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Cesium Carboxylate-Promoted Iridium Catalyzed C−H Amidation/Cyclization with 2,2,2-Trichloroethoxycarbonyl Azide

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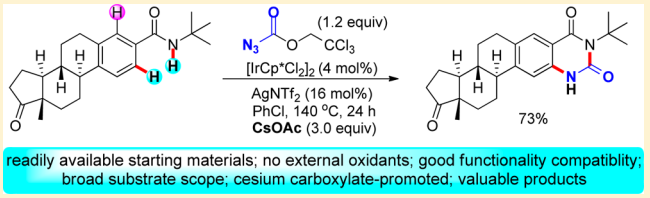
Supporting Information

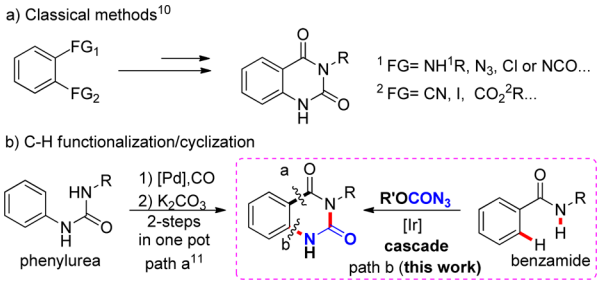
ABSTRACT: An Ir(III)-catalyzed direct C−H amidation/cyclization of benzamides using 2,2,2-trichloroethoxycarbonyl azide ($TrocN_3$) as the aminocarbonyl source is reported. With the aid of cesium carboxylate, the reactions proceed efficiently and with high regioselectivity, producing various functionalized quinazoline-2,4(1*H*,3*H*)-diones, which are important building blocks and key synthetic intermediates for biologically and medicinally important compounds. During the reactions, two new C−N bonds were formed by breaking C−H and N−H bonds sequence.



Transition-metal catalyzed C−H amination allows simplification and abbreviation of synthetic procedures and has been proved to be a powerful approach to the construction of valuable amine derivatives from starting materials devoid of functional groups.[1,2] This approach has achieved significant advances, although most available procedures require stoichiometric quantities of external oxidants and/or bases. Recently, C−H amination directed by functional groups using organic azides as amino sources has been less explored.[3,4] The advantages of this approach include its dependence on easily prepared organic azides, N_2 as the sole byproduct, high tolerance of functional groups and the nonoxidative reaction conditions that are used. Various type of organic azides, such as sulfonyl,[4a−c] carbonyl,[4d−f] phosphoryl,[4g,h] phenyl[4i−k] and alkyl azides[4l−n] have been utilized with an appropriate combination of chelate groups and metal catalysts. In spite of their many benefits, these reported protocols still suffer from some substrate scope limitations and reaction efficiency. For example, alkoxycarbonyl azides have shown low reactivity and thus been rarely used possibly due to their electrophilicity which is weaker than that of sulfonyl or carbonyl azides,[5] notwithstanding the fact that alkoxycarbonyl groups on an amino group are removable and readily susceptible to subsequent transformations. The cascade strategy combining C−H amination has been rarely applied,[4d] despite the fact that the cascade reaction has drawn much interest due to its high efficiency in constructing multiple new bonds in a simple one-pot operation.[6]

Quinazoline-2,4(1*H*,3*H*)-dione, a scaffold embedded in a variety of natural quinolone, quinazoline and acridone alkaloids,[7] contains a benzene ring and a fused pyrimidine ring with carbonyl groups at the 2 and 4 positions, and is recognized as the benzo-annulated analogue of the RNA and DNA nucleotide bases uracil and thymine. Its derivatives have drawn much attention due to their various biological activities[8] and are widely used as key structures in the production of medicinal agents.[9] There are a number of synthetic methods available for the preparation of quinazoline-2,4(1*H*,3*H*)-diones,[10] and *o*-aminobenzoic acid and its analogues are commonly used starting materials (Scheme 1a). Major drawbacks in these methods include the presence of multistep procedures, and the use of less available and expensive 1,2-difunctionalized arene reagents. Consequently, a new facile and effective method preferably using readily available starting materials is urgently needed. A functional group directed C−H activation would be useful because of its inherent advantage of producing 1,2-difunctionalized arenes derived from monofunctionalized arenes. But only one example based on metal catalytic C−H activation strategy has been reported (Path a in Scheme 1b).[11] This method proceeded through a stepwise palladium-catalyzed *ortho* C−H carboxylation of phenylurea

Scheme 1. Methods for the Synthesis of Quinazoline-2,4(1*H*,3*H*)-diones



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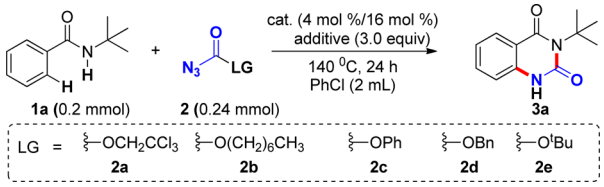
followed by base promoted cyclization, and represented one of the most efficient pathways for the synthesis of quinazoline-2,4(1*H*,3*H*)-dione. Here, we describe an alternative synthesis of quinazoline-2,4(1*H*,3*H*)-diones (Path b in Scheme 1b) from readily available benzamides with 2,2,2-trichloroethoxycarbonyl azide ($TrocN_3$)[12] as the aminocarbonyl source by a cesium carboxylate-promoted cascade C−H amidation/cyclization reaction.

Inspired by the Ir-catalyzed C−H amination of arenes with organic azides developed by Chang[4a−f,h] and others,[4g] and by our previous studies in C−H amination using different organic azides including $TrocN_3$ as amino soures,[4i,l,12,13] we began our investigation by examining reactions of benzamides with $TrocN_3$ (**2a**) (Table 1, and Table S1 in Supporting Information [SI]). Using $[IrCp^*Cl_2]_2$/$AgNTf_2$ (4 mol %/16 mol %) to catalyze the reaction,[4f] the amidated product was formed in only 29% yield (Table S1) with trace amount of the desired cyclic product **3a** even at 140 °C (Table 1, entry 1). Upon screening a variety of additives (entries 2−8), the desired product **3a** was obtained efficiently when cesium carboxylate was used as the additive (entries 7, 8). A variety of alkoxycarbonyl azides with different leaving groups (LG) were tested (entries 8−12), and $TrocN_3$ was found to be the best choice (entry 8). Further screening indicated [Ru(*p*-cymene)$Cl_2]_2$/$AgNTf_2$ was not an ideal catalyst (entry 13) and no desired product was formed with other catalysts such as $[RhCp^*Cl_2]_2$/$AgSbF_6$, $Pd(OAc)_2$, $Co(acac)_2$ and $Ni(OTf)_2$ (Table S1).

Table 1. Optimization of Reaction Conditions[a]

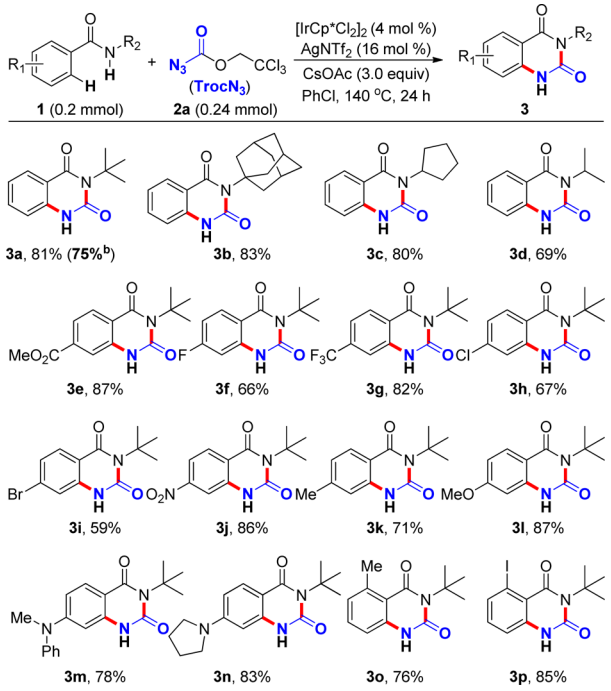


entry	2	cat.	additive	3a (%)
1	2a	$[IrCp^*Cl_2]_2$/$AgNTf_2$	–	<5
2	2a	$[IrCp^*Cl_2]_2$/$AgNTf_2$	Cs_2CO_3	–
3	2a	$[IrCp^*Cl_2]_2$/$AgNTf_2$	AgOAc	10
4	2a	$[IrCp^*Cl_2]_2$/$AgNTf_2$	NaOAc	62
5	2a	$[IrCp^*Cl_2]_2$/$AgNTf_2$	K_2CO_3	<5
6	2a	$[IrCp^*Cl_2]_2$/$AgNTf_2$	KO^{t}Bu	–
7	2a	**$[IrCp^*Cl_2]_2$/$AgNTf_2$**	**CsOPiv**	77
8	2a	**$[IrCp^*Cl_2]_2$/$AgNTf_2$**	**CsOAc**	**85**
9	2b	$[IrCp^*Cl_2]_2$/$AgNTf_2$	CsOAc	5
10	2c	$[IrCp^*Cl_2]_2$/$AgNTf_2$	CsOAc	52
11	2d	$[IrCp^*Cl_2]_2$/$AgNTf_2$	CsOAc	21
12	2e	$[IrCp^*Cl_2]_2$/$AgNTf_2$	CsOAc	11
13	2a	[Ru(p-cymene)$Cl_2]_2$/$AgNTf_2$	CsOAc	46

[a]Yield was calculated based on crude ^{1}H NMR using CH_2Br_2 as the standard.

A range of *ortho*- and *para*-substituted benzamides were employed under the optimized conditions, forming the corresponding quinazolinone derivatives effectively (Scheme 2). Benzamides with different *N*-alkyl substituents (**3a−d**), with electron-withdrawing (**3e−j**) and -donating groups (**3k−n**) at the *para*-position of the phenyl ring were well tolerated, the desired products being obtained in good yield. The *ortho* substitution of the phenyl ring does not affect the reactivity

Scheme 2. Scope of *ortho*- and *para*-Substituted Benzamides 1[a]



[a]Isolated yield. [b]**1a** (8.0 mmol), **2a** (9.6 mmol) was used, 1.311 g of product **3a** was obtained.

(**3o**,**p**). Various functional groups, such as ester (**3e**), halogens (**3f**, **3h**,**i**, **3p**), nitro (**3j**), methoxyl (**3l**) and amino (**3m**,**n**) groups were well tolerated, which is important for subsequent transformations. It could be noted that this cascade cyclization can be conducted on a gram-scale, the desired product **3a** being produced facilely.

Various *meta*-substituted benzamides were employed in this reaction (Scheme 3). Meta-substitution can affect both the steric and electron density of the reaction site, which can control the selectivity of C−H activation.[14] In this reaction, various electron-rich (**3q−s**) and -deficient (**3t−w**) functional groups can control C−H amidation occurring at the less hindered position. The C−H bond at the 3-position of 2-naphthamide could also be activated to form benzo[*g*]-quinazoline-2,4(1*H*,3*H*)-dione (**3x**) in high yield and regioselectivity. However, when the meta-position of the benzamide was substituted with methoxyl or bromine, a mixture of regioisomers was isolated (**3y** and **3y′**, **3z** and **3z′**). This can be explained in terms of the *ortho* directing effect of the strongly electronegative substituents, which was also observed in other C−H activation reactions.[4l,14] Interestingly, in addition to reactivity, the carboxylate salts can control the regioselectivity. For example, C−H amidation took place selectively at the less hindered site when the cesium salt with bulkier carboxylate ligand (CsOPiv) was used as the additive (**3y**,**z**).

In addition to the diverse array of biological activities,[8] the quinazoline-2,4(1*H*,3*H*)-diones (**3**) formed could serve as valuable synthetic intermediates for applications in biology and medicine.[9] For example, **3r** is a key intermediate in the production of FK 31327[9a] and FK 366;[9b] **3w** is a key intermediate in the production of various drugs such as alfuzosin, prazosin, terazosin, doxazosin, and iodoazidoarylprazosin (IAAP).[9c−e] **3a** can also be efficiently converted to 2,4-

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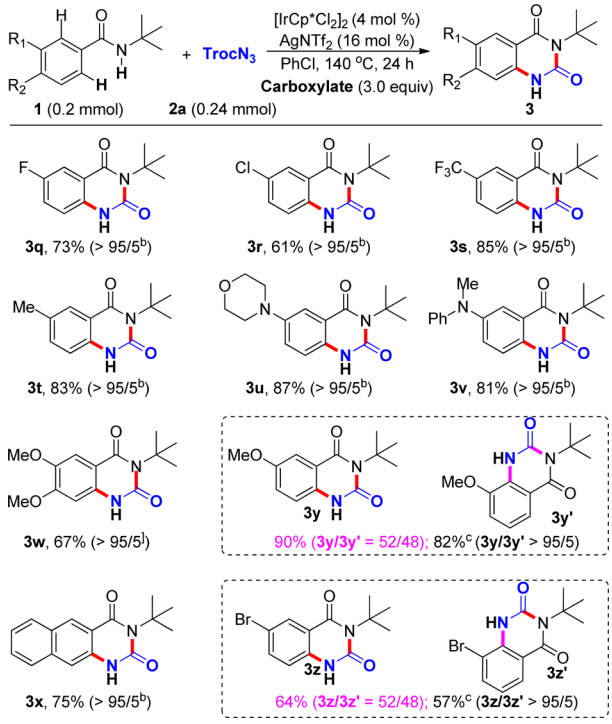
Scheme 3. Regioselectivity of C−H Amidation of *meta*-substituted Benzamides[a]

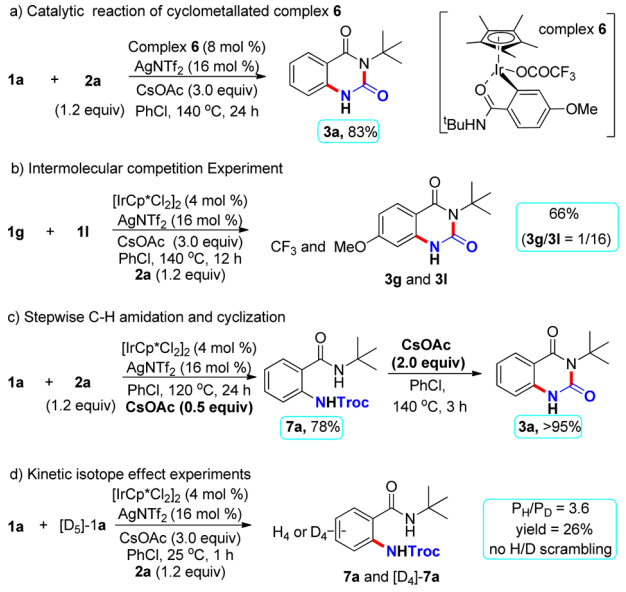


[a]Isolated yield. [b]The ratio of the products **3**/**3′**. [c]Using CsOPiv instead of CsOAc.

dichloroquinazoline (**8**), which is the key precursor of a vaccine adjuvant.[15] Furthermore, the nonoxidative reaction conditions may allow for direct use of substrates that are bioactive relevant. For example, amidation of the estrone-based substrate (**4a**) could provide the new quinazoline-2,4(1*H*,3*H*)-dione-based estrone derivative (**5a**) in good yield and with good regioselectivity (eq 1).

Several experiments have been performed to explore the mechanism of this reaction (Scheme 4). When the cyclometalated Ir(III) complex (**6**) was used as the catalyst, the desired product (**3a**) was obtained in 83% yield (Scheme 4a). This result suggests that an iridacyclic intermediate is involved in the catalytic cycle. The electronic effect on the phenyl ring was investigated through competition experiments, and the electron-rich benzamide (**1l**) was found to exhibit much higher reactivity (Scheme 4b). When the amount of CsOAc was reduced and the reaction temperature was lowered, the predominant product was anthranilamide (**7a**), a moiety found in many drugs and drug candidates,[16] and at the same time, less than 5% of the product (**3a**) was observed (Scheme 4c). Then, promoted by excess CsOAc (2.0 equiv), the amidated compound (**7a**) could easily cyclize to form product **3a** without side reactions. Finally, kinetic isotope effects were observed on the basis of an intermolecular competition experiment in one vessel (P_H/P_D = 3.6) with no H/D

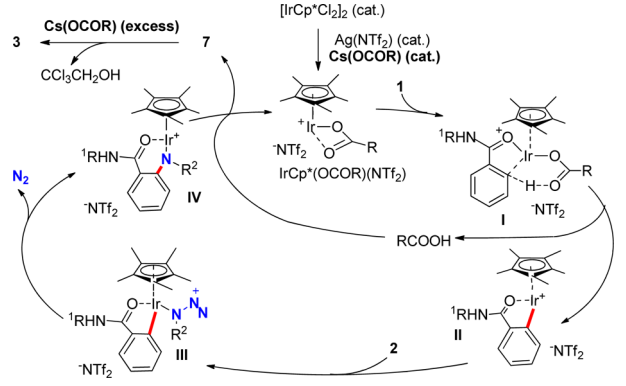
Scheme 4. Mechanistic Studies



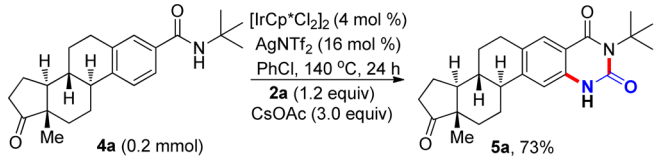
scrambling detected between substrates **1a** and [D_5]-**1a** (Scheme 4d), implying that C−H bond cleavage is likely to be the rate-limiting step.

In the experiments described above and previous studies,[4a,f−h] a possible mechanistic pathway has been proposed (Scheme 5). In this scheme, IrCp*(NTf) (OCOR) is formed

Scheme 5. Proposed Mechanistic Pathway



by the catalytic amount of [$IrCp^*Cl_2$]$_2$, $AgNTf_2$ and Cs(OCOR). This active species induces C−H bond cleavage through transition state I. In this step, both substrate and carboxylate control the regioselectivity of the reactions when using a *meta*-substituted benzamide as the substrate (Scheme 3). The cyclometalated Ir(III) complex II produced coordinates the azide (**2**) to form III, which undergoes migratory insertion and release of N_2 to give IV. Protonolysis of IV regenerates the active Ir species, completing the cycle. Meanwhile, it provides the amidation product (**7**) which forms the cyclic product (**3**)



(1)

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through an intramolecular substitution process with the aid of excess cesium carboxylate.

In summary, a cesium carboxylate-promoted Ir-catalyzed C−H amidation/cyclization using $TrocN_3$ as the aminocarbonyl source has been achieved. Various benzamides were selectively amidated/cyclized under nonoxidative reaction conditions with excellent regioselectivity and high functional-group tolerance. In this reaction, two new C−N bonds are formed by breaking C−H and N−H bonds sequence. This offers a direct and convenient route for the synthesis of functionalized quinazoline-2,4(1*H*,3*H*)-diones, which are important building blocks and key synthetic intermediates for applications in biology and medicine. The mechanistic investigation suggests that the reactions undergo C−H activation and SN_2 type intramolecular nucleophilic substitution.

EXPERIMENTAL SECTION

General Information. Unless otherwise mentioned, all commercial reagents and solvents were used without further purification. Thin layer chromatography (TLC) was performed on precoated silica gel GF254 plates. Visualization of TLC was achieved by the use of UV light (254 nm). Column chromatography was performed on silica gel (300−400 mesh) using a proper eluent. ^{1}H NMR was recorded on FT AM 400 (400 MHz). Chemical shifts were reported in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane or chloroform-*d* ($CDCl_3$) at 7.26 ppm. The following abbreviations were used to describe peak splitting patterns: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, ddd = doublet of doublet of doublet, m = multiplet. Coupling constants, *J*, were reported in hertz (Hz). The fully decoupled ^{13}C NMR was recorded on FT AM 400 (100 MHz). Chemical shifts were reported in ppm referenced to the center of a triplet at 77.0 ppm of chloroform-*d*. Infrared (IR) spectra were recorded neat in KBr cell. Frequencies are given in centimeter inverse (cm^{-1}) and only selected absorbance is reported. High resolution mass spectra were obtained by using the UHD Accurate-Mass Q-TOF.

General Procedure for the Preparation of Benzamides. To a solution of benzoyl chloride (5 mmol) in CH_2Cl_2 (20 mL) were slowly added alkylamine (6 mmol) and Et_3N (0.85 mL, 6 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was quenched with 1 N HCl (30 mL), extracted with CH_2Cl_2 for several times, and then dried over Na_2SO_4. The crude product was concentrated under reduced pressure and purified by recrystallization with *n*-hexane/CH_2Cl_2 to give the desired product. Physical and spectroscopic data are consistent with those reported in the literature.[4l]

*(8R,9S,13S,14S)-N-(tert-Butyl)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]-phenanthrene-3-carboxamide (**4a**).* TLC R_f = 0.70 (EA:PE = 1:1); yellowish solid; 1.33 g, 75% yield; mp 218−220 °C; $[\alpha]_D^{25}$ = +113.6 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 5.94 (s, 1H), 2.93 (dd, *J* = 10.8, 4.6 Hz, 2H), 2.50 (dd, *J* = 18.7, 8.6 Hz, 1H), 2.45−2.37 (m, 1H), 2.34−2.27 (m, 1H), 2.24−1.88 (m, 5H), 1.63−1.48 (m, 5H), 1.45 (s, 9H), 0.90 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 220.5, 166.8, 143.0, 136.8, 133.4, 127.6, 125.4, 123.8, 51.5, 50.5, 47.9, 44.5, 38.0, 35.8, 31.6, 29.3, 28.9, 26.3, 25.7, 21.6, 13.8; IR (neat) 2961, 2927, 2857, 1738, 1652, 1530, 1492, 1452, 1313, 1217, 1052, 757 cm^{-1}. HRMS (ESI) ([M + Na]$^+$) Calcd for $C_{23}H_{31}NO_2$: 376.2252, found 376.2252. The absolute configuration of compound **4a** was determined from the start material (8*R*,9*S*,13*S*,14*S*)-3-hydroxy-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one (CAS# 53−16−7), and The Procedure for the Preparation involved reaction of compound **4a** was found to proceed with stereo retention according to the existing reported in the literature.[17]

A screw-cap vial equipped with a magnetic stir bar was charged with the aryl halide (1.0 mmol), secondary amine (1.2 mmol), $Pd(OAc)_2$ (0.01 mmol), RuPhos (0.02 mmol), and powdered NaO^{t}Bu (1.2 mmol). The vial was transferred to a preheated oil bath (120 °C). After 4 h, the reaction mixture was cooled and dissolved in CH_2Cl_2/H_2O mixture (1:1). The organic phase was separated, the solvent was evaporated in vacuo, and the product (**3m**, **3n**, **3u** and **3v**) was isolated by flash chromatography on a silica gel column (CH_2Cl_2 or CH_2Cl_2/methyl *tert*-butyl ether). Physical and spectroscopic data are consistent with those reported in the literature.[4l]

General Procedure for the Preparation of Acyl Azides. To a well-stirred suspension of NaN_3 (1.95 g, 30 mmol) in acetone (40 mL) protected from light by aluminum foil was added acyl chloride (20 mmol) at room temperature. The reaction was monitored by TLC. After the reaction finished, the mixture was then poured into a flash chromatography column filled with Celite (dry) and was washed with methylene chloride until all the product was washed out. The filtrate was collected and concentrated by rotary evaporation at room temperature to give the product, which was further purified by flash chromatography column (silica gel). Physical and spectroscopic data are consistent with those reported in the literature.[12]

*Heptyl Carbonazidate (**2b**).* TLC R_f = 0.60 (EA:PE = 1:20); colorless oil; 3.33 g, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (t, *J* = 6.7 Hz, 2H), 1.71−1.62 (m, 2H), 1.37−1.23 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 68.8, 31.6, 28.8, 28.4, 25.5, 22.5, 14.0; IR (neat) 2959, 2931, 2859, 2186, 2136, 1759, 1733, 1237, 753 cm^{-1}; HRMS (DART) ([M + H]$^+$) Calcd for $C_8H_{15}N_3O_2$: 186.1237, found 186.1238.

General Procedure for the Ir-Catalyzed C−H Amidation/Cyclizition. To a screw capped vial equipped with a spinvane triangular-shaped Teflon stirbar were added benzamide (**1**, 0.2 mmol), Troc azides (**2**, 52.4 mg, 0.24 mmol), $[IrCp^*Cl_2]_2$ (6.4 mg, 4 mol %), $AgNTf_2$ (12.4 mg, 16 mol %), CsOAc (115.2 mg, 3 equiv)/ CsOPiv (140.4 mg, 3 equiv) and chlorobenzene (2 mL) under N_2 conditions. The reaction mixture was stirred in a preheated oil bath at 140 °C for 24 h. The reaction was cooled to room temperature, filtered through a pad of Celite and then washed with CH_2Cl_2 (10 mL × 3). The solvents were removed under reduced pressure and the crude reaction mixture was purified by silica gel column chromatography with *n*-Hexane/EtOAc as an eluent to give the desired product.

Spectroscopic Data of Compounds Obtained in this Study. *3-(tert-Butyl)quinazoline-2,4(1H,3H)-dione*[18] *(**3a**).* TLC R_f = 0.20 (EA:PE = 1:10); yellowish solid; 35.4 mg, 81% yield; mp 197−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.01 (d, *J* = 7.4 Hz, 1H), 7.57−7.51 (m, 1H), 7.18−7.13 (m, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 1.80 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 153.5, 138.2, 134.4, 128.1, 122.8, 117.0, 114.1, 62.1, 30.0; IR (neat) 3901, 3839, 3818, 3687, 2988, 1658, 1396, 1275, 1261, 764, 750 cm-1; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{12}H_{14}N_2O_2$: 217.0977, found 217.0976.

3-((3s,5s,7s)-Adamantan-1-yl)quinazoline-2,4(1H,3H)-dione[19] *(**3b**).* TLC R_f = 0.25 (EA:PE = 1:10); white solid; 49.2 mg, 83% yield; mp 233−234 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.56−7.50 (m, 1H), 7.18−7.11 (m, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 2.65 (d, *J* = 1.7 Hz, 6H), 2.19 (s, 3H), 1.82 (d, *J* = 11.8 Hz, 3H), 1.71 (d, *J* = 12.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 153.0, 138.0, 134.2, 128.1, 122.8, 117.5, 113.8, 65.6, 40.2, 36.5, 30.7; IR (neat) 3950, 3901, 3830, 3735, 3449, 2906, 1710, 1654, 1275, 1261, 764, 751 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{18}H_{20}N_2O_2$: 295.1447, found 295.1447.

3-Cyclopentylquinazoline-2,4(1H,3H)-dione[20] *(**3c**).* TLC R_f = 0.40 (DCM:PE:Et_2O = 10:10:1); white solid; 36.8 mg, 80% yield; mp 240−241 °C; ^{1}H NMR (400 MHz, Acetone) δ 10.15 (s, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.66−7.60 (m, 1H), 7.27−7.18 (m, 2H), 5.45−5.36 (m, 1H), 2.18 (dd, *J* = 11.8, 7.8 Hz, 2H), 2.00−1.92 (m, 2H), 1.87−1.78 (m, 2H), 1.65−1.56 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 152.3, 138.6, 134.8, 128.4, 123.2, 115.1, 114.7, 53.2, 28.6, 26.0; IR (neat) 3957, 3800, 3570, 3368, 2936, 1735, 1718, 1701, 1654, 1605, 1561, 1493, 1449, 1276, 1261, 763, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{13}H_{14}N_2O_2$: 229.0977, found 229.0977.

3-Isopropylquinazoline-2,4(1H,3H)-dione[18] *(**3d**).* TLC R_f = 0.38 (DCM:PE:Et_2O = 10:10:1); white solid; 28.2 mg, 69% yield; mp 187−

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188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 11.2, 4.2 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 5.29−5.40 (m, 1H), 1.58 (d, J = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 152.2, 138.7, 134.8, 128.4, 123.2, 115.1, 114.6, 45.8, 19.6; IR (neat) 3509, 3359, 3067, 3005, 2971, 2936, 1712, 1655, 1624, 1493, 1445, 1410, 1387, 1276, 1264, 1070, 861, 814, 746 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{11}H_{12}N_2O_2$: 203.0821, found 203.0820.

*Methyl 3-(tert-butyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (**3e**).* TLC R_f = 0.10 (DCM:PE:Et_2O = 10:10:1); white solid; 48.1 mg, 87% yield; mp 210−211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.67 (s, 1H), 3.99 (s, 3H), 1.81 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 163.5, 152.0, 137.7, 135.3, 128.6, 123.3, 120.1, 115.2, 62.5, 52.7, 29.8; IR (neat) 2954, 2925, 2854, 1721, 1668, 1605, 1520, 1436, 1398, 1366, 1294, 1233, 757 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{14}H_{16}N_2O_4$: 275.1032, found 275.1032.

*3-(tert-Butyl)-7-fluoroquinazoline-2,4(1H,3H)-dione (**3f**).* TLC R_f = 0.25 (DCM:PE:Et_2O = 10:10:1); white solid; 31.2 mg, 66% yield; mp 177−178 °C; ^{1}H NMR (400 MHz, Acetone) δ 10.02 (s, 1H), 7.96 (dd, J = 8.7, 6.1 Hz, 1H), 6.91 (ddd, J = 19.1, 9.5, 2.3 Hz, 2H), 1.71 (s, 9H); ^{13}C NMR (101 MHz, Acetone) δ 166.1 (d, J = 251.7 Hz, 2H), 163.1, 151.1, 140.82 (d, J = 12.9 Hz, 2H), 130.72 (d, J = 11.1 Hz, 3H), 113.56 (d, J = 2.0 Hz, 1H), 109.8 (d, J = 23.4 Hz, 1H), 100.3 (d, J = 26.5 Hz, 1H), 60.7, 29.1; ^{19}F NMR (376 MHz, Acetone) δ −105.9; IR (neat) 3424, 2930, 1720, 1655, 1618, 1496, 1381, 1292, 1169, 858, 766 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{12}H_{13}FN_2O_2$: 235.0883, found 235.0883.

*3-(tert-Butyl)-7-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione (**3g**).* TLC R_f = 0.25 (EA:PE = 1:10); white solid; 46.9 mg, 82% yield; mp 197−198 °C; ^{1}H NMR (400 MHz, Acetone) δ 10.13 (s, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.45 (d, J = 8.3 Hz, 1H), 1.73 (s, 9H); ^{13}C NMR (101 MHz, Acetone) δ 163.1, 150.8, 139.2, 134.7 (q, J = 32.6 Hz), 129.0, 123.6 (q, J = 273.2 Hz), 119.6, 118.1 (q, J = 3.6 Hz), 111.3 (q, J = 4.2 Hz), 61.0, 28.9; ^{19}F NMR (376 MHz, Acetone) δ −63.9; IR (neat) 3954, 3773, 3454, 3004, 1716, 1655, 1610, 1493, 1420, 1322, 1262, 1169, 1138, 882, 765, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{13}H_{13}F_3N_2O_2$: 285.0851, found 285.0855.

*3-(tert-Butyl)-7-chloroquinazoline-2,4(1H,3H)-dione (**3h**).* TLC R_f = 0.35 (EA:PE = 1:10); white solid; 33.9 mg, 67% yield; mp 189−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.12 (dd, J = 8.5, 1.7 Hz, 1H), 6.98 (d, J = 1.8 Hz, 1H), 1.78 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 152.8, 140.5, 138.8, 129.7, 123.5, 115.4, 113.8, 62.5, 29.9; IR (neat) 3005, 2990, 2303, 1654, 1467, 1275, 1261, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{12}H_{13}ClN_2O_2$: 251.0588, found 251.0588.

*7-Bromo-3-(tert-butyl)quinazoline-2,4(1H,3H)-dione (**3i**).* TLC R_f = 0.20 (DCM:PE:Et_2O = 10:10:1); white solid; 35.1 mg, 59% yield; mp 199−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.29−7.26 (m, 1H), 7.17 (d, J = 1.6 Hz, 1H), 1.79 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163., 153.0, 138.9, 129.7, 128.9, 126.3, 116.9, 115.8, 62.5, 29.9; IR (neat) 2923, 1709, 1654, 1601, 1412, 1367, 1276, 1261, 1140, 858, 805, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{12}H_{13}BrN_2O_2$: 295.0082, found 295.0083.

*3-(tert-Butyl)-7-nitroquinazoline-2,4(1H,3H)-dione (**3j**).* TLC R_f = 0.35 (DCM:PE:Et_2O = 10:10:1); yellowish solid; 45.3 mg, 86% yield; mp 348−349 °C; ^{1}H NMR (400 MHz, CDCl3) δ 10.19 (s, 1H), 8.20 (d, J = 8.6 Hz, 1H), 7.97 (dd, J = 8.6, 2.0 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 1.81 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 152.6, 151.4, 138.4, 130.2, 121.1, 117.1, 109.5, 63.2, 29.8; IR (neat) 3901, 3688, 2931, 1720, 1667, 1537, 1421, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{12}H_{13}N_3O_4$: 262.0828, found 262.0828.

*3-(tert-Butyl)-7-methylquinazoline-2,4(1H,3H)-dione (**3k**).* TLC R_f = 0.25 (EA:PE = 1:10); yellowish solid; 33.0 mg, 71% yield; mp 173−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.88 (d, J = 8.1 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.78 (s, 1H), 2.40 (s, 3H), 1.80 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 153.5, 145.5, 138.2, 128.0, 124.2, 114.6, 114.0, 61.9, 30.0, 21.9; IR (neat) 3974, 3848, 3800, 3726, 3705, 3635, 2977, 1708, 1654, 1605, 1483, 1412, 1366, 1288, 1177, 1139, 1021, 867, 773 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{13}H_{16}N_2O_2$: 231.1134, found 231.1135.

*3-(tert-Butyl)-7-methoxyquinazoline-2,4(1H,3H)-dione (**3l**).* TLC R_f = 0.20 (EA:PE = 1:3); white solid; 43.2 mg, 87% yield; mp 159−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 6.70 (dd, J = 8.8, 2.3 Hz, 1H), 6.43 (d, J = 2.3 Hz, 1H), 3.85 (s, 3H), 1.79 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 164.0, 153.7, 134.0, 130.0, 111.0, 110.3, 97.1, 61.9, 55.6, 30.1; IR (neat) 3950, 3688, 3026, 2973, 2939, 1707, 1652, 1608, 1517, 1423, 1364, 1216, 1177, 1129, 1021, 832, 773, 708 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{13}H_{16}N_2O_3$: 247.1083, found 247.1087.

*3-(tert-Butyl)-7-(methyl(phenyl)amino)quinazoline-2,4(1H,3H)-dione (**3m**).* TLC R_f = 0.45 (EA:PE = 1:5); white solid; 50.4 mg, 78% yield; mp 193−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.28−7.19 (m, 3H), 6.51 (dd, J = 8.9, 2.1 Hz, 1H), 6.13 (d, J = 2.1 Hz, 1H), 3.35 (s, 3H), 1.71 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 153.8, 153.6, 146.9, 139.7, 123.0, 129.2, 126.6, 126.2, 110.1, 107.2, 96.2, 61.5, 40.3, 30.2; IR (neat) 3506, 3454, 3259, 2922, 1701, 1654, 1625, 1590, 1561, 1493, 1420, 1389, 1276, 1261, 765, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{19}H_{21}N_3O_2$: 322.1556, found 322.1556.

*3-(tert-Butyl)-7-(pyrrolidin-1-yl)quinazoline-2,4(1H,3H)-dione (**3n**).* TLC R_f = 0.30 (EA:PE = 1:5); white solid; 47.7 mg, 83% yield; mp 360−361 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.59 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 6.36 (dd, J = 8.9, 2.1 Hz, 1H), 5.99 (d, J = 2.0 Hz, 1H), 3.26 (t, J = 6.5 Hz, 4H), 1.96 (t, J = 6.5 Hz, 4H), 1.64 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 164.1, 152.2, 151.8, 140.8, 129.1, 108.2, 104.8, 93.8, 60.0, 47.8, 30.3, 25.4; IR (neat) 3415, 3334, 2956, 1735, 1701, 1618, 1483, 1414 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{16}H_{21}N_3O_2$: 286.1556, found 286.1558.

*3-(tert-Butyl)-5-methylquinazoline-2,4(1H,3H)-dione (**3o**).* TLC R_f = 0.30 (EA:PE = 1:10); yellowish solid; 35.3 mg, 76% yield; mp 212−213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.36 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 2.67 (s, 3H), 1.77 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 153.0, 141.1, 139.0, 133.0, 125.8, 115.9, 112.2, 61.1, 29.7, 22.0; IR (neat) 2923, 1710, 1654, 1617, 1561, 1438, 1396, 1275, 1261, 764, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{13}H_{16}N_2O_2$: 231.1134, found 231.1139.

*3-(tert-Butyl)-5-iodoquinazoline-2,4(1H,3H)-dione (**3p**).* TLC R_f = 0.40 (EA:PE = 1:5); yellowish solid; 58.5 mg, 85% yield; mp 219−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.13 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 1.76 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 152.5, 139.4, 136.7, 134.1, 117.5, 114.8, 93.5, 61.9, 29.6; IR (neat) 3187, 3119, 2977, 2924, 1715, 1665, 1600, 1583, 1430, 1363, 1276, 1224, 1128, 790 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{12}H_{13}IN_2O_2$: 342.9944, found 342.9944.

*3-(tert-Butyl)-6-fluoroquinazoline-2,4(1H,3H)-dione (**3q**).* TLC R_f = 0.35 (EA:PE = 1:10); white solid; 34.5 mg, 73% yield; mp 213-214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.33−7.27 (m, 1H), 7.08 (td, J = 8.1, 4.8 Hz, 1H), 1.77 (s, 9H); ^{13}C NMR (101 MHz, CDCl3) δ 163.3, 151.5, 148.6 (d, J = 247.7 Hz), 127.2 (d, J = 14.1 Hz), 123.4 (d, J = 3.8 Hz), 122.3 (d, J = 6.4 Hz), 119.3 (d, J = 16.6 Hz), 118.9 (d, J = 1.7 Hz), 62.4, 29.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −135.3; IR (neat) 2923, 1715, 1660, 1458, 1387, 1275, 1261, 764, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{12}H_{13}FN_2O_2$: 235.0883, found 235.0885.

*3-(tert-Butyl)-6-chloroquinazoline-2,4(1H,3H)-dione (**3r**).* TLC R_f = 0.40 (EA:PE = 1:10); yellowish solid; 30.8 mg, 61% yield; mp 171−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.99 (d, J = 2.3 Hz, 1H), 7.48 (dd, J = 8.5, 2.3 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 1.77 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.2, 136.3, 134.5, 128.4, 127.8, 118.1, 115.3, 62.5, 29.8; IR (neat) 3747, 3006, 1275, 1261, 764, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{12}H_{13}ClN_2O_2$: 251.0588, found 251.0587.

*3-(tert-Butyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione (**3s**).* TLC R_f = 0.20 (EA:PE = 1:10); yellowish solid; 48.7 mg, 85% yield; mp 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.32 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 1.80 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.8, 140.3, 131.0 (q,

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J = 3.5 Hz), 126.2 (q, J = 4.1 Hz), 125.4 (q, J = 34.1 Hz), 122.3, 116.8, 114.6, 62.8, 29.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.2; IR (neat) 3954, 3800, 3602, 3418, 2926, 1734, 1671, 1618, 1367, 1320, 1299, 1256, 1129, 1067, 841, 786 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{13}H_{13}F_3N_2O_2$: 285.0851, found 285.0859.

*3-(tert-Butyl)-6-methylquinazoline-2,4(1H,3H)-dione (**3t**).* TLC R_f = 0.20 (EA:PE = 1:10); yellowish solid; 38.6 mg, 83% yield; mp 189−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.80 (s, 1H), 7.35 (dd, J = 8.2, 1.2 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 2.36 (s, 3H), 1.79 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 153.4, 136.0, 135.4, 132.5, 127.6, 116.8, 114.0, 61.9, 30.0, 20.8; IR (neat) 3935, 3357, 2974, 1719, 1655, 1519, 1427, 1365, 1275, 1261, 822, 764, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{13}H_{16}N_2O_2$: 231.1134, found 231.1137.

*3-(tert-Butyl)-6-morpholinoquinazoline-2,4(1H,3H)-dione (**3u**).* TLC R_f = 0.50 (EA:PE = 1:1); yellowish solid; 52.8 mg, 87% yield; mp 189−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.47 (d, J = 2.6 Hz, 1H), 7.21 (dd, J = 8.8, 2.7 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 3.90−3.83 (m, 4H), 3.18−3.10 (m, 4H), 1.78 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 152.8, 147.4, 131.8, 124.3, 117.5, 115.0, 113.2, 66.8, 62.0, 50.0, 30.0; IR (neat) 3207, 2962, 2924, 2854, 1710, 1660, 1622, 1516, 1431, 1368, 1264, 1121, 892, 813 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{16}H_{21}N_3O_3$: 302.1505, found 302.1488.

*3-(tert-Butyl)-6-(methyl(phenyl)amino)quinazoline-2,4(1H,3H)-dione (**3v**).* TLC R_f = 0.45 (EA:PE = 1:5); yellowish solid; 52.4 mg, 81% yield; mp 185−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.64 (d, J = 2.5 Hz, 1H), 7.27 (dt, J = 8.1, 6.5 Hz, 3H), 6.97 (t, J = 6.9 Hz, 3H), 6.89 (d, J = 8.7 Hz, 1H), 3.32 (s, 3H), 1.79 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 152.9, 148.9, 144.8, 132.7, 129.4, 128.5, 121.6, 120.3, 118.1, 117.8, 114.9, 62.1, 40.6, 30.0; IR (neat) 3201, 3065, 3030, 2955, 2925, 1712, 1662, 1625, 1515, 1496, 1433, 1367, 1284, 1188, 1111, 695 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{19}H_{21}N_3O_2$: 322.1556, found 322.1552.

*3-(tert-Butyl)-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione (**3w**).* TLC R_f = 0.10 (EA:PE = 1:3); yellowish solid; 37.3 mg, 67% yield; mp 180−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.40 (s, 1H), 6.45 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 1.80 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 155.0, 153.6, 145.7, 133.8, 109.0, 108.2, 96.3, 62.1, 56.3, 56.2, 30.2; IR (neat) 3345, 3145, 2938, 1704, 1650, 1510, 1423, 1275, 1260, 764, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{14}H_{18}N_2O_4$: 277.1189, found 277.1197.

*3-(tert-Butyl)benzo[g]quinazoline-2,4(1H,3H)-dione (**3x**).* TLC R_f = 0.10 (EA:PE = 1:10); yellowish solid; 40.2 mg, 75% yield; mp 223−224 °C; ^{1}H NMR (400 MHz, Acetone) δ 9.96 (s, 1H), 8.57 (s, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.60−7.55 (m, 1H), 7.52 (s, 1H), 7.47−7.41 (m, 1H), 1.75 (s, 9H); ^{13}C NMR (101 MHz, Acetone) δ 164.0, 151.1, 136.6, 134.9, 129.4, 129.2, 129.0, 128.8, 126.7, 124.7, 118.0, 109.1, 60.4, 29.1; IR (neat) 3953, 3601, 3508, 3369, 1703, 1660, 1417, 1396, 1188, 873, 779, 761, 737 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{16}H_{16}N_2O_2$: 267.1134, found 267.1134.

*3-(tert-Butyl)-6-methoxyquinazoline-2,4(1H,3H)-dione (**3y**).* TLC R_f = 0.30 (EA:PE = 1:5); yellowish solid; 40.7 mg, 82% yield; mp 186−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.46 (d, J = 2.8 Hz, 1H), 7.15 (dd, J = 8.8, 2.9 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 3.84 (s, 3H), 1.80 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 155.5, 153.0, 132.3, 123.9, 117.5, 115.5, 108.9, 62.1, 55.8, 30.0; IR (neat) 2958, 2925, 1713, 1659, 1515, 1368, 1265, 1189, 1109, 1034, 822, 754, 680 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{13}H_{16}N_2O_3$: 247.1083, found 247.1089.

*3-(tert-Butyl)-8-methoxyquinazoline-2,4(1H,3H)-dione (**3y′**).* TLC R_f = 0.30 (EA:PE = 1:5); yellowish solid; 21.4 mg, 43% yield; mp 180−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.07 (t, J = 7.9 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 3.93 (s, 3H), 1.76 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 151.6, 145.1, 128.5, 122.3, 119.1, 117.4, 113.7, 61.9, 56.1, 29.9; IR (neat) 2945, 2925, 1716, 1656, 1520, 1270, 1109, 1035, 820, 754 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{13}H_{16}N_2O_3$: 247.1083, found 247.1089.

*6-Bromo-3-(tert-butyl)quinazoline-2,4(1H,3H)-dione (**3z**).* TLC R_f = 0.30 (EA:PE = 1:10); yellowish solid; 33.9 mg, 57% yield; mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.14 (d, J = 1.8 Hz, 1H), 7.62 (dd, J = 8.5, 2.1 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 1.77 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 152.5, 137.2, 136.8, 130.8, 118.5, 115.7, 115.4, 62.5, 29.8; IR (neat) 3402, 2932, 1735, 1719, 1701, 1685, 1654, 1617, 1561, 1512, 1500, 1483, 1421, 1366, 1276, 750 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{12}H_{13}BrN_2O_2$: 295.0082, found 295.0082.

*8-Bromo-3-(tert-butyl)quinazoline-2,4(1H,3H)-dione (**3z′**).* TLC R_f = 0.50 (EA:PE = 1:10); yellowish solid; 18.4 mg, 31% yield; mp 169−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.8 Hz, 1H), 7.83 (s, 1H), 7.72 (dd, J = 7.9, 1.1 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H), 1.75 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 150.5, 137.0, 135.9, 127.8, 123.5, 118.2, 107.4, 62.3, 29.7; IR (neat) 3392, 2930, 1726, 1716, 1680, 1620, 1555, 1512, 1500, 1480, 1370, 1266, 755 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{12}H_{13}BrN_2O_2$: 295.0082, found 295.0080.

*(3aS,3bR,11bS,13aS)-8-(tert-Butyl)-13a-methyl-3,3a,4,5,8,10,11b,12,13,13a-decahydro-1H-cyclopenta[5,6]-naphtho[2,1-g]quinazoline-1,7,9(2H,3bH)-trione (**5a**).* TLC R_f = 0.55 (EA:PE = 1:1); yellowish solid; 57.6 mg, 73% yield; mp 233−234 °C; $[\alpha]_D^{25}$ = +91.2 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.71 (s, 1H), 6.90 (s, 1H), 2.99−2.87 (m, 2H), 2.52 (dd, J = 18.7, 8.6 Hz, 1H), 2.36−2.28 (m, 2H), 2.20−1.95 (m, 5H), 1.78 (s, 9H), 1.60−1.47 (m, 5H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.4, 164.4, 153.2, 147.5, 136.0, 131.7, 127.7, 114.9, 110.5, 61.9, 50.6, 47.8, 44.6, 37.6, 35.8, 31.5, 30.0, 28.5, 26.3, 25.5, 21.6, 13.8; IR (neat) 3196, 3111, 3061, 3028, 2251, 1740, 1712, 1659, 1629, 1421, 1366, 1187, 913, 732 cm^{-1}; HRMS (ESI) ([M − H]$^+$) Calcd for $C_{24}H_{30}N_2O_3$: 393.2178, found 393.2162. The absolute configuration of compound **5a** was determined from the start material (8*R*,9*S*,13*S*,14*S*)-3-hydroxy-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one (CAS# 53−16−7) and compound **4a**. The Procedure for the Preparation involved reaction of compound **5a** was found to proceed with stereo retention according to the existing reported in the literature.[17]

*2,2,2-Trichloroethyl (2-(tert-butylcarbamoyl)phenyl)carbamate (**7a**).* TLC R_f = 0.50 (EA:PE = 1:10); white solid, 57.4 mg, 78% yield; mp 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.06 (s, 1H), 4.82 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 152.0, 138.8, 132.2, 126.6, 122.5,121.9, 120.3, 95.4, 74.3, 52.2, 28.8. IR (neat) 3351, 2968, 2927, 1751, 1648, 1590, 1522, 1448, 1208, 1114, 756 cm^{-1}; HRMS (ESI) ([M + Na]$^+$) Calcd for $C_{14}H_{17}Cl_3N_2O_3$: 389.0202, found 389.0192.[4f]

Preparation of Cyclometalated Complex and Catalytic Reaction. Complex **6** was prepared according to literature report.[21] To a screw capped vial equipped with a spinvane triangular-shaped Teflon stirbar were added benzamide (**1a**, 35.4 mg, 0.2 mmol), Troc azides (**2a**, 52.4 mg, 0.24 mmol), Complex **6** (5.2 mg, 4 mol %), $AgNTf_2$ (12.4 mg, 16 mol %), CsOAc (115.2 mg, 3 equiv) and chlorobenzene (2 mL) under N_2 conditions. The reaction mixture was stirred in a preheated oil bath at 140 °C for 24 h. The reaction was cooled to room temperature, filtered through a pad of Celite and then washed with CH_2Cl_2 (10 mL × 3). The solvents were removed under reduced pressure, and the crude yield was measured by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

Intermolecular Competition Experiments. To a screw capped vial equipped with a spinvane triangular-shaped Teflon stirbar were added *N*-tertbutyl-4-(trifluoromethyl)benzamide (**1g**, 49.0 mg, 0.2 mmol), *N*-tertbutyl-4-(methoxyphenyl)benzamide (**1l**, 41.5 mg, 0.2 mmol), Troc azides (**2a**, 52.4 mg, 0.24 mmol), $[IrCp^*Cl_2]_2$ (6.4 mg, 4 mol %), $AgNTf_2$ (12.4 mg, 16 mol %), CsOAc (115.2 mg, 3 equiv) and chlorobenzene (2 mL) under N_2 conditions. The reaction mixture was stirred in an oil bath at 140 °C for 12 h with vigorous stirring. The reaction mixture was cooled to room temperature, filtered through a pad of Celite and then washed with CH_2Cl_2 (10 mL × 3). The solvents were removed under reduced pressure and ^{1}H NMR yield of the desired product was determined by integration using CH_2Br_2 as an internal standard.

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Synthetic Transformations of Compound 3a. In a screw capped vial equipped with a spinvane triangular-shaped Teflon stirbar was placed compound **3a** (43.7 mg, 0.2 mmol) in Phosphoryl trichloride (2 mL), and then the solution were slowly added DIPEA (33.1 μL, 0.2 mmol) under air conditions. The reaction mixture was stirred at 100 °C for 4 h, then allow to cool to room temperature, and poured on ice. The water layer was extracted with EtOAc (10 mL × 3). The organic layer was dried on $MgSO_4$, and the solvent was evaporated. Purification by flash column chromatography with DCM as the eluent provided the compound **8** as a white solid in 93% yield (37.0 mg).

*2,4-Dichloroquinazoline (**8**).* TLC R_f = 0.50 (DCM:PE = 2:1); white solid, 37.0 mg, 93% yield; mp 119−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.05−7.95 (m, 2H), 7.75 (ddd, *J* = 8.2, 5.3, 2.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 155.2, 152.4, 136.1, 129.2, 128.0, 126.1, 122.4; IR (neat) 2925, 1611, 1544, 1480, 1446, 1371, 1340, 1267, 1185, 766, cm^{-1}.[22]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00818.

Experimental details, characterization data for the products, and NMR spectra. (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews of C−H amination through a C−H insertion pathway, see: (a) Starkov, P.; Jamison, T. F.; Marek, I. *Chem. - Eur. J.* **2015**, *21*, 5278. (b) Driver, T. G. *Nat. Chem.* **2013**, *5*, 736. (c) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911. (d) Dequirez, G.; Pons, V.; Dauban, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 7384. (e) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926. (f) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (g) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (h) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

(2) For reviews of C−H amination through a C−H activation pathway, see: (a) Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, *6*, 610. (b) Subramanian, P.; Rudolf, G. C.; Kaliappan, K. P. *Chem. - Asian J.* **2016**, *11*, 168. (c) Louillat, M. L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. (d) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (e) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29. (f) Song, G. Y.; Wang, F.; Li, X. W. *Chem. Soc. Rev.* **2012**, *41*, 3651. (g) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068.

(3) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040.

(4) For examples of metal catalyzed C−H amination using azides as amino sources. Sulfonyl Azides: (a) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 4141. (b) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 2492. (c) Kim, J. Y.; Park, S. H.; Ryu, J.; Hwan, S.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110 and references cited therein. Carbonyl azides: (d) Peng, J.; Xie, Z.; Chen, M.; Wang, J.; Zhu, Q. *Org. Lett.* **2014**, *16*, 4702. (e) Shin, K.; Ryu, J.; Chang, S. *Org. Lett.* **2014**, *16*, 2022. (f) Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. *J. Am. Chem. Soc.* **2013**, *135*, 12861. Porphoryl azides: (g) Pan, C. D.; Jin, N.; Zhang, H. L.; Han, J.; Zhu, C. J. *J. Org. Chem.* **2014**, *79*, 9427. (h) Kim, H.; Park, J.; Kim, J. G.; Chang, S. *Org. Lett.* **2014**, *16*, 5466. Aryl azides: (i) Ali, M. A.; Yao, X.; Li, G.; Lu, H. *Org. Lett.* **2016**, *18*, 1386. (j) Wang, N. C.; Li, R. H.; Li, L. N.; Xu, S. S.; Song, H. B.; Wang, B. Q. *J. Org. Chem.* **2014**, *79*, 5379. (k) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 9904. Alkyl azides: (l) Zhang, T.; Hu, X.; Wang, Z.; Yang, T. T.; Sun, H.; Li, G.; Lu, H. *Chem. - Eur. J.* **2016**, *9*, 2920. (m) Shin, K.; Chang, S. *J. Org. Chem.* **2014**, *79*, 12197. (n) Shin, K.; Baek, Y.; Chang, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8031.

(5) Only one example was reported using 2,2,2-trichloroethoxycarbonyl azide as the amino source in $[IrCp^*Cl_2]_2$/$AgNTf_2$ cataltyzed C−H amidation of benzamide, forming **7a** in 23% yield, see ref 4f.

(6) For selected recent reviews: (a) Ardkhean, R.; Caputo, D. F. J.; Morrow, S. M.; Shi, H.; Xiong, Y.; Anderson, E. A. *Chem. Soc. Rev.* **2016**, *45*, 1557. (b) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. *Chem. Rev.* **2015**, *115*, 5301. (c) Zhang, B.; Studer, A. *Chem. Soc. Rev.* **2015**, *44*, 3505.

(7) (a) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223. (b) Rivero, I. A.; Espinoza, K.; Somanathan, R. *Molecules* **2004**, *9*, 609.

(8) For selected recent examples, see: (a) Akgun, H.; Yilmaz, D. U.; Atalay, R. C.; Gozen, D. *Lett. Drug. Des. Discovery* **2016**, *13*, 64. (b) Ji, Q. G.; Wang, D. W.; Lin, H. Y.; Cao, R. J.; Ming, Z. Z.; Chen, T.; Hao, G. F.; Yang, W. C.; Yang, G. F. *Pest Manage. Sci.* **2015**, *71*, 1122. (c) Yang, D.; Deng, Q.; Ge, Z. Q.; Yuan, L. J. *Med. Chem. Res.* **2014**, *23*, 2169. (d) Wang, D. W.; Lin, H. Y.; Cao, R. J.; Yang, S. G.; Chen, Q.; Hao, G. F.; Yang, W. C.; Yang, G. F. *J. Agric. Food Chem.* **2014**, *62*, 11786. (e) Zhou, X. L.; Xie, X. L.; Liu, G. *Mol. Diversity* **2013**, *17*, 197.

(9) (a) Andrus, M. B.; Mettath, S. N.; Song, C. *J. Org. Chem.* **2002**, *67*, 8284. (b) Mohri, S. *Yuki Gosei Kagaku Kyokaishi* **2001**, *59*, 514. (c) Goto, S.; Tsuboi, H.; Kagara, K. *Chem. Exp.* **1993**, *8*, 761. (d) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49. (e) Manoury, P. M.; Binet, J. L.; Dumas, A. P.; Lefsvre-Borg, F.; Cavero, I. *J. Med. Chem.* **1986**, *29*, 19.

(10) For recent examples: (a) Jiarong, L.; Xian, C.; Daxin, S.; Shuling, M.; Qing, L.; Qi, Z.; Jianhong, T. *Org. Lett.* **2009**, *11*, 1193. (b) Dou, G.; Wang, M.; Shi, D. *J. Comb. Chem.* **2009**, *11*, 151. (c) Li, Z.; Huang, H.; Sun, H.; Jiang, H.; Liu, H. *J. Comb. Chem.* **2008**, *10*, 484.

(11) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830.

(12) $TrocN_3$ was readily synthesized from the commercially available $CCl_3CH_2OC(O)Cl$ and NaN_3; it decomposes at 157 °C based on DSC, see: Lu, H.; Subbarayan, V.; Tao, J.; Zhang, X. P. *Organometallics* **2010**, *29*, 389.

(13) (a) Lu, H.; Li, C. Q.; Jiang, H.; Lizardi, C. L.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 7028. (b) Lu, H. J.; Zhang, X. P. *Chem. Soc. Rev.* **2011**, *40*, 1899.

(14) (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) Punji, B.; Song, W. F.; Shevchenko, G. A.; Ackermann, L. *Chem. - Eur. J.* **2013**, *19*, 10605. (c) Schinkel, D.-C. M.; Marek, I.; Ackermann, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 3977. (d) Webb, N. J.; Marsden, S. P.; Raw, S. A. *Org. Lett.* **2014**, *16*, 4718. (e) Zhang, Y.; Wang, D. H.; Cui, S. L. *Org. Lett.* **2015**, *17*, 2494.

(15) Yoo, E.; Salunke, D. B.; Sil, D.; Guo, X.; Salyer, A. C. D.; Hermanson, A. R.; Kumar, M.; Malladi, S. S.; Balakrishna, R.; Thompson, W. H.; Tanji, H.; Ohto, U.; Shimizu, T.; David, S. A. *J. Med. Chem.* **2014**, *57*, 7955.

(16) For selected examples: betrixaban (CID 10275777) and tariquidar (CID 148201).

(17) (a) Feng, C.; Loh, T.-P. *Org. Lett.* **2014**, *16*, 3444. (b) Rosen, B. R.; Simke, L. R.; Thuy-Boun, P. S.; Dixon, D. D.; Yu, J.-Q.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7317.

(18) Houlden, C.; Hutchby, M.; Bailey, C.; Ford, J.; Tyler, S.; Gagne, M.; Lloyd-Jones, G.; Booker-Milburn, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830.

DOI: 10.1021/acs.joc.6b00818
J. Org. Chem. 2016, 81, 4898−4905

(19) Au, T.; Badyar, A.; Boyd, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2884.
(20) Roberts, B.; Liptrot, D.; Luker, T.; Stocks, M.; Barber, C.; Webb, N.; Dods, R.; Martin, B. *Tetrahedron Lett.* **2011**, *52*, 3793.
(21) Kim, H.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 5904.
(22) (a) Verbeeck, S.; Herrebout, W. A.; Gulevskaya, A. V.; Veken, B.; Maes, B. U. W. *J. Org. Chem.* **2010**, *75*, 5126. (b) Yoo, E.; Salunke, D.; Sil, D.; Guo, X.; Salyer, A.; Hermanson, A.; Kumar, M.; Malladi, S.; Balakrishna, R.; Thompson, W.; Tanji, H.; Ohto, U.; Shimizu, T.; David, S. *J. Med. Chem.* **2014**, *57*, 7955.

DOI: 10.1021/acs.joc.6b00818
J. Org. Chem. 2016, 81, 4898−4905