JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Visible-Light-Mediated Radical Aryldifluoroacetylation of Alkynes with Ethyl Bromodifluoroacetate for the Synthesis of 3-Difluoroacetylated Coumarins

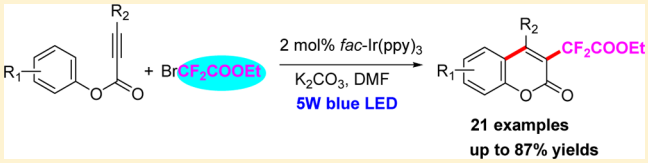
Weijun Fu,*[,†] Mei Zhu,[†] Guanglong Zou,[‡] Chen Xu,[†] Zhiqiang Wang,[†] and Baoming Ji[†]

[†]College of Chemistry and Chemical Engineering, Luoyang Normal University, Luoyang 471022, People's Republic of China

[‡]The College of Chemistry and Environmental Science, Guizhou Minzu Univeristy, Guiyang 550025, People's Republic of China

Supporting Information

ABSTRACT: A mild and efficient method for the synthesis of 3-difluoroacetylated coumarins through visible-light-promoted aryldifluoroacetylation of alkynes with ethyl bromodifluoroacetate has been developed. The reaction allows the direct formation of C_{sp^2}–CF_2COOEt and C–C bonds via a proposed tandem radical cyclization process.



The difluoromethylene group (CF_2) is an intriguing structural motif that has great potential for many applications in medicinal, agricultural, and material sciences.[1] It has been realized that the CF_2 group can act as a bioisostere for mimicking the steric and electronic features of an oxygen atom or a carbonyl group. In this field, the development of efficient methods for the introduction of a difluoromethylated group into diverse organic molecules has attracted much attention.[2] Among these difluorinated moieties, CF_2CO_2Et is extremely appealing because the moiety can undergo further modification into various CF_2-containing functional groups. Recently, transition-metal-mediated or transition-metal-catalyzed difluoroacetylation of aryl halides and aryl boronic acids to construct a C_{sp^2}–CF_2COOEt bond has been intensively studied.[3] Poisson and Pannecoucke also reported an elegant process for the direct difluoroacetylation of enamides, furans, and benzofurans through copper-catalyzed C–H functionalization.[4] Another frequently used strategy is the utilization of high reactivity of the CF_2COOEt radical.[5−7] For example, visible light photocatalyzed radical addition of the $BrCF_2CO_2Et$ reagent to heteroarenes,[5] alkenes,[6] and isocyanides[7] has been well-established by the several groups. However, the application of such a photocatalytic strategy for direct and regiospecific difluoroacetylation of alkynes is still quite limited.

Over the past few years, transition-metal-catalyzed difunctionalization of alkynes in alkynoates involving the direct aryl C(sp^2)–H functionalization has attracted considerable attention.[8] Various functionalized coumarins could be constructed by this efficient protocol. For example, Huang and co-workers described Ag_2CO_3-catalyzed carbon phosphorylation to form phosphorated coumarins.[9] The Lu group reported the synthesis of trifluoromethylated coumarins through a CF_3 radical.[10] Very recently, Wang and co-workers developed a method for the direct difunctionalization of alkynoates with sulfonylhydrazides under metal-free conditions using *tert*-butyl hydroperoxide.[11] Mechanistic studies demonstrated that these reactions could be initiated by the reaction of radicals with C≡C bonds followed by intramolecular radical cyclization onto the aryl substituent. Consistent with these findings and with our ongoing studies on the synthesis of fluorinated heterocycles,[12] we hypothesized that similar reactions could be carried out using a CF_2COOEt radical generated from ethyl bromodifluoroacetate under visible light irradiation to construct difluoroacetylated coumarins. This transformation allows the direct formation of a C_{sp^2}–CF_2COOEt bond and the construction of a coumarin ring in one reaction.

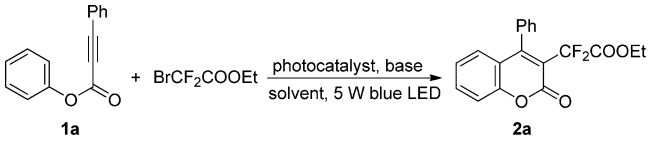
In our preliminary experiments, phenyl alkynoate **1a** and $BrCF_2CO_2Et$ were chosen as the model substrates to optimize the reaction conditions. Initially, we examined our previous reaction conditions, which were developed for photocatalyzed aryldifluoroacetylation of *N*-arylacrylamides[6e] (Table 1, entry 1). Gratifyingly, the desired coumarin **2a** was obtained as the major product in 60% yield. Considering that the catalysts usually play an important role in photoredox catalysis, several typical photocatalysts such as $[Ir(ppy)_2(dtbbpy)]PF_6$, $Ru(bpy)_3(PF_6)_2$, and eosin Y were investigated to improve the reaction efficiency (Table 1, entries 2–4). Unfortunately, none of them gave better results than [*fac*-Ir($ppy)_3$]. It was observed that the use of inorganic bases such as K_2CO_3, Cs_2CO_3, K_3PO_4, and $NaHCO_3$ promoted the reactions and K_2CO_3 gave the best result. Other bases were tested including NaOAc and organic base (Et_3N), all of which gave poor yields of **2a** (Table 1, entries 5–10). Further investigations revealed that dimethylformamide (DMF) was found to be the solvent of choice (Table 1, entries 11–13). In the control experiments, the reaction was found to be completely restrained without the catalyst or light irradiation (Table 1, entries 14 and 15).

To study the scope and limitations of this approach, various alkynoates **1b–t** were reacted with $BrCF_2CO_2Et$ under optimized reaction conditions to the corresponding coumarins

Received: February 10, 2015
Published: April 3, 2015

DOI: 10.1021/acs.joc.5b00305
J. Org. Chem. 2015, 80, 4766–4770

Table 1. Optimization of Reaction Conditions for 2a[a]



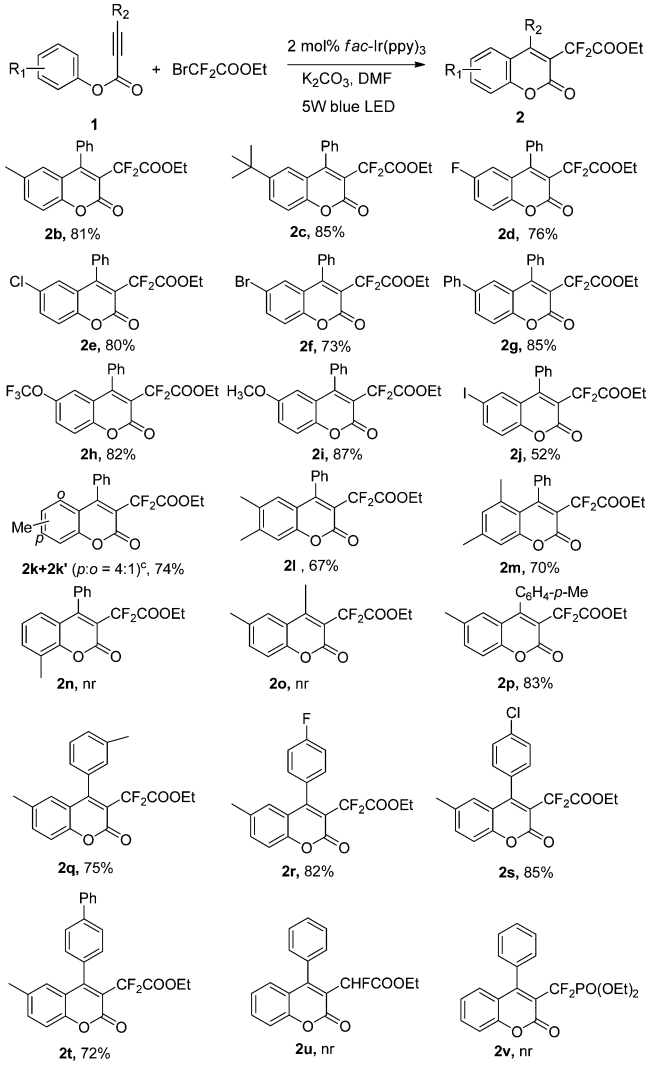
entry	catalyst	base	solvent	yield[b] (%)
1	*fac*-Ir(ppy)$_3$	Na_2HPO_4	DMF	60
2	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	Na_2HPO_4	DMF	43
3	Ru(bpy)$_3$(PF$_6$)$_2$	Na_2HPO_4	DMF	trace
4	eosin Y	Na_2HPO_4	DMF	0
5	*fac*-Ir(ppy)$_3$	K_2CO_3	DMF	78
6	*fac*-Ir(ppy)$_3$	Cs_2CO_3	DMF	63
7	*fac*-Ir(ppy)$_3$	K_3PO_4	DMF	68
8	*fac*-Ir(ppy)$_3$	$NaHCO_3$	DMF	72
9	*fac*-Ir(ppy)$_3$	NaOAc	DMF	54
10	*fac*-Ir(ppy)$_3$	Et_3N	DMF	38
11	*fac*-Ir(ppy)$_3$	K_2CO_3	CH_3CN	47
12	*fac*-Ir(ppy)$_3$	K_2CO_3	CH_2Cl_2	30
13	*fac*-Ir(ppy)$_3$	K_2CO_3	DMSO	65
14[c]	none	K_2CO_3	DMF	NR
15[d]	*fac*-Ir(ppy)$_3$	K_2CO_3	DMF	NR

[a]Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), $BrCF_2COOEt$ (0.6 mmol, 2.0 equiv), base (0.6 mmol, 2.0 equiv), and photocatalyst (0.006 mmol, 2.0 mol %) in indicated solvent (3.0 mL) were irradiated with a 5 W blue LED for 48 h. [b]Isolated yield. [c]Without photocatalyst irradiation. [d]Without visible light irradiation.

2b–t (Table 2). Initially, both moderate electron-withdrawing groups and electron-donating groups located in the *para* position of aryl 3-phenylpropiolates did not compromise the reaction efficiency, affording the desired coumarins (**2b–i**) in moderate to good yields. However, a substrate-bearing iodine (**2j**) atom on the aromatic ring resulted in relatively poor yield. The use of *meta*-substituted substrate **1k** resulted in a mixture of the products **2k** and **2k′** with moderate regioselectivity (4:1). By contrast, the 3,4-dimethyl substrate **1l** underwent this transformation to afford **2l** as the major regioisomer. In addition, 3,5-dimethyl-substituted substrate **1m** could also participate in this transformation to give the desired product (**2m**) in 70% yield. The reaction was more sensitive to the position of the substituents. For *ortho*-substituted substrate (**1n**), no product was obtained due to the steric effect. We have extended this radical cyclization reaction into various substituents on the alkynyl, as well. Disappointingly, no desired product was observed when methylpropiolate (**1o**) was employed in the reaction. For all arylpropiolates tested in this series, the corresponding coumarins (**2p–t**) were obtained in good yields. We further extended the work to the addition of CHFCOOEt or $CF_2PO(OEt)_2$ radical. However, the reaction of phenyl alkynoate **1a** with ethyl bromodifluoroacetate and diethyl bromodifluoromethylphosphonates failed to produce the expected product (**2u**,**v**) under the optimized reaction conditions.

To gain mechanistic insight into the photo-redox-catalyzed cyclization, the reaction was performed in the presence of the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy). Under these conditions, the reaction was completely restrained. To our delight, the TEMPO–CF_2COOEt adduct was formed as estimated by ESI-HRMS and ^{19}F NMR analysis, thus providing straightforward evidence of a CF_2COOEt radical formation (Scheme 1).

Table 2. Cyclization of Various Alkynoates 1 with $BrCF_2COOEt$[a,b]



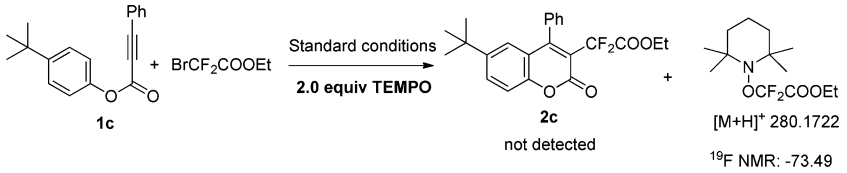
[a]Reaction conditions: **1** (0.3 mmol), $BrCF_2COOEt$ (0.6 mmol, 2.0 equiv), K_2CO_3 (0.6 mmol, 2.0 equiv), and *fac*-Ir(ppy)$_3$ (0.006 mmol, 2.0 mol %) in DMF (3.0 mL) were irradiated with a 5 W blue LED for 48 h. [b]Isolated yield. [c]The ratio of regioisomers based on isolated yields.

On the basis of the experimental results and literature,[9−11] a catalytic cycle is proposed for this transformation (Scheme 2). First, the photocatalyst [*fac*-Ir(III)(ppy)$_3$] is irradiated to the excited state [*fac*-Ir(III)(ppy)$_3$*], which is oxidatively quenched by $BrCF_2COOEt$ with the generation of a [*fac*-Ir(IV)(ppy)$_3$]$^+$ complex and a $\bullet CF_2COOEt$ radical species **A**. The radical **A** adds to alkynoates **1** to produce the radical intermediate **B**, which undergoes intramolecular homolytic aromatic substitution to give the radical intermediate **C**. The intermediate **C** is then oxidized by [*fac*-Ir(IV)(ppy)$_3$]$^+$ to form the cyclohexadienyl cation **D** and regenerates [*fac*-Ir(III)(ppy)$_3$]. Ultimately, deprotonation assisted by base yields the product **2**.

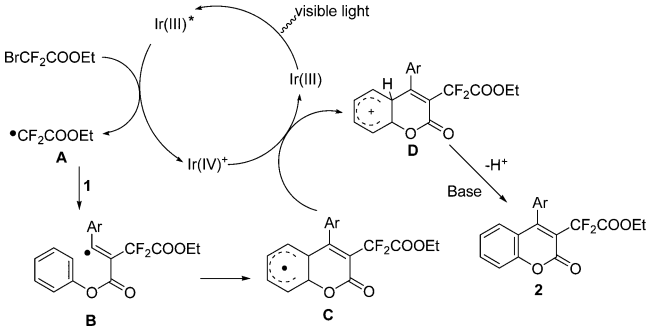
In summary, we have reported a facile assembly of 3-difluoroacetylated coumarins through visible-light-promoted tandem aryldifluoroacetylation of alkynoates with $BrCF_2CO_2Et$. The reaction was found to tolerate a wide range of functional groups. Most importantly, the difluoroester group

DOI: 10.1021/acs.joc.5b00305
J. Org. Chem. 2015, 80, 4766−4770

Scheme 1. Experiment for Mechanistic Study



Scheme 2. Plausible Reaction Mechanism



(CF_2COOEt) could be easily introduced into the scaffold of coumarin under mild and environmentally friendly conditions.

EXPERIMENTAL SECTION

General. All reactions were performed in a 20 mL tube equipped with a rubber septum at room temperature. Photoirradiation was carried out with a 5 W blue LED (light-emitting diode). Solvents were purified or dried in a standard manner. ^1H NMR spectra, ^{13}C NMR spectra, and ^{19}F NMR spectra were measured in $CDCl_3$ and recorded on 400 or 500 MHz NMR spectrometers with trimethylsilane as an internal standard. HRMS analyses were recorded on a Q-TOF global mass spectrometer. Alkynoates were prepared according to the literature.[13]

General Procedure for the Synthesis of Difluoroacetylated Coumarins. To a mixture of alkynoate **1** (0.30 mmol), $BrCF_2COOEt$ (0.6 mmol), and K_2CO_3 (0.6 mmol) in 3.0 mL of DMF was added *fac*-$Ir(ppy)_3$ (0.006 mmol, 2.0 mol %) under N_2 atmosphere. The solution was stirred at room temperature under 5 W blue LED irradiation for 48 h. Then the reaction mixture was diluted by adding EtOAc and brine. The aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate 8:1 as the eluant) on silica gel to give the desired coumarins.

*Ethyl 2,2-Difluoro-2-(2-oxo-4-phenyl-2H-chromen-3-yl)acetate (**2a**):* White solid (80.5 mg, 78%); mp 83−84 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60−7.63 (m, 1 H), 7.51−7.52 (m, 3 H), 7.41 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.32−7.33 (m, 2 H), 7.20−7.24 (m, 1 H), 7.07 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 4.35 (q, 2 H, J = 7.0 Hz), 1.34 (t, 3 H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7 (t, J = 32.0 Hz), 159.0 (t, J = 4.0 Hz), 156.1, 153.1, 133.5, 132.8, 129.1, 128.8, 128.3, 127.6 (t, J = 2.5 Hz), 124.9, 120.2, 118.0 (t, J = 22.5 Hz), 116.9, 111.8 (t, J = 251.5 Hz), 63.3, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.8 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{19}H_{15}F_2O_4$ 345.0933, found 345.0929.

*Ethyl 2,2-Difluoro-2-(6-methyl-2-oxo-4-phenyl-2H-chromen-3-yl)acetate (**2b**):* White solid (87.0 mg, 81%); mp 105−106 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.51 (m, 3 H), 7.30−7.32 (m, 2 H), 7.21 (s, 1 H), 7.02 (d, 1 H, J = 8.0 Hz), 6.93 (d, 1 H, J = 8.4 Hz), 4.35 (q, 2 H, J = 7.2 Hz), 2.46 (s, 3 H), 1.33 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8 (t, J = 32.0 Hz), 159.3 (t, J = 4.3 Hz), 156.2, 153.2, 145.3, 133.1, 129.0, 128.5, 128.2, 127.6 (t, J = 2.2 Hz), 126.1, 117.8, 117.0, 116.8 (t, J = 22.8 Hz), 111.9 (t, J = 251.4 Hz), 63.2, 21.7, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.6 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{20}H_{17}F_2O_4$ 359.1090, found 359.1092.

*Ethyl 2-(6-tert-Butyl-2-oxo-4-phenyl-2H-chromen-3-yl)-2,2-difluoroacetate (**2c**):* White solid (102.1 mg, 85%); mp 96−98 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50−7.51 (m, 3 H), 7.42 (d, 1 H, J = 2.0 Hz), 7.31−7.33 (m, 2 H), 7.26 (dd, 1 H, J_1 = 8.5 Hz, J_2 = 2.0 Hz), 7.00 (d, 1 H, J = 8.5 Hz), 4.34 (q, 2 H, J = 7.5 Hz), 1.34 (s, 9 H), 1.33 (t, 3 H, J = 7.5 Hz).^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8 (t, J = 32.1 Hz), 159.4 (t, J = 4.3 Hz), 158.4, 156.0, 153.2, 133.1, 129.0, 128.4, 128.2, 127.6 (t, J = 2.5 Hz), 122.4, 117.7, 117.0 (t, J = 22.8 Hz), 113.6, 112.0 (t, J = 251.0 Hz), 63. 2, 35.4, 30.9, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.7 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{23}H_{23}F_2O_4$ 401.1559, found 401.1558.

*Ethyl 2,2-Difluoro-2-(6-fluoro-2-oxo-4-phenyl-2H-chromen-3-yl)-acetate (**2d**):* White solid (82.5 mg, 76%); mp 109−110 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.53 (m, 3 H), 7.30−7.32 (m, 2 H), 7.06−7.15 (m, 2 H), 6.93−6.95 (m, 1 H), 4.35 (q, 2 H, J = 7.2 Hz), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 164.3, 162.6 (t, J = 31.9 Hz), 158.7 (t, J = 4.3 Hz), 155.7, 154.3 (d, J = 13.4 Hz), 132.7, 130.9 (d, J = 10.4 Hz), 129.2, 128.4, 127.5 (t, J = 2.4 Hz), 117.0 (t, J = 23.1 Hz), 113.1 (d, J = 22.4 Hz), 111.8 (t, J = 251.9 Hz), 104.4 (d, J = 25.6 Hz), 63.3, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.8 (s, 2 F), 102.3 (s, 1 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{19}H_{14}F_3O_4$ 363.0839, found 363.0836.

*Ethyl 2-(6-Chloro-2-oxo-4-phenyl-2H-chromen-3-yl)-2,2-difluoroacetate (**2e**):* White solid (90.7 mg, 80%); mp 98−100 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.53 (m, 3 H), 7.42 (d, 1 H, J = 2.0 Hz), 7.29−7.32 (m, 2 H), 7.17−7.20 (m, 1 H), 7.00 (d, 1 H, J = 8.8 Hz), 4.35 (q, 2 H, J = 7.2 Hz), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 (t, J = 31.9 Hz), 158.4 (t, J = 4.5 Hz), 155.5, 153.3, 139.6, 132.4, 129.8, 129.3, 128.4, 127.5 (t, J = 2.4 Hz), 125.4, 118.9, 117.9 (t, J = 22.9 Hz), 117.1, 111.7 (t, J = 251.9 Hz), 63.4, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 98.0 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{19}H_{14}ClF_2O_4$ 379.0543, found 379.0538.

*Ethyl 2-(6-Bromo-2-oxo-4-phenyl-2H-chromen-3-yl)-2,2-difluoroacetate (**2f**):* White solid (92.4 mg, 73%); mp 121−123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 1 H, J = 1.6 Hz), 7.52 (t, 3 H, J = 3.2 Hz), 7.29−7.35 (m, 3 H), 6.92 (d, 1H, J = 3.2 Hz), 4.35 (q, 2 H, J = 7.2 Hz), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 (t, J = 32.0 Hz), 158.3 (t, J = 4.4 Hz), 155.6, 153.2, 132.4, 129.8, 129.3, 128.4, 128.3, 127.8, 127.5 (t, J = 2.4 Hz), 120.0, 119.2, 118.2 (t, J = 22.9 Hz), 111.7 (t, J = 252.0 Hz), 63.3, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 98.0 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{19}H_{14}BrF_2O_4$ 423.0038, found 423.0042.

*Ethyl 2,2-Difluoro-2-(2-oxo-4,6-diphenyl-2H-chromen-3-yl)-acetate (**2g**):* White solid (107.1 mg, 85%); mp 102−104 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 3 H, J = 7.2 Hz), 7.44−7.54 (m, 7 H), 7.36 (t, 2 H, J = 3.6 Hz), 7.12 (d, 1 H, J = 8.4 Hz), 4.36 (q, 2 H, J = 7.2 Hz), 1.35 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8 (t, J = 31.8 Hz), 159.2, 156.0, 153.6, 146.6, 138.6, 132.9, 129.23, 129.17, 129.1, 129.0, 128.3, 127.6 (t, J = 2.4 Hz), 127.3, 123.6, 119.1, 117.5 (t, J = 23.6 Hz), 114.9, 111.9 (t, J = 251.6 Hz), 63.3, 13.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.7 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{25}H_{19}F_2O_4$ 421.1246, found 421.1240.

*Ethyl 2,2-Difluoro-2-(2-oxo-4-phenyl-6-(trifluoromethoxy)-2H-chromen-3-yl)acetate (**2h**):* White solid (105.3 mg, 82%); mp 89−90 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.54 (m, 3 H), 7.31−7.33 (m, 2 H), 7.28 (s, 1 H), 7.13 (d, 1 H, J = 7.2 Hz), 7.07 (d, 1 H, J = 8.8 Hz), 4.35 (q, 2 H, J = 7.2 Hz), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5 (t, J = 31.8 Hz), 158.4 (t, J = 4.3 Hz), 155.3, 153.8, 152.4, 132.4, 130.5, 129.3, 128.4, 127.5 (t, J = 2.3 Hz), 120.2 (q, J = 257.8 Hz), 118.6, 118.0 (t, J = 22.6 Hz), 116.8, 111.6 (t, J = 252.1 Hz), 108.7, 63. 4, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 98.1

DOI: 10.1021/acs.joc.5b00305
J. Org. Chem. 2015, 80, 4766−4770

(s, 2 F), 57.8 (s, 3 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{20}H_{14}F_5O_5$ 429.0756, found 429.0759.

*Ethyl 2,2-Difluoro-2-(6-methoxy-2-oxo-4-phenyl-2H-chromen-3-yl)acetate (**2i**):* White solid (97.6 mg, 87%); mp 77−79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.50 (m, 3 H), 7.30−7.32 (m, 2 H), 6.95 (d, 1 H, J = 9.2 Hz), 6.87 (d, 1 H, J = 2.4 Hz), 6.76 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 2.4 Hz), 4.35 (q, 2 H, J = 7.2 Hz), 3.89 (s, 3 H), 1.33 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 163.0 (t, J = 32.1 Hz), 159.4 (t, J = 4.3 Hz), 156.4, 155.1, 133.2, 130.0, 129.0, 128.2, 127.6 (t, J = 2.5 Hz), 114.6 (t, J = 23.2 Hz), 113.6, 113.1, 112.1 (t, J = 250.8 Hz), 100.5, 63.2, 56.0, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.1 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{20}H_{17}F_2O_5$ 375.1039, found 375.1035.

*Ethyl 2,2-Difluoro-2-(6-iodo-2-oxo-4-phenyl-2H-chromen-3-yl)-acetate (**2j**):* White solid (73.3 mg, 52%); mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 1 H, J = 1.2 Hz), 7.51−7.55 (m, 4 H), 7.28−7.30 (m, 2 H), 6.74 (d, 1 H, J = 8.8 Hz), 4.35 (q, 2 H, J = 7.2 Hz), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 (t, J = 32.0 Hz), 158.2 (t, J = 4.5 Hz), 155.7, 152.8, 134.2, 132.4, 129.6, 129.3, 128.4, 127.5 (t, J = 2.5 Hz), 126.0, 119.7, 118.4 (t, J = 23.0 Hz), 111.7 (t, J = 252.1 Hz), 99.7, 63.4, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 98.0 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{19}H_{14}F_2IO_4$ 470.9900, found 470.9904.

*Ethyl 2,2-Difluoro-2-(7-methyl-2-oxo-4-phenyl-2H-chromen-3-yl)acetate (**2k**):* White solid (63.6 mg, 59%); mp 91−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (t, 3 H, J = 3.2 Hz), 7.41 (d, 1 H, J = 8.4 Hz), 7.29−7.33 (m, 3 H), 6.82 (s, 1 H), 4.35 (q, 2 H, J = 7.2 Hz), 2.28 (s, 3 H),1.33 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8 (t, J = 31.9 Hz), 159.2 (t, J = 4.5 Hz), 156.1, 151.3, 134.7, 134.6, 133.0, 129.0, 128.4, 128.2, 127.6(t, J = 2.4 Hz), 119.8, 117.9 (t, J = 22.5 Hz), 116.6, 111.9 (t, J = 251.5 Hz), 63.2, 20.9, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.8 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{20}H_{17}F_2O_4$ 359.1090, found 359.1089.

*Ethyl 2,2-Difluoro-2-(5-methyl-2-oxo-4-phenyl-2H-chromen-3-yl)acetate (**2k′**):* Oil (15.8 mg, 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, 3 H, J = 3.2 Hz), 7.46 (d, 1 H, J = 7.2 Hz), 7.30−7.32 (m, 2 H), 7.10 (t, 1 H, J = 7.2 Hz), 6.89 (d, 1 H, J = 8.0 Hz), 4.35 (q, 2 H, J = 7.2 Hz), 2.50 (s, 3 H),1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8 (t, J = 32.1 Hz), 159.1 (t, J = 4.6 Hz), 156.4, 151.5, 134.7, 133.2, 128.9, 128.2, 127.6 (t, J = 2.6 Hz), 126.5, 126.4, 124.7, 120.0, 117.7 (t, J = 22.6 Hz), 111.9 (t, J = 251.5 Hz), 63.2, 15.5, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.8 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{20}H_{17}F_2O_4$ 359.1090, found 359.1093.

*Ethyl 2,2-Difluoro-2-(6,7-dimethyl-2-oxo-4-phenyl-2H-chromen-3-yl)acetate (**2l**):* White solid (74.8 mg, 67%); mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, 3 H, J = 3.2 Hz), 7.29−7.32 (m, 2 H), 7.19 (s, 1 H), 6.75 (s, 1 H), 4.34 (q, 2 H, J = 7.2 Hz), 2.36 (s, 3 H), 2.17 (s, 3 H), 1.33 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (t, J = 32.1 Hz), 159.4 (t, J = 4.5 Hz), 156.2, 151.6, 144.1, 133.8, 133.2, 128.9, 128.5, 128.2, 127.6 (t, J = 2.4 Hz), 117.8, 117.4, 116.8 (t, J = 22.9 Hz), 120.0 (t, J = 251.0 Hz), 63.1, 20.3, 19.4, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.6 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{21}H_{19}F_2O_4$ 373.1246, found 373.1245.

*Ethyl 2,2-Difluoro-2-(5,7-dimethyl-2-oxo-4-phenyl-2H-chromen-3-yl)acetate (**2m**):* White solid (78.1 mg, 70%); mp 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.51 (m, 3 H), 7.28−7.31 (m, 3 H), 6.64 (s, 1 H), 4.35 (q, 2 H, J = 7.2 Hz), 2.46 (s, 3 H), 2.23 (s, 3 H), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (t, J = 32.0 Hz), 159.3, 156.5, 149.7, 136.0, 134.0, 133.3, 128.9, 128.2, 127.6 (t, J = 2.4 Hz), 126.09, 126.06, 119.7, 117.5 (t, J = 22.6 Hz), 111.9 (t, J = 251.2 Hz), 63.2, 20.9, 15.5, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.8 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{21}H_{19}F_2O_4$ 373.1246, found 373.1248.

*Ethyl 2,2-Difluoro-2-(6-methyl-2-oxo-4-p-tolyl-2H-chromen-3-yl)-acetate (**2p**):* White solid (92.6 mg, 83%); mp 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, 2 H, J = 7.6 Hz), 7.17−7.21 (m, 3 H), 6.98−7.03 (m, 2 H), 4.34 (q, 2 H, J = 7.2 Hz), 2.46 (s, 3 H), 2.45 (s, 3 H), 1.33 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (t, J = 32.1 Hz), 159.3 (t, J = 4.5 Hz), 156.6, 153.2, 145.1, 139.0, 130.1, 128.9, 128.5, 127.6 (t, J = 2.5 Hz), 126.0, 117.9, 116.9, 116.8 (t, J = 22.6 Hz), 112.0 (t, J = 251.0 Hz), 63.1, 21.7, 21.4, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.5 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{21}H_{19}F_2O_4$ 373.1246, found 373.1249.

*Ethyl 2,2-Difluoro-2-(6-methyl-2-oxo-4-m-tolyl-2H-chromen-3-yl)acetate (**2q**):* White solid (83.7 mg, 75%); mp 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, 1 H, J = 7.6 Hz), 7.29 (d, 1H, J = 8.4 Hz), 7.20 (s, 1 H), 7.11 (d, 2 H, J = 7.6 Hz), 7.02 (d, 1 H, J = 8.4 Hz), 6.96 (d, 1 H, J = 8.4 Hz), 4.35 (q, 2 H, J = 7.2 Hz), 2.46 (s, 3 H), 2.42 (s, 3 H), 1.33 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (t, J = 31.9 Hz), 159.3 (t, J = 4.3 Hz), 156.4, 153.2, 145.2, 138.0, 133.0, 128.9, 129.7, 128.6, 128.09 (t, J = 2.3 Hz), 128.06, 126.0, 124.7 (t, J = 2.4 Hz), 117.9, 117.0, 116.7 (t, J = 22.8 Hz), 111.9 (t, J = 251.0 Hz), 63.1, 21.7, 21.5, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.7 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{21}H_{19}F_2O_4$ 373.1246, found 373.1243.

*Ethyl 2,2-Difluoro-2-(4-(4-fluorophenyl)-6-methyl-2-oxo-2H-chromen-3-yl)acetate (**2r**):* White solid (92.5 mg, 82%); mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.32 (m, 2 H), 7.18−7.23 (m, 3 H), 7.04 (d, 1 H, J = 8.0 Hz), 6.93 (d, 1 H, J = 8.0 Hz), 4.35 (q, 2 H, J = 7.2 Hz), 2.47 (s, 3 H), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (t, J = 32.1 Hz), 159.3 (t, J = 4.5 Hz), 156.6, 153.2, 145.1, 139.0, 130.1, 128.9, 128.5, 127.6 (t, J = 2.5 Hz), 126.0, 117.9, 116.9, 116.8 (t, J = 22.6 Hz), 112.0 (t, J = 251.0 Hz), 63.1, 21.7, 21.4, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.5 (s, 2 F), 112.0 (s, 1 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{20}H_{16}F_3O_4$ 377.0995, found 377.0997.

*Ethyl 2-(4-(4-Chlorophenyl)-6-methyl-2-oxo-2H-chromen-3-yl)-2,2-difluoroacetate (**2s**):* White solid (100.1 mg, 85%); mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 2 H, J = 8.4 Hz), 7.26 (d, 2 H, J = 8.4 Hz), 7.22 (s, 1 H), 7.04 (d, 1 H, J = 8.0 Hz), 6.92 (d, 1 H, J = 8.0 Hz), 4.35 (q, 2 H, J = 7.2 Hz), 2.47 (s, 3 H), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7 (t, J = 32.0 Hz), 159.0 (t, J = 4.5 Hz), 154.9, 153.2, 145.5, 135.2, 131.5, 129.1 (t, J = 2.5 Hz), 128.6, 128.1, 126.2, 117.4, 117.2 (t, J = 22.8 Hz), 117.1, 111.9 (t, J = 251.4 Hz), 63.2, 21.8, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.4 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{20}H_{16}ClF_2O_4$ 393.0699, found 393.0701.

*Ethyl 2,2-Difluoro-2-(6-methyl-2-oxo-4-biphenyl-2H-chromen-3-yl)acetate (**2t**):* White solid (93.7 mg, 72%); mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, 2 H, J = 8.0 Hz), 7.67 (d, 2 H, J = 7.6 Hz), 7.49 (t, 2 H, J = 7.6 Hz), 7.40 (t, 3 H, J = 8.0 Hz), 7.23 (s, 1 H), 7.04 (s, 2 H), 4.36 (q, 2 H, J = 7.2 Hz), 2.47 (s, 3 H), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (t, J = 32.1 Hz), 159.3 (t, J = 4.5 Hz), 156.1, 153.3, 145.3, 141.8, 140.0, 132.0, 129.0, 128.5, 128.2 (t, J = 2.6 Hz), 127.8, 127.1, 126.8, 126.1, 117.8, 117.1, 117.0 (t, J = 22.8 Hz), 112.0 (t, J = 251.4 Hz), 63.2, 21.8, 13.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ 97.4 (s, 2 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{26}H_{21}F_2O_4$ 435.1403, found 435.1406.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wjfu@lynu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (Project Nos. U1204205, 21202078, and 21363004) and Program for Innovative Research Team (in Science and Technology) in University of Henan Province (14IRTSTHN008).

DOI: 10.1021/acs.joc.5b00305
J. Org. Chem. 2015, 80, 4766−4770

REFERENCES

(1) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626. (c) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868. (d) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (e) Aráoz, R.; Anhalt, E.; René, L.; Badet-Denisot, M.-A.; Courvalin, P.; Badet, B. *Biochemistry* **2000**, *39*, 15971. (f) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465.

(2) (a) Iida, T.; Hashimoto, R.; Aikawa, K.; Ito, S.; Mikami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 9535. (b) Ge, S.; Arlow, S. I.; Mormino, M. G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 14401. (c) Zhou, Q.; Ruffoni, A.; Gianatassio, R.; Fujiwara, Y.; Sella, E.; Shabat, D.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3949. (d) Ma, G.; Wan, W.; Hu, Q.; Jiang, H.; Wang, J.; Zhu, S.; Hao, J. *Chem. Commun.* **2014**, *50*, 7527. (e) Fujita, T.; Sanada, S.; Chiba, Y.; Sugiyama, K.; Ichikawa, J. *Org. Lett.* **2014**, *16*, 1398. (f) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494. (g) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524. (h) Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090. (i) Feng, Z.; Chen, F.; Zhang, X. *Org. Lett.* **2012**, *14*, 1938.

(3) (a) Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 1669. (b) Belhomme, M.; Poisson, T.; Pannecouke, X. *Org. Lett.* **2013**, *15*, 3428. (c) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **2004**, *125*, 509. (d) Leung, L.; Linclau, B. *J. Fluorine Chem.* **2008**, *129*, 986. (e) Ma, G.; Wan, W.; Li, J.; Hu, Q.; Jiang, H.; Zhu, S.; Wang, J.; Hao, J. *Chem. Commun.* **2014**, *50*, 9749.

(4) (a) Caillot, G.; Dufour, J.; Belhomme, M.-C.; Poisson, T.; Grimaud, L.; Pannecoucke, X.; Gillaizeau, I. *Chem. Commun.* **2014**, *50*, 5887. (b) Belhomme, M. C.; Poisson, T.; Pannecoucke, X. *J. Org. Chem.* **2014**, *79*, 7205.

(5) (a) Lin, Q.; Chu, L.; Qing, F.-L. *Chin. J. Chem.* **2013**, *31*, 885. (b) Jung, J.; Kim, E.; You, Y.; Cho, E. J. *Adv. Synth. Catal.* **2014**, *356*, 2741.

(6) (a) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (b) Wallentin, C. J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875. (c) Jiang, H.; Huang, C.; Guo, J.; Zeng, C.; Zhang, Y.; Yu, S. *Chem.—Eur. J.* **2012**, *18*, 15158. (d) Yu, C.; Iqbal, N.; Park, S.; Cho, E. J. *Chem. Commun.* **2014**, *50*, 12284. (e) Fu, W.; Zhu, M.; Zou, G.; Xu, C.; Wang, Z. *Asian J. Org. Chem.* **2014**, *3*, 1273.

(7) Sun, X.; Yu, S. *Org. Lett.* **2014**, *16*, 2938.

(8) (a) Walkinshaw, A. J.; Xu, W.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 12532. (b) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332. (c) Beccalli, E. M.; Broggini, G.; Gazzolab, S.; Mazzaa, A. *Org. Biomol. Chem.* **2014**, *12*, 6767. (d) Iqbal, N.; Jung, J.; Park, S.; Cho, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 539. (e) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882. (f) Xiong, Y.; Wu, M.; Zhang, X.; Ma, C.; Huang, L.; Zhao, L.; Tan, B.; Liu, X. *Org. Lett.* **2014**, *16*, 1000. (g) Gao, P.; Shen, Y.; Fang, R.; Hao, X.; Qiu, Z.; Yang, F.; Yan, X.; Wang, Q.; Gong, X.; Liu, X.; Liang, Y.-M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7629. (h) Xu, J.; Wang, Y. L.; Gong, T. J.; Xiao, B.; Fu, Y. *Chem. Commun.* **2014**, *50*, 12915. (i) Hua, H.; He, Yu.; Qiu, Yi.; Li, Y.; Song, B.; Gao, P.; Song, X.; Guo, D.; Liu, X.; Liang, Y.-M. *Chem.—Eur. J.* **2015**, *21*, 1468. (j) Mi, X.; Wang, C.; Huang, M.; Wu, Y.; Wu, Y. *J. Org. Chem.* **2015**, *80*, 148. (k) Yan, K.; Yang, D.; Wei, W.; Wang, F.; Shuai, F.; Li, Q.; Wang, H. *J. Org. Chem.* **2015**, *80*, 1550.

(9) Mi, X.; Wang, C.; Huang, M.; Zhang, J.; Wu, Y.; Wu, Y. *Org. Lett.* **2014**, *16*, 3356.

(10) Li, Y.; Lu, Y.; Qiu, G.; Ding, Q. *Org. Lett.* **2014**, *16*, 4240.

(11) Wei, W.; Wen, J.; Yang, D.; Guo, M.; Wang, Y.; You, J.; Wang, H. *Chem. Commun.* **2015**, *51*, 768.

(12) (a) Fu, W.; Xu, F.; Fu, Y.; Xu, C.; Li, S.; Zou, D. *Eur. J. Org. Chem.* **2014**, 709. (b) Fu, W.; Zhu, M.; Xu, F.; Fu, Y.; Xu, C.; Zou, D. *RSC Adv.* **2014**, *4*, 17226. (c) Fu, W.; Xu, F.; Fu, Y.; Zhu, M.; Yu, J.; Xu, C.; Zou, D. *J. Org. Chem.* **2013**, *78*, 12202. (d) Fu, W.; Zhu, M.; Zou, G.; Xu, C.; Wang, Z. *Synlett* **2014**, *25*, 2513.

(13) Song, C. E.; Jung, D.-U.; Choung, S. Y.; Roh, E. J.; Lee, S.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6183.

DOI: 10.1021/acs.joc.5b00305
J. Org. Chem. 2015, 80, 4766−4770