

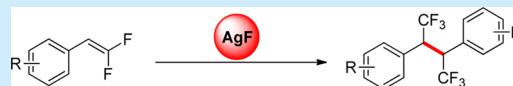
# AgF-Mediated Fluorinative Homocoupling of *gem*-Difluoroalkenes

Bing Gao, Yanchuan Zhao, Chuanfa Ni, and Jinbo Hu\*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China

**S** Supporting Information

**ABSTRACT:** A novel silver(I)-fluoride-mediated homocoupling reaction of  $\beta,\beta$ -difluorostyrene derivatives is described. The transformation is initiated via nucleophilic addition of silver(I) fluoride to  $\beta,\beta$ -difluorostyrenes, which is followed by dimerization of the corresponding benzylsilver intermediates. The reaction shows good substrate scope, functional group tolerance, and represents the first report on the reactivity of ( $\alpha$ -trifluoromethyl)benzylsilver species.

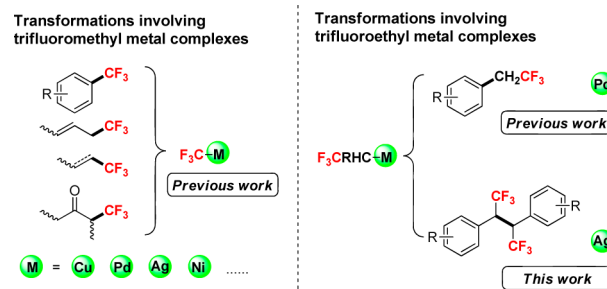


Selectively fluorinated or fluoroalkylated organic molecules often possess unique physical, chemical, and biological properties, making them of special importance in agrochemicals, pharmaceuticals, as well as functional materials.<sup>1</sup> Transition-metal-mediated fluorination and fluoroalkylation, which provide fast and mild access to fluorine-containing organic molecules, have become the subject of tremendous research activity over the past decade.<sup>2</sup> The preparation and characterization of the corresponding  $R_f$ -M organometallic complexes were carried out by several groups, the majority of which mainly focused on “ $CF_3$ -Pd(II/III/IV)”,<sup>3</sup> “ $CF_3$ -Cu(I/III)”,<sup>4</sup> “ $CF_3$ -Ag(I/III)”,<sup>5</sup> and other “ $CF_3$ -M” (M = Ni, Pt, Ru, Rh) species.<sup>6</sup> These trifluoromethyl metallic complexes are generally stable at low oxidation states and isolable with proper ligands.

Despite these important examples of trifluoromethyl metallic compounds, there are very few studies on partially fluorinated alkyl organometallic compounds.<sup>7</sup> The introduction of fluorine atom(s) might dramatically change the chemical properties of corresponding organometallic species. For instance,  $CH_3$ -PdAr(DPPBz) and  $PhCH_2$ -PdAr(DPPBz) species [DPPBz: 1,2-bis(diphenylphosphino)benzene] undergo complete reductive elimination within 4 h at 40 °C, while the reductive elimination of  $CF_3CH_2$ -PdAr(DPPBz) has to be conducted at 110 °C for 36 h.<sup>8a</sup> Recently, our group reported a palladium-catalyzed 2,2,2-trifluoroethylation of organoboronic derivatives that was accomplished within 12 h at 80 °C; a bulky phosphine ligand (Xantphos) was employed to accelerate the crucial reductive elimination step as well as the whole catalytic cycle consequently.<sup>8b</sup> Encouraged by this success, we sought to explore other related fluoroalkyl metallic complexes with different central metal atoms. Herein, we disclose our results on the study of an  $\alpha$ -trifluoromethylated benzylsilver species [ $CF_3CH(Ar)-Ag^I$ ] (Scheme 1).

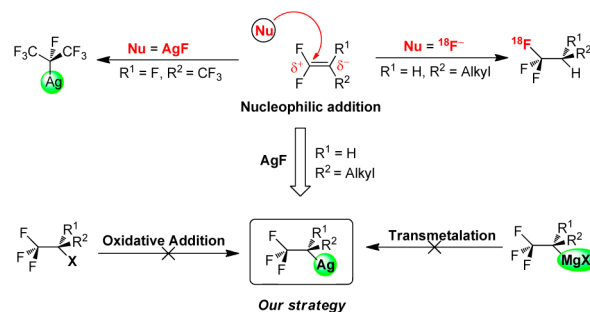
Currently, the development of practical approaches toward  $\alpha$ -trifluoromethylated alkylsilver compounds still remains a challenging task. Unlike  $R$ -Pd<sup>II</sup> (R = alkyl, alkenyl, and aryl) species, the  $R$ -Ag<sup>I</sup> compounds are inaccessible via direct oxidative addition of alkyl halide to metal ( $Ag^0$ ) on the benchtop,<sup>9,10</sup> and a facile  $\beta$ -fluoride elimination of  $CF_3CHR-$

## Scheme 1. Variations from Trifluoromethyl Metallic Complexes to $\alpha$ -Trifluoromethylated Alkyl Metallic Complexes



$Mg^{II}X_n$  species makes the transmetalation from the corresponding Grignard reagents to silver metal center difficult (Scheme 2).<sup>1a,b</sup> Traditionally, the nucleophilic addition of AgF to perfluoroalkenes provides an alternative approach to perfluoroalkylsilver compounds ( $R_f-Ag^I$ ), taking advantage of the high electrophilicity of perfluoroalkenes.<sup>11a</sup> *gem*-Difluoroalkenes, on the other hand, although less electron-deficient, have also been employed to synthesize <sup>18</sup>F-labeled  $CF_3$ -containing molecules

## Scheme 2. Proposed Strategy for the Preparation of $\alpha$ -Trifluoromethylated Alkylsilver Compounds



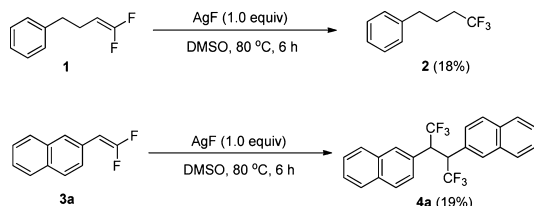
Received: October 26, 2013

Published: December 2, 2013

for positron emission tomography (PET) with [ $^{18}\text{F}$ ]KF under relatively harsh reaction conditions.<sup>11b</sup> Therefore, we envisioned that it could be possible to use *gem*-difluoroalkenes as precursors for the preparation of  $\text{CF}_3\text{CHR}-\text{Ag}^{\text{I}}$  compounds (Scheme 2).

Alkyl-substituted *gem*-difluoroalkene **1** was first examined with 1.0 equiv of AgF in DMSO at 80 °C for 6 h, as shown in Scheme 3. However, only hydrofluorination product **2**, rather

### Scheme 3. Impact of Substituents of *gem*-Difluoroalkenes



than the corresponding metallic compound, was obtained in 18% yield with 73% of **1** being recovered. Poor thermal stability of alkylsilver compound was considered to be responsible for the failure of **1**, and the introduction of an aromatic functionality seemed necessary for two reasons: (1)  $\beta,\beta$ -difluorostyrene derivatives are more electrophilic and therefore should facilitate the nucleophilic addition at relatively low temperatures; (2) the newly formed C–Ag<sup>I</sup> bond can be stabilized by the aromatic ring. Accordingly, 2-(2,2-difluorovinyl)naphthalene (**3a**) was next employed as a model precursor that was treated under the same reaction conditions. Nevertheless, no benzylsilver compound, but homocoupling product **4a** (19%), was observed along with hydrofluorination side product (Scheme 3).

It was reported that alkylsilver compounds could readily undergo homocoupling to give alkyl dimers, and general methodologies of silver-catalyzed oxidative homocoupling of Grignard reagents have been developed.<sup>9</sup> Although the homocoupling products of perfluoroalkylsilver compounds were observed during their decomposition process,<sup>11a</sup> its low efficiency could be a hurdle for practical applications. On the other hand, the synthetic transformations based on  $\alpha$ -trifluoromethylated benzylsilver species still remain unrevealed, which stimulated us to explore such a transformation.

The optimization of the reaction conditions was commenced using **3a** as the model substrate, as shown in Table 1. The transformation proceeded very slowly below 80 °C but turned messy at 130 °C, giving 80 °C as a preferred option. The yield of **4a** was increased to 39% by increasing the amount of AgF to 4.0 equiv, and further screening of the solvents revealed that the transformation could also proceed in  $\text{CH}_3\text{CN}$ , HMPA, and pyridine. It should be noted that although  $\text{CH}_3\text{CN}$  was extensively used in the preparation of perfluoroalkylsilver metallic compounds,<sup>11a</sup> pyridine proved to be even better in this case, which might serve as both solvent and ligand for the organosilver intermediate (entry 7).<sup>12</sup> Apolar solvents like dioxane and toluene were inefficient owing to the insolubility of AgF in these solvents (entries 8 and 9). On the other hand, decomposition of AgF was observed in pyridine, and the addition of THF as cosolvent (1:1 in volume) was expected to slow such a process (entry 8). Additives like molecular sieves gave a slightly higher yield (63%, entry 11). Finally, the reaction was performed on both 0.5 mmol scale (0.1 M in concentration) and 1.0 mmol scale (0.2 M in concentration)

Table 1. Optimization of Reaction Conditions

entry <sup>a</sup>	AgF (equiv)	solvent (0.1 M)	temp (°C)	time (h)	yield <sup>b</sup> (%)
1	1.0	DMSO	80	6	19
2	4.0	DMSO	80	6	39
3	4.0	DMSO	130	6	27
4	4.0	$\text{CH}_3\text{CN}$	80	6	15
5	4.0	HMPA	80	6	37
6	4.0	pyridine	80	6	49
7 <sup>c</sup>	4.0	toluene	80	6	0
8 <sup>c</sup>	4.0	dioxane	80	6	0
9	4.0	pyridine–THF (1:1)	80	6	58
10 <sup>d</sup>	4.0	pyridine–THF (1:1)	80	6	63
11 <sup>e</sup>	3.0	pyridine–THF (1:1)	80	6	62
12 <sup>f</sup>	3.0	pyridine–THF (1:1)	80	6	61
13 <sup>g</sup>	3.0	pyridine–THF (1:1)	80	6	25

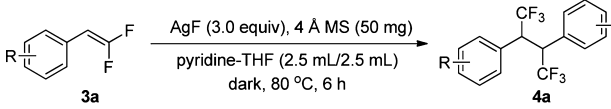
<sup>a</sup>All reactions were run on 0.2 mmol scale of substrate **3a**. <sup>b</sup>NMR yield determined by  $^{19}\text{F}$  spectroscopy with 1,3,5-trifluorobenzene as an internal standard. <sup>c</sup>Starting material **3a** was quantitatively recovered. <sup>d</sup>Molecular sieves was added (10 mg/mL). <sup>e</sup>The reaction was run on 0.5 mmol scale. <sup>f</sup>The reaction was run on 1.0 mmol scale. <sup>g</sup>The reaction was run with a concentration of 0.0125 M.

with only 3.0 equiv of AgF being used, both providing reproducible results. Attempts to lower the concentration to 0.0125 M decreased the yield to 25%. Moreover, it should be mentioned that all reactions were conducted under the protection from light to suppress the decomposition of AgF.

With the optimal reaction conditions in hand, the substrate scope of the homocoupling reaction was explored. As summarized in Table 2, a variety of  $\beta,\beta$ -difluorostyrene derivatives bearing different substituents were examined with satisfactory results. For precursors (**3b–3d**) with electron-donating substituents, such as  $-\text{NPh}_2$ ,  $-\text{OMe}$ , and  $-\text{SMe}$  *para* to the  $\beta,\beta$ -difluorovinyl functionality, the transformation proceeded smoothly. Linear alkyl-substituted compound **4e** was obtained in good yield (65%, entry 5), indicating the tolerance of ester. Halogen substituents such as iodo and bromo were also tolerated under the current conditions (**4f**, **4j**), which allows further elaborations of these interesting products (e.g., palladium-catalyzed polymerization for the preparation of functional materials).<sup>13</sup> Switching the position of substituents would affect the reaction output as **4k** was obtained in 40% yield while **4g** was isolated in 65%. It could be ascribed to the steric repulsion between bromine and the  $\beta,\beta$ -difluorovinyl group. Diastereoisomers of the majority of products, albeit in poor diastereoselectivity, could be separated via column chromatography. One diastereoisomer of **4m**, characterized by X-ray crystallography, was confirmed with a *syn* configuration, and the *syn/anti* ratios of other products were determined accordingly.

In general, the introduction of electron-deficient substituents should facilitate the electron polarization of the  $\pi$ -orbital of *gem*-difluoroalkenes and thus favor the nucleophilic addition of AgF.<sup>1b</sup> However, when **3m** was treated under our standard

Table 2. Survey of Substrate Scope



entry <sup>a</sup>	alkene 3	product 4	yield (syn:anti) <sup>b,c</sup>
1			48% (52:48)
2			76% (48:52)
3			67% (51:49)
4			75% (51:49)
5			65% (49:51)
6			67% (53:47)
7			65% (53:47)
8			67% (51:49)
9			78% (48:52)
10			47% (51:49)
11			40% (56:44)

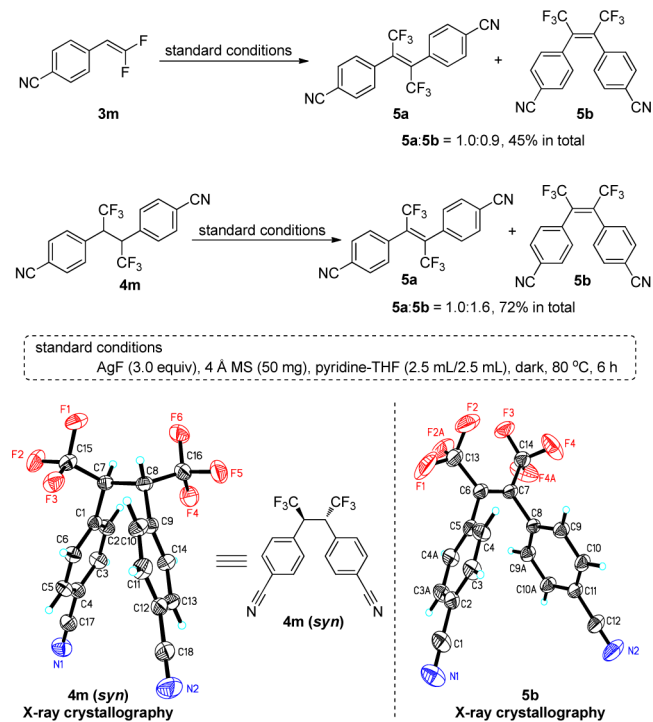
<sup>a</sup>In all cases, the reactions were run on 1.0 mmol scale using 3.0 equiv of AgF and 50 mg of molecular sieves in cosolvent of pyridine and THF (2.5 mL:2.5 mL) without light. <sup>b</sup>Isolated yield. <sup>c</sup>Diastereoselectivity determined by <sup>19</sup>F spectroscopy is given in parentheses.

reaction conditions, compounds **5a** and **5b** were formed instead of the expected homocoupling product **4m** (Scheme 4). **5b** was further confirmed by X-ray crystallography with a *Z* configuration. We assumed that **5a** and **5b** might derive from the oxidation of **4m** by excess AgF in the reaction system since **4m**, **5a**, and **5b** were all observed when the amount of AgF was minimized to 1.5 equiv.

To gain further mechanistic insights, **4m** was separately prepared<sup>14</sup> and treated with standard homocoupling conditions. A full conversion of **4m** into **5a** and **5b** with a ratio of 1.0:1.6 was observed. However, **4c** could not be oxidized under identical conditions. Although the detailed oxidation mechanism was still unclear, our experiments indicate that AgF acts as both an oxidant and a base throughout the transformation.<sup>15</sup> The different performances between **4c** and **4m** was ascribed to the high acidity of the benzylic C–H bond of **4m** caused by the –CN group.

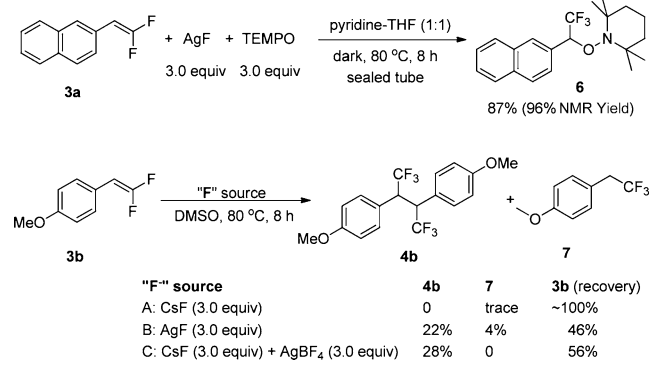
According to previous reports,<sup>9</sup> perfluoroalkylsilver compounds were relatively stable at room temperature in polar solvents and were therefore capable of participating in synthetic transformations. In sharp contrast, although the addition of salts (LiBr, MgBr<sub>2</sub>) could increase their stability, neat alkylsilver species were extremely unstable and would undergo quick decomposition even below 0 °C. This might explain why our endeavor to directly observe a benzy silver intermediate proved unsuccessful.

Two plausible mechanistic pathways have been proposed for the homocoupling of alkylsilver compounds: (1) homolytic

Scheme 4. Unexpected Result of Alkene **3m**

cleavage of the C–Ag bond followed by random radical reactions, and (2) concerted process involving both C–Ag bond breaking and C–C bond formation.<sup>9</sup> In our reaction, when 3.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-oxyl-piperidine) was added under standard reaction conditions with **3a** as substrate, homocoupling was completely inhibited and **6** was isolated in 87% yield (Scheme 5), which might

Scheme 5. Mechanistic Study of the Homocoupling Reaction



support a free radical pathway. However, a concerted pathway could not be ruled out since, in pyridine, an aggregation state of perfluoroalkylsilver species has also been proposed based on NMR study.<sup>12</sup>

Moreover, we were wondering whether the incorporation of F<sup>–</sup> source and other silver salts could replace AgF to promote the same transformation.<sup>16</sup> When **3b** was treated with conditions A (CsF), B (AgF), and C (CsF and AgBF<sub>4</sub>), the hydrofluorination product **7**, homocoupling product **4b**, and unreacted **3b** were observed, the yields of which were determined by <sup>19</sup>F NMR (as illustrated in Scheme 5). According to these experimental results, *gem*-difluoroalkene

**3b** should be inert to the nucleophilic addition of  $F^-$  anion at 80 °C, and a synergetic addition of AgF to double bond proved crucial for the generation of benzylsilver intermediate. The combination of CsF and  $AgBF_4$  provided an alternative approach to AgF.

In conclusion, we have developed an efficient fluorinative homocoupling reaction of *gem*-difluoroalkenes. Both the generality of substrate scope and functional group tolerance are demonstrated. The dimers possess unique chemical structure, which might find applications in life science- and materials-science-related fields.<sup>17</sup> Although the key intermediate is unstable at the temperature necessary for its formation, to our knowledge, it is the first example in which the chemistry of  $\alpha$ -trifluoromethylated benzylsilver species is demonstrated. Further development of new methodologies based on this unique species is underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: jinbohu@sioc.ac.cn.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the National Basic Research Program of China (2012CB821600, 2012CB215500), the National Natural Science Foundation of China (21372246, 20825209), and the Chinese Academy of Sciences.

## ■ REFERENCES

(1) (a) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004. (b) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, UK, 2006. (c) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, UK, 2009. (d) Petrov, V. A. *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry and Applications*; Wiley: Hoboken, NJ, 2009.

(2) For recent reviews and selective papers, see: (a) Ye, Y.-D.; Sanford, M. S. *Synlett* **2012**, 2005. (b) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (c) Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8610. (d) Deb, A.; Manna, S.; Modak, A.; Patra, T.; Maity, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 9747. (e) Danoun, G.; Bayarmagnai, B.; Gruenberg, M. F.; Goossen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7972. (f) Zeng, Y.-W.; Zhang, L.-J.; Zhao, Y.-C.; Ni, C.-F.; Zhao, J.-W.; Hu, J.-B. *J. Am. Chem. Soc.* **2013**, *135*, 2955. (g) Dai, J.-J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.-J.; Lu, X.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8436. (h) Wang, X.; Xu, Y.; Mo, F.-Y.; Ji, G.-J.; Qiu, D.; Feng, J.-J.; Ye, Y.-X.; Zhang, S.-N.; Zhang, Y.; Wang, J.-B. *J. Am. Chem. Soc.* **2013**, *135*, 10330. (i) Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948. (j) Hu, M.-Y.; Ni, C.-F.; Hu, J.-B. *J. Am. Chem. Soc.* **2012**, *134*, 15257. (k) He, Z.-B.; Hu, M.-Y.; Luo, T.; Li, L.-C.; Hu, J.-B. *Angew. Chem., Int. Ed.* **2012**, *51*, 11545.

(3) For Pd, see selective examples: (a) Powers, D. C.; Lee, E.; Ariafard, A.; Sanford, M. S.; Yates, B. F.; Cauty, A. J.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 12002. (b) Bakhmutov, V. I.; Bozoglian, F.; Gomez, K.; Gonzalez, G.; Grushin, V. V.; MacGregor, S. A.; Martin, E.; Miloserdov, F. M.; Novikov, M. A.; Panetier, J. A.; Romashov, L. V.

*Organometallics* **2012**, *31*, 1315. (c) Racowski, J. M.; Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18022. (d) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.

(4) For Cu, see: (a) Zhao, T. S. N.; Szabo, K. J. *Org. Lett.* **2012**, *14*, 3966. (b) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901. (c) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3793. (d) Yang, Z.-Y.; Burton, D. J. *J. Fluorine Chem.* **2000**, *102*, 89.

(5) For Ag, see: (a) Kremlev, M. M.; Mushta, A. I.; Tyrra, W.; Yagupolskii, Y. L.; Naumann, D.; Moeller, A. *J. Fluorine Chem.* **2012**, *133*, 67. (b) Weng, Z.; Lee, R.; Jia, W.; Yuan, Y.; Wang, W.; Feng, X.; Huang, K.-W. *Organometallics* **2011**, *30*, 3229. (c) Naumann, D.; Wessel, W.; Hahn, J.; Tyrra, W. *J. Organomet. Chem.* **1997**, *547*, 79.

(6) For other  $R_f$ -M compounds, see: (a) Kieltsch, I.; Dubinina, G. G.; Hamacher, C.; Kaiser, A.; Torres-Nieto, J.; Hutchison, J. M.; Klein, A.; Budnikova, Y.; Vivic, D. A. *Organometallics* **2010**, *29*, 1451. (b) Burton, D. J.; Lu, L. *Top. Curr. Chem.* **1997**, *193*, 45. (c) Rosevear, D. T.; Stone, F. G. A. *J. Chem. Soc., A* **1968**, 164. (d) Krause, L. J.; Morrison, J. A. *J. Chem. Soc., Chem. Commun.* **1981**, 1282. (e) Appleton, T. G.; Chisholm, M. H.; Clark, H. C.; Manzer, L. E. *Inorg. Chem.* **1972**, *11*, 1786. (f) Taw, F. L.; Clark, A. E.; Mueller, A. H.; Janicke, M. T.; Cantat, T.; Scott, B. L.; Hay, P. J.; Hughes, R. P.; Kiplinger, J. L. *Organometallics* **2012**, *31*, 1484. (g) Goodman, J.; Grushin, V. V.; Larichev, R. B.; Macgregor, S. A.; Marshall, W. J.; Roe, D. C. *J. Am. Chem. Soc.* **2009**, *131*, 4236. (h) Zhang, C.-P.; Wang, H.; Klein, A.; Biewer, C.; Stirnat, K.; Yamaguchi, Y.; Xu, L.; Gomez-Benitez, V.; Vivic, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 8141. (i) Dubinina, G. G.; Brennessel, W. W.; Miller, J. L.; Vivic, D. A. *Organometallics* **2008**, *27*, 3933.

(7) (a) Burton, D. J.; Hartgraves, G. A. *J. Fluorine Chem.* **2007**, *128*, 1198. (b) Eujen, R.; Hoge, B.; Brauer, D. J. *J. Organomet. Chem.* **1996**, *519*, 7. (c) Hughes, R. P.; Meyer, M. A.; Tawa, M. D.; Ward, A. J.; Williamson, A.; Rheingold, A. L.; Zakharov, L. N. *Inorg. Chem.* **2004**, *43*, 747.

(8) (a) Culkun, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398. (b) Zhao, Y.-C.; Hu, J.-B. *Angew. Chem., Int. Ed.* **2012**, *51*, 1033.

(9) Michael, H. *Silver in Organic Chemistry*; Wiley: Hoboken, NJ, 2010 and references therein.

(10) Klabunde, K. J. *J. Fluorine Chem.* **1976**, *7*, 95.

(11) (a) Miller, W. T.; Burnard, R. J. *J. Am. Chem. Soc.* **1968**, *90*, 7367. (b) Riss, P. J.; Aigbirhio, F. I. *Chem. Commun.* **2011**, *47*, 11873.

(12) Polishchuk, V. R.; Fedorov, L. A.; Okulevich, P. O.; German, L. S.; Knunyants, I. L. *Tetrahedron Lett.* **1970**, *11*, 3933.

(13) (a) Muroga, T.; Sakaguchi, T.; Hashimoto, T. *Polymer* **2012**, *53*, 4380. (b) Chen, L.; Zhang, B.; Cheng, Y.; Xie, Z.; Wang, L.; Jing, X.; Wang, F. *Adv. Funct. Mater.* **2010**, *20*, 3143.

(14) A systematic study of this reaction will be published in another manuscript.

(15) (a) Pandey, G.; Lakshmaiah, G. *Tetrahedron Lett.* **1993**, *34*, 4861. (b) Tyrra, W. *Heteroat. Chem.* **2002**, *13*, 561.

(16) Dyatkin, B. L.; Martynov, B. I.; Martynova, L. G.; Kizim, N. G.; Sterlin, S. R.; Stumbrevichute, Z. A.; Fedorov, L. A. *J. Organomet. Chem.* **1973**, *57*, 423.

(17) Prinsell, M. R.; Everson, D. A.; Weix, D. J. *Chem. Commun.* **2010**, *46*, 5743 and references therein.