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## Silver-catalyzed decarboxylative homocoupling reaction for the construction of tetrafluoroethylene-bridging aromatic compounds

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#### ABSTRACT

The Ag(l)-catalyzed decarboxylative homocoupling from the difluoroacetate has been developed to the synthesis of symmetric  $CF_2-CF_2$ containing dimers. This radical dimerization overpasses the prefunctionalization of the substrate and provides a direct and efficient method for construction of tetrafluoroethylene bridge-linked homodimers.

#### **GRAPHICAL ABSTRACT**



### ARTICLE HISTORY

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#### **KEYWORDS**

Decarboxylative homocoupling; difluoroacetate; radical dimerization; tetrafluoroethylene bridge

#### Introduction

Organofluorine compounds have attracted much attention because of their remarkable applications in medicinal, agrochemical and new-material chemistries.<sup>[1]</sup> Among various fluorinated moieties, *gem*-difluoromethylene unit (CF<sub>2</sub>), which has a steric profile similar to the methylene unit, is of great interest due to its unique stability and isosteric property as an ethereal oxygen atom or a carbonyl group.<sup>[2]</sup> Moreover, the dimeric moiety of tetrafluoroethylene bridge ( $-CF_2CF_2-$ ) has been regarded as a key structure in insecticides,<sup>[3]</sup> chemical vapor deposition (CVD) precursors of thin-film polymers,<sup>[4]</sup> as well as in the liquid-crystalline compounds because of its potential to influence the physical properties of these materials, such as clearing point, mesophase sequence, and rotational viscosity.<sup>[5]</sup> Thus, the development of an efficient and straightforward method to the formation of tetrafluoroethylene bridge has been in high demand.

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This Work: Decarboxylative Homo-coupling



Scheme 1. Strategies for transition-metal-catalyzed decarboxylative homo-coupling to form symmetrical difluoromethylated derivatives.

In general, the construction of a tetrafluoroethylene-bridging structure  $ArCF_2CF_2Ar'$  is achieved by fluorination of a carbon-carbon triple bond with  $F_2$  gas or via the deoxo-fluorination of 1,2-diketones with a fluorination reagent such as DAST (Scheme 1a).<sup>[6,7]</sup> Recently, Hu disclosed a fluoroalkylation process through a copper(0) mediated reductive cross-coupling between aryl idoides with structurally diverse 1-bromo-1,1,2,2-teta-fluoroethyl compounds  $RCF_2CF_2Br$ .<sup>[8]</sup> Ogoshi described an efficient construction of a tetrafluoroethylene-bridging structure through a copper-mediated transformation of tetrafluoroethylene (TFE) into aromatic compounds by the carbocupration of TFE with arylboronates in the presence of [CuO<sup>*t*</sup>-Bu] (Scheme 1b).<sup>[9]</sup> However, these methods have drawbacks including low functional group tolerance, the use of toxic, costly fluorination reagents, or the requirement of prefunctionalization of the substrates, which limit the widespread application of the protocols in synthesis and industrial production.

Since the pioneering work of Myers and Goossen, catalyzed decarboxylative coupling reactions have emerged as a powerful tool for the formation of C–C bonds in the past decade.<sup>[10]</sup> Decarboxylative homocoupling has been applied as an efficient protocol to construct the symmetrical molecules, which constitute an important motif in chiral ligands, monomers of conductive polymers, liquid crystal precursors, natural products, pharmaceuticals, and pesticides.<sup>[11]</sup> Transition metal-mediated decarboxylative homocouplings have been highly successful in the formation of symmetrical molecules, which are mainly related to the tethering of sp<sup>2</sup> or sp hybridized carbon centers.<sup>[12]</sup>

Due to its notable advantages, transition-metal-catalyzed oxidative decarboxylative radical *gem*-difluoromethylenation has recently emerged as an attractive and alternative approach for the direct construction of the  $C-CF_2$  bond, because of the ready availability and low cost of difluorocarboxylic acids as well as the extrusion of innocuous  $CO_2$  as a by-product in these reactions.<sup>[13]</sup> Very recently, our group developed a mild and

efficient method for the Ag(I) or Pd(II)-catalyzed oxidative decarboxylative gemdifluoromethylenation, affording  $C_{sp2}$ -CF<sub>2</sub> bond and  $C_{sp3}$ -CF<sub>2</sub> bonds in the construction of meta-C-H/difluoromethylenated aromatic derivatives, as well as phenanthridine and 2-oxindoles.<sup>[14]</sup> Hashmi and Wu described an efficient and direct decarboxylative cross-coupling of  $\alpha,\alpha$ -difluoroarylacetic acids and ethynylbenziodoxolone reagents to give difluoromethylated alkynes, providing the  $C_{sp}$ -CF<sub>2</sub> bond.<sup>[15]</sup> Qing developed a visible-light-induced hydroaryl difluoromethylenation of alkenes with  $\alpha,\alpha$ -difluoroarylacetic acids through decarboxylation and subsequent radical hydroaryldifluoromethylenation to form  $C_{sp3}$ -CF<sub>2</sub> bond.<sup>[16]</sup>

During our study on the reactivity of difluoromethyl radical generated from the readily available difluoroacetic acids through the oxidative decarboxylative process, we envisaged that the difluoromethyl radical intermediates could be applied to construct the  $C_{(sp3)}F_2-C_{(sp3)}F_2$  bond through the valuable and effective tool of homocoupling reaction by radical dimerization (Scheme 1c). To the best of our knowledge, the construction of  $C_{sp3}F_2-C_{sp3}F_2$  bonds through decarboxylative homocoupling strategy of difluoroacetate has not been reported. Such an environmental-friendly methodology would provide easy access to a variety of symmetric tetrafluoroethylene bridge-linked homodimers starting from inexpensive and stable aryl difluorocarboxylic acids with only innocuous carbon dioxide as a by-product.

#### **Results and discussion**

Our investigation commenced by taking the decarboxylative homocoupling of difluoroacetate 1a as the model reaction in the presence of catalyst and oxidant for the optimization studies. As we expected, decarboxylative homocoupling of la in dry DMSO under a nitrogen atmosphere at 80 °C for 2 h afforded the desired homodimer in modest yield of 31% (Table 1, entry 1). Among the silver salts and oxidants examined, the combination of  $AgNO_3$  and  $(NH_4)_2S_2O_8$  turned out to be the most effective, which afforded up to 48% yield (entries 2-8). Using Ag<sub>2</sub>CO<sub>4</sub>, AgBF<sub>4</sub>, AgOAc or AgSO<sub>3</sub>CF<sub>3</sub> as the catalysts and K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> or PhI(OAC)<sub>2</sub> as oxidant instead of AgNO<sub>3</sub> and (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> led to the decreased yields. Replacement of silver salts with copper (I) or (II) salts completely suppressed reaction (entry 9). Sequential screening of solvents revealed that DMSO was crucial for this reaction, while other solvents, such as DMF, NMP, 1,4dioxane or toluene, were of no use for this transformation. The optimal temperature for the current reaction was found to be 120 °C, giving good conversion to the expected product in 68% yield (entries 10-12). Lowering the reaction temperature reduced conversion and gave low yield (entry 13). The influence of bases, such as KHCO<sub>3</sub>, KOH, K<sub>2</sub>CO<sub>3</sub>, and Cs<sub>2</sub>CO<sub>3</sub> were further investigated. Other bases except for KHCO<sub>3</sub> or the absence of base reduced the reaction efficiency (entries 14-17). Longer or shorter reaction times also gave negative results (entries 18-21). Increasing AgNO<sub>3</sub> loading to two equivalents or lowering AgNO<sub>3</sub> loading to 0.3 equivalents was also found to be counterproductive. Control experiments revealed that the reaction still gave 34% yield even without Ag(I) catalyst (entry 22). However, no reaction occurred in the absence of the oxidant (entry 23).

	MeO	<mark>₹,                                    </mark>	Ag(I) Oxidant Base DMSO 120 °C	MeO F	C F OMe	
	1a			2	а	
Entry	Catalyst	Oxidant	Base	Temp. (°C)	Time (h)	Yield (%) <sup>b</sup>
1	AgNO <sub>3</sub>	PhI(OAC) <sub>2</sub>	KHCO <sub>3</sub>	80	2	31
2	AgNO <sub>3</sub>	$Na_2S_2O_8$	KHCO <sub>3</sub>	80	2	42
3	AgNO <sub>3</sub>	$K_2S_2O_8$	KHCO <sub>3</sub>	80	2	34
4	Ag <sub>2</sub> CO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	80	2	30
5	AgBF <sub>4</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	80	2	43
6	AgOAc	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	80	2	34
7	AgSO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	80	2	36
8	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	80	2	48
9	Cu(I) or Cu(II)	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	80	2	0
10	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	100	2	49
11	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	120	2	68
12	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	140	2	46
13	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	60	2	12
14	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	K <sub>2</sub> CO <sub>3</sub>	120	2	40
15	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	KOH	120	2	38
16	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	$Cs_2CO_3$	120	2	36
17 <sup>c</sup>	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	_	120	2	28
18	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	120	4	51
19	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	120	6	40
20	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	120	1	33
21	AgNO <sub>3</sub>	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	120	1/3	31
22 <sup>d</sup>	_	$(NH_4)_2S_2O_8$	KHCO <sub>3</sub>	120	2	34
23 <sup>e</sup>	AgNO <sub>3</sub>	_	KHCO <sub>3</sub>	120	2	0

#### Table 1. Optimization of reaction conditions.<sup>a</sup>

<sup>a</sup>Reaction conditions: difluoroacetate (0.6 mmol, 1.0 equiv.), AgNO<sub>3</sub> (0.3 mmol, 0.5 equiv.),  $(NH_4)_2S_2O_8$  (1.2 mmol, 2.0 equiv.), KHCO<sub>3</sub> (0.3 mmol, 0.5 equiv.) under N<sub>2</sub> atmosphere.

<sup>b</sup>Yields determined by <sup>19</sup>F NMR analysis with PhCF<sub>3</sub> as the internal standard;

without base;

<sup>d</sup>without catalyst;

<sup>e</sup>without oxidant.

With the optimized reaction conditions in hand (Table 1, entry 11), the decarboxylative homocoupling reactions of difluoroacetates were explored in order to study the substrate scope and limitation of this transformation. As depicted in Table 2, a variety of substrates with para-substituted groups, such as electron-donating groups (CH<sub>3</sub>, OCH<sub>3</sub>, t-Bu) 2a, 2b, 2c or electron-withdrawing halogen groups (F, Cl, Br) 2d, 2e, 2f afforded the homodimers in moderate to satisfactory yields. The halogen moiety provided the possibility for further modification. A mere 9% yield of the product dimer 2g was obtained when the extremely electron-poor cyano group CN was incorporated in the para-position of the aromatic ring. Phenyl difluoromethyl radicals released from phenyldifluoroacetate 1h combined more effectively to furnish diphenyl perfluoroethane 2h in yield of 48%. The substrates with ortho-substituted methyl or methoxyl group 2i and 2j also afforded moderate yield. It was interesting to find that though dimethylated substrate 1k gave a moderate yield of 46%, the trimethylated substrate 1l produced the desired dimer 2l in excellent yield (85%), indicative of the insensitivity of this transformation to steric hindrance. Increasing the size of the aromatic units with naphthalenyl difluoroacetate 1m gave a reasonable yield of 32%. In this work, the possibility of



 Table 2. Synthesis of symmetric tetrafluoroethylene bridge-linked homodimers.<sup>a,b</sup>

<sup>b</sup>Yields of isolated products.

the homocoupling of aryldifluoromethyl radicals and/or the reaction of aryldifluoromethyl radicals with aryldifluoroacetate derivatives could occur on their benzene rings, resulting in these regioisomers undergoing aromatization to afford bis(difluoromethyl)biaryls and/or (difluoromethylaryl)aryldifluoromethanes. However, only homocoupling products have been observed according to the careful <sup>19</sup>F NMR analysis. Unfortunately, an attempt to employ furan derivative 1n failed to return any dimer. The starting material **1n** was found to be completely consumed according to the <sup>19</sup>F NMR analysis, but only thiophene-2-carboxylic acid was obtained. The acid was probably formed by hvdrolvsis of the free difluoromethyl radical. To our surprise, while the mono-methyoxylated phenyldifluoroacetate la and lj gave the corresponding tetrafluoroethylene-linked dimers in moderate yields, the substrate of 2,4-dimethoxyphenyl-2,2-difluoroacetate 20 afforded instead the 2,4-dimethoxybenzoic acid as the main product, along with, for the first time, a minor product of defluoro homocoupling product after decarboxylative hydrolysis under the standard reaction conditions (See Supporting Information).

To figure out whether the *in situ* generated aryl difluoromethyl radical (ArCF2<sup>-</sup>) is involved in the reaction, some inhibition experiments using 2,2,6,6-tetramethyl-1-

<sup>&</sup>lt;sup>a</sup>Reaction condition: difluoroacetate (0.6 mmol, 1.0 equiv.), AgNO<sub>3</sub> (0.3 mmol, 0.5 equiv.), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (1.2 mmol, 2.0 equiv.), KHCO<sub>3</sub> (0.3 mmol, 0.5 equiv.) under N<sub>2</sub> atmosphere at 120 °C.

Entry 1

2

3

4

#### Table 3. Effect of additives on Ag(I)-catalyzed decarboxylative homocoupling reaction.<sup>a</sup>

2.0 equiv. TEMPO



0

<sup>a</sup>Reaction condition: **1a** (0.6 mmol), AgNO<sub>3</sub> (0.3 mmol), and (NH<sub>4</sub>)S<sub>2</sub>O<sub>8</sub> (1.2 mmol), KHCO<sub>3</sub> (0.3 mmol) under N<sub>2</sub> at 120  $^{\circ}$ C for 2 h.

<sup>b</sup>Yields determined by <sup>19</sup>F NMR analysis with PhCF<sub>3</sub> as the internal standard.



**Scheme 2.** Proposed mechanism for transition-metal-catalyzed decarboxylative homo-coupling reaction.

piperidinyloxy (TEMPO), 1,4-dinitro-benzene and hydroquinone as the radical scavenger were applied under the standard reaction conditions (Table 3). Significant suppression of the formation of the desired product **2a** suggested that the ArCF2<sup>·</sup> radical species acts as an important role in the current reaction. Additionally, control experiments (Table 1, entries 22, 23) provided evidence of the importance of the combination of AgNO<sub>3</sub> and (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> for the efficient generation of ArCF2<sup>·</sup> radical intermediate.

A plausible mechanism for this decarboxylative homocoupling reaction can be proposed (Scheme 2).<sup>[17]</sup> Initially, the active  $Ag^{2+}$  species is generated by oxidation of the  $Ag^+$  species with persulfate. Subsequently, the difluoroacetate undergoes single electron oxidative decarboxylation with the active  $Ag^{2+}$  species to afford the difluoromethyl radical intermediate and regenerate the  $Ag^+$  species. Finally, termination occurs by homocoupling of two difluoromethyl radicals producing the desired homodimer containing  $CF_2-CF_2$  bridge.

#### Conclusion

In summary, the decarboxylative homocoupling reaction in this work provides a valuable and effective tool for the synthesis of symmetric dimers linked by tetrafluoroethylene-bridge. This decarboxylative homocoupling from the difluoroacetate bypasses the prefunctionalization of the substrate to efficiently construct the  $CF_2-CF_2$  containing homodimers. The primary mechanistic investigation suggests that the aryl difluoromethyl radical is involved in the homocoupling process.

#### **Experimental section**

#### General

The reagents used for experiments were commercially available and were used as received unless otherwise noted. Column chromatography was performed on silica gel 300–400 mesh. <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR spectra were recorded in CDCl<sub>3</sub> on a Bruker AV-500 spectrometer (Bruker, Billerica, MA). Chemical shifts for <sup>1</sup>H NMR spectra are reported in ppm relative to residual CHCl<sub>3</sub> as internal reference ( $\delta$  7.26 ppm for <sup>1</sup>H) downfield from TMS, chemical shifts for <sup>13</sup>C NMR spectra are reported in ppm relative to residual CHCl<sub>3</sub> as internal reference ( $\delta$  7.26 ppm for <sup>1</sup>H) downfield from TMS, chemical shifts for <sup>13</sup>C NMR spectra are reported in ppm relative to internal CDCl<sub>3</sub> ( $\delta$  77.16 ppm for <sup>13</sup>C). <sup>19</sup>F NMR chemical shifts are determined relative to CFCl<sub>3</sub> at  $\delta$  0.0 as the outside standard and low field is positive. Coupling constants (*J*) are given in Hertz (Hz). The terms m, s, d, t, q refer to multiplet, singlet, doublet, triplet, quartet, respectively; br refers to a broad signal. High-resolution mass spectra (HRMS) and Mass spectra (MS) were recorded using an Electron impact (EI) or Electrospray ionization (ESI) techniques. High-resolution mass spectra (HRMS) was recorded on Agilent G6500 iFunnel Q-TOF LC/MS (Agilent, Santa Clara, CA).

# Typical procedure for the decarboxylative homocoupling of difluoroacetates to homodimers

A mixture of aryl difluoroacetates (0.6 mmol), AgNO<sub>3</sub> (0.3 mmol), and  $(NH_4)S_2O_8$  (1.2 mmol), and KHCO<sub>3</sub> (0.3 mmol) was added to in 3.0 mL of DMSO under N<sub>2</sub> atmosphere. The solution was stirred at 120 °C for 2 h. Then the reaction mixture was quenched by water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give the desired homodimers (**2a–2m**) with ethyl acetate/petroleum ether as eluent.

#### 1,2-bis(4-methylphenyl)-1,1,2,2-tetrafluoroethane (2b)

White solid, mp 137–140 °C, 53% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 7.33 (d, J = 8.3 Hz, 4H), 7.21 (d, J = 8.3 Hz, 4H), 2.39 (s, 6H). <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$ : –111.36 (s, 4F, CF<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 141.0, 128.8, 128.1–128.3 (m), 126.9 (m), 116.8 (tt,  $1J_{CF} = 250.7$  Hz,  $2J_{CF} = 36.4$  Hz), 21.4. HRMS (EI): calcd. for C<sub>16</sub>H<sub>14</sub>F<sub>4</sub> (M<sup>+</sup>) 282.1026; found 282.1029.

Full experimental details of <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra can be found through the "Supplementary Content" section of this article's webpage.

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#### **Disclosure statement**

We state that none of the authors have any conflict of interest in the context of this communication.

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10 😧 Y. WANG ET AL.

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