Communication

Ag-Catalyzed Chemoselective Decarboxylative Mono- and gem-Di-Fluorination of Malonic Acid Derivatives

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Ag-Catalyzed Chemoselective Decarboxylative Mono- and *gem*-Di-Fluorination of Malonic Acid Derivatives

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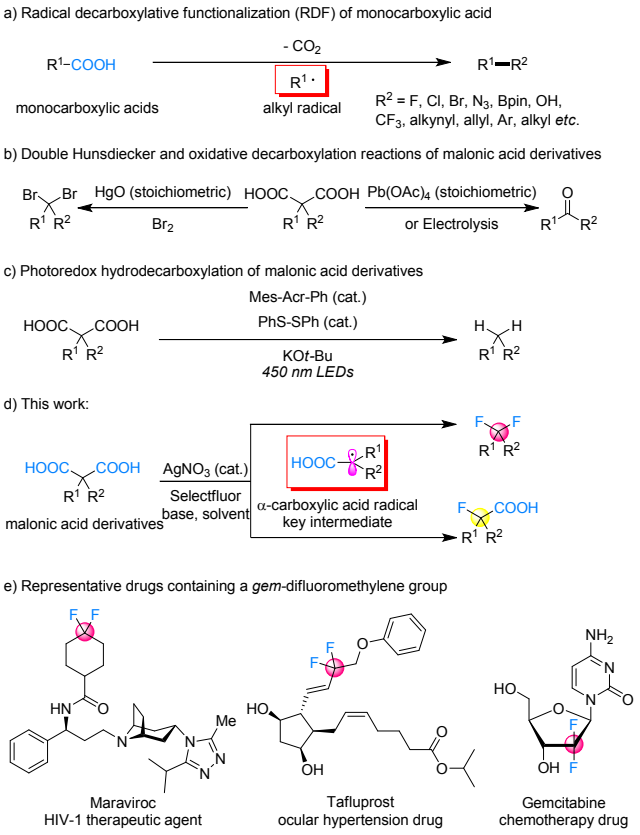
Supporting Information Placeholder

ABSTRACT: Malonic acid derivatives have been successfully applied in a Ag-catalyzed decarboxylative fluorination reaction, providing an unprecedented route to either *gem*-difluoroalkanes or α-fluorocarboxylic acids by the judicious selection of base and solvent. This reaction features the use of readily available starting materials, tunable chemoselectivity and good functional group compatibility as well as gram-scale synthetic capability. The advantage of using malonic acid derivatives in this radical decarboxylative functionalization is further highlighted by the facile transformations of the α-fluorocarboxylic acid to valuable fluorine-containing compounds. Preliminary mechanistic studies suggest that an α-carboxylic acid radical is involved in this reaction.

Carboxylic acids are appealing starting materials because of their stability, broad availability and low cost. Recently, the development of novel transformations with carboxylic acids as starting materials has attracted much attention.[1] Among them, radical decarboxylative functionalization (RDF) has emerged as a powerful strategy to efficiently construct carbon-carbon and carbon-heteroatom bonds (Scheme 1a).[2] The strength of this methodology lies in its ability to generate alkyl radicals through a radical decarboxylation and capture the carbon radicals under mild conditions. Nevertheless, the carboxylic acids used in RDFs have been predominantly restricted to monocarboxylic acids. Malonic acid derivatives are classical building blocks, which can be readily accessible via alkylations of malonic ester and subsequent hydrolysis;[3] however, the corresponding RDFs of malonic acids have rarely been reported. Early studies demonstrated that disubstituted malonic acid derivatives could undergo double Hunsdiecker or oxidative decarboxylation reactions in the presence of excess toxic metals or under electrochemical conditions (Scheme 1b).[4,5] A notable example was reported by the Nicewicz group, who applied *gem*-dicarboxylic acids in a photoredox hydrodecarboxylation reaction, but the increased oxidation potential caused by the second carboxylic acid moiety through hydrogen bonding makes them challenging substrates, and a strong base was necessary for this transformation (Scheme 1c).[6] Being aware that the utilization of malonic acid derivatives in RDF remains largely elusive, especially in a catalytic manner, we are particularly interested in exploring their novel radical decarboxylative reactions and exploiting malonic acid as a promising synthon in organic synthesis.

gem-Difluoromethylene group is a valuable fluorinated motif that is widely present in pharmaceuticals and biologically active compounds (Scheme 1e).[7,8] As a result, great efforts have been dedicated toward the incorporation of *gem*-difluoromethylene group into small molecules. However, achievements have mainly



Scheme 1. Radical Decarboxylative Functionalization and Representative Drugs Containing a *gem*-Difluoromethylene Group

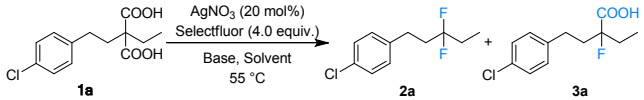
been made in the formation of aryl-CF_2R bonds,[8] but methods for the synthesis of *gem*-difluoroalkanes (Csp^3-CF_2-Csp^3) are less developed. Conventional approaches for preparing difluoroalkylated alkanes include deoxyfluorination of ketones and hydrofluorination of alkynes.[9,10] Alternatively, *gem*-difluoroalkanes can be obtained via a light-induced difluoroalkylation or a nickel-catalyzed tandem difluoroalkylation-arylation of activated alkenes.[11,12] Despite recent advances, the limitations of the aforementioned methods such as harsh reaction conditions, poor functional group tolerance, poor availability of starting materials and limited scope have impeded their applications in organic synthesis to a certain extent. Given their

significance in medicinal chemistry, the exploration of a general and practical approach for the efficient synthesis of *gem*-difluoroalkanes is highly desirable.

Although the application of monocarboxylic acids in radical decarboxylative fluorinations has been well-documented,[13] to the best of our knowledge, the generation of α-carboxylic acid radicals through radical decarboxylation of malonic acid derivatives and subsequent trapping of the resulting radicals with a fluorine reagent is unprecedented. Herein, we describe the successful application of malonic acid derivatives in a silver-catalyzed decarboxylative fluorination. The chemoselectivity of this reaction was tunable, providing valuable access to either *gem*-difluoroalkanes or α-fluorocarboxylic acids (Scheme 1d).

Inspired by Li's elegant work on the Ag-catalyzed decarboxylative fluorination of monocarboxylic acids,[13a] we commenced our study with the reaction of 2-(4-chlorophenethyl)-2-ethylmalonic acid (**1a**) and Selectfluor in the presence of $AgNO_3$ (20 mol%) in aqueous acetone or acetonitrile at 55 °C. Delightfully, *gem*-difluorinated product **2a** and monofluorinated product **3a** were produced after 12 h, albeit in low yields and poor ratios of **2a**/**3a** (Table 1, entries 1 and 2). Next, we examined the effect of base on this reaction. Generally, the addition of base could promote the formation of **2a** (entries 4-9), except for KOH (entry 3). When $PhCO_2K$ or $PhCO_2Na$ were employed, **2a** was produced as the major product in a 31% yield with the ratio of **2a**/**3a** being 84/16 (entries 6 and 7). The investigation of the solvents with $PhCO_2Na$ as the base revealed that the solvent played an important role in controlling the chemoselectivity (entry 7 vs entries 10-13). Interestingly, when biphasic systems (CH_2Cl_2/H_2O or CPME/H_2O) were employed, the monofluorinated product **3a** was generated exclusively (entries 10 and 13).

Table 1. Optimization of Reaction Conditions[a]



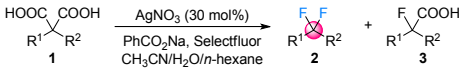
1a 2a 3a

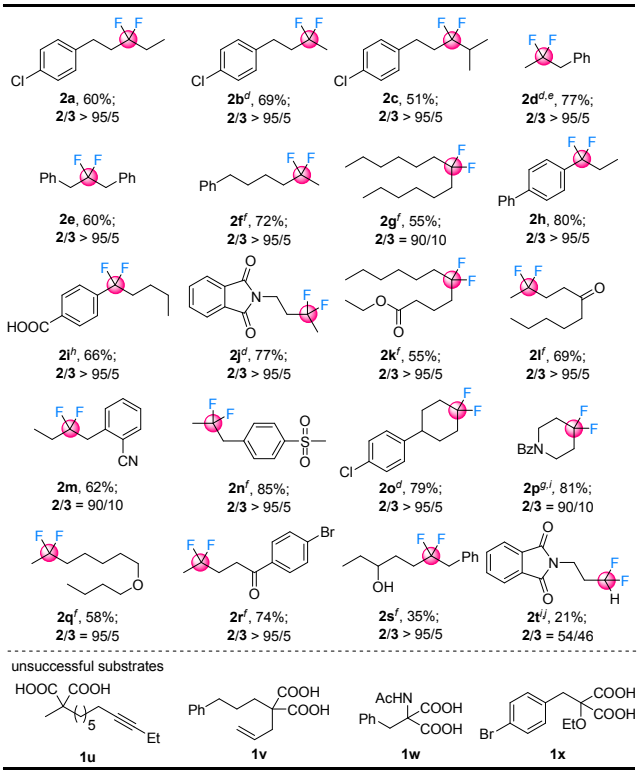
entry	base (equiv)	solvent (V/V)	ratio (2/3)	2a yield (%)[b]	3a yield (%)[b]
1	-	Acetone/H_2O (1/1)	48/52	10	11
2	-	CH_3CN/H_2O (1/1)	21/79	4	15
3	KOH (2.0)	Acetone/H_2O (1/1)	32/68	6	13
4	K_3PO_4 (2.0)	Acetone/H_2O (1/1)	76/24	16	5
5	K_2HPO_4 (2.0)	Acetone/H_2O (1/1)	71/29	17	6
6	$PhCO_2K$ (2.0)	Acetone/H_2O (1/1)	84/16	31	6
7	$PhCO_2Na$ (2.0)	Acetone/H_2O (1/1)	84/16	31	6
8	K_2CO_3 (2.0)	Acetone/H_2O (1/1)	59/41	10	7
9	Et_3N (2.0)	Acetone/H_2O (1/1)	63/37	17	10
10	$PhCO_2Na$ (2.0)	DCM/H_2O (1/1)	0/100	0	18
11	$PhCO_2Na$ (2.0)	CH_3CN/H_2O (1/1)	21/79	4	15
12	$PhCO_2Na$ (2.0)	*n*-Hex/H_2O (1/1)	27/73	6	16
13	$PhCO_2Na$ (2.0)	CPME/H_2O (1/1)	4/96	1	25
14[c]	K_2HPO_4 (4.0)	CPME/H_2O (1/1)	2/98	1	**56 (54)**
15[d]	$PhCO_2Na$ (3.0)	CH_3CN/H_2O/*n*-Hex (1/1/3)	100/0	**69 (60)**	0
16[d]	$PhCO_2Na$ (3.0)	CPME/H_2O (1/1)	7/93	1	14
17[e]	K_2HPO_4 (4.0)	CPME/H_2O (1/1)	0	0	0
18[e]	$PhCO_2Na$ (3.0)	CH_3CN/H_2O/*n*-Hex (1/1/3)	0	0	0

[a]Reaction conditions: **1a** (0.1 mmol), $AgNO_3$ (0.02 mmol), Selectfluor (0.4 mmol), base, solvent (2 mL), 55 °C, 12 h under N_2. [b]^{19}F NMR yield with 4-fluorobenzoic acid as the internal standard, isolated yield in parentheses. [c]Selectfluor (0.2 mmol), rt. [d]**1a** (0.1 mmol), $AgNO_3$ (0.03 mmol), Selectfluor (0.6 mmol), base, solvent (1.5 mL). [e]Without $AgNO_3$. CPME = cyclopentyl methyl ether; *n*-Hex = *n*-hexane.

Based on the above findings, an extensive study of the reaction parameters was conducted to further improve the yields. Ultimately, the *gem*-difluorinated compound **2a** could be obtained predominantly in an isolated yield of 60% by the reaction of **1a** (0.1 mmol) with Selectfluor (0.6 mmol) in a mixed solvent of CH_3CN/H_2O/*n*-Hex (1/1/3) in the presence of $AgNO_3$ (30 mol%) by using $PhCO_2Na$ (3.0 equiv) as the base (entry 15). When the base was changed to K_2HPO_4, the reaction in CPME/H_2O (1/1) at room temperature exclusively provided α-fluorocarboxylic acid **3a** in an isolated yield of 54% (entry 14). This tunable chemoselectivity realized by simply varying the reaction conditions offers an expedient way of selectively introducing fluorine atoms into small molecules. Control experiments showed that the solvent had a substantial impact on the chemoselectivity of this reaction (entries 15 and 16) and the silver catalyst was essential for these transformations (entries 17 and 18).

Table 2. Scope of Decarboxylative *gem*-Difluorination[a-c]





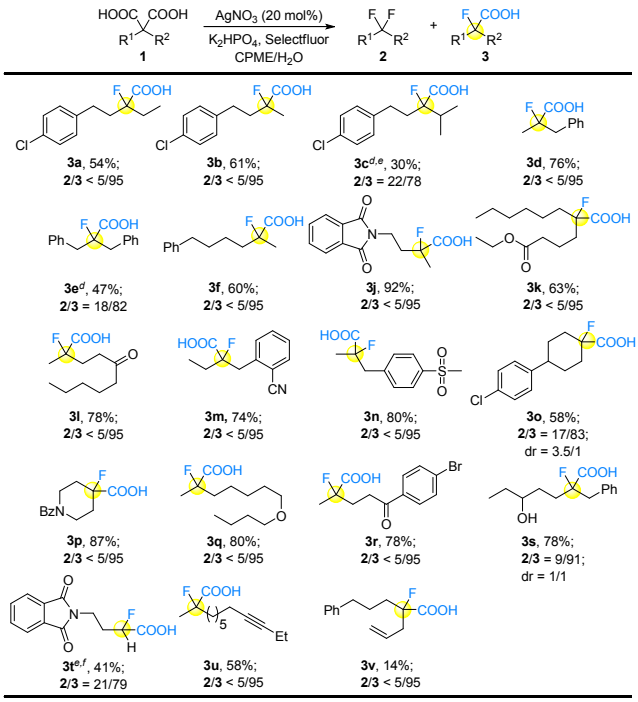
[a]Reaction condition: **1** (0.2 mmol), $AgNO_3$ (0.06 mmol), Selectfluor (1.2 mmol), $PhCO_2Na$ (0.5 mmol), CH_3CN (0.6 mL), H_2O (0.6 mL), *n*-hexane (1.8 mL), 55 °C, under N_2. [b]Isolated yield. [c]The **2**/**3** ratio was determined by ^{19}F NMR. [d]K_2HPO_4 (0.4 mmol) instead of $PhCO_2Na$. [e]^{19}F NMR yield with 4-fluorobenzoic acid as the internal standard. [f]$PhCO_2Na$ (0.7 mmol), CH_3CN (1.0 mL), H_2O (1.0 mL) and *n*-hexane (3.0 mL) as solvent, rt. [g]$AgNO_3$ (0.04 mmol), K_2HPO_4 (0.6 mmol). [h]K_2CO_3 (0.6 mmol), DCE (2.0 mL) and H_2O (2.0 mL). [i]CH_3CN (2.0 mL) and H_2O (2.0 mL) were used as the solvent. [j]Selectfluor (1.6 mmol), K_2HPO_4 (0.8 mmol).

With the optimal conditions established, the substrate scope of decarboxylative *gem*-difluorination was examined (Table 2). Generally, for disubstituted malonic acids, the reaction proceeded smoothly, affording *gem*-difluorinated compounds **2** in moderate to good yields with excellent chemoselectivities. The reactions of simple dialkyl-substituted *gem*-dicarboxylic acids exclusively produced *gem*-difluoroalkanes **2a**-**2g** in 51-77% yields. Increasing the steric hindrance at the α-position of the malonic acids had no obvious deleterious effects on the reactivity or selectivity (**2a**-**2c**). Aryl- and alkyl-substituted malonic acids were tolerated in this transformation, and two fluoro substituents could be effectively installed at the benzylic position (**2h** and **2i**). In addition, cyclic malonic acids were also suitable substrates, furnishing **2o** and **2p** in good yields. Notably, malonic acids bearing functional groups, including phthalimide (**2j**), ester (**2k**), ether (**2q**), sulfone (**2n**), benzoic acid (**2i**), cyanide (**2m**), amide (**2p**) and ketone (**2l** and **2r**) were well tolerated in this system, providing *gem*-difluoro compounds **2** in 55-85% yields with excellent chemoselectivities.

Secondary alcohol partially survived to afford product **2s** in 35% yield, along with 33% yield of corresponding ketone product.[14] Alkynyl and alkenyl groups (**1u** and **1v**) were not compatible with such oxidative conditions. Only oxidative decarboxylation products were observed for the α-heteroatom substituted malonic acids (**1w** and **1x**).[5] Furthermore, the decarboxylative *gem*-difluorination of monosubstituted malonic acid was also examined; unfortunately, product **2t** was obtained in a low yield with poor chemoselectivity.[15]

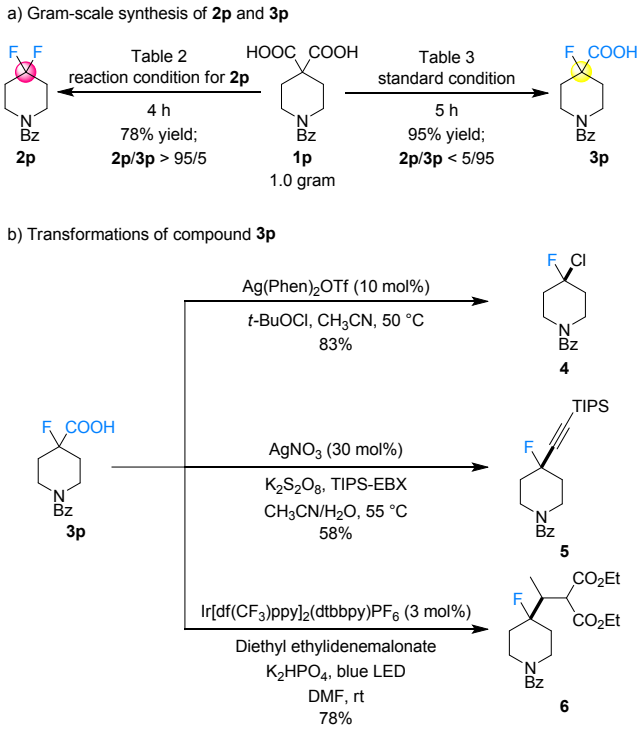
Subsequently, we turned our attention to extending the substrate scope of decarboxylative monofluorination. As illustrated in Table 3, the substrates that can participate in the decarboxylative *gem*-difluorination are also suitable for this monofluorination reaction, predominately producing α-fluorocarboxylic acids in 30-92% yields;[16] the exception is aryl-substituted malonic acids, which only produced *gem*-difluorides (**2h** and **2i**). We attribute the different chemoselectivity of aryl-substituted malonic acids in this system to the reaction rate of the second decarboxylative fluorination being accelerated due to the stabilization of the corresponding benzylic radical. In contrast to the decarboxylative *gem*-difluorination, introduction of sterically encumbered groups at the α-position of the malonic acids compromised the reaction efficiency (**3c** vs **3b** and **3e** vs **3d**), but **3c** and **3e** could still be obtained in synthetically useful yields. Generally, methods for accessing tertiary α-fluorocarboxylic acid derivatives rely on electrophilic fluorination of the corresponding ester enolates and subsequent hydrolysis;[17] however, the harsh reaction conditions of these protocols showed limited functional group compatibility. In comparison, our mild reaction conditions for α-fluorocarboxylic acids accommodate a variety of functional groups, such as aryl halide (**3a-3c**, **3o** and **3r**), phthalimide (**3j**), ester (**3k**), ether (**3q**), sulfone (**3n**), cyanide (**3m**), amide (**3p**), ketone (**3l** and **3r**), alcohol (**3s**) and alkyne (**3u**). Substrates **1v-1x** are not viable for this transformation. Pleasingly, the reaction of monosubstituted malonic acid delivered product **3t** in 41% yield with a **2**/**3** ratio of 21/79.

Table 3. Scope of Decarboxylative Monofluorination[a-c]

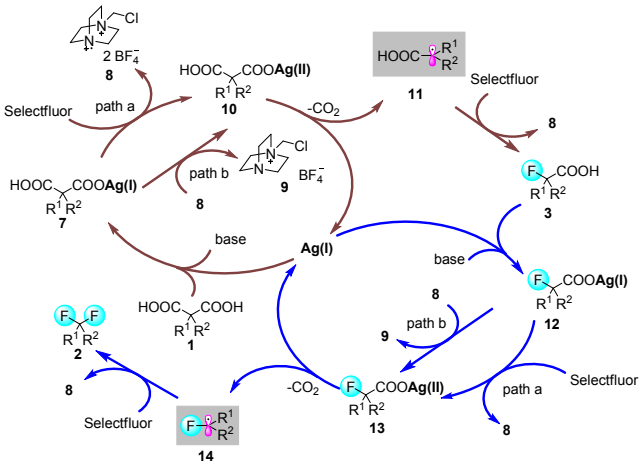


[a]Reaction condition: **1** (0.2 mmol), $AgNO_3$ (0.04 mmol), Selectfluor (0.4 mmol), K_2HPO_4 (0.8 mmol), CPME (2.0 mL), H_2O (2.0 mL), rt under N_2. [b]Isolated yield for the corresponding methyl ester. [c]The ratio of **2**/**3** was determined by ^{19}F NMR. [d]$AgNO_3$ (0.06 mmol), Selectfluor (0.8 mmol), $PhCO_2Na$ (0.7 mmol), CPME (9.0 mL), CH_3CN (1.0 mL), *n*-hexane (3.0 mL), H_2O (1.0 mL), rt. [e]55 °C. [f]$AgNO_3$ (0.06 mmol), Selectfluor (1.2 mmol), CH_3CN (0.8 mL), H_2O (3.2 mL).

To demonstrate the practical utility of this unprecedented decarboxylative fluorination, gram-scale reactions were carried out (Scheme 2a). From the same starting material **1p**, *gem*-difluoroalkane **2p** and α-fluorocarboxylic acid **3p** were obtained in good yields and excellent selectivities. Notably, α-fluorocarboxylic acids **3** are of particular versatility, as the remaining carboxylic acid group provides spacious room for further elaboration. The utility of the α-fluorocarboxylic acid has been showcased by the facile conversions of compound **3p** to a series of valuable fluorine-containing building blocks, such as *gem*-chloro fluoroalkane **4**,[2a,18] tertiary propargylic fluoride **5**[2b,19] and γ-fluoride Michael adduct **6**[2g] via radical decarboxylative functionalization (Scheme 2b). These results clearly demonstrate the potential applications of this protocol for the late-stage diversification of fluorinated bioactive compounds.



Scheme 2. Synthetic Applications

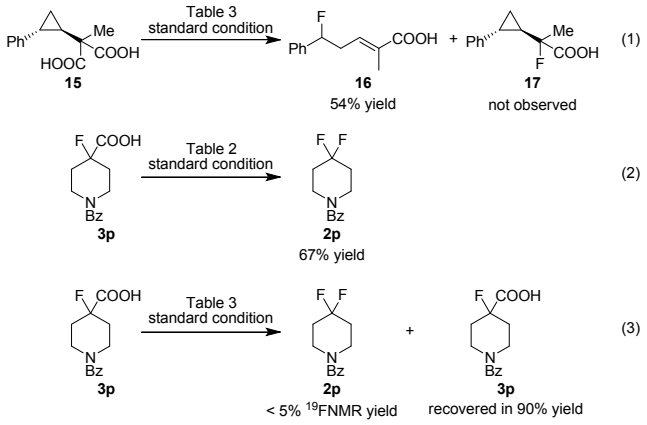


Scheme 3. Proposed Mechanism

Based upon our experimental results and literature precedents,[13a,20] a tentative reaction mechanism was proposed (Scheme 3). Initially, facilitated by a weak base, malonic acid **1**

reacts with a catalytic amount of Ag(I) to form malonic acid monosilver(I) salt **7**,[21] which is readily oxidized to Ag(II) **10** by Selectfluor with concomitant generation of **8**; alternatively, the newly formed Selectfluor radical cation **8** is also capable of oxidizing Ag(I) to Ag(II).[20] Then, the carboxylate anion loses an electron to Ag(II), and subsequent CO_2 extrusion delivers an α-carboxylic acid radical **11** and regenerates Ag(I). The resulting radical **11** abstracts a fluorine atom from Selectfluor to give product **3**. In the decarboxylative monofluorination, the reaction ceases at this stage and α-fluorocarboxylic acid **3** is the final product. In the decarboxylative *gem*-difluorination, compound **3** would undergo a second decarboxylative fluorination (**3** → **12** → **13** → **14** → **2**) to eventually produce *gem*-difluorinated product **2.**

Although the mechanism of the silver-catalyzed decarboxylative fluorination of monocarboxylic acids has been well studied,[20] the radical decarboxylation of malonic acid derivatives to generate α-carboxylic acid radicals in a Ag(I)/Selectfluor system is unknown. To support the above mechanistic hypothesis, radical clock **15** was subjected to our standard decarboxylative monofluorination conditions, and the ring-opening product **16** was obtained in 54% yield (Scheme 4, eq 1), which suggested the involvement of α-carboxylic acid radical **11** in this transformation. Moreover, the successful conversion of **3p** to *gem*-difluoroalkane **2p** (eq 2) and the observation of monofluorinated product **3** as a side product in the decarboxylative *gem*-difluorination (Table 2) implied that α-fluorinated carboxylic acid **3** was the intermediate in the formation of *gem*-difluoroalkanes.[22] Additionally, **3p** could not be converted to **2p** by decarboxylative monofluorination (eq 3). Although the origin of this intriguing chemoselectivity is not yet clear,[23] a detailed mechanistic study of this reaction is underway in our laboratory.



Scheme 4. Mechanistic Experiments

In summary, we have successfully developed a silver-catalyzed decarboxylative fluorination reaction of malonic acid derivatives. Tunable chemoselectivity was realized by the judicious selection of base and solvent, which offers an expedient way to access *gem*-difluoroalkanes and α-fluorocarboxylic acids. The advantage of using malonic acid derivatives in RDF was further highlighted by the facile transformations of the α-fluorocarboxylic acid to some valuable fluorine-containing compounds. More importantly, this work constitutes the first example of the generation of α-carboxylic acid radicals through the decarboxylation of malonic acid derivatives in a Ag(I)/Selectfluor system. Given the operational simplicity and good functional group tolerance as well as the use of readily available starting materials, we believe that the present protocol will provide a powerful tool for the preparation of valuable fluorinated compounds.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data, and analytical data are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) This was further confirmed by the time course study of the decarboxylative *gem*-difluorination of substrate **1p**, see supporting information for details.

(23) Since the chemoselectivity was mainly caused by the different reactivities of α-fluorocarboxylic acid **3** (Scheme 3) in decarboxylative mono- and *gem*-difluorination, we speculate that the contrasting reactivity behavior of **3** under different conditions might be due to different existing forms of corresponding silver α-fluorocarboxylate salt, in which the number of coordinated carboxylate ligands and different coordinated solvents with silver might affect the redox potential of the Ag(I)/Ag(II) couple, see: Kumar, A.; Neta, P. Complexation and oxidation of glycine and related compounds by silver(II). *J. Am. Chem. Soc.* **1980**, *102*, 7284.

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