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Preparation of 3-Acyl-4-aryl-coumarins via Metal-free Tandem Oxidative Acylation/Cyclization between Alkynoates with Aldehydes

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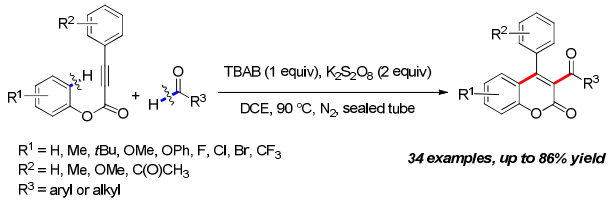


ABSTRACT

A new and efficient metal-free tandem acylation/cyclization of alkynoates with aldehydes was developed for the synthesis of 3-acyl-4-aryl-coumarins. The reaction was achieved by the addition of acyl radical to alkynes and a C-H bond functionalization to form two new C-C bonds simultaneously.

INTRODUCTION

Coumarins, an important class of heterocycles, are commonly found in natural compounds[1], pharmaceuticals[2], dyes[3], and as versatile synthetic blocks[4] in organic synthesis. Among these compounds, 3-acyl derivatives (coumarin-chalcone hybrid compounds) have received considerable attention since they display important biological activities[5] such as antioxidant activity, monoamine oxidase (MAO) inhibitor, antimalarial, antitumor, and antiinflammatory. Because of these important applications, various methods for their synthesis have been reported (Fig. 1, eqn (1), (2), (3), (4)).[6, 7, 8, 9] However, these protocols can suffer from several drawbacks, such as inaccessible substrates and catalysts, tedious performances, hazardous reagents, low atom economy, and limited substrate scope. Therefore, the development of general, highly efficient and direct strategies to access 3-acylcoumarins is still desirable in synthetic chemistry.

Recently, oxidative coupling involving a C-H functionalization process has begun to emerge as an alternative route for C-C bond formation.[10] The current

protocol enables the direct construction of target molecules by avoiding the prefunctionalization of the coupling partners, and serves as an elegant example of an atom economy approach. A lot of efforts have been devoted to the oxidative coupling with an aldehyde C(sp^2)-H bond to introduce a carbonyl group, and significant improvements have been made in recent years. Many groups successfully developed the transition-metal-catalyzed direct arylation of aldehydes.[11] The direct oxidative coupling of aldehyde C(sp^2)-H bonds with alkenes has been employed to furnish saturated ketones[12], β-peroxy ketones[13] or unsaturated ketones[14]. In addition, alkynes have been widely used in oxidative transformations catalyzed by the transition-metal complexes (especially Rh^I catalysts) to obtain the α-alkenyl ketones via hydroacylation.[15]Recently, transition-metal-free cross-coupling has been employed as an environmentally friendly and alternative approach to the metal catalyzed/mediated transformations.[16] In this context, Liang and Li respectively demonstrated the tandem oxidative coupling of alkynes with aldehydes via a single-electron-transfer (SET) process to produce fluorine and 3-acylspiro[4,5]trienone derivatives.[17] Inspired by these works and based on our previous study,[18] herein, we describe a metal-free TBAB-mediated oxidative tandem coupling of alkynoates with aldehydes for selective synthesis of biologically attractive 3-acylcoumarins (Fig. 1, eqn (5)). This method was achieved by sequential acylation and carbocyclization to form two new C-C bonds simultaneously, providing a new, efficient and atom-economic route to 3-acyl-4-aryl-coumarins.

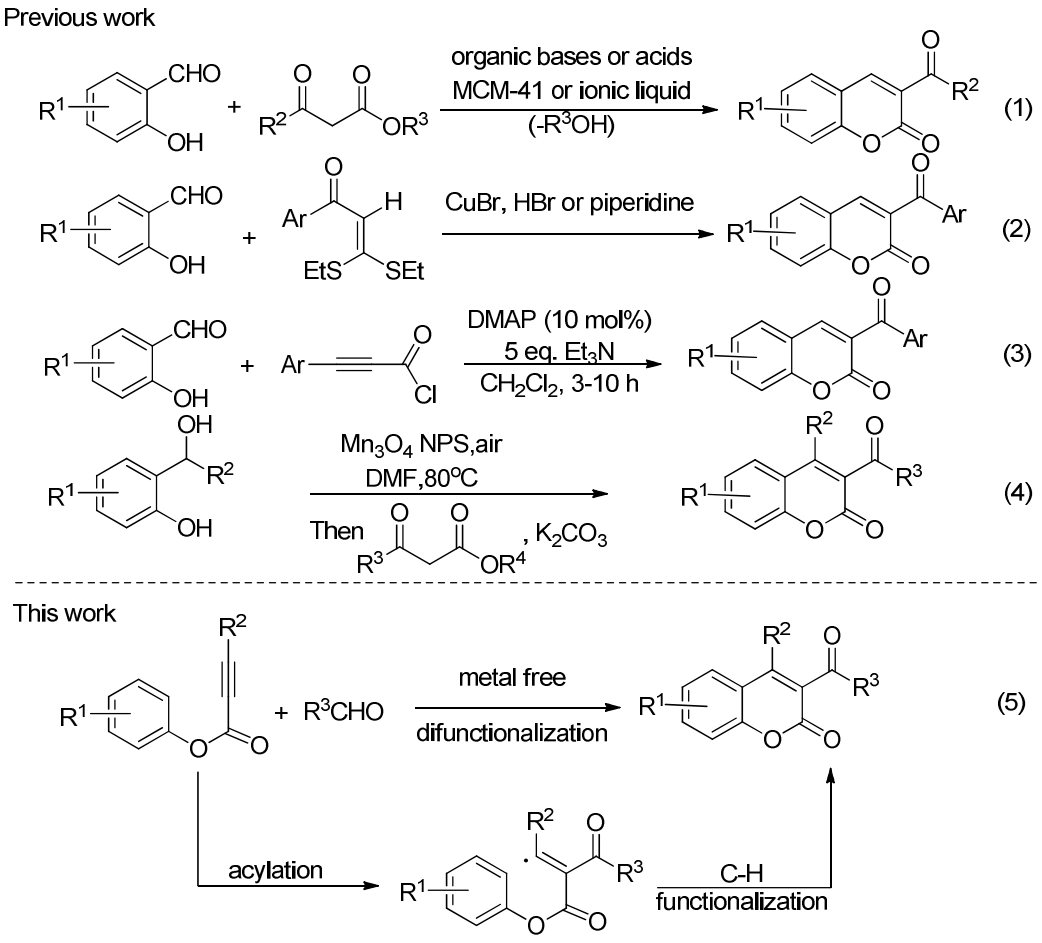


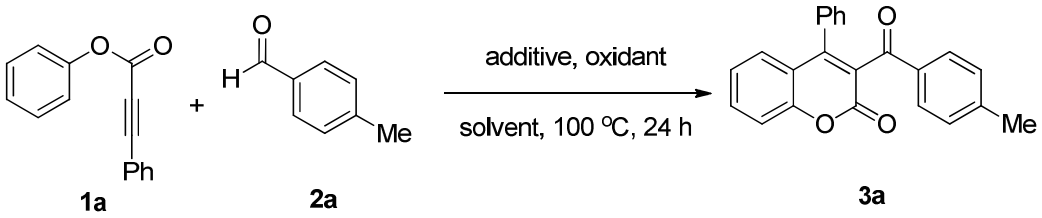
Figure1 Synthesis of 3-acylcoumarins

RESULTS AND DISCUSSION

At the outset of our investigation, the reaction conditions were optimized by using phenyl 3-phenylpropiolate (**1a**) and diethyl *p*-tolualdehyde (**2a**). According to the protocol by Liang et al. on fluorine derivatives formation from TBHP/PivOH system,[17a] the desired product **3a** was only obtained in 37% yield (Table 1, entry 1). Fortunately, the first breakthrough was achieved when we replaced PivOH with TBAB as an additive (Table 1, entry 2). Next, various oxidants were examined in the presence of TBAB, and $K_2S_2O_8$ was found to be the most efficient oxidant for this reaction (Table 1, entries 3-5). Other quaternary ammonium salts (Bu_4NF, Bu_4NCl, and Et_4NBr) led to a slight decrease in product yield of **3a** (Table 1, entries 6-8). Notably, *n*-Bu_4NI as an efficient catalyst[19] in radical chemistry showed negligible activity (Table 1, entry 9), and no product **3a** was formed without TBAB (Table 1, entry 10). Various solvents were also surveyed, revealing that DCE is the best suited solvent as compared to other solvents such as CH_3CN, dioxane, toluene,

chlorobenzene and H_2O (Table 1, entries 11-15). The yield was increased to 73% by using 4 equiv of **2a** (Table 1, entry 16). Lowering the reaction temperature to 90 °C was feasible, however, reducing further to 80 °C led to a lower yield (Table 1, entries 17, 18). The yields were markedly decreased when the amount of TBAB was reduced to 0.5 equiv (Table 1, entry 19). In addition, the structure of **3a** was confirmed by X-ray analysis (see supporting information).[20]

Table 1. Optimization of Conditions[a]



entry	additive	oxidant	yield[b] (%)
1[c]	PivOH	TBHP	37
2[c]	TBAB	TBHP	51
3	TBAB	$K_2S_2O_8$	59
4	TBAB	$Na_2S_2O_8$	55
5	TBAB	$(NH_4)_2S_2O_8$	55
6	TBAC	$K_2S_2O_8$	57
7	TBAF	$K_2S_2O_8$	34
8	TEAB	$K_2S_2O_8$	52
9	TBAI	$K_2S_2O_8$	trace
10	-	$K_2S_2O_8$	nr
11[d]	TBAB	$K_2S_2O_8$	nr
12[e]	TBAB	$K_2S_2O_8$	nr
13[f]	TBAB	$K_2S_2O_8$	17
14[g]	TBAB	$K_2S_2O_8$	25

15[h]	TBAB	$K_2S_2O_8$	32
16[i]	TBAB	$K_2S_2O_8$	73
17[i, j]	TBAB	$K_2S_2O_8$	75
18[i, k]	TBAB	$K_2S_2O_8$	62
19[i, l]	TBAB	$K_2S_2O_8$	65

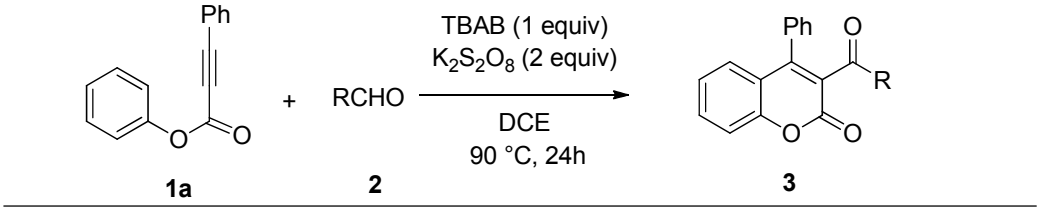
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), additive (0.25 mmol), oxidant (0.5 mmol), 1,2-dichloroethane (DCE, 1.5 mL) in a sealed tube under N_2 at 100 °C (oil bath) for 24 h, PivOH: pivalic acid; TBAF: *n*-Bu_4NF; TBAC: *n*-Bu_4NCl; TBAB: *n*-Bu_4NBr; TBAI: *n*-Bu_4NI; TEAB: Et_4NBr. [b] Isolated yields. [c] 70 % aq. [d] CH_3CN as solvent. [e] Dioxane as solvent. [f] Toluene as solvent. [g] Chlorobenzene as solvent. [h] H_2O as solvent. [i] 4 equiv of **2a** (2.0 mmol). [j] 90 °C (oil bath). [k] 80 °C (oil bath). [l] 0.5 equiv TBAB.

Under the optimal conditions, various aldehydes were firstly evaluated with phenyl 3-phenylpropiolate (**1a**). As demonstrated in Scheme 1, the metal-free acylation/cyclization reaction could proceed well to give corresponding products in moderate to good yields. The substrates bearing electron-donating groups at the *para*-position of the aromatic rings work more efficiently than those bearing electron-withdrawing groups (**3a**-**3g**) except product **3d**. Although *meta*-substituted benzaldehydes were also suitable for this transformation, generally, a slight decrease in product yields was found (**3h**-**3k**). Due to the steric effect, *ortho*-substituted benzaldehydes gave target products only in moderate yields (**3l**-**3n**). Alkyl and cyclic aldehydes could also be used as the coupling partners to provide the corresponding products in moderate yields (**3o**-**3q**).

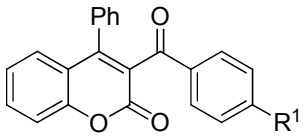
Encouraged by above results, we next focused our attention on the scope of aryl alkynoates (Scheme 2). Generally, the reactions with either electron-rich or electron-poor groups at the 4-positions of phenoxy ring proceeded well, and the corresponding products were furnished in good yields except **4c** (**4a**-**4g**). With a strong electron-withdrawing group (CF_3) on the phenoxy ring, the product **4g** was only obtained in 38% yield. It was found that the steric effect on the phenoxy ring was distinct. A moderate yield (57%) was obtained with the reaction of 3,5-dimethyl substituted aryl phenylpropiolate (**4i**). Furthermore, no product was formed for *ortho*-substituted system (**4j**). Upon using substrates with methyl group at the meta-position of the phenoxy ring, a mixture of two regioisomers **4k** and **4k'** were formed in a ratio of 1.6:1, however, aryl alkynoates bearing *meta*-methoxyl substituted phenoxy ring gave the product **4l** in 76% yield with complete regiocontrol.

In addition, different substituted aryl groups linked with the alkynyl could also be used to construct the 3-acyl-4-arylcoumarin derivatives in moderate to good yields (**4m**-**p**). Disappointingly, no desired product was observed when phenyl 2-octynoate was employed in the reaction.

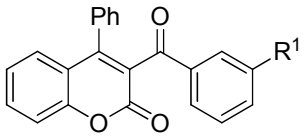
Scheme 1. Cyclization of Phenyl Alkynoate **1a** with Various Aldehydes **2**[a,b]



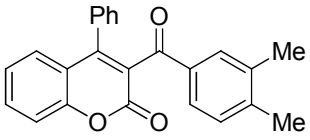
1a **2** **3**



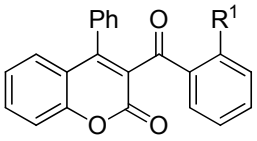
3a, R^1 = Me (75%)
3b, R^1 = H (77%)
3c, R^1 = OMe (86%)
3d, R^1 = F (85%)
3e, R^1 = Cl (70%)
3f, R^1 = Br (69%)
3g, R^1 = CF_3 (38%)



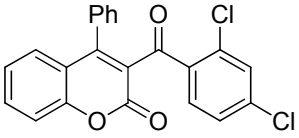
3h, R^1 = Me (75%)
3i, R^1 = OMe (72%)
3j, R^1 = Cl (49%)



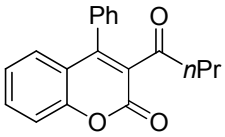
3k (55%)



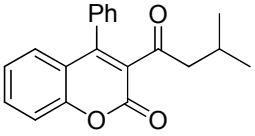
3l, R^1 = Me (67%)
3m, R^1 = OH (55%)



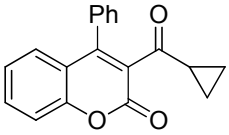
3n (52%)



3o (57%)



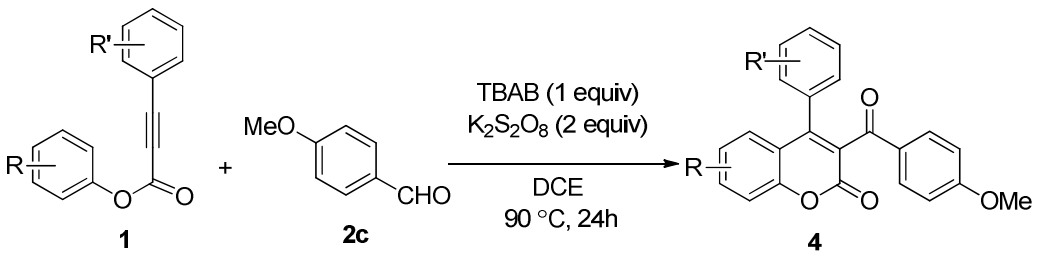
3p (61%)

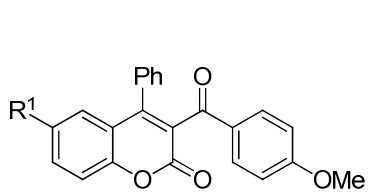


3q (37%)

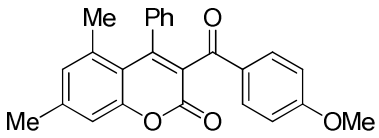
[a] Reaction conditions: **1a** (0.25 mmol), **2** (1.0 mmol), TBAB (0.25 mmol), $K_2S_2O_8$ (0.5 mmol), DCE (1.5 mL) in a sealed tube under N_2 at 90 °C (oil bath) for 24 h. [b] Isolated yields.

Scheme 2. Cyclization of Various Alkynoates **1** with 4-Methoxybenzaldehyde **2c**[a, b]

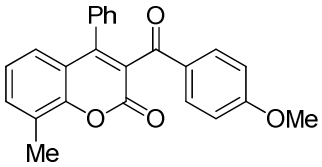




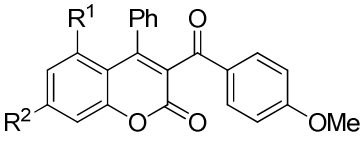
4a, R^1 = Me (80%)
4b, R^1 = *t*Bu (77%)
4c, R^1 = OMe (41%)
4d, R^1 = OPh (79%)
4e, R^1 = F (79%)
4f, R^1 = Cl (70%)
4g, R^1 = Br (74%)
4h, R^1 = CF_3 (54%)



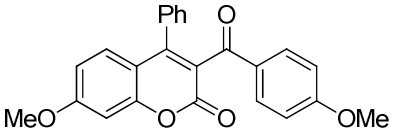
4i (57%)



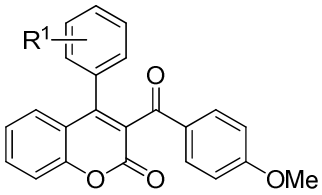
4j (0%)



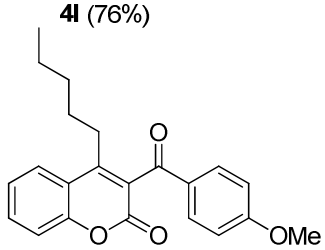
4k, R^1 = H, R^2 = Me
4k', R^1 = Me, R^2 = H
75%, **4k**:**4k'** = 1.6:1



4l (76%)



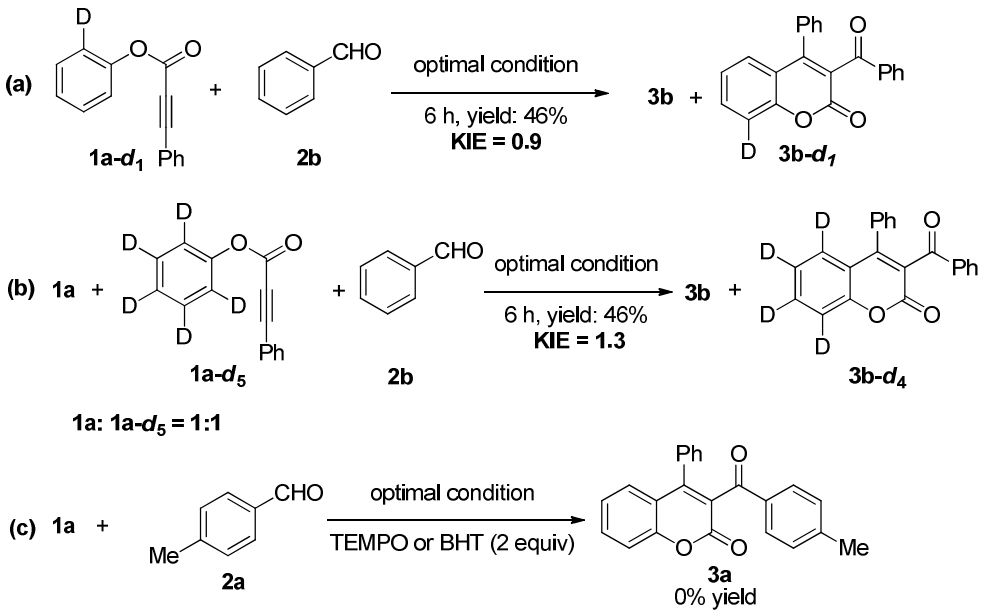
4m, R^1 = 4-OMe (60%)
4n, R^1 = 4-Me (70%)
4o, R^1 = 4-$COCH_3$ (53%)
4p, R^1 = 2-Me (80%)



4q (nr)

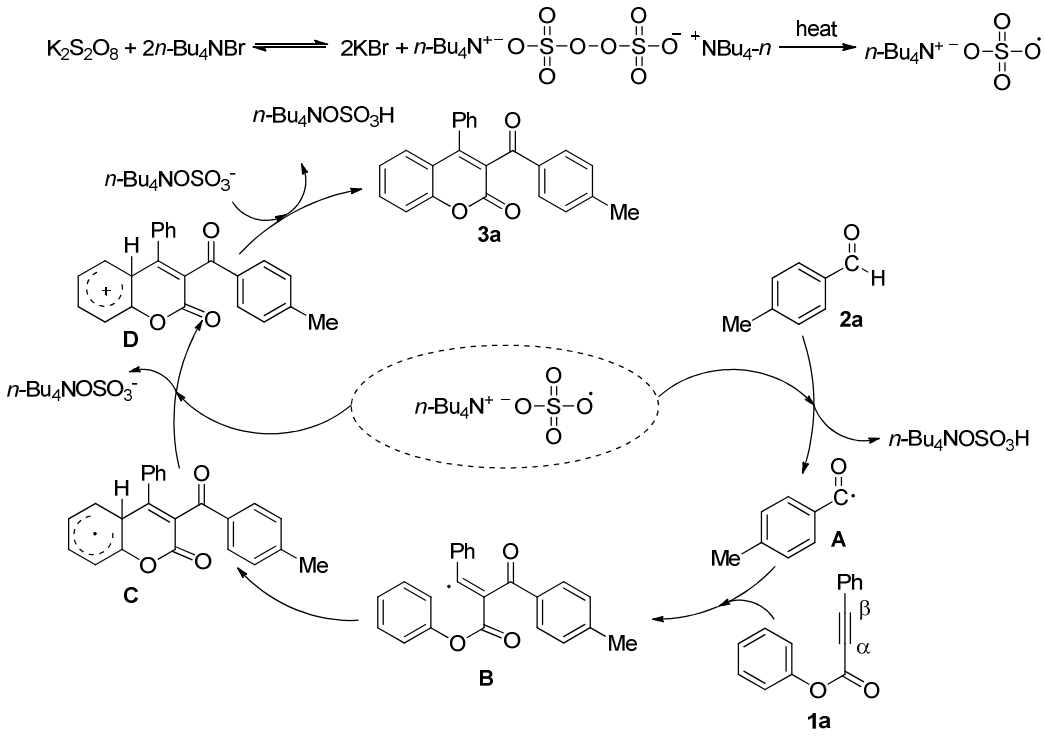
[a] Reaction conditions: **1** (0.25 mmol), **2c** (4-methoxybenzaldehyde, 1.0 mmol), TBAB (0.25 mmol), $K_2S_2O_8$ (0.5 mmol), DCE (1.5 mL) in a sealed tube under N_2 at 90 °C (oil bath) for 24 h. [b] Isolated yields.

Scheme 3. Control Experiments.



To obtain a detailed mechanism for this transformation, some control experiments were performed. The intramolecular and intermolecular kinetic isotope effects (k_H/k_D = 0.9 and 1.3) were measured by using the deuterium labeled substrates [D_1]-**1a** and [D_5]-**1a** in competing experiments (Scheme 3). The observed low k_H/k_D values imply that the C-H bond cleavage is not the rate-limiting step in this process. Subsequently, a radical scavenger TEMPO or BHT (2,2,6,6-tetramethylpiperidinooxy or 2,6-di-tert-butyl-4-methylphenol) was added to the reaction mixture. The formation of **3a** was suppressed, and an adduct of *p*-tolualdehyde (**2a**) with TEMPO or BHT was detected from ESI-MS analysis (see supporting information). Thus, we inferred that the acylation/cyclization reaction may involve a radical mechanism.

Scheme 4. Possible Mechanism



Based on the results above and previous reports[13, 17], a plausible reaction mechanism via free-radical-type process is depicted in Scheme 4. Initially, the peroxydisulfate was reacted with TBAB to generate the bis(tetrabutylammonium) peroxydisulfate which could be readily converted into the tetrabutylammonium sulfate radical anions at high temperature.[11k, 21] The tetrabutylammonium sulfate radical reacted with **2a** to form an acyl radical **A**. Selective addition of the radical **A** to the α-position of the C=O bond in alkynoate **1a** generated the vinyl radical **B**. The intermediate **B** then cyclized to the arene to form the radical intermediate **C**. Subsequently, a single electron transfer from intermediate **C** to another sulfate radical could give cation **D** which was deprotonated by formed sulfate dianion to give the product **3a** and another bisulfate anion.

In summary, we have demonstrated a novel approach to the synthesis of biologically attractive 3-acyl-4-aryl-coumarins starting with readily prepared alkynoates and the commercially available aldehydes. Various 3-acyl-4-aryl-coumarins were selectively prepared in moderate to high yields. This method comprises an acylation with concomitant arene formation, providing a new, efficient and atom-economic route to the coumarin core structure. We anticipate further development of the presented method and its application towards systhesis of bioactive compounds.

EXPERIMENTAL SECTION

General Information. All reactions were performed under a N_2 atmosphere. Solvents were dried and degassed by standard methods before use. All alkynoates were synthesized according to reported procedures.[22] Purification of the reaction products was carried out by column chromatography using silica gel. Analytical TLC was performed on a silica gel GF 254 Plate. NMR spectra were recorded on a 400MHz NMR spectrometer (400MHz for ^{1}H and 100MHz for ^{13}C) using $CDCl_3$ and DMSO-d_6 as solution. Chemical shifts δ are reported in ppm relative to Me_4Si or residual $CHCl_3$. The multiplicity of signals is designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). High resolution mass spectra (HRMS) were obtained on an MSD-Trap spectrometer with micromass MS software using electrospray ionisation (ESI). X-ray analysis were obtained with a X-ray single crystal diffractometer. Melting points were measured on microscopic apparatus and are uncorrected.

General Procedure for Carbon-cyclization of Alkynoates and Aldehydes. Compound **1** (0.25 mmol), TBAB (0.25 mmol), $K_2S_2O_8$ (0.5 mmol) were added to a 25mL dried Schlenk tube with a magnetic bar and degassed with N_2 three times. Degassed 1,2-dichloroethane (1.5 mL) was added followed by the addition of aldehyde **2** (1.0 mmol). The tube was sealed and was stirred at 90 ^{o}C for the indicated time. The reaction mixture was diluted with EtOAc and filtered. The filtrate was concentrated under reduced pressure and then was purified by chromatography on silica gel (elute: EtOAc/ Petroleum ether (bp 60-90 °C) 1/1 - 1/10, v/v) to give the desired product.

*3-(4-Methylbenzoyl)-4-phenyl-2H-chromen-2-one (**3a**)*: 63.8 mg, 75%; yellow solid; mp 146-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.1 Hz, 2H), 7.65-7.60 (m, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.37-7.35 (m, 3H), 7.32-7.26 (m, 4H), 7.18 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 191.0, 158.2, 152.9, 152.1, 144.4, 133.1, 132.1, 131.7, 128.9, 128.8, 128.7, 128.0, 127.9, 127.3, 125.3, 124.2, 118.8, 116.4, 21.2. HRMS (ESI): calcd for $C_{23}H_{17}O_3^+$ $[M+H]^+$ m/z 341.1172, found 341.1173.

*3-Benzoyl-4-phenyl-2H-chromen-2-one (**3b**)*: 62.8 mg, 77%; yellow solid; mp 146-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.3 Hz, 2H), 7.63-7.58 (m, 1H), 7.51-7.44 (m, 2H), 7.37-7.29 (m, 5H), 7.28-7.22 (m, 4H), 7.18 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6): δ 192.1, 158.7, 153.7, 152.9, 136.1, 133.8, 132.6, 132.2, 129.4, 129.2, 128.6, 128.5, 128.5, 127.9, 125.9, 124.6, 119.4, 117.1. HRMS (ESI): calcd for $C_{22}H_{15}O_3^+$ $[M+H]^+$ m/z 327.1016, found 327.1018.

*3-(4-Methoxybenzoyl)-4-phenyl-2H-chromen-2-one (**3c**)*: 81.3 mg, 86%; yellow solid; mp 121-123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.8 Hz, 2H), 7.62-7.58 (m, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.34-7.32 (m, 3H), 7.29-7.22 (m, 4H), 6.83 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$+ -DMSO-d_6): δ

190.1, 163.8, 158.5, 153.2, 152.1, 132.2, 131.9, 131.3, 129.1, 128.9, 128.2, 128.1, 127.5, 125.7, 124.3, 119.0, 116.6, 113.5, 55.1. HRMS (ESI): calcd for $C_{23}H_{16}O_4^+$ $[M+Na]^+$ m/z 379.0941, found 379.0937.

*3-(4-Flurobenzoyl)-4-phenyl-2H-chromen-2-one (**3d**)*: 73.1 mg, 85%; yellow solid; mp 179-181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.80 (m, 2H), 7.65-7.60 (m, 1H), 7.47 (d, J = 8.3 Hz, 3H), 7.36-7.34 (m, 3H), 7.31-7.24 (m, 4H), 7.03 (d, J = 8.3 Hz, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 166.1 (d, $J_{C\text{-}F}$ = 254.9 Hz), 158.7, 153.7, 153.1, 132.8, 132.7 (d, $J_{C\text{-}F}$ = 3.1 Hz), 132.2, 131.9 (d, $J_{C\text{-}F}$ = 9.6 Hz), 129.6, 128.6, 128.6, 127.9, 125.6, 124.7, 119.3, 117.2, 115.8 (d, $J_{C\text{-}F}$ = 22.0 Hz). HRMS (ESI): calcd for $C_{22}H_{14}FO_3^+$ $[M+H]^+$ m/z 345.0921, found 345.0922.

*3-(4-Chlorobenzoyl)-4-phenyl-2H-chromen-2-one (**3e**)*: 63.0 mg, 70%; yellow solid; mp 180-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.6 Hz, 2H), 7.64-7.59 (m, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.36-7.31 (m, 5H), 7.29-7.23 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 158.6, 153.7, 153.3, 140.3, 134.5, 132.9, 132.1, 130.5, 129.6, 128.9, 128.6, 128.6, 127.9, 125.4, 124.7, 119.3, 117.2. HRMS (ESI): calcd for $C_{22}H_{14}ClO_3^+$ $[M+H]^+$ m/z 361.0626, found 361.0627.

*3-(4-Bromobenzoyl)-4-phenyl-2H-chromen-2-one (**3f**)*: 69.7 mg, 69%; yellow solid; mp 182-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.60 (m, 3H), 7.51-7.45 (m, 3H), 7.36-7.34 (m, 3H), 7.32-7.23 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 158.7, 153.7, 153.4, 134.9, 132.9, 132.1, 131.9, 130.6, 129.7, 129.2, 128.7, 128.6, 128.0, 125.4, 124.7, 119.3, 117.2. HRMS (ESI): calcd for $C_{22}H_{14}BrO_3^+$ $[M+H]^+$ m/z 405.0121, found 405.0120.

*4-Phenyl-3-(4-trifluromethylbenzoyl)-2H-chromen-2-one (**3g**)*: 37.4 mg, 38%; yellow solid; mp 169-171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.0 Hz, 2H), 7.66-7.61 (m, 3H), 7.36-7.32 (m, 3H), 7.30-7.25 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 158.6, 153.9, 153.8, 138.9, 134.8 (q, $J_{C\text{-}F}$ = 32.5 Hz), 133.1, 132.1, 129.7, 129.4, 128.7, 128.6, 128.1, 125.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 125.2, 124.8, 123.4 (q, $J_{C\text{-}F}$ = 271.6 Hz), 119.3, 117.3. HRMS (ESI): calcd for $C_{23}H_{14}F_3O_3^+$ $[M+H]^+$ m/z 395.0890, found 395.0893.

*3-(3-Methylbenzoyl)-4-phenyl-2H-chromen-2-one (**3h**)*: 63.8 mg, 75%; yellow solid; mp 99-100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.57 (m, 3H), 7.47 (d, J = 8.2 Hz, 1H), 7.34-7.33 (m, 3H), 7.30 (s, 1H), 7.28-7.22 (m, 5H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 158.7, 153.6, 152.7, 138.3, 136.1, 134.6, 132.6, 132.3, 129.5, 129.4, 128.6, 128.5, 128.4, 127.9, 126.6, 126.1, 124.6, 119.4, 117.1, 21.1. HRMS (ESI): $C_{23}H_{17}O_3^+$ $[M+H]^+$ m/z 341.1172, found 341.1174.

*3-(3-Methoxybenzoyl)-4-phenyl-2H-chromen-2-one (**3i**)*: 64.0 mg, 72%; yellow solid; mp 100-101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.59 (m, 1H), 7.47-7.44 (m, 1H), 7.37-7.33 (m, 5H), 7.30-7.24 (m, 5H), 7.06-7.03 (m, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 159.7, 158.7, 153.6, 152.8, 137.4, 132.6, 132.2, 129.5, 129.4, 128.6, 128.5, 127.9, 125.9, 124.6, 122.4, 120.5, 119.3, 117.1, 112.7, 55.3. HRMS (ESI): calcd for $C_{23}H_{17}O_4^+$ $[M+H]^+$ m/z 357.1121, found 357.1122.

*3-(3-Chlorobenzoyl)-4-phenyl-2H-chromen-2-one (**3j**)*: 44.1 mg, 49%; yellow solid; mp 110-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.67-7.61 (m, 2H),

7.48-7.44 (m, 2H), 7.36-7.34 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 7.26-7.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 158.6, 153.7, 153.5, 127.7, 134.8, 133.6, 132.9, 132.1, 129.9, 129.6, 128.9, 128.6, 128.6, 128.0, 127.3, 125.2, 124.7, 119.2, 117.2. HRMS (ESI): calcd for $C_{22}H_{14}ClO_3^+$ $[M+H]^+$ m/z 361.0626, found 361.0628.

*3-(3,4-Dimethylbenzoyl)-4-phenyl-2H-chromen-2-one (**3k**)*: 48.7 mg, 55%; yellow solid; mp 180-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.58 (m, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.35-7.33 (m, 3H), 7.30-7.25 (m, 3H), 7.23 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 2.26 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 158.8, 153.6, 152.5, 143.7, 136.9, 134.1, 132.5, 132.4, 130.1, 129.8, 129.3, 128.6, 128.5, 127.9, 127.2, 126.2, 124.5, 119.5, 117.1, 20.1, 19.6. HRMS (ESI): calcd for $C_{24}H_{19}O_3^+$ $[M+H]^+$ m/z 355.1329, found 355.1330.

*3-(2-Methylbenzoyl)-4-phenyl-2H-chromen-2-one (**3l**)*: 57.0 mg, 67%; yellow solid; mp 160-162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.55 (m, 2H), 7.45 (d, J = 8.3 Hz, 1H), 7.33-7.29 (m, 4H), 7.23-7.19 (m, 4H), 7.14 (d, J = 7.6 Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 158.8, 153.7, 152.2, 140.1, 135.9, 132.6, 132.4, 132.4, 131.9, 131.0, 129.3, 128.5, 128.4, 127.5, 125.5, 125.4, 124.6, 119.6, 117.1, 21.2. HRMS (ESI): calcd for $C_{23}H_{17}O_3^+$ $[M+H]^+$ m/z 341.1172, found 341.1172.

*3-(2-Hydroxylbenzoyl)-4-phenyl-2H-chromen-2-one (**3m**)*: 47.0 mg, 55%; yellow solid; mp 179-181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.51 (s, 1H), 7.65-7.61 (m, 1H), 7.51-7.45 (m, 2H), 7.42-7.24 (m, 8H), 6.89 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 197.0, 162.1, 158.1, 153.1, 152.8, 136.9, 132.7, 131.7, 131.6, 129.4, 128.3, 128.1, 127.7, 124.5, 123.9, 119.3, 118.9., 118.7, 117.8, 116.8. HRMS (ESI): calcd for $C_{22}H_{15}O_4^+$ $[M+H]^+$ m/z 343.0965, found 343.0972.

*3-(2,4-Dichlorobenzoyl)-4-phenyl-2H-chromen-2-one (**3n**)*: 51.2 mg, 52%; yellow solid; mp 119-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.58 (m, 1H), 7.46-7.43 (m, 2H), 7.29 (d, J = 1.8 Hz, 1H), 7.24-7.22 (m, 4H), 7.15 (dd, J_1 = 8.4 Hz, J_2 = 1.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 158.3, 153.7, 138.8, 134.9, 133.5, 133.0, 132.4, 130.3, 129.5, 128.6, 128.3 (2C), 128.2, 127.3, 126.6, 124.6, 119.5, 117.1. HRMS (ESI): calcd for $C_{22}H_{13}Cl_2O_3^+$ $[M+H]^+$ m/z 395.0236, found 395.0235.

*3-Butyryl-4-phenyl-2H-chromen-2-one (**3o**)*: 41.6 mg, 57%; yellow solid; mp 72-73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.55 (m, 1H), 7.50-7.49 (m, 3H), 7.40 (d, J = 8.0 Hz, 1H), 7.32-7.31 (m, 2H), 7.25-7.22 (m, 2H), 2.45 (t, J = 7.2 Hz, 2H), 1.52-1.42 (m, 2H), 0.70 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 158.5, 153.4, 151.3, 132.5, 132.4, 129.6, 128.8, 128.7, 128.4, 127.9, 124.5, 119.4, 117.0, 45.5, 16.5, 13.3. HRMS (ESI): calcd for $C_{19}H_{17}O_3^+$ $[M+H]^+$ m/z 293.1172, found 293.1178.

*3-(3-Methylbutanoyl)-4-phenyl-2H-chromen-2-one (**3p**)*: 46.7 mg, 61%; yellow solid; mp 107-109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.55 (m, 1H), 7.51-7.49 (m, 3H), 7.40 (d, J = 8.0 Hz, 1H), 7.33-7.31 (m, 2H), 7.21 (d, J = 4.2 Hz, 2H), 2.36 (d, J = 6.8 Hz, 2H), 2.09-2.01 (m, 1H), 0.70 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 158.5, 153.3, 151.2, 132.5, 132.3, 129.6, 128.8, 128.7, 128.0, 127.9,

124.5, 119.4, 116.9, 52.4, 23.4, 22.2. HRMS (ESI): calcd for $C_{20}H_{19}O_3^+$ $[M+H]^+$ m/z 307.1329, found 307.1337.

*3-(Cyclopropanecarbonyl)-4-phenyl-2H-chromen-2-one (**3q**)*: 26.8 mg, 37%; yellow solid; mp 127-128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.56 (m, 1H), 7.50-7.48 (m, 3H), 7.29 (d, J = 8.0 Hz, 1H), 7.35-7.32 (m, 2H), 7.29-7.20 (m, 2H), 2.08-2.02 (m, 1H), 0.99-0.94 (m, 1H), 0.83-0.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5, 158.4, 153.5, 151.9, 132.9, 132.6, 129.5, 128.8, 128.1 (2C), 124.5, 119.4, 117.0, 23.1, 12.7. HRMS (ESI): calcd for $C_{19}H_{15}O_3^+$ $[M+H]^+$ m/z 291.1016, found 291.1016.

*3-(4-Methoxybenzoyl)-6-methyl-4-phenyl-2H-chromen-2-one (**4a**)*: 74.0 mg, 80%; yellow solid; mp 80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.8 Hz, 2H), 7.33-7.31 (m, 3H), 7.26-7.24 (m, 3H), 7.15 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 163.9, 159.1, 153.7, 152.5, 143.9, 132.6, 131.6, 129.4, 129.3, 128.6, 128.4, 127.5, 125.7, 124.9, 117.2, 116.9, 113.8, 55.4, 21.6. HRMS (ESI): calcd for $C_{24}H_{19}O_4^+$ $[M+H]^+$ m/z 371.1278, found 371.1284.

*6-t-Butyl-3-(4-methoxybenzoyl)-4-phenyl-2H-chromen-2-one (**4b**)*: 79.3 mg, 77%; yellow solid; mp 106-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.8 Hz, 2H), 7.46 (s, 1H), 7.33-7.26 (m, 6H), 7.21 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 163.9, 159.2, 157.2, 153.7, 152.4, 132.6, 131.6, 129.5, 129.3, 128.6, 128.4, 127.4, 125.2, 122.1, 116.9, 113.8, 113.8, 55.4, 35.2, 30.9. HRMS (ESI): calcd for $C_{27}H_{25}O_4^+$ $[M+H]^+$ m/z 413.1747, found 413.1751.

*3-(4-Methoxybenzoyl)-6-methoxyl-4-phenyl-2H-chromen-2-one (**4c**)*: 39.6 mg, 41%; yellow solid; mp 155-156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.8 Hz, 2H), 7.33-7.31 (m, 3H), 7.26-7.22 (m, 2H), 7.17 (d, J = 8.9 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.83-6.78 (m, 3H), 3.90 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 163.9, 163.3, 159.2, 155.5, 152.9, 132.8, 131.7, 129.7, 129.3, 128.9, 128.6, 128.4, 122.9, 113.8, 112.9, 112.8, 100.9, 55.9, 55.4. HRMS (ESI): calcd for $C_{24}H_{19}O_5^+$ $[M+H]^+$ m/z 387.1227, found 387.1230.

*3-(4-Methoxybenzoyl)-6-phenoxyl-4-phenyl-2H-chromen-2-one (**4d**)*: 88.4 mg, 79%; yellow solid; mp 145-146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.8 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.34-7.32 (m, 3H), 7.26-7.25 (m, 3H), 7.21 (d, J = 8.9 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 2.3 Hz, 1H), 6.87 (dd, J_1 = 8.8 Hz, J_2 = 2.3 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 164.1, 161.9, 158.9, 155.2, 154.9, 152.6, 132.7, 131.7, 130.2, 129.6, 129.4, 129.3, 128.6, 128.5, 128.3, 125.3, 123.9, 120.4, 119.2, 114.5, 114.4, 113.8, 105.1, 55.5. HRMS (ESI): calcd for $C_{29}H_{21}O_5^+$ $[M+H]^+$ m/z 449.1384, found 449.1386.

*6-Fluoro-3-(4-methoxybenzoyl)-4-phenyl-2H-chromen-2-one (**4e**)*: 73.8 mg, 79%; yellow solid; mp 143-144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.8 Hz, 2H), 7.35-7.33 (m, 3H), 7.29-7.26 (m, 3H), 7.17 (dd, J_1 = 8.8 Hz, J_2 = 2.3 Hz, 1H), 6.87 (td, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 190.1, 164.8 (d, J = 254.1 Hz), 164.2, 158.5, 154.8 (d, J = 15.8 Hz), 152.1, 132.3, 131.7, 129.7 (d, J = 10.2 Hz), 129.6, 129.3, 128.6, 128.5, 125.1 (d, J = 2.9 Hz), 116.3 (d, J = 2.8 Hz), 113.9, 112.7 (d, J = 22.3 Hz), 104.6 (d, J = 25.5 Hz), 55.4. HRMS (ESI): calcd for $C_{23}H_{16}FO_4^+$ $[M+H]^+$ m/z 375.1027, found 375.1027.

*6-Chloro-3-(4-methoxybenzoyl)-4-phenyl-2H-chromen-2-one (**4f**)*: 68.3 mg, 70%; yellow solid; mp 171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.7 Hz, 2H), 7.45 (s, 3H), 7.34-7.29 (m, 3H), 7.25-7.20 (m, 4H), 6.82 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 164.2, 158.2, 153.8, 151.8, 138.5, 132.0, 131.7, 129.6, 129.1, 128.8, 128.6, 128.5, 126.0, 125.1, 118.1, 117.3, 113.9, 55.4. HRMS (ESI): calcd for $C_{23}H_{16}ClO_4^+$ $[M+H]^+$ m/z 391.0732, found 391.0734.

*6-Bromo-3-(4-methoxybenzoyl)-4-phenyl-2H-chromen-2-one (**4g**)*: 80.3 mg, 74%; yellow solid; mp 147-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 1.4 Hz, 1H), 7.37-7.33 (m, 4H), 7.25 (t, J = 4.1 Hz, 2H), 7.13 (d, J = 8.6 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 164.2, 158.2, 153.7, 151.9, 131.9, 131.7, 129.6, 129.1, 128.8, 128.6, 128.5, 127.9, 126.6, 126.2, 120.3, 118.5, 113.9, 55.4. HRMS (ESI): calcd for $C_{23}H_{16}BrO_4^+$ $[M+H]^+$ m/z 435.0226, found 435.0231.

*3-(4-Methoxybenzoyl)-4-phenyl-6-trifluoromethyl-2H-chromen-2-one (**4h**)*: 57.2 mg, 54%; yellow solid; mp 141-142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.8 Hz, 2H), 7.70 (s, 3H), 7.47 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.37-7.35 (m, 3H), 7.27-7.26 (m, 2H), 6.83 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 164.3, 157.9, 153.2, 151.1, 133.9 (d, $J_{C\text{-}F}$ = 33.4 Hz), 132.3, 131.7, 130.2, 129.8, 128.7, 128.7, 128.6, 122.2, 123.0 (d, $J_{C\text{-}F}$ = 271.3 Hz), 121.0 (d, $J_{C\text{-}F}$ = 3.5 Hz), 114.5 (d, $J_{C\text{-}F}$ = 4.0 Hz), 114.0, 113.7, 55.5. HRMS (ESI): calcd for $C_{24}H_{16}F_3O_4^+$ $[M+H]^+$ m/z 425.0995, found 425.0997.

*5,7-Dimethyl-3-(4-methoxybenzoyl)-4-phenyl-2H-chromen-2-one (**4i**)*: 54.7 mg, 57%; yellow solid; mp 188-189 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.8 Hz, 2H), 7.33-7.31 (m, 3H), 7.27-7.24 (m, 3H), 6.85 (s, 1H), 6.81 (d, J = 8.9 Hz, 1H), 3.80 (s, 3H), 2.49 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 163.9, 159.1, 152.7, 150.1, 134.9, 133.6, 132.7, 131.7, 129.4, 129.1, 128.6, 128.3, 126.2, 125.8, 125.2, 118.9, 113.7, 55.4, 20.8, 15.5. HRMS (ESI): calcd for $C_{25}H_{21}O_4^+$ $[M+H]^+$ m/z 385.1434, found 385.1436.

*3-(4-Methoxybenzoyl)-7-methyl-4-phenyl-2H-chromen-2-one (**4k**)* and *3-(4-Methoxybenzoyl)-5-methyl-4-phenyl-2H-chromen-2-one (**4k'**)*: 78.6 mg, 85%; yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.45-7.38 (m, 2H), 7.35-7.30 (m, 7H), 7.30-7.26 (m, 4H), 7.15-7.08 (m, 2H), 7.03 (s, 1H), 6.82 (d, J = 8.8 Hz, 4H), 3.80 (s, 3H), 2.53 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 190.6, 164.1, 159.0, 158.9, 152.8, 152.4. 151.9, 151.8, 134.4, 133.8, 133.5, 132.8, 132.6, 131.7, 131.7, 129.4, 129.3, 129.2, 128.6, 128.5, 128.4, 127.5, 126.6, 126.1, 125.6, 123.9, 119.2, 119.2, 116.9, 113.8, 113.8, 55.4, 20.9, 15.7. HRMS (ESI): calcd for $C_{24}H_{19}O_4^+$ $[M+H]^+$ m/z 371.1278, found 371.1281.

*3-(4-Methoxybenzoyl)-7-methoxyl-4-phenyl-2H-chromen-2-one (**4l**)*: 73.3 mg, 76%; yellow solid; mp 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 1H), 7.32-7.26 (m, 4H), 7.16 (dd, J_1 = 8.8 Hz, J_2 = 2.9 Hz, 1H), 6.80 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 2.9 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 164.0, 158.9, 156.1, 152.1, 147.9, 132.4, 131.6, 129.4, 129.3, 128.5, 126.4, 119.9, 119.6, 117.9, 113.8, 110.6, 55.7, 55.4. HRMS (ESI): calcd for $C_{24}H_{19}O_5^+$ $[M+H]^+$ m/z 387.1227, found 387.1230.

*3-(4-Methoxybenzoyl)-4-(4-methoxyphenyl)-2H-chromen-2-one (**4m**)*: 57.8 mg, 60%, yellow solid; mp 150-151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.7 Hz, 2H), 7.60-7.56 (m, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.24-7.20 (m, 3H), 6.85-6.80 (m, 4H), 3.80 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 164.0, 160.3, 158.9, 153.6, 152.2, 132.4, 131.7, 130.2, 129.3, 127.9, 125.9, 124.5 (2H), 119.6, 117.1, 114.0, 113.8, 55.4, 55.2. HRMS (ESI): calculated for $C_{24}H_{19}O_5^+$ $[M+H]^+$ m/z 387.1227, found 387.1228.

*3-(4-Methoxybenzoyl)-4-(4-methylphenyl)-2H-chromen-2-one (*__4n__): 64.7 mg, 70%, yellow solid; mp 132-133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.8 Hz, 2H), 7.61-7.57 (m, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.34-7.31 (m, 1H), 7.27-7.22 (m, 1H), 7.18-7.12 (m, 4H), 6.84 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 164.2, 159.0, 153.7, 152.8, 139.6, 132.5, 131.8, 129.5, 129.5, 129.3, 128.7, 128.0, 126.1, 124.6, 119.7, 117.2, 113.9, 55.5, 21.4. HRMS (ESI): calculated for $C_{24}H_{19}O_4^+$ $[M+H]^+$ m/z 371.1278, found 371.1279.

*4-(4-Acetylphenyl)-3-(4-methoxybenzoyl)-2H-chromen-2-one (**4o**)*: 52.7 mg, 53%, yellow solid; mp 157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H), 7.65-7.60 (m, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.41-7.39 (m, 2H), 7.25 (d, J = 7.4 Hz, 1H), 7.18 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.83 (s, 3H), 2.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 190.0, 164.4, 158.6, 153.7, 151.4, 137.6, 137.2, 132.8, 131.8, 129.2, 129.1, 128.5, 127.6, 126.6, 124.8, 119.1, 117.3, 114.1, 55.5, 26.6. HRMS (ESI): calculated for $C_{25}H_{19}O_5^+$ $[M+H]^+$ m/z 399.1227, found 399.1227.

*3-(4-Methoxybenzoyl)-4-(2-methylphenyl)-2H-chromen-2-one (**4p**)*: 74.0 mg, 80%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.8 Hz, 2H), 7.60-7.56 (m, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.24-7.18 (m, 3H), 7.11-6.98 (m, 3H), 6.84 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 164.1, 159.0, 153.4, 153.2, 135.8, 132.5, 131.9, 131.5, 130.2, 129.3, 129.3, 128.2, 127.4, 126.5, 125.7, 124.7, 119.3, 117.0, 113.8, 55.4, 19.9. HRMS (ESI): calculated for $C_{24}H_{19}O_4^+$ $[M+H]^+$ m/z 371.1278, found 371.1279.

Intramolecular Kinetic Isotope Effect (KIE) Study (Scheme 3). To a 25 mL dried Schlenk tube were added alkynoate [D_1]-**1a** (0.25 mmol), TBAB (0.25 mmol), $K_2S_2O_8$ (0.5 mmol), benzaldehyde **2b** (1.0 mmol), and DCE (1.5 mL) under a N_2 atmosphere. After sealing the tube, the reaction mixture was stirred at 90 ^{o}C for 6 hours after which time the reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the desired product

in 46% yield. The ratio of deuterium to hydrogen was determined from the ^{1}H NMR relative integration values of H_a (7.26 ppm) based on H_b (7.61 ppm). (see Figure S1)

Intermolecular Kinetic Isotope Effect (KIE) Study (Scheme 3). To a 25mL dried Schlenk tube were added alkynoate **1a** (0.125 mmol), [D_1]-**1a** (0.125 mmol), TBAB (0.25 mmol), $K_2S_2O_8$ (0.5 mmol), benzaldehyde **2b** (1.0 mmol), and DCE (1.5 mL) under a N_2 atmosphere. After sealing the tube, the reaction mixture was stirred at 90 ^{o}C for 6 hours after which time the reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the desired product in 46% yield. The ratio of deuterium to hydrogen was determined from the ^{1}H NMR relative integration values of H_b (7.61 ppm) based on $H_{a'}$ (7.79 ppm). (see Figure S2)

Radical-trapping Experiments (Scheme 3). Two equivalents of radical scavenger (2,2,6,6-tetramethylpiperidinooxy or 2,6-di-tert-butyl-4-methylphenol) was added to the reaction of **1a** with **2a** in the standard conditions. After two hours, the reaction mixture was cooled to room temperature. The crude reaction mixture was detected by ESI-MS, and no peak of the desired product was found. An adduct of aldehyde with radical scavenger was detected shown in Figure S3 and S4.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of compounds **3** and **4** and crystal structure and data of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Borges, F.; Roleira, F.; Milhazes, N.; Uriarte, E.; Santana, L. *Front. Med. Chem.* **2009**, *4*, 23.

(2) (a) Goth, A. *Science* **1945**, *101*, 383. (b) Eckardt, T.; Hagen, V.; Schade, B.; Schmidt, R.; Schweitzer, C.; Bendig, J. *J. Org. Chem.* **2002**, *67*, 703. (c) Wang, C. J.; Hsieh, Y. J.; Chu, C. Y.; Lin, Y. Y.; Tseng, T. H. *Cancer Lett.* **2002**, *183*, 163. (d) Zhao, Y.; Zheng, Q.; Dakin, K.; Xu, K.; Martinez, M. L.; Li, W. H. *J. Am. Chem. Soc.* **2004**, *126*, 4653. (e) Komatsu, K.; Urano, Y.; Kojima, H.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 13447. (f) Signore, G.; Nifosi, R.; Albertazzi, L.; Storti, B.; Bizzarri, R. *J. Am. Chem. Soc.* **2010**, *132*, 1276. (g) Wang, C.; Wu, C.; Zhu, J.; Miller, R. H.; Wang, Y. *J. Med. Chem.*, **2011**, *54*, 2331. (h) Matos, M. J.; Vazquez-Rodriguez, S.; Santana, L.; Uriarte, E.; Fuentes-Edfuf, C.; Santos, Y.; Munoz-Crego, A. *Molecules*, **2013**, *18*, 1394.

(3) (a) Christie, R. M.; Lui, C. H. *Dyes Pigm.* **2000**, *47*, 79. (b) Schiedel, M. S.; Briehn, C. A.; Bauerle, P. *Angew. Chem. Int. Ed.* **2001**, *40*, 4677. (c) Uchiyama, S.; Takehira, K.; Yoshihara, T.; Tobita, S.; Ohwada, T. *Org. Lett.* **2006**, *8*, 5869. (d) Hirano, T.; Hiromoto, K.; Kagechika, H. *Org. Lett.* **2007**, *9*, 1315. (e) Turki, H.; Abid, S.; Fery-Forgues, S.; El Gharbi, R. *Dyes Pigm.* **2007**, *73*, 311.

(4) (a) Sastry, V. D. N.; Seshadri, T. R. *Proc. Ind. Acad. Sci.* 1942, *16A*, 29; *Chem. Abstr.* **1943**, *37*, 880. (b) Yamashita, M.; Okuyama, K.; Kawajiri, T.; Takada, A.; Inagaki, Y.; Nakano, H.; Tomiyama, M.; Ohnaka, A.; Teryama, I.; Kawasaki, I.; Ohta, S. *Tetrahedron* **2002**, *58*, 1497. (c) Nemeryuk, M. P.; Dimitrova, V. D.; Anisimova, O. S.; Sedov, A. L.; Soloveva, N. P.; Traven, V. F. *Chem. Heterocycl. Comp* **2003**, *39*, 1454.

(5) (a) Sandhu, S.; Bansal, Y.; Silakari, O.; Bansal, G. *Bioorg. Med. Chem.* **2014**, *22*, 3806. (b) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887.

(6) (a) Specht, D.-P.; Martic, P.-A.; Farid, S. *Tetrahedron* **1982**, *38*, 1203. (b) Raju, B.-C.; Tiwari, A.-K.; Kumar, J.-K.; Ali, A.-Z.; Agawane, S.-B.; Saidachary, G.; Madhusudana, K. *Bioorg. Med. Chem.* **2010**, *18*, 358. (c) Heravi, M.-M.; Poormohammad, N.; Beheshtiha, Y.-S.; Baghernejad, B.; Malakooti, R. *Chin. J. Chem.* **2009**, *27*, 968. (d) Heravi, M.-M.; Sadjadi, S.; Oskooie, H.-A.; Shoar, R.-H.; Bamoharram, F.-F. *Catal. Commun.* **2008**, *9*, 270. (e) Ranu, B.-C.; Jana, R. *Eur. J. Org. Chem.* **2006**, 3767. (f) Ajania, O. O.; Nwinyi, O. C. *J. Heterocycl. Chem.* **2010**, *47*, 179. (g) Tang, X.; Blake, A.-J.; Lewis, W.; Woodward, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1881.

(7) (a) Surya P. R., H.; Sivakumar, S. *J. Org. Chem.* **2006**, *71*, 8715. (b) Yuan, H.-J.; Wang, M.; Liu, Y.-J.; Liu, Q. *Adv. Synth. Catal.* **2009**, *353*, 112. (c) Yuan, H.; Wang, M.; Liu, Y.; Wang, L.; Liu, J.; Liu, Q. *Chem. Eur. J.* **2010**, *16*, 13450.

(8) Majumdar, K.C.; Samanta, S.; Ansary, I.; Roy, B. *RSC Adv.* **2012**, *1*, 2137.

(9) Sun, H.; Zhang, Y,; Guo, F.; Yan, Y.; Wan, C.; Zha, Z.; Wang, Z. *Eur. J. Org. Chem.* **2012**, 480.

(10) (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Mcglacken, G. P.; Bateman, L. M.; Bateman, L. *Chem. Soc. Rev.* **2009**, *38*, 2447. (c) Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (d) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540. (e) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (f) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (g) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (h) Xie, Y.-X.; Song, R.-J.; Xiang, J.-N.; Li, J.-H. *Chin. J. Org. Chem.* **2012**, *32*, 1555.

(11) For reviews, see: (a) Pan, C.; Jia, X.; Cheng, J. *Synthesis* **2012**, *44*, 677. For selected examples, see: (b) Tang, B.-X.; Song, R.-J.; Wu, C.-Y.; Liu, Y.; Zhou, M.-B.; Wei, W.-T.; Deng, G.-B.; Yin D.-L.; Li, J.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8900. (c)

Jia, X.; Zhang, S.; Wang,;W.; Luoand, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120. (d) Chan, C.-W.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 3926. (e) Basle, O.; Bidange, J.; Shuai, Q.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1145. (f) Wang, P.; Rao, H.; Hua, R.; Li, C.-J. *Org. Lett.* **2012**, *14*, 902. (g) Zhou, B.; Yang, Y.; Li, Y. *Chem. Commun.* **2012**, *48*, 5163. (h) Park, J.; Park, E.; Kim, A.; Lee, Y.; Chi, K.-W.; Kwak, J.; Jung, Y.; Kim, I. *Org. Lett.* **2011**, *13*, 4390. (i) Sharma, S.; Park, E.; Park, J.; Kim, I. *Org. Lett.* **2012**, *14*, 906. (j) Li, C.; Wang, L.; Li, P.; Zhou, W. *Chem. Eur. J.* **2011**, *17*, 10208. (k) Shi, Z.; Glorius, F. *Chem. Sci.* **2013**, *4*, 829. (l) Chan, C.-W.; Zhou, Z.; Yu, W.-Y. *Adv. Synth. Catal.* **2011**, *353*, 2999. (m) Sharma, S.; Park, J.; Park, E.; Kim, A.; Kim, M.; Kwak, J.-H.; Jung, Y.-H.; Kim, I.-S. *Adv. Synth. Catal.* **2013**, *355*, 332. (n) Yang, Y.; Zhou, B.; Li, Y. *Adv. Synth. Catal.* **2012**, *354*, 2916. (o) Matcha, K.; Antonchick, A.-P. *Angew. Chem. Int. Ed.* **2013**, *52*, 2082. (p) Li, X.-A.; Wang, H.-L.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 1794. (q) Wertz, S.; Leifert, D.; Studer, A. *Org. Lett.* **2013**, *15*, 928.

(12) (a) Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat. Chem.* **2010**, *2*, 592. (b) Fitzmaurice, R. J.; Ahern, J.; Caddick, S. *Org. Biomol. Chem.* **2009**, *7*, 235. (c) Tsujimoto, S.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2001**, 2352. (d) Tsujimoto, S.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, *44*, 5601. (e) Zhou, M.-B.; Song, R.-J.; Ouyang, X.-H.; Liu, Y.; Wei, W.-T.; Deng, G.-B.; Li, J.-H. *Chem. Sci.* **2013**, *4*, 2690.

(13) Liu, W.; Li, Y.; Liu, K.; Li, Z. *J. Am. Chem. Soc.* **2011**, *133*, 10756.

(14) (a) Shi, Z.; Schrcder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 8092. (b) Wang, J.; Liu, C.; Yuan, J.; Lei, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2256.

(15) For reviews, see: (a) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667. (b) Jun, C.-H.; Hong, J.-B.; Lee, D. L. *Synlett* **1999**, 1. (c) Jun, C.-H.; Jo, E.-A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, 1869. (d) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (e) Gonzalez-Rodriguez, C.; Willis, M. C. *Pure Appl. Cem.* **2011**, *83*, 577. (f) Leung, J. C.; Krische, M. J. *Chem. Sci.* **2012**, *3*, 2202.

(16) For reviews, see: (a) Ouyang, K.; Xi, Z. *Acta Chim. Sin.* **2013**, *71*, 13. (b) Shirakawa, E.; Hayashi, R. *Chem. Lett.* **2012**, *41*, 130. (c) Yanigasawa, S. Itami, K. *Chem. Cat. Chem.* **2011**, *3*, 827. (d) Wang, Y. *Synlett.* **2011**, 2901.

(17) (a) Luo, J.-Y.; Hua, H.-L.; Chen, Z.-S.; Zhou, Z.-Z.; Yang, Y.-F.; Zhou, P.-X.; He, Y.-T.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2014**, *50*, 1564. (b) Ouyang, X.-H.; Song, R.-J.; Li, Y.; Liu, B.; Li, J.-H. *J. Org. Chem.* **2014**, *79*, 4582.

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

(19) For selected examples, see: (a) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem. Eur. J.* **2011**, *17*, 4085. (b) Wei, W.; Zhang, C.; Xu,

Y.; Wan, X. *Chem. Commun.* **2011**, *47*, 10827. (c) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 3231.

(20) This crystal was deposited in the Cambridge Crystallographic Data Centre and assigned as CCDC 1022899.

(21) (a) Zhu, X.; Shi, Y.; Mao, H; Cheng Y.; Zhu, C. *Adv. Synth. Catal.* **2013**, *355*, 3558. (b) Yang, S.-G.; Hwang, J.-P.; Park, M.-Y.; Lee, K.; Kim, Y.-H. *Tetrahedron* **2007**, *63*, 5184.

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