


# C–H and N–H Bond Annulation of Benzamides with Isonitriles Catalyzed by Cobalt(III)

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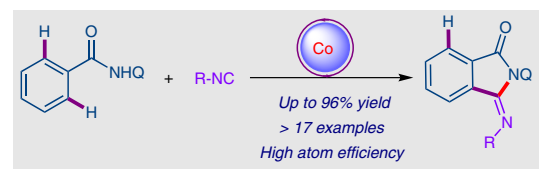
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In memory of Prof. Shunsuke Murahashi for pioneering work in cobalt-catalyzed C–H bond functionalization



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**Abstract** A simple efficient, atom-economical procedure was developed for the cobalt-catalyzed C–H bond annulation of benzamides with isonitriles under mild conditions. The reaction tolerates a variety of functional group including heterocycles. Diverse 3-(alkylimino)-2-quinolin-8-yl-2,3-dihydro-1*H*-isoindol-1-ones were synthesized using isonitriles as the C1 source through C–H and N–H bond annulation via C–H bond activation in a ‘green’ solvent. Vinylamides were also used similarly with *tert*-butyl isonitrile to give 3-(*tert*-butylimino)-1-quinolin-8-yl-1*H*-pyrrol-2(5*H*)-ones.

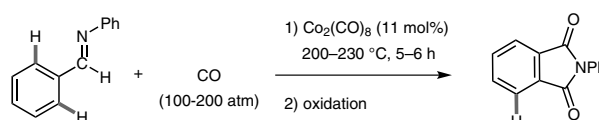
**Key words** cobalt, annulation, isonitrile, C–H activation, iminoisoindolinone

C–H bond functionalization has become an integral part of various transformations ranging from simple to complex molecules in a few steps.<sup>1</sup> Although these transformations operate well with the utilization of a directing group strategy, improved synthetic applications have led to significant developments in this field. Among the directing groups, amides have proven to improve the synthetic applications through C–H bond activation with good reactivity and selectivity.<sup>1f,2</sup> Since the early 2000s, Noble metals have been exploited for this process. However, due to economical concerns, the use of inexpensive first-row transition metals for C–H bond functionalizations has become an emerging target.<sup>3</sup> In 1955, Murahashi reported the first cobalt-catalyzed carbonylation of azobenzene via C–H bond activation using a low valent cobalt–carbonyl complex (Scheme 1, Ia).<sup>4</sup> In a different approach, Daugulis reported the C–H carbonylative annulation of benzamide using high valent Co(III) under mild conditions (Scheme 1, Ib).<sup>5</sup> In 2017, our group<sup>6a</sup> and the Gaunt group<sup>6b</sup> independently reported the carbonylative cyclization of aliphatic amides using a similar direct-

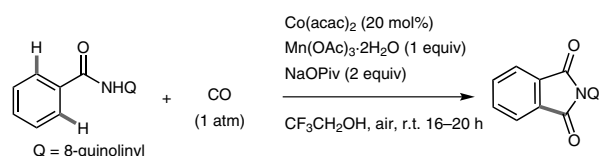
ing group strategy (Scheme 1, II). In continuation of our previous work, we envisaged replacing carbon monoxide by isonitriles as the C1 source for the formal [4+1] C(sp<sup>2</sup>)–H bond annulation of benzamides (Scheme 1, III). Isonitriles are versatile building blocks and a unique C1 source, which facilitates transformations that could not be achieved with carbon monoxide with very high atom efficiency.<sup>7</sup> Only

## I) Cobalt-catalyzed carbonylation of C(sp<sup>2</sup>)–H bonds

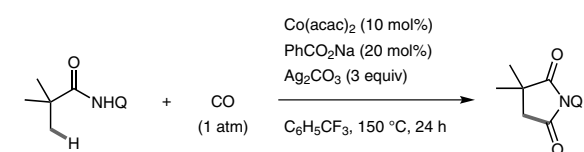
### a) Co(0)-catalyzed carbonylation of aldimine:<sup>4</sup>



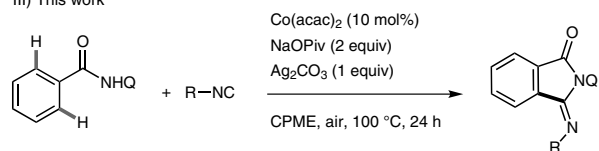
### b) In situ Co(III)-catalyzed carbonylation of benzamide:<sup>5</sup>



## II) Previous work: Cobalt-catalyzed carbonylation of C(sp<sup>3</sup>)–H bonds<sup>6a,b</sup>



## III) This work



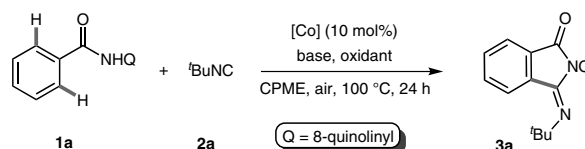
**Scheme 1** Overview of Co-catalysis for formal [4+1] C–H bond annulation

very few examples were reported for the annulation of benzamide with isocyanides under oxidative conditions.<sup>8</sup> Within our program for C–H bond functionalization using first row transition metal catalysts,<sup>6a,9–11</sup> we wish to report the cobalt-catalyzed formal [4+1] annulation of benzamides and isocyanides using CPME as a ‘green’ solvent under mild conditions.<sup>12,13</sup>

We began our investigation by screening various reaction parameters using the eco-friendly solvent cyclopentyl methyl ether (CPME) as the reaction medium, with benzamide **1a** and *tert*-butyl isocyanide (**2a**) as model substrates; the results are summarized in Table 1. Iminoisoindolinone **3a** was isolated in 80% yield, when cobalt(II) acetate was used as a catalyst precursor, along with sodium pivalate as the base and silver carbonate as the oxidant at 100 °C for 24 h (entry 1). Reduction in the amount of silver carbonate significantly lower the yield of **3a**, suggesting that excess oxidant is required to access high product formation (entry 2). The reaction was performed under oxygen and air atmo-

spheres. Both gave similar yields as to that obtained under argon (entries 3 and 4). Replacement of silver carbonate with another commonly used oxidant in cobalt catalysis, such as Mn(OAc)<sub>3</sub>, gave a lower yield (entry 5). Several cobalt catalysts were screened for further improvement. Among them, Co(acac)<sub>2</sub> is an effective catalyst that provides complete conversion with the isolated yield of **3a** in 95% (entries 6–9). Changing CPME to another eco-friendly solvent, dimethyl carbonate, gave a lower yield (entry 10). Further lower the quantity of oxidant or base gave satisfactory results (entries 11–13). Our control experiments reveal that the catalyst, base, oxidant, and quinoline for bidentate chelation were crucial for the reaction to proceed (entries 14–18). Other solvents were not efficient under the standard reaction conditions. With the best reaction conditions in hand, we next examined the scope of amides and results are given in Scheme 2.

**Table 1** Reaction Optimization<sup>a</sup>



Entry	[Co]	Base (equiv)	Oxidant (equiv)	Yield (%)
1	Co(OAc) <sub>2</sub>	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (2)	80 <sup>b</sup>
2	Co(OAc) <sub>2</sub>	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	53 <sup>b</sup>
3	Co(OAc) <sub>2</sub>	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	78 <sup>c</sup>
4	Co(OAc) <sub>2</sub>	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	85
5	Co(OAc) <sub>2</sub>	NaOPiv (2)	Mn(OAc) <sub>3</sub> (1)	29 <sup>c</sup>
6	Co(acac) <sub>2</sub>	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	95
7	Co(acac) <sub>3</sub>	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	41
8	Co(acac) <sub>3</sub>	–	Ag <sub>2</sub> CO <sub>3</sub> (2)	70
9	Cp*Co(CO)I <sub>2</sub>	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	58
10	Co(OAc) <sub>2</sub>	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	70 <sup>d</sup>
11	Co(acac) <sub>2</sub>	NaOPiv (1)	Ag <sub>2</sub> CO <sub>3</sub> (1)	78
12	Co(acac) <sub>2</sub>	NaOPiv (1)	Ag <sub>2</sub> CO <sub>3</sub> (0.5)	68
13	Co(acac) <sub>2</sub>	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (0.5)	80
14	Co(acac) <sub>2</sub>	NaOPiv (2)	–	17
15	Co(acac) <sub>2</sub>	–	Ag <sub>2</sub> CO <sub>3</sub> (1)	21
16	–	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	n.d.
17	Co(acac) <sub>2</sub>	NaOPiv (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	n.d. <sup>e</sup>
18	Co(acac) <sub>2</sub>	NaOPiv (2)	AgNO <sub>3</sub> (1)	41

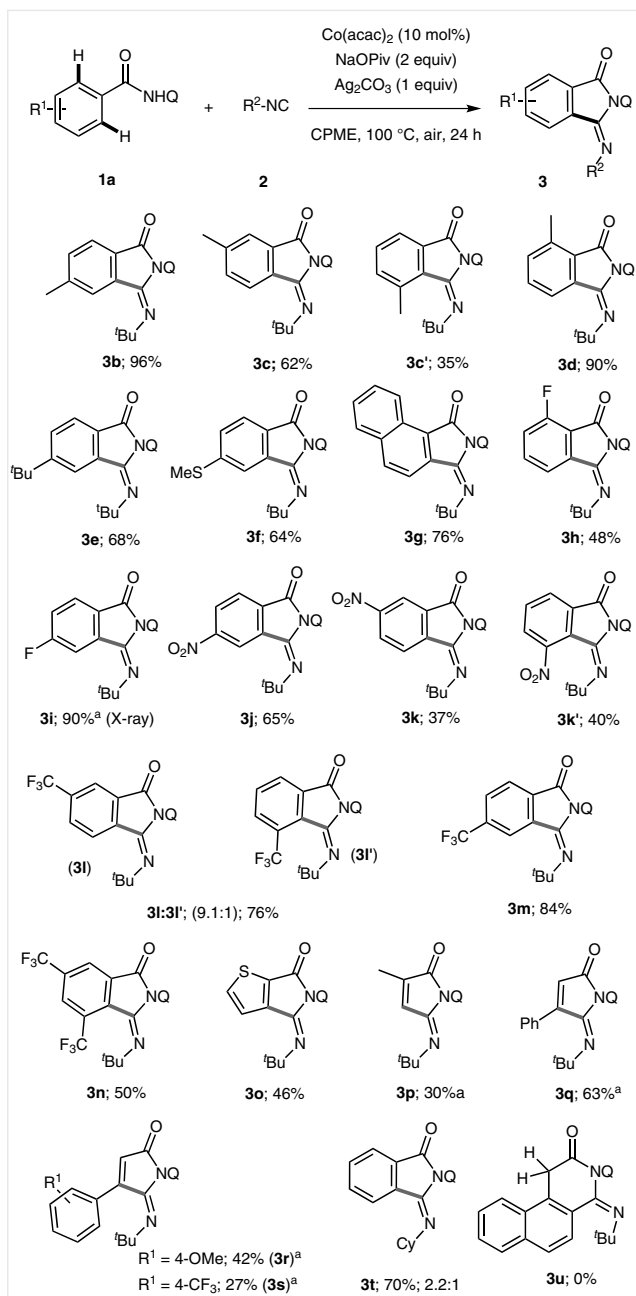
<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Co] (0.02 mmol), base (0.2–0.4 mmol), oxidant (0.1–0.4 mmol), CPME (1 mL), air atmosphere, 100 °C (oil bath temperature), 24 h; n.d. = not determined.

<sup>b</sup> Reaction performed under argon atmosphere.

<sup>c</sup> Under O<sub>2</sub> atmosphere.

<sup>d</sup> Dimethyl carbonate (DMC) (1 mL) was used as solvent.

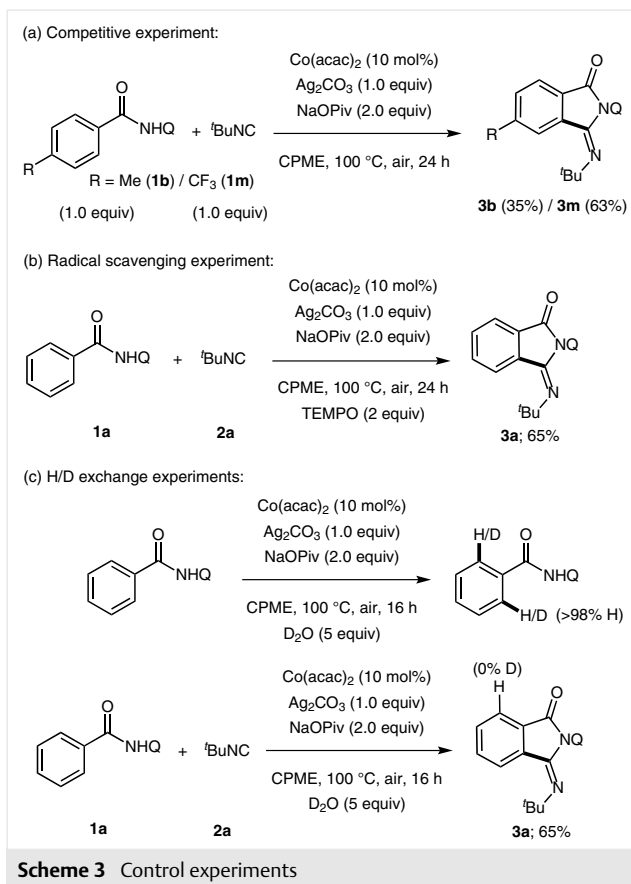
<sup>e</sup> PhCONHOMe was used as amide instead of **1a**.



A methyl substituent at *o*-, *m*-, and *p*-positions of the arene gave good to excellent yields of **3b–d**. Arylamides with electron-rich (*t*-Bu, SMe) and electron-deficient (F, CF<sub>3</sub>, Ar) functional groups at different positions work equally well giving **3e–n** in moderate to excellent yields. We next examined *m*-substituted benzamides, which possess two electronically and sterically biased *ortho*-protons. Functionalization of *ortho*-C–H bonds provides two regioisomers, of which the major product **3c,l** obtained is from the sterically less hindered C–H bond. On the other hand, a 1:1

ratio of **3k/3k'** was obtained, when the NO<sub>2</sub> group was placed at the *meta* position perhaps due to stereoelectronic reasons. Annulation with *tert*-butyl isocyanide (**2a**) was further extended to amides derived from thiophene-2-carboxylic acid, which led to 46% of **3o**. Next we extended the scope to access  $\gamma$ -lactams through  $\beta$ -C–H bond activation by employing  $\alpha,\beta$ -unsaturated amides derived from the parent carboxylic acids. Gratifyingly, all substituted vinylamides provide the cycloaddition products **3p–s** however with moderate efficiency. Further, cyclohexyl isocyanide (**2b**) was used in place of *tert*-butyl isocyanide (**2a**) with benzamide **1a** under standard conditions provides corresponding iminoisoindolinone **3t** in good yield as a mixture of *E/Z*-stereoisomers in 2.2:1 ratio.

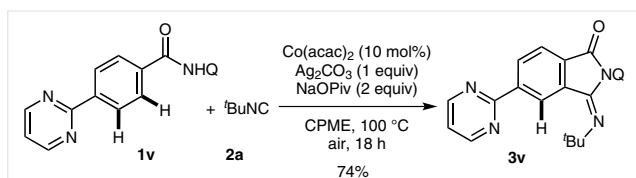
Notably, benzamide **1u** derived from naphthaleneacetic acid did not give the cycloaddition product **3u**, this may be due to the incompetence to form a six-membered cobaltacycle. To understand the reaction pathways, some control experiments were carried out and the results are presented in Scheme 3. A competitive experiment was performed with electron-rich and -poor amides. An equimolar amount of amide **1b** and **1m** was subjected under standard conditions, 63% of **3m** and 35% of **3b** was isolated, suggesting that electrophilic activation is unlikely (Scheme 3, a). A radical trapping experiment was carried out with TEMPO (2 equiv)



Scheme 3 Control experiments

and this gave 65% of **3a**, indicating that the  $1e^-$  process may not be involved (Scheme 3, b). To shed light on the cleavage of C–H bonds, further H/D exchange experiments were conducted using  $D_2O$  as the deuterium source. Under the standard conditions, no deuterium incorporation was observed with or without **2a** indicating that the C–H bond cleavage is irreversible (Scheme 3, c).

Finally, we have also shown the selective C–H bond functionalization of amide containing strongly coordinating pyrimidine **1v** provide the expected iminoisoindolinone **3v** in 74% yield (Scheme 4).



**Scheme 4** Overcoming the limitation of strongly chelating directing groups

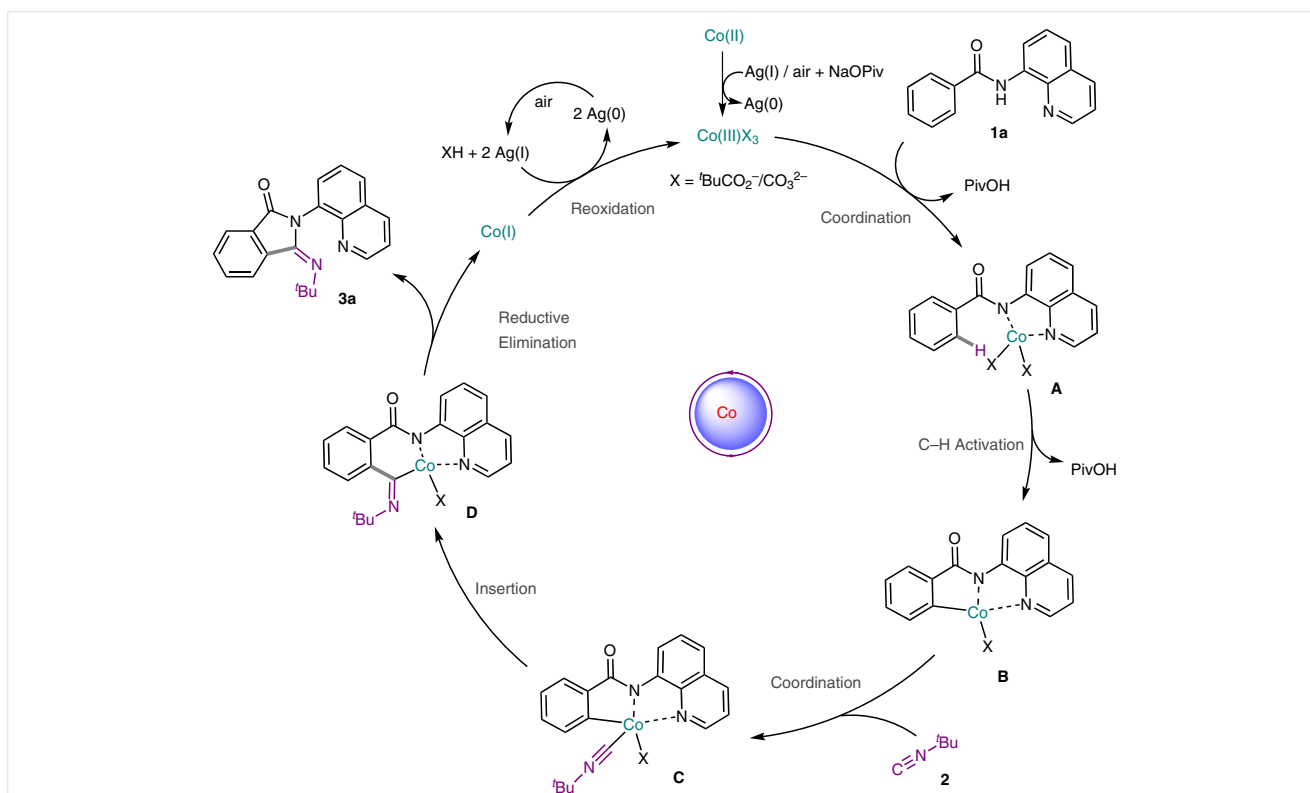
Based on the above experiment, a plausible mechanism is proposed in Scheme 5.

Initial oxidation of Co(II) to Co(III) is facilitated by silver(I) under air followed by N,N-coordination of benzamide **1a** leading to intermediate **A**, which undergoes irreversible

C–H bond activation that leads to cobaltacycle **B**. Further coordination of isocyanide **2a** with **B** followed by insertion leads to intermediate **D**. Reductive elimination of **D** gives iminoisoindolinone **3a** along with Co(I). Co(III) is regenerated by oxidation of Co(I) mediated by silver(I) for the next catalytic cycle. Silver(I) will possibly be recycled by oxidation of Ag(0) under air/oxygen.

In conclusion, we have reported a new method for the preparation of isoindolinone, a highly useful intermediates for bioactive compounds,<sup>14</sup> catalyzed by high-valent cobalt(III) under mild conditions. The scope of the reaction reveals that the reaction is regioselective with very high functional group tolerance. Our preliminary control experiments suggest that C–H bond cleavage is irreversible and the reaction did not proceed through  $1e^-$  pathway. Also, stoichiometric oxidant was necessary to re-oxidize the Co(I) to Co(III) in order to regenerate active catalyst. Further isolation of reactive organometallic intermediates is currently pursued in our laboratory.

Unless otherwise mentioned, all catalytic reactions were carried out under an  $O_2$ /air atmosphere; starting materials were prepared under an argon atmosphere. HPLC grade  $CH_2Cl_2$  and reagent grade CPME and DMC were used as such from commercial sources, as were all other chemicals.  $^1H$  and  $^{13}C$  NMR were recorded on a Jeol (400 and 500 MHz) using  $CDCl_3$  with the solvent signals used as references ( $CDCl_3$ :



**Scheme 5** Proposed mechanism

$\delta_c = 77$ ; residual  $\text{CHCl}_3$  in  $\text{CDCl}_3$ :  $\delta_H = 7.26$ ). All the reactions were monitored by analytical TLC using commercial aluminum sheets pre-coated with silica gel. Chromatography was conducted on silica gel (Merck, 100–200 mesh). ESI-MS was recorded on a Waters-Micro-mass Quattro Micro triple-quadrupole mass spectrometer. GC-MS was used to analyze our samples on a Shimadzu GC 2010 plus and MS 2010SE system. LC-MS was recorded on a Agilent technologies 6120 Quadrupole LC/MS. IR samples were analyzed on a Perkin Elmer FTIR spectrophotometer.

### 5-(Alkylimino)-1-quinolin-8-yl-1H-pyrrol-2(5H)-one Derivatives 3a–t, v; General Procedure

To an oven-dried Schlenk tube charged with magnetic stirrer was added benzamide/vinylamide (0.2 mmol),  $\text{Co}(\text{acac})_2$  (0.02 mmol, 10 mol%), sodium pivalate (0.4 mmol, 2.0 equiv), and  $\text{Ag}_2\text{CO}_3$  (0.2 mmol, 1.0 equiv) and finally CPME (1 mL) as the solvent. To this mixture, *tert*-butyl isonitrile (**2a**, 0.3 mmol, 1.5 equiv) was added under air. The closed Schlenk tube containing the mixture was placed in pre-heated oil bath at 100 °C for 24 h. The mixture was allowed to cool to r.t. The solvent was removed and the residue was purified by flash column chromatography (silica gel, EtOAc/hexane) to afford iminoisoindolinones and iminopyrrolones **3** in good yield.

#### (E)-3-(*tert*-Butylimino)-5-(methylthio)-2-quinolin-8-yl-2,3-dihydro-1H-isoindol-1-one (3f)

Following the general procedure on a 0.2-mmol scale with purification by flash column chromatography (EtOAc/hexane, 30:70) gave **3f** as a pale white solid; yield: 48 mg (64%);  $R_f = 0.4$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.82$  (dd,  $J = 4.1, 1.6$  Hz, 1 H), 8.18 (dd,  $J = 8.1, 1.6$  Hz, 1 H), 7.92 (d,  $J = 8.0$  Hz, 2 H), 7.87 (dd,  $J = 8.0, 1.5$  Hz, 1 H), 7.69 (dd,  $J = 7.1, 1.4$  Hz, 1 H), 7.64–7.60 (m, 1 H), 7.48 (dd,  $J = 7.8, 1.5$  Hz, 1 H), 7.37 (dd,  $J = 8.2, 4.1$  Hz, 1 H), 2.60 (s, 3 H), 1.31 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 167.34, 150.09, 146.80, 144.89, 144.81, 135.91, 133.13, 131.08, 130.39, 130.38, 128.90, 128.27, 127.82, 125.74, 123.93, 123.83, 121.11, 53.61, 30.56, 15.51$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_3\text{OS}$ : 376.1484; found: 376.1481.

#### (E)-3-(*tert*-Butylimino)-2-quinolin-8-yl-2,3-dihydro-1H-benzo[e]isoindol-1-one (3g)

Following the general procedure on a 0.2-mmol scale with purification by flash column chromatography (EtOAc/hexane, 30:70) gave **3g** as a bright yellow solid; yield: 58 mg (76%);  $R_f = 0.45$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 9.29$  (d,  $J = 8.2$  Hz, 1 H), 8.83 (dd,  $J = 4.1, 1.6$  Hz, 1 H), 8.19–8.12 (m, 3 H), 7.94 (d,  $J = 8.3$  Hz, 1 H), 7.89 (dd,  $J = 8.0, 1.1$  Hz, 1 H), 7.78 (dd,  $J = 7.2, 1.3$  Hz, 1 H), 7.70–7.60 (m, 3 H), 7.37 (dd,  $J = 8.2, 4.1$  Hz, 1 H), 1.34 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 169.33, 150.94, 150.28, 145.20, 135.98, 134.51, 133.57, 132.89, 131.21, 131.48, 128.98, 128.84, 128.66, 128.33, 127.99, 127.86, 127.56, 125.82, 125.64, 122.52, 121.19, 53.98, 31.04$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}$ : 380.1763; found: 380.1768.

#### (E)-3-(*tert*-Butylimino)-5-fluoro-2-quinolin-8-yl-2,3-dihydro-1H-isoindol-1-one (3i)

Following the general procedure on a 0.2-mmol scale using  $\text{Ag}_2\text{CO}_3$  (2 equiv) with purification by flash column chromatography (EtOAc/hexane, 20:80) gave **3i** as a yellow solid; yield: 63 mg (90%);  $R_f = 0.4$  (EtOAc/hexane). NMR data are in accordance with the literature.<sup>3</sup>

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.82$  (dd,  $J = 4.0, 1.6$  Hz, 1 H), 8.17–8.14 (m, 1 H), 8.02 (dd,  $J = 8.1, 5.5$  Hz, 1 H), 7.86–7.84 (m, 1 H), 7.77 (dd,  $J = 9.1, 2.0$  Hz, 1 H), 7.69 (dd,  $J = 7.5, 1.6$  Hz, 1 H), 7.63–7.59 (m, 1 H), 7.37–7.32 (m, 2 H), 1.30 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta = 166.6, 166.37, 163.85, 150.19, 144.77, 136.0, 132.97, 131.07, 129.88, 128.96, 128.46, 125.79, 125.70, 121.21, 118.35, 118.11, 114.62, 53.79, 30.57$ .

$^{19}\text{F NMR}$  ( $\text{CDCl}_3$ , 471 MHz):  $\delta = -104.99$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{21}\text{H}_{19}\text{FN}_3\text{O}$ : 348.1512; found: 348.1518.

#### (E)-3-(*tert*-Butylimino)-5-nitro-2-quinolin-8-yl-2,3-dihydro-1H-isoindol-1-one (3j)

Following the general procedure on a 0.2-mmol scale with purification by flash column chromatography (EtOAc/hexane, 25:75) gave **3j** as a yellow solid; yield: 49 mg (65%);  $R_f = 0.5$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.95$  (d,  $J = 1.8$  Hz, 1 H), 8.80 (dd,  $J = 4.2, 1.8$  Hz, 1 H), 8.53 (dd,  $J = 8.2, 1.8$  Hz, 1 H), 8.19–8.16 (m, 2 H), 7.99 (dd,  $J = 8.1, 1.3$  Hz, 1 H), 7.72 (dd,  $J = 7.3, 1.4$  Hz, 1 H), 7.64 (m, 1 H), 7.38 (dd,  $J = 8.2, 4.1$  Hz, 1 H), 1.32 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 165.62, 150.48, 150.34, 148.53, 144.55, 144.45, 138.31, 136.05, 132.50, 130.92, 128.95, 128.86, 126.23, 125.79, 124.69, 121.88, 121.41, 54.29, 30.76$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{21}\text{H}_{19}\text{N}_4\text{O}_3$ : 375.1457; found: 375.1454.

#### (E)-3-(*tert*-Butylimino)-6-nitro-2-quinolin-8-yl-2,3-dihydro-1H-isoindol-1-one (3k)

Following the general procedure on a 0.3-mmol scale with purification by flash column chromatography (EtOAc/hexane, 10:90) gave **3k** as a yellow solid; yield: 42 mg (37%);  $R_f = 0.55$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.73$  (dd,  $J = 4.1, 1.7$  Hz, 1 H), 8.25–8.20 (m, 2 H), 7.89 (dd,  $J = 8.2, 0.52$  Hz, 1 H), 7.72 (dd,  $J = 8.2, 1.2$  Hz, 1 H), 7.61–7.57 (m, 1 H), 7.39 (dd,  $J = 8.3, 4.1$  Hz, 1 H), 7.26 (dd,  $J = 7.2, 1.3$  Hz, 1 H), 6.90–6.89 (m, 1 H), 1.96 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 166.68, 150.59, 150.17, 150.04, 145.20, 140.07, 137.47, 136.14, 130.38, 129.28, 126.81, 126.42, 123.82, 123.70, 121.70, 119.87, 117.50, 59.89, 29.54$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{21}\text{H}_{19}\text{N}_4\text{O}_3$ : 375.1457; found: 375.1454.

#### (E)-3-(*tert*-Butylimino)-4-nitro-2-quinolin-8-yl-2,3-dihydro-1H-isoindol-1-one (3k')

Following the general procedure on a 0.3-mmol scale with purification by flash column chromatography (EtOAc/hexane, 20:90) gave **3k'** as a yellow solid; yield: 45 mg (40%);  $R_f = 0.55$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.84$ –8.82 (m, 2 H), 8.59–8.56 (m, 1 H), 8.27 (d,  $J = 8.6$  Hz, 1 H), 8.21 (dd,  $J = 8.3, 1.7$  Hz, 1 H), 7.92 (dd,  $J = 8.1, 1.4$  Hz, 1 H), 7.72 (dd,  $J = 7.2, 1.5$  Hz, 1 H), 7.67–7.64 (m, 1 H), 7.41 (dd,  $J = 8.2, 4.0$  Hz, 1 H), 1.29 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 150.44, 150.40, 149.36, 144.46, 143.76, 141.77, 136.25, 132.50, 131.07, 129.03, 128.94, 127.60, 127.19, 127.17, 125.89, 121.50, 119.02, 54.42, 30.76$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{21}\text{H}_{19}\text{N}_4\text{O}_3$ : 375.1457; found: 375.1454.



**(E)-3-(tert-Butylimino)-2-quinolin-8-yl-4-(trifluoromethyl)-2,3-dihydro-1H-isoindol-1-one (3I) and (E)-3-(tert-Butylimino)-2-quinolin-8-yl-6-(trifluoromethyl)-2,3-dihydro-1H-isoindol-1-one (3I')**

Following the general procedure on a 0.2-mmol scale with purification by flash column chromatography (EtOAc/hexane, 20:80) gave **3I/3I'** as a yellow oil; yield: 60 mg (76%); ratio **3I/3I'** 9.1:1.0;  $R_f = 0.45$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.80$  (dd,  $J = 4.0, 1.6$  Hz, 1 H), 8.32 (m, 1 H), 8.23 (d,  $J = 8.1$  Hz, 1 H), 8.17 (dd,  $J = 8.3, 1.7$  Hz, 1 H), 7.99–7.97 (m, 1 H), 7.87 (dd,  $J = 8.2, 1.4$  Hz, 1 H), 7.71 (dd,  $J = 7.4, 1.5$  Hz, 1 H), 7.65–7.61 (m, 1 H), 7.36 (dd,  $J = 8.2, 4.3$  Hz, 1 H), 1.32 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 166.34, 150.29, 144.59, 136.68, 136.03, 134.30, 133.98, 132.67, 131.03, 128.95, 128.69, 128.14, 125.78, 124.89, 124.28, 123.71, 122.17, 121.32, 54.0, 30.62$ .

$^{19}\text{F NMR}$  ( $\text{CDCl}_3$ , 471 MHz):  $\delta = -62.64$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{22}\text{H}_{19}\text{F}_3\text{N}_3\text{O}$ : 398.1480; found: 398.1483.

**(E)-3-(tert-Butylimino)-2-quinolin-8-yl-5-(trifluoromethyl)-2,3-dihydro-1H-isoindol-1-one (3m)**

Following the general procedure on a 0.2-mmol scale with purification by flash column chromatography (EtOAc/hexane, 15:85) gave **3m** as a pale yellow solid; yield: 67 mg (84%);  $R_f = 0.45$  (EtOAc/hexane). NMR data are in accordance with the literature.<sup>3</sup>

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.81$  (dd,  $J = 4.2, 1.7$  Hz, 1 H), 8.35 (s, 1 H), 8.17 (t,  $J = 7.8$  Hz, 2 H), 7.96–7.87 (m, 2 H), 7.71 (dd,  $J = 7.3, 1.5$  Hz, 1 H), 7.65–7.61 (m, 1 H), 7.39–7.36 (m, 1 H), 1.32 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 166.37, 150.29, 144.59, 136.68, 136.03, 134.62, 134.30, 133.98, 133.65, 132.67, 131.03, 128.95, 128.69, 128.14, 125.78, 124.89, 124.28, 123.78, 122.17, 121.32, 54.0, 30.62$ .

$^{19}\text{F NMR}$  ( $\text{CDCl}_3$ , 471 MHz):  $\delta = -62.39$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{22}\text{H}_{19}\text{F}_3\text{N}_3\text{O}$ : 398.1480; found: 398.1483.

**(E)-3-(tert-Butylimino)-2-quinolin-8-yl-4,6-bis(trifluoromethyl)-2,3-dihydro-1H-isoindol-1-one (3n)**

Following the general procedure on a 0.2-mmol scale with purification by flash column chromatography (EtOAc/hexane, 10:90) gave **3n** as a yellow oil; yield: 47 mg (50%);  $R_f = 0.50$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.81$  (dd,  $J = 4.1, 1.5$  Hz, 1 H), 8.38 (s, 1 H), 8.28 (s, 1 H), 8.21 (dd,  $J = 8.1, 1.5$  Hz, 1 H), 7.97 (dd,  $J = 8.3, 1.3$  Hz, 1 H), 7.84 (dd,  $J = 7.1, 1.3$  Hz, 1 H), 7.71–7.67 (m, 1 H), 7.42 (dd,  $J = 8.4, 3.9$  Hz, 1 H), 0.79 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 168.51, 151.14, 148.69, 145.23, 140.22, 136.17, 135.51, 134.67, 132.89, 132.85, 132.55, 131.67, 129.76, 129.13, 128.48, 127.03, 125.86, 123.57, 122.07, 55.66, 30.68$ .

$^{19}\text{F NMR}$  ( $\text{CDCl}_3$ , 471 MHz):  $\delta = -59.42, -62.57$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{23}\text{H}_{18}\text{F}_6\text{N}_3\text{O}$ : 466.1354; found: 466.1354.

**(E)-5-(tert-Butylimino)-3-methyl-1-quinolin-8-yl-1H-pyrrol-2(5H)-one (3p)**

Following the general procedure on a 0.3-mmol scale using  $\text{Ag}_2\text{CO}_3$  (2 equiv) with purification by flash column chromatography flash column chromatography (EtOAc/hexane, 40:60) gave **3p** as a brown oil; yield: 27 mg (30%);  $R_f = 0.50$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.85$  (dd,  $J = 4.1, 1.7$  Hz, 1 H), 8.13 (dd,  $J = 8.3, 1.7$  Hz, 1 H), 7.81 (dd,  $J = 7.7, 1.8$  Hz, 1 H), 7.62–7.55 (m, 2 H), 7.35 (dd,  $J = 8.2, 4.2$  Hz, 1 H), 6.95–6.94 (m, 1 H), 2.16 (d,  $J = 1.7$  Hz, 3 H), 1.26 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 170.38, 152.42, 150.12, 144.13, 141.44, 135.97, 132.42, 130.88, 129.04, 128.15, 125.82, 122.95, 121.15, 55.40, 32.18, 11.48$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{18}\text{H}_{20}\text{N}_3\text{O}$ : 294.1606; found: 294.1615.

**(E)-5-(tert-Butylimino)-4-phenyl-1-quinolin-8-yl-1H-pyrrol-2(5H)-one (3q)**

Following the general procedure on a 0.2-mmol scale using  $\text{Ag}_2\text{CO}_3$  (2 equiv) with purification by flash column chromatography (EtOAc/hexane, 20:80) gave **3q** as a yellow solid; yield: 45 mg (63%);  $R_f = 0.45$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.86$  (dd,  $J = 4.2, 1.6$  Hz, 1 H), 8.18 (dd,  $J = 8.2, 1.6$  Hz, 1 H), 7.93–7.89 (m, 3 H), 7.81 (dd,  $J = 7.2, 1.3$  Hz, 1 H), 7.67–7.63 (m, 1 H), 7.44–7.42 (m, 3 H), 7.40 (dd,  $J = 8.3, 4.2$  Hz, 1 H), 6.75 (m, 1 H), 0.79 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 173.86, 151.92, 150.89, 145.77, 144.42, 136.02, 135.83, 132.07, 130.07, 129.44, 129.09, 129.02, 128.82, 127.87, 125.83, 122.00, 121.76, 55.45, 30.87$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}$ : 356.1763; found: 356.1765.

**(E)-5-(tert-Butylimino)-4-(4-methoxyphenyl)-1-quinolin-8-yl-1H-pyrrol-2(5H)-one (3r)**

Following the general procedure on a 0.2-mmol scale using  $\text{Ag}_2\text{CO}_3$  (2 equiv) with purification by flash column chromatography (EtOAc/hexane, 40:60) gave **3r** as a yellow solid; yield: 32.5 mg (42%);  $R_f = 0.40$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.86$  (dd,  $J = 4.2, 1.7$  Hz, 1 H), 8.18 (dd,  $J = 8.3, 1.7$  Hz, 1 H), 7.96–7.92 (m, 2 H), 7.90 (dd,  $J = 8.3, 1.5$  Hz, 1 H), 7.80 (dd,  $J = 7.3, 1.4$  Hz, 1 H), 7.65 (dd,  $J = 8.1, 7.3$  Hz, 1 H), 7.39 (dd,  $J = 8.3, 4.1$  Hz, 1 H), 6.97–6.94 (m, 2 H), 6.67 (s, 1 H), 3.87 (s, 3 H), 0.79 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 174.15, 160.80, 151.46, 150.89, 145.85, 144.75, 136.03, 136.01, 132.14, 131.61, 129.11, 128.96, 125.85, 124.61, 121.75, 119.97, 113.43, 55.42, 55.30, 30.89$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_2$ : 386.1869; found: 386.1866.

**(E)-5-(tert-Butylimino)-1-quinolin-8-yl-4-[4-(trifluoromethyl)phenyl]-1H-pyrrol-2(5H)-one (3s)**

Following the general procedure on a 0.2-mmol scale using  $\text{Ag}_2\text{CO}_3$  (2 equiv) with purification by flash column chromatography (EtOAc/hexane, 20:80) gave **3s** as a brown solid; yield: 23 mg (27%);  $R_f = 0.40$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz):  $\delta = 8.86$ –8.85 (m, 1 H), 8.19 (d,  $J = 8.0$  Hz, 1 H), 8.02 (d,  $J = 7.7$  Hz, 2 H), 7.92 (d,  $J = 8.0$  Hz, 1 H), 7.81 (d,  $J = 7.3$  Hz, 1 H), 7.69–7.64 (m, 3 H), 7.41 (dd,  $J = 7.9, 4.0$  Hz, 1 H), 6.81 (s, 1 H), 0.785 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 173.40, 150.99, 150.51, 145.68, 144.05, 136.11, 135.56, 135.44, 135.43, 132.09, 130.26, 129.23, 129.14, 125.88, 124.76, 124.72, 123.27, 121.89, 55.63, 30.85$ .

$^{19}\text{F NMR}$  ( $\text{CDCl}_3$ , 471 MHz):  $\delta = -62.65$ .

HRMS:  $m/z$  [M + H] calcd for  $\text{C}_{24}\text{H}_{21}\text{F}_3\text{N}_3\text{O}$ : 424.1637; found: 424.1633.

**(E)-3-(Cyclohexylimino)-2-quinolin-8-yl-2,3-dihydro-1H-isoindol-1-one (3t) and (Z)-3-(Cyclohexylimino)-2-quinolin-8-yl-2,3-dihydro-1H-isoindol-1-one (3t')**

Following the general procedure on a 0.2-mmol scale using cyclohexyl isonitrile with purification by flash column chromatography (EtOAc/hexane, 25:75) gave **3t/3t'** as a colorless oil; yield: 50 mg (70%); ratio *E/Z* 2.28:1.0;  $R_f = 0.45$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 8.87\text{--}8.84$  (m, 1 H), 8.22–8.16 (m, 1 H), 8.04 (d,  $J = 7.7$  Hz, 1 H), 7.96 (d,  $J = 7.3$  Hz, 1 H), 7.91–7.86 (m, 1 H), 7.73–7.61 (m, 4 H), 7.38–7.35 (m, 1 H), 4.28–4.23 (m, 1 H), 1.85–1.82 (m, 1 H), 1.74–1.65 (m, 2 H), 1.64–1.58 (m, 1 H), 1.45–1.18 (m, 6 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 167.51$ , 150.30, 149.80, 144.70, 136.05, 133.13, 133.04, 132.35, 131.31, 130.95, 130.12, 129.80, 129.09, 128.59, 125.65, 123.96, 121.27, 57.59, 34.03, 25.47, 24.50.

HRMS:  $m/z$  [ $M + H$ ] calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}$ : 356.1763; found: 356.2.

**(E)-3-(tert-Butylimino)-5-pyrimidin-2-yl-2-quinolin-8-yl-2,3-dihydro-1H-isoindol-1-one (3v)**

Following the general procedure on a 0.2-mmol scale with purification by flash column chromatography (EtOAc/hexane, 40:60) gave **3v** as a white solid; yield: 60 mg (74%);  $R_f = 0.50$  (EtOAc/hexane).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta = 9.31$  (s, 1 H), 8.88–8.79 (m, 4 H), 8.19 (dd,  $J = 8.2$ , 1.7 Hz, 1 H), 8.14 (d,  $J = 8.0$  Hz, 1 H), 7.88 (dd,  $J = 8.1$ , 1.3 Hz, 1 H), 7.73 (dd,  $J = 7.4$ , 1.5 Hz, 1 H), 7.66–7.63 (m, 1 H), 7.38 (dd,  $J = 8.2$ , 4.2 Hz, 1 H), 7.30–7.26 (m, 1 H), 1.42 (s, 9 H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 101 MHz):  $\delta = 167.2$ , 163.4, 157.4, 150.1, 147.3, 144.8, 141.5, 136.0, 135.7, 133.0, 131.1, 130.8, 130.0, 128.9, 128.3, 127.1, 125.8, 123.8, 121.1, 119.8, 53.9, 30.6.

HRMS:  $m/z$  [ $M + H$ ] calcd for  $\text{C}_{25}\text{H}_{22}\text{N}_5\text{O}$ : 408.1824; found: 408.1825.

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## Supporting Information

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