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Silver-Catalyzed Oxidative Decarboxylation of Difluoroacetates: Efficient Access to C-CF₂ Bond Formation

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A mild, versatile and efficient method for the silver(I)-catalyzed oxidative decarboxylative *gem*-difluoromethylenation has been developed. The radical cascade reaction comprises addition of an oxidatively generated difluoromethylene radical to the isonitrile functionality and subsequent homolytic aromatic substitution. It provides a novel and efficient access to the C-CF₂ bond formation.

Among various fluorinated moieties, gem-difluoromethylene group (CF₂) is of particular interest due to its unique stability, isosteric property as an ethereal oxygen atom or a carbonyl group, as well as its critical role in some enzyme inhibitors.¹ In progress the contrast to significant strong of difluoromethylation (CF_2H) and trifluoromethylation (CF_3) few years,² the analogous within the last aemdifluoromethylenation is much less explored.³

Though the development of decarboxylative trifluoromethylation has caught great attention during the past decades,⁴ decarboxylative *gem*-difluoromethylenation protocol for direct introduction of a difluoromethyl moiety into molecule has scarcely been explored, due to the shortage of the difluoromethyl source and the instability of the difluoromethylating reagents. Very recently, Gouverneur reported a Ag(I)-catalyzed decaboxylative fluorination through the treatment of α -fluoroarylacetic acids with electrophilic Selectfluor (Scheme 1a).⁵ Hu described a Cu(II)-catalyzed decarboxylative gem-difluoromethylenation strategy by using a Togni-type electrophilic sulfonyldifluoromethylating agent and decarboxylation of aliphatic carboxylic acids.⁶ Despite these important advances, the current strategies for the difluoromethylenation using fluorinedecarboxvlative containing electrophiles are still suffering from one or more limitations, such as using toxic and expensive electrophilic fluorinating reagents of Selectfluor or Togni-type sulfonyl

difluoroalkylate, a limited substrate scope and generality of vinylic or allylic carboxylic acids. The decarboxylative *gem*-difluoromethylenation remains to be a formidable challenge.

Compared with the decarboxylative electrophilic fluoroalkylation, the radical-mediated decarboxylative difluoroalkylation would be an attractive alternative to address these issues. Diarylisonitriles have been regarded as known radical acceptors in cascade reaction for the construction of phenanthridines,⁷ which are key skeleton compounds in the studies of several biological activities.⁸ However, most efforts on the synthesis of difluoroalkylated phenathridines have been focused on photocatalyzed reactions or a Pd-catalyzed singleelectron-transfer pathway (Scheme 1b).⁹ It is known that α, α difluoroacetates are versatile fluorine-containing compounds, which are conveniently available and can be readily converted to other useful fluorinated compounds. We envisaged that radical gem-difluoromethylenation could be accomplished through the reactivity of diarylisonitriles towards the gemdifluoromethyl radical, which might be generated from the readily available α, α -difluoroacetates through the oxidative decarboxylative process (Scheme 1c).

a) Gouverneur, Catalytic decarboxylative fluorination

b) Zhang, Pd-catalyzed radical difluoroalkylation of isocyanides



c) This study, Oxidative decarboxylative radical gem-difluoromethylenation



Scheme 1. Strategies for Silver (I)-Catalyzed Oxidative Decarboxylative gem-Difluoromethylenation of Difluoroacetates

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The catalytzed decarboxylative cross-coupling reactions have emerged as a powerful tool for the formation of C-C bond in the past several years.¹⁰ To the best of our knowledge, the Ag(I)-catalyzed oxidative decarboxylative radical gem-difluoromethylenation has never been considered for the direct construction of gem-difluormethylenated arenes from aryl α, α -difluoroacetic acid precursors. This protocol has several notable advantages: 1) difluoroacetates are inexpensive and conveniently available, easy to store and simple to handle. 2) only one equivalent byproduct of carbon dioxide is produced, which is nonflammable, nontoxic, and easily removed from the reaction medium, thus making these decarboxylative gemdifluoromethylenation amongst the greenest alternative to strategy for the preparation of difluoroalkylated arenes. 3) this radical gem-difluoromethylenation proceeds under mild reaction conditions without using excess quantities of difluoroalkylating reagents, which are typically used to compensate for the decomposition of difluoroalkylating intermediates in the conventional difluoroalkylation reactions, providing a direct and atom economic approach to gemdifluoromethylenated (hetero) arenes.

Initially, we examined the feasibility of the oxidative decarboxylation of difluoroactetae **1a** in the presence of AgNO₃ as catalyst and Na₂S₂O₈ as oxidant (Table 1, entry 1). To our delight, the cascade *gem*-difluoromethylenation-annulation reaction between difluoroacteate **1a** and isocyanide **2a** could proceed smoothly to afford the desired 6-*gem*-difluoromethylenated phenanthridine **3aa**, albeit with a low yield of 39% (Table 1, entry 1). The structure of **3aa** (CCDC 1058835) was unambiguously confirmed by single-crystal X-ray diffraction analysis.

With this delightful result, a survey of the reaction factors, such as solvents, silver sources and bases, was further conducted. It was found that switching the Ag(I) salts from Ag₂CO₃, AgOAc, AgBF₄, AgSbF₆ to Ag₂O as the catalyst could also afforded similar but a little lower catalytic activity under the same conditions (entries 2-6). Investigation of other oxidants such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, showed that $(NH_4)_2S_2O_8$ was the best choice. The transformation did not proceed in such solvents as DMPU, NMP, while DMF gave only very low yield (entries 9-11). Lowering the temperature down to 80 $^{\circ}$ C gave good conversion to the expected product in 73% yield (entries 13). The influence of the bases, such as K₂CO₃, KOH, Et₃N, KHCO₃ were further investigated (entries 15-18). Interestingly, the yield of the reaction marginally improved to 87% with the use of $KHCO_3$ (0.5 equiv) as base (entry 18). High loading of KHCO₃ would apparently affect the reaction efficiency (entries 19-20). Reducing the oxidant loading was found to be counterproductive (entries 21). It was also found that raising the amount of catalyst up to 30% could afford a slight better yield (entry 22, 23).

Encouraged by these results, a variety of difluoroarylacetates **1a-o** and biarylisonitrile **2a** were prepared and reacted under the optimized reaction conditions, in order to study the scope and limitation of this transformation. As revealed in Table 2, a broad range of difluoroacteates **1a-o** reacted smoothly with 2isocyanobiphenyl compound **2a** to generate the corresponding
 Table 1 Optimization of reaction conditions for the silver (I)-catalyzed oxidative decarboxylation of difluoroacetates



				ORTEP dr		rawing of 3aa	
Entry	Catalyst	Oxidant	Base	Solvent	Tem	Yield	
	[mol %]	[equiv]	[equiv]		p[°C	[%]	
1	AgNO ₃ (10)	$Na_{2}S_{2}O_{8}(2)$		DMSO	120	39	
2	AgCO ₃ (10)	$Na_{2}S_{2}O_{8}(2)$		DMSO	120	35	
3	Ag ₂ O (10)	$Na_{2}S_{2}O_{8}(2)$		DMSO	120	34	
4	AgBF ₄ (10)	$Na_{2}S_{2}O_{8}(2)$		DMSO	120	29	
5	AgSbF ₆ (10)	$Na_{2}S_{2}O_{8}(2)$		DMSO	120	21	
6	AgOAc (10)	$Na_{2}S_{2}O_{8}(2)$		DMSO	120	34	
7	AgNO ₃ (10)	(NH ₄) ₂ S ₂ O ₈ (2)		DMSO	120	48	
8	AgNO ₃ (10)	(NH ₄) ₂ S ₂ O ₈ (2)		DMSO	120	56	
9	AgNO ₃ (10)	$(NH_4)_2S_2O_8$ (2)		DMF	120	8	
10	AgNO ₃ (10)	(NH ₄) ₂ S ₂ O ₈ (2)		DMPU	120	0	
11	AgNO ₃ (10)	$(NH_4)_2S_2O_8$ (2)		NMP	120	0	
12	AgNO ₃ (10)	(NH ₄) ₂ S ₂ O ₈ (2)		DMSO	100	66	
13	AgNO ₃ (10)	$(NH_4)_2S_2O_8$ (2)		DMSO	80	73	
14	AgNO ₃ (10)	(NH ₄) ₂ S ₂ O ₈ (2)		DMSO	60	65	
15	AgNO ₃ (10)	(NH ₄) ₂ S ₂ O ₈ (2)	K ₂ CO ₃ (0.5)	DMSO	80	43	
16	AgNO ₃ (10)	$(NH_4)_2S_2O_8$ (2)	KOH (0.5)	DMSO	80	62	
17	AgNO ₃ (10)	(NH ₄) ₂ S ₂ O ₈ (2)	Et ₃ N (0.5)	DMSO	80	60	
18	AgNO ₃ (10)	(NH ₄) ₂ S ₂ O ₈ (2)	KHCO₃ (0.5)	DMSO	80	87	
19	AgNO ₃ (10)	(NH ₄) ₂ S ₂ O ₈ (2)	KHCO₃ (1)	DMSO	80	64	
20	AgNO ₃ (10)	$(NH_4)_2S_2O_8$ (2)	KHCO₃ (2)	DMSO	80	44	
21	AgNO ₃ (10)	$(NH_4)_2S_2O_8$ (1)	KHCO ₃ (0.5)	DMSO	80	53	
22	AgNO ₃ (20)	(NH ₄) ₂ S ₂ O ₈ (2)	KHCO₃ (0.5)	DMSO	80	92	
23	AgNO ₃ (30)	(NH ₄) ₂ S ₂ O ₈ (2)	KHCO ₃ (0.5)	DMSO	80	97	

^{*a*} Reaction conditions: potassium difluoroacetate **1a** (0.5 mmol), 2isocyanobiphenyl **2a** (2.5 mmol), Ag(I) salt, oxidant and base in solvent (3.0 mL) under N₂ atmosphere; ^{*b*} Yields determined by ¹⁹F NMR analysis with PhCF₃ as the internal standard;

gem-difluoromethylenated phenanthridine derivatives 3aa-oa. It was found that electro-neutral, electro-rich, and sterically hindered aryl difluoroacetates could be successfully converted gem-difluoromethylenated the corresponding to phenanthridines 3aa-ja in good to excellent yields. Notably, the aromatic heterocycle could be incorporated into the phenanthridine scaffold in moderate yield by using α , α difluoro-2-thiophenyl acetate (1k), which made this methodology more useful for the preparation of pharmaceuticals and gem-difluoromethylene linked twin drugs. However, the aryl difluoroacetates bearing electronwithdrawing substituents, such as trifluoromethyl, cyano, afforded the gem-difluoroalkylenated phenanthridines 3ma-na with much lower yields, due to the instability of the

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difluoromethyl intermediates. Fluorinated alkanoate were also applied for this transformation. Unfortunately, reaction of potassium trifluoroacetate **10** with isocyanide **2a** failed to give the product.

We further turned our attention to explore the scope of biarylisonitriles 2a-r as shown in Table 3. All the isocyanides bearing either electron-rich or electron-deficient substituent at the para position of benzene ring A underwent the reactions smoothly to afford the corresponding gem-difluoromethylenated products 3ab-ah in good to excellent yields. Many synthetically important functional groups, such as chloro, carbonyl and cyano groups, are well tolerated under the present oxidative decarboxylative reactions, thus providing potential possibility for further functionalization. It was found that the isocyanide having an electron-deficient pyridine ring instead of the benzene ring A (2i) was compatible in the annulation reaction and the desired gem-difluoromethylenated product 3ai was isolated in 51% yield. In general, slightly lower but still good yields were achieved for the substrates with electron-deficient ring A (3af-ai). It should be noted that compound 3aj could be observed in 52% yield with good regioselectivity, determined by ¹⁹F-NMR study, when an isocyanide bearing a 2-naphthyl group (2j) was employed. It

Table 2. Scope of Ag(I)-Catalyzed Decarboxylative gem-Difluoromethylenation of Difluoroacetates with $2a^{a,b}$



afforded two regiosiomers 3aj and 3aj' in a ratio of 5 : 1. Further extension of π -system was readily accomplished by modifying the 2-aryl group with anthracene, affording pentacyclic azaarene (3ak). To highlight the utility of this transformation, we also varied substituents at the arene moiety that has the isonitrile functionality (ring B). An increased functional group tolerance was observed and the efficiency of the reaction was not affected in the presence of halides, ether and alkyl groups for all biaryl tested in this gem-difluormethylenated series. The corresponding phenanthridines 3al-aq were obtained in satisfactory yields. To our surprise and delight, 2-isocyanoacrylate 2r could also react smoothly with the difluoromethylating intermediate, providing isoquinoline **3ar** without significant loss in the yield (72%). These results exhibit the robustness of our method with respect to the substitution pattern of the starting biphenyls.





^o Reaction condition: **1a** (0.3 mmol, 1.0 equiv), isocyanides **2** (0.75 mmol, 2.5 equiv), and AgNO₃ (0.06 mmol, 0.2 equiv), (NH₄)₂S₂O₈ (0.6 mmol, 2.0 equiv), KHCO₃ (0.15 mmol, 0.5 equiv), 4 Å M.S. (60 mg) under N₂ atmosphere at 80 °C. ^b
 Yields of isolated products.

^{*a*} Reaction condition: difluoroacetate (0.3 mmol, 1.0 equiv), **2a** (0.75 mmol, 2.5 equiv), and AgNO₃ (0.06 mmol, 0.2 equiv), (NH₄)₂S₂O₈ (0.6 mmol, 2.0 equiv), KHCO₃ (0.15 mmol, 0.5 equiv), 4 Å M.S. (60 mg) under N₂ atmosphere at 80 °C. ^{*b*} Yields of isolated products. ^{*c*} AgNO₃ (0.09 mmol, 0.3 equiv).

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To figure out whether the in situ generated aryl difluoroemthylene radical (ArCF₂⁻) would be involved in the reaction, we conducted the inhibition experiment of **1a** with the addition of the known radical scavenger of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), **1**, 4-dinitrobenzene or hydroquinone under the standard reaction condition (see ESI). Significant suppression of the formation of the desired product **3aa** suggested that a ArCF₂⁻ radical species would act as an important role in the current reaction condition.

To obtain some information on the reaction pathway, we also investigated the control experiments and revealed that the reaction still gave 12% yield even without Ag(I) catalyst (see ESI). No reaction occurred in the absence of an oxidant. The possible formation of $ArCF_2$ radical species generated independently from AgNO₃ was ruled out. The control experiments authenticated the importance of the combination of both of AgNO₃ and (NH₄)₂S₂O₈.

On the basis of these results and previous reports,^{7a, 11} a postulated mechanism is depicted in Scheme 2. We believe that in this work, Ag(I) is initially oxidized by the persulfate $((NH_4)_2S_2O_8)$ to generate the Ag(II) cation in situ, which could obtain a single electron from difluoroacetate to produce the carboxyl radical. Quick decarboxylation of the carboxyl radical with the loss of CO2 provides the corresponding gemdifluoromethylene radical A, which undergoes intermolecular addition to isonitrile functionality to form the imidoyl radical B. Subsequent intramolecular attack of the imidoyl radical on the pendant aromatic ring generates a cyclohexadienyl-type radical C, which gets oxidized by sulphate radical anion through a single electron transfer (SET) process to afford the cyclohexadienyl cation D. Finally, aromatiztion of D through deprotonation leads to the desired gem-difluoromethylenated phenanthridine E.



Scheme 2. Proposed Mechanism

In summary, we have demonstrated the simple and practical protocol for the generation of aryl difluoroemthylene radicals through the Ag(I)-catalyzed oxidative decarboxylation of aryl difluoroacetates. This transition-metal-catalyzed oxidative decarboxylative *gem*-difluoromethylenation might reasonably be expected to become a novel and convenient synthetic strategy for constructing *gem*-difluoromethylenated phenanthridine, due to the stability, easy availability of difluoroacetates and catalyst, the mild experimental conditions and the wide functional group compatibility.

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