Regiocontrolled Heptafluoroisopropylation of Aromatic Halides by Copper(I) Carboxylates with Heptafluoroisopropyl-Zinc Reagents

Soichiro Ono, Yuki Yokota, Shigekazu Ito, and Koichi Mikami*®

Organic

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: Copper(I)-mediated heptafluoroisopropylation of aryl halides (ArX: X = I, Br) is demonstrated using copper(I) carboxylates and a bis(heptafluoroisopropyl)zinc reagent $Zn(i-C_3F_7)_2(dmf)_2$, prepared from heptafluoroisopropyl iodide and diethylzinc. The air-tolerant solid heptafluoroisopropylzinc reagent is advantageous to conduct simple synthetic operations and successful to give the corresponding heptafluor-



oisopropyl arene derivatives via transmetalation to copper(I) center. The newly developed copper(I)-mediated heptafluoroisopropylation process can be advanced to the copper(I)-catalysis by silver carboxylate salts and complementary to the precedent radical-based processes.

In synthetic organofluorine chemistry, the introduction of fluoroalkyl functional groups into lead/sead organic compounds poses a long-standing challenge due to unique fluoroalkyl functionalities.¹ Among them, heptafluoroisopropyl arenes have attracted current interests in agrochemical^{2a,b} and organocatalysis^{2c} fields. For instance, flubendiamide and pyrifluquinazon are in market as insecticides with excellent activity against a broad spectrum of pests. As for organocatalysis, hetero-Diels–Alder reactions can be catalyzed by heptafluoroisopropylated binaphthyl bis-sulfonimide to give high enantioselectivities. In addition, heptafluoroisopropyl compounds have also been applied as liquid crystals.^{2d}

Fluoroalkyl groups should be directly introduced into target molecular units both on early (starting) and very late (last) stages.³ However, the methods for heptafluoroisopropylation were rarely of precedence (Scheme 1). For instance, McLoughlin and Ishikawa reported Ullmann-type heptafluoroisopropylations separately (eq 1).⁴ The reaction can be performed only at high (125 °C) temperature and with large excess (7.0 equiv) of copper powder. Nihon Nohyaku Co., Ltd. reported radical-type heptafluoroisopropylations leading to flubendiamide (eq 2).⁵ The reaction requires substrates containing strongly electron-donating amino groups and proceeds only at para-position. Recently, Wu and Gong reported oxidative heptafluoroisopropylations using aryl boronic acids (eq 3).⁶ They require excess reagents (2.0 equiv of Ag salt and 1.0 equiv of Cu salt). Burton et al. attempted heptafluoroisopropylation with heptafluoroisopropyl cadmium complex that afforded heptafluoroisopropyl copper complex via transmetalation. However, this process has not been employed for synthesis of heptafluoroisopropyl arene products.

Herein, we report copper(I)-mediated aromatic heptafluoroisopropylation with heptafluoroisopropylzinc reagents under mild reaction conditions (eq 4). Recently, we reported trifluoromethylation of aryl iodides catalyzed by copper(I)







iodide with bis(trifluoromethyl)zinc in N,N'-dimethylpropyleneurea (DMPU).⁸ The catalytic reaction provides moderateto-high yields of trifluoromethyl products from aromatic halide.

First, we tried to synthesize⁹ stable but reactive bis-(heptafluoroisopropyl)zinc reagents prepared from diethylzinc and heptafluoroisoropyl iodide (Table 1). In hexane, the desired zinc reagent was obtained but in low yields (entry 1–

Received: December 29, 2018

Table 1. Preparation of Bis(heptafluoroisopropyl)zinc Reagents*

ZnEt ₂	<i>i</i> -C ₃ F ₇ I (2.5 equiv) cosolvent (Solv) (2.0 e solvent, temp °C, tim) quiv) <mark>→</mark> Zn(<i>i-</i> C e h	3F ₇) ₂ (Solv) ₂ 1	cos 1a 1b 1c	olvent (Solv) DMF DMPU DME
entry	cosolvent (Solv)	solvent	temp	time	yield ^a (%)
1	DMF	hexane	-20	48	22
2	DMPU	hexane	-20	48	20
3 ^b	DME	hexane	-20	48	18
4 ^{<i>c</i>}	DMF	CH_2Cl_2	-20	48	71
5	DMF	CH_2Cl_2	0	3	96
sk:			,		

*Conditions: Diethylzinc (5.0 mmol), *i*- C_3F_7I (12.5 mmol), cosolvent (Solv) (10 mmol) in solvent (10 mL). ^{*a*}Isolated yield. ^{*b*}1.0 equiv of DME was used. ^{*c*}5.0 equiv of *i*- C_3F_7I was used.

3). Although Zn(*i*-C₃F₇)₂(dmpu)₂ **1b** was air-sensitive at room temperature, the DMF- and DME-coordinated zinc complexes showed almost no decomposition in air at room temperature. However, $Zn(i-C_3F_7)_2(dme)_2$ **1c** could not be purified by crystallization, and further investigation with DMPU and DME was not carried out. In dichloromethane including DMF as a cosolvent, $Zn(i-C_3F_7)_2(dmf)_2$ **1a** was isolated in higher yields (entry 4–5). The DMF-coordinated zinc complex **1a** was obtained after workup procedures with >97% purity (¹⁹F NMR). Crystalline **1a** showed slight instability to moisture but could be stored at –30 °C under inert atmosphere at least one month.

Thermal stability of 1a was examined by ¹⁹F NMR spectroscopic analysis (Table S1). In DMF, 1a was decomposed at 70 and 90 °C in 20 and 10 min, respectively. In the decomposition process, hexafluoropropene via fluoride elimination was not observed, but heptafluoropropane was detected together with unidentified byproducts. However, in 1,4-dioxane, 1a showed relatively high stability as compared in DMF, and only small amount of hexafluoropropene and heptafluoropropane were observed upon heating at 90 °C for 1 h.

Compound 1a showed melting point (decomp.) of 78 °C, which is lower than $Zn(i-C_3F_7)_2(CH_3CN)_2$ (121 °C).⁹ Thus, the lower thermal stability of 1a might correspond to the useful reactivity for aromatic heptafluoroisopropylation (*vide infra*). No report on $Zn(i-C_3F_7)_2(CH_3CN)_2$ has been known in synthetic application.

The copper(I)-mediated heptafluoroisopropylation of aryl iodides was executed with the zinc reagent 1a (Table 2). A stoichiometric amount of copper(I) iodide was first employed for the reaction of ethyl 2-iodobenzoate (2a) as a model substrate with 1a in DMF at 70 °C for 18 h. Unfortunately, heptafluoroisopropyl product was not obtained (entry 1). However, by employing copper(I) acetate, the product (3a) was obtained in a low yield (entry 2). This finding encouraged us to optimize the reaction conditions. Entries 3-9 examined the solvents, and 1,4-dioxane gave higher yields (entry 4). However, the yield was not substantially improved even at higher temperatures (entries 10-12). To our delight, the use of copper(I) thiophene-2-carboxylate (CuTC) improved the yield dramatically (entries 13-16). We concluded that the conditions with CuTC at 70 °C in 1,4-dioxane should be employed for further studies (entry 16).

Under the optimized conditions in 1,4-dioxane, the substrate scope was investigated (Scheme 2). Aryl iodides bearing

 Table 2. Copper(I)-Mediated Heptafluoroisopropylation of

 Ethyl 2-Iodobenzoate

		1a (2.0 equiv) Cu salt (1.5 equiv)	(^``	<i>i</i> -C ₃ F ₇
	CO ₂ Et	solvent, temp °C, 18 h		CO ₂ Et
2a				3a -
entry	Cu salt	solvent	temp	yield ^a (%)
1 ^{<i>b,c</i>}	CuI	DMF	70	0
2	CuOAc	DMF	70	20
3	CuOAc	toluene	70	0
4	CuOAc	1,4-dioxane	70	43
5	CuOAc	DMPU	70	0
6	CuOAc	DCE	70	36
7	CuOAc	THF	70	20
8	CuOAc	diglyme	70	36
9	CuOAc	DMI	70	4
10	CuOAc	1,4-dioxane	80	47
11	CuOAc	1,4-dioxane	90	47
12	CuOAc	1,4-dioxane	100	32
13	CuTC	1,4-dioxane	80	69
14	CuTC	1,4-dioxane	90	81
15 ^b	CuTC	1,4-dioxane	90	60
16 ^{b,d}	CuTC	1,4-dioxane	70	82

^{*}Conditions: **2a** (0.10 mmol), **1a** (0.20 mmol), Cu salt (0.15 mmol) in solvent (0.30 mL). ^{*a*}Yields based on **2a** were determined by ¹⁹F NMR analysis by using BTF as an internal standard. ^{*b*}1.0 equiv of zinc reagents **1a** was used. ^{*c*}1.0 equiv of Cu salt was used. ^{*d*}Reaction time was 48 h.

Scheme 2. Scope of Substrates*



^{*}Conditions: **2** (0.10 mmol), **1a** (0.10 mmol), CuTC (0.15 mmol) in 1,4-dioxane (0.3 mL). Yields based on **2** were determined by 19 F NMR analysis by using BTF as an internal standard. Isolated yields are shown in parentheses. 1.0 mmol scale experiment. ^{*a*}1.0 mmol scale experiment.

carbonyl substituents at *ortho*-position, such as ester, ketone, and amide, afforded the heptafluoroisopropyl products (3a-3c) in good yields. However, the absence of *ortho*-carbonyl substituent reduced the yields of heptafluoroisopropyl products (3d, 3g), suggesting that the *ortho*-carbonyl groups might facilitate the oxidative addition via intramolecular coordination on copper(I) center.¹⁰ Thiophene and bithiophene iodides also gave products (3e, 3f) in moderate to good yields.

The reaction was further examined with low yielding *para*ethoxycarbonyl substrate 2g (Table 3). In 1,4-dioxane at 70 and 90 °C, the reaction resulted in low yields. However, the small amount of product 3g in entries 1 and 2 prompted us to optimize the reaction conditions. In diglyme, the yields remained low (entries 3, 4). In DMF, the reaction gave an Table 3. Copper(I)-Mediated Heptafluoroisopropylation of Ethyl 4-Iodobenzoate*

	1a (1.0 equiv) CuTC (1.5 equiv)		<i>i</i> -C ₃ F ₇	
EtO ₂ C	solvent, temp	o °C, 18 h EtC	EtO ₂ C	
2g			3g	
entry	solvent	temp	yield ^a (%)	
1 ^b	1,4-dioxane	70	8	
2	1,4-dioxane	90	16	
3	diglyme	90	10	
4	diglyme	120	16	
5	DMF	80	22	
6	DMF	90	38	
7	DMF	100	22	
8	DMF	120	7	
9 ^c	DMF	90	92	

^{*}Conditions: **2g** (0.10 mmol), **1a** (0.10 mmol), CuTC (0.15 mmol) in solvent (0.30 mL). ^{*a*}Yields based on **2g** were determined by ¹⁹F NMR analysis by using BTF as an internal standard. ^{*b*}Reaction time was 48 h. ^{*c*}**2g** (0.30 mmol), **1a** (0.30 mmol), CuTC (0.45 mmol) in DMF (0.60 mL), using oven-dried glassware, reaction time was 7 h.

increased (38%) yield at 90 °C (entry 6). Using oven-dried glassware and higher concentration [0.50 mol/L], the reaction reproductively gave the product **3g** in 92% yield (entry 9). We concluded that the conditions in DMF at 90 °C for 7 h should be employed for further studies (entry 9).

Under the optimized conditions in DMF, the substrate scope was investigated (Scheme 3). Aryl iodides bearing

Scheme 3. Scope of Substrates*



^{*}Conditions: Aryl iodides 2 (0.30 mmol), 1a (0.30 mmol), CuTC (0.45 mmol) in DMF (0.6 mL). Yields based on 2 were determined by ¹⁹F NMR analysis by using BTF as an internal standard. Isolated yields are shown in parentheses. ^a0.5 equiv of 1a was used. ^bAryl bromides 2' were used instead of aryl iodides 2. ^c0.6 mmol scale experiment.

electron-withdrawing substituents in *para-* and *meta-*positions, such as ester, cyano, nitro, and trifluoromethyl, afforded the products in excellent yields. Electron-donating substituents in *para-* and *meta-*position, such as methoxy and *tert-*butyl groups, also afforded excellent yields. Electron-withdrawing and -donating substituents in *ortho-*position gave moderate yields.

As for thiophene derivatives, the products were obtained in moderate yields. Even aryl bromides were also applicable to give good yields (3h, 3k, 3l). It should be noted here that the use of just 0.5 equiv of 1a led to excellent yield (3g, 90%), equally high to that obtained with 1.0 equiv of 1a (92%).

In order to develop Cu-catalyzed reaction system (*vide infra*), we employed silver(I) carboxylate salt (Scheme 4). The

Scheme 4. Catalytic Reactions*



^{*}Conditions: 2 (0.10 mmol), 1a (0.10 mmol), CuI (0.01 mmol), silver(I) acetate (0.15 mmol) in 1,4-dioxane (0.30 mL). Yields based on 2 were determined by ¹⁹F NMR analysis by using BTF as an internal standard. ^{*a*}1.0 equiv of silver(I) acetate was used. ^{*b*}0.6 equiv of silver(I) acetate was used. ^{*c*}2f (1.0 mmol), 1a (1.0 mmol), CuTC (0.1 mmol), silver(I) acetate (1.5 mmol) in 1,4-dioxane (3.0 mL).

heptafluoroisopropyl products (**3a**, **3b**, **3f**) were obtained in good to excellent (73–98%) yields with a catalytic amount of copper(I) iodide or thiophenecarboxylate (10 mol %) and 1.0-1.5 equiv of silver(I) acetate. The heptafluoroisopropyl silver(I) complex⁶ was not observed in the reaction of **1a** and silver(I) acetate in 1,4-dioxane.

In order to clarify the reaction mechanism, transmetalation of the heptafluoroisopropyl group from the zinc reagent 1a to copper(I) salts such as CuI, CuOAc, and CuTC was monitored by ¹⁹F NMR spectroscopic analysis (Scheme 5,

Scheme 5. Transmetalation to Copper(I) Salts from Zinc Reagent 1a

CuX 1a (1.0 equiv) 1,4-dioxane or DMF	$Cu(i-C_3F_7) \xrightarrow{4a}$	Cu(<i>i</i> -C ₃ F ₇)2 [⊖] 4b
in 1,4-dioxane:	δ _F = -69.6, -214.0 ppm	$\delta_{\rm F}$ = -69.2, -217.8 ppm
X = I, OAc, TC	δ _F = -69.5, -213.8 ppm ↓ 2a/2g	δ _F = -69.6, -218.4 ppm
	3a/3g	

Table S2). Transmetalation to copper(I) iodide was not observed at all in a wide range of temperatures $(50-90 \ ^{\circ}C)$ and either 1,4-dioxane or DMF. However, copper(I) carboxylates gave monoheptafluoroisopropyl copper(I) complex⁷ 4a at 70 $^{\circ}C$ in 1,4-dioxane. The mixture containing 4a in 1,4-dioxane was reacted with aryl iodide 2a to give the heptafluoroisopropyl product 3a. In DMF, the reaction of a copper(I) carboxylate and 1a gave mainly bis-heptafluoroisopropyl copper(I) complex 4b at room temperature. The mixture did not react with 2g at room temperature. On heating the mixture at 90 $^{\circ}C$, the amount of monoheptafluoroisopropyl copper(I) complex 4a was increased and the reaction with 2g proceeded to afford the heptafluoroisopropyl product 3g (see Table S3). It is thus likely that 4b is not reactive¹¹ but a

Organic Letters

reservoir of 4a that can react with 2 affording 3. Significantly, both 4a and 4b were found to be stable even at 90 $^{\circ}$ C.

On the basis of these NMR studies, the proposed mechanism of the catalytic cycle is visualized in Scheme 6

Scheme 6. Plausible Reaction Mechanisms



with energy profiles (by DFT calculations; see SI). The cycle starts from transmetalation¹² of 1a to copper(I) carboxylates affording monoheptafluoroisopropyl 4a together with bisheptafluoroisopropyl 4b. Compound 4a would react with 2 via oxidative addition. The Cu(III) intermediate could cause reductive elimination to give the heptafluoroisopropyl product 3 and copper(I) iodide. Although copper(I) iodide is inert to transmetalation, anion exchange with silver(I) carboxylates provides the copper(I) carboxylates, which would close the catalytic cycle.

In 1,4-dioxane, 4a shows low reactivity, but *ortho*-carbonyl coordinated heptafluoroisopropyl copper(I) complex has higher reactivity¹⁰ (by DFT calculations; see SI). Therefore, the substrate scope was limited only on coordinating/ activating substrates. In DMF, 4a has higher reactivity because DMF coordinated on the copper(I) center.¹³ Therefore, the heptafluoroisopropylation in DMF realizes wide substrate scope.

Our heptafluoroisopropylation should find applications in agrochemical, pharmaceutical, and material developments (Scheme 7). We established the convergent and copper(I)-catalyzed synthesis of heptafluoroisopropyl quaterthiophene in high yield (*vide supra*). In comparison with perfluorophenyl or

Scheme 7. Synthesis of Quaterthiophene



"NMR yield based on **2f** were determined by ¹⁹F NMR analysis by using BTF as an internal standard. *n*-perfluoroalkyl derivatives, 14,15 installation of *iso*-heptafluoropropyl substituents to quaterthiophene would be advantageous in term of easy fabrication based on high solubility.

In summary, we have succeeded in the first copper(I)catalyzed heptafluoroisopropylation of aryl halides with the organozinc reagent $Zn(i-C_3F_7)_2(dmf)_2$ 1a, prepared from heptafluoroisopropyl iodide and diethylzinc. The air-tolerant zinc reagent is applicable to develop easy synthetic operations for various heptafluoroisopropyl aryl products. The copper(I)mediated heptafluoroisopropylation should thus be complementary to the radical processes. Material developments are in progress for demand installation of heptafluorooisopropyl and other fluoro-functional units.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b04147.

Experimental procedures, compound characterization data and DFT calculation data(PDF) NMR data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: mikami.k.ab@m.titech.ac.jp. ORCID [®]

Koichi Mikami: 0000-0002-7093-2642

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Nippon Soda Co., Ltd. for generous gift of heptafluoroisopropyl iodide. This research was supported by the Japan Science and Technology Agency (JST) (ACT-C: Creation of Advance Catalytic Transformation for the Sustainable Manufacturing at Low Energy, Low Environmental Load).

REFERENCES

(1) (a) Kirsch, P. Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications, 2nd completely revised and enlarged ed.; Wiley-VCH, Weinheim, 2013. (b) Ojima, I. Fluorine in Medicinal Chemistry and Chemical Biology; Wiley-Blackwell, Chichester, 2009. (c) Petrov, V. A. Fluorinated Heterocyclic Compounds: Synthesis Chemistry and Applications; Wiley, Hoboken, 2009. (d) Uneyama, K. Organofluorine Chemistry; Blackwell, Oxford, 2006.

(2) (a) Tohnishi, M.; Nakao, H.; Furuya, T.; Seo, A.; Kodama, H.; Tsubata, K.; Fujioka, H.; Hirooka, T.; Nishimatsu, T. J. Pestic. Sci. **2005**, 30, 354. (b) Kimura, M.; Morimoto, M.; Uehara, M.; Watanabe, M.; Yoshida, M. Jpn. Kokai Tokkyo Koho JP 2001342186, 2001;. (c) Guin, J.; Rabalakos, C.; List, B. Angew. Chem., Int. Ed. **2012**, 51, 8859. (d) Okumura, K. Jpn. Kokai Tokkyo Koho JP 2007308483 A, 2007.

(3) (a) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, R. F. Beilstein J. Org. Chem. 2013, 9, 2476. (b) Liang, T. C. N.; Neumann, C. N.; Ritter, T. Angew. Chem., Int. Ed. 2013, 52, 8214.
(c) Tomashenko, O. A.; Grushin, V. V. Chem. Rev. 2011, 111, 4475.
(d) Burton, D. J.; Yang, Z.-Y. Tetrahedron 1992, 48, 189.

(4) (a) McLoughlin, V. C. R.; Thrower, J. Tetrahedron 1969, 25, 5921. (b) Ishikawa, N.; Ochiai, M. Nippon Kagaku Kaishi 1973, 12, 2351.

Organic Letters

(5) Onishi, M.; Yoshiura, A.; Kohno, E.; Tsubata, K. Jpn. Kokai Tokkyo Koho JP 2001122836 A, 2001.

(6) Li, Y.; Wang, X.; Guo, Y.; Zhu, Z.; Wu, Y.; Gong, Y. Chem. Commun. 2016, 52, 796.

(7) Nair, H. K.; Burton, D. J. J. Fluorine Chem. 1992, 56, 341.

(8) (a) Aikawa, K.; Nakamura, Y.; Yokota, Y.; Toya, W.; Mikami, K. *Chem. - Eur. J.* **2015**, *21*, 96. (b) Nakamura, Y.; Fujiu, M.; Murase, T.; Itoh, Y.; Serizawa, H.; Aikawa, K.; Mikami, K. *Beilstein J. Org. Chem.* **2013**, *9*, 2404. (c) Also see the 1,10-phenanthroline ligand system: Wang, X.; Hirano, K.; Kurauchi, D.; Kato, H.; Toriumi, N.; Takita, R.; Uchiyama, M. *Chem. - Eur. J.* **2015**, *21*, 10993.

(9) Naumann, D.; Schorn, C.; Tyrra, W. Z. Z. Anorg. Allg. Chem. 1999, 625, 827.

(10) (a) Konovalov, A. I.; Lishchynskyi, A.; Grushin, V. V. J. Am. Chem. Soc. 2014, 136, 13410. (b) Komoda, K.; Kubota, Y.; Sugiishi, R.; Serizawa, H.; Aikawa, K.; Mikami, K.; Amii, H. Ann. Meeting of Chem. Soc.. Jpn. No. 96, Kyoto, Japan, March 2016.

(11) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. J. Am. Chem. Soc. 2005, 127, 4120.

(12) Transmetalation may be exemplified via: (a) Six-membered Zimmerman-Traxler-like transition state: Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Burlington, 2005. (b) Activation of zinc reagents with carboxylates: Aikawa, K.; Toya, W.; Nakamura, Y.; Mikami, K. *Org. Lett.* **2015**, *17*, 4996.



(13) DMF-coordinated sterically congested copper species: Lishchynskyi, A.; Novikov, M. A.; Martin, E.; Escudero-Adan, E. C.; Novak, P.; Grushin, V. V. J. Org. Chem. **2013**, 78, 11126.

(14) Reviews of organic semiconductors: (a) Murphy, A. R.; Fréchet, J. M. *Chem. Rev.* **2007**, *107*, 1066. (b) Mishra, A.; Ma, C.-Q.; Bauerle, P. *Chem. Rev.* **2009**, *109*, 1141.

(15) Perfluorophenyl or *n*-perfluoroalkyl substituted quaterthiophenes: (a) Facchetti, A.; Yoon, M.-Y.; Stern, C. L.; Katz, H. E.; Marks, T. J. Angew. Chem., Int. Ed. **2003**, 42, 3900. (b) Yoon, M.-Y.; Facchetti, A.; Stern, C. E.; Marks, T. J. J. Am. Chem. Soc. **2006**, 128, 5792. (c) Facchetti, A.; Mushrush, M.; Katz, H. E.; Marks, T. Adv. Mater. **2003**, 15, 33.

Letter