JOC The Journal of Organic Chemistry

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Organocatalytic Direct *N*-Acylation of Amides with Aldehydes under Oxidative Conditions

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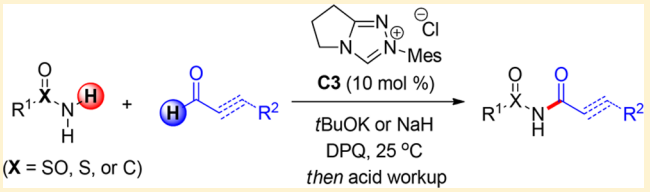
Supporting Information

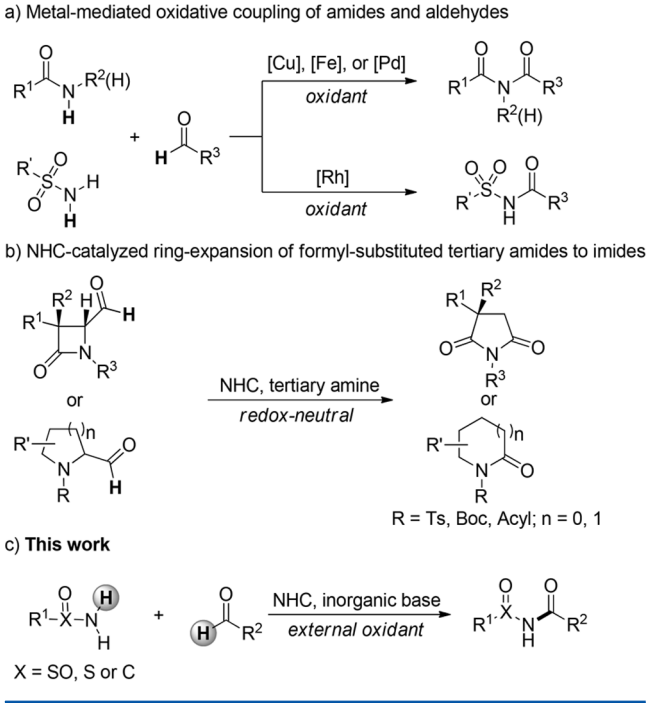
ABSTRACT: The direct oxidative *N*-acylation reaction of primary amides with aryl/α,β-unsaturated aldehydes was achieved in the presence of azolium salt **C3** and an inorganic base using 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone as the oxidant, thus providing an efficient approach for the synthesis of three types of imide compounds including *N*-sulfonylcarboxamides, *N*-sulfinylcarboxamides, and dicarboxyimides in good yield.



The increasing significance of imide motifs in natural products and medical and material molecules[1] has prompted chemists to develop novel methods for their efficient synthesis during the past decades.[2] As a complementary alternative to classical methodology focused on the condensation[3] of carboxylic acid or its derivatives with amides to imides, *N*-acylation of amides using aldehydes as acyl sources possesses several practical advantages and has attracted the growing interest of specialists in this class of transformation. The limited successful precedents based on such a cross-coupling strategy were accomplished mainly via metal-catalyzed oxidative coupling routes (Scheme 1a),[4,5] such as Rh(II)-catalyzed direct sulfamidation of aldehydes,[5a] copper- and iron-based C−H functionalization of aldehydes with primary or secondary carboxamides assisted by bromine-containing reagents,[5b,c] and palladium-mediated *N*-acylation of picolinamides with aldehydes.[5d] However, these elegant methods appear to be developed specifically for derivatization of sulfonamides or carboxamides, respectively, giving access to corresponding imide products.

On the other hand, significant progress has recently been made in the *N*-heterocyclic carbene (NHC) catalyzed oxidative conversions of aldehydes to carboxamides,[6,7] even though the addition of nucleophilic additives[7d−f] or a two-step reaction procedure involving an activated ester intermediate[6d,7g] was generally required for simple amines to circumvent problems like competing imine formation and the weak nucleophilicity of amines.[7h] Notably, NHC-catalyzed redox-neutral cyclization reactions of imine compounds with α,β-unsaturated aldehydes provide a robust protocol to forge a variety of *N*-substituted lactams containing tertiary imide scaffolds.[8] In this regard, ring expansion of some special formyl-substituted tertiary amides to imides has also been realized upon NHC-mediated redox ring-opening and ring-closure cascades (Scheme 1b).[9] Despite these advances, to our knowledge, the NHC-catalyzed intermolecular oxidative coupling of amides and aldehydes has remained elusive in the literature.[10] As a part of our studies on NHC-catalyzed transformation,[11] herein we present an organocatalytic approach for the direct oxidative *N*-acylation of primary amides with aryl/α,β-unsaturated aldehydes to produce a variety of imide compounds (Scheme 1c).

Scheme 1. Formation of Imides via *N*-Acylation of Amides with Aldehydes

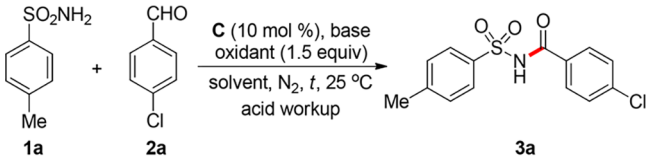


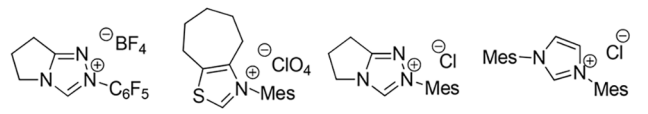
The coupling of 4-methylbenzenesulfonamide (**1a**) with 4-chlorobenzaldehyde (**2a**) was initially explored in the presence of a set of NHC precursors **C** and bases under oxidative conditions (Table 1). The treatment of **1a** and **2a** with

Received: February 25, 2017
Published: June 8, 2017

DOI: 10.1021/acs.joc.7b00457
J. Org. Chem. 2017, 82, 6940−6945

Table 1. Optimization of Reaction Conditions[a]





C1 C2 C3 C4

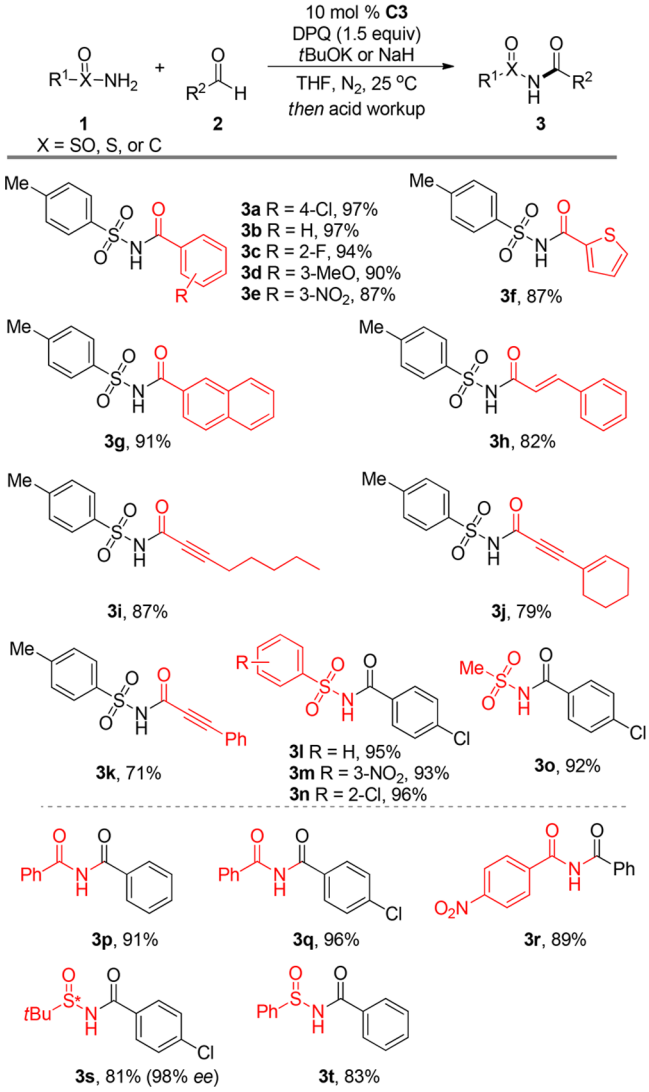
entry	C	oxidant	base (equiv)	solvent	time (h)	yield[b] (%)
1[c]	C1	$PhI(OAc)_2$	DBU (4.0)	DCM	16	45
2[c]	C1	$PhI(OAc)_2$	DBU (4.0)	DCM	16	42
3[c]	C2	$PhI(OAc)_2$	DBU (4.0)	DCM	16	10
4	C3	DPQ	NaH	THF	0.5	94
5	C3	BQ	NaH	THF	0.5	10
6	C3	DDQ	NaH	THF	0.5	trace
7		DPQ	NaH	THF	12	trace
8	C1	DPQ	NaH	THF	0.5	11
9	C2	DPQ	NaH	THF	0.5	6
10	C4	DPQ	NaH	THF	0.5	25
11	C3	DPQ	NaH	THF	2	75
12	C3	DPQ	*t*-BuOK	THF	1	97
13	C3	DPQ	Cs_2CO_3	THF	8	45
14	C3	DPQ	*t*-BuOK	DCM	12	50
15	C3	DPQ	*t*-BuOK	PhMe	12	94

[a]Unless otherwise noted, reactions were conducted on a 0.4 mmol scale of **1a** with **2a** (0.6 mmol), catalyst **C** (10 mol %), oxidant (1.5 equiv), and base (2.0 equiv) in solvent (4 mL) under N_2. [b]Isolated yield. [c]4 Å MS (100 mg) was added. DPQ = 3,3′,5,5′-tetra-*tert*-butyl[1,1′-bi(cyclohexylidene)]-2,2′,5,5′-tetraene-4,4′-dione, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. BQ = benzoquinone.

triazolium salt **C1** and DBU furnished *N*-tosylcarboxamide **3a** in 45% yield by using $PhI(OAc)_2$ as the oxidant (Table 1, entry 1).[12] Further attempts to improve the yield of **3a** by dropping amide **1a** slowly into the reaction mixtures or switching **C1** to thiazolium salt **C2** were unsuccessful, partially due to the competing oxidation of **1a** to PhI=NTs by $PhI(OAc)_2$ (Table 1, entries 2 and 3). When a less acidic triazolium salt **C3** and NaH were used to generate the NHC catalyst, a survey of common quinone compounds (Table 1, entries 4–6) revealed that DPQ was the oxidant of choice to give **3a** in 94% yield. In sharp contrast, neither benzoquinone nor 2,3-dichloro-5,6-dicyano-1,4-benzoquinone could conduct this reaction well. Meanwhile, the reaction almost did not occur at all in the absence of **C3**, and several other azolium salts proved less effective, albeit with DPQ as the oxidant (Table 1, entries 7–10). It was found that imide **3a** was labile in the reaction mixtures and would convert to other unidentified byproducts, resulting in a reduced yield (Table 1, entries 4 versus 11). While the use of *t*-BuOK as the base instead proceeded smoothly in THF to furnish the desired product **3a** in almost quantitative yield, the use of Cs_2CO_3 led to a moderate product yield (Table 1, entries 12 and 13). Finally, when the solvent THF was switched to CH_2Cl_2 or toluene, respectively, **3a** was isolated in 50 and 94% yield after 12 h (Table 1, entries 14 and 15).

Having the optimized reaction conditions established (Table 1, entry 12), the scope of the *N*-acylation of primary amides with aldehydes was investigated (Scheme 2). A scope of aryl aldehydes bearing several substituents (−F, −Cl, −OMe, and

Scheme 2. Substrate Scope of the *N*-Acylation of Primary Amides 1 with Aldehydes 2 to Imides 3[a]



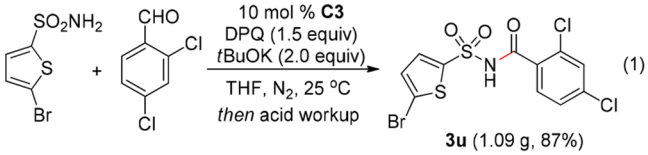
[a]Reaction conditions: **1** (0.4 mmol), **2** (0.6 mmol), **C3** (10 mol %), DPQ (0.6 mmol), and *t*-BuOK (0.8 mmol) in THF (4 mL) under N_2, 25 °C; quenched by 1 M HCl aqueous solution. Isolated yields are given. NaH (1.2 mmol) was used instead of *t*-BuOK to form **3p–r**. The absolute configuration of chiral **3s** was not determined, and the ee value was detected by chiral HPLC analysis.

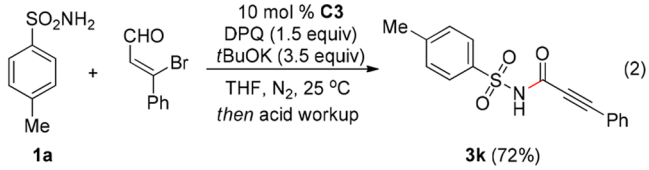
$-NO_2$) at different positions (2-, 3-, and 4-positions) of the benzene ring partook in the reaction with tosylamide (**1a**) to give the corresponding *N*-tosylcarboxamides **3a–e** in high yields. This transformation was easily carried out by both thiophene-2-carbaldehyde and 2-naphthaldehyde, leading to imides **3f** and **3g** in 92% and 91% yields, respectively. Moreover, *α,β*-unsaturated aldehydes including enals and ynals were also suitable partners in this direct *N*-acylation of tosylamide. Whereas ynals were previously employed as suitable substrates in the NHC-catalyzed redox reaction, notably, a wide scope of conjugated ynals containing an aliphatic or an aromatic substituent underwent this oxidative reaction to produce the desired imides **3i–k** in 71–87% yields, respectively. Unfortu-

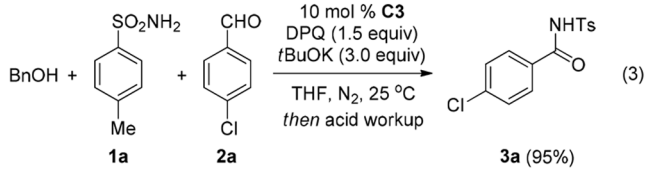
DOI: 10.1021/acs.joc.7b00457
J. Org. Chem. 2017, 82, 6940–6945

nately, simple alkyl-substituted aldehydes could not afford the corresponding imide products under the current conditions, probably due to the competing enolization of aldehyde substrates. To exploit the synthetic feasibility of this protocol, variation of the amide component was tested next. Electron-rich and -poor aryl sulfonamides reacted with aldehyde **2a** readily, giving rise to products **3l–n** in excellent yields. Methanesulfonamide was also a competent partner to furnish *N*-sulfonylcarboxamide **3o** (92%). In addition, benzamide and 4-nitrobenzamide could be employed with ease for the formation of dicarboxyimide **3p–r** by using NaH (3.0 equiv) as the base instead of *t*-BuOK, owing to the weaker acidity of carboxamides compared with sulfonylamides. Of particular interest, (*S*)-*tert*-butylsulfinamide (99% ee) accomplished this reaction efficiently and yielded (+)-*N*-(*tert*-butylsulfinyl)-4-chlorobenzamide (**3s**) with almost completely retained ee values. These preliminary studies further demonstrated the versatility of this NHC-catalyzed oxidative *N*-acylation reaction in secondary imide synthesis.

The oxidative *N*-acylation reaction could be easily manipulated on a multigram scale, for example, to form an antitumor agent of LY573636 (**3u**) in 87% yield (eq 1).[13] However, the





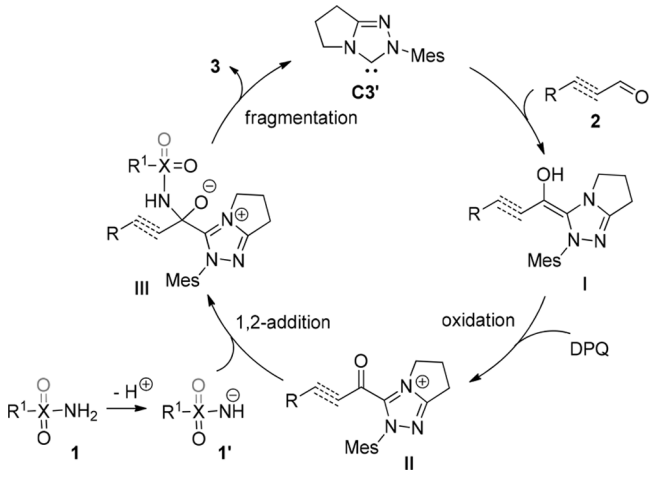


use of 3.5 equiv of *t*-BuOK delivered yne imide **3k** in 72% yield from the reaction of (*Z*)-3-bromo-3-phenylacrylaldehyde and amide **1a** accompanied by the elimination of HBr (eq 2). In addition, a competition experiment using **1a** (1.0 equiv) and **2a** (1.5 equiv) in the presence of phenylmethanol (1.0 equiv) still afforded imide **3a** in 95% yield (eq 3), indicating that *N*-acylation is preferred over ester formation under the current conditions.[14]

On the basis of these results and our previous reports,[6,11b] a postulated catalytic cycle is depicted in Scheme 3. The nucleophilic addition of in situ generated carbene **C3′** to aldehydes **2** initially affords Breslow intermediates **I**, which are oxidized to form acylazolium species **II** upon treatment with DPQ.[14] Attacked by deprotonated amide compounds **1′**, presumably via 1,2-adducts **III**, the azolium intermediates **II** undergo a subsequent fragmentation sequence to give imides **3** along with liberation of the carbene catalyst.

In summary, we have developed an organocatalytic approach for the direct *N*-acylation reaction of primary amides with a variety of aromatic or α,β-unsaturated aldehydes upon oxidative NHC catalysis strategy. This study provides a versatile protocol

Scheme 3. Proposed Catalytic Cycle



for the efficient construction of several types of imides including *N*-sulfonylcarboxamides, *N*-sulfinylcarboxamides, and dicarboxyimide at room temperature in good yield.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out under N_2 atmosphere with dry, freshly distilled solvents in anhydrous conditions. Tetrahydrofuran and toluene were distilled from sodium, while dichloromethane was distilled from CaH_2 immediately prior to use. All chemicals were used without further purification as commercially available unless otherwise noted. Thin-layer chromatography was performed on silica gel plates (60F-254) using UV light (254 and 365 nm). Flash chromatography was conducted on silica gel (300–400 mesh). Melting points were determined on an X-5 Data microscopic melting point apparatus. NMR (400 MHz for ^{1}H NMR, 100 for ^{13}C NMR) spectra were recorded in $CDCl_3$ or acetone-d_6 with TMS as the internal standard. High-resolution mass spectral analyses were measured using EI (electron impact) with a Q-TOF mass analyzer. The enantiomeric excess (ee) of the products was determined by HPLC using a Chiralcel OD-H column with 2-propanol/hexane = 5/95 as the eluent, and UV detection was monitored at 254 nm.

General Procedure for the Synthesis of Imides 3. To a suspension of **C3** (10.5 mg, 0.04 mmol) in THF (4 mL) was added *t*-BuOK (89.1 mg, 0.8 mmol) or NaH (29.0 mg, 1.2 mmol) for **3p–r** under N_2. After the sustpension was stirred at 25 °C for 5 min, aldehyde **2** (0.6 mmol), DPQ (245.2 mg, 0.6 mmol), and amide **1** (0.4 mmol) were added. The resulting mixture was stirred for 0.5–3 h. After the complete consumption of **1** as detected by TLC, the mixture was quenched with a cold aqueous solution of HCl (1 M, 10 mL), extracted with CH_2Cl_2 (10 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel with hexane/acetone (v/v = 5:1) as the eluent to give the product **3**.

*4-Chloro-N-tosylbenzamide (**3a**).*[15] Yield 119.8 mg (97%) from 68.4 mg (0.4 mmol) of amide **1a** and 84.1 mg (0.6 mmol) of aldehyde **2a** stirred for 0.5 h as a white solid: mp 172–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 9.17 (s, 1H), 8.04–8.02 (m, 2H), 7.78–7.76 (m, 2H), 7.40–7.35 (m, 4H), 2.44 ppm (s, 3H); HRMS (EI) *m*/*z* calcd for $C_{14}H_{12}ClNO_3S$ $[M]^+$ 309.0226, found 309.0219.

*N-Tosylbenzamide (**3b**).*[15] Yield 106.7 mg (97%) from 68.5 mg (0.4 mmol) of amide **1a** and 63.8 mg (0.6 mmol) of benzaldehyde stirred for 0.5 h as a white solid: mp 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 9.03 (s, 1H), 8.06–8.04 (m, 2H), 7.82–7.80 (m, 1H), 7.59–7.53 (m, 1H), 7.37 (d, 2H), 7.28–7.23 (m, 1H), 7.19–7.13 (m, 1H), 2.44 ppm (s, 3H); HRMS (EI) *m*/*z* calcd for $C_{14}H_{13}NO_3S$ $[M]^+$ 275.0616, found 275.0619.

DOI: 10.1021/acs.joc.7b00457
J. Org. Chem. 2017, 82, 6940–6945

*2-Fluoro-N-tosylbenzamide (**3c**).*[16] Yield 110.2 mg (94%) from 68.4 mg (0.4 mmol) of amide **1a** and 74.7 mg (0.6 mmol) of 2-fluorobenzaldehyde stirred for 0.5 h as a white solid: mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 9.03 (s, 1H), 8.06−8.04 (m, 1H), 7.59−7.53 (m, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.28−7.24 (m, 1H), 7.35 (t, J = 7.8 Hz, 2H), 7.19−7.13 (m, 1H), 2.44 ppm (s, 3H); HRMS (EI) m/z calcd for $C_{14}H_{12}FNO_3S$ $[M]^+$ 293.0522, found 293.0523.

*3-Methoxy-N-tosylbenzamide (**3d**).*[17] Yield 109.8 mg (90%) from 68.4 mg (0.4 mmol) of amide **1a** and 81.9 mg (0.6 mmol) of 3-methoxybenzaldehyde stirred for 2 h as a white solid: mp 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 9.52 (s, 1H), 8.05 (d, J = 8.8 Hz, 2H), 7.40−7.28 (m, 5H), 7.08−7.06 (m, 1H), 3.76 (s, 3H), 2.43 ppm (s, 3H); HRMS (EI) m/z calcd for $C_{15}H_{15}NO_4S$ $[M]^+$ 305.0722, found 305.0729.

*3-Nitro-N-tosylbenzamide (**3e**).*[18] Yield 111.3 mg (87%) from 67.4 mg (0.4 mmol) of amide **1a** and 90.6 mg (0.6 mmol) of 3-nitrobenzaldehyde stirred for 3 h as a white solid: mp 171−173 °C; ^{1}H NMR (400 MHz, acetone-d_6, 25 °C, TMS) δ 11.4 (s, 1H), 8.75−8.74 (m, 1H), 8.49−8.48 (m, 1H), 8.47−8.46 (m, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.85 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 2.46 ppm (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6, 25 °C, TMS) δ 164.0, 149.2, 145.9, 137.5, 135.1, 134.5, 131.3, 130.4, 129.4, 128.3, 123.9; HRMS (EI) m/z calcd for $C_{14}H_{12}N_2O_5S$ $[M]^+$ 320.0467, found 320.0461.

*N-Tosylthiophene-2-carboxamide (**3f**).*[15] Yield 97.8 mg (87%) from 67.4 mg (0.4 mmol) of amide **1a** and 67.9 mg (0.6 mmol) of thiophene-2-carbaldehyde stirred for 2.5 h as a white solid: mp 175−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 9.52 (s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.75−7.74 (m, 1H), 7.62−7.61 (m, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.10−7.08 (m, 1H), 2.46 ppm (s, 3H); HRMS (EI) m/z calcd for $C_{12}H_{11}NO_3S_2$ $[M]^+$ 281.0180, found 281.0178.

*N-Tosyl-2-naphthamide (**3g**).*[16] Yield 118.2 mg (91%) from 67.9 mg (0.4 mmol) of amide **1a** and 93.8 mg (0.6 mmol) of 2-naphthaldehyde stirred for 1 h as a white solid: mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 9.62 (s, 1H), 8.39 (s, 1H), 8.11 (d, J = 8.4 Hz, 2H), 7.88−7.82 (m, 4H), 7.59−7.52 (m, 2H), 7.35 (d, J = 8.4 Hz, 2H), 2.42 ppm (s, 3H); HRMS (EI) m/z calcd for $C_{18}H_{15}NO_3S$ $[M]^+$ 325.0773, found 325.0779.

*N-Tosylcinnamamide (**3h**).*[15] Yield 98.8 mg (82%) from 67.8 mg (0.4 mmol) of amide **1a** and 79.3 mg (0.6 mmol) of cinnamaldehyde stirred for 1 h with hexane/acetone (v/v = 8:1) as a white solid: mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 9.22 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 15.6 Hz, 1H), 7.40−7.38 (m, 2H), 7.31−7.19 (m, 4H), 6.42 (d, J = 15.6 Hz, 2H), 2.35 ppm (s, 3H); HRMS (EI) m/z calcd for $C_{16}H_{15}NO_3S$ $[M]^+$ 301.0773, found 301.0770.

*N-Tosyloct-2-ynamide (**3i**).* Yield 102.1 mg (87%) from 67.8 mg (0.4 mmol) of amide **1a** and 74.5 mg (0.6 mmol) of oct-2-ynal stirred for 2 h with hexane/ethyl acetate (v/v = 6:1) as a colorless oil: ^{1}H NMR (400 MHz, acetone-d_6, 25 °C, TMS) δ 11.16 (s, 1H), 7.92−7.90 (m, 2H), 7.46−7.44 (m, 2H), 2.45 (s, 3H), 2.35 (t, J = 7.2 Hz, 2H), 1.54−1.50 (m, 2H), 1.37−1.28 (m, 4H), 0.87 ppm (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6, 25 °C, TMS) δ 150.9, 145.9, 137.5, 130.4, 129.1, 92.9, 74.9, 31.7, 27.9, 22.7, 21.6, 18.9, 14.2 ppm; HRMS (EI) m/z calcd for $C_{15}H_{19}NO_3S$ $[M]^+$ 293.1086, found 293.1092.

*3-(Cyclohex-1-en-1-yl)-N-tosylpropiolamide (**3j**).* Yield 95.8 mg (79%) from 67.8 mg (0.4 mmol) of amide **1a** and 80.6 mg (0.6 mmol) of 3-(cyclohex-1-en-1-yl)propiolaldehyde stirred for 2 h with hexane/ethyl acetate (v/v = 6:1) as a colorless oil: ^{1}H NMR (400 MHz, acetone-d_6, 25 °C, TMS) δ 7.93−7.90 (m, 2H), 7.47−7.44 (m, 2H), 2.45 (s, 3H), 2.17−2.13 (m, 2H), 2.12−2.08 (m, 2H), 1.66−1.56 ppm (m, 4H); ^{13}C NMR (100 MHz, acetone-d_6, 25 °C, TMS) δ 151.2, 145.9, 143.7, 137.5, 130.4, 129.1, 119.1, 91.1, 80.4, 28.5, 26.6, 22.5, 21.7, 21.6 ppm; HRMS (EI) m/z calcd for $C_{16}H_{17}NO_3S$ $[M]^+$ 303.0929, found 303.0935.

*3-Phenyl-N-tosylpropiolamide (**3k**).* Yield 84.5 mg (71%) from 67.8 mg (0.4 mmol) of amide **1a** and 78.6 mg (0.6 mmol) of 3-phenylpropiolaldehyde stirred for 2 h with hexane/ethyl acetate (v/v = 7:1) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.99 (d, J = 8.4 Hz, 2H), 7.53−7.51 (m, 2H), 7.47−7.45 (m, 1H), 7.39−7.34 (m, 1H), 2.44 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 149.7, 145.6, 135.2, 133.0, 131.2, 129.7, 128.7, 128.6, 118.8, 81.0, 21.8 ppm; HRMS (EI) m/z calcd for $C_{16}H_{13}NO_3S$ $[M]^+$ 299.0616, found 299.0622.

From (*Z*)-3-bromo-3-phenylacrylaldehyde (126.7 mg, 0.6 mmol), *t*-BuOK (157.1 mg, 1.4 mmol), and 68.2 mg (0.4 mmol) of amide **1a** was isolated 85.7 mg (72%) of imide **3k**.

*4-Chloro-N-(phenylsulfonyl)benzamide (**3l**).*[5a] Yield 112.1 mg (95%) from 62.9 mg (0.4 mmol) of benzenesulfonamide and 84.1 mg (0.6 mmol) of aldehyde **2a** stirred for 1.5 h with hexane/acetone (v/v = 4:1) as a white solid: mp 162−164 °C; ^{1}H NMR (400 MHz, acetone-d_6, 25 °C, TMS) δ 11.10 (s, 1H), 8.13−8.11 (m, 2H), 7.96−7.94 (m, 2H), 7.76−7.72 (m, 1H), 7.68−7.63 (m, 2H), 7.56−7.53 ppm (m, 2H); HRMS (EI) m/z calcd for $C_{13}H_{10}ClNO_3S$ $[M]^+$ 295.0070, found 295.0077.

*4-Chloro-N-((3-nitrophenyl)sulfonyl)benzamide (**3m**).*[19] Yield 103.4 mg (93%) from 80.1 mg (0.4 mmol) of 3-nitrobenzenesulfonamide and 84.9 mg (0.6 mmol) of aldehyde **2a** stirred for 2.5 h with hexane/acetone (v/v = 2:1) as a yellow solid: mp 215−216 °C; ^{1}H NMR (400 MHz, acetone-d_6, 25 °C, TMS) δ 11.33 (s, 1H), 8.89 (t, J = 1.6 Hz, 1H), 8.61−8.59 (m, 1H), 8.55−8.52 (m, 1H), 8.03−7.96 (m, 3H), 7.56−7.54 ppm (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6, 25 °C, TMS) δ 165.1, 149.1, 142.0, 140.1, 135.2, 131.8, 131.1, 131.0, 129.8, 129.2, 124.4 ppm; HRMS (EI) m/z calcd for $C_{13}H_9ClN_2O_5S$ $[M]^+$ 339.9921, found 339.9917.

*4-Chloro-N-((2-chlorophenyl)sulfonyl)benzamide (**3n**).*[5a] Yield 126.7 mg (96%) from 84.2 mg (0.4 mmol) of 2-chlorobenzenesulfonamide and 84.6 mg (0.6 mmol) of aldehyde **2a** stirred for 1 h with hexane/acetone (v/v = 4:1) as a white solid: mp 189−191 °C; ^{1}H NMR (400 MHz, acetone-d_6, 25 °C, TMS) δ 11.41 (s, 1H), 8.34−8.31 (m, 1H), 8.01−7.99 (m, 2H), 7.75−7.71 (m, 1H), 7.67−7.63 (m, 2H), 7.57−7.55 ppm (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6, 25 °C, TMS) δ 164.9, 140.0, 137.8, 136.0, 133.9, 132.6, 132.3, 131.3, 131.0, 129.9, 128.4 ppm; HRMS (EI) m/z calcd for $C_{13}H_9Cl_2NO_3S$ $[M]^+$ 328.9680, found 328.9686.

*4-Chloro-N-(methylsulfonyl)benzamide (**3o**).*[20] Yield 85.5 mg (92%) from 38.1 mg (0.4 mmol) of methanesulfonamide and 84.5 mg (0.6 mmol) of aldehyde **2a** stirred for 1 h with hexane/acetone (v/v = 3:1) as a white solid: mp 135−136 °C; ^{1}H NMR (400 MHz, acetone-d_6, 25 °C, TMS) δ 10.75 (s, 1H), 8.04−8.03 (m, 2H), 7.60−7.58 (m, 2H), 3.41 ppm (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6, 25 °C, TMS) δ 166.0, 139.8, 131.7, 131.0, 129.8, 41.7 ppm; HRMS (EI) m/z calcd for $C_8H_8ClNO_3S$ $[M]^+$ 232.9913, found 232.9920.

*N-Benzoylbenzamide (**3p**).*[5b] Yield 81.9 mg (91%) from 48.6 mg (0.4 mmol) of benzamide and 63.6 mg (0.6 mmol) of benzaldehyde stirred for 2 h with hexane/acetone (v/v = 6:1) as a white solid: mp 149−150 °C; ^{1}H NMR (400 MHz, acetone-d_6, 25 °C, TMS) δ = 10.4 (s, 1H), 8.00−7.98 (m, 4H), 7.64−7.61 (m, 2H), 7.54−7.50 ppm (m, 4H); ^{13}C NMR (100 MHz, acetone-d_6, 25 °C, TMS) δ 167.8, 135.2, 133.4, 129.3, 129.3 ppm; HRMS (EI) m/z calcd for $C_{14}H_{11}NO_2$ $[M]^+$ 225.0790, found 225.0786.

*N-Benzoyl-4-chlorobenzamide (**3q**).*[5b] Yield 99.9 mg (96%) from 48.5 mg (0.4 mmol) of benzamide and 84.5 mg (0.6 mmol) of aldehyde **2a** stirred for 2 h with hexane/acetone (v/v = 6:1) as a white solid: mp 132−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.98 (s, 1H), 7.90−7.88 (m, 2H), 7.83−7.81 (m, 2H), 7.66−7.62 (m, 1H), 7.55−7.48 ppm (m, 4H); HRMS (EI) m/z calcd for $C_{14}H_{10}ClNO_2$ $[M]^+$ 259.0400, found 259.0405.

*N-Benzoyl-4-nitrobenzamide (**3r**).*[5b] Yield 96.1 mg (89%) from 66.5 mg (0.4 mmol) of 4-nitrobenzamide and 64.1 mg (0.6 mmol) of benzaldehyde stirred for 2 h with hexane/acetone (v/v = 4:1) as a white solid: mp 188−189 °C; ^{1}H NMR (400 MHz, acetone-d_6, 25 °C, TMS) δ 10.7 (s, 1H), 8.37−8.34 (m, 2H), 8.19−8.17 (m, 2H), 8.03−8.01 (m, 2H), 7.68−7.64 (m, 1H), 7.56−7.52 ppm (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6, 25 °C, TMS) δ 167.6, 167.4, 150.9, 141.1, 134.5, 133.8, 130.6, 129.4, 129.4, 124.3 ppm; HRMS (EI) m/z calcd for $C_{14}H_{10}N_2O_4$ $[M]^+$ 270.0640, found 270.0641.

*(+)-N-(tert-Butylsulfinyl)-4-chlorobenzamide (**3s**).* Yield 84.3 mg (81%, 98% ee) from 48.5 mg (0.4 mmol, 99% *ee*) of (*S*)-2-methylpropane-2-sulfinamide and 84.7 mg (0.6 mmol) of aldehyde **2a**

DOI: 10.1021/acs.joc.7b00457
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stirred for 1.5 h as a white solid: mp 149−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.48 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 1.19 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 161.5, 138.7, 132.5, 130.5, 129.3, 57.9, 22.6 ppm; HRMS (EI) m/z calcd for $C_{11}H_{14}ClNO_2S$ $[M]^+$ 259.0434, found 259.0439. Determined by HPLC with Chiralcel OD-H column at 254 nm (hexane/iPrOH = 95:5, flow rate = 0.8 mL/min), t_{minor} = 11.6 min, t_{major} = 7.8 min. $[\alpha]^{20}_D$ = +82.6 (c 0.80, $CHCl_3$).

*N-(Phenylsulfinyl)benzamide (**3t**).*[21] Yield 79.4 mg (81%) from 56.4 mg (0.4 mmol) of methanesulfonamide and 63.6 mg (0.6 mmol) of benzaldehyde stirred for 3 h with hexane/acetone (v/v = 3:1) as a white solid: mp 145−146 °C; ^{1}H NMR (400 MHz, acetone-d_6, 25 °C, TMS) δ 10.48 (s, 1H), 7.96−7.95 (m, 2H), 7.84−7.82 (m, 2H), 7.64−7.59 (m, 4H), 7.50−7.47 ppm (m, 2H); HRMS (EI) m/z calcd for $C_{13}H_{11}NO_2S$ $[M]^+$ 245.0510, found 245.0513.

*Synthesis of LY573636 (**3u**).*[13b] To a suspension of **C3** (79.5 mg, 0.3 mmol) in THF (25 mL) was added *t*-BuOK (673.3 mg, 6.0 mmol) under N_2. After being stirred for 10 min, 2,4-dichlorobenzaldehyde (787.4 mg, 4.5 mmol), DPQ (1.840 g, 4.5 mmol), and 5-bromothiophene-2-sulfonamide (718.8 mg, 3.0 mmol) were added. The resulting mixture was stirred for 3 h, quenched with a cold aqueous solution of HCl (1 M, 25 mL) at 0−5 °C, extracted with CH_2Cl_2 (30 mL × 3), and then dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The product was purified by column chromatography on silica gel with hexane/acetone (v/v = 4:1) as the eluent to afford **3s** (1.081 g, 87%) as as a white solid: mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 9.19 (s, 1H), 7.73−7.71 (m, 2H), 7.45 (d, J = 1.6 Hz, 1H), 7.37−7.34 (m, 1H), 7.13 ppm (d, J = 8.0 Hz, 1H); HRMS (EI) m/z calcd for $C_{11}H_6BrCl_2NO_3S_2$ $[M]^+$ 412.8350, found 412.8357.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00457.

Characterization data of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21372196 and 21572199) for generous financial support.

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