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Formal fluorine atom transfer radical addition: silver-catalyzed carbofluorination of unactivated alkenes with ketones in aqueous solution†

Lin Zhu,[a] He Chen,[b] Zijia Wang[b] and Chaozhong Li*[a,b]

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In this article, we report the first examples of carbofluorination of unactivated alkenes. Under catalysis by $AgNO_3$, the reactions of unactivated alkenes with Selectfluor reagent and active methylene compounds such as acetoacetates or 1,3-dicarbonyls in CH_2Cl_2–H_2O–HOAc solution afforded the corresponding three-component condensation products under mild conditions. Furthermore, with the promotion of NaOAc, the AgOAc-catalyzed carbofluorination of various unactivated alkenes with Selectfluor and acetone proceeded smoothly in aqueous solution at 50 °C. The carbofluorination was efficient and highly regioselective, and enjoyed a broad substrate scope and wide functional group compatibility. These formal fluorine atom transfer radical addition reactions provide a convenient entry to structurally divergent, polyfunctional organofluorine compounds as versatile synthetic intermediates.

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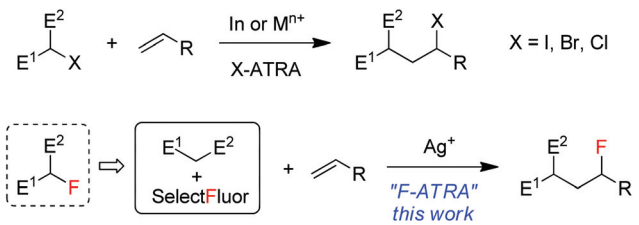
Introduction

Atom transfer radical addition (ATRA) reactions, discovered by Kharasch[1] and significantly promoted by Curran[2] and others, have been demonstrated to be a versatile tool in organic synthesis.[3] The most common ATRA processes are iodine-atom-transfer in which carbon–iodine bonds are added across alkenes or alkynes in the presence of a radical initiator. A representative example is the addition of iodinated active methylene compounds onto electron-rich alkenes, as shown in Scheme 1, a process driven partially by a radical polar effect.[4] Bromine and chlorine ATRA reactions have also been developed and can be catalyzed by a number of transition metal complexes such as copper and ruthenium *via* transition-metal-assisted Cl (or Br)-atom-transfer mechanism.[5] On the other hand, fluorine ATRA reactions are virtually unknown probably because of the much higher C–F bond dissociation energies. However, if one considers that monofluorinated active methylene compounds are typically prepared from the reactions of active methylene compounds with electrophilic fluorinating reagents such as Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclic[2.2.2]octane bis(tetrafluoroborate)),[6] it would be an interesting variant of F-ATRA to use directly a combination of the two starting materials as a substitute for their products (monofluorinated active methylene compounds) (Scheme 1). In view of the widespread and growing use[7] of organofluorine compounds in agrochemicals, pharmaceuticals and materials and the importance of ^{18}F-labeled organic compounds in positron emission tomography (PET),[8] this formal F-ATRA process should be advantageous in that it allows the rapid assembly of cheap and readily available substrates and fluorinating reagents into polyfunctional fluorinated molecules.[9] Herein we report silver-catalyzed formal F-ARTA reactions in aqueous solution.



Scheme 1 ATRA *versus* formal ATRA.

Results and discussion

We recently reported[10] that the combination of a catalytic amount of $AgNO_3$ with Selectfluor resulted in the decarboxylative fluorination of aliphatic carboxylic acids,[10a] the intramolecular aminofluorination of alkenes[10b] and the intermolecular phosphonofluorination of unactivated alkenes.[10c] During the

[a]*Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P. R. China. E-mail: clig@mail.sioc.ac.cn*
[b]*Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China*
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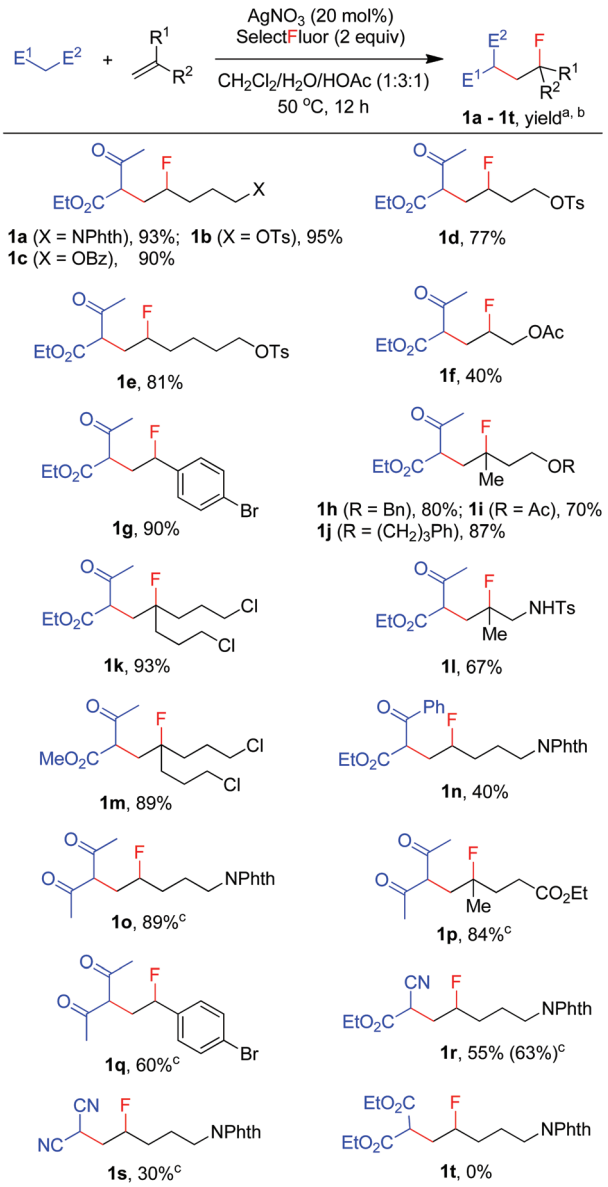
course of these studies, we noted that small amounts of hexane-2,5-dione could be detected by GC-MS in some cases when acetone was used as the co-solvent. This phenomenon implied that acetonyl radicals might be generated from the oxidation of acetone[11] by reaction with $AgNO_3$–Selectfluor. If this was the case, electrophilic α-keto radicals might be produced and trapped by electron-rich alkenes to give the adduct radicals as nucleophilic alkyl radicals. The subsequent fluorination of the adduct radicals would lead to the carbofluorination products. It should be pointed out that only a few examples of intermolecular carbofluorination have been reported and they dealt with activated alkenes such as styrenes or enamines.[12,13]

Thus, *N*-(pent-4-en-1-yl)phthalimide (**A-1a**) and ethyl acetoacetate, which is more prone to oxidation than acetone,[14] were used as the model substrates in the search for optimal reaction conditions (see Table S1 in the ESI† for details). We were delighted to find that, with catalysis by $AgNO_3$, the reaction of the two model substrates with Selectfluor proceeded smoothly in CH_2Cl_2–H_2O–HOAc (1 : 3 : 1) at reflux (~50 °C) leading to the expected F-ATRA product **1a** in 93% isolated yield. Control experiments indicated that $AgNO_3$ was necessary to initiate the reaction, while other silver(I) salts such as AgOAc showed similar effect. No fluorination took place when Selectfluor was switched to *N*-fluorobis-(benzenesulfonyl)imide (NSFI).[15] To the best of our knowledge, this is also the first example of intermolecular carbofluorination of *unactivated* alkenes.

We then moved on to examine the scope and limitation of this new method. As illustrated in Scheme 2, a number of electron-rich mono-substituted alkenes underwent F-ATRA to afford the expected products **1a–1f** in satisfactory yields. Styrenes were also excellent substrates for the condensation, as exemplified by the synthesis of **1g** in 90% yield. Di-substituted alkenes also exhibited a high reactivity (**1h–1l**). Functional groups such as ester, tosylate, sulfonamide and aryl or alkyl halide, were well tolerated. Active methylene compounds other than acetoacetates could also be employed for the carbofluorination. While the reactions of acetylacetone proceeded sluggishly under the above conditions, they were speeded up by the addition of $K_2S_2O_8$ (1 equiv.), furnishing the corresponding products (**1o–1q**) in high yields. The role of $K_2S_2O_8$ remains unclear at this moment.[16] Cyanoacetate was also a good substrate for the condensation, as proved by the synthesis of **1r** in good yield. On the other hand, malononitrile showed a low efficiency and diethyl malonate failed to give any carbofluorination product.[17] The results seem to indicate that the reactivity of active methylene compounds decreases in the order of acetoacetate > acetylacetone > cyanoacetate > malononitrile > malonate.

The above excellent performance of acetoacetates and 1,3-diketones urged us to examine the possibility of using ordinary ketones such as acetone in the carbofluorination. The condensation of acetone with alkene **A-1a** and Selectfluor under the above conditions gave only a trace amount of the expected carbofluorination product **2a**. We then went on to optimize the reaction conditions (Table 1). When acetone was directly used as the co-solvent, all the alkene **A-1a** was consumed and **2a** was



Scheme 2 Carbofluorination of alkenes with active methylene compounds. [a] Reaction conditions: alkene (1 mmol), ketone (3 mmol), Selectfluor (2 mmol), $AgNO_3$ (0.2 mmol), CH_2Cl_2 (2.5 mL), H_2O (7.5 mL), HOAc (2.5 mL), 50 °C, 12 h. [b] Isolated yield based on the alkene. [c] $K_2S_2O_8$ (1 equiv.) was used as the additive.

isolated in 17% yield (entry 4, Table 1). Switching $AgNO_3$ to AgOAc did not increase the product yield (entry 5, Table 1). However, a large portion (~60%) of alkene **A-1a** was now recovered. This unusual difference prompted us to check the effect of NaOAc. Indeed, with 3 equivalents of NaOAc as the additive, the product yield was increased to 90% (entry 8, Table 1). The reaction also proceeded smoothly when the catalyst loading was lowered to 10 mol% (entry 9, Table 1). Notably, with water as the only solvent and 3 equivalents of acetone as the substrate, the reaction also proceeded to give the product **2a** in 30% yield (entry 11, Table 1). While the role of NaOAc is not clear at this moment, it might act as a weak base to absorb the

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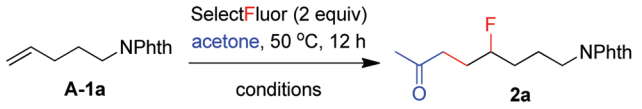
Table 1 Optimization of conditions for the synthesis of **2a**

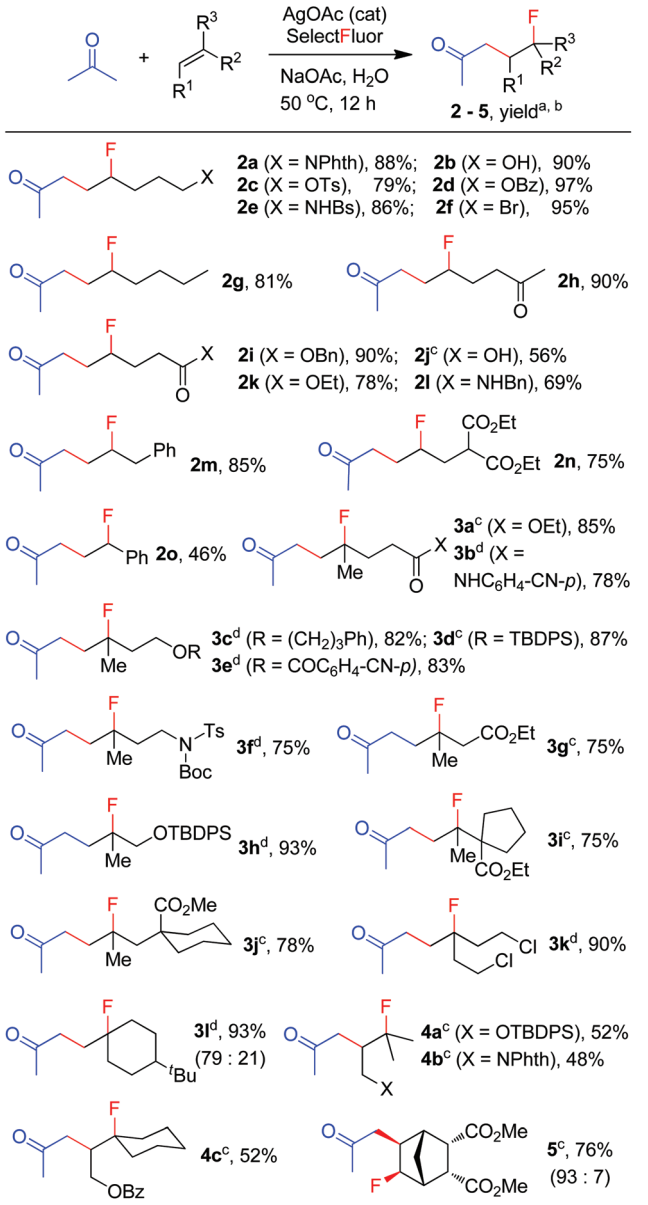


Entry[a]	Conditions	Yield[b] (%)
1[c]	$AgNO_3$ (20 mol %), acetone (3 equiv.), CH_2Cl_2–H_2O–HOAc (1 : 3 : 1)	Trace
2[c]	$AgNO_3$ (20 mol %), acetone (3 equiv.), CH_2Cl_2–H_2O (1 : 3)	Trace
3[c]	$AgNO_3$ (20 mol %), acetone (3 equiv.), CH_3CN–H_2O (1 : 3)	Trace
4	$AgNO_3$ (20 mol %), acetone–H_2O (1 : 1)	17
5	AgOAc (20 mol %), acetone–H_2O (1 : 1)	18
6	AgOAc (20 mol %), NaOAc (1 equiv.), acetone–H_2O (1 : 1)	59
7	AgOAc (20 mol %), NaOAc (2 equiv.), acetone–H_2O (1 : 1)	75
8	AgOAc (20 mol %), NaOAc (3 equiv.), acetone–H_2O (1 : 1)	90
9	**AgOAc (10 mol %), NaOAc (3 equiv.), acetone–H_2O (1 : 1)**	**88**
10	AgOAc (10 mol %), NaOAc (3 equiv.), acetone (10 equiv.), H_2O	63
11	AgOAc (10 mol %), NaOAc (3 equiv.), acetone (3 equiv.), H_2O	30
12	NaOAc (3 equiv.), acetone–H_2O (1 : 1)	0
13	AgOAc (10 mol %), KOAc (3 equiv.), acetone–H_2O (1 : 1)	84
14	AgOAc (10 mol %), $NaHCO_3$ (3 equiv.), acetone–H_2O (1 : 1)	0

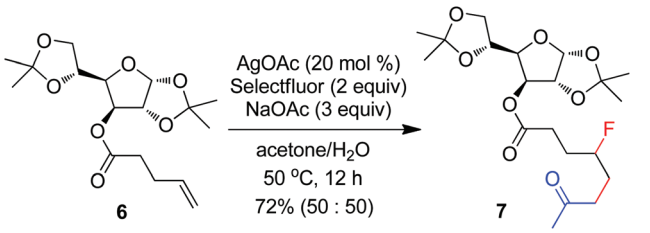
[a] Conditions: **A-1a** (0.2 mmol), Selectfluor (0.4 mmol), acetone, H_2O (2 mL), Ag(I) source, organic solvent and additive if applicable, 50 °C, 12 h. [b] Isolated yield based on **A-1a**. [c] Water (1.5 mL) was used.

acid generated during the reaction. KOAc showed an effect similar to NaOAc (entry 13, Table 1). However, the reaction was significantly retarded when NaOAc was replaced by $NaHCO_3$ (entry 14, Table 1).

The above optimization revealed that the F-ATRA with acetone proceeded nicely under much milder conditions. The procedure was particularly advantageous in that no other organic solvent was required and the condensation was conducted under almost neutral conditions. As a result, the carbofluorination enjoyed a broad substrate scope and wide functional group compatibility, as demonstrated in Scheme 3. Mono-, di- and even tri-substituted alkenes were all good acceptors, furnishing the corresponding products **2**, **3** and **4**, respectively. Various functional groups were well tolerated, including labile free carboxylic acid, unprotected hydroxyl group and primary alkyl bromide (in **2b**, **2j** and **2f**), a unique characteristic of ATRA reactions. In addition, the reactions were scalable and the products could be easily obtained in gram scale without any decrease in efficiency. Note that the reactions were not only efficient but also highly regioselective. The condensation could also be stereoselective, as indicated by the synthesis of bicyclic compound **5**. This method could be utilized in the direct modification of complex molecules. For example, the condensation of carbohydrate **6** with acetone and Selectfluor gave the product **7** in 72% yield (eqn (1)). In another case, steroid **8** underwent stereoselective carbofluorination to give **9** as the only stereoisomer isolated (eqn (2)).



Scheme 3 Carbofluorination of alkenes with acetone. [a] Reaction conditions: alkene (2 mmol), Selectfluor (4 mmol, 2 equiv.), AgOAc (0.2 mmol, 10 mol%), NaOAc (6 mmol), acetone (20 mL), H_2O (20 mL), 50 °C, 12 h. [b] Isolated yield based on the alkene. [c] AgOAc (20 mol%) and H_2O (10 mL) were used. [d] Selectfluor (3 equiv.) and AgOAc (15 mol%) were used.



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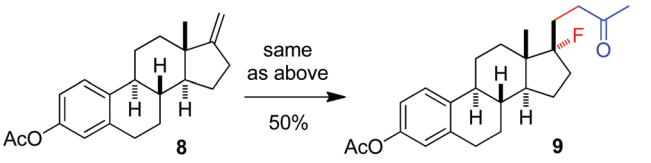
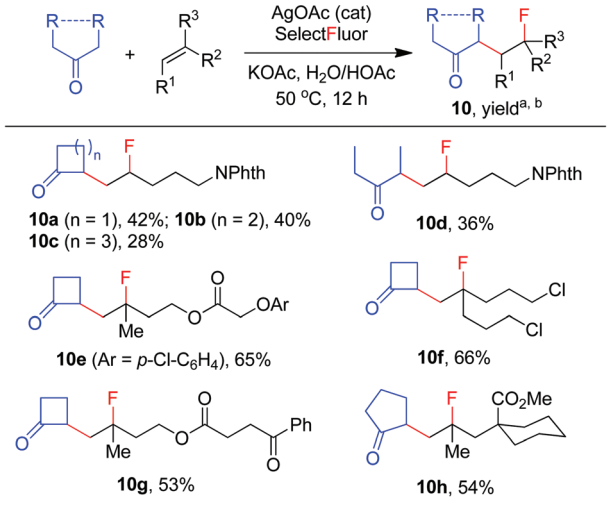


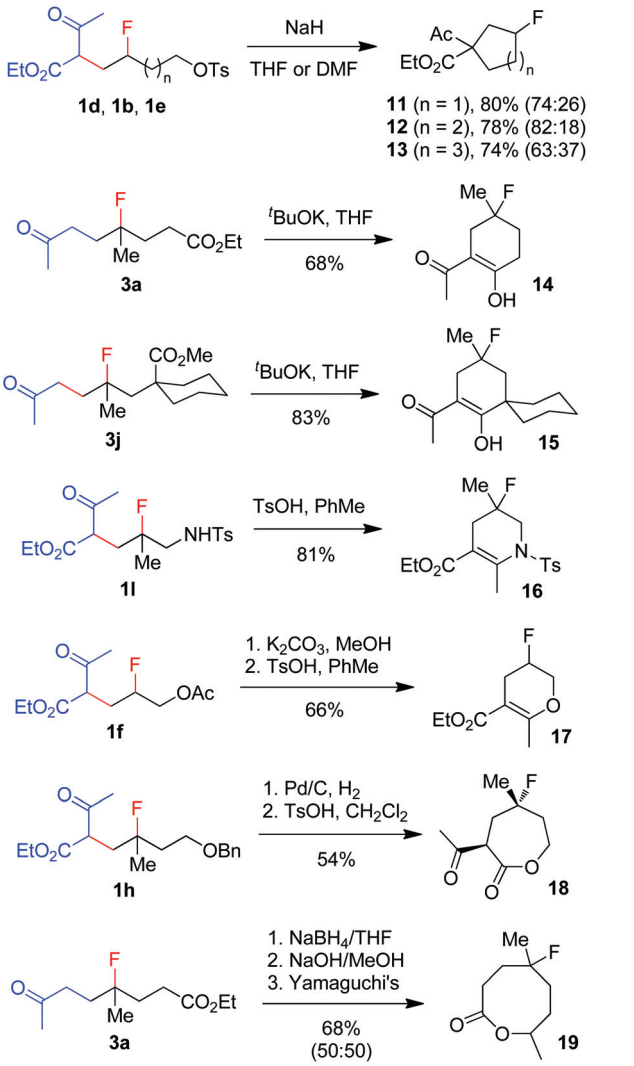
(2)

The carbofluorination could also be extended to the use of other ordinary ketones such as cycloalkanones and 3-pentanone, as depicted in Scheme 4. Under the re-optimized conditions, moderate to good efficiency was typically observed. Nevertheless, direct α-fluorination of ketones could now be detected in small extents, presumably due to the decreased electrophilicity of α-keto radicals (*vide infra*).

The broad substrate scope and excellent functional group compatibility of carbofluorination demonstrated above allow convenient access to divergent and polyfunctional organofluorine compounds, which should serve as versatile synthetic intermediates. For example, monofluorinated carbo- and heterocycles[18] can be easily prepared from the carbofluorination products (Scheme 5). Thus, fluorinated carbocycles **11–13** were readily prepared in one step from compounds **1d**, **1b** and **1e**, respectively, *via* intramolecular nucleophilic substitution. 4-Fluorocyclohexanones **14** and **15** were produced from **3a** and **3j** *via* base-promoted Dieckmann condensation. Cyclic enamine **16** and enol ether **17** were readily obtained from **1l** and **1f** *via* dehydration. Deprotection of benzyl ether **1h** followed by ester exchange afforded 7-membered lactone **18** as a single stereoisomer. Reduction of ketone **3a** followed by hydrolysis and subsequent Yamaguchi lactonization[16] produced 8-membered lactone **19**. It is conceivable that more new fluorinated cyclic compounds can be reached *via* similar strategies. Note that these cyclic compounds are also valuable building blocks in the synthesis of more complex fluorinated molecules.



Scheme 4 Carbofluorination of alkenes with simple ketones. [a] Reaction conditions: alkene (0.2 mmol), ketone (2 mmol), Selectfluor (0.4 mmol), AgOAc (0.04 mmol), KOAc (0.6 mmol), H_2O (1 mL), HOAc (0.4 mL), 50 °C, 12 h. [b] Isolated yield based on the alkene. If applicable, the products were obtained as ~1 : 1 mixture of stereoisomers.



Scheme 5 Conversion of carbofluorination products to fluorinated carbo- and heterocycles.

As indicated above, a radical fluorination[10,12c,19,20] mechanism might be involved in the carbofluorination of unactivated alkenes. More direct evidence was the reaction of 1,6-diene **20** with acetone in which the cyclization product **21** was isolated in 46% yield along with the recovery of diene **20** in 23% yield (eqn (3)). Furthermore, vinylcyclopropane **22** was designed as a radical probe.[21] The reaction of **22** with acetone under the above optimized conditions (Scheme 2) led to the ring-opening product **23** in 59% yield along with the recovery of **22** in 20% yield (eqn (4)). These experiments provide solid evidence for the intermediacy of α-carbonyl radicals in carbofluorination. To gain more insight into the mechanism, the following experiments were carried out. When Selectfluor was replaced by a combination of $K_2S_2O_8$ (2 equiv.) and KF (2 equiv.), the reaction of acetone with alkene **A-1a** gave the addition–hydrogenation product **24** in 68% yield while no

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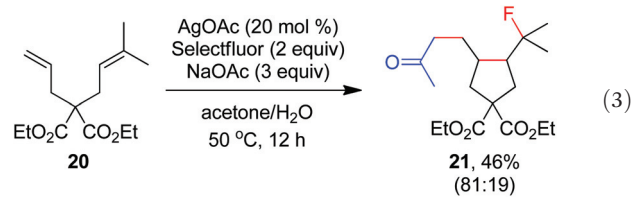
carbofluorination product **2a** could be detected (eqn (5)). This implied that Ag(II)F alone was unlikely to initiate the carbofluorination. When AgOAc was switched to divalent silver–1,10-phenanthroline complex $Ag(Phen)_2S_2O_8$, the reaction of acetone with **A-1a** and Selectfluor under various conditions also led to the formation of **24** rather than **2a**, indicating that the adduct radicals could not directly abstract fluorine atoms from Selectfluor.



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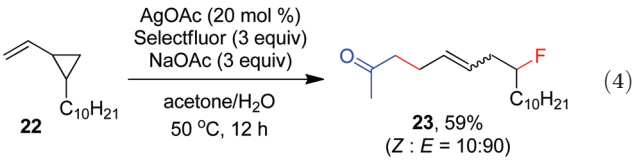

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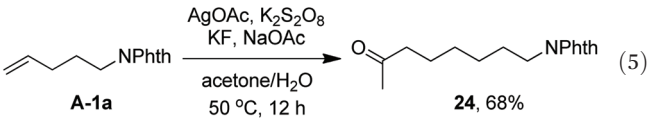

(5)

A plausible mechanism was thus proposed based on the above results as well as our previous findings.[10] As shown in Fig. 1, the interaction of Ag(I) with Selectfluor generates the Ag(III)–F intermediate, presumably *via* oxidative addition. The single electron transfer between acetone and Ag(III)–F gives Ag(II)–F and acetonyl radical cation. Deprotonation of the acetonyl radical cation affords the electrophilic α-carbonyl radical, which adds selectively to the electron-rich C=C bond to provide the adduct radical as a nucleophilic alkyl radical. The subsequent fluorine atom transfer from Ag(II)–F to the adduct radical leads to the carbofluorination product and regenerates the catalyst Ag(I), which enters into the next catalytic circle. This mechanism well explains the umpolung of ketones. Moreover, when α-keto radicals bear an alkyl substituent, they become less electrophilic and the efficiency of carbofluorination is lowered, consistent with our experimental observations. Note that the proposed mechanism is closely similar to that of transition-metal-assisted Cl-ATRA,[3b,5] thus justifying its classification as a F-ATRA process.

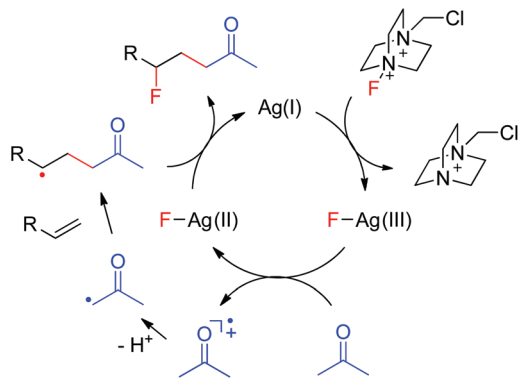

Fig. 1 Proposed mechanism of carbofluorination.

Conclusion

In conclusion, we have successfully developed silver-catalyzed formal F-ARTA reactions employing ketones and Selectfluor as a substitute for α-fluoroketones, allowing the three-component condensation of unactivated alkenes, ketones and Selectfluor in aqueous solution under mild conditions. The results significantly expand the scope of radical fluorination. Furthermore, they offer a new way of thinking for the practice of ATRA reactions, which should find important application both in radical chemistry and in organofluorine chemistry.

Experimental section

Typical procedure for silver-catalyzed carbofluorination of unactivated alkenes with active methylene compounds

N-(Pent-4-en-1-yl)phthalimide (**A-1a**, 215 mg, 1.0 mmol), $AgNO_3$ (34 mg, 0.20 mmol) and Selectfluor (706 mg, 2.0 mmol) were placed in a Schlenk tube under nitrogen atmosphere. Dichloromethane (2.5 mL), water (7.5 mL), acetic acid (2.5 mL) and ethyl acetoacetate (0.38 mL, 3.0 mmol) were added successively at room temperature. The reaction mixture was gently refluxed (at ~50 °C) with stirring for 12 h. The resulting mixture was cooled down to room temperature and extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined and dried over anhydrous Na_2SO_4. After the removal of solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with hexane–ethyl acetate (5 : 1, v : v) as the eluent to give the pure product **1a** as a colorless oil. Yield: 338 mg (93%). Ketone **1a** is in equilibrium with its enol form in $CDCl_3$ (in ~86 : 14 ratio at 20 °C), as indicated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.84 (m, 2H), 7.71–7.73 (m, 2H), 4.40–4.61 (m, 1H), 4.17–4.27 (m, 2H), 3.66–3.75 (m, 3H), 2.00–2.52 (m, 5H), 1.59–1.89 (m, 4H), 1.24–1.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3/202.2, 169.2/169.0, 168.2, 133.9, 131.9, 123.1, 91.6/91.5 (2d, J = 167.5 Hz), 61.5, 55.5/55.2 (2d, J = 2.3 Hz), 37.3, 33.3/33.1 (2d, J = 19.3 Hz), 32.5 (d, J = 20.5 Hz)/32.4 (d, J = 20.0 Hz), 29.5/29.0, 24.2 (d, J = 1.5 Hz)/24.1 (2d, J = 1.2 Hz), 13.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ −182.9/−183.5 (2m, 1F); IR (film): ν (cm^{-1}) 1772, 1713; ESI-MS: (m/z) 386.1 (M^+ + Na); HRMS calcd for $C_{19}H_{22}FNNaO_5$ (M + Na): 386.1374, found: 386.1361.

Typical procedure for silver-catalyzed carbofluorination of unactivated alkenes

N-(Pent-4-en-1-yl)phthalimide (**A-1a**, 431 mg, 2.0 mmol), AgOAc (34 mg, 0.20 mmol), Selectfluor (1.41 g, 4.0 mmol) and sodium acetate (489 mg, 6.0 mmol) were placed in a Schlenk tube under nitrogen atmosphere. Water (20 mL) and acetone

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(20 mL) were then added successively at room temperature. The reaction mixture was then stirred at 50 °C for 12 h. The resulting mixture was cooled down to room temperature and extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were combined and dried over anhydrous Na_2SO_4. After the removal of solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with hexane–ethyl acetate (10 : 1, v : v) as the eluent to give the pure product **2a** as a white solid. Mp: 56–58 °C. Yield: 512 mg (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.77 (m, 2H), 7.62–7.66 (m, 2H), 4.35–4.52 (m, 1H), 3.61–3.65 (m, 2H), 2.46–2.57 (m, 2H), 2.07 (s, 3H), 1.45–1.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 168.3, 133.9, 132.0, 123.1, 92.8 (d, J = 167.0 Hz), 38.7 (d, J = 3.8 Hz), 37.4, 32.4 (d, J = 20.5 Hz), 29.9, 28.8 (d, J = 21.2 Hz), 24.3 (d, J = 3.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −183.7 (m, 1F); IR (KBr): ν (cm^{-1}) 1772, 1712, 1615; ESI-MS: (m/z) 314.1 (M^+ + Na); HRMS calcd for $C_{16}H_{18}FNNaO_3$ (M + Na): 314.1163, Found 314.1176.

Acknowledgements

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