JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis and Anti-inflammatory Evaluation of 2-Aminobenzaldehydes via Ir(III)-Catalyzed C−H Amidation of Aldimines with Acyl Azides

Saegun Kim,[†,∥] Prashant Chakrasali,[‡,§,∥] Hyo Sun Suh,[†] Neeraj Kumar Mishra,[†] Taeyoung Kim,[†] Sang Hoon Han,[†] Hyung Sik Kim,[†] Byung Mu Lee,*[,†] Soo Bong Han,*[,‡,§] and In Su Kim*[,†]

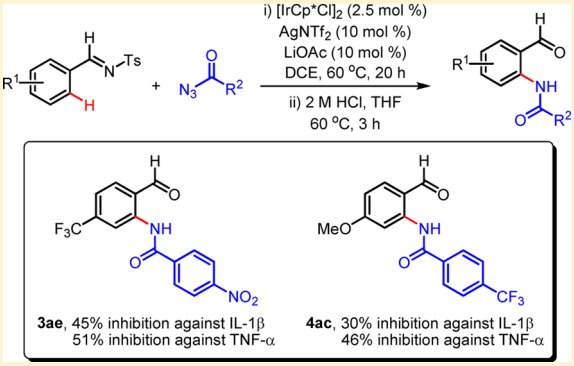
[†]School of Pharmacy, Sungkyunkwan University, Suwon 16419, Republic of Korea

[‡]Division of Bio & Drug Discovery, Korea Research Institute of Chemical Technology, Daejeon 305-600, Republic of Korea

[§]Department of Medicinal and Pharmaceutical Chemistry, University of Science and Technology, 217 Gajeongro, Yuseong, Daejeon 305-355, Republic of Korea

Supporting Information

ABSTRACT: The aldimine-directed C−H amidation of various arenes with *N*-acyl azides as amidation surrogates under cationic iridium(III) catalysis is described. This transformation efficiently provides a range of 2-aminobenzaldehyde derivatives with excellent site selectivity and functional group compatibility. The resulting 2-aminobenzaldehyde framework provides facile access to a range of biologically interesting heterocycles. In addition, all synthetic compounds were screened for anti-inflammatory activity against interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α) with lipopolysaccharide (LPS)-induced RAW264.7 cells. Generally, a range of *ortho*-amidated benzaldehydes displayed promising inhibitory activity against IL-1β and TNF-α compared to dexamethasone as a positive control. Notably, compounds (**3ae** and **4ac**) were found to exhibit potent anti-inflammatory activity stronger than that of dexamethasone.



INTRODUCTION

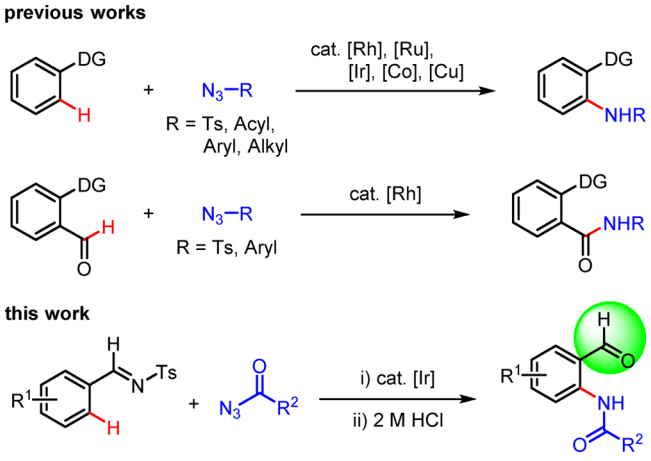
Transition-metal-catalyzed C−N bond formation reactions via C−H bond activation have been of great interest in organic and medicinal chemistry due to the prevalence of bioactive nitrogen-containing heterocycles.[1] In this area, various *N*-amidation surrogates, such as *N*-carboxylates, *N*-tosylates, organic azides, and dioxazolones, have been investigated as relevant sources for the C−H amidation reactions.[2] Particularly, *N*-acyl azides have been intensively studied in the direct C−N amidation reactions of sp^2 C−H bonds,[3] although *N*-acyl azides can be readily converted to aryl isocyanates through the Curtius rearrangement under thermal and photochemical conditions.[4] Chang reported a pioneering example on the C−H amidation reaction of arenes and alkenes with various *N*-acyl azides as amidating reagents under Ir(III) and Ru(II) catalysis.[3a,b] Zhu also disclosed a single example of the Cu(I)Tc-catalyzed C−N bond formation of phenylpyridine with 4-methylbenzoyl azide.[3c] König demonstrated the Ru(II)-catalyzed C−H amidation of heteroarenes with *N*-acyl azides in the presence of visible light.[3d] In addition, Zhou and Li presented the Ir(III)-catalyzed C7-amidation of indolines with acyl, sulfonyl, and aryl azides leading to a biologically important C7-aminated indolinic scaffold.[3e] Moreover, Ackermann described the inexpensive Co(III)-catalyzed C−H aminocarbonylation of unactivated (hetero)arenes and alkenes through the Curtius rearrangement of acyl azides.[3f] In sharp contrast, Zhou and Li disclosed the Rh(III)-catalyzed synthesis of amides from aldehydes and sulfonyl/aryl azides by chelation-assisted aldehydic C−H bond activation.[3g]

2-Aminobenzaldehydes have been utilized as ubiquitous precursors for the construction of various heterocycles such as quinolines, acridines, quinolinones, dibenzonaphthyridines, benzoxazin-4-ones, and natural neocryptolepine.[5] Furthermore, *N*-substituted *ortho*-aminobenzaldehydes have been employed for the formation of pharmaceutically relevant indoles.[6] Due to the weak coordinating ability of aldehydes to transition metals, aldimines have been recently applied as alternative directing groups to afford *ortho*-functionalized benzaldehydes.[7] In sharp contrast, aldimines were also used as electrophilic coupling partners in a C−H activation event leading to the corresponding secondary amine adducts.[8] In continuation of our recent work on site-selective C−H amidation of (hetero)-arenes,[9] we herein report the Cp*Ir(III)-catalyzed direct amidation of aldimines with *N*-acyl azides followed by in situ acidic hydrolysis affording *ortho*-amidobenzaldehydes (Scheme 1). It is noted that the resulting *ortho*-amidated benzaldehydes are readily converted to various biologically relevant hetero-

Received: May 24, 2017
Published: June 22, 2017

DOI: 10.1021/acs.joc.7b01280
J. Org. Chem. 2017, 82, 7555−7563

Scheme 1. Transition-Metal-Catalyzed C−H Amidation Reactions Using Organic Azides



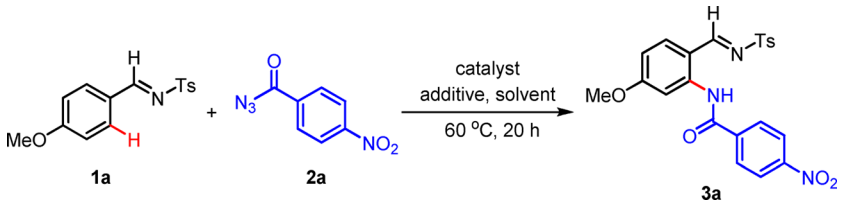
cycles such as 4*H*-1,3-benzoxazin-4-ones, quinazoline, and 1,2-dihydroquinoline. Additionally, synthesized *ortho*-amidated benzaldehydes and 4*H*-1,3-benzoxazin-4-ones were evaluated for anti-inflammatory activity against interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α) with lipopolysaccharide-induced RAW264.7 cells, and were found to display promising anti-inflammatory activity competitive with dexamethasone as a positive control.

RESULTS AND DISCUSSION

Our optimization was initiated by examining the coupling of *N*-sulfonyl aldimine **1a** and acyl azide **2a** under cationic Ir(III) catalysis, as shown in Table 1. To our pleasure, the desired *ortho*-amidated aldimine **3a** was formed in 30% yield (Table 1, entry 1). However, other catalysts such as Rh(III), Ru(II), and Co(III) were found to be unsuccessful in this transformation (Table 1, entries 2−4). Exchange of $AgSbF_6$ to $AgNTf_2$ displayed the slightly increased formation of the desired product **3a** in 35% yield (Table 1, entry 5). Control experiments indicated that both the Ir(III) catalyst and silver additive are highly required for the coupling reaction between **1a** and **2a** (Table 1, entries 6 and 7). Interestingly, a catalytic amount of LiOAc additive was found to display the remarkably increased reactivity to give **3a** in 85% yield (Table 1, entry 8). However, other additives, e.g., NaOAc, KOAc, CuOAc, AcOH, and Li_2CO_3, were less effective (Table 1, entries 9−13). In addition, various solvents were screened, and DCE solvent was found to be most effective in this reaction (Table 1, entries 14−17). Decreasing the amount of Ir(III) catalyst to 1 mol % provided 2-amido aldimine **3a** in 42% yield (Table 1, entry 18). In addition, increasing the amount of acyl azide **2a** was found to be comparable in this transformation to provide **3a** in 83% yield (Table 1, entry 19). Finally, it should be mentioned that the reaction temperature is quite important for the amidation reaction to furnish **3a** in high yield (Table 1, entries 20 and 21).

Meanwhile, we envisioned the in situ formation of 2-aminobenzaldehyde **3aa** under acidic hydrolysis conditions.

Table 1. Selected Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	additive (mol %)	solvent	yield (%)[b]
1	$[IrCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (10)	DCE	30
2	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (10)	DCE	N.R.
3	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5)	$AgSbF_6$ (10)	DCE	N.R.
4	$[CoCp^*(CO)I_2]$ (5)	$AgSbF_6$ (10)	DCE	N.R.
5	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	DCE	35
6	$[IrCp^*Cl_2]_2$ (2.5)		DCE	N.R.
7		$AgNTf_2$ (10)	DCE	N.R.
8	**$[IrCp^*Cl_2]_2$ (2.5)**	**$AgNTf_2$(10), LiOAc (10)**	**DCE**	**85**
9	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), NaOAc (10)	DCE	42
10	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), KOAc (10)	DCE	53
11	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), CuOAc (10)	DCE	40
12	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), AcOH (10)	DCE	62
13	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), Li_2CO_3 (10)	DCE	57
14	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), LiOAc (10)	MeOH	trace
15	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), LiOAc (10)	MeCN	N.R.
16	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), LiOAc (10)	toluene	N.R.
17	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), LiOAc (10)	THF	trace
18	$[IrCp^*Cl_2]_2$ (1)	$AgNTf_2$ (5), LiOAc (10)	DCE	42
19[c]	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), LiOAc (10)	DCE	83
20[d]	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), LiOAc (10)	DCE	70
21[e]	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (5), LiOAc (10)	DCE	45

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (quantity noted), additive (quantity noted), solvent (1 mL) under air at 60 °C for 20 h in pressure tubes. [b]Isolated yield by flash column chromatography. [c]**2a** (0.6 mmol) was used. [d]80 °C. [e]Room temperature.

DOI: 10.1021/acs.joc.7b01280
J. Org. Chem. 2017, 82, 7555−7563

Scheme 2. In Situ Formation of 2-Amidobenzaldehyde 3aa

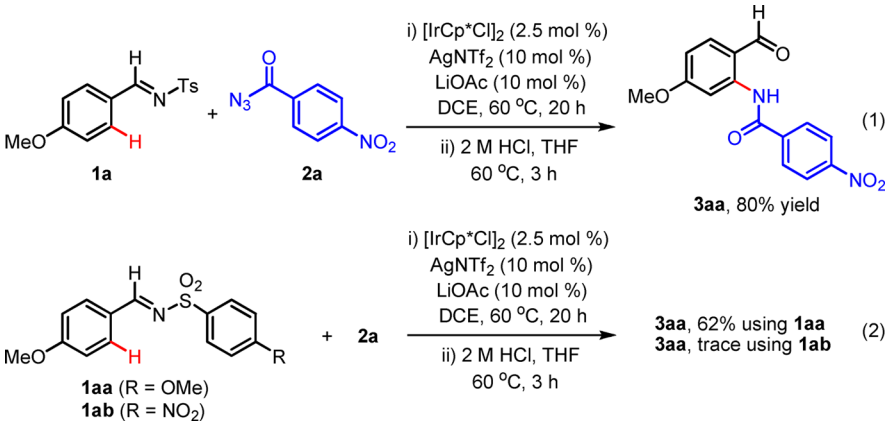
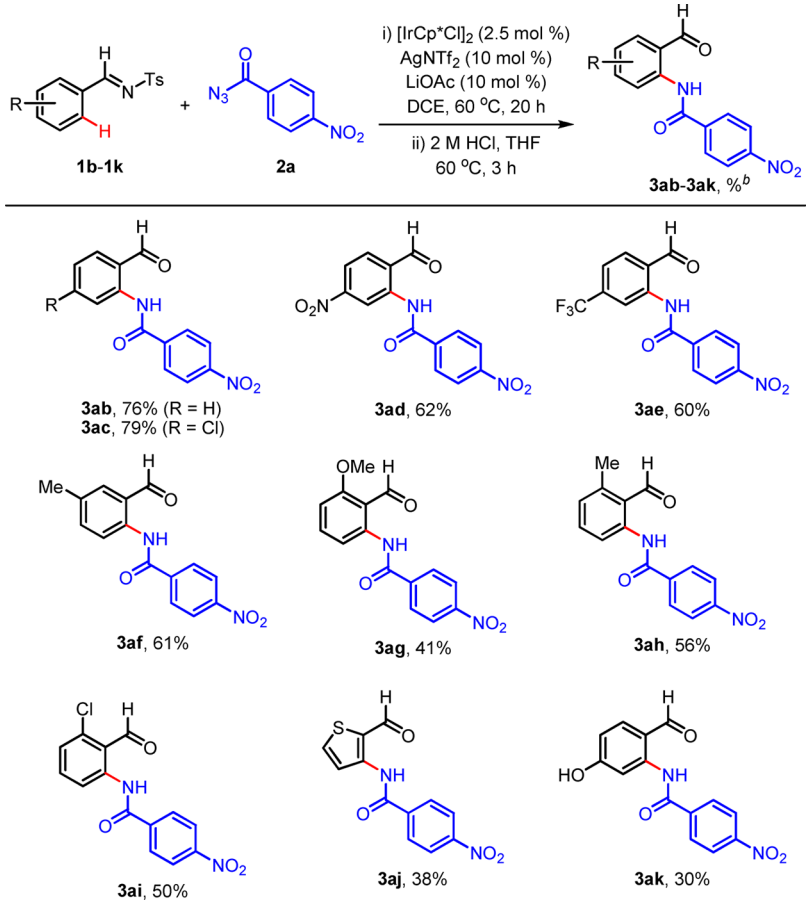


Table 2. Scope of Aldimines[a]



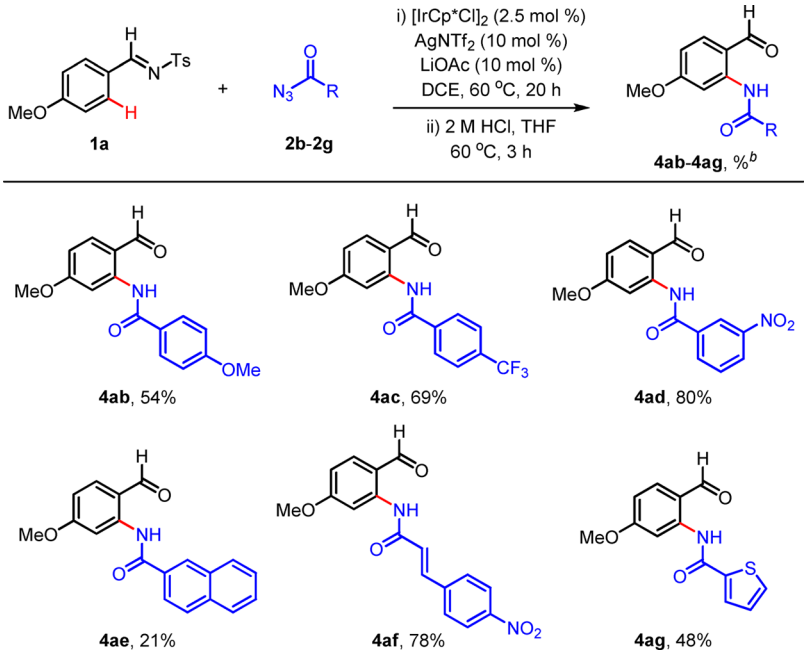
[a]Reaction conditions: (i) **1b**−**1k** (0.2 mmol), **2a** (0.3 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol %), $AgNTf_2$ (10 mol %), LiOAc (10 mol %), DCE (1 mL) under air at 60 °C for 20 h in pressure tubes; (ii) 2 M HCl (1 mL), THF (2 mL) under air at 60 °C for 3 h. [b]Isolated yield by flash column chromatography.

After screening of reaction conditions, we found that treatment of a reaction mixture with 2 M HCl in THF at 60 °C for 3 h afforded 2-aminobenzaldehyde **3aa** in 80% yield (Scheme 2, eq 1). Additionally, this reaction could be applied to another *N*-sulfonyl aldimine **1aa**, which was readily coupled with **2a** to provide **3aa** in 62% yield (Scheme 2, eq 2). However, the reaction of highly electron-deficient *N*-sulfonyl aldimine **1ab** was unsuccessful to deliver **3aa** under the current reaction conditions.

With the optimal reaction conditions in hand, the substrate scope of aldimines was examined, as shown in Table 2. The *para*-substituted aldimines **1b**−**1e** were found to display moderate to good reactivity furnishing the corresponding *ortho*-amidated benzaldehydes **3ab**−**3ae** in 60−79% yields. The coupling reaction of *meta*-substituted aldimine **1f** with acyl azide **2a** preferentially occurred at the less sterically congested position affording the amidated adduct **3af** as a single regioisomer. In addition, *ortho*-substituted aldimines **1g**−**1i**

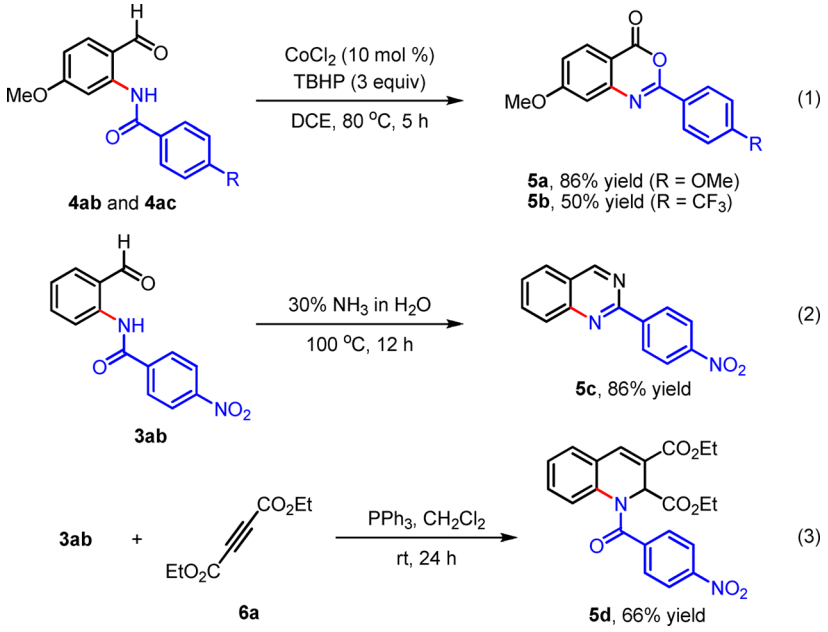
DOI: 10.1021/acs.joc.7b01280
J. Org. Chem. 2017, 82, 7555−7563

Table 3. Scope of Acyl Azides[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2b**−**2g** (0.3 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol %), $AgNTf_2$ (10 mol %), LiOAc (10 mol %), DCE (1 mL) under air at 60 °C for 20 h in pressure tubes; (ii) 2 M HCl (1 mL), THF (2 mL) under air at 60 °C for 3 h. [b]Isolated yield by flash column chromatography.

Scheme 3. Synthesis of Various Heterocycles Using *ortho*-Amidated Benzaldehydes



and heterocyclic aldimine **1j** showed relatively decreased reactivity under the current reaction conditions. It should be noted that aldimines **1k** having OH as a functional group were also tolerable in this transformation to provide **3ak** in 30% yield.

To further evaluate the substrate scope of this process, a range of *N*-acyl azides was tested under the optimal reaction conditions (Table 3). The *para*- and *meta*-substituted aroyl azides **2b**−**2d** were found to show good reactivity giving the corresponding *ortho*-amidated benzaldehyde derivatives **4ab**−**4ad** in moderate to high yields. However, acyl azide **2e** containing a naphthyl moiety displayed relatively decreased reactivity to afford **4ae** in 21% yield. To our pleasure, cinnamoyl azide **2f** was found to be highly reactive under the optimized reaction conditions to furnish the α,β-unsaturated amide **4af** in 78% yield. Additionally, heterocyclic *N*-acyl azide **2g** was also coupled with **1a** to provide the corresponding *ortho*-amidobenzaldehyde **4ag** in moderate yield.

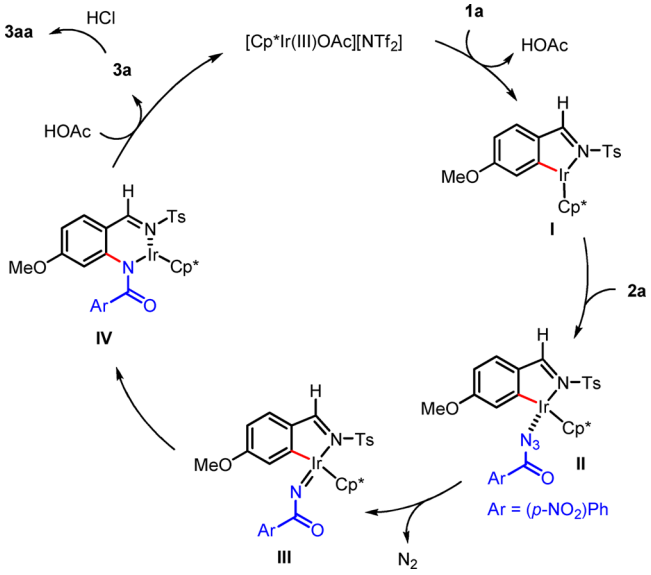
To show the synthetic utility of *N*-(2-formylphenyl)amide derivatives, we first performed the $CoCl_2$/TBHP-mediated intramolecular oxidative cyclization of **4ab** and **4ac** to deliver the corresponding 4*H*-1,3-benzoxazin-4-ones **5a** and **5b** in 86% and 50% yields, respectively (Scheme 3, eq 1).[5f] Notably, the 4*H*-1,3-benzoxazin-4-one skeleton has been found in a number

DOI: 10.1021/acs.joc.7b01280
J. Org. Chem. 2017, 82, 7555−7563

of physiologically and pharmaceutically important molecules such as a chymotrypsin inactivator and selective inhibitors of human leukocyte elastase and serine protease.[10] To further highlight the applicability of amide products, we exploited the formation of quinazoline and 1,2-dihydroquinoline derivatives. When *ortho*-amidated benzaldehyde **3ab** was reacted with 30% ammonia in water, 2-aryl quinazoline **5c** was smoothly formed in 86% yield through the Bischler cyclization (Scheme 3, eq 2).[11] In addition, **3ab** was also coupled with an internal alkyne **6a** to yield 1,2-dihydroquinoline **5d** via the vinyltriphenylphosphonium salt-mediated intramolecular Wittig reaction (Scheme 3, eq 3).[12] However, ethyl phenylpropiolate as an unsymmetrical acetylene did not give any coupling product under the identical reaction conditions, and most of starting material **3ab** was recovered.

Based on previous literatures,[7c,d] a proposed reaction mechanism is outlined in Scheme 4. A cationic Ir(III) complex

Scheme 4. Proposed Reaction Pathway



I is generated from the reaction between aldimine **1a** and [Cp*Ir(III)OAc][NTf_2] via the C−H activation process. Then coordination of acyl azide **2a** and subsequent formation of iridium N−Ts imine species **III** can occur in an oxidative manner to release the N_2 molecule. A C−N bond can be formed by migratory insertion of the N−Ts imine to deliver an Ir(III)−amino species **IV**, which undergoes a protonation step to provide *ortho*-amidated adduct **3a** and an active Ir(III) catalyst. Finally, the desired *ortho*-amidated benzaldehyde **3aa** is generated via hydrolysis with HCl solution.

Meanwhile, synthesized *ortho*-amidated benzaldehydes (**3aa**−**3ak** and **4ab**−**4ag**) and 4*H*-1,3-benzoxazin-4-ones (**5a** and **5b**) were evaluated for in vitro inhibitory activity against interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α) as cell signaling cytokines involved in a systemic inflammation process (Figure 1). The anti-inflammatory activity was analyzed by Western blot experiments using lipopolysaccharide (LPS)-stimulated RAW264.7 cells.[13] The intensity of immunoblot signaling was quantified using ImageJ software[14] and represents the inhibition % values of compounds compared with LPS-stimulated cells. Dexamethasone as an anti-inflammatory drug was chosen as a positive control.[15] A broad range of compounds (**3ac**−**3af**, **4ab**−**4ad**, and **4ag**) exhibited superior inhibitory activity to dexamethasone against IL-1β. Particulary, analogues (**4ad** and **4ag**) were found to display most potent inhibitory activities (47% inhibition for **4ad** and 55% inhibition for **4ag**) about 2-fold stronger than that of a positive control. Next, we screened the TNF-α inhibition activity of synthetic compounds using lipopolysaccharide (LPS)-stimulated RAW264.7 cells. Various *ortho*-amidated benzaldehydes (**3ac**, **3ae**−**3ag**, **3aj**, **3ak**, **4ab**, and **4ac**) were found to induce higher inhibition activity than that of dexamethasone. Interstingly, compounds (**3ae** and **4ac**) showed potent inhibitory activities against both IL-1β and TNF-α. In this stage, we are not clear about the structure−activity relationship (SAR) between synthetic compounds (**3ae** and **4ac**), but these results could be very useful for our future SAR studies to discover novel anti-inflammatory agents.

CONCLUSION

In conclusion, we described the iridium(III)-catalyzed C−H amidation reaction of various aldimines with *N*-acyl azides followed by hydrolysis affording *ortho*-amidated benzaldehydes. This transformation has been applied to a wide range of substrates and typically proceeds with excellent levels of site selectivity as well as with high functional group tolerance. The synthesized *ortho*-amidated benzaldehydes were readily transformed into biologically relevant heterocycles such as 4*H*-1,3-benzoxazin-4-ones, quinazoline, and 1,2-dihydroquinoline. In addition, all synthetic compounds were screened for an anti-inflammatory property against IL-1β and TNF-α with LPS-induced RAW264.7 cells. In general, a broad range of *ortho*-amidated benzaldehydes displayed promising inhibitory activity for IL-1β and TNF-α compared to dexamethasone as a positive control. Notably, compounds (**3ae** and **4ac**) were found to display potent anti-inflammatory activity stronger than that of dexamethasone.

EXPERIMENTAL SECTION

General Procedure for the Reaction of Aldimine with Acyl Azide (3a). To an oven-dried sealed tube charged with (*E*)-*N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (**1a**) (57.9 mg, 0.2 mmol, 100 mol %), [$IrCp^*Cl_2$]$_2$ (4.0 mg, 0.005 mmol, 2.5 mol %), $AgNTf_2$ (7.8 mg, 0.02 mmol, 10 mol %), and LiOAc (1.3 mg, 0.02 mmol, 10 mol %) were added 4-nitrobenzoyl azide (**2a**) (57.6 mg, 0.3 mmol, 150 mol %) and DCE (1 mL) under air. The reaction mixture was allowed to stir for 20 h at 60 °C. The reaction mixture was filtered, washed with MeOH (10 mL), and dried to afford **3a** (77.1 mg) in 85% yield without purification using flash column chromatography.

(E)-N-(5-Methoxy-2-((tosylimino)methyl)phenyl)-4-nitrobenzamide (3a). 77.1 mg (85%, *E*/*Z* = 7.8:1); yellow solid; mp = 235.0−255.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (br s, 1H), 9.12 (s, 1H), 8.31 (dt, *J* = 9.2, 2.4 Hz, 2H), 8.07−8.00 (m, 4H), 7.82 (dt, *J* = 8.8, 2.4 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 6.99 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.90 (s, 3H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.2, 165.8, 163.9, 149.6, 144.6, 142.7, 139.3, 138.1, 135.1, 130.1, 128.7, 127.6, 123.9, 114.4, 111.2, 106.7, 56.1, 21.0; IR (KBr) υ 3266, 3124, 2834, 2359, 1711, 1685, 1626, 1587, 1530, 1462, 1425, 1344, 1318, 1268, 1156, 1086, 1034, 914, 862, 843, 808, 744 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{22}H_{19}N_3O_6S$ $[M]^+$ 453.0995, found 453.0995.

Typical Procedure for the Reaction of Aldimines with Acyl Azides To Access the 2-Aminobenzaldehyde Derivatives (3aa−3ak and 4ab−4ag). To an oven-dried sealed tube charged with (*E*)-*N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (**1a**) (57.9 mg, 0.2 mmol, 100 mol %), [$IrCp^*Cl_2$]$_2$ (4.0 mg, 0.005 mmol, 2.5 mol %), $AgNTf_2$ (7.8 mg, 0.02 mmol, 10 mol %), and LiOAc (1.3 mg, 0.02 mmol, 10 mol %) were added 4-nitrobenzoyl azide (**2a**) (57.6 mg, 0.3 mmol, 150 mol %) and DCE (1 mL) under

DOI: 10.1021/acs.joc.7b01280
J. Org. Chem. 2017, 82, 7555−7563

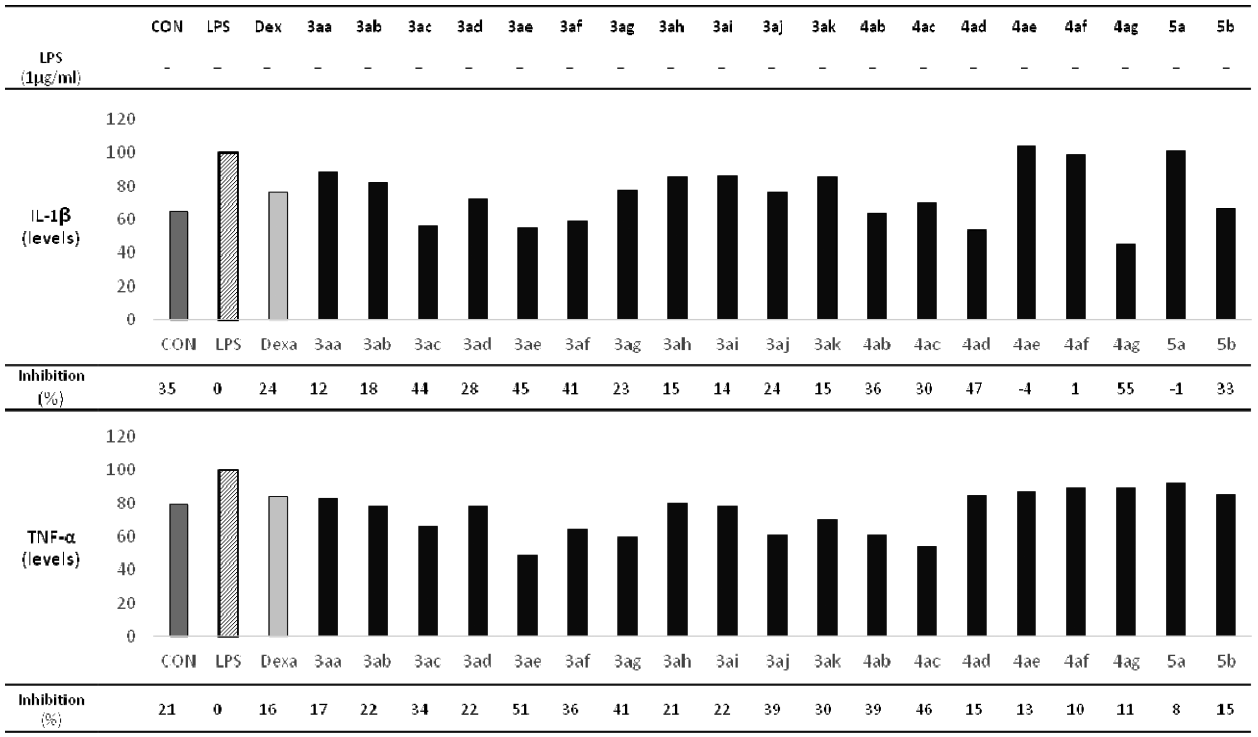


Figure 1. Anti-inflammatory activity of synthesized compounds against IL-1β and TNF-α.

air. The reaction mixture was allowed to stir for 20 h at 60 °C and cooled to room temperature. Then, 2 M HCl (1 mL) and THF (2 mL) were added to the resulting reaction mixture. The reaction mixture was allowed to stir for 3 h at 60 °C. The reaction mixture was cooled to room temperature, quenched with saturated $NaHCO_3$ solution (1 mL) to reach pH 7, and extracted with EtOAc (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 3:1) to afford **3aa** (48.2 mg) in 80% yield.

*N-(2-Formyl-5-methoxyphenyl)-4-nitrobenzamide (**3aa**).* 48.2 mg (80%); light yellow solid; mp = 208.6−209.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.55 (br s, 1H), 9.84 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.37 (dt, J = 9.6, 2.4 Hz, 2H), 8.22 (dt, J = 9.2, 2.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 1H), 6.80 (dd, J = 8.4, 2.4 Hz, 1H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.1, 166.2, 164.1, 150.0, 143.1, 139.7, 138.2, 128.7, 124.1, 116.2, 110.9, 104.2, 55.9; IR (KBr) υ 3200, 2925, 2363, 1686,1624, 3585, 1521, 1340, 1267, 1214, 1165, 1029, 856, 800, 740, 703 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{15}H_{12}N_2O_5$ $[M]^+$ 300.0746, found 300.0747.

*N-(2-Formylphenyl)-4-nitrobenzamide (**3ab**).*[11] 41.2 mg (76%); orange solid; mp = 200.3−206.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (br s, 1H), 10.02 (s, 1H), 8.92 (d, J = 8.4 Hz, 1H), 8.38 (dt, J = 9.2, 2.4 Hz, 2H), 8.22 (dt, J = 9.2, 2.4 Hz, 2H), 7.77 (dd, J = 7.6, 1.6 Hz, 1H), 7.74−7.70 (m, 1H), 7.34 (td, J = 8.4, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.2, 163.9, 150.0, 140.6, 139.8, 136.6, 136.3, 128.7, 124.1, 123.9, 122.1, 120.1; IR (KBr) υ 3005, 2365, 2358, 1715, 1667, 1602, 1587, 1513, 1418, 1363, 1322, 1222, 1095, 870, 763, 709 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{14}H_{10}N_2O_4$ $[M]^+$ 270.0641, found 270.0640.

*N-(5-Chloro-2-formylphenyl)-4-nitrobenzamide (**3ac**).* 48.4 mg (79%); yellow solid; mp = 167.4−170.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.31 (br s, 1H), 9.97 (s, 1H), 9.01 (s, 1H), 8.39 (dt, J = 9.2, 2.4 Hz, 2H), 8.22 (dt, J = 9.2, 2.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.0, 163.9, 150.1, 143.4, 141.4, 139.3, 137.1, 128.7, 124.2, 124.1, 120.4, 120.3; IR (KBr) υ 3273, 3106, 2918, 2850, 2358, 1684, 1660, 1600, 1579, 1516, 1460, 1424, 1400, 1350, 1308, 1268, 1201, 1137, 1098, 1080, 1014, 924, 902, 870, 856, 819, 794, 739, 701 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{14}H_9ClN_2O_4$ $[M]^+$ 304.0251, found 304.0249.

*N-(2-Formyl-5-nitrophenyl)-4-nitrobenzamide (**3ad**).* 39.1 mg (62%); yellow solid; mp = 104.6−107.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.28 (br s, 1H), 10.17 (s, 1H), 9.81 (d, J = 2.0 Hz, 1H), 8.42 (dt, J = 9.2, 2.4 Hz, 2H), 8.24 (dt, J = 9.2, 2.0 Hz, 2H), 8.14 (dd, J = 8.4, 2.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.2, 164.0, 152.2, 150.4, 141.6, 138.8, 136.9, 128.8, 124.9, 124.3, 118.0, 115.5; IR (KBr) υ 3105, 2926, 2852, 2358, 1702, 1597, 1582, 1508, 1342, 1267, 1196, 1169, 1106, 1007, 860, 813, 730, 703 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{14}H_9N_3O_6$ $[M]^+$ 315.0491, found 315.0491.

*N-(2-Formyl-5-(trifluoromethyl)phenyl)-4-nitrobenzamide (**3ae**).* 40.7 mg (60%); brown solid; mp = 110.1−113.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (br s, 1H), 10.11 (s, 1H), 9.27 (s, 1H), 8.40 (dt, J = 9.2, 2.4 Hz, 2H), 8.22 (dt, J = 9.2, 2.4 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.6, 164.0, 150.2, 140.9, 139.1, 137.4 (q, J_{C-F} = 33.3 Hz), 136.5, 128.7, 125.74 (q, J_{C-F} = 273.9 Hz), 124.2, 123.6, 120.3 (q, J_{C-F} = 3.9 Hz), 117.3 (q, J_{C-F} = 4.0 Hz); IR (KBr) υ 3356, 3261, 2361, 2342, 1671, 1626, 1600, 1544, 1492, 1439, 1399, 1331, 1303, 1270, 1252, 1161, 1129, 1111, 1073, 930, 902, 840, 815, 798, 740, 709 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{15}H_9F_3N_2O_4$ $[M]^+$ 338.0514, found 338.0516.

*N-(2-Formyl-4-methylphenyl)-4-nitrobenzamide (**3af**).* 34.9 mg (61%); brown solid; mp = 188.7−191.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.15 (br s, 1H), 9.97 (s, 1H), 8.80 (d, J = 8.4 Hz, 1H), 8.37 (dt, J = 9.2, 2.4 Hz, 2H), 8.21 (dt, J = 9.2, 2.0 Hz, 2H), 7.56−7.51 (m, 2H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.3, 163.7, 149.9, 139.9, 138.2, 137.3, 136.5, 133.7, 128.6, 124.1, 122.1, 120.1, 20.6; IR (KBr) υ 2923, 2852, 2361, 1684, 1657, 1600, 1540, 1555, 1469, 1391, 1345, 1321, 1260, 1242, 1157, 1109, 937, 864, 853, 833, 775, 751, 707 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{15}H_{12}N_2O_4$ $[M]^+$ 284.0797, found 284.0796.

*N-(2-Formyl-3-methoxyphenyl)-4-nitrobenzamide (**3ag**).* 24.9 mg (41%); brown solid; mp = 160.2−163.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.83 (br s, 1H), 10.58 (s, 1H), 8.47 (d, J = 8.8 Hz, 1H), 8.36 (dt, J = 9.2, 2.0 Hz, 2H), 8.24 (dt, J = 9.2, 2.0 Hz, 2H), 7.62 (t, J = 8.4 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR

DOI: 10.1021/acs.joc.7b01280
J. Org. Chem. 2017, 82, 7555−7563

(100 MHz, $CDCl_3$) δ 194.1, 164.1, 163.5, 152.7, 142.1, 140.0, 138.4, 128.7, 124.1, 112.2, 111.3, 106.1, 56.0; IR (KBr) υ 3250, 2921, 2850, 2370, 1677, 1654, 1611, 1600, 1582, 1513, 1474, 1439, 1404, 1348, 1325, 1301, 1271, 1195, 1127, 1112, 1071, 950, 871, 817, 791, 738, 705 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{15}H_{12}N_2O_5$ $[M]^+$ 300.0746, found 300.0743.

*N-(2-Formyl-3-methylphenyl)-4-nitrobenzamide (**3ah**).*[16] 32.2 mg (56%); yellow solid; mp = 209.6−211.1 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.74 (br s, 1H), 10.54 (s, 1H), 8.79 (d, J = 8.4 Hz, 1H), 8.38 (dt, J = 9.2, 2.4 Hz, 2H), 8.23 (dt, J = 9.2, 2.4 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 2.74 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.1, 164.0, 149.9, 143.7, 141.5, 140.1, 136.9, 128.7, 126.8, 124.1, 119.7, 118.6, 19.2; IR (KBr) υ 3112, 2924, 2357, 1681, 1644, 1601, 1578, 1541, 1520, 1466, 1396, 1345, 1304, 1276, 1200, 1174, 1111, 865, 853, 824, 790, 740, 700 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{15}H_{12}N_2O_4$ $[M]^+$ 284.0797, found 284.0796.

*N-(3-Chloro-2-formylphenyl)-4-nitrobenzamide (**3ai**).* 30.6 mg (50%); yellow solid; mp = 165.3−169.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.65 (br s, 1H), 10.64 (s, 1H), 8.84 (d, J = 8.4 Hz, 1H), 8.37 (dt, J = 9.2, 2.4 Hz, 2H), 8.21 (dt, J = 9.2, 2.4 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.24 (dd, J = 8.0, 1.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.0, 163.9, 150.1, 142.7, 140.5, 139.5, 137.2, 128.7, 125.5, 124.1, 119.1, 117.9; IR (KBr) υ 3113, 2364, 1686, 1654, 1604, 1579, 1530, 1489, 1450, 1397, 1346, 1267, 1197, 1102, 865, 852, 795, 741, 705 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{14}H_9ClN_2O_4$ $[M]^+$ 304.0251, found 304.0250.

*N-(2-Formylthiophen-3-yl)-4-nitrobenzamide (**3aj**).* 21.3 mg (38%); brown solid; mp = 204.8−207.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 11.76 (br s, 1H), 9.81 (s, 1H), 8.38 (dt, J = 8.8, 2.0 Hz, 2H), 8.32 (d, J = 5.6 Hz, 1H), 8.18 (dt, J = 8.8, 2.0 Hz, 2H), 7.81 (d, J = 5.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 184.9, 162.6, 150.2, 144.5, 138.6, 136.8, 128.8, 124.2, 123.1, 123.0; IR (KBr) υ 3258, 3058, 2925, 2851, 2358, 2337, 1684, 1625, 1600, 1572, 1517, 1438, 1404, 1374, 1345, 1251, 1179, 1111, 1073, 1006, 900, 866, 857, 801, 760, 740, 707 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{12}H_8N_2O_4S$ $[M]^+$ 276.0205, found 276.0202.

*N-(2-Formyl-5-hydroxyphenyl)-4-nitrobenzamide (**3ak**).* 17.2 mg (30%); yellow solid; mp = 211.7−213.9 °C; ^1H NMR (400 MHz, CD_3OD) δ 13.27 (br s, 1H), 10.45 (s, 1H), 9.26−9.23 (m, 2H), 9.00−8.97 (m, 2H), 8.76 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 201.3, 172.8, 158.9, 151.9, 149.4, 148.1, 138.1, 133.7, 122.8, 116.7, 112.2, 108.1; IR (KBr) υ 3261, 2361, 2332, 1634, 1601, 1557, 1524, 1473, 1452, 1399, 1323, 1269, 1159, 1109, 865, 810, 743, 709 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{14}H_{10}N_2O_5$ $[M]^+$ 286.0590, found 286.0587.

*N-(2-Formyl-5-methoxyphenyl)-4-methoxybenzamide (**4ab**).* 31.1 mg (54%); white solid; mp = 128.8−135.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.32 (br s, 1H), 9.82 (s, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.04 (dt, J = 10.0, 3.2 Hz, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.01 (dt, J = 9.6, 2.8 Hz, 2H), 6.72 (dd, J = 8.8, 2.4 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 193.8, 166.1, 166.0, 162.8, 144.1, 137.9, 129.5, 126.5, 115.9, 114.1, 110.4, 103.4, 55.8, 55.5; IR (KBr) υ 3283, 3132, 2921, 2851, 2777, 2671, 1710, 1683, 1650, 1622, 1606, 1579, 1535, 1508, 1439, 1409, 1336, 1298, 1255, 1224, 1195, 1173, 1145, 1119, 1091, 1031, 951, 903, 869, 814, 756 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{16}H_{15}NO_4$ $[M]^+$ 285.1001, found 285.1003.

*N-(2-Formyl-5-methoxyphenyl)-4-(trifluoromethyl)benzamide (**4ac**).* 44.8 mg (69%); white solid; mp = 108.6−111.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.49 (br s, 1H), 9.83 (s, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.18 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 8.4, 2.4 Hz, 1H), 3.96 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.0, 166.2, 164.9, 143.3, 138.1, 137.5, 134.0, 133.7, 127.9, 125.9 (q, J_{C-F} = 4.0 Hz), 116.2, 110.8, 104.0, 55.9; IR (KBr) υ 3231, 2845, 2359, 2340, 1687, 1655, 1616, 1579, 1531, 1463, 1430, 1403, 1323, 1294, 1267, 1240, 1209, 1168, 1126, 1086, 1064, 1030, 1015, 970, 903, 857, 811, 766, 742 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{16}H_{12}F_3NO_3$ $[M]^+$ 323.0769, found 323.0770.

*N-(2-Formyl-5-methoxyphenyl)-3-nitrobenzamide (**4ad**).* 48.3 mg (80%); yellow solid; mp = 158.1−161.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.60 (br s, 1H), 9.85 (s, 1H), 8.96 (t, J = 2.0 Hz, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.44−8.42 (m, 1H), 8.37 (dt, J = 8.0, 1.6 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 8.4, 2.4 Hz, 1H), 3.97 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.1, 166.2, 163.8, 148.7, 143.2, 138.1, 136.1, 132.8, 130.1, 126.7, 123.1, 116.2, 110.9, 104.2, 55.9; IR (KBr) υ 3056, 2923, 2849, 2358, 1675, 1652, 1625, 1585, 1529, 1476, 1348, 1267, 1212, 1174, 1104, 1021, 929, 857, 811, 740 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{15}H_{12}N_2O_5$ $[M]^+$ 300.0746, found 300.0741.

*N-(2-Formyl-5-methoxyphenyl)-2-naphthamide (**4ae**).* 12.9 mg (21%); brown solid; mp = 180.4−183.1 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 12.56 (br s, 1H), 9.87 (s, 1H), 8.66 (d, J = 2.0 Hz, 1H), 8.62 (s, 1H), 8.13 (dd, J = 8.5, 1.5 Hz, 1H), 8.04 (d, J = 7.5 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.61−7.56 (m, 2H), 6.77 (dd, J = 8.5, 2.0 Hz, 1H), 3.98 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.9, 166.5, 166.2, 143.9, 138.0, 135.2, 132.8, 131.5, 129.5, 128.8, 128.7, 128.1, 127.8, 126.9, 123.6, 116.2, 110.6, 103.8, 55.9; IR (KBr) υ 3235, 2922, 2848, 2758, 2363, 1681, 1655, 1617, 1579, 1529, 1457, 143, 1401, 1335, 1294, 1238, 1207, 1171, 1140, 1118, 1078, 1030, 970, 912, 862, 815, 772, 741 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{19}H_{15}NO_3$ $[M]^+$ 305.1052, found 305.1053.

*(E)-N-(2-Formyl-5-methoxyphenyl)-3-(4-nitrophenyl)acrylamide (**4af**).* 51.1 (78%); yellow solid; mp = 206.3−209.7 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 11.39 (br s, 1H), 9.89 (s, 1H), 8.27 (d, J = 8.5 Hz, 2H), 8.17 (s, 1H), 8.04 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 16.0 Hz, 1H), 7.17 (d, J = 15.5 Hz, 1H), 6.92 (dd, J = 8.5, 2.0 Hz, 1H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 193.6, 164.8, 163.9, 147.9, 141.8, 140.8, 139.4, 137.7, 129.3, 126.1, 123.9, 117.1, 109.5, 105.4, 55.8; IR (KBr) υ 3248, 3114, 2842, 2357, 1659, 1618, 1582, 1514, 1462, 1435, 1344, 1295, 1268, 1236, 1207, 1183, 1131, 1110, 1033, 982, 859, 839, 805, 740 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{17}H_{14}N_2O_5$ $[M]^+$ 326.0903, found 326.0904.

*N-(2-Formyl-5-methoxyphenyl)thiophene-2-carboxamide (**4ag**).* 25.2 mg (48%); yellow solid; mp = 155.2−158.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.35 (br s, 1H), 9.80 (s, 1H), 8.46 (d, J = 2.4 Hz, 1H), 7.83 (dd, J = 3.6, 1.2 Hz, 1H), 7.59 (dd, J = 4.8, 1.2 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.16 (dd, J = 5.2, 4.0 Hz, 1H), 6.72 (dd, J = 8.4, 2.4 Hz, 1H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 193.8, 166.0, 161.1, 143.6, 139.8, 137.9, 131.9, 128.9, 128.1, 115.7, 110.7, 103.4, 55.8; IR (KBr) υ 3227, 3121, 2995, 2840, 2361, 1670, 1650, 1619, 1583, 1537, 1455, 1435, 1415, 1403, 1354, 1294, 1274, 1228, 1201, 1175, 1151, 1094, 1042, 1031, 947, 885, 862, 808, 785, 718 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{13}H_{11}NO_3S$ $[M]^+$ 261.0460, found 261.0462.

Experimental Procedure and Characterization Data for the Synthesis of 5a and 5b. To an oven-dried sealed tube charged with *N*-(2-formyl-5-methoxyphenyl)-4-methoxybenzamide (**4ab**) (57.0 mg, 0.2 mmol, 100 mol %) in DCE (1 mL) were added $CoCl_2$ (2.6 mg, 0.02 mmol, 10 mol %) and TBHP (77.2 mg, 0.6 mmol, 300 mol %, 70% in H_2O) under air. The reaction mixture was stirred at 80 °C for 5 h. The resulting mixture was cooled, diluted with EtOAc (3 mL), and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 4:1) to afford **5a** (48.8 mg) in 86% yield.

*7-Methoxy-2-(4-methoxyphenyl)-4H-benzo[d][1,3]oxazin-4-one (**5a**).* 48.8 mg (86%); white solid; mp = 152.0−155.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.04−7.00 (m, 3H), 3.95 (s, 3H), 3.90 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 163.7, 158.9, 158.6, 149.0, 130.7, 130.3, 121.9, 117.2, 114.3, 109.2, 108.2, 55.9, 55.6; IR (KBr) υ 3059, 2921, 2850, 1763, 1606, 1569, 1491, 1446, 1411, 1352, 1322, 1283, 1246, 1204, 1169, 1125, 1109, 1071, 1028, 999, 853, 774, 738 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{16}H_{13}NO_4$ $[M]^+$ 283.0845, found 283.0844.

*7-Methoxy-2-(4-(trifluoromethyl)phenyl)-4H-benzo[d][1,3]-oxazin-4-one (**5b**).* 32.2 mg (50%); white solid; mp = 215.8−218.0

DOI: 10.1021/acs.joc.7b01280
J. Org. Chem. 2017, 82, 7555−7563

°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 2H), 8.16 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 7.10 (dd, J = 8.5, 2.0 Hz, 1H), 3.97 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.5, 158.7, 156.6, 149.0, 134.0 (q, J_{C-F} = 32.4 Hz), 133.7, 130.4, 128.7, 125.7 (q, J_{C-F} = 3.6 Hz), 123.7 (q, J_{C-F} = 271.4 Hz), 117.8, 109.9, 109.4, 55.9; IR (KBr) υ 3053, 2924, 2954, 1756, 1671, 1601, 1567, 1510, 1488, 1443, 1279, 1265, 1203, 1168, 1104, 1027, 839, 741 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{16}H_{10}F_3NO_3$ [M]$^+$ 321.0613, found 321.0614.

Experimental Procedure and Characterization Data for the Synthesis of 5c. To an oven-dried sealed tube charged with *N*-(2-formylphenyl)-4-nitrobenzamide (**3ab**) (54.0 mg, 0.2 mmol, 100 mol %) in H_2O (1.0 mL) was added a 30% aqueous solution of ammonia (1 mL). The reaction mixture was stirred at 100 °C for 12 h. The resulting mixture was cooled to room temperature and extracted with EtOAc (2 × 2 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 3:1) to afford **5c** (43.5 mg) in 86% yield.

*2-(4-Nitrophenyl)quinazoline (**5c**).* 43.5 mg (86%); white solid; mp = 215.8−218.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.84−8.81 (m, 2H), 8.38−8.35 (m, 2H), 8.17 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 7.6 Hz, 2H), 7.71 (td, J = 7.2, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.7, 158.5, 150.5, 149.3, 143.4, 143.3, 134.9, 129.5, 128.8, 128.5, 127.3, 123.8; IR (KBr) υ 3725, 2917, 2849, 2359, 1677, 1658, 1605, 1553, 1514, 1456, 1339, 1260, 1174, 846, 764, 707 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{14}H_9N_3O_2$ [M]$^+$ 251.0695, found 251.0697.

Experimental Procedure and Characterization Data for the Synthesis of 5d. To a stirred solution of *N*-(2-formylphenyl)-4-nitrobenzamide (**3ab**) (54.0 mg, 0.2 mmol, 100 mol %) and triphenylphosphine (52.5 mg, 0.2 mmol, 100 mol %) in CH_2Cl_2 (1 mL) were added dropwise a mixture of diethyl acetylenedicarboxylate (**6a**) (34.0 mg, 0.2 mmol, 100 mol %) and CH_2Cl_2 (1 mL) at 0 °C for 10 min. The reaction mixture was stirred for 24 h at room temperature. The resulting mixture was diluted with EtOAc (1 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 6:1) to afford **5d** (56.2 mg) in 66% yield.

*Diethyl 1-(4-Nitrobenzoyl)-1,2-dihydroquinoline-2,3-dicarboxylate (**5d**).* 56.2 mg (66%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.8 Hz, 2H), 7.67 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.35 (dd, J = 7.6, 1.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.03 (br s, 1H), 6.65 (br s, 1H), 6.42 (br s, 1H), 4.43−4.30 (m, 2H), 4.18−4.10 (m, 1H), 4.07−3.99 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.1, 167.3, 164.3, 148.9, 140.4, 136.2, 133.6, 130.1, 129.9, 129.1, 127.2, 127.1, 125.9, 125.3, 125.0, 123.6, 62.1, 61.5, 14.3, 13.9; IR (KBr) υ 3106, 3067, 2981, 2926, 2853, 1741, 1708, 1661, 1602, 1523, 1485, 1457, 1370, 1334, 1288, 1223, 1200, 1154, 1015, 863, 760, 735, 716 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{22}H_{20}N_2O_7$ [M]$^+$ 424.1271, found 424.1272.

Cell Culture and Cell Viability Assay. The Murine RAW 264.7 macrophage cell line was obtained from American Type Culture Collection (ATCC) and cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 1% penicillin-streptomycin at 37 °C in a humidified atmosphere containing 5% CO_2. Cell viability was determined by 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) reduction assay. In brief, RAW264.7 cells were preincubated overnight in 96-well plates at a density of 1 × 10^4 cells per well. After 24 h, cells were treated with various concentrations of synthetic compounds for another 24 h. The mediums then were removed, and MTT was then added to each well at a final concentration of 0.5 mg/mL. The cells were incubated for 4 h at 37 °C, supernatants were removed, and dimethyl sulfoxide was added to each well. The optical density was measured at 540 nm using a microplate reader.

Western Blot Analysis. After pretreatment with synthetic compounds, RAW 264.7 cells were stimulated with LPS (1 μg/mL) for 24 h. After treatment, cells were harvested on ice, washed twice using ice-cold PBS, and suspended in lysis buffer supplemented with protease inhibitor. After incubating on ice for 25 min, cell extracts were subjected to centrifugation (12 000 rpm) at 4 °C for 5 min to get cell protein and quantified using a BCA protein assay. Protein samples were separated by SDS-polyacrylamide gel (PAGE), electro-transferred to polyvinylidene difluoride (PVDF) membranes, and then hybridized with the specific antibodies. Blots were normalized by use of β-actin to correct for differences in loading of the proteins. The intensity of protein bands were quantified with densitometry using ImageJ software.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01280.

Western blot analysis data and ^{1}H and ^{13}C NMR copies of all products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: bmlee@skku.edu (B.M.L.).
*E-mail: sbhan@krict.re.kr (S.B.H.).
*E-mail: insukim@skku.edu (I.S.K.).

ORCID

Soo Bong Han: 0000-0002-7831-1832
In Su Kim: 0000-0002-2665-9431

Author Contributions

‖S.K. and P.C. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (Nos. 2016R1A4A1011189 and 2017R1A2B2004786).

■ REFERENCES

(1) (a) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Ackermann, L. *Org. Lett.* **2013**, *15*, 3286. (b) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (c) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (d) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (e) Kim, H.; Chang, S. *ACS Catal.* **2016**, *6*, 2341. (f) Raghuvanshi, K.; Zell, D.; Rauch, K.; Ackermann, L. *ACS Catal.* **2016**, *6*, 3172.

(2) For recent reviews on C−H amidation reactions using various amidation sources, see: (a) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29. (b) Liang, Y.; Liang, Y.-F.; Jiao, N. *Org. Chem. Front.* **2015**, *2*, 403. (c) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040. (d) Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, *6*, 610. (e) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, DOI: 10.1021/acs.chemrev.6b00644.

(3) (a) Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. *J. Am. Chem. Soc.* **2013**, *135*, 12861. (b) Shin, K.; Ryu, J.; Chang, S. *Org. Lett.* **2014**, *16*, 2022. (c) Peng, J.; Xie, Z.; Chen, M.; Wang, J.; Zhu, Q. *Org. Lett.* **2014**, *16*, 4702. (d) Brachet, E.; Ghosh, T.; Ghosh, I.; König, B. *Chem. Sci.* **2015**, *6*, 987. (e) Hou, W.; Yang, Y.; Ai, W.; Wu, Y.; Wang, X.; Zhou, B.; Li, Y. *Eur. J. Org. Chem.* **2015**, *2015*, 395. (f) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8551. (g) Zhou, B.; Yang, Y.; Shi, J.; Feng, H.; Li, Y. *Chem. - Eur. J.* **2013**, *19*, 10511.

(4) (a) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023. (b) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (c) Lebel, H.; Leogane, O.; Huard, K.; Lectard, S. *Pure Appl. Chem.* **2006**, *78*, 363.

(5) (a) Friedländer, P. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2572. (b) Rogness, D. C.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 2289. (c) Zhang, Y.; Zhang, T.; Zhan, H.; Li, X. *Chin. J. Catal.* **2014**, *35*,

DOI: 10.1021/acs.joc.7b01280
J. Org. Chem. 2017, 82, 7555−7563

1840. (d) Yang, T.; Zhang, T.; Yang, S.; Chen, S.; Li, X. *Org. Biomol. Chem.* **2014**, *12*, 4290. (e) Okuma, K.; Koga, T.; Ozaki, S.; Suzuki, Y.; Horigami, K.; Nagahora, N.; Shioji, K.; Fukuda, M.; Deshimaru, M. *Chem. Commun.* **2014**, *50*, 15525. (f) Yu, J.; Zhang-Negrerie, D.; Du, Y. *Eur. J. Org. Chem.* **2016**, *2016*, 562. (g) Vecchione, M. K.; Sun, A. X.; Seidel, D. *Chem. Sci.* **2011**, *2*, 2178.

(6) Zhao, Y.; Li, D.; Zhao, L.; Zhang, J. *Synthesis* **2011**, *2011*, 873.

(7) (a) Zhang, T.; Wu, L.; Li, X. *Org. Lett.* **2013**, *15*, 6294. (b) Mei, S.-T.; Wang, N.-J.; Ouyang, Q.; Wei, Y. *Chem. Commun.* **2015**, *51*, 2980. (c) Li, Y.; Feng, Y.; Xu, L.; Wang, L.; Cui, X. *Org. Lett.* **2016**, *18*, 4924. (d) Zhang, Y.-F.; Wu, B.; Shi, Z.-J. *Chem. - Eur. J.* **2016**, *22*, 17808.

(8) For selected reviews on the use of aldimines as electrophilic coupling partners, see: (a) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.6b00661. (b) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468.

(9) (a) Shin, Y.; Han, S.; De, U.; Park, J.; Sharma, S.; Mishra, N. K.; Lee, E.-K.; Lee, Y.; Kim, H. S.; Kim, I. S. *J. Org. Chem.* **2014**, *79*, 9262. (b) Jeong, T.; Han, S.; Mishra, N. K.; Sharma, S.; Lee, S.-Y.; Oh, J. S.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 7243. (c) Han, S.; Mishra, N. K.; Sharma, S.; Park, J.; Choi, M.; Lee, S.-Y.; Oh, J. S.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 8026. (d) Mishra, N. K.; Oh, Y.; Jeon, M.; Han, S.; Sharma, S.; Han, S. H.; Um, S. H.; Kim, I. S. *Eur. J. Org. Chem.* **2016**, *2016*, 4976. (e) Jeon, M.; Mishra, N. K.; De, U.; Sharma, S.; Oh, Y.; Choi, M.; Jo, H.; Sachan, R.; Kim, H. S.; Kim, I. S. *J. Org. Chem.* **2016**, *81*, 9878. (f) Mishra, N. K.; Jeon, M.; Oh, Y.; Jo, H.; Park, J.; Han, S.; Sharma, S.; Han, S. H.; Jung, Y. H.; Kim, I. S. *Org. Chem. Front.* **2017**, *4*, 241.

(10) (a) Hedstrom, L.; Moorman, A. R.; Dobbs, J.; Abeles, R. H. *Biochemistry* **1984**, *23*, 1753. (b) Stein, R. L.; Strimpler, A. M.; Viscarello, B. R.; Wildonger, R. A.; Mauger, R. C.; Trainor, D. A. *Biochemistry* **1987**, *26*, 4126. (c) Krantz, A.; Spencer, R. W.; Tam, T. F.; Liak, T. J.; Copp, L. J.; Thomas, E. M.; Rafferty, S. P. *J. Med. Chem.* **1990**, *33*, 464. (d) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpalli, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. *J. Med. Chem.* **1998**, *41*, 1060.

(11) Zhang, L.; Gao, Z.; Peng, C.; Bin, Z.-Y.; Zhao, D.; Wu, J.; Xu, Q.; Li, J.-X. *Mol. Diversity* **2012**, *16*, 579.

(12) Yavari, I.; Ramazani, A.; Esmaili, A. A. *J. Chem. Res., Synop.* **1997**, 208.

(13) (a) Huang, G.-J.; Reddy, M. V. B.; Kuo, P.-C.; Huang, C.-H.; Shih, H.-C.; Lee, E.-J.; Yang, M.-L.; Leu, Y.-L.; Wu, T.-S. *Eur. J. Med. Chem.* **2012**, *48*, 371. (b) Xu, X.; Yin, P.; Wan, C.; Chong, X.; Liu, M.; Cheng, P.; Chen, J.; Liu, F.; Xu, J. *Inflammation* **2014**, *37*, 956.

(14) (a) Jin, J.; Teng, P.; Liu, H.-L.; Wu, J.; Liu, Y.-M.; Xu, Q.; Li, J.-X. *Eur. J. Med. Chem.* **2013**, *62*, 280. (b) Tang, M.-L.; Zhong, C.; Liu, Z.-Y.; Peng, P.; Liu, X.-H.; Sun, X. *Eur. J. Med. Chem.* **2016**, *113*, 63.

(15) (a) Oh, Y.-C.; Jeong, Y. H.; Cho, W.-K.; Ha, J.-H.; Gu, M. J.; Ma, J. Y. *Int. J. Mol. Sci.* **2015**, *16*, 1232. (b) Li, Q.; Dong, D.-D.; Huang, Q.-P.; Li, J.; Du, Y.-Y.; Li, B.; Li, H.-Q.; Huyan, T. *Pharm. Biol.* **2017**, *55*, 799.

(16) Mu, D.; Wang, X.; Chen, G.; He, G. *J. Org. Chem.* **2017**, *82*, 4497.

DOI: 10.1021/acs.joc.7b01280
J. Org. Chem. 2017, 82, 7555−7563