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Intermolecular Iodofluoroalkylation of Unactivated Alkynes and Alkenes Mediated by Manganese Catalysts

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Abstract: An approach for iodofluoroalkylation of unactivated alkynes and alkenes facilitated by an earth-abundant and inexpensive manganese catalyst, $Mn_2(CO)_{10}$, is reported. This protocol employs visible light as the energy input and shows a wide substrate scope and high functional-group compatibility. A variety of synthetically useful fluoroalkylated alkyl and alkenyl iodides can be prepared in moderate to excellent yields. The reaction features high efficiency, operational simplicity, scalability, as well as excellent chemo-, regio-, and *E*/*Z* selectivities.

Keywords: Radicals; Iodofluoroalkylation; Manganese; Visible light; Synthetic methods

Introduction

The fluoroalkyl group is a privileged and prominent structural unit found in many drugs and drug candidates.[1] The introduction of fluoroalkyl groups can dramatically enhance the pharmacological profile of biologically active molecules, such as lipophilicity, metabolic stability, and bioavailability.[2] Accordingly, fluoroalkylation of organic molecules has become an important strategy for improvement of the biological activity of potential drug candidates. In light of the importance of this group, significant efforts have been directed toward development of methods for efficient fluoroalkylation reactions.[3] One of the most powerful and straightforward strategies toward incorporating fluoroalkyl substituents into organic molecules is the additions of fluoroalkyl radicals to alkynes and alkenes, which are both ubiquitous feedstock materials.[4] In particular, atom transfer radical addition (ATRA) reactions of fluoroalkyl halides to alkynes is an effective and atom-economical methodology, in which new C-C and C-X bonds (X = I, Br) are simultaneously forged in a single operation, thus rapidly generating molecular complexity. In established ATRA reactions of fluoroalkyl halides to alkynes, fluoroalkyl radicals are usually generated by use of radical initiators, such as AIBN,[5e] $Na_2S_2O_4$/$NaHCO_3$,[5b] Et_3B/O_2,[5a,f] SmI_2,[5c] or by use of UV light irradiation.[5d,g] However, these protocols also revealed some drawbacks such as narrow substrate scope, poor selectivity, and harsh reaction conditions. Besides employing radical initiators, several transition metal-catalyst systems based on Fe,[6] Cu,[7] and Co,[8] have recently been established to promote such ATRA reactions. Despite these achievements, these methods are associated with one or more limitations such as the use of additives (e.g., metal reducing agents and bases), the need for ligands, elevated reaction temperatures and so on. Furthermore, in some alkyne substrates only moderate *E*/*Z* selectivities were obtained.

In recent years, photoredox catalysis enabled by visible light has been recognized as a reliable synthetic avenue to generate carbon-centered radicals in an environment- and user-friendly manner.[9] Fluoroalkyl radicals can be delivered from the corresponding fluoroalkyl halides by oxidative quenching of photoredox catalysts. Stephenson and co-workers reported a photoredox-mediated ATRA reaction of fluoroalkyl halides to alkynes and alkenes using $Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ [dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] or $Ru(bpy)_3Cl_2$ (bpy = 2,2'-bipyridine) as a photocatalyst.[10] The Che group disclosed a Pt(II) photoredox-catalyzed ATRA reaction of iododifluoroacetate to terminal alkynes with moderate to good *E*/*Z* selectivities.[11] However, these elegant photochemical reactions suffer from the use of a precious metal catalyst. Recent attempt to replace expensive metal catalysts, such Ir, Ru, and Pt, with a cheap transition metal, such as Cu, in photoredox-catalyzed ATRA reaction of perfluoroalkyl iodides to alkynes and alkenes has been reported by the group of Reiser,[12] but the photocatalyst $[Cu(dap)_2]Cl$ [dap = 2,9-di(*p*-anisyl)-1,10-phenanthroline] used in this method is not commercially available which needs to be prepared from a multistep procedure. Therefore, a new method allowing for conveniently installing a

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broad range of fluoroalkyl substituents to various organic molecules promoted by readily available and nonprecious metal catalysts under simple and mild reaction conditions will be of high value to the fields of synthetic and medicinal chemistry.

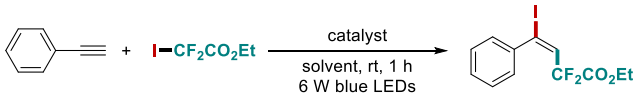
Given our continued interests in the development of sustainable radical transformations employing inexpensive manganese as a high-performance atom transfer catalyst,[13] we reason that a different photochemical reaction strategy in which fluoroalkyl radicals are formed by replacing the fluoroalkyl halide reduction step with a halogen abstraction process through a manganese-catalyzed atom transfer mechanism can nicely complement current protocols for halofluoroalkylation reactions. Manganese is a very ideal candidate for molecular catalysis, since manganese is the twelfth most abundant element and the third most abundant transition metal.[14] Manganese-catalyzed/promoted atom transfer reactions have been shown to be an efficient tool to produce alkyl radicals that can participate in various radical reactions.[15] Yet, ATRA reaction of fluoroalkyl halides to alkenes and alkynes facilitated by manganese catalysts has not been developed thus far. Herein, we disclosed the first example of manganese-mediated iodofluoroalkylation reactions of unactivated alkynes and alkenes. The mild and easy-to-conduct protocol displays excellent chemo-, regio-, and stereoselectivities, and is suited for the late-stage functionalization of complex natural product and drug derivatives.

Results and Discussion

We first selected phenylacetylene **1** as the model substrate and ethyl iododifluoroacetate **2** as the difluoromethyl radical precursor for reaction optimization (Table 1). On the basis of our previous studies,[13] commercially available and cheap $Mn_2(CO)_{10}$ was used as the atom transfer catalyst, and the reaction was conducted in CH_2Cl_2 at room temperature. After 1 h of irradiation with 6 W blue LEDs lights, the expected product **3** was formed in 71% yield with 96:4 *E*/*Z* selectivity (entry 1). The influence of various solvents on this ATRA reaction was then evaluated, and the results identified cyclohexane as the optimal solvent, giving rise to **3** in 85% yield (entries 2-6). A catalyst screening showed that $Mn_2(CO)_{10}$ is the best catalyst (entries 7-12). Lowering $Mn_2(CO)_{10}$ loading to 5 mol% results in a slight decrease in yield (entry 13). Notably, the yield was not affected when the reaction was run open to the air (entry 14). Without a catalyst, the reaction did not proceed (entry 15). Additionally, this ATRA progression was completely suppressed when the reaction was carried out in the absence of visible light irradiation (entry 16). These results confirmed that both $Mn_2(CO)_{10}$ and visible light are indispensable for product formation.

Having established optimal reaction conditions, we next explore the scope of the reaction. As

Table 1. Optimization of the reaction conditions.[a]



1 2 3

Entry	Catalyst (mol%)	Solvent	Yield [%][b]
1	$Mn_2(CO)_{10}$ (10)	CH_2Cl_2	71
2	$Mn_2(CO)_{10}$ (10)	CH_3CN	76
3	$Mn_2(CO)_{10}$ (10)	EtOAc	74
4	$Mn_2(CO)_{10}$ (10)	MeOH	69
5	$Mn_2(CO)_{10}$ (10)	decalin	77
6	$Mn_2(CO)_{10}$ (10)	cyclohexane	85
7	$Mn(CO)_5Br$ (10)	cyclohexane	60
8	$Fe_2Cp_2(CO)_4$ (10)	cyclohexane	43
9	$Mn(OAc)_3$ (10)	cyclohexane	0
10	$Mn(acac)_3$ (10)	cyclohexane	0
11	$Co_2(CO)_8$ (10)	cyclohexane	0
12	$Re_2(CO)_{10}$ (10)	cyclohexane	0
13	$Mn_2(CO)_{10}$ (5)	cyclohexane	80
14[c]	$Mn_2(CO)_{10}$ (10)	cyclohexane	85
15	none	cyclohexane	0
16[d]	$Mn_2(CO)_{10}$ (10)	cyclohexane	0

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), and catalyst in solvent (2.0 mL) were irradiated with 6 W blue LEDs at room temperature under N_2 for 1 h. [b] Isolated yields. *E*/*Z* = 96:4 (by ^{19}F NMR spectroscopy). [c] The reaction was performed under air. [d] The reaction was performed in the dark. acac = acetylacetonate.

summarized in Table 2, the protocol showed a very broad substrate scope, and a number of alkynes were successfully transformed into iododifluoromethylated products in high yields. The ATRA reaction is *E* selective, with an *E*/*Z* ratio larger than 90:10. A wide range of phenylacetylene derivatives containing electron-donating and electron-withdrawing substituents, such as methyl (**4**, **13**, **15**), methoxyl (**5**, **17**), fluoro (**6**), chloro (**7**, **14**), bromo (**8**, **16**), trifluoromethoxy (**9**), ester (**10**), phenyl (**11**), and aldehyde (**12**), worked well, thus affording the desired products in 66-95% yields with 93:7 to 98:2 *E*/*Z* selectivities. Both electron-rich and electron-deficient heterocycles also participated in the reaction to furnish the targeted products with excellent *E*/*Z* selectivities (**18** and **19**). Apart from aromatic terminal alkynes, aliphatic terminal alkynes proved to be viable substrates and reacted with high stereoselectivities to deliver the corresponding products in good yields. It is important to note that a broad range of functional groups including alkenyl (**21**), phenyl (**22**), carboxylic acid (**23**), ether (**24**), ester (**25**), phthalimide (**26**), and alcohol (**27**) moieties are compatible with this process. Moreover, the substrate scope could be expanded to symmetrical internal alkynes, as exemplified by the successful preparation of **28**. When an unsymmetrical internal alkyne such as prop-1-yn-1-ylbenzene was used, the desired product **29** was obtained in 90% yield with complete regioselectivity and excellent stereoselectivity.

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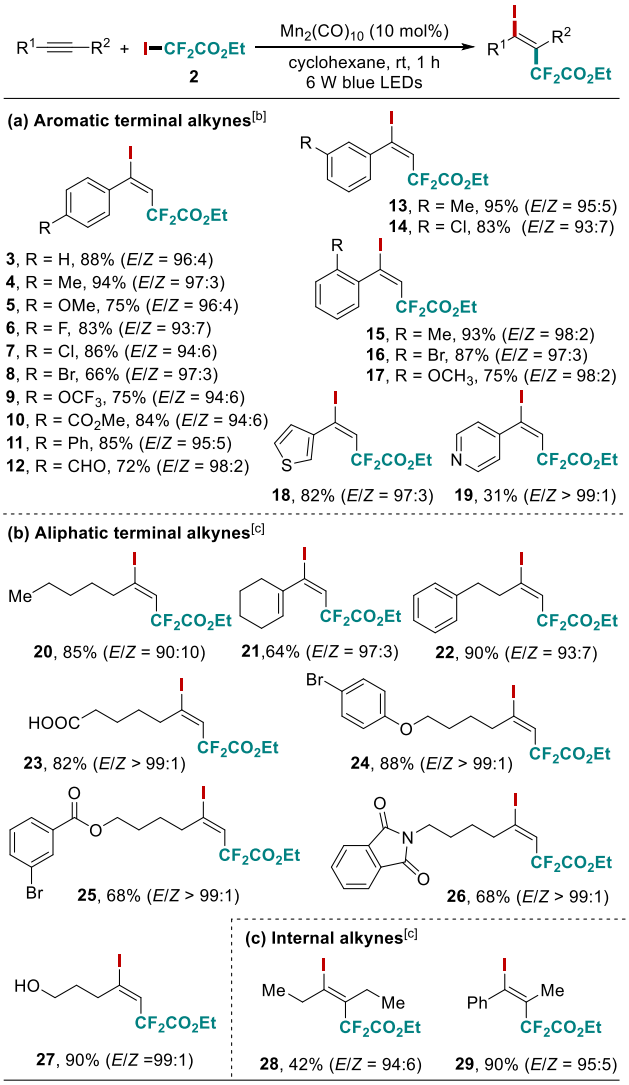
Table 2. Scope of the manganese-mediated iododifluoromethylation of alkynes.[a]

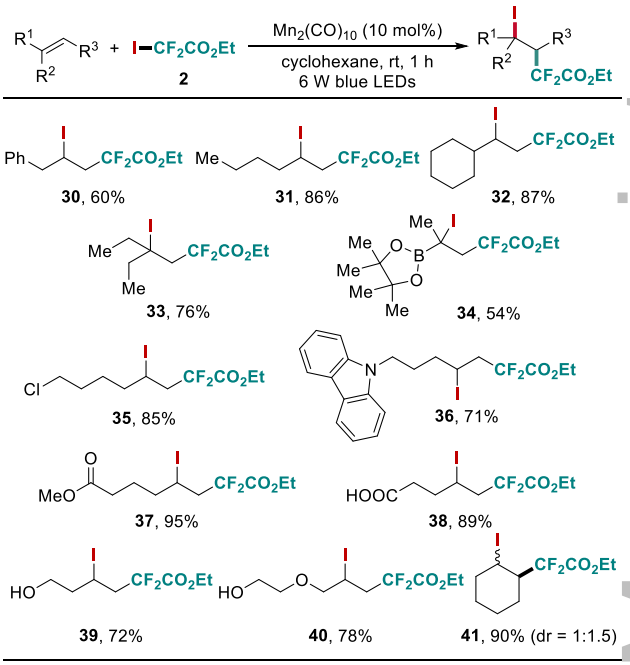


[a] Isolated yields. [b] The *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy. [c] The *E*/*Z* ratios were determined by ^{19}F NMR spectroscopy.

Next, we switched to alkenes as substrates to study the iododifluoromethylation of alkenes (Table 3). We were delighted to find that a diverse set of simple terminal olefins including monsubstituted (**30**, **31**, **32**) and 1,1-disubstituted olefins (**33**, **34**) reacted smoothly with ethyl iododifluoroacetate **2** to produce the corresponding iododifluoromethylated products under the standard reaction conditions. Again, the manganese-mediated method exhibits exceptional functional-group compatibility. A variety of common functionalities including boryl (**34**), primary alkyl chloride (**35**), carbazole (**36**), ester (**37**), carboxylic acid (**38**), alcohol (**39**, **40**), and ether (**40**) were well-tolerated. In addition, an internal olefin such as cyclohexene proved reactive by providing **41** in 90% yield, albeit with low diastereoselectivity.

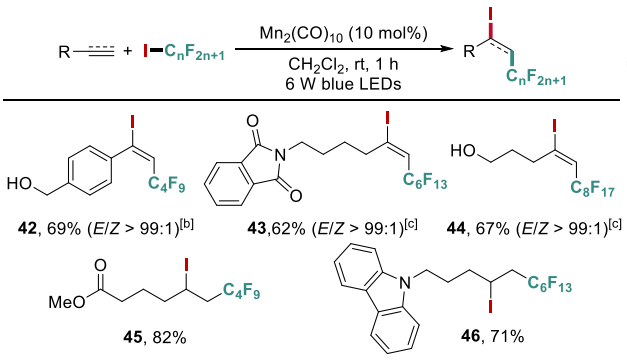
Encouraged by the above success, we decided to apply the method to the iodoperfluoroalkylations of unactivated alkynes and alkenes. As showed in Table 4, the iodoperfluoroalkylation of alkynes with commercially available perfluoroalkyl iodides, such as C_4F_9I, $C_6F_{13}I$, and $C_8F_{17}I$, could be efficiently accomplished by using CH_2Cl_2 as the solvent, leading to products **42-44** in good yields with excellent stereoselectivities. Moreover, we found that the iodoperfluoroalkylation of alkenes proceeded well, and the corresponding products **45** and **46** were obtained in 82% and 71% isolated yields, respectively.

Table 3. Scope of the manganese-mediated iododifluoromethylation of alkenes.[a]



[a] Isolated yields.

Table 4. Scope of the manganese-mediated iodoperfluoroalkylation of alkynes and alkenes.[a]



[a] Isolated yields. [b] The *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy. [c] The *E*/*Z* ratios were determined by ^{19}F NMR spectroscopy.

In light of operational convenience and mild reaction conditions of the method, we anticipate that the manganese-mediated protocol might be applied to the late-stage functionalization of complex small molecules. To this end, a portfolio of natural product and drug derivatives were subjected to the optimized reaction conditions (Table 5). For examples, the steroidal substrate prepared from cholestanol was

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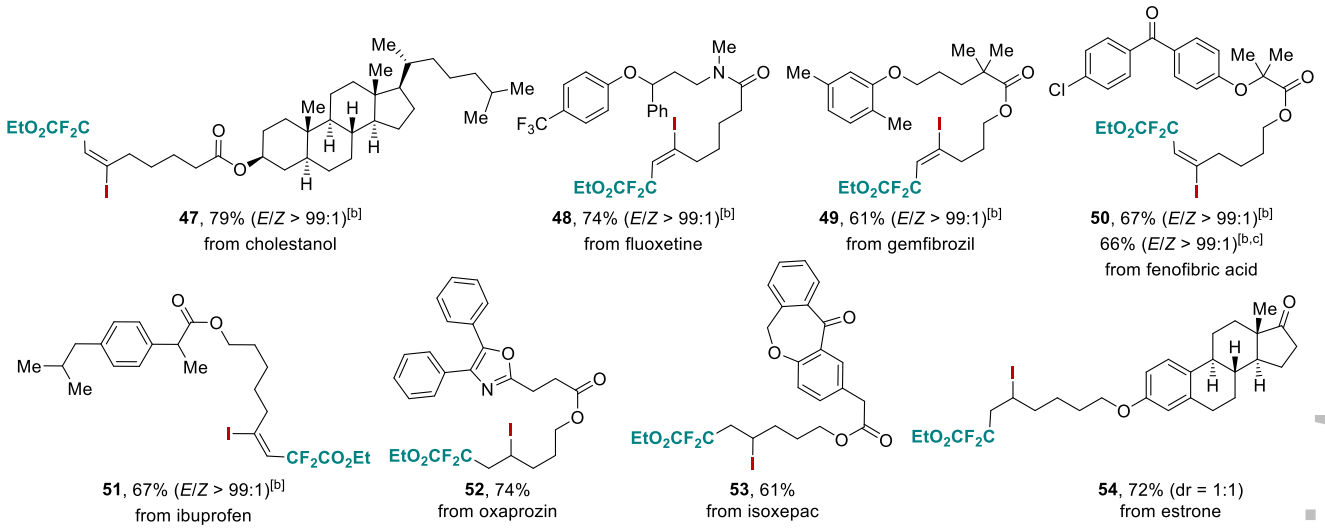
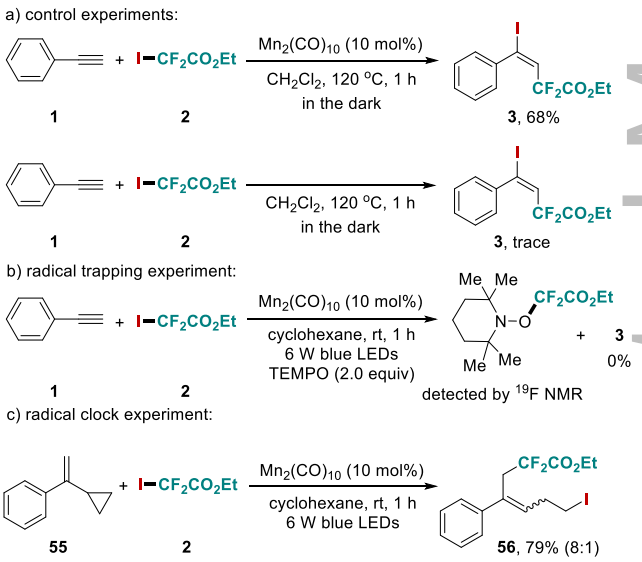
Table 5. Late-stage functionalization of complex molecules.[a]



[a] Isolated yields. [b] The *E*/*Z* ratios were determined by ^{19}F NMR spectroscopy. [c] 0.858 g of **50** prepared.

readily converted to product **47** in 79% yield with >99:1 *E*/*Z* selectivity. Several drug derived substrates, such as fluoxetine, gemfibrozil, fenofibric acid, and ibuprofen, furnished the corresponding products **48**-**51** in synthetically useful yields with excellent stereoselectivities. Remarkably, the transformation allowed the larger-scale synthesis of **50** with retention of the yield and stereoselectivity, thus showing the practicality and efficiency of this methodology. Furthermore, an olefin derived from drug oxaprozin underwent late-stage modification to afford product **52** in 74% yield. An isoxepac derived olefin was also found to be compatible with this methodology to provide the expected product **53** in 61% yield. Finally, an estrone derivative was successfully functionalized to deliver product **54** in good yield. Taken together, the results illustrated in Table 2, 3, 4, and 5 highlighted the high chemo-, regio-, and stereoselectivities of our method.

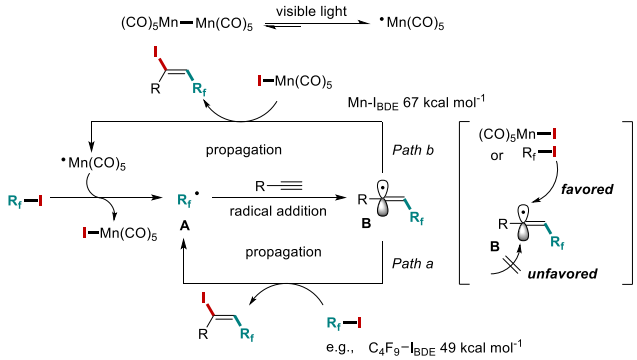
To probe the mechanism of the iodofluoroalkylation process, we carried out a series of mechanistic experiments (Scheme 1). The Mn-Mn bond in $Mn_2(CO)_{10}$ has the low bond dissociation energy (BDE of Mn-Mn bond = 15 kcal mol^{-1}).[16] It was reported that $Mn_2(CO)_{10}$ generated $^{\cdot}Mn(CO)_5$ through thermal homolysis of its Mn-Mn bond.[17] To verify whether our reaction can take place under heating conditions, we ran a reaction of **1** with **2** at 120 °C without visible light, and product **3** was isolated in 68% yield. Performing the reaction in the absence of $Mn_2(CO)_{10}$ afforded traces of **3** (Scheme 1a). These results suggest that $^{\cdot}Mn(CO)_5$ is capable to trigger the iodofluoroalkylation. Next, we performed radical trapping experiment and radical clock experiment. When 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the standard reaction conditions, the reaction was completely shut down, while TEMPO-CF_2CO_2Et adduct could be detected by ^{19}F NMR (Scheme 1b). Upon using radical clock substrate **55**, the ring-opened product **56** was isolated in 79% yield (Scheme 1c). These observations provided solid evidence for a fluorolkyl radical addition pathway. Finally, we conducted the reaction in the presence of some nucleophiles such as MeOH and H_2O. As expected, no corresponding adduct product was detected, thus implying that iodine atom transfer to a C-radical intermediate rather than carbocation is operative.



Scheme 1. Mechanistic studies.

Based on these experimental results, a plausible reaction mechanism is proposed in Scheme 2 (with the iodofluoroalkylation of alkynes as an example). Under visible-light irradiation, $Mn_2(CO)_{10}$ is homolyzed to $^{\cdot}Mn(CO)_5$.[13,15h-j] Then, the formed $^{\cdot}Mn(CO)_5$ can abstract the iodine atom from the C-I bond of fluoroalkyl iodide (R_fI) to generate the fluoroalkyl radical **A**, which further adds to the less sterically hindered terminal carbon of alkyne to yield the vinyl radical **B**. Finally, radical **B** abstracts the iodine atom from R_fI (*path a*) or $IMn(CO)_5$ (*path b*) to deliver the desired iodofluoroalkylation product with concurrent regeneration of fluoroalkyl radical **A**

or ·Mn(CO)$_5$, thereby sustaining the radical chain. For *path a* and *path b*, we currently consider that *path a* might be a major reaction pathway due to the low BDE of R_f-I bond (Mn-I bond BDE = 67 kcal mol^{-1} vs C_4F_9-I bond BDE = 49 kcal mol^{-1})[15i,16] and the low concentration of IMn(CO)$_5$ compared to R_fI. However, the possibility of *path b* can be not completely excluded, and this process is likely to represent a minor reaction pathway. The high *E*-selectivity of the reaction can be rationalized by the electrostatic repulsion of the R_f group and the incoming R_fI or IMn(CO)$_5$ during the iodine atom transfer process.[18]



Scheme 2. Proposed reaction mechanism.

Conclusion

In conclusion, we have developed the first ATRA reaction of fluoroalkyl iodides to unactivated alkynes and alkenes by employing a commercially available and inexpensive manganese catalyst. The operationally simple and redox-neutral method proceeds with high functional-group tolerance under mild reaction conditions, allowing for the preparation of a broad scope of synthetically valuable fluoroalkylated alkyl and alkenyl iodides with excellent chemo-, regio-, and *E*/*Z* selectivities. Additionally, the robust and practical nature of this methodology is demonstrated by the late-stage functionalization of complex molecules and the larger-scale synthesis. These transformations that combine earth-abundant 3d-non-noble metals and visible light meet the criteria for green and sustainable synthetic chemistry. Further application of manganese catalyst in ATRA reactions are currently in progress in our laboratory.

Experimental Section

General procedure for manganese-mediated ATRA reaction of ethyl iododifluoroacetate to alkynes:

Alkyne (0.2 mmol, 1.0 equiv), ethyl iododifluoroacetate (0.3 mmol, 1.5 equiv), and $Mn_2(CO)_{10}$ (0.02 mmol, 0.1 equiv) were placed in a 10 mL Schlenk tube under air. Then cyclohexane (2.0 mL) was added with a syringe. The reaction mixture was stirred and irradiated by using 6 W blue LEDs at room temperature for 1 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford the product.

General procedure for manganese-mediated ATRA reaction of ethyl iododifluoroacetate with alkenes:

Alkene (0.2 mmol, 1.0 equiv), ethyl iododifluoroacetate (0.3 mmol, 1.5 equiv), and $Mn_2(CO)_{10}$ (0.02 mmol, 0.1 equiv) were placed in a 10 mL Schlenk tube under air. Then cyclohexane (2.0 mL) was added with a syringe. The reaction mixture was stirred and irradiated by using 6 W blue LEDs at room temperature for 1 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford the product.

General procedure for manganese-mediated ATRA reaction of perfluoroalkyl iodides with alkynes:

Alkyne (0.2 mmol, 1.0 equiv), perfluoroalkyl iodide (0.3 mmol, 1.5 equiv), and $Mn_2(CO)_{10}$ (0.02 mmol, 0.1 equiv) were placed in a 10 mL Schlenk tube under air. Then CH_2Cl_2 (2.0 mL) was added with a syringe. The reaction mixture was stirred and irradiated by using 6 W blue LEDs at room temperature for 1 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford the product.

General procedure for manganese-mediated ATRA reaction of perfluoroalkyl iodides with alkenes:

Alkene (0.2 mmol, 1.0 equiv), perfluoroalkyl iodide (0.3 mmol, 1.5 equiv), and $Mn_2(CO)_{10}$ (0.02 mmol, 0.1 equiv) were placed in a 10 mL Schlenk tube under air. Then CH_2Cl_2 (2.0 mL) was added with a syringe. The reaction mixture was stirred and irradiated by using 6 W blue LEDs at room temperature for 1 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford the product.

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FULL PAPER

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