JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

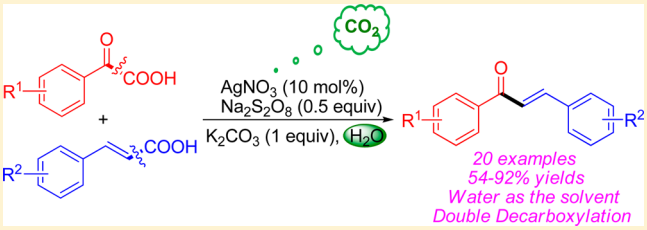
Silver-Catalyzed Double-Decarboxylative Cross-Coupling of α-Keto Acids with Cinnamic Acids in Water: A Strategy for the Preparation of Chalcones

Ning Zhang, Daoshan Yang,* Wei Wei, Li Yuan, Fafa Nie, Laijin Tian, and Hua Wang*

The Key Laboratory of Life-Organic Analysis and Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, Shandong P. R. China

Supporting Information

ABSTRACT: A silver-catalyzed double-decarboxylative protocol has been proposed for the construction of chalcone derivatives via cascade coupling of substituted α-keto acids with cinnamic acids under the mild aqueous conditions. The developed method for constructing C−C bonds via double-decarboxylative reactions is efficient, practical, and environmentally benign by using the readily available starting materials. It should provide a promising synthesis candidate for the formation of diverse and useful chalcone derivatives in the fields of synthetic and pharmaceutical chemistry.



Seeking mild, green, and selective approaches for the formation of C−C bonds has been of growing interest in organic chemistry.[1] Historically, the C−C bond forming reactions were mainly conducted by nucleophilic additions, substitutions, Diels−Alder reactions, and Friedel−Crafts-type reactions.[2] Recently, the transition-metal catalyzed or mediated coupling reactions have been emerging as the powerful tools for the C−C bond formation. In this respect, prefunctionalized substrates such as organometallic reagents, organohalides, or pseudo halides are coupled in these transformations under an aerobic conditions.[3] As an alternative, decarboxylative reactions have been introduced by Goossen,[4] Myers,[5] and other research groups.[6] Recently, tremendous progress has been made in the decarboxylative-coupling transformations using carboxylic acids as the substrates owing to that such coupling partners are easy to store and handle.[7] Notably, cinnamic acids and α-keto acids have been standing out as the remarkable coupling partners in decarboxylative transformations. In recent years, using α-keto acids as substrates in the decarboxylative reactions has been extensively studied, such as the visible-light-mediated amidations,[8] difunctionalization of activated alkenes,[9] and decarboxylative acylation of aromatic C−H bonds.[10] On the other hand, decarboxylation of cinnamic acids has also been investigated, such as the transition-metal catalyzed decarboxylative coupling of aryl or vinyl halides with cinnamic acids,[11] and radical pathways to formation of a C−C bond,[12] C−N bond,[13] and C−S bond.[14] Meanwhile, α-keto acids and cinnamic acids are the cheap and readily prepared chemical materials. In 2013, a Cu/Ag cocatalyzed double-decarboxylative coupling method for C−C bond formation was initially reported by Mai and coworkers.[15] Nevertheless, to the best of our knowledge, the direct double-decarboxylative cross-coupling of α-keto acids with cinnamic acids to form C−C bonds has never been exploited.

Chalcones as the biologically active molecules are ubiquitous in natural products and widely used as the important building blocks in the organic transformations.[16] However, a literature survey indicated that the synthetic methods for the construction of chalcone skeletons are rare. The traditional methods for chalcones synthesis are mainly focus on the Claisen−Schmidt reactions.[17] In 2013, Miura, Satoh, and coworkers described the decarboxylative arylation of 3-acylacrylic acids for the synthesis of chalcones in the presence of palladium catalysis.[18] Very recently, Su's group developed an elegant palladium-catalyzed decarboxylative coupling between aryl carboxylic acids and saturated propiophenones to access to chalcones.[19] However, it remains a challenging, but attractive, task to develop more practical and environmentally benign approaches for the synthesis of the useful chalcone derivatives.

In view of green chemistry, water as an ideal reaction media with environmentally benign and nontoxic characters has been attracting considerable attention. Besides that, water has been proven to affect the selectivity of lots of organic reactions and to enhance the reaction rates.[20] Herein, we report a novel and efficient strategy for the construction of chalcones via silver-catalyzed double-decarboxylative cross-coupling of α-keto acids with cinnamic acids in water (Scheme 1).

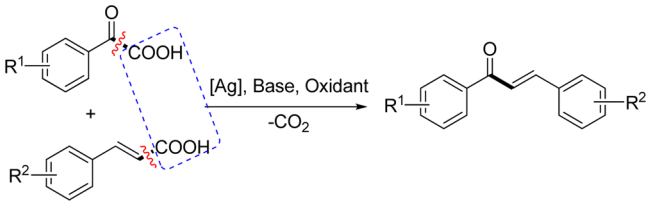
First, 2-oxo-2-phenylacetic acid (**1a**) and cinnamic acid (**2a**) were used as the model substrates to screen the reaction conditions, including the oxidants, catalysts, solvents, and reaction temperatures under a nitrogen atmosphere. As shown in Table 1, three oxidants such as $K_2S_2O_8$, $Na_2S_2O_8$, and

Received: November 19, 2014
Published: February 20, 2015

ACS Publications © 2015 American Chemical Society

DOI: 10.1021/jo502642n
J. Org. Chem. 2015, 80, 3258−3263

Scheme 1. Strategy to Chalcones via Decarboxylative Reaction of α-Keto Acids with Cinnamic Acids



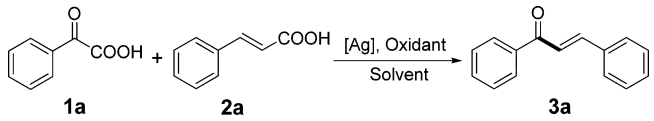
$(NH_4)_2S_2O_8$ were investigated at 50 °C by using 0.1 equiv of $AgNO_3$ as the catalyst, 2 equiv of K_2CO_3 as the base in 2 mL of CH_3CN/H_2O (v_1/v_2 = 1:1), and $Na_2S_2O_8$, which gave the highest yield (21%) (entries 1−3); no product was obtained in the absence of the oxidant (entry 15). The common silver salts, $AgNO_3$, Ag_2CO_3, Ag_2O, and AgOAc were tested in CH_3CN/H_2O (entries 2, 4−6) using $Na_2S_2O_8$ as the oxidant at 50 °C, and $AgNO_3$ was observed to be the most effective catalyst (entry 1, 4−6). Notably, the reaction did not proceed without the catalyst (entry 14). We attempted to use different solvents (compare entries 1, 7−9), and H_2O was superior to the other solvents (entry 1). Moreover, various reaction temperatures were examined (entries 9−12), and 100 °C was discovered to be more suitable for this reaction (entry 11). In addition, different amounts of K_2CO_3 were employed in the reactions (compare entries 12 and 13), and 2 equiv of K_2CO_3 provided the highest yield (entry 12). After the optimization process of oxidants, catalysts, temperature, and solvents, the various chalcone derivatives were synthesized under the optimized conditions: 10 mol % $AgNO_3$ as the catalyst, 1 equiv of $Na_2S_2O_8$ as the oxidant, 2 equiv of K_2CO_3 as the base, and H_2O as the solvent at 100 °C under a nitrogen atmosphere

As shown in Table 2, the scope and generality of this reaction was investigated under the optimized conditions. As expected, a series of chalcones could be efficiently obtained by this developed double-decarboxylative reaction. Generally, cinnamic acids with electron-donating or electron-withdrawing groups on the aryl ring could be smoothly transformed into the chalcones in moderate to good yields (Table 2, **3a**−**3t**). Cinnamic acids with the electron-donating group, such as a methoxy and a methyl group, could give good yields as compared to the cinnamic acids with the electron-withdrawing substituents. Furthermore, the effects of the substituent on α-keto acids was investigated. The catalytic efficiency was not obviously affected by steric hindrance in α-keto acids (Table 2, **3f**, **3g**, and **3p**−**3r**). Unfortunately, the α-keto acids bearing strong electron-withdrawing groups, and aliphatic ones, were the poor coupling partners in this new transformation (Table 2, **3u**−**3w**). Besides that, aliphatic conjugated acids, such as crotonic acid, did not work in the reaction (Table 2, **3x**). The silver-catalyzed double-decarboxylative reactions could tolerate some functional groups such as C−Cl bonds, C−Br bonds, and alkyl groups, which could be used for further transformations.

To investigate the mechanism further, the coupling of 2-oxo-2-phenylacetic acid (**1a**) with cinnamic acid (**2a**) was tested in the presence of a radical inhibitor, such as TEMPO (2,2,6,6-tetramethylpiperidine 1-oxy). The formation of **3a** was completely inhibited in the reaction [eq (1), Scheme 2], thereby indicating that a radical process might be involved. Treatment of benzaldehyde (**4a**) with 2-oxo-2-phenylacetic acid (**2a**) did not afford the product (**3a**) [eq (2), Scheme 2]. Besides that, the desired product (**3a**) was not observed when 2-oxo-2-phenylacetic acid (**1a**) was reacted with styrene (**5a**) under the standard conditions [eq (3), Scheme 2]. These preliminary results indicated that benzaldehyde (**4a**) and styrene (**5a**) might not be the important intermediates in the present transformations.

On the basis of these experimental results above, together with literature reports,[21] we proposed the tentative mechanism in Scheme 3. First, Ag(I) cation was oxidized to Ag(II) cation by peroxodisulfate. Then, α-keto acids anion **A** reacted with the Ag(II) cation to generate acyl radical **B** with releasing one

Table 1. Sliver-Catalyzed Coupling Reaction of 2-Oxo-2-phenylacetic Acid (1a) with Cinnamic Acid (2b) Leading to (*E*)-Chalcone (3a): Optimization of Conditions[a]

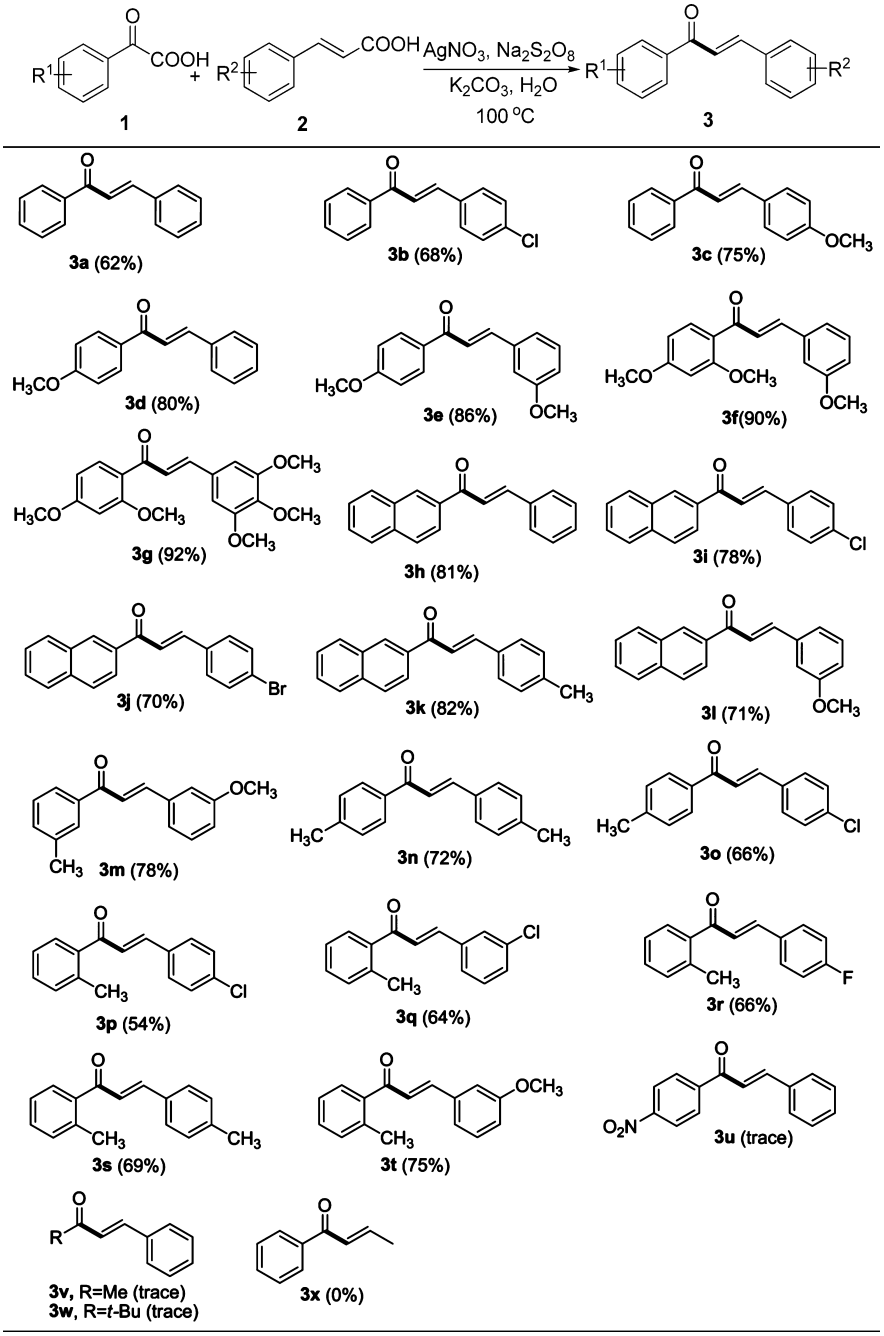


entry	cat.	oxidant	solvent	temp. [°C]	yield [%][b]
1	$AgNO_3$	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	50	13
2	$AgNO_3$	$Na_2S_2O_8$	CH_3CN/H_2O (1:1)	50	21
3	$AgNO_3$	$(NH_4)_2S_2O_8$	CH_3CN/H_2O (1:1)	50	16
4	Ag_2CO_3	$Na_2S_2O_8$	CH_3CN/H_2O (1:1)	50	9
5	Ag_2O	$Na_2S_2O_8$	CH_3CN/H_2O (1:1)	50	8
6	AgOAc	$Na_2S_2O_8$	CH_3CN/H_2O (1:1)	50	11
7	$AgNO_3$	$Na_2S_2O_8$	dioxane/H_2O (1:1)	50	25
8	$AgNO_3$	$Na_2S_2O_8$	acetone/H_2O (1:1)	50	16
9	$AgNO_3$	$Na_2S_2O_8$	H_2O	50	39
10	$AgNO_3$	$Na_2S_2O_8$	H_2O	25	0
11	$AgNO_3$	$Na_2S_2O_8$	H_2O	80	51
12	**$AgNO_3$**	**$Na_2S_2O_8$**	**H_2O**	**100**	**62**
13	$AgNO_3$	$Na_2S_2O_8$	H_2O	100	49[c]
14		$Na_2S_2O_8$	H_2O	100	0
15	$AgNO_3$		H_2O	100	0

[a]Reaction conditions: 2-oxo-2-phenylacetic acid (**1a**) (0.24 mmol), cinnamic acid (**2a**) (0.2 mmol), catalyst (0.02 mmol), oxidant (0.1 mmol), K_2CO_3(0.4 mmol), solvent (1.0 mL), reaction time (24 h) under nitrogen atmosphere. [b]Isolated yield. [c]In the presence of K_2CO_3 (1 equiv).

DOI: 10.1021/jo502642n
J. Org. Chem. 2015, 80, 3258−3263

Table 2. Sliver-Catalyzed Synthesis of Chalcone Derivatives via Decarboxylative Coupling of α-Keto Acids with Cinnamic Acids[a,b,c]



[a]Reaction conditions: under a nitrogen atmosphere, substituted α-keto acids (0.6 mmol), cinnamic acids (0.5 mmol), $AgNO_3$(0.05 mmol), $Na_2S_2O_8$ (0.25 mmol), H_2O (2.0 mL). [b]Isolated yield. [c]Reaction time (24 h).

molecule of CO_2 and Ag(I) cation. Subsequently, the addition of acyl radical **B** to the α-position of the double bond of cinnamate anion **C** led to the formation of intermediate **D**. Finally, this was followed by the loss of carbon dioxide and Ag(I) cation, which resulted in the chalcone products **E**.

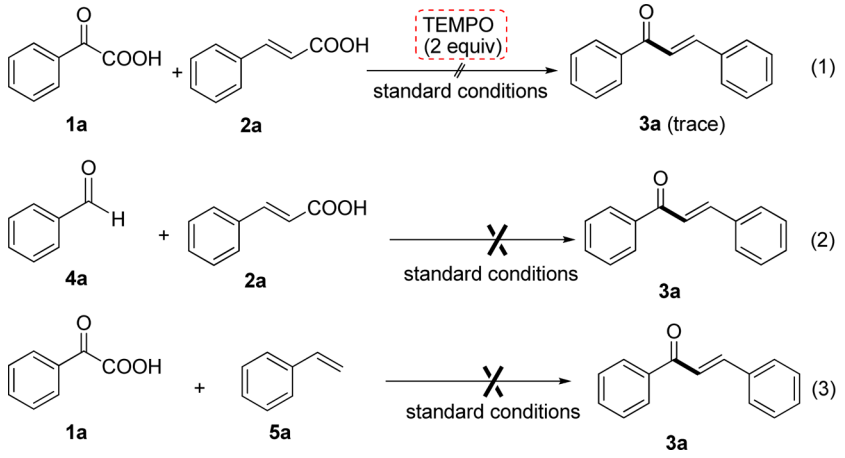
In summary, a novel and efficient protocol has been initially developed for the synthesis of chalcone derivatives via silver-catalyzed decarboxylative coupling of readily prepared α-keto acids and cinnamic acids in water. A series of chalcone frameworks could be efficiently obtained in moderate to good yields under the mild aqueous conditions.The easy and efficient approach could extend the scope of synthetic methods for the preparation of diverse chalcones, and it would attract much attention in synthetic and pharmaceutical chemistry.

■ EXPERIMENTAL SECTION

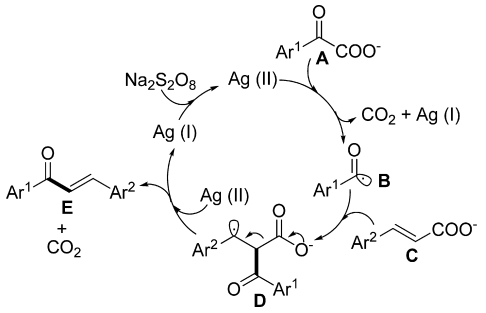
General. All commercially available reagent and chemicals were purchased from chemical suppliers and used as received without further purification. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as internal standard (400 MHz ^1H, 100 MHz ^{13}C) at room temperature. Mass analyses and HRMS were obtained by ESI on a TOF mass analyzer. Column chromatography was performed on silica gel (200−300 mesh).

DOI: 10.1021/jo502642n
J. Org. Chem. 2015, 80, 3258−3263

Scheme 2. Investigations of the Mechanism



Scheme 3. Possible Mechanism for the Synthesis of Chalcones



General Experimental Procedures. A 25 mL Schlenk tube was charged with $AgNO_3$ (8.5 mg, 0.05 mmol), potassium carbonate (69 mg, 1.0 mmol), α-keto acids (0.6 mmol), and cinnamic acids (0.5 mmol). After the reaction vessel was evacuated thrice and backfilled with nitrogen, 2 mL of H_2O was added to the solution by syringe under a stream of nitrogen. The tube was sealed, and then the mixture was stirred at 100 °C for 24 h. After completion of the reaction determined by TLC, the reaction solution was cooled down to room temperature; then the mixture was extracted with ethyl acetate or dichloromethane (3 × 4 mL). The combined organic phase was concentrated by a rotary evaporator, and the residue was purified by column chromatography on silica gel (200−300 mesh) to provide the desired product (**3**).

*(E)-Chalcone (**3a**):*[18] Following the general procedure, the product was isolated in 62% yield (64.5 mg). Eluent petroleum ether/ethyl acetate (30:1). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.05 (d, 2H, J = 8.0 Hz), 7.84 (d, 2H, J = 16.0 Hz), 7.68 (dd, 2H, J = 8.0 Hz), 7.62−7.52 (m, 4H), 7.46−7.44 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 190.6, 144.85, 134.93, 132.8, 130.6, 128.9, 128.6, 128.5, 128.4, 122.1. HRMS m/z calcd. for $C_{15}H_{12}O$ $[M + H]^+$: 209.0966, found: 209.0965.

*(E)-3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one (**3b**):*[22] Following the general procedure, the product was isolated in 68% yield (82.3 mg). Eluent petroleum ether/ethyl acetate (20:1). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.04 (d, 2H, J = 8.0 Hz), 7.79 (d, 2H, J = 16.0 Hz), 7.63−7.60 (m, 3H), 7.56−7.52 (m, 3H), 7.42 (d, 2H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 190.3, 143.3, 138.1, 136.5, 133.4, 132.9, 129.6, 129.3, 128.7, 128.5, 122.5. HRMS m/z calcd. for $C_{15}H_{11}ClO$ $[M + H]^+$: 243.0577, found: 243.0569.

*(E)-3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (**3c**):*[23] Following the general procedure, the product was isolated in 75% yield (89.2 mg). Eluent petroleum ether/ethyl acetate (30:1). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.04 (d, 2H, J = 8.0 Hz), 7.80 (d, 2H, J = 16.0 Hz), 7.62 (t, 1H, J = 8.0 Hz), 7.55 (s, 1H), 7.53 (d, 2H, J = 8.0 Hz), 7.37 (t, 1H, J = 8.0 Hz), 7.27 (d, 1H, J = 8.0 Hz), 7.18 (s, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 190.6, 160.0, 144.8, 138.2, 136.3, 132.8, 130.0, 128.6, 128.5, 122.5, 121.1, 116.3, 113.5, 55.4. HRMS m/z calcd. for $C_{16}H_{14}O_2$ $[M + H]^+$: 239.1072, found: 239. 1068.

*(E)-1-(4-Methoxyphenyl)-3-phenylprop-2-en-1-one (**3d**):*[24] Following the general procedure, the product was isolated in 80% yield (95.2 mg). Eluent petroleum ether/ethyl acetate (20:1). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.07 (d, 2H, J = 8.0 Hz), 7.83 (d, 1H, J = 16.0 Hz), 7.67 (dd, 2H, J = 8.0 Hz), 7.57 (d, 1H, J = 16.0 Hz), 7.45−7.43 (m, 2H), 7.82 (d, 2H, J = 8.0 Hz), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 188.8, 163.5, 144.0, 135.1, 131.1, 130.8, 130.3, 128.9, 128.4, 121.9, 113.9, 55.5. HRMS m/z calcd. for $C_{16}H_{14}O_2$ $[M + H]^+$: 239.1072, found: 239.1068.

*(E)-3-(3-Methoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**3e**):*[25] Following the general procedure, the product was isolated in 86% yield (115.2 mg). Eluent petroleum ether/ethyl acetate (20:1). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.96 (d, 2H, J = 8.0 Hz), 7.67 (d, 1H, J = 16.0 Hz), 7.46 (d, 1H, J = 16.0 Hz), 7.26−7.21 (m, 1H), 7.15 (d, 2H, J = 8.0 Hz), 7.08 (s, 1H), 6.90−6.85 (m, 3H), 3.79 (s, 3H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 188.4, 170.8, 163.4, 159.9, 143.7, 136.4, 131.0, 130.7, 129.8, 122.1, 120.9, 116.0, 113.7, 113.3, 55.3, 55.1. HRMS m/z calcd. for $C_{17}H_{16}O_3$ $[M + H]^+$: 269.1178, found: 269.1171.

*(E)-1-(2,4-Dimethoxyphenyl)-3-(3-methoxyphenyl)prop-2-en-1-one (**3f**):* Following the general procedure, the product was isolated in 90% yield (134 mg). Eluent petroleum ether/ethyl acetate (30:1). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.78 (d, 2H, J = 8.0 Hz), 7.66 (d, 1H, J = 16.0 Hz), 7.51 (d, 1H, J = 16.0 Hz), 7.33 (t, 1H, J = 8.0 Hz), 7.20 (d, 2H, J = 8.0 Hz), 7.14 (s, 1H), 6.95 (d, 2H, J = 8.0 Hz), 6.59 (dd, 1H, J = 8.0 Hz), 6.52 (s, 1H), 3.92 (s, 3H), 3.89(s, 3H), 3.86(s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 190.5, 164.2, 160.5, 160.0, 141.9, 137.0, 132.9, 129.8, 127.6, 122.2, 120.9, 115.6, 113.5, 105.3, 98.7, 55.8, 55.6, 55.3. HRMS m/z calcd. for $C_{18}H_{18}O_4$ $[M + H]^+$: 299.1283, found: 299.1276.

*(E)-1-(2,4-Dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**3g**):*[26] Following the general procedure, the product was isolated in 92% yield (164.6 mg). Eluent petroleum ether/ethyl acetate (20:1). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.76 (d, 2H, J = 8.0 Hz), 7.59 (d, 1H, J = 16.0 Hz), 7.39 (d, 1H, J = 16.0 Hz), 6.85 (s, 2H), 6.59 (d, 2H, J = 8.0 Hz), 6.53 (s, 1H), 3.92−3.90 (m, 15H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 190.6, 164.1, 160.3, 153.4, 142.3, 132.7, 131.0, 126.7, 122.3, 105.6, 105.2, 98.8, 60.9, 56.2, 55.8, 55.6. HRMS m/z calcd. for $C_{20}H_{22}O_6$ $[M + H]^+$: 359.1495, found: 359.1489

*(E)-1-(Naphthalen-2-yl)-3-phenylprop-2-en-1-one (**3h**):*[27] Following the general procedure, the product was isolated in 80% yield (103.2 mg). Eluent petroleum ether/ethyl acetate (20:1). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.35 (d, 1H, J = 8.0 Hz), 7.03 (d, 1H, J = 8.0 Hz), 7.95 (d, 1H, J = 8.0 Hz), 7.62−7.57 (m, 6H), 7.44−7.42 (m, 3H), 7.34 (d, 1H, J = 16.0 Hz), 6.53 (s, 1H), 3.92−3.90 (m, 15H). ^{13}C

DOI: 10.1021/jo502642n
J. Org. Chem. 2015, 80, 3258−3263

NMR ($CDCl_3$, 100 MHz, ppm) δ 195.8, 146.0, 137.1, 134.7, 133.9, 131.6, 130.7, 130.5, 129.0, 128.5, 128.4, 127.5, 127.2, 127.1, 126.5, 125.7, 124.5. HRMS m/z calcd. for $C_{19}H_{14}O$ $[M + H]^+$: 259.1123, found: 259.1121.

(E)-3-(4-Chlorophenyl)-1-(naphthalen-2-yl)prop-2-en-1-one ***(3i)***:[27] Following the general procedure, the product was isolated in 78% yield (113.8 mg). Eluent petroleum ether/ethyl acetate (10:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.36 (d, 1H, J = 8.0 Hz), 8.03 (d, 1H, J = 8.0 Hz), 7.94 (d, 1H, J = 8.0 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.61−7.51 (m, 6H), 7.39 (d, 1H, J = 8.0 Hz), 7.30 (d, 1H, J = 16.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 195.3, 144.3, 137.1, 136.9, 136.6, 133.9, 133.2, 131.8, 130.5, 129.6, 129.3, 128.5, 127.6, 127.5, 127.2, 126.6, 125.6, 124.5. HRMS m/z calcd. for $C_{19}H_{13}ClO$ $[M + H]^+$: 293.0733, found: 293.0730.

(E)-3-(4-Bromophenyl)-1-(naphthalen-2-yl)prop-2-en-1-one ***(3j)***:[27] Following the general procedure, the product was isolated in 75% yield (126.0 mg). Eluent petroleum ether/ethyl acetate (10:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.36 (d, 1H, J = 8.0 Hz), 8.03 (d, 1H, J = 8.0 Hz), 7.94 (d, 1H, J = 8.0 Hz), 7.60−7.55 (m, 6H), 7.46 (d, 1H, J = 8.0 Hz), 7.31 (d, 1H, J = 16.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 195.3, 144.3, 136.9, 133.9, 133.6, 132.3, 131.8, 130.8, 130.5, 129.8, 128.8, 128.5, 127.6, 127.2, 126.6, 125.6, 125.0, 124.5. HRMS m/z calcd. for $C_{19}H_{13}BrO$ $[M + H]^+$: 336.0150, 338.0129, found: 336.0155, 338.0136.

(E)-1-(Naphthalen-2-yl)-3-p-tolylprop-2-en-1-one ***(3k)***:[28] Following the general procedure, the product was isolated in 82% yield (111.5 mg). Eluent petroleum ether/ethyl acetate (10:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.33 (d, 1H, J = 8.0 Hz), 8.02 (d, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.62−7.54 (m, 4H), 7.50 (d, 2H, J = 8.0 Hz), 7.30 (d, 1H, J = 16.0 Hz), 7.23 (d, 2H, J = 8.0 Hz), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 196.0, 146.2, 141.3, 137.3, 133.9, 131.9, 131.4, 130.5, 129.7, 128.8, 128.5, 128.4, 127.4, 127.0, 126.3, 125.7, 124.5, 21.5. HRMS m/z calcd. for $C_{20}H_{16}O$ $[M + H]^+$: 273.1279, found: 273.1282.

(E)-3-(3-Methoxyphenyl)-1-(naphthalen-2-yl)prop-2-en-1-one ***(3l)***:[29] Following the general procedure, the product was isolated in 71% yield (102.2 mg). Eluent petroleum ether/ethyl acetate (20:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.36 (d, 1H, J = 8.0 Hz), 8.03 (d, 1H, J = 8.0 Hz), 7.94 (d, 1H, J = 8.0 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.62−7.55 (m, 4H), 7.36−7.30 (m, 2H), 7.20 (d, 1H, J = 8.0 Hz), 7.12 (s, 1H), 7.69 (d, 2H, J = 8.0 Hz), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 195.6, 160.0, 145.9, 137.1, 136.0, 133.8, 131.6, 130.5, 130.0, 128.5, 127.5, 127.4, 127.2, 126.5, 125.7, 124.5, 121.2, 116.7, 113.3, 55.4. HRMS m/z calcd. for $C_{20}H_{16}O_2$ $[M + H]^+$: 289.1229, found: 289.1232.

(E)-3-(3-Methoxyphenyl)-1-m-tolylprop-2-en-1-one ***(3m)***: Following the general procedure, the product was isolated in 78% yield (98.3 mg). Eluent petroleum ether/ethyl acetate (20:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.85−7.83 (m, 2H), 7.79 (d, 1H, J = 16.0 Hz), 7.53 (d, 1H, J = 16.0 Hz), 7.43−7.41 (m, 2H), 7.36 (t, 1H, J = 8.0 Hz), 7.28−7.26 (m, 2H), 7.19 (s, 1H), 6.99 (d, 2H, J = 8.0 Hz), 3.88 (s, 3H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 190.7, 160.0, 144.6, 138.5, 138.3, 136.4, 133.6, 130.0, 129.1, 128.5, 125.7, 122.6, 121.1, 116.2, 113.5, 55.4, 21.4. HRMS m/z calcd. for $C_{17}H_{16}O_2$ $[M + H]^+$: 253.1229, found: 253.1219.

(E)-1,3-Di-p-tolylprop-2-en-1-one ***(3n)***:[30] Following the general procedure, the product was isolated in 72% yield (84.9 mg). Eluent petroleum ether/ethyl acetate (20:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.84 (d, 2H, J = 8 Hz), 7.65 (d, 1H, J = 16 Hz), 7.34 (d, 2H, J = 8 Hz), 7.32−7.29 (m, 3H), 6.85 (d, 1H, J = 16 Hz), 2.46 (s, 3H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 190.1, 144.3, 142.2, 138.8, 137.9, 132.4, 131.9, 129.9, 129.1, 128.9, 127.7, 127.4, 125.8, 21.6, 21.3. HRMS m/z calcd. for $C_{17}H_{16}O$ $[M + H]^+$: 273.1279, found: 273.1279.

(E)-3-(4-Chlorophenyl)-1-p-tolylprop-2-en-1-one ***(3o)***:[31] Following the general procedure, the product was isolated in 66% yield (79.4 mg). Eluent petroleum ether/ethyl acetate (20:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.96 (d, 2H, J = 8.0 Hz), 7.77 (d, 1H, J = 16.0 Hz), 7.60 (d, 2H, J = 8.0 Hz), 7.53 (d, 1H, J = 16.0 Hz), 7.41 (d, 2H, J = 8.0 Hz), 7.33 (d, 2H, J = 8.0 Hz), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 189.7, 143.9, 142.9, 136.3, 135.5, 133.5, 129.6, 129.4, 129.2, 128.7, 122.5, 21.7. HRMS m/z calcd. for $C_{16}H_{13}ClO$ $[M + H]^+$: 257.0733, found: 257.0726.

(E)-3-(4-Chlorophenyl)-1-o-tolylprop-2-en-1-one ***(3p)***:[32] Following the general procedure, the product was isolated in 54% yield (69.1 mg). Eluent petroleum ether/ethyl acetate (20:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.52−7.51 (m, 3H), 7.47−7.39 (m, 4H), 7.31 (d, 1H, J = 8.0 Hz), 7.14 (d, 1H, J = 16.0 Hz), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 196.1, 144.2, 138.9, 137.1, 136.6, 133.2, 131.4, 130.6, 129.6, 129.3, 128.1, 127.1, 125.5, 20.3. HRMS m/z calcd. for $C_{16}H_{13}ClO$ $[M + H]^+$: 257.0733, found: 257.0726.

(E)-3-(3-Chlorophenyl)-1-o-tolylprop-2-en-1-one ***(3q)***: Following the general procedure, the product was isolated in 64% yield (82.0 mg). Eluent petroleum ether/ethyl acetate (20:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.57 (s, 1H), 7.53 (d, 1H, J = 8.0 Hz), 7.47−7.41 (m, 3H), 7.39−7.21 (m, 4H), 7.15 (d, 1H, J = 16.0 Hz) 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 195.9, 143.9, 138.7, 137.2, 136.5, 135.0, 131.5, 130.8, 130.4, 130.2, 128.2, 128.1, 127.8, 126.6, 125.6, 20.3. HRMS m/z calcd. for $C_{16}H_{13}ClO$ $[M + H]^+$: 257.0733, found: 257.0726.

(E)-3-(4-Fluorophenyl)-1-o-tolylprop-2-en-1-one ***(3r)***: Following the general procedure, the product was isolated in 66% yield (79.2 mg). Eluent petroleum ether/ethyl acetate (20:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.60−7.56 (m, 2H), 7.53−7.39 (m, 3H), 7.29 (d, 2H, J = 8.0 Hz), 7.14−7.07 (m, 3H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 196.3, 165.4, 162.9, 144.5, 140.1, 139.0, 131.6, 131.4, 130.5, 130.3(d, J = 160 Hz), 128.1, 127.4, 126.5(d, J = 12 Hz), 125.8, 125.5, 116.3, 116.1, 20.2. HRMS m/z calcd. for $C_{16}H_{13}FO$ $[M + H]^+$: 241.1029, found: 241.1032.

(E)-1-o-Tolyl-3-p-tolylprop-2-en-1-one ***(3s)***: Following the general procedure, the product was isolated in 69% yield (81.4 mg). Eluent petroleum ether/ethyl acetate (20:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.51−7.38 (m, 5H), 7.31−7.29 (m, 2H), 7.23 (d, 2H, J = 8.0 Hz), 7.11(d, 2H, J = 16.0 Hz), 2.46 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 196.8, 146.1, 141.2, 139.3, 136.8, 131.9, 131.3, 130.3, 129.7, 128.5, 128.0, 125.9, 125.4, 21.5, 20.1. HRMS m/z calcd. for $C_{17}H_{16}O$ $[M + H]^+$: 237.1279, found: 237.1280.

(E)-3-(3-Methoxyphenyl)-1-o-tolylprop-2-en-1-one ***(3t)***: Following the general procedure, the product was isolated in 75% yield (94.5 mg). Eluent petroleum ether/ethyl acetate (20:1). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.52 (d, 2H, J = 8.0 Hz), 7.45 (d, 1H, J = 16.0 Hz), 7.38 (d, 2H, J = 8.0 Hz), 7.36−7.30 (m, 3H), 7.19−7.10 (m, 3H), 6.69 (d, 1H, J = 8.0 Hz), 3.86 (s, 3H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 196.6, 160.0, 145.8, 139.1, 137.0, 136.0, 131.3, 130.5, 130.0, 128.1, 127.1, 125.5, 121.1, 116.6, 113.2, 55.3, 20.2. HRMS m/z calcd. for $C_{17}H_{16}O_2$ $[M + H]^+$: 253.1229, found:253.1226.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yangdaoshan@tsinghua.org.cn (D.Y.).
*E-mail: huawang_qfnu@126.com (H.W.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (Nos. 21302110, 21302109, and 21375075), the Taishan Scholar Foundation of Shandong Province, the Natural Science Foundation of Shandong Province (ZR2013BQ017 and ZR2013M007), and the Project of Shandong Province Higher Educational Science and Technology Program (J13LD14).

DOI: 10.1021/jo502642n
J. Org. Chem. 2015, 80, 3258−3263

REFERENCES

(1) (a) Corey, E. J.; Cheng, X. M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989; pp 1−91. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; pp 49−89.

(2) (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095−3165. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318−5365.

(3) (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59. (b) Knochel, P.; Singer, R. *Chem. Rev.* **1993**, *93*, 2117−2188. (c) Negishi, E. I. *Acc. Chem. Res.* **1982**, *15*, 340−348. (d) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846.

(4) (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662−664. (b) Goossen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824−4833. (c) Goossen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100−3120. (d) Goossen, L. J.; Rodríguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248−15249. (e) Goossen, L. J.; Lange, P. P.; Rodríguez, N.; Linder, C. *Chem.—Eur. J.* **2010**, *16*, 3906−3909. (f) Tang, J.; Gooßen, L. J. *Org. Lett.* **2014**, *16*, 2664−2667. (g) Dzik, W. I.; Lange, P. P.; Gooßen, L. J. *Chem. Sci.* **2012**, *3*, 2671−2678. (h) Lange, P. P.; Goossen, L. J.; Podmore, P.; Underwood, T.; Sciammetta, N. *Chem. Commun.* **2011**, *47*, 3628−3630. (i) Song, B.; Knauber, T.; Goossen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2954−2958.

(5) (a) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323−10333. (b) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250−11251.

(6) For selected examples, see: (a) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350−11351. (b) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006−14008. (c) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395−3409. (d) Jafarpour, F.; Zarei, S.; Olia, M. B. A.; Jalalimanesh, N.; Rahiminejadan, S. *J. Org. Chem.* **2013**, *78*, 2957−2964. (e) Zhang, F.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 4745−4747. (f) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 2735−2738. (g) Shang, R.; Yang, Z.-W.; Wang, Y.; Zhang, S.-L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391−14393. (h) Li, C.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 862−865.

(7) (a) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030−5048. (b) Zhang, Y.; Patel, S.; Mainolfi, N. *Chem. Sci.* **2012**, *3*, 3196−3199. (c) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846−1913. (d) Goossen, L. J.; Rudolphi, F.; Oppel, C.; Rodriguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043−3045.

(8) Liu, J.; Liu, Q.; Yi, H.; Qin, C.; Bai, R.; Qi, X.; Lan, Y.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 502−506.

(9) (a) Wang, H.; Guo, L.-N.; Duan, X.-H. *Chem. Commun.* **2014**, *50*, 7382−7384. (b) Wang, H.; Guo, L.-N.; Duan, X.-H *Adv. Synth. Catal.* **2013**, *355*, 2222−2226.

(10) (a) Fang, P.; Li, M.; Ge, H. *J. Am. Chem. Soc.* **2010**, *132*, 11898−11899. (b) Kim, M.; Park, J.; Sharma, S.; Kim, A.; Park, E.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Chem. Commun.* **2013**, *49*, 925−927. (c) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett.* **2012**, *14*, 4358−4361. (d) Li, Z.-Y.; Li, D.-D.; Wang, G.-W. *J. Org. Chem.* **2013**, *78*, 10414−10420.

(11) (a) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 592−595. (b) Wang, Z.; Ding, Q.; He, X.; Wu, J. *Org. Biomol. Chem.* **2009**, *7*, 863−865.

(12) (a) Yang, H.; Sun, P.; Zhu, Y.; Yan, H.; Lu, L.; Qu, X.; Li, T.; Mao, J. *Chem. Commun.* **2012**, 7847−7849. (b) Cui, Z.; Shang, X.; Shao, X.-F.; Liu, Z.-Q. *Chem. Sci.* **2012**, *3*, 2853−2858. (c) Li, Z.; Cui, Z.; Liu, Z.-Q. *Org. Lett.* **2013**, *15*, 406−409. (d) Rong, G.; Liu, D.; Lu, L.; Yan, H.; Zheng, Y.; Chen, J.; Mao, J. *Tetrahedron.* **2014**, *70*, 5033−5037. (e) Zhao, J.; Fang, H.; Han, J.; Pan, Y. *Beilstein J. Org.Chem.* **2013**, *9*, 1718−1723.

(13) Manna, S.; Jana, S.; Saboo, T.; Maji, A.; Maiti, D. *Chem. Commun.* **2013**, 5286−5288.

(14) (a) Xu, Y.; Tang, X.; Hu, W.; Wu, W.; Jiang, H. *Green Chem.* **2014**, *16*, 3720−3723. (b) Rokade, B. V.; Prabhu, K. R. *J. Org. Chem.* **2014**, *79*, 8110−8117. (c) Li, H.-S.; Liu, G. *J. Org. Chem.* **2014**, *79*, 509−516.

(15) Mai, W.-P.; Song, G.; Sun, G.-C.; Yang, L.-R.; Yuan, J.-W.; Xiao, Y.-M.; Mao, P.; Qu, L.-B. *RSC Adv.* **2013**, *3*, 19264−19267.

(16) (a) Nowakowska, Z. *Eur. J. Med. Chem.* **2007**, *42*, 125−137. (b) Cabrera, M.; Simoens, M.; Falchi, G.; Lavaggi, M. L.; Piro, O. E.; Castellano, E. E.; Vidal, A.; Azqueta, A.; Monge, A.; Lopez, A.; Sagrera, G.; Seoane, G.; Cerecetto, H.; Gonzalez, M. *Bioorg. Med. Chem.* **2007**, *15*, 3356−3367. (c) Rao, Y. K.; Fang, S.-H.; Tzeng, Y.-M. *Bioorg. Med. Chem.* **2004**, *12*, 2679−2686. (d) Liu, M.; Wilairat, P.; Croft, S. L.; Tan, A. L.-C.; Go, M.-L. *Bioorg. Med. Chem.* **2003**, *11*, 2729−2738. (e) Weber, W. M.; L. Hunsaker, A. S.; Abcouwer, F.; Deck, L. M.; Jagt, D. L. V. *Bioorg. Med. Chem.* **2005**, *13*, 3811−3820. (f) Anto, R. J.; Sukumaran, K.; Kuttan, G.; Rao, M. N. A.; Subbaraju, V.; Kuttan, R. *Cancer Lett.* **1995**, *97*, 33−37.

(17) (a) Choudary, B. M.; Kantam, M. L.; Ranganath, K. V. S.; Mahendar, K.; Sreedhar, B. *J. Am. Chem. Soc.* **2004**, *126*, 3396−3397. (b) Fang, D.; Cheng, J.; Fei, Z.; Gong, K.; Liu, Z. *Catal. Commun.* **2008**, *9*, 1924−1927.

(18) Unoh, Y.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2013**, *78*, 5096−5102.

(19) Zhou, J.; Wu, G.; Zhang, M.; Jie, X.; Su, W. *Chem.—Eur. J.* **2012**, *18*, 8032−8036.

(20) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725−748.

(21) (a) Anderson, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 1651−1653. (b) Fontana, F.; Minisci, F.; Claudia, M.; Barbosa, N.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866−2869.

(22) Wang, P.; Liu, C.-R.; Sun, X.-L.; Chen, S.-S.; Li, J.-F.; Xie, Z.; Tang, Y. *Chem. Commun.* **2012**, *48*, 290−292.

(23) Chang, M.-Y.; Tsai, C.-Y.; Wu, M.-H. *Tetrahedron* **2013**, *69*, 6364−6370.

(24) Jacubert, M.; Provot, O.; Peyrat, J.-F.; Hamze, A.; Brion, J.-D.; Alami, M. *Tetrahedron* **2010**, *66*, 3775−3787.

(25) Kumar, A.; Sharma, S.; Tripathi, V. D.; Srivastava, S. *Tetrahedron* **2010**, *66*, 6445−9449.

(26) Bandgar, B. P.; Gawande, S. S.; Bodadec, R. G.; Totre, J. V.; Khobragad, C. N. *Bioorg. Med. Chem.* **2010**, *18*, 1364−1370.

(27) Winter, E.; Chiarad, L. D.; Cordova, C. A. S.; José Nunes, R.; Yunes, R. A.; Creczynski-Pasaa, T. B. *Bioorg. Med. Chem.* **2010**, *18*, 8026−8034.

(28) Li, X.; Zou, D.; Leng, F.; Sun, C.; Li, J.; Wu, Y.; Wu, Y. *Chem. Commun.* **2013**, *49*, 312−314.

(29) Chang, M.-Y.; Chan, C.-K.; Lin, S.-Y.; Wu, M.-H. *Tetrahedron* **2013**, *69*, 9616−9624.

(30) Yang, J.-X.; Tao, X.-T.; Yuan, C.; Yan, Y.; Wang, L.; Liu, Z.; Ren, Y.; Jiang, M. *J. Am. Chem. Soc.* **2005**, *127*, 3278−3279.

(31) Madapa, S.; Sridhar, D.; Yadav, G. P.; Maulik, P.- R.; Batra, S. *Eur. J. Org. Chem.* **2007**, 4343−4351.

(32) Cardia, M.-C.; Sanna, M.-L.; Meleddu, R.; Distinto, S.; Yañez, M.; Viña, D.; Lamela, M.; Maccioni, E. *J. Heterocycl. Chem.* **2013**, *50*, E87−E92.

NOTE ADDED AFTER ASAP PUBLICATION

The toc/abstract graphic and Table 2 footnote were corrected March 3, 2015.

DOI: 10.1021/jo502642n
J. Org. Chem. 2015, 80, 3258−3263