Tetrahedron xxx (2013) 1–6

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Cobalt-catalyzed cross-coupling reaction of arylzinc reagents with ethyl bromodifluoroacetate

Keisuke Araki, Munenori Inoue *

Sagami Chemical Research Institute (SCRI), 2743-1 Hayakawa, Ayase, Kanagawa 252-1193, Japan

ARTICLE INFO

Article history:
Received 27 November 2012
Received in revised form 5 March 2013
Accepted 9 March 2013
Available online xxx

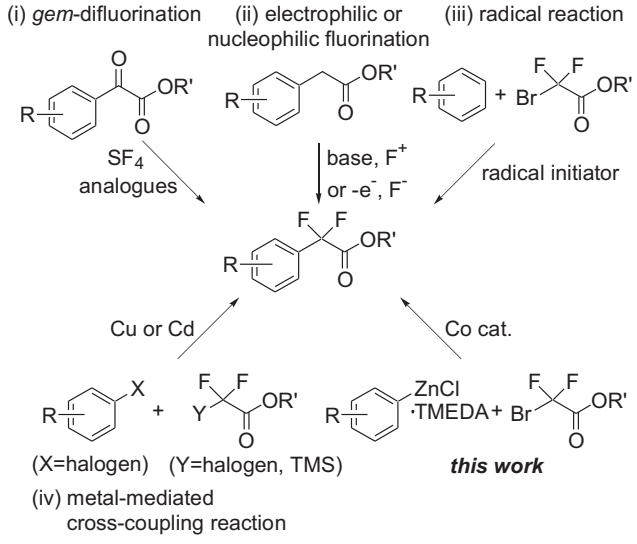
Keywords:
Cobalt-catalyzed
Cross-coupling
Arylzinc reagent
Alkoxycarbonyldifluoromethylation
Ethyl aryldifluoroacetate

ABSTRACT

Transition metal-catalyzed cross-coupling reactions of arylmetal reagents with ethyl bromodifluoroacetate have been explored. After intensive investigations, we have successfully found that a cobalt-catalyzed cross-coupling reaction (catalytic alkoxycarbonyldifluoromethylation) of arylzinc reagents with ethyl bromodifluoroacetate smoothly proceeded to afford the corresponding ethyl aryldifluoroacetates in moderate to good yields.

1. Introduction

Organofluorine compounds have attracted considerable attention from the fields of medicinal chemistry, agricultural chemistry, and material science because they show unique chemical, physical, and biological properties.[1] Therefore, the selective introduction of a fluorine-containing functional group at the desired position of organic substrates to synthesize various kinds of organofluorine compounds is one of the most important topics in current organic chemistry. Among them, aryldifluoroacetic acid derivatives have been known as important biological active and functionalized compounds[2] and, to date, several synthetic methods to prepare aryldifluoroacetic acid derivatives have been disclosed as follows (Scheme 1): (i) *gem*-difluorination of arylglyoxylic acid derivatives with sulfur tetrafluoride (SF_4) analogues, such as diethylaminosulfur trifluoride (DAST),[3a,b] bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor),[3c] diethylaminodifluorosulfinium tetrafluoroborate (XtalFluor-E),[3d] and 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead),[3e] (ii) α-fluorination of arylacetates with electrophilic or nucleophilic fluorinating reagents,[4] (iii) radical-mediated alkoxycarbonyldifluoromethylation using difluorohaloacetates,[5] and (iv) metal-mediated cross-coupling reaction using difluorohaloacetates or α-silyldifluoroacetates.[6,7] While transition-metal catalyzed cross-coupling reactions play an important role in the formation of carbon–carbon bonds in organic synthesis, most of the metal-mediated cross-coupling reactions of difluorohaloacetates with arylmetal species or halogenated aromatics proceeded in the presence of stoichiometric amounts of Cu or Cd metals.[6] Recently,



Scheme 1. Methods for the preparation of aryldifluoroacetic acid derivatives.

* Corresponding author. Tel.: +81 467 77 4208; fax: +81 467 77 4113.
e-mail address: inoue@sagami.or.jp (M. Inoue).

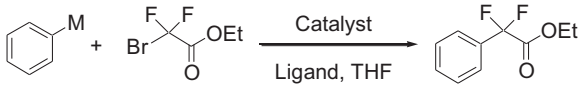
0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.03.041

Amii et al. disclosed copper-catalyzed cross-coupling reactions of aryl iodides with α-silyldifluoroacetates and they demonstrated the conversion of the resulting aryldifluoroacetates to the corresponding α,α-difluorotoluene derivatives.[7] While several methods are available to synthesize aryldifluoroacetic acid derivatives, it is still required to develop a facile method to access to those compounds. During the course of our development of the transition-metal catalyzed introduction of a fluorine-containing functional group to aromatic rings,[8] we initiated a project to develop a novel catalytic alkoxycarbonyldifluoromethylation reaction.[9] Herein, we would like to report a cobalt-catalyzed cross-coupling reaction of arylzinc reagents **3** with ethyl bromodifluoroacetate (**4**).

2. Results and discussion

At the beginning, we investigated the cross-coupling reactions between various phenylmetal species **1a**–**3a** and ethyl bromodifluoroacetate (**4**) as shown in Table 1. The initial attempts of alkoxycarbonyldifluoromethylation reactions catalyzed by Pd,[10] Fe,[11] or Ni[12] complexes gave disappointing results, leading to the formation of trace amounts (<5%) of the expected coupling product (entries 1–3) even though the corresponding cross-coupling reactions with ethyl bromoacetate under the same reaction conditions were reported to proceed in good yield.[10–12] Fortunately, taking advantage of Yorimitsu and Oshima's procedure,[13] the cobalt-catalyzed cross-coupling reaction[14,15] of phenylmagnesium bromide (**2a**) with **4** in the presence of cobalt (II) chloride and *trans*-1,2-bis(dimethylamino)cyclohexane (**6**) gave promising results (entry 4), furnishing the desired ethyl 2,2-difluoro-2-phenylacetate (**5a**) in 22% yield (based on ^{19}F NMR).

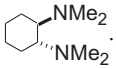
Table 1
Metal-catalyzed cross-coupling reaction of ethyl bromodifluoro-acetate with phenylmetal species



1a: M=B(OH)$_2$
2a: M=MgBr
3a: M=ZnCl

4 **5a**

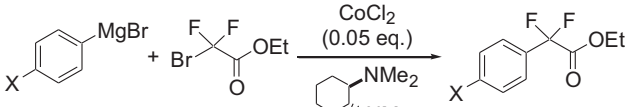
Entry	Ph–M	Catalyst, ligand	Conditions	Yield[a]
1	**1a** (1.2 equiv)	Pd (OAc)$_2$ (0.03 equiv) P (*o*-Tol)$_3$ (0.09 equiv) K_2CO_3 (5.0 equiv)	rt, 20 h	<5%
2	**2a** (1.2 equiv)	$FeCl_3$ (0.05 equiv) TMEDA (1.2 equiv)	0 °C, 1 h	<5%
3	**3a** (2.0 equiv)	Ni(acac)$_2$ (0.01 equiv) PPh_3 (0.01 equiv)	0 °C, dropwise for 30 min; 10 min	<5%
4	**2a** (1.2 equiv)	$CoCl_2$ (0.05 equiv) **6** (0.06 equiv)	0 °C, 5 min; rt, 20 min	22%

6 : 

[a] ^{19}F NMR yield (benzotrifluoride was used as an internal standard).

Thus, we decided to focus on the cobalt-catalyzed cross-coupling reaction and a further investigation was carried out as depicted in Table 2. While increasing the amount of the Grignard reagent to 2.4 equiv raised the yield slightly (entry 1), the yield was dramatically improved by slow addition of the Grignard reagent to a mixture of ethyl bromodifluoroacetate (**4**) and the cobalt catalyst in THF, leading to produce a 70% yield of **5a** (entry 2). Next, we employed other Grignard reagents under the slow addition condition. The reaction using 4-fluorophenylmagnesium bromide (**2b**) possessing an electron-withdrawing group produced ethyl 2,2-difluoro-2-(4-fluorophenyl)acetate (**5b**) in 71% yield (entry 3), however, the use of 4-methoxyphenylmagnesium bromide (**2c**) having an electron-donating group diminished the yield of ethyl 2,2-difluoro-2-(4-methoxyphenyl)acetate (**5c**) (42%, entry 4). We reasoned that the relative high reactivity of **2c** may cause side reactions such as an addition of the Grignard reagent to the carbonyl group of ethyl bromodifluoroacetate and the bromine–magnesium exchange reaction,[16] lowering the yield of the desired product.

Table 2
Co-catalyzed cross-coupling reaction of ethyl bromodifluoro-acetate with Grignard reagents



2a: X=H
2b: X=F
2c: X=OMe

4

6 (0.06 eq.)
THF

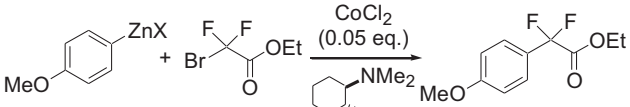
5a: X=H
5b: X=F
5c: X=OMe

Entry	Ar–MgBr	Conditions	Yield[a]
1	**2a** (2.4 equiv)	0 °C, 5 min; rt, 20 min	34%
2	**2a** (1.3 equiv)	0 °C, dropwise for 30 min; 0 °C, 10 min	70%
3	**2b** (1.3 equiv)	rt, dropwise for 2 h; rt, 10 min	71%
4	**2c** (1.3 equiv)	rt, dropwise for 2 h; rt, 10 min	42%

[a] ^{19}F NMR yield (benzotrifluoride was used as an internal standard).

To avoid these unwanted side reactions, instead of using Grignard reagents we then explored the Co-catalyzed reaction of arylzinc reagents[14d] having low nucleophilicity toward the carbonyl group and the bromine atom of **4** (Table 3). The first attempt using 4-methoxyphenylzinc chloride (**3c**), prepared from **2c** and zinc chloride, unfortunately did not proceed (entry 1), but any undesired side reaction was not observed. To enhance the reactivity of the zinc reagent, *N*-methyl-2-pyrrolidone (NMP) was employed as an additive,[17] however, the yield was not improved (entry 2). To our delight, we found that the coupling reaction took place to produce the desired product **5c** in moderate yield when **3c**–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) complex, prepared by transmetalation of **2c** with $ZnCl_2$–TMEDA complex, was used as an arylzinc reagent (entry 3).[18] After further optimization (entries 4 and 5), the reaction performed in the presence of 2 equiv of the arylzinc reagent **3c**–TMEDA complex at room temperature afforded the best result, yielding a 79% of **5c**.[19] Furthermore several amine ligands were explored under the reaction

Table 3
Co-catalyzed cross-coupling reaction of ethyl bromodifluoro-acetate with *p*-methoxyphenylzinc halides



3c (X=Cl)
3c' (X=Br)

4

6 (0.06 eq.)
Additive, THF

5c

Entry	Ar–ZnX	Additive	Conditions	Yield[a]
1	**3c** (1.2 equiv)	—	0 °C, dropwise for 30 min; rt, 30 min	5%
2	**3c'** (1.2 equiv)	NMP	0 °C, dropwise for 30 min; rt, 4 h	0%
3	**3c** (1.2 equiv)	TMEDA	0 °C, dropwise for 30 min; rt, 4 h	33%
4	**3c** (1.2 equiv)	TMEDA	rt, 4 h	43% (isolated 50%)
5	**3c** (2.0 equiv)	TMEDA	rt, 4 h	64% (isolated 79%)

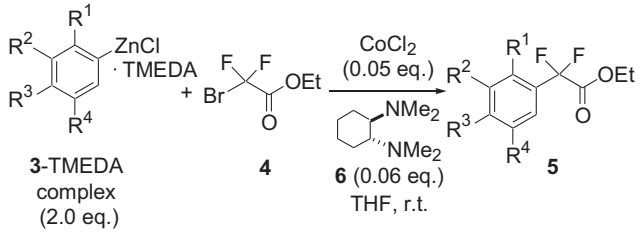
[a] ^{19}F NMR yield (benzotrifluoride was used as an internal standard).

Please cite this article in press as: Araki, K.; Inoue, M., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.03.041

condition in entry 5. While 1,10-phenanthroline as a ligand in place of **6** gave a disappointing result (6%), other amine ligands (no ligand, 1,3-bis(dimethylamino)propane, 1,4-bis(dimethylamino) butane, or 2,3-bis(dimethylamino)naphthalene) gave moderate yields (57–70%) of the desired product **5c**. We decided that further investigations would be carried out using the best reaction condition (2 equiv of ArZnCl–TMEDA, 1 equiv of **4**, 0.05 equiv of $CoCl_2$, and 0.06 equiv of *trans*-1,2-bis(dimethylamino)cyclohexane in THF at rt).

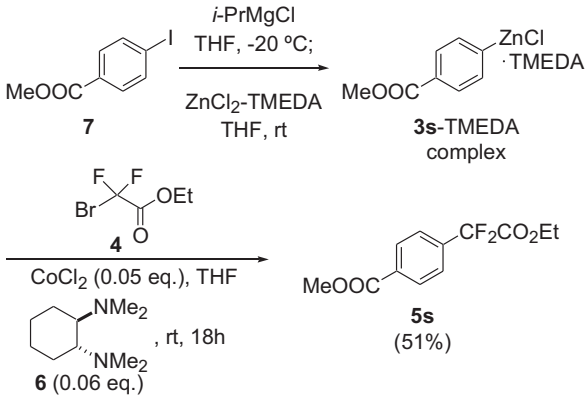
With the optimized reaction condition in hand, the substrate scope was evaluated by using several arylzinc reagent **3**–TMEDA complexes as depicted in Table 4. The developed reaction could tolerate various functional groups, such as alkyl and phenyl groups, electron-withdrawing substituents (fluorine, chlorine, and bromine atoms, and trifluoromethyl group), and electron-donating groups (methoxy, phenoxy, and methylthio groups). The *o*-substituted substrate also worked well for this coupling (entry 16). This method was applicable to prepare ethyl 2,2-difluoro-2-(4′-methoxy-4-biphenylyl)acetate (**5k**), an important synthetic intermediate for the liver X-receptor modulating effector (entry 11).[2b]

Table 4
Co-catalyzed cross-coupling reaction of ethyl bromodifluoro-acetate with arylzinc reagents



Entry	Product	R^1	R^2	R^3	R^4	Time	Yield
1	**5a**	H	H	H	H	22 h	74%
2	**5b**	H	H	F	H	4 h	70%
3	**5c**	H	H	MeO	H	4 h	79%
4	**5d**	H	H	Me	H	16 h	70%
5	**5e**	H	H	Ph	H	13 h	73%
6	**5f**	H	H	CF_3	H	20 h	59%
7	**5g**	H	H	Br	H	16 h	54%
8	**5h**	H	H	Cl	H	19 h	48%
9	**5i**	H	H	PhO	H	17 h	72%
10	**5j**	H	H	MeS	H	19 h	57%
11	**5k**	H	H	*p*-$MeOC_6H_4$	H	16 h	68%
12	**5l**	H	H	$(EtO)_2CH$	H	13 h	50%
13	**5m**	H	Me	F	H	16 h	69%
14	**5n**	H	F	F	H	12 h	58%
15	**5o**	H	MeO	H	H	24 h	79%
16	**5p**	Me	H	H	H	14 h	61%
17	**5q**	H	MeO	H	MeO	13 h	69%
18	**5r**	H		H	H	13 h	53%

The cross-coupling reaction of 4-(methoxycarbonyl)phenylzinc reagent **3s**–TMEDA complex, prepared via Knochel direct magnesiation,[20] also proceeded in 51% yield (Scheme 2). Unfortunately, all attempts using alkyl-, alkenyl-, and alkynyl-zinc reagents in place of arylzinc reagents under the same manner failed. Yorimitsu and Oshima proposed that cobalt-mediated cross-coupling reactions of ArMgX with alkyl halides involved an electron transfer (ET) process[13b] and we regarded that our developed reactions also proceeded via the same reaction mechanism except for the use of arylzinc reagents.



Scheme 2. Co-catalyzed cross-coupling reaction of ethyl bromodifluoroacetate with arylzinc reagent **3s** prepared via Knochel direct magnesiation.

3. Conclusion

In summary, we have accomplished the Co-catalyzed cross-coupling reaction of arylzinc reagents with ethyl bromodifluoroacetate. This method is very mild and applicable to various arylzinc reagents, having alkyl and phenyl groups, electron-withdrawing substituents (fluorine, chlorine, and bromine atoms, trifluoromethyl, and methoxycarbonyl groups), and electron-donating groups (methoxy, phenoxy, and methylthio groups), to afford variety of the corresponding ethyl aryldifluoroacetates, which are important intermediates in the fields of the medicinal, agricultural, and material sciences.

4. Experimental

4.1. General methods

All reactions involving air- and moisture-sensitive reagents were carried out using oven-dried glassware and standard syringe-septum cap techniques. Routine monitoring of reaction was carried out using glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60 N (spherical, neutral 40–50 μm). All solvents and reagents were obtained from commercial suppliers and were used without further purification. Melting points were taken on a Mettler Toledo MP70 melting point system and were uncorrected. ^1H, ^{13}C, and ^{19}F NMR spectra were measured with a Bruker DRX-250 or a Bruker AVANCE III spectrometers. Chemical shifts are expressed in parts per million using tetramethylsilane (δ=0, ^1H NMR) and $CFCl_3$ (δ=0, ^{19}F NMR) as standard substances. ^{19}F NMR spectra were recorded with ^1H decoupling. Multiplicities are indicated by s (singlet), br s (broad singlet), d (doublet), br d (broad doublet), t (triplet), br t (broad triplet), q (quartet), dd (doublet of doublet), br dd (broad doublet of doublet), dt (doublet of triplet), and m (multiplet). Infrared (IR) spectral measurements were carried out with a HORIBA FT-720 spectrometer.

4.2. General procedure for Co-catalyzed cross-coupling reaction of ethyl bromodifluoroacetate (4) with arylmagnesium bromide 2

To a stirred solution of anhydrous cobalt (II) chloride (6.5 mg, 0.050 mmol) in anhydrous THF (3.0 ml) was added *trans*-1,2-bis(dimethylamino)cyclohexane (**6**) (10.2 mg, 0.060 mmol) and ethyl bromodifluoroacetate (**4**) (0.13 ml, 1.0 mmol) sequentially at room temperature under Ar and the resulting mixture was stirred at room temperature for 5 min. To the resulting mixture was added

dropwise a solution of ArMgBr **2** in anhydrous THF (1.0 M, 1.3 ml, 1.3 mmol) for 2 h at room temperature and the resulting mixture was stirred at room temperature for 10 min. Benzotrifluoride was added as an internal standard and the resulting solution was subjected to quantitative analysis by ^{19}F NMR.

4.3. General procedure for Co-catalyzed cross-coupling reaction of ethyl bromodifluoroacetate (4) with arylzinc reagent 3–TMEDA complex

To a stirred suspension of $ZnCl_2$–TMEDA (505 mg, 2.0 mmol) in anhydrous THF (0.50 ml) was added dropwise a solution of ArMgX in anhydrous THF or Et_2O (2.0 equiv) at 0 °C under Ar and the resulting mixture was stirred at room temperature for 30 min to prepare arylzinc reagent **3**–TMEDA complex. To a solution of anhydrous cobalt (II) chloride (6.5 mg, 0.050 mmol) in anhydrous THF (3.0 ml) was added *trans*-1,2-bis(dimethylamino)cyclohexane (**6**) (10.2 mg, 0.060 mmol) and ethyl bromodifluoroacetate (**4**) (0.13 ml, 1.0 mmol) sequentially at room temperature under Ar and the resulting mixture was stirred at room temperature for 5 min. To this resulting mixture was added dropwise the above prepared mixture of arylzinc reagent **3**–TMEDA complex in THF at 0 °C and the resulting mixture was stirred at room temperature for an indicated reaction time. The reaction mixture was quenched with 13% aqueous NH_4Cl solution (2.0 ml) and extracted with ether (4.0 ml×3). The extract was washed with water (4.0 ml) and brine (4.0 ml), then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by silica gel column chromatography (hexane/ethyl acetate) to give ethyl 2-aryl-2,2-difluoroacetate **5**.

*4.3.1. Ethyl 2,2-difluoro-2-phenylacetate (**5a**).*[3b] The reaction was carried out for 22 h according to the general procedure using phenylmagnesium bromide in THF (2.8 ml, 2.0 mmol) as ArMgX. Colorless oil (148 mg, 74%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.62 (br d, J=8.0 Hz, 2H), 7.52–7.44 (m, 3H), 4.31 (q, J=7.5 Hz, 2H), 1.31 (t, J=7.5 Hz, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −104.2 (2F).

*4.3.2. Ethyl 2,2-difluoro-2-(4-fluorophenyl)acetate (**5b**).*[3b] The reaction was carried out for 4 h according to the general procedure using 4-fluorophenylmagnesium bromide in THF (2.0 ml, 2.0 mmol) as ArMgX. Colorless oil (152 mg, 70%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.64 (br dd, J=8.8 Hz, J_{HF}=5.3 Hz, 2H), 7.16 (br dd, J=8.8 Hz, J_{HF}=8.8 Hz, 2H), 4.32 (q, J=7.0 Hz, 2H), 1.33 (t, J=7.0 Hz, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −103.6 (d, J_{FF}=2.8 Hz, 2F), −109.3 (t, J_{FF}=2.8 Hz, 1F).

*4.3.3. Ethyl 2,2-difluoro-2-(4-methoxyphenyl)acetate (**5c**).* The reaction was carried out for 4 h according to the general procedure using 4-methoxyphenylmagnesium bromide in THF (4.0 ml, 2.0 mmol) as ArMgX. Colorless oil (182 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (br d, J=9.0 Hz, 2H), 6.95 (br d, J=9.0 Hz, 2H), 4.29 (q, J=7.0 Hz, 2H), 3.84 (s, 3H), 1.31 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (t, J_{CF}=36 Hz), 161.6 (br s), 127.0 (t, J_{CF}=5.9 Hz, 2C), 124.9 (t, J_{CF}=26 Hz), 114.0 (2C), 113.6 (t, J_{CF}=251 Hz), 63.0, 55.3, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.6 (2F); IR (neat) 2983, 2941, 2910, 2843, 1761, 1614, 1587, 1516, 1466, 1444, 1421, 1371, 1290, 1271, 1250, 1178, 1138, 1095, 1032, 1018, 989, 858, 833, 794, 758, 704, 642 cm^{-1}; Anal. Calcd for $C_{11}H_{12}F_2O_3$: C, 57.39; H, 5.25. Found: C, 57.39; H, 5.25.

*4.3.4. Ethyl 2,2-difluoro-2-(4-methylphenyl)acetate (**5d**).* The reaction was carried out for 16 h according to the general procedure using *p*-tolylmagnesium chloride in THF (2.0 ml, 2.0 mmol) as ArMgX. Colorless oil (150 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (br d, J=8.3 Hz, 2H), 7.24 (br d, J=8.3 Hz, 2H), 4.28 (q, J=7.3 Hz, 2H), 2.38 (s, 3H), 1.29 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (t, J_{CF}=36 Hz), 141.2 (t, J_{CF}=1.7 Hz), 130.0 (t, J_{CF}=26 Hz), 124.3 (2C), 125.3 (t, J_{CF}=5.9 Hz, 2C), 113.5 (t, J_{CF}=252 Hz), 63.0, 21.3, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.4 (2F); IR (neat) 2987, 2970, 2941, 2929, 1763, 1616, 1516, 1448, 1371, 1300, 1267, 1213, 1188, 1140, 1095, 1028, 1014, 991, 860, 840, 821, 748, 700, 638 cm^{-1}; Anal. Calcd for $C_{11}H_{12}F_2O_2$: C, 61.68; H, 5.65. Found: C, 61.83; H, 5.61.

*4.3.5. Ethyl 2-(4-biphenylyl)-2,2-difluoroacetate (**5e**).*[7a] The reaction was carried out for 13 h according to the general procedure using 4-biphenylylmagnesium bromide in THF (4.0 ml, 2.0 mmol) as ArMgX. Colorless oil (201 mg, 73%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72–7.63 (m, 4H), 7.59 (br d, J=8.0 Hz, 2H), 7.51–7.35 (m, 3H), 4.33 (q, J=7.5 Hz, 2H), 1.33 (t, J=7.5 Hz, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −103.9 (2F).

*4.3.6. Ethyl 2,2-difluoro-2-[4-(trifluoromethyl)phenyl]acetate (**5f**).*[3a] The reaction was carried out for 20 h according to the general procedure using 4-(trifluoromethyl)phenylmagnesium bromide in THF (2.3 ml, 2.0 mmol) as ArMgX. Colorless oil (157 mg, 59%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.79–7.70 (m, 4H), 4.32 (q, J=7.3 Hz, 2H), 1.33 (t, J=7.3 Hz, 3H); ^{19}F NMR (250 MHz, $CDCl_3$) δ −63.3 (3F), −104.8 (2F).

*4.3.7. Ethyl 2-(4-bromophenyl)-2,2-difluoroacetate (**5g**).*[7a] The reaction was carried out for 16 h according to the general procedure using 4-bromophenylmagnesium bromide in THF (2.0 ml, 2.0 mmol) as ArMgX. Colorless oil (151 mg, 54%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.70–7.40 (m, 4H), 4.30 (q, J=7.0 Hz, 2H), 1.33 (t, J=7.0 Hz, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −104.1 (2F).

*4.3.8. Ethyl 2-(4-chlorophenyl)-2,2-difluoroacetate (**5h**).*[4b] The reaction was carried out for 19 h according to the general procedure using 4-chlorophenylmagnesium bromide in Et_2O (2.0 ml, 2.0 mmol) as ArMgX. Colorless oil (112 mg, 48%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65–7.55 (br d, J=8.0 Hz, 2H), 7.49–7.44 (br d, J=8.0 Hz, 2H), 4.30 (q, J=7.0 Hz, 2H), 1.30 (t, J=7.0 Hz, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −104.1 (2F).

*4.3.9. Ethyl 2,2-difluoro-2-(4-phenoxyphenyl)acetate (**5i**).* The reaction was carried out for 17 h according to the general procedure using 4-phenoxyphenylmagnesium bromide in THF (4.0 ml, 2.0 mmol) as ArMgX. Colorless oil (210 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (br d, J=8.8 Hz, 2H), 7.38 (br dd, J=8.5, 7.5 Hz, 2H), 7.17 (br t, J=7.5 Hz, 1H), 7.06–7.01 (m, 4H), 4.31 (q, J=7.1 Hz, 2H), 1.32 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (t, J_{CF}=36 Hz), 160.0 (br s), 155.9, 130.0 (2C), 127.3 (t, J_{CF}=6.1 Hz, 2C), 127.1 (t, J_{CF}=26 Hz), 124.3, 119.9 (2C), 118.0 (2C), 113.4 (t, J_{CF}=252 Hz), 63.1, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.8 (2F); IR (neat) 2987, 1763, 1589, 1508, 1489, 1238, 1199, 1170, 1138, 1095, 1022, 991, 870, 837, 750, 692 cm^{-1}; Anal. Calcd for $C_{16}H_{14}F_2O_3$: C, 65.75; H, 4.83. Found: C, 66.14; H, 5.09.

*4.3.10. Ethyl 2,2-difluoro-2-[4-(methylthio)phenyl]acetate (**5j**).* The reaction was carried out for 19 h according to the general procedure using 4-(methylthio)phenylmagnesium bromide in THF (2.0 ml, 2.0 mmol) as ArMgX. Colorless oil (141 mg, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J=8.7 Hz, 2H), 7.28 (d, J=8.7 Hz, 2H), 4.29 (q, J=7.2 Hz, 2H), 2.50 (s, 3H), 1.30 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (t, J_{CF}=36 Hz), 142.8 (br s), 129.1 (t, J_{CF}=26 Hz), 125.9 (t, J_{CF}=6.0 Hz, 2C), 125.7 (2C), 113.3 (t, J_{CF}=252 Hz), 63.1, 15.1, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.6 (2F); IR (neat) 2985, 2924, 1761, 1601, 1495, 1437, 1402, 1371, 1267,

Please cite this article in press as: Araki, K.; Inoue, M., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.03.041

1142, 1092, 1011, 989, 822, 762, 739, 690 cm^{-1}; Anal. Calcd for $C_{11}H_{12}F_2O_2S$: C, 53.65; H, 4.91. Found: C, 53.59; H, 4.93.

*4.3.11. Ethyl 2,2-difluoro-2-(4′-methoxy-4-biphenylyl)acetate (**5k**).* The reaction was carried out for 16 h according to the general procedure using (4′-methoxy-4-biphenylyl)magnesium bromide in THF (10 ml, 2.0 mmol) as ArMgX. White solid (207 mg, 68%); mp 95–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (br d, J=8.9 Hz, 2H), 7.62 (br d, J=8.9 Hz, 2H), 7.54 (br d, J=8.8 Hz, 2H), 6.99 (br d, J=8.8 Hz, 2H), 4.32 (q, J=7.2 Hz, 2H), 3.86 (s, 3H), 1.32 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (t, J_{CF}=35 Hz), 159.8, 143.6 (br s), 132.4, 131.0 (t, J_{CF}=26 Hz), 128.3 (2C), 126.8 (2C), 125.9 (t, J_{CF}=6.1 Hz, 2C), 114.4 (2C), 113.5 (t, J_{CF}=252 Hz), 63.1, 55.4, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.5 (2F); IR (neat) 3006, 2842, 1765, 1603, 1581, 1533, 1294, 1265, 1203, 1149, 1120, 1103, 1030, 1012, 989, 825, 809, 766, 719, 694 cm^{-1}; Anal. Calcd for $C_{17}H_{16}F_2O_3$: C, 66.66; H, 5.27. Found: C, 66.52; H, 5.19.

*4.3.12. Ethyl 2-[4-(diethoxymethyl)phenyl]-2,2-difluoroacetate (**5l**).* The reaction was carried out for 13 h according to the general procedure using 4-(diethoxymethyl)phenylmagnesium bromide in THF (4.3 ml, 2.0 mmol) as ArMgX. Colorless oil (151 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.51 (m, 4H), 5.52 (s, 1H), 4.29 (q, J=7.2 Hz, 2H), 3.70–3.50 (m, 4H), 1.30 (t, J=7.2 Hz, 3H), 1.24 (t, J=7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (t, J_{CF}=36 Hz), 142.2 (br s), 132.8 (t, J_{CF}=26 Hz), 127.1 (2C), 125.4 (t, J_{CF}=6.1 Hz, 2C), 113.4 (t, J_{CF}=252 Hz), 101.5, 63.1, 61.3 (2C), 15.2 (2C), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.7 (2F); IR (neat) 2976, 2924, 2879, 1766, 1444, 1392, 1371, 1335, 1267, 1093, 1053, 837, 806 cm^{-1}; Anal. Calcd for $C_{15}H_{20}F_2O_4$: C, 59.59; H, 6.67. Found: C, 59.33; H, 6.50.

*4.3.13. Ethyl 2,2-difluoro-2-(4-fluoro-3-methylphenyl)acetate (**5m**).* The reaction was carried out for 16 h according to the general procedure using (4-fluoro-3-methylphenyl)magnesium bromide in THF (2.0 ml, 2.0 mmol) as ArMgX. Colorless oil (160 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.38 (m, 2H), 7.07 (dd, J=8.8, 8.8 Hz, 1H), 4.30 (q, J=7.1 Hz, 2H), 2.31 (br s, 3H), 1.31 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (t, J=26 Hz), 162.8 (dt, J_{CF}=249, 2.2 Hz), 128.9 (dt, J_{CF}=6.1, 6.1 Hz), 128.5 (dt, J_{CF}=26, 3.5 Hz), 125.7 (d, J_{CF}=18 Hz), 125.0 (dt, J_{CF}=8.9, 6.3 Hz), 115.4 (d, J_{CF}=23 Hz), 113.1 (t, J_{CF}=252 Hz), 63.2, 14.6 (d, J=3.4 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.0 (d, J_{FF}=2.6 Hz, 2F), −113.4 (t, J_{FF}=2.6 Hz, 1F); IR (neat) 2987, 2935, 1763, 1601, 1504, 1290, 1263, 1168, 1097, 1032, 991, 823, 754, 651 cm^{-1}; Anal. Calcd for $C_{11}H_{11}F_3O_2$: C, 56.90; H, 4.77. Found: C, 56.78; H, 4.69.

*4.3.14. Ethyl 2-(3,4-difluorophenyl)-2,2-difluoroacetate (**5n**).*[3a] The reaction was carried out for 12 h according to the general procedure using 3,4-difluorophenylmagnesium bromide in THF (2.2 ml, 2.0 mmol) as ArMgX. Colorless oil (138 mg, 58%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53–7.21 (m, 3H), 4.34 (q, J=7.0 Hz, 2H), 1.34 (t, J=7.0 Hz, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −103.6 (d, J=2.4 Hz, 2F), −133.5 (dt, J=21, 2.4 Hz, 1F), −135.7 (d, J=21 Hz, 1F).

*4.3.15. Ethyl 2,2-difluoro-2-(3-methoxyphenyl)acetate (**5o**).*[2c] The reaction was carried out for 24 h according to the general procedure using 3-methoxyphenylmagnesium bromide in THF (2.0 ml, 2.0 mmol) as ArMgX. Colorless oil (181 mg, 79%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (dd, J=8.3, 8.3 Hz, 1H), 7.21–7.10 (m, 2H), 7.01 (br d, J=8.3 Hz, 1H), 4.30 (q, J=7.3 Hz, 2H), 3.83 (s, 3H), 1.31 (t, J=7.3 Hz, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −104.0 (2F).

*4.3.16. Ethyl 2,2-difluoro-2-(2-methylphenyl)acetate (**5p**).* The reaction was carried out for 14 h according to the general procedure using 2-methylphenylmagnesium bromide in THF (2.0 ml, 2.0 mmol) as ArMgX. Colorless oil (131 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (br d, J=7.5 Hz, 1H), 7.37 (br dd, J=7.5, 7.5 Hz, 1H), 7.27 (br dd, J=7.5, 7.5 Hz, 1H), 7.23 (br dd, J=7.5, 7.5 Hz, 1H), 4.32 (q, J=7.0 Hz, 2H), 2.42 (t, J=2.2 Hz, 3H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (t, J_{CF}=35 Hz), 136.4 (t, J_{CF}=2.9 Hz), 131.9, 131.1 (t, J_{CF}=24 Hz), 130.8 (br s), 126.1 (t, J_{CF}=8.8 Hz), 125.9 (s), 114.3 (t, J_{CF}=252 Hz), 63.1, 19.7 (t, J_{CF}=2.6 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.3 (2F); IR (neat) 2985, 2970, 2944, 1763, 1608, 1458, 1458, 1448, 1371, 1284, 1252, 1203, 1140, 1080, 1053, 1014, 989, 858, 838, 783, 742, 725, 667 cm^{-1}; Anal. Calcd for $C_{11}H_{12}F_2O_2$: C, 61.68; H, 5.65. Found: C, 61.46; H, 5.59.

*4.3.17. Ethyl 2-(3,5-dimethoxyphenyl)-2,2-difluoroacetate (**5q**).* The reaction was carried out for 13 h according to the general procedure using 3,5-dimethoxyphenylmagnesium bromide in THF (4.8 ml, 2.0 mmol) as ArMgX. Colorless oil (179 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J=2.3 Hz, 2H), 6.55 (t, J=2.3 Hz, 1H), 4.30 (q, J=7.1 Hz, 2H), 3.81 (s, 6H), 1.31 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1 (t, J_{CF}=35 Hz), 161.0 (2C), 134.8 (t, J_{CF}=26 Hz), 113.2 (t, J_{CF}=252 Hz), 103.5 (t, J_{CF}=6.4 Hz, 2C), 103.1 (br s), 63.2, 55.6 (2C), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.9 (2F); IR (neat) 3006, 2943, 2843, 1763, 1599, 1460, 1429, 1354, 1335, 1294, 1205, 1157, 1101, 1059, 1024, 852, 746, 683 cm^{-1}; Anal. Calcd for $C_{12}H_{14}F_2O_4$: C, 55.38; H, 5.42. Found: C, 55.25; H, 5.34.

*4.3.18. Ethyl 2-[3-(1,3-dioxolan-2-yl)phenyl]-2,2-difluoroacetate (**5r**).* The reaction was carried out for 13 h according to the general procedure using 3-(1,3-dioxolan-2-yl)phenylmagnesium bromide in THF (2.3 ml, 2.0 mmol) as ArMgX. Colorless oil (144 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.64–7.59 (m, 2H), 7.47 (br dd, J=7.8, 7.7 Hz, 1H), 5.84 (s, 1H), 4.29 (q, J=7.2 Hz, 2H), 4.17–4.02 (m, 4H), 1.30 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1 (t, J_{CF}=35 Hz), 138.9, 133.1 (t, J_{CF}=26 Hz), 132.2 (br s), 128.8, 126.3 (t, J_{CF}=6.0 Hz), 123.7 (t, J_{CF}=6.0 Hz), 113.3 (t, J_{CF}=252 Hz), 103.0, 65.4 (2C), 63.2, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.7 (2F); IR (neat) 2985, 2893, 1763, 1448, 1371, 1284, 1194, 1095, 1076, 1028, 943, 804, 710 cm^{-1}; Anal. Calcd for $C_{13}H_{14}F_2O_4$: C, 57.35; H, 5.18. Found: C, 57.45; H, 5.04.

4.4. Co-catalyzed cross-coupling reaction of ethyl bromodifluoroacetate (4) with (4-methoxycarbonylphenyl)zinc chloride (3s)–TMEDA complex to synthesize methyl 4-[(ethoxycarbonyl)difluoromethyl]benzoate (5s)

To a stirred solution of methyl 4-iodobenzoate (**7**) (524 mg, 2.0 mmol) in anhydrous THF (4 ml) was added dropwise a solution of *i*-propylmagnesium chloride in THF (2.0 M, 1.0 ml, 2.0 mmol) at −20 °C under Ar and the resulting mixture was stirred at −20 °C for 1 h. To the resulting solution of 4-(methoxycarbonyl)phenylmagnesium chloride in THF was added $ZnCl_2$–TMEDA (505 mg, 2.0 mmol) and the resulting mixture was stirred at room temperature for 30 min. To a stirred suspension of anhydrous cobalt (II) chloride (6.5 mg, 0.050 mmol) in anhydrous THF (3.0 ml) was added *trans*-1,2-bis(dimethylamino)cyclohexane (**6**) (10.2 mg, 0.060 mmol) and ethyl bromodifluoroacetate (**4**) (0.13 ml, 1.0 mmol) sequentially at room temperature under Ar and the resulting mixture was stirred at room temperature for 5 min. To the resulting mixture was added dropwise the above prepared solution of (4-methoxycarbonylphenyl)zinc chloride (**3s**)–TMEDA complex in THF at 0 °C and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with 13% aqueous NH_4Cl solution (2.0 ml) and extracted with ether (4.0 ml×3). The extract was washed with water (4.0 ml) and brine (4.0 ml), then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by silica gel column chromatography (hexane/ethyl acetate=10/1) to give methyl 4-[(ethoxycarbonyl)difluoromethyl]benzoate (**5s**) (131 mg, 51%) as

a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J=8.0 Hz, 2H), 7.69 (d, J=8.0 Hz, 2H), 4.30 (q, J=7.1 Hz, 2H), 3.95 (s, 3H), 1.30 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 163.7 (t, J_{CF}=35 Hz), 137.0 (t, J_{CF}=26 Hz), 132.6 (br s), 129.9 (2C), 125.7 (t, J_{CF}=6.0 Hz, 2C), 113.0 (t, J_{CF}=252 Hz), 63.4, 52.4, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.5 (2F); IR (neat) 2987, 2956, 1765, 1728, 1437, 1410, 1277, 1192, 1099, 1012, 993, 862, 841, 825, 785, 742, 715 cm^{-1}; Anal. Calcd for $C_{12}H_{12}F_2O_4$: C, 55.82; H, 4.68. Found: C, 56.00; H, 4.85.

Acknowledgements

We thank Mrs. A. Sato at A Rabbit Science Co., Ltd. for elemental analysis.

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Please cite this article in press as: Araki, K.; Inoue, M., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.03.041