RSC Advances

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

www.rsc.org/advances

RSC Advances

Dynamic Article Links▶

COMMUNICATION

Regioisomerized atom transfer radical addition (ATRA) of olefins with dichlorofluorocarbons

Bo Zhao,[a] Ju-You Lu,[a] Yang Li,[a] Dong-Huai Tu,[a] Zhao-Tie Liu,*[b] Zhong-Wen Liu[b] and Jian Lu*[a]
Received (in XXX, XXX) XthXXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

The Cu(I) catalysed atom transfer radical addition of dichlorofluorocarbons to olefins via C-Cl bond homolysis is successfully carried out. Isomerization of *vic* into *gem*-dichlorofluorocarbons is observed by using CuCl as a catalyst
10 and TPMA as a ligand, indicating a radical addition mechanism of this reaction procedure.
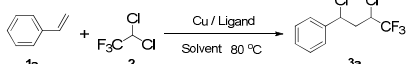
Introduction

Fluorinated compounds have played an important role in the field of pharmaceutical chemistry, agrochemistry, and material
15 science.[1,2] Significant efforts have been made to incorporate fluorinated groups into organic compounds. Atom transfer radical addition (ATRA) reaction between halofluorocarbons and olefins is a direct and atom economic way for constructing carbon-halogen and carbon-carbon bonds.[3,4] The resulting 1,3-adducts of
20 ATRA can introduce both halogen and the fluoroalkyl groups into the carbon backbone, which are easily transformed into aralkanes,[5] conjugated dienes[6] or cyclopropanes.[7]

Current ATRA methods for introduction of fluorinated groups into olefins are not many. Okano and co-workers found the
25 reaction of aryltrifluoroethyl bromides with terminal olefins in the presence of Cu(I)/amine complex at 180 °C.[8] Domowski[9] and Severin[10] reported that halothane could undergo addition to olefins with sodium dithionite (Na$_2$S$_2$O$_4$) or Cp*RuCl$_2$(PPh$_3$) as initiators. Here, we disclose a copper catalysed
30 difunctionalization of olefins with commercial available dichlorofluorocarbons under mild conditions, and several diastereomixtures were obtained. An interesting regioisomerization process was observed, indicating that the reaction follows a radical addition mechanism. The fluorinated
35 products could be readily converted to synthetic useful compounds such as fluoride containing cyclopropanes.

Results and discussion

Initially, the addition of dichlorotrifluoroethane (**2**) to styrene was chosen as a model reaction. A solution of styrene (**1a**) and **2**
40 in DMF was stirred using CuCl (3 mol%) as a catalyst. In the absence of ligand, 1,3-dichloro-4,4,4-trifluorobutyl benzene (**3a**) was formed in a poor yield of 5% (Table 1, entry 1). Then the influence of ligands was examined, tris(2-pyridylmethyl)amine (TPMA) was found to be the best ligand for the reaction, other
45 nitrogen ligands such as tetramethylethylenediamine (TMEDA), 2,2'-bipyridine (Bpy), 1,10-phenanthroline (Phen), 1,1,2,3,3-pentamethyldiethylenetriamine (PMEDTA), 1,1,4,7,10,10-

hexamethyltriethylenetetraamine (HMTETA) and tris(2-dimethylaminoethyl)amine (Me$_6$TREN) were less effective
50 (Table 1, entries 2-8). Next, a variety of solvents was explored with *N,N*-dimethylformamide (DMF) giving the best yield (Table 1, entries 9-13). Further, we studied the influence of copper sources on the reaction, and CuCl was the best for the reaction (Table 1, entries 14-17). Finally, we investigated the temperature
55 and catalyst loading. Raising temperature to 90 °C, resulted in the formation of **3a** in an excellent yield of 93% (Table 1, entry 18). Reducing the loading of CuCl and TPMA to 2 mol%, the yield decreased to 74% (Table 1, entry 19). It should be mentioned that similar yield was obtained with CuCl$_2$ instead of CuCl in the
60 presence of suitable amount of ascorbic acid (Table 1, entry 20-22).
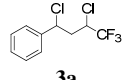
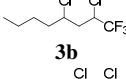**Table 1** Optimization of the reaction conditions[a]
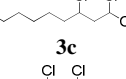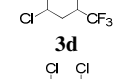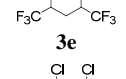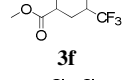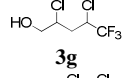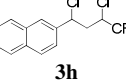
entry	ligand	solvent	Cu source	Yield[b] (%)
1	-	DMF	CuCl	5
2	TMEDA[c]	DMF	CuCl	47
3	Bpy[c]	DMF	CuCl	51
4	Phen[c]	DMF	CuCl	84
5	PMEDTA[d]	DMF	CuCl	73
6	HMTETA[d]	DMF	CuCl	71
7	Me$_6$TREN[d]	DMF	CuCl	49
8	TPMA[d]	DMF	CuCl	88
9	TPMA	CH$_3$CN	CuCl	78
10	TPMA	MeOH	CuCl	52
11	TPMA	DCM	CuCl	76
12	TPMA	Toluene	CuCl	81
13	TPMA	DMSO	CuCl	10
14	TPMA	DMF	Cu	66
15	TPMA	DMF	CuBr	76
16	TPMA	DMF	CuI	37
17	TPMA	DMF	CuCl$_2$	0
18[e]	TPMA	DMF	CuCl	93
19[f]	TPMA	DMF	CuCl	74
20[g]	TPMA	DMF	CuCl$_2$/VC	14
21[h]	TPMA	DMF	CuCl$_2$/VC	35
22[i]	TPMA	DMF	CuCl$_2$/VC	94

Reaction conditions: [a] **1a** (33 mmol), **2** (100 mmol), catalyst (3 mol%),
65 solvent (10 mL), 80 °C, 6 h. [b] yields determined by GC. [c] ligand (6 mol%). [d] ligand (3 mol%). [e] reaction temperature 90 °C. [f] catalyst (2 mol%). [g] **1a** (33 mmol), **2** (100 mmol), catalyst (3 mol%), solvent (10 mL), 90 °C, 6 h, ascorbic acid (6 mol%), [h] ascorbic acid (15 mol%), [i] ascorbic acid (24 mol%).

70 This strategy was applicable to a variety of terminal alkenes,

giving the desired products with various functional groups. The results are summarized in Table 2. Generally, substrates bearing an electron donating group afforded higher yields (Table 2, **3a-3c**) than those substitutes with electron-withdrawing group. For instance, the yield of **3a** was significantly higher than **3e**. The additions to halide or pseudohalide alkenes produced lower yields of the monoadducts (Table 2, **3d** and **3f**). This was presumably due to a compete addition between trifluorochloroethyl and its monoadduct radical.[11] Functional groups such as ester group and hydroxyl group (Table 2, **3f** and **3g**) were well tolerated, and 2-vinylnaphthalene (Table 2, **3h**) underwent addition with an impressive 95% yield.

Table 2 Radical addition of **2** into various alkenes catalysed by copper[a]

entry	alkenes	products	Yield[b] (%)
1	**1a**	**3a**	93
2	**1b**	**3b**	59
3	**1c**	**3c**	63
4	**1d**	**3d**	31
5	**1e**	**3e**	15
6	**1f**	**3f**	53
7	**1g**	**3g**	36
8	**1h**	**3h**	95
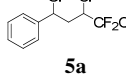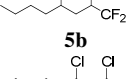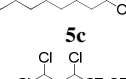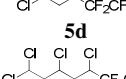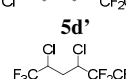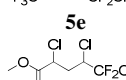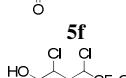
[a] Reaction conditions: alkene (33 mol), **2** (100 mol), catalyst (3 mol%), ligand (3 mol%), DMF (10 mL), 90 °C, 6 h. [b] isolated yields.

In order to further demonstrate the utility of this protocol, dichloropentafluoropropane (**4**) was examined. Largely used for cleaning applications, **4** contained almost equal amounts of two isomers exhibited very similar properties.[12] Interestingly, the reaction of olefins with **4** afforded a sole product of **5**, and this procedure was further investigated at lower temperatures. Apparent variation in isomeric ratio could be detected from the initial formation of monoadducts, and it seems that only *gem*-dichloropentafluoropropane would undergo ATRA as abstract energy was much lower. A dimer by-product (Table 3, **5d'**) was successfully isolated from the addition to chloroethylene.

This regioisomerized radical addition process was further explored by the reaction of 1,2-dichlorotetrafluoroethane (**6**) with olefins.[13] Compound **7** was obtained as the major product in these reactions (Table 4). An elevated temperature used in the process, which simultaneously increased the propagation rate constants of olefin, as a result, the target monoadducts were complicated by

polymers. For simple olefins (Table 4, **7b** and **7c**) with less polymeric liability in free radical process, adducts obtained in moderated yield, halide or alcohol olefins provided **7** in dropping yield (Table 4, **7d** and **7g**) which can be attributed to incomplete conversions, and significantly higher catalyst loadings were required for more active alkenes such as styrene (Table 4, **7a**) and methyl acrylate (Table 4, **7f**). It is reasonable to assume that regioisomerization was promoted by radical from *gem*-dichlorocarbons, and ceased at the end of addition.

Table 3 Radical addition of **4** into various alkenes catalysed by copper[a]

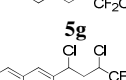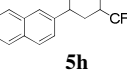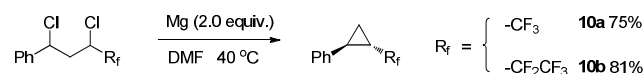| entry	alkenes	products	Yield[b] (%)
1	**1a**	**5a**	95
2	**1b**	**5b**	67
3	**1c**	**5c**	64
4	**1d**	**5d**	29
		5d'	13
5	**1e**	**5e**	18
6	**1f**	**5f**	46
7	**1g**	**5g**	45
8	**1h**	**5h**	92

[a] Reaction conditions: alkene (33 mmol), **4** (100 mmol), catalyst (3 mol%), ligand (3 mol%), DMF (10 mL), 80 °C, 6 h. [b] isolated yields.

In respect that trifluoromethyl group always withdraw electron and strongly affects chemical reactivity,[14] dichlorofluorocarbon without trifluoromethyl group (**8**) was investigated. An elevating temperature to 130 °C furnished the desired halogenated product (Table 5) even in a low yield due to less stable radical species. As expected, electron-deficient and sterically hindered substrates hardly proceeded, aliphatic olefins (Table 5, **9b** and **9c**) were moderated converted to the corresponding fluorinated products, and chloroethene (Table 5, **9d**) was less reactive because of volatile nature. Owning to free radical polymerization, addition was inefficient in the case of methyl acrylate (Table 5, **9f**).

$$\text{Ph-CHCl-CH}_2\text{-CHCl-R}_f \xrightarrow[\text{DMF } 40\,^{\circ}\text{C}]{\text{Mg (2.0 equiv.)}} \text{Ph-cyclopropane-R}_f$$

R_f = { -CF₃ **10a** 75% ; -CF₂CF₃ **10b** 81% }

Scheme 1 Dechlorination into cyclopropane

The addition products could be readily converted to fluoride

containing cyclopropanes (Scheme 1). Conventional method for generation of cyclopropane has been developed by treating 1,3-dichlorides with reducing agents.[15] Accordingly, **3a** or **4a** in combination with magnesium (Mg) was used for dechlorination (Scheme 1). In contrast to reported work, a slightly excess of Mg was required to produce mainly *trans* cyclopropanes.

Conclusions

In summary, difunctionalization of olefins with commercial dichlorofreons over a simple copper catalyst was developed, featuring an interesting regioisomerization process. The reactions could be carried out at a relatively large scale, allowing for the synthesis of a variety of fluorine containing compounds. Further efforts to improve catalytic performance and dechlorination of the addition products are underway in our laboratory.

Table 4 Radical addition of **6** into various alkenes catalysed by copper [a]

entry	alkenes	products	Yield[b] (%)
1[c]	**1a**	**7a**	32
2	**1b**	**7b**	51
3	**1c**	**7c**	53
4	**1d**	**7d**	20
5[c]	**1f**	**7f**	11
6	**1g**	**7g**	17

Reaction conditions: [a] alkene (33 mmol), **6** (100 mmol), catalyst (3 mol%), ligand (3 mol%), DMF (10 mL), 110 °C, 10 h. [b] isolated yields. [c] catalyst (5 mol%), ligand (5 mol%).

Table 5 Radical addition of **8** into various alkenes catalysed by copper [a]

entry	alkenes	products	Yield[b] (%)
1	**1b**	**9b**	46
2	**1c**	**9c**	45
3	**1d**	**9d**	15
4[c]	**1f**	**9f**	17

Reaction conditions: [a] alkene (33 mmol), **8** (100 mmol), catalyst (3 mol%), ligand (3 mol%), DMF (10 mL), 130 °C, 14 h. [b] isolated yields. [c] catalyst (5 mol%), ligand (5 mol%).

Notes and references

[a] Department of Catalysis, Xi'an Modern Chemistry Research Institute, Xi'an, 710065, China. Tel: 86 29 88291213. E-mail: lujian204@263.net
[b] Key Laboratory of Applied Surface and Colloid Chemistry (Ministry of Education), School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an, 710119, China. Tel: 86 29 81530802. E-mail: ztliu@snnu.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, ^{1}H, ^{13}C, ^{19}F NMR, IR and MS spectra. See DOI: 10.1039/b000000x/

1 (a) P. Jeschke, *Chem. Bio. Chem.*, 2004, **5**, 570-589; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320-330; (c) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. D. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432-2506; (d) C. Zhang, *Adv. Synth. Catal.*, 2014, **356**, 2895-2906.

2 (a) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214-231; (b) M. Schlosser, *Angew. Chem., Int. Ed.*, 2006, **45**, 5432-5438; (c) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881-1886; (d) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359-4369.

3 (a) M. J. W. Taylor, W. T. Eckenhoff and T. Pintauer, *Dalton Trans.*, 2010, **39**, 11475-11482; (b) M. N. C. Balili and T. Pintauer, *Dalton Trans.*, 2011, **40**, 3060-3066; (c) W. T. Eckenhoff and T. Pintauer, *Dalton Trans.*, 2011, **40**, 4909-4917.

4 (a)Y. Sawama, R. Nakatani, T. Imanishi, Y. Fujiwara, Y. Monguchi and H. Sajiki, *RSC Adv.*, 2014, **4**, 8657-8660; (b) D. Motoda, H. Kinoshita, H. Shinokubo and K. Oshima, *Adv. Synth. Catal.*, 2002, **344**, 261-265.

5 (a) Y. Xu and W. R. Dolbier, Jr., *J. Org. Chem.*, 1997, **62**, 6503-6506; (b) Y. Xu, W. R. Dolbier, Jr. and X. X. Rong, *J. Org. Chem.*, 1997, **62**, 1576-1577. (c) X. J. Tang and Q. Y. Chen, *Org. Lett.*, 2012, **14**, 6214-6217; (d) X. J. Tang and Q. Y. Chen, *J. Fluor. Chem.*, 2015, **169**, 1-5.

6 T. Okano, H. Sugiura, M. Fumoto, H. Matsubara, T. Kusukawa and M. Fujita, *J. Fluor. Chem.*, 2002, **114**, 91-98.

7 W. Dmowski and K. Piasecka-Maciejewska, *J. Fluor. Chem.*, 2005, **126**, 877-882.

8 K.Thommes, G.Kiefer, R. Scopelliti and K. Severin, *Angew. Chem. Int. Ed.*, 2009, **48**, 8115–8119.

9 J. Ignatowska and W. Dmowski, *J. Fluor. Chem.*, 2006, **127**, 720-729.

10 J. Risse, M. A. Fernández-Zúmel, Y. Cudré and K. Severin, *Org. Lett.*, 2012, **14**, 3060-3063.

11 (a) W. Jakubowski, N. V. Tsarevsky, T. Higashihara, R. Faust and K. Matyjaszewski, *Macromolecules*, 2008, **41**, 2318-2323; (b) K. Matyjaszewski, *Macromolecules*, 2012, **45**, 4015-4039. (c) K. Schröder, R. T. Mathers, J. Buback, D. Konkolewicz, A. J. D. Magenau and K. Matyjaszewski, *Macro. Lett.*, 2012, **1**, 1037-1040; (d) R. M. Johnson, C. Ng, C. C. M. Samson and C. L. Fraser, *Macromolecules*, 2000, **33**, 8618-8628; (e) W, A. Braunecker, N. V. Tsarevsky, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2009, **42**, 6348-6360.

12 (a) Y. Tanaka, Y. F. Xiao, S. Matsuo and T. Makita, *Fluid Phase Equilibria*, 1994, **97**, 155-165; (b) B. Kanegsberg and E. Kanegsberg, *Metal Finishing*, 2012, **110**, 28-29.

13 (a) H. Bozorgzadeh, E. Kemnitz, M. Nickkho-Amiry, T. Skapin and J. M. Winfield, *J. Fluor. Chem.*, 2001, **107**, 45-52; (b) N. V. Ignat'ev, U. Welz-Biermann, U. Heider, A. Kucheryna, S. von Ahsen, W. Habel, P. Sartori and H. Willner, *J. Fluor. Chem.*, 2003, **124**, 21-37.

14 (a) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470-477; (b) A. Studer, *Angew. Chem. Int. Ed.*, 2012, **51**, 8950-8958; (c) C. Feng and T. P. Loh, *Angew. Chem. Int. Ed.*, 2013, **52**, 12414-12417.

15 (*a*) F. Diaba, A. Martínez-Laporta, J. Bonjoch, A. Pereira, J. M.
       Muñoz-Molina, P. J. Pérez and T. R. Belderrain, *Chem. Commun.*,
       2012, **48**, 8799-8801; (*b*) M. Braun and M. Christl, *Org. Biomol.
       Chem.*, 2012, **10**, 4400; (*c*) M. A. Fernández-Zúmel, C. Buron and
 5   K. Severin, *Eur. J. Org. Chem.*, 2011, 2272–2277.

This journal is © The Royal Society of Chemistry [year]