zn(CF_2H)_2$ (2b)	DMPU	0	60	0
10	$(DMPU)_2Zn(CF_2H)_2$ (2b)	DMF	10	60	61
11	$(DMPU)_2Zn(CF_2H)_2$ (2b)	NMP	10	60	3
12	$(DMPU)_2Zn(CF_2H)_2$ (2b)	DMSO	10	60	5
13	$(DMPU)_2Zn(CF_2H)_2$ (2b)	MeCN	10	60	2
14	$(DMPU)_2Zn(CF_2H)_2$ (2b)	THF	10	60	0
15	$(DMPU)_2Zn(CF_2H)_2$ (2b)	toluene	10	60	0

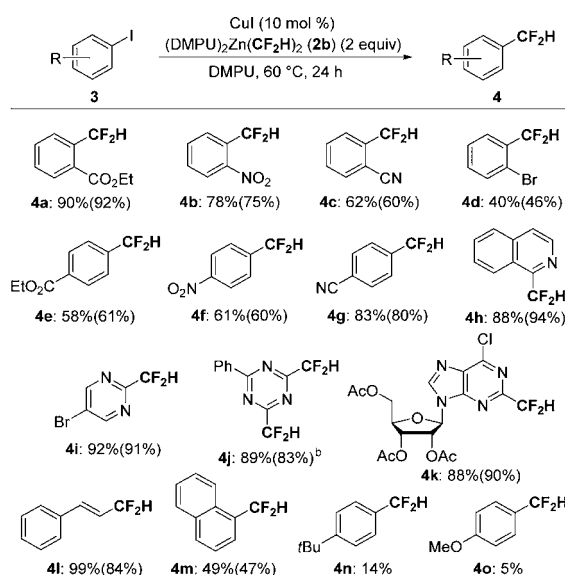
^aConditions: **3a** (0.3 mmol), zinc reagent (~0.5 M DMPU solution: 0.6 mmol), CuI (X mol %) in solvent (2 mL). ^b $(DMF)_2Zn(CF_2H)I$ and $L_2Zn(CF_2H)_2$ (L = DMF, DMPU) prepared according to methods shown in Schemes 2 and 3 were employed, respectively. ^cYield was determined by ¹⁹F NMR spectroscopy. ^dGram-scale experiment, isolated yield. ^eZinc reagents (~0.5 M DMF solution) were employed. ^fReaction time was 48 h.

stoichiometric amount of CuI was first employed for the reaction of ethyl 2-iodobenzoate (**3a**) as a model substrate with 2 equiv of $(DMPU)_2Zn(CF_2H)_2$ in DMPU at 60 °C for 24 h, providing the difluoromethyl coupling product (**4a**) in 75% yield (entry 1). Significantly, the reduction of the amount of CuI to 10 mol % led to the higher yield of product up to 90% (entry 2). The gram-scale reaction also proceeded smoothly. The $(DMF)_2Zn(CF_2H)_2$ derivative afforded moderate yield, and $(DMF)_2Zn(CF_2H)I$ gave only a small amount of the product (entries 3 and 4).

Temperatures lower or higher than 60 °C gave slightly lower yields, respectively (entries 5 and 6). Even a reduction in catalyst amount up to 5 and 2 mol % also led to satisfactory yields (entries 7 and 8). Control experiments clarified the requirement of copper catalyst (entry 9). Additionally, a dramatic solvent effect was observed in the present reaction. Except for DMPU and DMF (entries 2 and 10), the difluoromethylation did not efficiently proceed in NMP,⁸ DMSO,^{7a,13} MeCN,¹⁰ THF, and toluene (entries 11–15). Therefore, the reaction conditions in entry 2 were set to be the best.

Under the best reaction conditions, the substrate scope in the reaction was investigated (Scheme 4). Aryl iodides with electron-

Scheme 4. Scope of Substrates^a

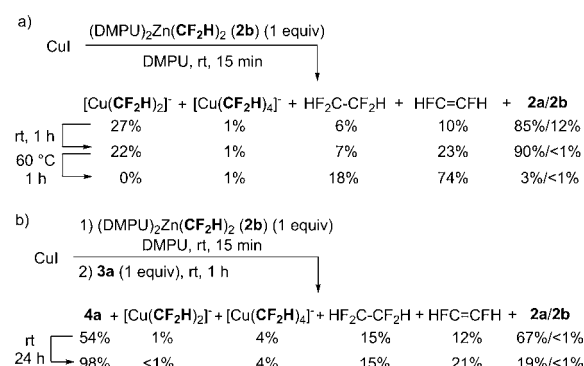


^aConditions: **3** (0.3 mmol), zinc reagent (~0.5 M DMPU solution: 0.6 mmol), CuI (10 mol %) in DMPU (2 mL). $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ prepared according to the method shown in Scheme 3 was employed. The yield was determined by ¹⁹F NMR spectroscopy, and the value in parentheses is the isolated yield. ^b $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ (4 equiv) was employed.

withdrawing substituents in the *ortho*-position of the ring, such as nitro, cyano, and bromo, afforded the difluoromethylated products **4b–d** in moderate to good yields. The reaction of aryl iodides bearing electron-withdrawing substituents in the *para*-position of the ring also proceeded to give the desired products **4e–g** in moderate to good yields. Furthermore, difluoromethylation of heteroaromatics such as isoquinoline, pyrimidine, and triazine provided high yields of the products (**4h–j**). The nucleoside analogue and vinylic substrate also afforded the products **4k,l** in high yields. 1-Iodonaphthalene also led to the corresponding product (**4m**) in moderate yield, but unfortunately, aryl iodides with electron-donating substituents such as *tert*-butyl and methoxy gave low yields (**4n,o**).

In order to shed light on the mechanism of the present copper-catalyzed difluoromethylation, transmetalation of the CF_2H group from the zinc reagent to CuI was monitored by ¹⁹F NMR spectroscopy (Scheme 5a).¹⁸ After 15 min at room temperature, the progress of the transmetalation was observed to give two types of (difluoromethyl)copper species, cuprates $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ (−114.9 ppm, $J_{\text{F-H}} = 44.8$ Hz)^{8,17,20} and $[\text{Cu}(\text{CF}_2\text{H})_4]^-$ (−116.3 ppm, $J_{\text{F-H}} = 49.6$ Hz),²⁰ in 27% and 1% yields, respectively, along with $\text{HF}_2\text{C-CF}_2\text{H}$ and HFC=CFH . The

Scheme 5. Stoichiometric Experiments in Difluoromethylation^a



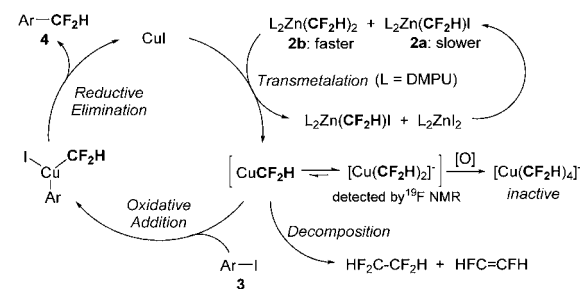
^aConditions: CuI (0.1 mmol), zinc reagent (~0.5 M DMPU solution: 0.1 mmol), **3a** (0.1 mmol) in DMPU (1 mL). $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ prepared according to the method shown in Scheme 3 was employed. Yield was determined by ¹⁹F NMR spectroscopy.

neutral CuCF_2H in equilibrium, which has been suggested as a reactive species,^{8,9} was not observed due to the instability at room temperature.^{17,20} After an additional 1 h at room temperature and then at 60 °C, the increase of $\text{HF}_2\text{C-CF}_2\text{H}$ and HFC=CFH was observed at the same time that $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ decomposed. Furthermore, it was found that transmetalation of the CF_2H group by $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ (**2b**) was faster than that by $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})\text{I}$ (**2a**) because **2a** (85–90%) remained at room temperature.

The reaction of aryl iodide **3a** with the copper difluoromethyl species after transmetalation was also investigated (Scheme 5b). Even at room temperature for 1 h, the peak of $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ almost disappeared and the formation of coupling product **4a** was observed in 54% yield with complete conversion of $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ (**2b**) to $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})\text{I}$ (**2a**). Subsequently, the reaction slowly ended after 24 h to afford **4a** in 98% yield because of the slower transmetalation of the CF_2H group by **2a** at room temperature. The ratio of stable complex $[\text{Cu}(\text{CF}_2\text{H})_4]^-$,²⁰ which is inert species in the reaction, did not change during the course of reaction.

On the basis of these results by ¹⁹F NMR analysis, the mechanism of the catalytic reaction is visualized in Scheme 6.

Scheme 6. Plausible Reaction Mechanism



Initially, transmetalation of the CF_2H group from $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ to CuI triggers the catalytic reaction to produce neutral CuCF_2H and cuprate $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ in equilibrium that should shift to the more stable $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ observed in ¹⁹F NMR analysis. In fact, Hartwig has suggested that cuprate $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ can function as a stable reservoir for the unstable and active species CuCF_2H .⁸ The reaction of CuCF_2H with aryl

iodide **3** bearing an electron-withdrawing substituent leads to oxidative addition of the C–I bond with formation of the corresponding copper(III) species. A final reductive elimination in the copper(III) species closes the catalytic cycle to provide the difluoromethylated arene **4** and to reproduce CuI. In sharp contrast, the oxidative addition of aryl iodide with an electron-donating substituent is relatively slow, and consequently, the decomposition of CuCF_2H mainly occurs to produce $\text{HF}_2\text{C}-\text{CF}_2\text{H}$ and $\text{HFC}=\text{CFH}$.

In summary, we have succeeded in the first copper-catalyzed difluoromethylation of aryl iodides with the organozinc reagent $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ in DMPU at 60 °C. It was also demonstrated that transmetalation of the CF_2H group from the zinc reagent to copper catalyst can proceed efficiently even at room temperature, generating not neutral CuCF_2H but cuprate $[\text{Cu}(\text{CF}_2\text{H})_2]^-$. Moreover, aryl iodides bearing electron-withdrawing substituents underwent the reaction to provide the difluoromethylated products in moderate to high yields. The reaction proceeded without use of any ligands for copper catalyst (e.g., 1,10-phenanthroline and 2,2'-bipyridine derivatives) and activators for zinc reagent (e.g., KF, CsF, and $\text{NaO}-t\text{-Bu}$). Development of Pd-catalyzed difluoromethylation of aryl halides bearing not only electron-withdrawing substituents but also electron-donating substituents is the topic of our following paper (DOI: [10.1021/acs.orglett.6b01734](https://doi.org/10.1021/acs.orglett.6b01734)).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b01733](https://doi.org/10.1021/acs.orglett.6b01733).

Experimental procedures and compound characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mikami.k.ab@m.titech.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by JST (ACT-C: Advanced Catalytic Transformation program for Carbon utilization) and JSPS KAKENHI Grant No. 26620078.

■ REFERENCES

- (1) (a) 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. (b) O'Hagan, D.; Deng, H. *Chem. Rev.* **2015**, *115*, 634. (c) Tirota, L.; Dichiarante, V.; Pigliacelli, C.; Cavallo, G.; Terraneo, G.; Bombelli, F. B.; Metrangola, P.; Resnati, G. *Chem. Rev.* **2015**, *115*, 1106.
- (2) For selected reviews, see: (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (b) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (c) Sugiishi, T.; Amii, H.; Aikawa, K.; Mikami, K. *Beilstein J. Org. Chem.* **2015**, *11*, 2661. (d) Zeng, Y.; Ni, C.; Hu, J. *Chem. - Eur. J.* **2016**, *22*, 3210.
- (3) For selected reviews, see: (a) Hu, J.; Wang, F. *Chem. Commun.* **2009**, 7465. (b) Hu, J. *J. Fluorine Chem.* **2009**, *130*, 1130. (c) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842. (d) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765.
- (4) (a) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, *132*, 18199. (b) Fujimoto, T.; Becker, F.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 1041.
- (5) The radical difluoromethylation, see: (a) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494. (b) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95. For Sandmeyer-type difluoromethylation, see: (c) Matheis, C.; Jouvin, K.; Goossen, L. J. *Org. Lett.* **2014**, *16*, 5984. For the difluoromethylation-containing difluorocarbene pathway, see: (d) Feng, Z.; Min, Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44.
- (6) For a review, see: Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. - Eur. J.* **2015**, *21*, 12836.
- (7) For selected examples of the direct introduction of functionalized difluoromethyl ($-\text{CF}_2\text{R}$) groups to arenes: (a) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560. (b) Ohtsuka, Y.; Yamakawa, T. *Tetrahedron* **2011**, *67*, 2323. (c) Min, Q.-Q.; Yin, Z.; Feng, Z.; Guo, W.-H.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 1230. (d) Ge, S.; Chaladaj, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4149. (e) Xiao, Y.-L.; Guo, W.-H.; He, G.-Z.; Pan, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 9909. (f) Arlow, S. I.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 4567. (g) Xiao, Y.-L.; Min, Q.-Q.; Xu, C.; Wang, R.-W.; Zhang, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 5837.
- (8) (a) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524. Qing has succeeded in improving Hartwig's reaction conditions; see: (b) Jiang, X.-L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. *Org. Chem. Front.* **2014**, *1*, 774.
- (9) Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swaback, J. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090.
- (10) (a) Gu, Y.; Leng, X.-B.; Shen, Q. *Nat. Commun.* **2014**, *5*, 5405. (b) Chang, D.; Gu, Y.; Shen, Q. *Chem. - Eur. J.* **2015**, *21*, 6074.
- (11) (a) Mikami, K.; Nakamura, Y.; Aikawa, K. Japanese Patent Application 2012-113898, May 18, 2012. (b) Mikami, K.; Nakamura, Y.; Negishi, K.; Aikawa, K. Japanese Patent Application 2013-180007, Aug 30, 2013. (c) Nakamura, Y.; Fujita, M.; Murase, T.; Itoh, Y.; Serizawa, H.; Aikawa, K.; Mikami, K. *Beilstein J. Org. Chem.* **2013**, *9*, 2404. (d) Aikawa, K.; Nakamura, Y.; Yokota, Y.; Toya, W.; Mikami, K. *Chem. - Eur. J.* **2015**, *21*, 96. (e) Aikawa, K.; Toya, W.; Nakamura, Y.; Mikami, K. *Org. Lett.* **2015**, *17*, 4996.
- (12) (a) Serizawa, H. Doctor Thesis, Tokyo Institute of Technology, Dec 21, 2015. (b) Mikami, K. Presented at Pacificchem 2015, Honolulu, HI, Dec 15–20, 2015.
- (13) Xu, L.; Vicić, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 2536.
- (14) Recent examples of perfluoroalkylations using (perfluoroalkyl) zinc reagents: (a) Kaplan, P. T.; Xu, L.; Chen, B.; McGarry, K. R.; Yu, S.; Wang, H.; Vicić, D. A. *Organometallics* **2013**, *32*, 7552. (b) Kaplan, P. T.; Chen, B.; Vicić, D. A. *J. Fluorine Chem.* **2014**, *168*, 158. (c) Kato, H.; Hirano, K.; Kurauchi, D.; Toriumi, N.; Uchiyama, M. *Chem. - Eur. J.* **2015**, *21*, 3895. (d) Wang, X.; Hirano, K.; Kurauchi, D.; Kato, H.; Toriumi, N.; Takita, R.; Uchiyama, M. *Chem. - Eur. J.* **2015**, *21*, 10993.
- (15) Previous reports on the stable solid reagent mono(trifluoromethyl)zinc prepared from CF_3Br and zinc dust: (a) Naumann, D.; Tyrre, W.; Kock, B.; Rudolph, W.; Wilkes, B. *J. Fluorine Chem.* **1994**, *67*, 91. (b) Tyrre, W.; Naumann, D.; Pasenok, S. V.; Yagupolskii, Y. L. *J. Fluorine Chem.* **1995**, *70*, 181. (c) Kremlev, M. M.; Tyrre, W.; Mushta, A. I.; Naumann, D.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2010**, *131*, 212.
- (16) Previous reports on bis(trifluoromethyl)zinc and bis(perfluoroalkyl)zinc prepared from R_2I and dialkylzinc: (a) Lange, H.; Naumann, D. *J. Fluorine Chem.* **1984**, *26*, 435. (b) Schorn, C.; Naumann, D.; Scherer, H.; Hahn, J. *J. Fluorine Chem.* **2001**, *107*, 159.
- (17) The preparation of (difluoromethyl)zinc has been reported by Burton, via the reaction of zinc dust with bromodifluoromethane in DMF to afford $\text{Zn}(\text{CF}_2\text{H})\text{Br}$ and $\text{Zn}(\text{CF}_2\text{H})_2$ in an 88:12 ratio in 73–85% yield: Burton, D. J.; Hartgraves, G. A. *J. Fluorine Chem.* **2007**, *128*, 1198.
- (18) See the Supporting Information.
- (19) By treatment of HCF_2I and diethylzinc in a 1:1 ratio, the formation of both $\text{Zn}(\text{CF}_2\text{H})\text{Et}$ and $\text{Zn}(\text{CF}_2\text{H})_2$ was confirmed by Charette: Beaulieu, L.-P. B.; Schneider, J. K.; Charette, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 7819.
- (20) Eujen, R.; Hoge, B.; Brauer, D. J. *J. Organomet. Chem.* **1996**, *519*, 7.