JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

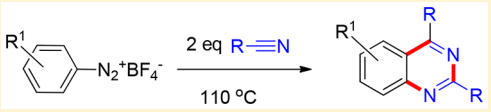
Preparation of Quinazolines via a 2+2+2 Annulation from Aryldiazonium Salts and Nitriles

Mani Ramanathan and Shiuh-Tzung Liu*

Department of Chemistry, National Taiwan University, Taipei 106, Taiwan

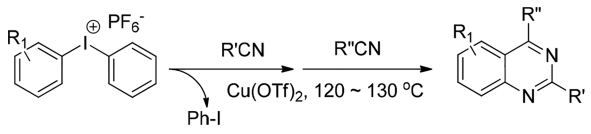
Supporting Information

ABSTRACT: A (2+2+2) modular synthesis of multisubstituted quinazolines has been realized by the direct reaction of aryldiazonium salts with two equivalent of nitriles. Reaction of aryldiazonium salt with a nitrile provides the initial formation of a reactive nitrilium ion, which is attacked by another molecule of nitrile followed by electrophilic cyclization to deliver the desired product. Notable flexibility in the substitution patterns, readily available substrates, short reaction time, transition metal-free, and gram-scale synthesis are the advantages of this method.



Substituted quinazolines are one of the privileged classes of fused *N*-heterocyclic cores present in many natural products[1] and biologically active molecules[2] including anti-inflammatory,[3] anticonvulsant,[4] anti-HIV,[5] antimicrobial activities,[6] lung cancer drugs, and therapeutic agents for pneumonia and post-traumatic stress or anxiety disorders.[7−10] In addition, quinazoline derivatives are used as fragments in the functionalized materials.[11] There are numerous reported methodologies for synthesis of quinazolines starting from *ortho*-functionalized anilines or derivatives, which generally involve multiple-step reactions.[12,13] Despite these advancements, there is still a need to develop a convenient and efficient preparation leading to the quinazoline core from simple starting materials. Recently, Chen et al. described a synthesis of quinazolines via Cu(II) catalyzed (2+2+2) cascade annulation of diaryliodinium salts and two molecules of nitriles at elevated temperature (Scheme 1).[14]

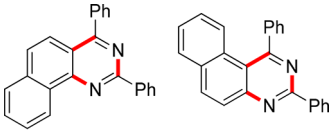
Scheme 1. Chen's Approach To Prepare Quinazolines



This method clearly demonstrated the use of two molecules of nitrile, a simple starting material, to construct the desired heterocyclic core, but it still requires the use of metal catalysts and synthesis of diaryliodinium salts. Inspired by this work, combined with our recent studies of aryldiazonium salt in synthetic applications,[15] herein we disclose an intermolecular cascade annulation route for 2,4-disubtituted quinazolines. We propose that *N*-arylnitrilium ion, generated *in situ* from the reaction of aryldiazonium salt and nitrile,[16] could react further with another nitrile component via tandem addition/electrophilic cyclization to yield 2,4-disubstituted quinazolines in an atom-economic fashion (Scheme 2).

To validate our hypothesis, initially we considered anhydrous PhCN for this cascade annulation (Table 1). Treatment of phenyldiazonium tetrafluoroborate (**1a**) in anhydrous PhCN (**2**) at ambient temperature overnight gave no desired product. By running the reaction at 80 °C, the desired compound **3a** was isolated in 63% yield. After significant screening efforts, we found that the reaction of **1a** with anhydrous PhCN at 110 °C for 3 h gave the desired product **3a** in 72% isolated yield as the sole product (Table 1, entry 3). Carrying out the reaction in various solvents provided inferior results (Table 1, entries 5−8).

With the optimized conditions, we investigated the scope and limitations for various arenediazonium salts. The results obtained are summarized in Table 2. Various aryldiazonium tetrafluoroborates with electron-donating and/or withdrawing groups at different positions in the ring were reacted smoothly with anhydrous benzonitrile to produce the corresponding quinazolines in moderate to good yields. Reaction of benzonitrile with *para*- or *ortho*-substituted phenyldiazonium salts gave the corresponding 2,4,6-trisubstituted quinazolines in good yields (**3a**−**3f** and **3h**) except the nitro substituent (**3g**). Multiple substituted phenyldiazonium salts also provided the desired products in good yields (Table 2, entries **3i**−**3j**). Annulation of *meta*-bromophenyldiazonium salt with PhCN gave a mixture of regio-isomers (**3k** and **3k′**). However, *p*-(aminocarbonyl)phenyldiazonium salt and *o*-(acetyl)-phenyldiazonium were led to complicated mixtures with no desired product formation. To our delight, 1-naphthyl and 2-naphthyldiazonium salts furnished benzo[*h*]quinazoline (**3l**) (69%) and benzo[*f*] quinazoline (**3m**) (57%), respectively, in synthetically useful yields.



3l (69%) **3m** (57%)

Received: May 30, 2017
Published: July 12, 2017

ACS Publications © 2017 American Chemical Society

DOI: 10.1021/acs.joc.7b01325
J. Org. Chem. 2017, 82, 8290−8295

Scheme 2. Our Approach in Preparation of Quinazolines without Metal-Catalyzed Reactions

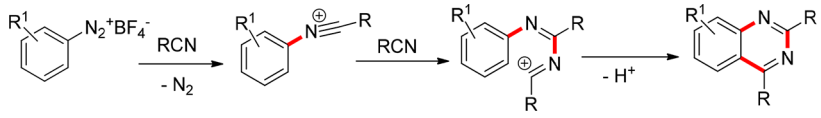
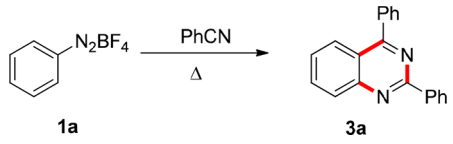


Table 1. Reaction Optimzation[a]

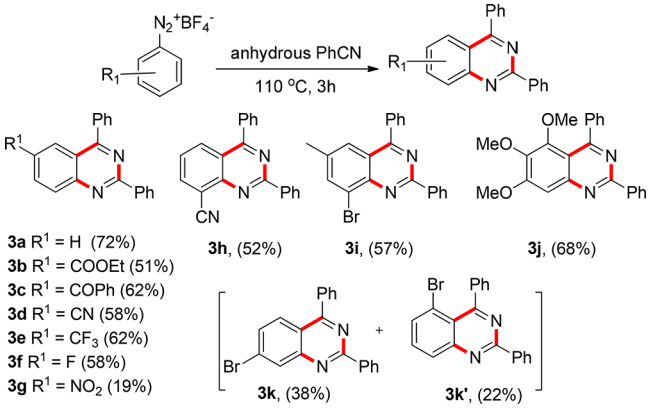


1a 3a

entry	solvent	temp (°C)	time (h)	yield
1	neat (1 mL)	rt	12	NR
2	neat (1 mL)	80	8	63%
3	neat (1 mL)	110	3	72%
4	neat (1 mL)	110	12	66%
5[d]	toluene	110	3	trace
6[d]	THF	reflux	3	[c]
7[d]	DMSO	110	3	[c]
8[d]	$ClCH_2CH_2Cl$	reflux	3	6%[b]

[a]Reaction conditions: A mixture of **1a** (0.52 mmol) and benzonitrile (**2**) in a reaction tube was heated. [b]Yields given are determined by ^1H NMR. [c]Trace *N*-phenylbenzamide was obtained. [d]PhCN (2.6 mmol) in solvent (1 mL).

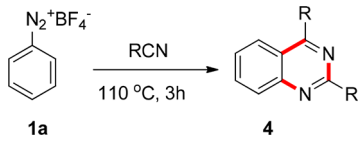
Table 2. Quinazolines from Reaction of Various Aryldiazonium Salts with PhCN[a]



[a]ArN_2BF_4 (0.52 mmol) in anhydrous benzonitrile (1 mL) was heated at 110 °C for 3 h; isolated yields given in parentheses.

We then contemplated the scope of the reaction with varieties of readily available aliphatic and aromatic nitriles (Table 3). All aromatic nitriles reacted with phenyldiazonium salt **1a** to render the desired quinazolines in good yields (Table 3, entries 1−8). This facile introduction of various substituents illustrates the great flexibility and generality of this method. It is noticed that 1- or 2-naphthylenecarbonitrile and 2-thiophenecarbonitrile are also suitable substrates for this annulation. Alkyl nitrile compounds bearing a 2°, 3°, or cyclic aliphatic group smoothly participated and furnished the 2,4-dialiphatic quinazolines in moderate yield (Table 3, entries 9−11). Unfortunately, reaction of acetonitrile with **1a** led to no desired product presumably due to the lower boiling point of acetonitrile, whereas on using bromoacetonitrile as a substrate, only 11% of the desired product **4m** was obtained (Table 3, entry 13). However, with the use of activated aryldiazonium salt, such as **5** and **6**, to facilitate the electrophilic aromatic cyclization, the annulation with acetonitrile proceeded to give 2,4-dimethyl substituted quinazolines in poor yields (Scheme 3). Similarly, reaction of 1-naphthyldiazonium tetrafluoroborate with acetonitrile gave 2,4-dimethylbenzo[*h*]quinazoline (**9**) in 38% yield.[16c]

Table 3. Substrate Scope with Various Nitriles[a]

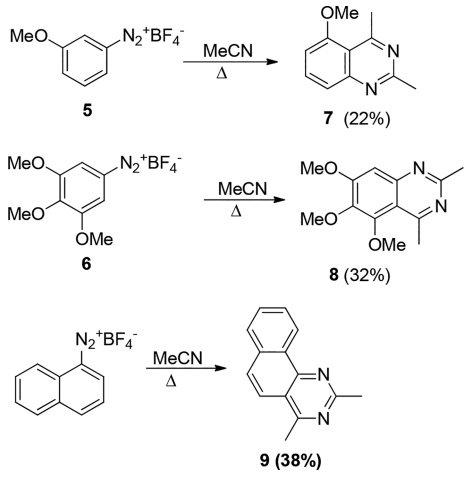


1a 4

entry	Product	Isolated yield
1	**4a**, R = *p*-MeC_6H_4-	71%
2	**4b**, R = *p*-FC_6H_4-	69%
3	**4c**, R = *m*-$MeOC_6H_4$-	57%
4	**4d**, R = *m*-BrC_6H_4-	73%
5	**4e**, R = *o*-BrC_6H_4-	62%
6	**4f**, R = 1-naphthyl	52%
7	**4g**, R = 2-naphthyl	54%
8	**4h,** R = 	69%
9	**4i**, R = isopropyl	41%
10	**4j**, R = cyclopropyl	44%
11	**4k**, R = *t*-butyl	38%
12	**4l**, R = CH_3-	0
13	**4m**, R = $BrCH_2$-	11%

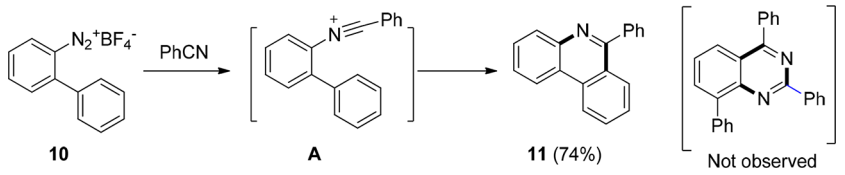
[a]**1a** (0.52 mmol) in anhydrous nitrile (1 mL) was heated at 110 °C for 3 h.

Scheme 3. Reaction of Acetonitrile with Aryldiazonium Salts



DOI: 10.1021/acs.joc.7b01325
J. Org. Chem. 2017, 82, 8290−8295

Scheme 4



Notably, when aryldiazonium salt **8**, with a phenyl group adjacent to the diazonium center, employed in this reaction, the intermediate **A** rapidly underwent an intramolecular cyclization to deliver 6-phenylphenanthridine (**11**) exclusively (Scheme 4). Evidently, the rate of the intramolecular sequence is more rapid than that of the electrophilic addition of *N*-arylnitrilium ion toward the second nitrile molecule. In addition, these results confirmed the formation of *N*-arylnitrilium ion as the intermediate.

The practical application of presented annulation strategy was further demonstrated by a gram scale synthesis. Phenyldiazonium tetrafluoroborate (**1a**) on a 1 g scale was treated with anhydrous PhCN (10 mL) under the optimized conditions yielding the 2,4-diphenylquinazoline **3a** in 74% isolated yield. Notably, PhCN was recovered in 84% by simple hexane wash of the crude reaction mixture in analytically pure form, thus making the overall procedure economic.

In summary, a transition metal free and one-pot approach is developed to construct multiple substituted quinazolines from the reaction of aryldiazonium salts and nitriles. This convenient approach tolerates a variety of functional groups and represents an atom-efficient, facile, and easy-handle procedure, illustrating the possibilities for industrial application.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR were recorded in a 400 MH_Z spectrometer in $CDCl_3$ and CD_3CN referenced to TMS. Acetonitrile and other liquid nitriles were dried over activated 3 and 4 Å molecular sieves, respectively, whereas solid nitriles were dried under vacuum. All the anilines were commercially purchased and used for diazotization without further purification. Other chemicals were used as purchased. Flash chromatography was performed using silica gel 230−400 mesh. In cases of known compounds, their ^{1}H and ^{13}C NMR values were compared with the literature values. Melting points were determined on a Fargo MP-1D instrument. Unless otherwise noted, all the reactions were performed without any special precautions.

General Procedure for Preparing Aryldiazonium Tetrafluoroborate. All the substituted aryldiazonium salts were synthesized by following the reported methods. Spectral data of the compounds are in agreement with those reported in the literature. A typical procedure for preparing benzenediazonium tetrafluoroborate is shown below.[15a] The corresponding aniline (10 mmol) was dissolved in a mixture of water (4 mL) and 50% aqueous hydrofluoroboric acid (19.3 mmol, 1.92 equiv). The mixture was cooled to 0 °C and a solution of $NaNO_2$ (10 mmol in 1.5 mL of water) was added slowly. The resulting reaction mixture was stirred at 0 °C for 30 min and the precipitate was collected by filtration. The solid product was dissolved in minimum acetone and reprecipitated using diethyl ether to yield aryldiazonium tetrafluoroborate which was dried under vacuum without further purification.

General Procedure for the Preparation of 2,4-Disubstituted Quinazolines. In a dry 10 mL glass sealed tube, aryldiazonium tetrafluoroborate (0.52 mmol) was mixed with anhydrous nitrile (1 mL). The tube was sealed with a Teflon screw cap and heated in an oil bath (110 °C) for 3 h. After cooling to room temperature, reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ solution (5 mL). Aqueous layer was extracted with CH_2Cl_2 (10 mL). Combined organic layers were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the residue was chromatographed (SiO_2, EA-hexane, 5%) to yield 2,4-disubstituted quinazoline.

*2,4-Diphenylquinazoline (**3a**).*[13c] 105 mg, 72%, white solid: mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 8.0 Hz, 2H), 8.15 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.89−7.85 (m, 3H), 7.59−7.57 (m, 3H), 7.55−7.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 160.2, 151.9, 138.1, 137.6, 133.5, 130.5, 130.1, 129.9, 129.1, 128.6, 128.5 (3C), 126.9, 121.6; HRMS (ESI-TOF) calcd. for $C_{20}H_{15}N_2$ $(M+H)^+$ m/z = 283.1235, found 283.1231.

*Ethyl 2,4-Diphenylquinazoline-6-carboxylate (**3b**).* 68 mg, 51%, white solid: mp 186−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 1.2 Hz, 1H), 8.71−8.69 (m, 2H), 8.43 (dd, J = 8.8, 1.6 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 7.92−7.89 (m, 2H), 7.62−7.60 (m, 3H), 7.54−7.50 (m, 3H), 4.40 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 165.7, 161.7, 154.0, 137.7, 137.1, 132.9, 131.0, 130.4, 130.3, 130.1, 129.4 (2C), 128.9, 128.7, 128.6, 120.9, 61.5, 14.3; HRMS (ESI-TOF) calcd. for $C_{23}H_{19}N_2O_2$ $(M+H)^+$ m/z = 355.1447, found 355.1472.

*(2,4-Diphenylquinazolin-6-yl) Phenyl Ketone (**3c**).* 81 mg, 62%, off-white solid: mp 160−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, J = 7.6, 4.0 Hz, 2H), 8.56 (d, J = 1.2 Hz, 1H), 8.31−8.24 (m, 2H), 7.89−7.87 (m, 2H), 7.82 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 7.2 Hz. 1H), 7.56−7.54 (m, 4H), 7.52−7.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 169.8, 161.7, 153.6, 137.5, 137.1, 137.0, 135.7, 133.6, 132.8, 131.2, 130.6, 130.5, 130.3, 130.0, 129.3, 129.0, 128.7, 128.6, 128.5, 120.8; HRMS (ESI-TOF) calcd. for $C_{27}H_{19}N_2O$ $(M+H)^+$ m/z = 387.1497, found 387.1516.

*2,4-Diphenylquinazoline-6-carbonitrile (**3d**)*[17a]. 82 mg, 58%, off-white solid: mp 226−227 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, J = 6.0, 2.4 Hz, 2H), 8.47 (d, J = 1.6 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.98 (dd, J = 8.8, 1.6 Hz, 1H), 7.85 (dd, J = 5.6, 2.0 Hz, 2H), 7.63 (dd, J = 5.2, 2.0 Hz, 3H), 7.53−7.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.4, 153.3, 137.2, 136.4, 134.0, 133.6, 131.5, 130.8, 130.7, 130.1, 129.1, 128.9, 128.7, 121.1, 118.2, 110.3; HRMS (ESI-TOF) calcd. for $C_{21}H_{14}N_3$ $(M+H)^+$ m/z = 308.1188, found 308.1172.

*2,4-Diphenyl-6-(trifluoromethyl)quinazoline (**3e**).*[13c] 112 mg, 62%, white solid: mp 157−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (t, J = 4.0 Hz, 2H), 8.41 (s, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.87 (dd, J = 2.8, 1.2 Hz, 2H), 7.63 (d, J = 2.8 Hz, 3H), 7.53−7.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 161.8, 153.2, 137.5, 136.8, 131.1, 130.4 (d, J = 4.0 Hz), 130.1, 129.1 (d, J = 3.0 Hz), 128.9, 128.8, 128.7, 128.6, 128.4, 125.1 (d, J = 5.0 Hz), 122.3, 120.7; HRMS (ESI-TOF) calcd. for $C_{21}H_{14}F_3N_2$ $(M+H)^+$ m/z = 351.1109, found 351.1123.

*6-Fluoro-2,4-diphenylquinazoline (**3f**).*[13c] 83 mg, 58%, white solid: mp 168−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67−8.64 (m, 2H), 8.14 (dd, J = 9.2, 5.6 Hz, 1H), 7.87−7.83 (m, 2H), 7.23 (dd, J = 9.6, 3.2 Hz, 1H), 7.67−7.63 (m, 1H), 7.62−7.57 (m, 3H), 7.54−7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8 (d, J = 5.0 Hz), 161.6, 159.9, 159.1, 149.2, 137.9, 137.3, 131.8 (d, J = 8.0 Hz), 130.6, 130.1, 129.9, 128.7, 128.6, 123.8 (d, J = 26 Hz), 122.1 (d, J = 9.0 Hz), 110.3 (d, J = 24 Hz); HRMS (ESI-TOF) calcd. for $C_{20}H_{14}FN_2$ $(M+H)^+$ m/z = 301.1141, found 301.1136.

*6-Nitro-2,4-diphenylquinazoline (**3g**).*[17] 28 mg, 19%, off-white solid: mp 230−231 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, J = 2.4 Hz, 1H), 8.70 (dd, J = 6.0, 2.0 Hz, 2H), 8.61 (dd, J = 9.2, 2.4 Hz, 1H), 8.23 (d, J = 9.2 Hz. 1H), 7.89 (dd, J = 5.6, 2.0 Hz, 2H), 7.66−7.63 (m, 3H), 7.53 (dd, J = 5.6, 2.4 Hz, 3H); ^{13}C NMR (100 MHz,

DOI: 10.1021/acs.joc.7b01325
J. Org. Chem. 2017, 82, 8290−8295

$CDCl_3$) δ 170.4, 162.9, 154.5, 145.4, 137.1, 136.4, 131.7, 131.0, 130.9, 130.2, 129.2, 129.0, 128.7, 126.9, 124.2, 120.5; HRMS (ESI-TOF) calcd. for $C_{20}H_{14}N_3O_2$ $(M+H)^+$ m/z = 328.1086, found 328.1087.

2,4-Diphenylquinazoline-8-carbonitrile (**3h**). 73 mg, 52%, off-white solid: mp 168−169 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, J = 6.4, 2.8 Hz, 2H), 8.32 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 6.8 Hz, 1H), 7.85−7.83 (m, 2H), 7.61−7.59 (m, 3H), 7.56−7.54 (m, 1H), 7.52−7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 161.6, 151.7, 139.1, 136.9, 136.6, 131.9, 131.5, 130.5, 130.1, 129.2, 128.7, 128.6, 125.9, 121.5, 116.4, 113.0; HRMS (ESI-TOF) calcd. for $C_{21}H_{14}N_3$ $(M+H)^+$ m/z = 308.1188, found 308.1192.

8-Bromo-6-methyl-2,4-diphenylquinazoline (**3i**). 111 mg, 57%, off-white solid: mp 171−172 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 6.4 Hz, 2H), 8.02 (s, 1H), 7.83 (d, J = 3.6 Hz, 2H), 7.79 (s, 1H), 7.64−7.58 (m, 3H), 7.53−7.46 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 159.9, 147.7, 138.9, 137.8, 137.6, 137.4, 130.7, 130.1, 129.9, 128.8, 128.52, 128.50, 125.5, 124.4, 122.7, 21.5; HRMS (ESI-TOF) calcd. for $C_{21}H_{16}{}^{79}BrN_2$ $(M+H)^+$ m/z = 375.0497, found 375.0504; HRMS (ESI-TOF) calcd. for $C_{21}H_{16}{}^{81}BrN_2$ $(M+H)^+$ m/z = 377.0477, found 377.0487.

5,6,7-Trimethoxy-2,4-diphenylquinazoline (**3j**). 89 mg, 68%, off-white solid: mp 127−128 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62−8.59 (m, 2H), 7.65−7.62 (m, 2H), 7.50−7.47 (m, 6H), 7.42 (s, 1H), 4.07 (s, 3H), 3.92 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 159.6, 159.1, 150.1, 148.8, 142.1, 141.1, 137.4, 130.5, 129.0, 128.9, 128.6, 128.4, 127.2, 112.9, 103.6, 61.3, 61.0, 56.4; HRMS (ESI-TOF) calcd. for $C_{23}H_{21}N_2O_3$ $(M+H)^+$ m/z = 373.1552, found 373.1557.

7-Bromo-2,4-diphenylquinazoline (**3k**).[17] 51 mg, 38%, off-white solid: mp 155−156 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66−8.64 (m, 2H), 8.32 (d, J = 2.0 Hz, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.84−7.82 (m, 2H), 7.60−7.55 (m, 4H), 7.53−7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 161.0, 152.7, 137.7, 137.2, 131.5, 130.8, 130.5, 130.2, 130.1, 128.7, 128.6, 128.5, 128.4, 128.3, 120.3; HRMS (ESI-TOF) calcd. for $C_{20}H_{14}{}^{79}BrN_2$ $(M+H)^+$ m/z = 361.0340, found 361.0340; HRMS (ESI-TOF) calcd. for $C_{20}H_{14}{}^{81}BrN_2$ $(M+H)^+$ m/z = 363.0320, found 363.0313.

5-Bromo-2,4-diphenylquinazoline (**3k′**). 29 mg, 22%, off-white solid: mp 156−157 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64−8.62 (m, 2H), 8.12 (dd, J = 8.4, 1.2 Hz, 1H), 7.80 (dd, J = 7.6, 1.2 Hz, 1H), 7.68−7.64 (m, 1H), 7.63−7.61 (m, 2H), 7.52−7.50 (m, 3H), 7.49−7.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 159.0, 153.8, 139.6, 137.1, 133.6, 133.4, 130.8, 129.9, 129.5, 129.1, 128.8, 128.5, 127.9, 121.6, 119.8; HRMS (ESI-TOF) calcd. for $C_{20}H_{14}{}^{79}BrN_2$ $(M+H)^+$ m/z = 361.0340, found 361.0337; HRMS (ESI-TOF) calcd. for $C_{20}H_{14}{}^{81}BrN_2$ $(M+H)^+$ m/z = 363.0320, found 363.0350.

2,4-Diphenylbenzo[h]quinazoline (**3l**).[13c] 94 mg, 69%, white solid: mp 153−154 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54−9.52 (m, 1H), 8.84 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.8 Hz, 1H), 7.90−7.88 (m, 3H), 7.81−7.74 (m, 3H), 7.62−7.58 (m, 3H), 7.56−7.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 160.0, 151.8, 138.4, 138.0, 135.0, 130.7, 130.4, 130.2, 130.0, 129.6, 128.6 (2C), 128.5, 127.8, 127.7, 127.2, 125.3, 122.7, 119.2; HRMS (ESI-TOF) calcd. for $C_{24}H_{17}N_2$ $(M+H)^+$ m/z = 333.1392, found 333.1391.

1,3-Diphenylbenzo[f]quinazoline (**3m**).[17] 78 mg, 57%, white solid: mp 146−147 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, J = 8.0, 1.6 Hz, 2H), 8.03 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.62 (dd, J = 6.8, 1.2 Hz, 2H), 7.47−7.44 (m, 4H), 7.42−7.38 (m, 3H), 7.16−7.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 159.7, 154.3, 141.8, 137.6, 135.5, 132.7, 130.5, 129.5, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 127.7, 127.2, 127.0, 126.3, 119.3; HRMS (ESI-TOF) calcd. for $C_{24}H_{17}N_2$ $(M+H)^+$ m/z = 333.1392, found 333.1403.

2,4-Di-p-tolylquinazoline (**4a**).[14] 113 mg, 71%, white solid: mp 128−129 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 8.4 Hz, 2H), 8.11 (dd, J = 8.4, 0.8 Hz, 2H), 7.84 (dt, J = 7.2, 1.6 Hz, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.49 (dt, J = 8.0, 0.8 Hz, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 2.48 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 160.2, 151.9, 140.6, 140.0, 135.5, 134.9, 133.3, 130.1, 129.2, 129.1, 129.0, 128.6, 127.0, 126.6, 121.6, 21.49, 21.43; HRMS (ESI-TOF) calcd. for $C_{22}H_{19}N_2$ $(M+H)^+$ m/z = 311.1548, found 311.1563.

2,4-Bis(4-fluorophenyl)quinazoline (**4b**).[17] 114 mg, 69%, white solid: mp 168−169 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69−8.64 (m, 2H), 8.11 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.89−7.84 (m, 3H), 7.55−7.51 (m, 1H), 7.29−7.24 (m, 2H), 7.20−7.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 165.6 (d, J = 70 Hz), 163.0 (d, J = 70 Hz), 159.2, 151.9, 134.2 (d, J = 2.0 Hz), 133.7, 133.6 (d, J = 3.0 Hz), 132.1 (d, J = 9.0 Hz), 130.7 (d, J = 8.0 Hz), 129.1, 127.1, 126.7, 121.4, 115.6 (d, J = 45 Hz), 115.5 (d, J = 3.0 Hz); HRMS (ESI-TOF) calcd. for $C_{20}H_{13}F_2N_2$ $(M+H)^+$ m/z = 319.1047, found 319.1048.

2,4-Bis(3-methoxyphenyl)quinazoline (**4c**). 101 mg, 57%, sticky white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (dt, J = 8.0, 1.2 Hz, 1H), 8.27 (dd, J = 2.8, 1.6 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.13 (dd, J = 8.8, 1.2 Hz, 1H), 7.87 (dt, J = 7.6, 1.6 Hz, 1H), 7.53 (dt, J = 7.8, 1.2 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.44−7.40 (m, 3H), 7.12−7.10 (m, 1H), 7.06−7.03 (m, 1H), 3.93 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 160.0, 159.9, 159.7, 151.7, 139.4, 138.9, 133.6, 129.5 (2C), 129.0, 127.1, 127.0, 122.6, 121.7, 121.4, 117.0, 115.6, 114.7, 113.4; 55.4; HRMS (ESI-TOF) calcd. for $C_{22}H_{19}N_2O_2$ $(M+H)^+$ m/z = 343.1447, found 343.1459.

2,4-Bis(3-bromophenyl)quinazoline (**4d**). 170 mg, 73%, white solid: mp 135−136 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.59 (d, J = 7.6 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H), 7.89 (dt, J = 4.0, 0.8 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.61−7.54 (m, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 158.6, 151.8, 140.0, 139.3, 133.9, 133.4, 132.9, 132.8, 131.5, 130.0 (2C), 129.3, 128.7, 127.6, 127.1, 126.5, 122.8, 122.7, 121.6; HRMS (ESI-TOF) calcd. for $C_{20}H_{13}{}^{79}Br_2N_2$ $(M+H)^+$ m/z = 438.9468, found 438.9468; HRMS (ESI-TOF) calcd. for $C_{20}H_{13}{}^{81}Br_2N_2$ $(M+H)^+$ m/z = 440.9425, found 440.9444.

2,4-Bis(2-bromophenyl)quinazoline (**4e**). 141 mg, 62%, sticky white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 1H), 7.92 (dt, J = 7.8, 1.2 Hz, 1H), 7.83 (dd, J = 7.6, 1.6 Hz, 1H), 7.73−7.67 (m, 3H), 7.57 (dt, J = 7.4, 1.2 Hz, 1H), 7.51−7.45 (m, 2H), 7.43 (dd, J = 7.6, 1.2 Hz, 1H), 7.39−7.35 (m, 1H), 7.27 (ddd, J = 15.4, 7.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 162.1, 150.8, 140.1, 138.0, 134.2, 133.5, 133.0, 131.6, 130.9, 130.7 (2C), 130.3, 128.9, 127.9, 127.4, 127.3, 126.9, 122.0, 121.8; HRMS (ESI-TOF) calcd. for $C_{20}H_{13}{}^{79}Br_2N_2$ $(M+H)^+$ m/z = 438.9445, found 438.9446; HRMS (ESI-TOF) calcd. for $C_{20}H_{13}{}^{81}Br_2N_2$ $(M+H)^+$ m/z = 440.9425, found 440.9428.

2,4-Di(naphthalen-1-yl)quinazoline (**4f**).[14] 102 mg, 52%, pale yellow solid:: mp 155−156 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 8.0 Hz, 1H), 8.27 (t, J = 7.2 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.97−7.89 (m, 4H), 7.69 (d, J = 7.2 Hz, 2H), 7.66−7.62 (m, 2H), 7.61−7.57 (m, 1H), 7.56−7.54 (m, 1H), 7.52−7.46 (m, 3H), 7.41 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 162.9, 151.1, 136.3, 134.7, 134.2, 134.1, 133.7, 131.6, 131.3, 130.3, 129.9, 129.8, 129.0, 128.5, 128.4, 127.9, 127.5, 127.3, 126.8, 126.7, 126.2, 126.0, 125.8, 125.7, 125.3, 125.1, 122.9; HRMS (ESI-TOF) calcd. for $C_{28}H_{19}N_2$ $(M+H)^+$ m/z = 383.1548, found 383.1569.

2,4-Di(naphthalen-2-yl)quinazoline (**4g**). 108 mg, 54%, off-white solid: mp 175−176 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.85 (dd, J = 8.8, 1.6 Hz, 1H), 8.39 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.10−8.04 (m, 3H), 8.02−7.97 (m, 3H), 7.92−7.89 (m, 2H), 7.64−7.58 (m, 2H), 7.57−7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 160.1, 152.0, 133.5, 135.0, 134.7, 133.9, 133.6, 133.4, 132.9, 130.3, 129.2, 129.1, 129.0, 128.7, 128.3, 128.1, 127.8, 127.7, 127.2 (2C), 127.0 (2C), 126.9, 126.6, 126.1, 125.6, 121.9; HRMS (ESI-TOF) calcd. for $C_{28}H_{19}N_2$ $(M+H)^+$ m/z = 383.1548, found 383.1542.

2,4-Di(thiophen-2-yl)quinazoline (**4h**).[14] 105 mg, 69%, pale yellow solid: mp 99−100 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, J = 8.4, 0.8 Hz, 1H), 8.09 (dd, J = 4.0, 1.2 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.79 (dd, J = 3.6, 0.8 Hz, 1H), 7.75−7.71 (m, 1H), 7.55 (dd, J = 4.8, 0.8 Hz, 1H), 7.44 (dt, J = 8.0, 1.2 Hz, 1H), 7.41 (dd, J = 4.8, 1.2 Hz, 1H), 7.15 (dd, J = 5.2, 3.6 Hz, 1H), 7.09 (dd, J = 5.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 156.9, 152.2, 143.9, 141.4,

DOI: 10.1021/acs.joc.7b01325
J. Org. Chem. 2017, 82, 8290−8295

133.6, 131.2, 130.6, 129.8, 129.2, 128.9, 128.2, 128.0, 127.0, 126.0, 120.3; HRMS (ESI-TOF) calcd. for $C_{16}H_{11}N_2S_2$ $(M+H)^+$ m/z = 295.0364, found 295.0361.

*2,4-Diisopropylquinazoline (**4i**).*[17] 46 mg, 41%, Colorless Oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.08 (m, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.77 (dt, J = 7.8, 1.2 Hz, 1H), 7.51 (dt, J = 7.8, 1.2 Hz, 1H), 3.86 (sept, J = 6.8 Hz, 1H), 3.31 (sept, J = 6.8 Hz, 1H), 1.41 (d, J = 0.8 Hz, 6 H), 1.39 (d, J = 0.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 170.8, 149.8, 133.0, 128.5, 126.3, 123.9, 121.2, 37.8, 31.0, 21.75, 21.70; HRMS (ESI-TOF) calcd. for $C_{14}H_{19}N_2$ $(M+H)^+$ m/z = 215.1548, found 215.1563.

*2,4-Dicyclopropylquinazoline (**4j**).* 48 mg, 44%, Colorless Oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.75 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 2.67 (sept, J = 4.4 Hz, 1H), 2.27 (sept, J = 4.4 Hz, 1H), 1.31−1.28 (m, 2H), 1.19−1.07 (m, 4H), 1.04−0.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 167.0, 149.4, 133.2, 127.7, 125.7, 124.2, 122.5, 18.2, 12.6, 11.9, 10.0; HRMS (ESI-TOF) calcd. for $C_{14}H_{15}N_2$ $(M+H)^+$ m/z = 211.1235, found 211.1241.

*2,4-Ditert-butylquinazoline (**4k**).* 45 mg, 38%, Colorless Oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37−8.34 (m, 1H), 8.01−7.98 (m, 1H), 7.72 (dt, J = 7.4, 1.2 Hz, 1H), 7.46 (dt, J = 7.8, 1.2 Hz, 1H), 1.61 (s, 9H), 1.47 (9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 171.5, 151.5, 131.6, 130.0, 126.2, 125.0, 120.7, 40.4, 39.6, 30.6, 29.5; HRMS (ESI-TOF) calcd. for $C_{16}H_{23}N_2$ $(M+H)^+$ m/z = 243.1861, found 243.1875.

*2,4-Bis(bromomethyl)quinazoline (**4m**).* Eighteen mg, 11%, off-white solid: mp 164−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.91 (dt, J = 7.8, 0.8 Hz, 1H), 7.70 (dt, J = 7.6, 0.8 Hz, 1H), 4.90 (s, 2H), 4.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 161.7, 151.2, 134.5, 129.3, 128.4, 124.6, 121.1, 34.2, 28.7; HRMS (ESI-TOF) calcd. for $C_{10}H_9{}^{79}Br_2N_2$ $(M+H)^+$ m/z = 314.9132, found 314.9142; HRMS (ESI-TOF) calcd. for $C_{10}H_9{}^{81}Br_2N_2$ $(M+H)^+$ m/z = 316.9112, found 316.9097.

*5-Methoxy-2,4-dimethylquinazoline (**7**).* 18 mg, 21%, pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.11 (dd, J = 9.2, 2.4 Hz, 1H), 3.90 (s, 3H), 2.80 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 164.1, 163.7, 152.4, 126.2, 119.5, 117.4, 105.9, 55.64, 55.62, 26.3, 21.4; HRMS (ESI-TOF) calcd. for $C_{11}H_{13}N_2O$ $(M+H)^+$ m/z = 189.1028, found 189.1035.

*5,6,7-Trimethoxy-2,4-dimethylquinazoline (**8**).* 28 mg, 32%, pale yellow solid:: mp 60−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 4.00 (s, 3H), 3.97 (s, 3H), 3.92 (s, 3H), 2.97 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 162.8, 158.9, 149.8, 149.1, 141.6, 113.4, 103.2, 61.1, 61.0, 56.2, 26.1, 26.0; HRMS (ESI-TOF) calcd. for $C_{13}H_{17}N_2O_3$ $(M+H)^+$ m/z = 249.1239, found 249.1242.

*2,4-Dimethylbenzo[h]quinazoline (**9**).*[17] 32 mg, 38%, brown solid: mp 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, J = 2.4 Hz, 1H), 7.88−7.85 (m, 2H), 7.70−7.78 (m, 3H) 2.91 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.8, 150.0, 135.0, 130.2, 129.7, 127.7, 127.3, 127.2, 125.0, 120.9, 119.5, 26.6, 21.8; HRMS (ESI-TOF) calcd. for $C_{14}H_{13}N_2$ $(M+H)^+$ m/z = 209.1079 found 209.1092.

*6-Phenylphenanthridine (**11**).* 70 mg, 74%, white solid: mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 8.4 Hz, 1H), 8.59 (dd, J = 8.4, 1.2 Hz, 1H), 8.25 (dd, J = 8.0, 1.2 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.85−7.81 (m, 1H), 7.76−7.71 (m, 3H), 7.67 (d, J = 8.4, 1.2 Hz, 1H), 7.61−7.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 143.7, 129.7, 133.4, 130.5, 130.3, 129.7, 128.9, 128.8, 128.6, 128.4, 127.0, 12.9, 125.2, 123.7, 122.1, 121.9; HRMS (ESI-TOF) calcd. for $C_{19}H_{14}N$ $(M+H)^+$ m/z = 256.1126, found 256.1124.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01325.

Spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stliu@ntu.edu.tw

ORCID

Shiuh-Tzung Liu: 0000-0002-0544-006X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Taiwan (Grant No.MOST103-2113-M-002-002-MY3) for the financial support. We also thank "National Taiwan University Mass Spectrometry-based Proteomics Core Facility" for the measurement of ESI mass data.

■ REFERENCES

(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166. (b) Witt, A.; Bergman. *Curr. Org. Chem.* **2003**, *7*, 659. (c) Bansal, Y.; Silakari, O. *Bioorg. Med. Chem.* **2012**, *20*, 6208 and references therein..

(2) (a) Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. *Eur. J. Med. Chem.* **2015**, *90*, 124. (b) Colotta, V.; Catarzi, D.; Varano, F.; Lenzi, O.; Filacchioni, G.; Costagli, C.; Galli, A.; Ghelardini, C.; Galeotti, N.; Gratteri, P.; Sgrignani, J.; Deflorian, F.; Moro, S. *J. Med. Chem.* **2006**, *49*, 6015 and references therein..

(3) (a) Alafeefy, A. M.; Kadi, A.; Al-Deeb, O. A.; El-Tahir, K. E.; Al-Jaber, N. A. *Eur. J. Med. Chem.* **2010**, *45*, 4947. (b) Chao, Q.; Deng, L.; Shih, H.; Leoni, L. M.; Genini, D.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **1999**, *42*, 3860. (c) Balakumar, C.; Lamba, P.; Kishore, D. P.; Narayana, B. L.; Rao, K. V.; Rajwinder, K.; Rao, A. R.; Shireesha, B.; Narsaiah, B. *Eur. J. Med. Chem.* **2010**, *45*, 4904.

(4) Ugale, V. G.; Bari, S. B. *Eur. J. Med. Chem.* **2014**, *80*, 447.

(5) (a) Machara, A.; Lux, V.; Kozisek, M.; Grantz-Saskova, K.; Stepanek, O.; Kotora, M.; Parkan, K.; Pavova, M.; Glass, B.; Sehr, P.; et al. *J. Med. Chem.* **2016**, *59*, 545.

(6) (a) Jafari, E.; Khajouei, M. R.; Hassanzadeh, G.; Hakimelahi, G. H.; Khodarahmi, G. A. *Res. Pharm. Sci.* **2016**, *11*, 1. (b) Kumar, A.; Sharma, P.; Kumari, P.; Kalal, B. L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4656.

(7) (a) Sordella, R.; Bell, D. W.; Haber, D. A.; Settleman, J. *Science* **2004**, *305*, 1163. (b) Assiddiq, B. F.; Tan, K. Y.; Toy, W.; Chan, S. P.; Chong, P. K.; Lim, Y. P. J. *Proteome Res.* **2012**, *11*, 4110.

(8) Sos, M. L.; Koker, M.; Weir, B. A.; Heynck, S.; Rabinovsky, R.; Zander, T.; Seeger, J. M.; Weiss, J.; Fischer, F.; Frommolt, P.; Michel, K.; Peifer, M.; Mermel, C.; Girard, L.; Peyton, M.; Gazdar, A. F.; Minna, J. D.; Garraway, L. A.; Kashkar, H.; Pao, W.; Meyerson, M.; Thomas. *Cancer Res.* **2009**, *69*, 3256.

(9) Bolognesi, M. L.; Budriesi, R.; Chiarini, A.; Poggesi, E.; Leonardi, A.; Melchiorre, C. *J. Med. Chem.* **1998**, *41*, 4844.

(10) Short, C. E. S.; Gilleece, Y. C.; Fisher, M. J.; Churchill, D. R. *AIDS* **2009**, *23*, 1287.

(11) (a) Zhao, D.; Shen, Q.; Zhou, Y. R.; Li, J. X. *Org. Biomol. Chem.* **2013**, *11*, 5908. (b) Zhang, Y. L.; Sheets, M. R.; Raja, E. K.; Boblak, K. N.; Klumpp, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 8467. (c) Achelle, S.; Rodriguez-Lopez, J.; Robin-le Guen, F. *J. Org. Chem.* **2014**, *79*, 7564. (d) Wilson, J. N.; Liu, W.; Brown, A. S.; Landgraf, R. *Org. Biomol. Chem.* **2015**, *13*, 5006. (e) Liu, D.; Zhang, Z.; Zhang, H.; Wang, Y. *Chem. Commun.* **2013**, *49*, 10001.

(12) (a) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153. (b) Maheswari, C. U.; Kumar, G. S.; Venkateshwar, M.; Kumar, R. A.; Kantam, M. L.; Reddy, K. R. *Adv. Synth. Catal.* **2010**, *352*, 341. (c) Han, B.; Yang, X. L.; Wang, C.; Bai, Y. W.; Pan, T. C.; Chen, X.; Yu, W. *J. Org. Chem.* **2012**, *77*, 1136. (d) Yan, Y.; Zhang, Y.; Feng, C.; Zha, Z.; Wang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 8077. (e) Zhang, J.; Yu, C.; Wang, S.; Wan, C.; Wang, Z. *Chem. Commun.* **2010**, *46*, 5244. (f) Zhang, J.; Zhu, D.; Yu, C.; Wan, C.; Wang, Z. *Org. Lett.* **2010**, *12*, 2841. (g) Han, B.; Wang, C.; Han, R.-

DOI: 10.1021/acs.joc.7b01325
J. Org. Chem. 2017, 82, 8290−8295

F.; Yu, W.; Duan, X.-Y.; Fang, R.; Yang, X.-L. *Chem. Commun.* **2011**, *47*, 7818.
(13) (a) Kumar, V.; Mohan, C.; Gupta, M.; Mahajan, M. P. *Tetrahedron* **2005**, *61*, 3533. (b) Lin, J.-P.; Zhang, F.-H.; Long, Y.-Q. *Org. Lett.* **2014**, *16*, 2822. (c) Shen, Z.-C.; Yang, P.; Tang, Y. *J. Org. Chem.* **2016**, *81*, 309−317. (d) Wang, Y.; Wang, H.; Peng, J.; Zhu, Q. *Org. Lett.* **2011**, *13*, 4604. (e) Xu, L.; Li, H.; Liao, Z.; Lou, K.; Xie, H.; Li, H.; Wang, W. *Org. Lett.* **2015**, *17*, 3434. (f) McGowan, M. A.; McAvoy, C. Z.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 3800. (g) Ohta, Y.; Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2010**, *12*, 3963.
(14) Su, X.; Chen, C.; Wang, Y.; Chen, J.; Lou, Z.; Li, M. *Chem. Commun.* **2013**, *49*, 6752.
(15) (a) Ramanathan, M.; Liu, S. T. *J. Org. Chem.* **2015**, *80*, 5329. (b) Ramanathan, M.; Wang, Y. H.; Liu, S. T. *Org. Lett.* **2015**, *17*, 5886.
(16) (a) Wang, H.; Xu, Q.; Shen, S.; Yu, S. *J. Org. Chem.* **2017**, *82*, 770. (b) Youn, S. W.; Lee, E. M. *Org. Lett.* **2016**, *18*, 5728. (c) Petterson, R. C.; Bennett, J. T.; Lankin, D. C.; Lin, G. W.; Mykytka, J. P.; Troendle, T. G. *J. Org. Chem.* **1974**, *39*, 1841−1845.
(17) Xia, Z.; Zhu, Q. *Org. Lett.* **2013**, *15*, 4110.

■ NOTE ADDED AFTER ASAP PUBLICATION

Reference 16c, a highly analogous precedent for this work, was added on July 25, 2017.

DOI: 10.1021/acs.joc.7b01325
J. Org. Chem. 2017, 82, 8290−8295