JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Copper(II)-Mediated Aerobic Oxidation of Benzylimidates: Synthesis of Primary α-Ketoamides

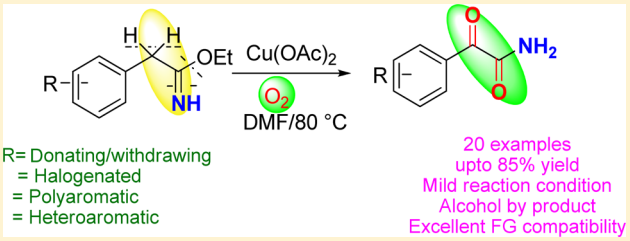
Yogesh Kumar,[†] Mukta Shaw,[†] Rima Thakur,[‡] and Amit Kumar*[,†]

[†]Department of Chemistry, Indian Institute of Technology Patna, Bihta 801103, Bihar, India

[‡]Department of Chemistry, National Institute of Technology Patna, Patna 800005, Bihar, India

Supporting Information

ABSTRACT: A simple and straightforward method for the synthesis of primary α-ketoamides has been discovered. The reaction represents the first example of benzylimidates directly converting to primary α-ketoamides by using sustainable molecular oxygen as an oxidant. This reaction proceeds in the presence of copper(II) salt via cleavage of benzylic C−H and C−O bonds of the benzylimidates with liberation of alcohols as the only byproduct. A wide substrate scope, operationally mild conditions, the use of single substrates, and a reaction scaled up to grams make this strategy very attractive and practical. Furthermore, mechanistic studies illustrate that the imidate group adjacent to the benzylic position plays crucial role in facilitating this chemical process.



INTRODUCTION

The ubiquitous presence of α-ketoamides as a key structural feature in many biologically active natural compounds such as tacrolimus (FK506), rapamycin, eurystatin A and B, and poststatin (Figure 1) makes this an attractive target for organic chemists.[1−3] Moreover, they serve as building blocks for a variety of functional group transformations, particularly the primary α-ketoamides.[4]

Because of their importance, preparation of this class of compounds has attracted a considerable amount of attention in recent years.[5,6] While synthetic methods toward secondary[7,8] and tertiary α-ketoamides[9−11] have been well studied, there are only limited reports about the synthesis of primary α-ketoamides.[12] Scheme 1 summarizes some of the well-established methods for the synthesis of primary α-ketoamides. (a) Zinc chloride promoted formal oxidative coupling of aromatic aldehydes and isocyanides, followed by treatment with TFA in DCM to provide primary α-ketoamides (Scheme 1a).[13a] (b) Electrochemical oxidative synthesis was performed from acetophenones with ammonium acetate (Scheme 1b).[13b] (c) I_2-catalyzed oxidative cross-coupling amidation was performed between aryl methyl ketones and formamidine hydrochloride (Scheme 1c).[13c]

The methods mentioned above require two substrates, where external nitrogen sources were used to obtain free amine and suffer the drawback of involving multiple steps to generate the target molecules. Thus, there is a need to develop an improved strategy for primary α-ketoamides that should meet the following criteria: (a) use of a single substrate, where nitrogen should be preinstalled, (b) an environmentally friendly oxidant, and (c) liberation of less harmful byproducts, which ease the purification process and could also explain the high isolated yields. Pursuing this challenge, we envisioned that readily synthesized benzylimidates **1a**, in which the benzyl group is attached to imidate (NH) at the α-position, could serve as an ideal substrate. To the best of our knowledge, use of benzylimidates as a key precursor for straightforward synthesis of primary α-ketoamides has not been reported previously. Herein, we report copper(II)-mediated direct synthesis of primary α-ketoamides using molecular oxygen as an oxidant from benzylimidates (Scheme 1d).

RESULTS AND DISCUSSION

To test our hypothesis, we have selected copper as a catalyst because it is less toxic than other transition metals, and because of its ability to coordinate with imines,[14,15] benzylimidate **1a** was selected as the model substrate to optimize the reaction conditions. To our delight, the reaction of **1a** in the presence of molecular oxygen (1 atm pressure)[16] as the oxidant[15a] and copper(II) acetate (0.1 equiv) as the metal catalyst in DMF afforded the desired primary α-ketoamide **2a**, albeit in a low yield of 10% (Table 1, entry 1). It is noteworthy that 2-oxo-phenylacetate **3a** was also formed as a byproduct in 7% isolated yield in this case (Table 1, entry 1), and the rest of the starting material was recovered. However, it was observed that when reaction was performed in the absence of copper salt, no desired product was obtained (entry 2). On the basis of the initial result, different copper salts were surveyed (Table 1). Copper(II) acetate turned out to be the best choice (entry 13) among other copper salts such as copper(II) acetate monohydrate, copper(I) thiophene-2-carboxylate, copper(I) bromide, copper(I) chloride, and copper(I) cyanide (Table 1, entries 4−12). Moreover, loading of copper salts plays a critical

Received: May 26, 2016
Published: June 27, 2016

DOI: 10.1021/acs.joc.6b01262
J. Org. Chem. 2016, 81, 6617−6625

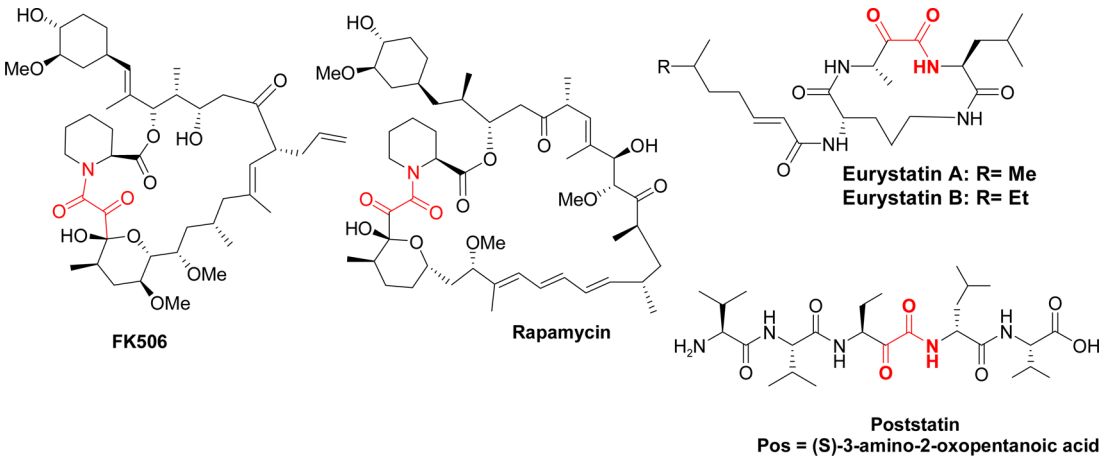
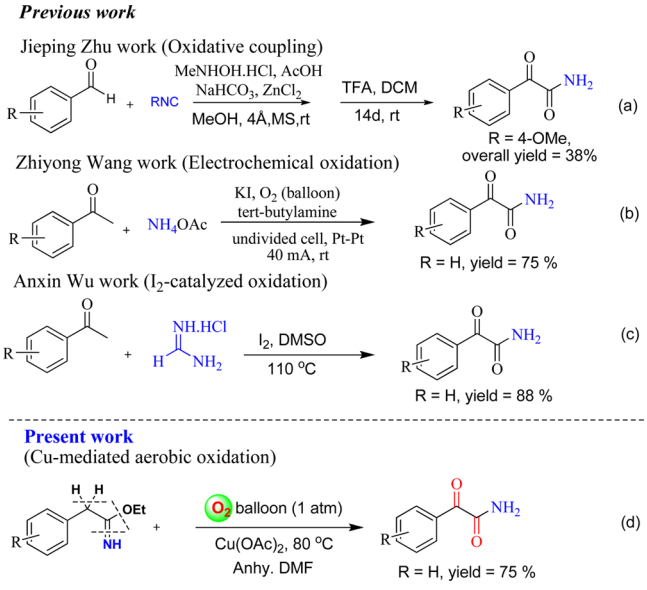


Figure 1. α-Ketoamides in bioactive natural molecules.

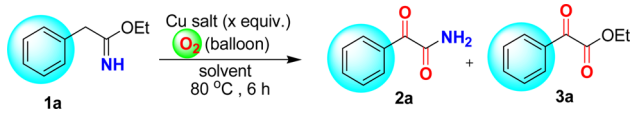
Scheme 1. Different Approaches to Primary α-Ketoamides



role in enhancing the efficiency of the reaction. An increase in the loading of copper(II) acetate from 1 to 2 equiv resulted in a higher yield (74%) of the desired product (Table 1, entry 14). A further increase in loading of the catalyst from 2 to 2.5 equiv was futile; there was no improvement in yield (Table 1, entry 22). The effects of different solvents (polar and nonpolar) on the reaction were screened, and DMF was found to be the most suitable (entries 15−21). Apart from copper(II) salts, other transition metals such as iron(III), nickel(II), and palladium(II) proved to be inefficient in this transformation (Table 1, entries 23−25, respectively). After different parameters had been extensively screened, the yield of the desired primary α-ketoamide **2a** was improved to 74% (entry 14), in which chemoselectivity was strongly controlled with only a trace amount of 2-oxo-phenylacetate **3a** formation.

The reactivity of different *O*-alkyl in the alkoxy group of α-phenyl-acetimidates **1** was next investigated (Table 2) under the established reaction conditions. It was observed that the reaction was compatible with different alkyl substituents, and among them, the ethyl substituent (entry 1) displayed better results as compared to those of methyl (entry 2), *n*-propyl (entry 3), and isopropyl (entry 4) derivatives.

Table 1. Optimization of the Reaction Conditions[a]



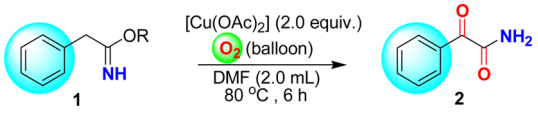
entry	catalyst	solvent	equiv	yield of **2a**[b] (%)	yield of **3a**[b] (%)
1	$Cu(OAc)_2$	DMF	0.10	10	7
2	none	DMF	–	–	–
3	$Cu(OAc)_2$	DMF	0.20	17	10
4	$Cu(OAc)_2{\cdot}H_2O$	DMF	1.0	54	8
5	$Cu(OTf)_2$	DMF	1.0	34	–
6	CuCl	DMF	1.0	35	trace
7	$CuCl_2$	DMF	1.0	40	trace
8[c]	CuTc	DMF	1.0	45	trace
9	CuBr	DMF	1.0	40	8
10	CuCN	DMF	1.0	5	–
11	CuI	DMF	1.0	–	trace
12	Cu_2O	DMF	1.0	–	–
13	$Cu(OAc)_2$	DMF	1.0	60	–
14	$Cu(OAc)_2$	DMF	2.0	74	trace
15	$Cu(OAc)_2$	ACN	2.0	52	9
16	$Cu(OAc)_2$	1,4-dioxane	2.0	20	8
17	$Cu(OAc)_2$	DCE	2.0	16	10
18	$Cu(OAc)_2$	toluene	2.0	24	15
19	$Cu(OAc)_2$	chlorobenzene	2.0	18	10
20	$Cu(OAc)_2$	NMP	2.0	46	4
21	$Cu(OAc)_2$	DMSO	2.0	48	4
22	$Cu(OAc)_2$	DMF	2.5	73	trace
23	$Fe(NO_3)_3{\cdot}9H_2O$	DMF	2.0	trace	–
24	$Ni(OAc)_2{\cdot}4H_2O$	DMF	2.0	–	–
25	$Pd(OAc)_2$	DMF	2.0	–	–

[a]Reaction conditions: **1a** (0.2 mmol), copper salts (x equiv), O_2 balloon (1 atm), and solvent (2.0 mL) at 80 °C for 6 h. [b]Isolated yield of the products. [c]CuTc = copper(I) thiophene-2-carboxylate.

Having optimized the reaction conditions, we examined the scope of copper-mediated aerobic oxidative amidation of α-aryl/heteroaryl-*O*-alkyl acetimidates, and results are presented in Table 3. The results indicated that benzylimidates with both an electron-donating group (-OMe, 3,4-OCH_2O, and -Me) at various positions (*ortho*-, *meta*-, and *para*-substituted) and electronically neutral substrates (-Ph) at the *para* position were smoothly transformed into the desired products in moderate to

DOI: 10.1021/acs.joc.6b01262
J. Org. Chem. 2016, 81, 6617−6625

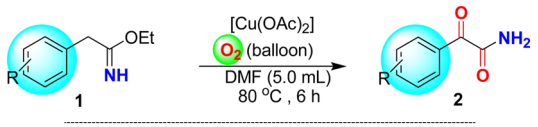
Table 2. Effect of Alkyl in the Alkoxy Group in the Benzylimidates[a]

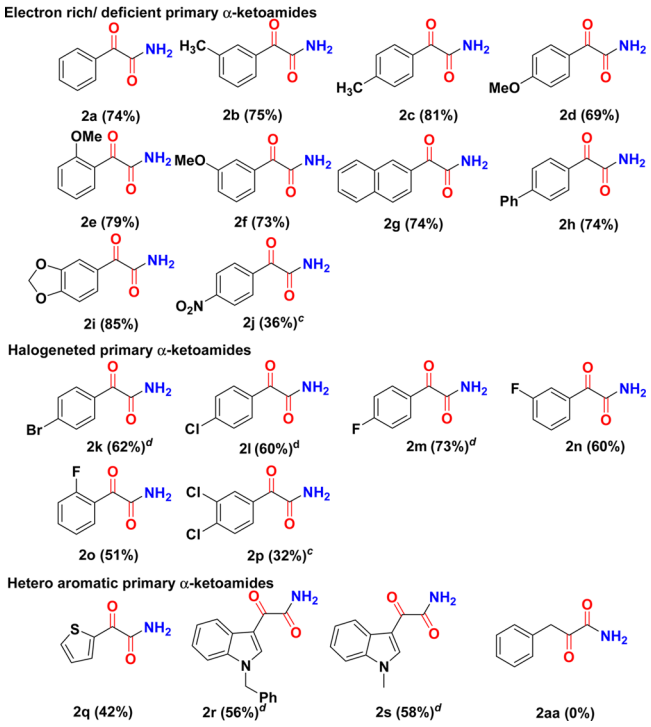


entry	R	yield[b] (%)
1	$-CH_2CH_3$	74
2	$-CH_3$	70
3	$-CH_2CH_2CH_3$	68
4	$-CH(CH_3)_2$	64

[a]For reaction conditions, see entry 14 of Table 1. [b]Isolated yield of the products.

Table 3. Substrate Scope of 2-Arylacetimidates for the Formation of Primary α-Ketoamides[a,b]





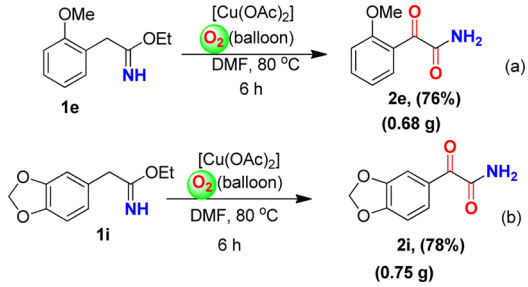
[a]For reaction conditions, see entry 14 of Table 1. [b]Isolated yields of the products are given in parentheses. [c]The reaction was run for 12 h. [d]The reaction was run for 10 h.

good yields [69–85% (Table 3, entries **2a–2i**)]. However, it was observed that the presence of a strong electron-withdrawing group, such as the nitro group, had a negative effect on the reaction yield. An only 36% yield of the desired product (**2j**) was obtained.

It is noteworthy that benzylimidates possessing halo groups (*bromo*, *chloro*, and *fluoro*) survived well, leading to halo-substituted α-ketoamides (entries **2k–2p**). These products can act as potential intermediates in organic synthesis. It should be mentioned that when dichlorobenzylimidate was treated under similar conditions, we obtained a slightly lower yield of product **2p**. These results reveal that benzylimidates bearing electron-donating substituents give yields higher than the yields of those bearing electron-withdrawing groups. The plausible reason could be stabilization of benzylic radical by electron-donating groups. At the same time, electron-withdrawing groups destabilized the benzylic radical to afford the target products in lower yields.[17] Correspondingly, we expanded the scope of this methodology toward the synthesis of heteroaryl α-ketoamide derivatives (entries **2q–2s**), which were procured in moderate yields. On the other hand, attempts to obtain alkyl-substituted α-ketoamide by the established protocol failed to give desired product **2aa**. This result clearly demonstrates that benzylic hydrogen adjacent to the imidate group is essential for the success of this transformation.

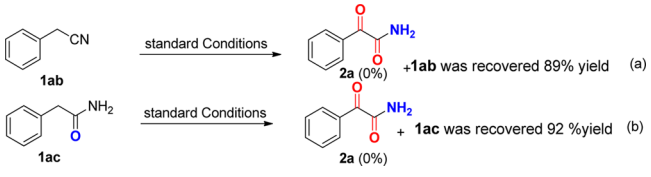
Recently, Wu and co-workers have reported an efficient route for the synthesis of primary α-ketoamides via iodine-catalyzed oxidative amidation of aryl methyl ketones in the presence of formamidine hydrochloride.[13c] In their work, there is a major limitation in the use of formamidine hydrochloride as an external source to generate a free amine, which makes this strategy less attractive for gram scale synthesis. To demonstrate the feasibility and effectiveness of our developed method, gram scale synthesis of α-ketoamides was performed under standard conditions. The reactions involving 5.0 mmol of 2-methoxy-benzylimidate **1e** (Scheme 2a) and 3,4-(methylenedioxy)-benzylimidate **1i** (Scheme 2b) as substrates were investigated under optimized conditions. Subsequently, products **2e** and **2i** were procured in 0.68 g (76%) and 0.75 g (78%) yields, respectively. Yields of the desired products are comparable to those of earlier literature reports,[13] and milder conditions and the use of a single easily synthesized (preinstalled nitrogen) starting material make this methodology applicable in synthetic as well as medicinal chemistry.

Scheme 2. Scale-up Experiment of 2-Methoxy-benzylimidate and 3,4-(Methylenedioxy)-benzylimidate



To illustrate the reaction mechanism, we conducted a series of additional experiments. First, 2-phenylacetonitrile **1ab** was treated under the optimized reaction conditions, but there was no formation of desired product **2a** (Scheme 3a). Further, we assumed that 2-phenylacetamide **1ac** could be a potential intermediate and hence was subjected to the standard reaction conditions (Scheme 3b). However, product **2a** was not

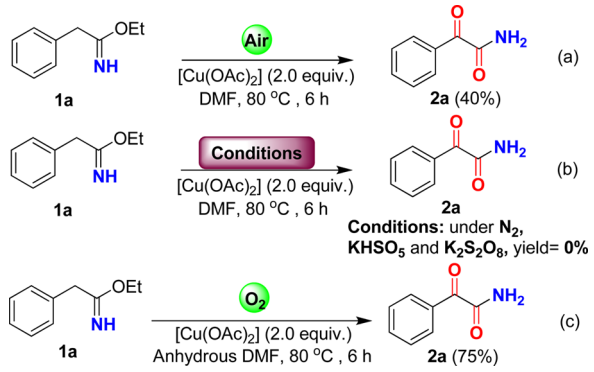
Scheme 3. Identification of Possible Intermediates



DOI: 10.1021/acs.joc.6b01262
J. Org. Chem. 2016, 81, 6617–6625

obtained. These results clearly indicate that **1ab** and **1ac** might not be the possible intermediates in this oxidative transformation. Subsequently, to investigate the role of molecular O_2, the following control experiments were performed as shown in Scheme 4. When the reaction was performed under

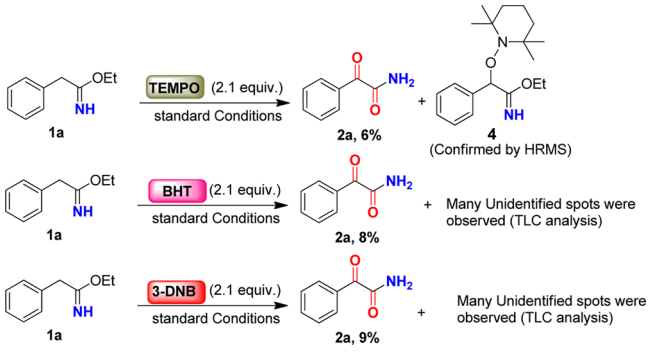
Scheme 4. Control Experiments



an open air atmosphere instead of under pure molecular oxygen, the required product was obtained in moderate yield (Scheme 4a). Similarly, benzylimidate **1a** was reacted under a nitrogen atmosphere, and no desired product was obtained. Next, when reactions were performed in the absence of molecular oxygen using other chemical oxidants, such as $K_2S_2O_8$ and $KHSO_5$ under standard reaction conditions, no further success was achieved (Scheme 4b), and the starting material was intact (TLC analysis). Hence, we concluded that the presence of molecular oxygen is necessary for this transformation. To rule out the indispensable effect of water, the reaction was conducted using anhydrous DMF under standard conditions. Interestingly, the desired product was isolated in good yield (Scheme 4c). Thus, this observation revealed that there is no participation of water in the reaction medium.

To confirm possible radical pathways involved in the reaction mechanism, radical scavenger (2,2,6,6-tetramethyl-1-piperidin-1-yl)oxyl (TEMPO) was added to the model reaction mixture under the standard condition (Scheme 5, eq 1). To our

Scheme 5. Radical Inhibition Experiments



surprise, primary α-ketoamide **2a** was obtained in low yield, and interestingly, a TEMPO adduct was observed via HRMS analysis (see the Supporting Information).[18] When another alternative radical scavenger such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 1,3-dinitrobenzene (3-DNB) was added to the model reaction mixture, as anticipated, desired product **2a** was obtained in low yield (Scheme 5, eqs 2 and 3). Although the radical-trapping adducts were not isolated in either case, the observed results indicate that the reaction is likely to involve a radical pathway. Also, the formation of the superoxide radical was detected by electron paramagnetic resonance (EPR) measurements (Figure 2), by using 5,5-dimethyl-1-pyrroline-

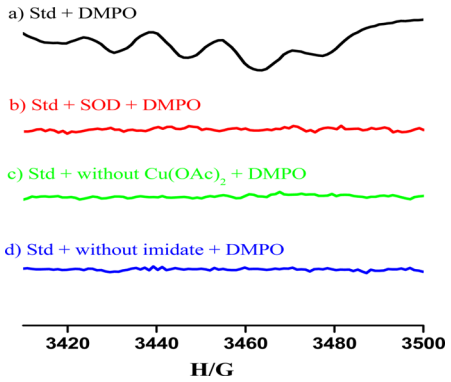


Figure 2. EPR spectra (X-band, 9.4 GHz, room temperature) of the reaction under the standard condition [**1a**, $Cu(OAc)_2$, O_2 balloon (1 atm), toluene, 80 °C] (a) in the presence of a radical trapping reagent, DMPO (5×10^{-2} M) at 25 °C (the calculated hyperfine splitting is g_{av} = 2.0037), (b) the same solution with the addition of SOD (5×10^{-2} M) and DMPO (5×10^{-2} M) at 25 °C, (c) the same reaction condition without $Cu(OAc)_2$, and (d) the same reaction condition without imidate. All spectra were analyzed by EPR at 25 °C.

N-oxide (DMPO) as a selective superoxide free radical trapping reagent. The EPR signal corresponding to the DMPO–superoxide adduct was identified (Figure 2a), and the calculated *g* value is g_{av} (2.0037).[8b] Moreover, the signal of the DMPO–superoxide adduct disappeared in the presence of superoxide dismutase (SOD) (Figure 2b) or by the removal of the copper(II) salt or benzylimidate (Figure 2c,d). These results additionally support the idea that the reaction must have proceeded through a radical pathway.

Aware of the fact that alcohol is liberated as a byproduct, we decided to conduct a few ^{1}H NMR experiments. A 0.20 mmol solution of benzylimidate (**1d**) in DMSO-d_6 placed in a NMR tube (Figure 3) was subjected to standard reaction conditions. Continued monitoring of the reaction (intervals of 3, 6, and 9 h) showed (Figure 3b–d) shows the significant appearance of a new peak and complete reduction of the benzylic peak at δ 3.46. New peaks at δ 3.74 (m, -*CH*) and δ 1.01 (d, -CH_3) correspond to the isopropyl alcohol. This method satisfies the aforementioned criteria set by us, and the reaction proceeds through cleavage of two benzylic C–H bonds and one C–O bond of the benzylimidates with liberation of alcohol as a byproduct.

Mechanistic Considerations. On the basis of the exploratory experiments described above and earlier literature reports,[8b,15b] we propose a plausible mechanism for the copper-mediated aerobic oxidative amidation of benzylimidates (Scheme 6). To initiate the reaction, copper(II) salt coordinates with the -NH group of benzylimidate to generate aminiminyl copper(II) species **A**.[15b] Subsequently, species **A** could be oxidized to superoxide radical **B**[8b] via radical pathway I under molecular oxygen, which eventually would form six-membered transition state **C**. Another pathway, II, may exist, according to earlier reports.[14a,15b] Iminyl copper(II) complex **A** will be oxidized in the presence of O_2 to form highly reactive

DOI: 10.1021/acs.joc.6b01262
J. Org. Chem. 2016, 81, 6617–6625

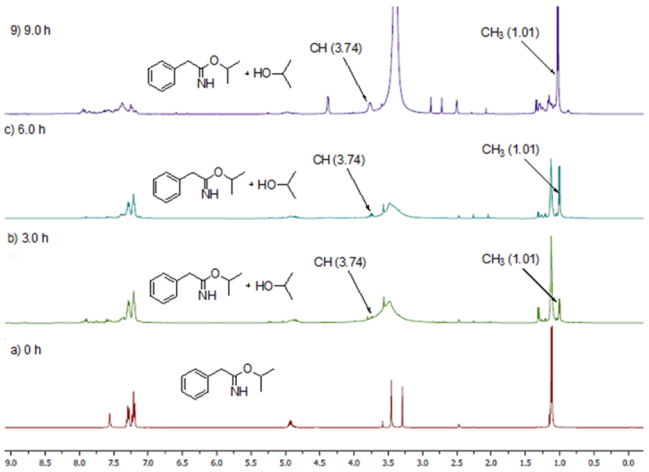
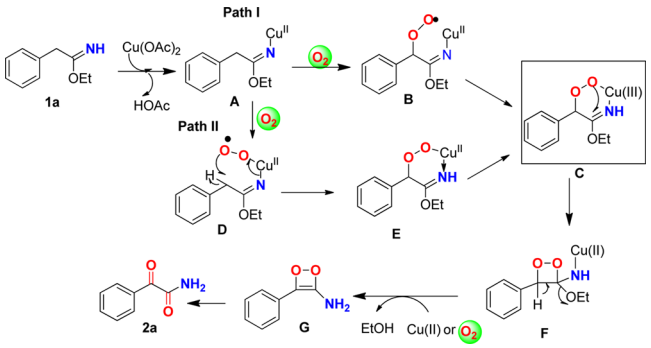


Figure 3. Monitoring the reaction of benzylimidate (**1d**) (0.2 mmol), $Cu(OAc)_2$ (0.02 mmol), and an O_2 balloon (1 atm) at 80 °C in DMSO-d_6 by NMR: (a) ^{1}H NMR spectrum of **1d** in DMSO-d_6, (b) ^{1}H NMR spectrum of the reaction mixture after 3.0 h, (c) ^{1}H NMR spectrum of the reaction mixture after 6.0 h, and (d) ^{1}H NMR spectrum of the reaction mixture after 9.0 h.

Scheme 6. A Proposed Reaction Mechanism for the Formation of Primary α-Ketoamides



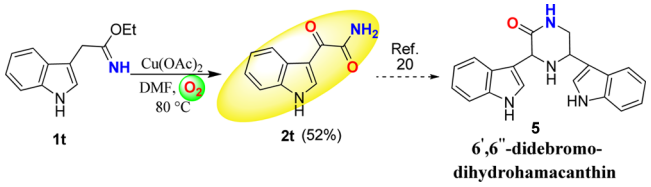
copper(III)-superoxide species **D**, which will rapidly undergo an intramolecular 1,3-hydrogen shift leading to formation of peroxycopper species **E**. Copper(II) would thus coordinate with the -NH group of benzylimidate to generate six-membered transition state **C**. This highly reactive copper(III) species may undergo intramolecular addition to imine, forming corresponding aminyl species **F**.[8b,19] Further, species **F** would undergo hydrogen abstraction assisted by copper(II) or O_2, resulting in intermediate **G**. Finally, fragmentation of **G** would produce desired primary α-ketoamide **2a**.

The established protocol was correspondingly employed in the formal synthesis of a marine sponge dihydrohamacanthins **5**.[20] This compound belongs to the family of bisindole alkaloids that exhibit many interesting biological properties like antitumor and cytotoxic activities.[20b,c] Thus, the crucial intermediate 2-(1*H*-indol-3-yl)-2-oxoacetamide **2t** was prepared directly (Scheme 7) from indolylimidate **1t** in moderate yield (52%). Compound **2t** has been reported in the literature[20c] for the total synthesis of dihydrohamacanthins.

CONCLUSION

In conclusion, we have developed a simple and efficient strategy for the synthesis of primary α-ketoamides from easily obtained benzylimidate derivatives using copper(II) acetate-mediated

Scheme 7. Formal Total Synthesis of Dihydrohamacanthins



aerobic oxidative amidation. The exclusivity of this strategy lies in the use of benzylimidates as a single substrate, which directly converts into primary α-ketoamides. Also, mechanistic studies show that the imidate group adjacent to the benzylic position plays a crucial role in this transformation. The reaction circumvents the need for two substrates and the use of ligands and bases. The advantages of this methodology include a high substrate efficiency, straightforward operation, and liberation of alcohol as the only byproduct. The synthetic application of this approach is currently under investigation in our laboratory.

EXPERIMENTAL SECTION

General Information. All substrates, reagents, and solvents were commercially available and used without further purification. All the reactions were monitored by TLC followed by exposure of mixtures to UV light and/or using an iodine chamber for visualization. Column chromatography was performed using silica gel [ethyl acetate/hexane (in different ratios) solvent system]. FTIR spectra were recorded with absorption in cm^{-1}. ^{1}H NMR (400 MHz) and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 as the solvent at room temperature. Chemical shifts (in parts per million) were reported using tetramethylsilane (δ 0) as an internal standard in $CDCl_3$ (δ 7.26) or DMSO-d_6 (δ 2.49) solvent. Data are reported as follows: chemical shift (in parts per million), multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br s, broad singlet), coupling constants (*J*, in hertz). ^{13}C NMR spectra were recorded with $CDCl_3$ (δ 77.0) or DMSO-d_6 (δ 39.7) as an internal reference. EPR data were recorded with 9.4 GHz spectrometers. The modulation frequency was 100 kHz and the modulation amplitude 10 G. DMPO (5,5-dimethyl-1-pyrroline-*N*-oxide) was used as a selective superoxide free radical trapping reagent. HRMS spectra were recorded using the ESI (Q-TOF, positive ion) technique. Melting points were recorded with an automated melting point apparatus without correction.

General Procedure for the Preparation of Imidates Hydrochloride.[21a] The reaction flask containing a solution of a nitrile (1 mmol) and an alcohol (12 mmol) was cooled to 0 °C under a nitrogen atmosphere. Then, AcCl (8 mmol) was added drop by drop to the stirring solution by syringe. The reaction was monitored after a certain time interval with the help of TLC. When the reaction was completed (monitored by TLC), the volatile solvents were removed under reduced pressure. The compound was dried under reduced pressure to isolate the imidate hydrochloride salt. Further, the imidate hydrochloride salt was dissolved in 20 mL of EtOAc and cooled to 0 °C. A cooled saturated aqueous $NaHCO_3$ solution was added slowly to the salt solution, until CO_2 gas evolution had ceased. The product was extracted with EtOAc (3 × 10 mL) and water, and the organic solution was washed with H_2O (10 mL) and brine (10 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the pure imidates.

*Ethyl-2-phenylacetimidate Hydrochloride (**1a**).*[21a] White solid: yield 180 mg, 90%; IR (ATR) 3377, 2922, 1659, 1496, 1447, 1389, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.67 (br s, 1H), 11.62 (br s, 1H), 7.27−7.19 (m, 5H), 4.07 (q, *J* = 8.0 Hz, 2H), 3.54 (s, 2H), 1.18 (t, *J* = 8.0 Hz, 3H).

*Ethyl-2-m-tolylacetimidate Hydrochloride (**1b**).*[22a] White solid: yield 196 mg, 92%; IR (ATR) 3332, 2923, 2853, 1668, 1461, 1389, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.66 (br s, 1H), 11.64 (br s, 1H), 7.22−7.12 (m, 3H), 7.10−7.07 (m, 1H), 4.62 (q, *J* = 8.0 Hz, 2H), 4.0 (s, 2H), 2.35 (s, 3H), 1.44 (t, *J* = 8.0 Hz, 3H).

DOI: 10.1021/acs.joc.6b01262
J. Org. Chem. 2016, 81, 6617−6625

*Ethyl-2-p-tolylacetimidate Hydrochloride (**1c**).*[22a] White solid: yield 204 mg, 95%; IR (ATR) 3310, 2995, 2755, 1646, 1565, 1379, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.62 (br s, 1H), 11.61 (br s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.60 (q, J = 8.0 Hz, 2H), 3.99 (s, 2H), 2.34 (s, 3H), 1.43 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(4-methoxyphenyl)acetimidate Hydrochloride (**1d**).*[22a] White solid: yield 183 mg, 80%; IR (ATR) 3220, 2806, 1654, 1565, 1510, 1341, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.60 (br s, 1H), 11.59 (br s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 4.60 (q, J = 8.0 Hz, 2H), 3.97 (s, 2H), 3.80 (s, 3H), 1.43 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(2-methoxyphenyl)acetimidate Hydrochloride (**1e**).*[22a] White solid: yield 197 mg, 86%; IR (ATR) 2804, 1639, 1584, 1494, 1389, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.16 (br s, 1H), 11.68 (br s, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 4.64 (q, J = 8.0 Hz, 2H), 4.06 (s, 2H), 3.84 (s, 3H), 1.38 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(3-methoxyphenyl)acetimidate Hydrochloride (**1f**).*[22a] White solid: yield 205 mg, 89%; IR (ATR) 2996, 2786, 1651, 1574, 1455, 1385, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.67 (br s, 1H), 11.65 (br s, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.04 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 4.62 (q, J = 8.0 Hz, 2H), 4.01 (s, 2H), 3.82 (s, 3H), 1.44 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(naphthalene-2-yl)acetimidate Hydrochloride (**1g**).*[21b] White solid: yield 214 mg, 86%; IR (ATR) 2911, 2760, 1647, 1571, 1442, 1386, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.81 (br s, 1H), 11.75 (br s, 1H), 7.91 (s, 1H), 7.85−7.82 (m, 3H), 7.54−7.48 (m, 3H), 4.63 (q, J = 8.0 Hz, 2H), 4.23 (s, 2H), 1.42 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(biphenyl-4-yl)acetimidate Hydrochloride (**1h**).*[21c] White solid: yield 242 mg, 88%; IR (ATR) 3384, 2922, 1658, 1498, 1386, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.74 (br s, 1H), 11.73 (s, 1H), 7.57−7.51 (m, 6H), 7.44 (t, J = 8.0 Hz, 2H), 7.37−7.34 (m, 1H), 4.65 (q, J = 8.0 Hz, 2H), 4.10 (s, 2H), 1.47 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(benzo[d][1,3]dioxol-5-yl)acetimidate Hydrochloride (**1i**).*[22a] White solid: yield 218 mg, 90%; IR (ATR) 3298, 2993, 2818, 1643, 1569, 1498, 1354, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.51 (br s, 1H), 11.52 (br s, 1H), 6.85 (s, 2H), 6.71 (d, J = 8.0 Hz, 1H), 5.90 (s, 2H), 4.55 (q, J = 8.0 Hz, 2H), 3.88 (s, 2H), 1.38 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(4-nitrophenyl)acetimidate Hydrochloride (**1j**).*[21c] Light yellowish solid: yield 195 mg, 80%; IR (ATR) 3310, 2806, 1654, 1510, 1386, 1341 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.84 (br s, 1H), 11.78 (br s, 1H), 8.17 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 4.59 (q, J = 8.0 Hz, 2H), 4.13 (s, 2H), 1.40 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(4-bromophenyl)acetimidate Hydrochloride (**1k**).*[22b] White solid: yield 250 mg, 90%; IR (ATR) 3306, 2993, 2732, 1652, 1566, 1381 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.75 (br s, 1H), 11.70 (br s, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.62 (q, J = 8.0 Hz, 2H), 4.01 (s, 2H), 1.44 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(4-chlorophenyl)acetimidate Hydrochloride (**1l**).*[22a] White solid: yield 186 mg, 80%; IR (ATR) 3435, 3215, 2923, 2852, 1658, 1584, 1464, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.75 (br s, 1H), 11.70 (br s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.62 (q, J = 8.0 Hz, 2H), 4.03 (s, 2H), 1.44 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(4-fluorophenyl)acetimidate Hydrochloride (**1m**).*[22d] White solid: yield 182 mg, 84%; IR (ATR) 3362, 3114, 2988, 1652, 1486, 1390 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.71 (br s, 1H), 11.67 (br s, 1H), 7.45−7.42 (m, 2H), 7.07−7.03 (m, 2H), 4.62 (q, J = 8.0 Hz, 2H), 4.03 (s, 2H), 1.45 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(3-fluorophenyl)acetimidate Hydrochloride (**1n**).*[22d] White solid: yield 190 mg, 87%; IR (ATR) 3368, 3112, 2980, 1654, 1480, 1386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.26 (m, 1H), 7.06−6.98 (m, 3H), 4.16 (q, J = 8.0 Hz, 2H), 3.61 (s, 2H), 1.26 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(2-fluorophenyl)acetimidate Hydrochloride (**1o**).*[22d] White solid: yield 191 mg, 88%; IR (ATR) 3362, 3116, 2986, 2828, 1737, 1655, 1493, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.30 (br s, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.36−7.31 (m, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 4.64 (q, J = 8.0 Hz, 2H), 4.16 (s, 2H), 1.41 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(3,4-dichlorophenyl)acetimidate Hydrochloride (**1p**).*[22b] White solid: yield 213 mg, 80%; IR (ATR) 3128, 2983, 2844, 1657, 1471, 1397, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.81 (br s, 1H), 11.80 (br s, 1H), 7.55 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 4.64 (q, J = 8.0 Hz, 2H), 4.03 (s, 2H), 1.47 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(thiophen-2-yl)acetimidate Hydrochloride (**1q**).*[22e] Brownish solid: yield 164 mg, 80%; IR (ATR) 2995, 2774, 1644, 1573, 1444, 1386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.69 (br s, 1H), 11.76 (br s, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.99 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 4.66 (q, J = 8.0 Hz, 2H), 4.29 (s, 2H), 1.48 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(1-benzyl-1H-indol-3-yl)acetimidate Hydrochloride (**1r**).*[21e] Brownish solid: yield 275 mg, 84%; IR (ATR) 2983, 2779, 1645, 1570, 1454, 1358, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.37 (br s, 1H), 11.64 (br s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.27−7.23 (m, 4H), 7.17−7.09 (m, 4H), 5.29 (s, 2H), 4.59 (q, J = 8.0 Hz, 2H), 4.20 (s, 2H), 1.41 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(1-methyl-1H-indol-3-yl)acetimidate Hydrochloride (**1s**).*[21e] White solid: yield 196 mg, 78%; IR (ATR) 2986, 2780, 1644, 1576, 1458, 1342, 1150 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.62 (br s, 1H), 11.61 (br s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.66−7.64 (m, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 4.40 (q, J = 8.0 Hz, 2H), 4.11 (s, 2H), 3.87 (s, 3H), 1.41 (t, J = 8.0 Hz, 3H).

*Ethyl-2-(1H-indol-3-yl)acetimidate Hydrochloride (**1t**).*[21e] Brownish solid: yield 190 mg, 80%; IR (ATR) 3457, 3268, 3119, 2974, 1651, 1574, 1455, 1385, 1098 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.96 (br s, 1H), 11.17 (br s, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.20−7.18 (m, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 4.44 (q, J = 8.0 Hz, 2H), 4.11 (s, 2H), 1.34 (t, J = 8.0 Hz, 3H).

*Ethyl-3-phenylpropanimidate Hydrochloride (**1aa**).*[23b] White solid: yield 187 mg, 88%; IR (ATR) 2976, 2830, 1652, 1562, 1454, 1386, 1136 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.44 (br s, 1H), 11.49 (br s, 1H), 7.32−7.25 (m, 5H), 4.57 (q, J = 8.0 Hz, 2H), 3.07 (s, 4H), 1.40 (t, J = 8.0 Hz, 3H).

*Methyl-2-phenylacetimidate Hydrochloride (**1ad**).*[23a] White solid: yield 187 mg, 88%; IR (ATR) 2922, 1650, 1480, 1446, 1390, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.86 (br s, 1H), 11.79 (br s, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 8.0 Hz, 3H), 4.26 (s, 3H), 4.07 (s, 2H).

*Isopropyl-2-phenylacetimidate Hydrochloride (**1ae**).*[22a] White solid: yield 200 mg, 94%; IR (ATR) 3319, 2977, 1645, 1372, 1274, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.48 (br s, 1H), 11.65 (br s, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 8.0 Hz, 3H), 5.51−5.42 (m, 1H), 4.00 (s, 2H), 1.39 (d, J = 8.0 Hz, 6H).

*Propyl-2-phenylacetimidate Hydrochloride (**1af**).*[22a] White solid: yield 196 mg, 92%; IR (ATR) 3368, 2922, 1655, 1498, 1440, 1375, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.62 (br s, 1H), 11.58 (br s, 1H), 7.32−7.26 (m, 5H), 4.05 (t, J = 8.0 Hz, 2H), 3.62 (s, 2H), 1.67−1.60 (m, 2H), 0.91 (t, J = 8.0 Hz, 3H).

General Procedures for the Synthesis of Primary α-Ketoamides. Imidates (0.5 mmol, 1.0 equiv) and anhydrous $Cu(OAc)_2$ (1.0 mmol, 2.0 equiv) were placed in a 25 mL round-bottom flask, and DMF (5.0 mL) was added by syringe. The reaction flask was sealed with a rubber septum, and the reaction mixture was degassed and refilled with O_2 (1 atm) (repeated three times). Then the reaction mixture was heated to 80 °C in the preheated oil bath to drive the reaction to completion. When the reaction was completed (monitored by TLC), saturated aqueous Na_2CO_3 (10 mL) and EtOAc (20 mL) were added to the reaction mixture. The dark solid was removed by filtration through a Celite bed and washed with EtOAc (3 × 20 mL). The organic solution was washed with H_2O (10 mL) and a brine (10 mL) solution. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by using silica gel column chromatography and dried under vacuum.

DOI: 10.1021/acs.joc.6b01262
J. Org. Chem. 2016, 81, 6617−6625

*2-Oxo-2-phenylacetamide (**2a**).*[13c] Yellow solid: yield 60.4 mg, 74%; R_f (8:2 hexanes/EtOAc) = 0.5; mp 68−69 °C; IR (ATR) 3423, 3332, 3209, 1666, 1594, 1450, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 6.8 Hz, 2H), 7.64 (t, J = 6.0 Hz, 1H), 7.50 (t, J = 6.0 Hz, 2H), 6.97 (br s, 1H), 5.86 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 163.7, 134.6, 133.0, 131.1, 128.6.

*2-Oxo-2-(m-tolyl)acetamide (**2b**).*[13b] Yellow wax: yield 61.2 mg, 75%; R_f (8:2 hexanes/EtOAc) = 0.5; IR (ATR) 3406, 3332, 3210, 1668, 1583, 1461, 1256, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.09 (d, J = 6.0 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 6.98 (br s, 1H), 6.16 (br s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 164.1, 138.4, 135.4, 132.9, 131.4, 128.4, 128.3, 21.32.

*2-Oxo-2-p-tolylacetamide (**2c**).*[13c] White solid: yield 66.1 mg, 81%; R_f (8:2 hexanes/EtOAc) = 0.5; mp 133−134 °C; IR (ATR) 3409, 3190, 1682, 1652, 1603, 1407, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24−8.22 (m, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.97 (br s, 1H), 5.89 (br s, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 164.1, 145.8, 131.3, 130.5, 129.3, 21.9.

*2-(4-Methoxyphenyl)-2-oxoacetamide (**2d**).*[13c] Yellow solid: yield 61.5 mg, 69%; R_f (8:2 hexanes/EtOAc) = 0.5; mp 146−148 °C; IR (ATR) 3384, 3190, 2923, 2852, 2669, 2560, 1734, 1684, 1604, 1515, 1428, 1305, 1264 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 8.10 (br s, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.76 (br s, 1H), 7.01 (d, J = 8.0 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 188.5, 167.0, 163.9, 132.2, 125.6, 113.8, 55.4.

*2-(2-Methoxyphenyl)-2-oxoacetamide (**2e**).*[13c] Yellow solid: yield 70.5 mg, 79%; R_f (7:3 hexanes/EtOAc) = 0.2; mp 125−126 °C; IR (ATR) 3380, 3185, 2923, 1681, 1651, 1597, 1484, 1288, 1248 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 7.72 (br s, 1H), 7.64 (d, J = 9.2 Hz, 1H), 7.55 (t, J = 8.6 Hz, 1H), 7.30 (br s, 1H), 7.06−7.02 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 191.1, 167.1, 159.2, 134.4, 130.1, 124.0, 120.3, 111.9, 55.6.

*2-(3-Methoxyphenyl)-2-oxoacetamide (**2f**).*[13c] Yellow solid: yield 65.3 mg, 73%; R_f (7:3 hexanes/EtOAc) = 0.3; mp 94−95 °C; IR (ATR) 3423, 3332, 3184, 2923, 1666, 1596, 1580, 1485, 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89−7.87 (m, 1H), 7.71 (s, 1H), 7.32 (t, J = 9.0 Hz, 1H), 7.13−7.10 (m, 1H), 6.90 (br s, 1H), 6.02 (br s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 163.9, 159.6, 134.1, 129.6, 124.1, 121.5, 114.6, 55.4.

*2-(Naphthalen-2-yl)-2-oxoacetamide (**2g**).*[13c] Yellow solid: yield 73.1 mg, 74%; R_f (8:2 hexanes/EtOAc) = 0.5; mp 192−194 °C; IR (ATR) 3406, 3206, 1692, 1664, 1594, 1277 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 8.69 (s, 1H), 8.30 (br s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.01 (s, 2H), 7.97 (d, J = 8.4 Hz, 1H), 7.96 (br s, 1H), 7.70−7.66 (m, 1H), 7.63−7.59 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 190.2, 166.8, 135.4, 132.7, 131.8, 130.1, 129.6, 129.0, 128.4, 127.6, 126.9, 123.9.

*2-(Biphenyl-4-yl)-2-oxoacetamide (**2h**).*[13c] White solid: yield 83 mg, 74%; R_f (8:2 hexanes/EtOAc) = 0.5; mp 171−172 °C; IR (ATR) 3415, 3220, 2923, 1693, 1662, 1592, 1557, 1403, 1247 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 8.19 (d, J = 8.2 Hz, 2H), 8.06 (br s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.69 (br s, 1H), 7.66 (d, J = 7.4 Hz, 2H), 7.50−7.46 (m, 2H), 7.43−7.39 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 189.0, 166.1, 145.8, 138.8, 131.6, 130.5, 128.6, 128.1, 126.7, 126.6.

*2-(Benzo[d][1,3]dioxol-5-yl)-2-oxoacetamide (**2i**).*[13c] White solid: yield 82 mg, 85%; R_f (8:2 hexanes/EtOAc) = 0.5; mp 171−173 °C; IR (ATR) 3427, 3184, 2922, 1708, 1650, 1591, 1489, 1441, 1258 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 8.16 (br s, 1H), 7.81 (br s, 1H), 7.70−7.68 (m, 1H), 7.44 (s, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.14 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 188.3, 166.8, 152.5, 147.8, 127.3, 108.0, 102.1.

*2-(4-Nitrophenyl)-2-oxoacetamide (**2j**).*[13c] Yellow solid: yield 35 mg, 36%; R_f (8:2 hexanes/EtOAc) = 0.6; mp 155−157 °C; IR (ATR) 3447, 3223, 2923, 1712, 1685, 1524, 1348, 1221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 8.9 Hz, 2H), 8.32 (d, J = 8.9 Hz, 2H), 6.99 (br s, 1H), 5.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6, 164.1, 150.5, 137.5, 132.3, 123.5.

*2-(4-Bromophenyl)-2-oxoacetamide (**2k**).*[13c] Yellow solid: yield 70 mg, 62%; R_f (8:2 hexanes/EtOAc) = 0.6; mp 122−124 °C; IR (ATR) 3422, 3224, 1685, 1658, 1583, 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24−8.20 (m, 2H), 7.65−7.60 (m, 2H), 7.00 (br s, 1H), 5.97 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 163.3, 132.6, 131.9, 131.8, 131.7, 131.5 130.3.

*2-(4-Chlorophenyl)-2-oxoacetamide (**2l**).*[13c] Yellow solid: yield 55 mg, 60%; R_f (8:2 hexanes/EtOAc) = 0.6; mp 129−131 °C; IR (ATR) 3435, 3215, 1712, 1691, 1658, 1584, 1464, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32−8.29 (m, 2H), 7.48−7.45 (m, 2H), 7.0 (br s, 1H), 5.89 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.8, 163.3, 141.3, 132.6, 131.3, 128.9.

*2-(4-Fluorophenyl)-2-oxoacetamide (**2m**).*[13c] Yellow solid: yield 61 mg, 73%; R_f (8:2 hexanes/EtOAc) = 0.5; mp 150−151 °C; IR (ATR) 3455, 3202, 2923, 1718, 1671, 1579, 1501, 1228 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 8.23−8.18 (m, 2H), 8.01 (br s, 1H), 7.68 (br s, 1H), 7.24−7.18 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 187.5, 166.94, and 164.40 [d, $J_{(C-F)}$ = 254 Hz], 165.5, 132.9, and 132.8 [d, $J_{(C-F)}$ = 10 Hz], 129.4 and 129.3 [d, $J_{(C-F)}$ = 3 Hz], 115.4 and 115.2 [d, $J_{(C-F)}$ = 22 Hz].

*2-(3-Fluorophenyl)-2-oxoacetamide (**2n**).* Yellow wax: yield 50 mg, 60%; R_f (8:2 hexanes/EtOAc) = 0.5; IR (ATR) 3414, 3207, 3076, 1707, 1678, 1588, 1490, 1456, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 7.8 Hz, 1H), 8.05−8.02 (m, 1H), 7.50−7.45 (m, 1H), 7.36−7.32 (m, 1H), 7.00 (br s, 1H), 6.02 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.8, 163.70, and 161.24 [d, $J_{(C-F)}$ = 246 Hz], 163.2, 134.8, and 134.7 [d, $J_{(C-F)}$ = 6 Hz], 130.3 and 130.2 [d, $J_{(C-F)}$ = 7 Hz], 127.1 and 127.0 [d, $J_{(C-F)}$ = 3 Hz], 121.7 and 121.5 [d, $J_{(C-F)}$ = 22 Hz], 117.9 and 117.6 [d, $J_{(C-F)}$ = 23 Hz]; HRMS (ESI, TOF) calcd for $C_8H_6FNO_2^+$ $[M]^+$ 167.0383, found 167.0360.

*2-(2-Fluorophenyl)-2-oxoacetamide (**2o**).* Yellow wax: yield 42.1 mg, 51%; R_f (8:2 hexanes/EtOAc) = 0.5; IR (ATR) 3426, 3259, 3170, 1720, 1675, 1611, 1592, 1485, 1458, 1278 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−7.88 (m, 1H), 7.62−7.56 (m, 1H), 7.28−7.24 (m, 1H), 7.19−7.14 (m, 1H), 6.82 (br s, 1H), 6.06 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 163.3, 163.21, and 160.64 [d, $J_{(C-F)}$ = 257 Hz], 135.5 and 135.4 [d, $J_{(C-F)}$ = 9 Hz], 131.9 and 131.9 [d, $J_{(C-F)}$ = 1 Hz], 124.2 and 124.2 [d, $J_{(C-F)}$ = 4 Hz], 122.6 and 122.4 [d, $J_{(C-F)}$ = 12 Hz], 116.7 and 116.5 [d, $J_{(C-F)}$ = 21 Hz]; HRMS (ESI, TOF) calcd for $C_8H_6FNNaO_2^+$ $[M + Na]^+$ 190.0275, found 190.0246.

*2-(3,4-Dichlorophenyl)-2-oxoacetamide (**2p**).*[13c] Yellow solid: yield 35 mg, 32%; R_f (8:2 hexanes/EtOAc) = 0.6; mp 186−187 °C; IR (ATR) 3454, 3212, 2923, 1709, 1669, 1576, 1465, 1375, 1220 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 8.23 (s, 1H), 8.21 (br s, 1H), 8.06−8.01 (m, 1H), 7.94 (br s, 1H), 7.71 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 186.9, 164.9, 137.5, 132.8, 132.0, 131.5, 130.7, 129.4.

*2-Oxo-2-(thiophen-2-yl)acetamide (**2q**).*[13c] Brown solid: yield 34.8 mg, 46%; R_f (8:2 hexanes/EtOAc) = 0.5; mp 82−84 °C; IR (ATR) 3447, 3330, 2853, 1708, 1648, 1578, 1500, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41−8.40 (m, 1H), 7.84−7.83 (m, 1H), 7.20 (t, J = 4.8 Hz, 1H), 7.18 (br s, 1H), 5.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 162.8, 138.6, 138.2, 136.7, 128.3.

*2-(1-Benzyl-1H-indol-3-yl)-2-oxoacetamide (**2r**).*[13c] Brown solid: yield 77.1 mg, 56%; R_f (7:3 hexanes/EtOAc) = 0.6; mp 182−184 °C; IR (ATR) 3454, 3320, 2923, 1690, 1626, 1514, 1392, 1355, 1172 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 8.93 (s, 1H), 8.30−8.28 (m, 1H), 7.98 (br s, 1H), 7.67 (br s, 1H), 7.52−7.50 (m, 1H), 7.34−7.22 (m, 7H), 5.55 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 182.0, 165.4, 140.9, 136.4, 136.1, 128.5, 128.4, 127.6, 127.1, 127.0, 126.7, 123.3, 122.7, 121.6, 111.4, 111.1, 49.9.

*2-(1-Methyl-1H-indol-3-yl)-2-oxoacetamide (**2s**).*[13c] Yellow solid: yield 59.0 mg, 58%; R_f (7:3 hexanes/EtOAc) = 0.6; mp 179−181 °C; IR (ATR) 3369, 3186, 2926, 1705, 1625, 1593, 1517, 1463, 1346, 1205, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.44−8.40 (m, 1H), 7.40−7.33 (m, 4H), 5.65 (br s, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 164.8, 142.0, 137.0, 127.6, 123.9, 123.5, 122.6, 111.7, 109.9, 33.7.

*2-(1H-Indol-3-yl)-2-oxoacetamide (**2t**).*[13c] Brown solid: yield 48.7 mg, 52%; R_f (7:3 hexanes/EtOAc) = 0.5; mp 249−251 °C; IR (ATR)

DOI: 10.1021/acs.joc.6b01262
J. Org. Chem. 2016, 81, 6617−6625

3253, 2923, 1686, 1620, 1579, 1494, 1458 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 with $CDCl_3$) δ 12.10 (br s, 1H), 8.72 (d, J = 2.9 Hz, 1H), 8.26−8.24 (m, 1H), 7.94 (br s, 1H), 7.62 (br s, 1H), 7.51−7.49 (m, 1H), 7.26−7.20 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 with $CDCl_3$) δ 182.3, 165.6, 138.0, 136.1, 126.2, 123.1, 122.2, 121.2, 112.2, 112.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01262.

^1H NMR for starting materials, ^1H NMR and ^{13}C NMR for all the products, EPR analysis, and byproduct monitoring results (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: amitkt@iitp.ac.in or amitktiitk@gmail.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by CSIR [02(0229)/15/EMR-II], New Delhi, and the Indian Institute of Technology (IIT) Patna. Y.K. and M.S. thank IIT Patna for an Institute Research Fellowship. The authors also acknowledge SAIF-Panjab University for providing analytical facilities. The authors also express sincere thanks to Dr. C. S. Purohit (NISER-Bhubaneswar) for his timely help in providing the ^1H NMR facility. This work is dedicated to Prof. R. R. Schmidt (University of Konstanz, Konstanz, Germany) on the occasion of his 80th birthday.

■ REFERENCES

(1) For selected examples, see: (a) Xu, G. G.; Etzkorn, F. A. *Org. Lett.* **2010**, *12*, 696. (b) Wang, Z.; Bois-Choussy, M.; Jia, Y.; Zhu, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2018. (c) Shinohara, T.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 7334. (d) Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032. (e) Chiou, A.; Markidis, T.; Constantinou-Kokotou, V.; Verger, R.; Kokotos, G. *Org. Lett.* **2000**, *2*, 347. (f) Toda, S.; Kotake, C.; Tsuno, T.; Narita, Y.; Yamasaki, T.; Konishi, M. *J. Antibiot.* **1992**, *45*, 1580.

(2) (a) Fusetani, N.; Matsunaga, S.; Matsumoto, H.; Takebayashi, Y. *J. Am. Chem. Soc.* **1990**, *112*, 7053. (b) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031. (c) Aoyagi, T.; Nagai, M.; Ogawa, K.; Kojima, F.; Okada, M.; Ikeda, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1991**, *44*, 949. (d) Bierer, B. E.; Somers, P. K.; Wandless, T. J.; Burakoff, S. J.; Schreiber, S. L. *Science* **1990**, *250*, 556. (e) Rosen, M. K.; Standaert, R. F.; Galat, A.; Nakatsuka, M.; Schreiber, S. L. *Science* **1990**, *248*, 863.

(3) (a) Ovat, A.; Li, Z. Z.; Hampton, C. Y.; Asress, S. A.; Fernández, F. M.; Glass, J. D.; Powers, J. C. *J. Med. Chem.* **2010**, *53*, 6326. (b) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946. (c) Álvarez, S.; Álvarez, R.; Khanwalkar, H.; Germain, P.; Lemaire, G.; Rodríguez-Barrios, F.; Gronemeyer, H.; de Lera, Á. R. *Bioorg. Med. Chem.* **2009**, *17*, 4345. (d) Qian, J.; Cuerrier, D.; Davies, P. L.; Li, Z.; Powers, J. C.; Campbell, R. L. *J. Med. Chem.* **2008**, *51*, 5264. (e) Hagihara, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570.

(4) (a) Chen, Y.-H.; Zhang, Y.-H.; Zhang, H.-J.; Liu, D.-Z.; Gu, M.; Li, J.-Y; Wu, F.; Zhu, X.-Z.; Li, J.; Nan, F.-J. *J. Med. Chem.* **2006**, *49*, 1613. (b) Natarajan, A.; Wang, K.; Ramamurthy, V.; Scheffer, J. R.; Patrick, B. *Org. Lett.* **2002**, *4*, 1443.

(5) Only a few recent citations: (a) De Risi, C.; Pollini, G. P.; Zanirato, V. *Chem. Rev.* **2016**, *116*, 3241. (b) Wang, Z.; Liu, C.; Huang, Y.; Hu, Y.; Zhang, B. *Chem. Commun.* **2016**, *52*, 2960. (c) Guo, S.; Fang, Z.; Yang, Z.; Liu, C.; Dai, Z.; Zhao, L.; Guo, K. *RSC Adv.* **2016**, *6*, 1503. (d) Du, H.; Ruan, Q.; Qi, M.; Han, W. *J. Org. Chem.* **2015**, *80*, 7816. (e) Liu, L.; Du, L.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2014**, *16*, 5772. (f) Deshidi, R.; Kumar, M.; Devari, S.; Shah, B. A. *Chem. Commun.* **2014**, *50*, 9533 and references therein.

(6) For selected examples, see: (a) Kotha, S. S.; Chandrasekar, S.; Sahu, S.; Sekar, G. *Eur. J. Org. Chem.* **2014**, *2014*, 7451. (b) Zhao, Q.; Miao, T.; Zhang, X.; Zhou, W.; Wang, L. *Org. Biomol. Chem.* **2013**, *11*, 1867. (c) Li, D.; Wang, M.; Liu, J.; Zhao, Q.; Wang, L. *Chem. Commun.* **2013**, *49*, 3640. (d) Wei, W.; Shao, Y.; Hu, H.; Zhang, F.; Zhang, C.; Xu, Y.; Wan, X. *J. Org. Chem.* **2012**, *77*, 7157. (e) Nielsen, D. U.; Neumann, K.; Taaning, R. H.; Lindhardt, A. T.; Modvig, A.; Skrydstrup, T. *J. Org. Chem.* **2012**, *77*, 6155 and references therein.

(7) Only a few recent citations: (a) Sasaki, M.; Ando, M.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Org. Lett.* **2016**, *18*, 1598. (b) Sagadevan, A.; Ragupathi, A.; Lin, C.-C.; Hwu, J. R.; Hwang, K. C. *Green Chem.* **2015**, *17*, 1113. (c) Padala, A. K.; Mupparapu, N.; Singh, D.; Vishwakarma, R. A.; Ahmed, Q. N. *Eur. J. Org. Chem.* **2015**, *2015*, 3577. (d) Giustiniano, M.; Mercalli, V.; Cassese, H.; Di Maro, S.; Galli, U.; Novellino, E.; Tron, G. C. *J. Org. Chem.* **2014**, *79*, 6006. (e) Guin, S.; Rout, S. K.; Gogoi, A.; Ali, W.; Patel, B. K. *Adv. Synth. Catal.* **2014**, *356*, 2559. (f) Wu, X.; Gao, Q.; Liu, S.; Wu, A. *Org. Lett.* **2014**, *16*, 2888.

(8) For selected examples, see: (a) Shao, J.; Huang, X.; Wang, S.; Liu, B.; Xu, B. *Tetrahedron* **2012**, *68*, 573. (b) Zhang, C.; Xu, Z.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11088. (c) Mossetti, R.; Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2010**, *12*, 820. (d) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (e) Grassot, J.-M.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 947. (f) Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* **2003**, *68*, 6063 and references therein.

(9) Only a few recent citations: (a) Kotha, S. S.; Sekar, G. *Tetrahedron Lett.* **2015**, *56*, 6323. (b) Dutta, S.; Kotha, S. S.; Sekar, G. *RSC Adv.* **2015**, *5*, 47265. (c) Fan, W.; Shi, D.; Feng, B. *Tetrahedron Lett.* **2015**, *56*, 4638. (d) Zhang, L.; Pu, J.; Ren, J.; Li, Z.; Xiang, H.; Zhou, X. *Synth. Commun.* **2015**, *45*, 1848. (e) Mupparapu, N.; Khan, S.; Battula, S.; Kushwaha, M.; Gupta, A. P.; Ahmed, Q. N.; Vishwakarma, R. A. *Org. Lett.* **2014**, *16*, 1152. (f) Du, B.; Jin, B.; Sun, P. *Org. Biomol. Chem.* **2014**, *12*, 4586.

(10) For selected examples, see: (a) Zhou, M.; Song, Q. *Synthesis* **2014**, *46*, 1853. (b) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Biomol. Chem.* **2013**, *11*, 4573. (c) Zhang, X.; Wang, M.; Zhang, Y.; Wang, L. *RSC Adv.* **2013**, *3*, 1311. (d) Zhang, X.; Yang, W.; Wang, L. *Org. Biomol. Chem.* **2013**, *11*, 3649. (e) Mai, W.-P.; Wang, H.-H.; Li, Z.-C.; Yuan, J.-W.; Xiao, Y.-M.; Yang, L.-R.; Mao, P.; Qu, L.-B. *Chem. Commun.* **2012**, *48*, 10117.

(11) For selected examples, see: (a) Xing, Q.; Shi, L.; Lang, R.; Xia, C.; Li, F. *Chem. Commun.* **2012**, *48*, 11023. (b) Zhang, J.; Wei, Y.; Lin, S.; Liang, F.; Liu, P. *Org. Biomol. Chem.* **2012**, *10*, 9237. (c) Zhang, X.; Wang, L. *Green Chem.* **2012**, *14*, 2141. (d) Fukuyama, T.; Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I. *Org. Lett.* **2006**, *8*, 1383 and references therein.

(12) (a) Wang, G.; Yu, Q.; Chen, S.; Yu, X. *Org. Biomol. Chem.* **2014**, *12*, 414. (b) Takács, E.; Varga, C.; Skoda-Földes, R.; Kollár, L. *Tetrahedron Lett.* **2007**, *48*, 2453.

(13) (a) Bouma, M.; Masson, G.; Zhu, J. *J. Org. Chem.* **2010**, *75*, 2748. (b) Zhang, Z.; Su, J.; Zha, Z.; Wang, Z. *Chem. Commun.* **2013**, *49*, 8982. (c) Liu, S.; Gao, Q.; Wu, X.; Zhang, J.; Ding, K.; Wu, A. *Org. Biomol. Chem.* **2015**, *13*, 2239.

(14) (a) Sterckx, H.; De Houwer, J.; Mensch, C.; Caretti, I.; Tehrani, K. A.; Herrebout, W. A.; Van Doorslaer, S.; Maes, B. U. W. *Chem. Sci.* **2016**, *7*, 346. (b) McCann, S. D.; Stahl, S. S. *Acc. Chem. Res.* **2015**, *48*, 1756. (c) Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 2357. (d) Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *ACS Catal.* **2013**, *3*, 2599.

DOI: 10.1021/acs.joc.6b01262
J. Org. Chem. 2016, 81, 6617−6625

(15) (a) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234. (b) Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2011**, *13*, 1622 and references therein.
(16) For safe and controlled operation of O_2 mixing with flammable solvents, see: (a) Greene, J. F.; Preger, Y.; Stahl, S. S.; Root, T. W. *Org. Process Res. Dev.* **2015**, *19*, 858. (b) Osterberg, P. M.; Niemeier, J. K.; Welch, C. J.; Hawkins, J. M.; Martinelli, J. R.; Johnson, T. E.; Root, T. W.; Stahl, S. S. *Org. Process Res. Dev.* **2015**, *19*, 1537. (c) Steves, J. E.; Preger, Y.; Martinelli, J. R.; Welch, C. J.; Root, T. W.; Hawkins, J. M.; Stahl, S. S. *Org. Process Res. Dev.* **2015**, *19*, 1548. (d) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. *Acc. Chem. Res.* **2015**, *48*, 349. (e) Bourne, S. L.; Ley, S. V. *Adv. Synth. Catal.* **2013**, *355*, 1905. (f) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849.
(17) (a) Ma, B.; Zhang, Z.; Song, W.; Xue, X.; Yu, Y.; Zhao, Z.; Ding, Y. J. M. *J. Mol. Catal. A: Chem.* **2013**, *368*−*369*, 152. (b) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 6810.
(18) See the Supporting Information for the complete details of the experiment.
(19) (a) Liu, F.; Liu, K.; Yuan, X.; Li, C. *J. Org. Chem.* **2007**, *72*, 10231. (b) Guindon, Y.; Guerin, B.; Landry, S. R. *Org. Lett.* **2001**, *3*, 2293. (c) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans.1* **2000**, 1. (d) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (e) Speier, G.; Párkányi, L. *J. Org. Chem.* **1986**, *51*, 218.
(20) (a) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C.-O.; Cho, H. Y.; Jung, J. H. *J. Nat. Prod.* **2007**, *70*, 2. (b) Garg, N. K.; Stoltz, B. M. *Tetrahedron Lett.* **2005**, *46*, 2423. (c) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2002**, *4*, 941.
(21) (a) Yadav, V. K.; Babu, K. G. *Eur. J. Org. Chem.* **2005**, *2005*, 452. (b) Grella, G. E.; Cabras, M. C.; Murineddu, G.; Pau, A.; Pinna, G. A. *Eur. J. Pharm. Sci.* **2003**, *20*, 267. (c) McCarthy, J. R.; Wright, D. L.; Schuster, A. J.; Abdallah, A. H.; Shea, P. J.; Eyster, R. *J. Med. Chem.* **1985**, *28*, 1721. (d) Calcinari, R.; Case, N.; Guerrato, A.; Milanino, R.; Passarella, E.; Perchinunno, M.; Tamburini, B.; Sparatore, F. *J. Med. Chem.* **1981**, *24*, 632. (e) Kelarev, V. I.; Shvekhgeimer, G. A. *Khimiya Geterotsiklicheskikh Soedinenii* **1980**, *5*, 645.
(22) (a) Squarcialupi, L.; Colotta, V.; Catarzi, D.; Varano, F.; Betti, M.; Varani, K.; Vincenzi, F.; Borea, P. A.; Porta, N.; Ciancetta, A.; Moro, S. *Eur. J. Med. Chem.* **2014**, *84*, 614. (b) Tonelli, M.; Novelli, F.; Tasso, B.; Vazzana, I.; Sparatore, A.; Boido, V.; Sparatore, F.; La Colla, P.; Sanna, G.; Giliberti, G.; Busonera, B.; Farci, P.; Ibba, C.; Loddo, R. *Bioorg. Med. Chem.* **2014**, *22*, 4893. (c) Kahveci, B.; Mentese, E.; Özil, M.; Ülker, S.; Ertürk, M. *Monatsh. Chem.* **2013**, *144*, 993. (d) Bekircan, O.; Bektas, H. *Molecules* **2008**, *13*, 2126. (e) Litzinger, E. A.; Martásek, P.; Roman, L. J.; Silverman, R. B. *Bioorg. Med. Chem.* **2006**, *14*, 3185.
(23) (a) Connolly, D. J.; Lacey, P. M.; McCarthy, M.; Saunders, C. P.; Carroll, A.-M.; Goddard, R.; Guiry, P. J. *J. Org. Chem.* **2004**, *69*, 6572. (b) Ringom, R.; Axen, E.; Uppenberg, J.; Lundbäck, T.; Rondahl, L.; Barf, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4449.

DOI: 10.1021/acs.joc.6b01262
J. Org. Chem. 2016, 81, 6617−6625