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Copper-Catalyzed Intramolecular Benzylic C–H Amination for the Synthesis of Isoindolinones

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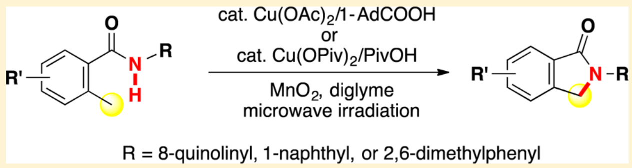
Supporting Information

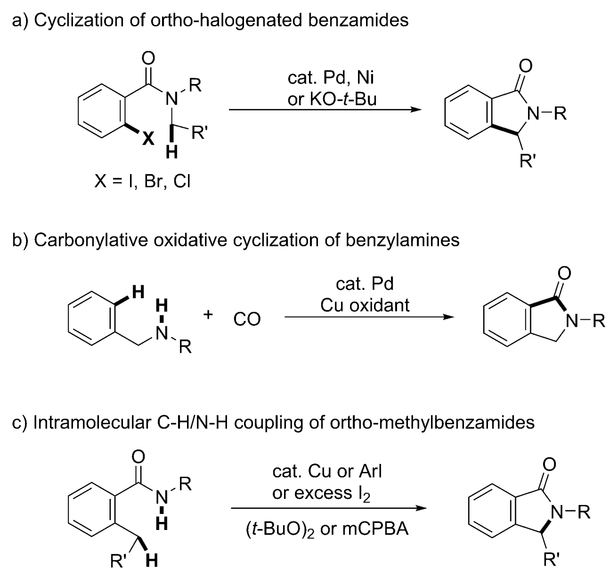
ABSTRACT: A copper-catalyzed intramolecular amination occurs at the benzylic C–H of 2-methylbenzamides to deliver the corresponding isoindolinones of great interest in medicinal chemistry. The mild and abundant MnO_2 works well as a terminal oxidant, and the reaction proceeds smoothly under potentially explosive organic peroxide-free conditions. Additionally, the directing-group-dependent divergent mechanisms are proposed: 8-aminoquinoline-containing benzamides include a Cu-mediated organometallic pathway whereas an aminyl radical-promoted Hofmann–Loffler–Freytag (HLF)-type mechanism can be operative in the case of N-naphthyl-substituted substrates.



■ INTRODUCTION

Isoindolinones are one of the prevalent nitrogen-containing heterocycles in natural and synthetic drug molecules. Such well-known compounds include indoprofen,[1] stachybotrin,[2] and staurosporine.[3] Additionally, some isoindolinone derivatives show unique biological activities, such as inhibitors for the production of tumor necrosis factor, MGR-1 antagonist, antitumor, and anti-inflammatory activities.[4] Thus, versatile strategies for the construction of the isoindolinone skeleton have been developed by many synthetic chemists. Traditional but reliable protocols largely rely on prefunctionalized starting materials, as exemplified by hydrosilane- or tin-mediated selective monoreduction of phthalimides[5] and Pd-catalyzed carbonylative cyclization of ortho-halogenated benzylamines.[6] Moreover, recent advances in C–H functionalization[7] can provide more atom- and step-economical approaches to the above target structure: Pd-, Ni-, and KO-*t*-Bu-mediated direct cyclizations of ortho-halogenated benzamides (Scheme 1a),[8] Pd-catalyzed carbonylative oxidative cyclization of benzylamines (Scheme 1b),[9] and intramolecular C–H/N–H coupling of ortho-methylbenzamides in the presence of Cu, iodoarene, or iodine promoter combined with organic peroxides (Scheme 1c).[10] The last scheme is particularly attractive because the C–N forming process occurs in a dehydrogenative manner and toxic CO gas is not necessary.[11] However, potentially explosive peroxide-based terminal oxidants are still required. Thus, there remains large demand for further improvements of the catalytic systems. Herein we report a Cu/Mn-catalyzed intramolecular C–H/N–H coupling of ortho-methylbenzamides directed toward the isoindolinones. Trivial, safe, and abundant MnO_2 worked well as the terminal oxidant, and the desired isoindolinoes are obtained in the dehydrogenative manner even without the use of organic peroxides. Additionally, the directing-group-dependent divergent mechanisms are observed: 8-aminoquinoline-containing benzamides include a Cu-mediated organometallic pathway whereas an aminyl radical-promoted Hofmann–Loffler–Freytag (HLF)-type mechanism can be operative in the case of *N*-naphthyl-substituted substrates (Scheme 2).

Scheme 1. C–H Functionalization Approaches to Isoindolinones



■ RESULTS AND DISCUSSION

We previously reported an 8-aminoquinoline-directed,[12] Cu-$(OAc)_2$-mediated oxidative coupling of benzamides and maleimides, giving the spirosuccinimides.[13] At an early stage of this study, we performed the reaction of the ortho-methylbenzamide **1a** with *N*-methylmaleimide and serendip-

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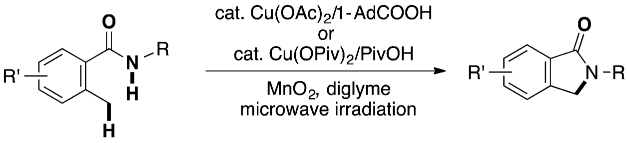
Scheme 2. Cu/Mn-Catalyzed Intramolecular C−H/N−H Coupling of ortho-Methylbenzamides Directed toward Isoindolinones (This Work)

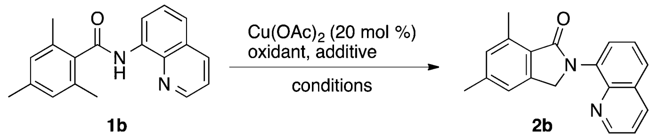


R = 8-quinolinyl, 1-naphthyl, or 2,6-dimethylphenyl

itously detected a small but significant amount of the isoindolinone **2a**, accompanied by the formation of the expected spirosuccinimide (Scheme 3). Apparently, the intramolecular amination occurred at the benzylic position of the benzamide **1a** without participation of the maleimide. The intriguing result prompted us to optimize catalytic conditions for the dehydrogenative cyclization with 2,4,6-trimethylbenzamide **1b** as the model substrate (Table 1). On the basis of our previous work on the copper-catalyzed intramolecular aromatic C−H amination,[14,15] we first tested an MnO_2 terminal oxidant (2.0 equiv), combined with 20 mol % of $Cu(OAc)_2$ and 1.0 equiv of PivOH, in DMF at 170 °C and pleasingly found the desired isoindolinone **2b** in 35% GC yield (entry 1). The structure of **2b** was unambiguously determined by NMR, HRMS, and X-ray analysis.[16] Other oxidants, such as silver salts and molecular oxygen (air), resulted in the negligible catalyst turnover (entries 2−4). As seen in previous studies,[14] microwave irradiation (μw; 200 °C, 1 h) accelerated the reaction and increased the GC yield to 47% (entry 5). Subsequent screening of acidic additives revealed that the carboxylic acids generally accelerated the reaction, with 1-AdCOOH proving to be optimal (entries 6−9). Some other copper carboxylates also promoted the C−H amination with the comparable efficiency, but $Cu(OAc)_2$ was still found to be best from the viewpoints of cost and availability.[17] An increase in the amount of MnO_2 further improved the yield, and in this case 1-AdCOOH could be decreased to 40 mol % (entries 10−12). Finally, treatment of **1b** with 20 mol % $Cu(OAc)_2$, 40 mol % 1-AdCOOH, and 6.0 equiv of MnO_2 in diglyme for 2 h afforded **2b** in 83% yield (entry 13). Additionally notable is that no reaction occurred in the absence of $Cu(OAc)_2$, thus confirming the operation of copper catalysis in this transformation (entry 14).

With conditions of entry 13 in Table 1, we initially investigated the effect of the substitution at the 4 position of 2,6-dimethylbenzamide substrates (Scheme 4). Electron-neutral as well as electron-donating substituents were well tolerated to form the corresponding isoindolinones **2c**, **2d**, and **2e**, in 80, 80, and 73% yields, respectively. The Cu/Mn catalysis was also

Table 1. Optimization Studies for Copper-Catalyzed Intramolecular Benzylic C−H Amination of Benzamide 1b Directed toward Isoindolinone 2b[a]



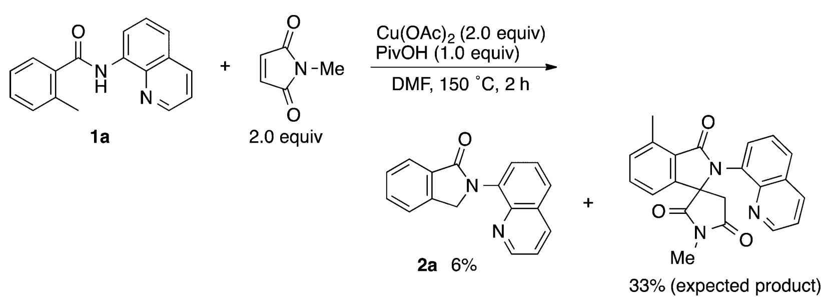
entry	oxidant (equiv)	additive (equiv)	conditions	yield (%)[b]
1	MnO_2 (2.0)	PivOH (1.0)	DMF, 170 °C, 16 h, N_2	(35)
2	Ag_2O (2.0)	PivOH (1.0)	DMF, 170 °C, 16 h, N_2	(21)
3	AgOAc (2.0)	PivOH (1.0)	DMF, 170 °C, 4 h, N_2	(18)
4	O_2 (air)	PivOH (1.0)	DMF, 170 °C, 14 h, air	(16)
5	MnO_2 (2.0)	PivOH (1.0)	DMF, μw, 200 °C, 1 h, N_2	(47)
6	MnO_2 (2.0)	AcOH (1.0)	DMF, μw, 200 °C, 1 h, N_2	(36)
7	MnO_2 (2.0)	1-AdCOOH (1.0)	DMF, μw, 200 °C, 1 h, N_2	(51)
8	MnO_2 (2.0)	MesCOOH (1.0)	DMF, μw, 200 °C, 1 h, N_2	(27)
9	MnO_2 (2.0)	none	DMF, μw, 200 °C, 1 h, N_2	(40)
10	MnO_2 (4.0)	1-AdCOOH (1.0)	DMF, μw, 200 °C, 1 h, N_2	(64)
11	MnO_2 (4.0)	1-AdCOOH (0.40)	DMF, μw, 200 °C, 1 h, N_2	(66)
12	MnO_2 (6.0)	1-AdCOOH (0.40)	DMF, μw, 200 °C, 1 h, N_2	(72)
13	MnO_2 (6.0)	1-AdCOOH (0.40)	diglyme, μw, 200 °C, 2 h, N_2	83
14[c]	MnO_2 (6.0)	1-AdCOOH (0.40)	diglyme, μw, 200 °C, 2 h, N_2	(0)

[a]Reaction conditions: **1b** (0.25 mmol), $Cu(OAc)_2$ (0.050 mmol), oxidant, additive, solvent (1.5 mL). [b]GC yields are in parentheses. [c]Without $Cu(OAc)_2$.

compatible with electron-withdrawing halogen functionalities, and we obtained **2f−h** in synthetically useful yields with chloride, bromide, and iodide moieties left intact, which can be useful synthetic handle for further manipulations. In the case of 2-methyl-6-pentylbenzamide **1i** that bears potentially reactive methyl and methylene benzylic C−Hs, the reaction occurred exclusively at the methyl C−H to deliver **2i** in 55% yield. Similarly, the 2-isopropyl-6-methylbenzamide **1j** afforded the methyl C−H aminated product as the sole product. On the other hand, expectedly, 2,6-dipentylbenzamide **1k** showed moderate reactivity (13% GC yield of **2k**).

We then tested the 2,5-dimethylbenzamide **1l** under the standard reaction conditions; however, the desired product **2l**

Scheme 3. Initial Finding



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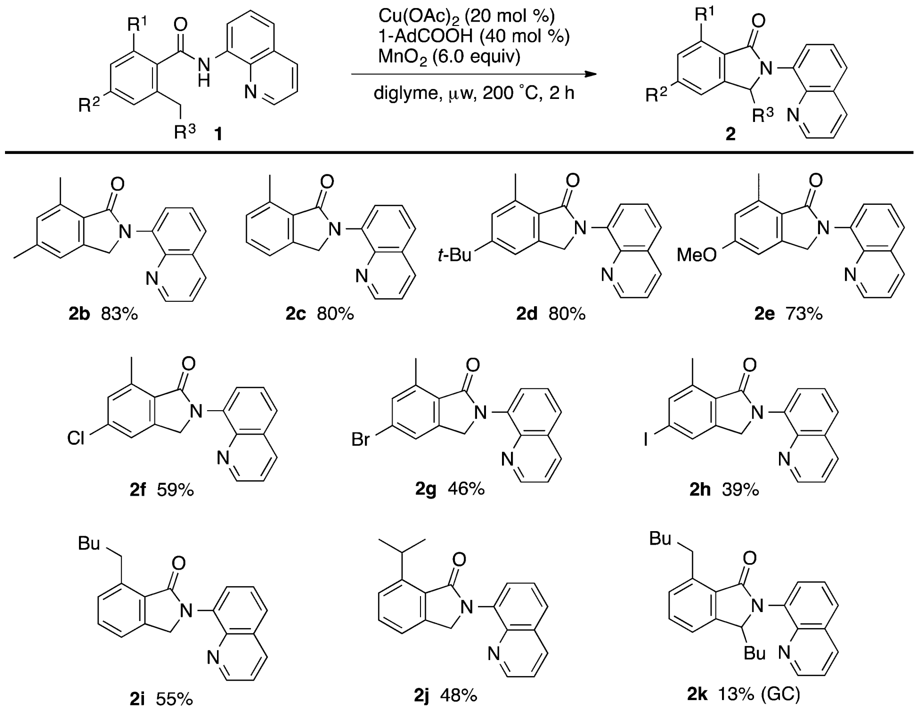
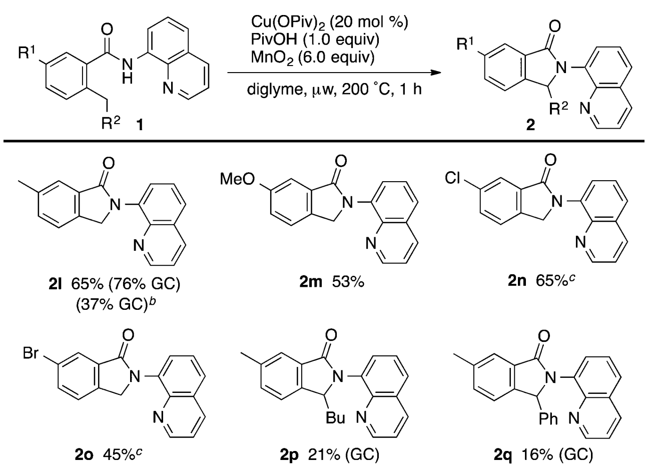
Scheme 4. Copper-Catalyzed Intramolecular Benzylic C−H Amination of Various 2,6-Disubstituted Benzamide 1 Directed toward Isoindolinone 2[a]



[a]Reaction conditions: **1** (0.25 mmol), $Cu(OAc)_2$ (0.050 mmol), 1-AdCOOH (0.10 mmol), MnO_2 (1.5 mmol), diglyme (1.5 mL), 200 °C, 2 h, microwave irradiation.

was formed in only 37% GC yield (Scheme 5). Thus, we performed additional optimization studies. To our delight, the yield was dramatically improved to 65% (76% GC yield) by using a combination of 20 mol % of $Cu(OPiv)_2$ and 1.0 equiv of PivOH instead of the $Cu(OAc)_2$/1-AdCOOH catalyst system. The second catalyst system was also effective for the

Scheme 5. Copper-Catalyzed Intramolecular Benzylic C−H Amination of Various 2,5-Disubstituted Benzamide 1 Directed toward Isoindolinone 2[a,b]



[a]Reaction conditions: **1** (0.25 mmol), $Cu(OPiv)_2$ (0.050 mmol), PivOH (0.25 mmol), MnO_2 (1.5 mmol), diglyme (1.5 mL), 200 °C, 1 h, microwave irradiation. [b]Reaction conditions: **1l** (0.25 mmol), $Cu(OAc)_2$ (0.050 mmol), 1-AdCOOH (0.10 mmol), MnO_2 (1.5 mmol), diglyme (1.5 mL), 200 °C, 2 h, microwave irradiation. [c]In diglyme (5.0 mL).

methoxy-, chloro-, and bromo-substituted substrates to furnish **2m−o** in acceptable yields. As shown in Scheme 4, the methyl benzylic C−H was most reactive: the C−H amination at the methylene C−Hs of the 2-pentyl- and 2-benzylbenzamides **1p** and **1q** proceeded insufficiently (**2p** and **2q**).

Under identical conditions, the methoxy-substituted quinoline also worked well as the substituent on the nitrogen: the benzamide **1r** underwent the intramolecular C−H amination to afford **2r** in 60% yield. Subsequent demethylation with BBr_3 was followed by oxidation with $PhI(TFA)_2$ to produce the NH isoindolinone **2r-H** in 51% yield (Scheme 6).[18]

To get mechanistic insight, deuterated **1l-*d*$_3$** was prepared, and some kinetic studies were carried out (Scheme 7). All the following experiments were performed under the conventional heating conditions with an oil bath (170 °C, N_2), because under microwave-irradiated conditions the reaction proceeded in the course of the preheating time, and the conversion at an early stage was difficult to trace. When the reaction stopped in 3 h, the cyclized product **2l-*d*$_2$** was formed in 34% yield, and the recovered starting material underwent no H/D scrambling, which was confirmed by ^1H and ^2H NMR analysis. Additionally, major kinetic isotope effect (KIE) value of 1.9 was obtained from the parallel reactions of **1l** and **1l-*d*$_3$** (see the Supporting Information for detailed kinetic profiles). The above outcomes suggest the irreversible and rate-limiting C−H cleavage at the benzylic position. On the other hand, addition of radical scavengers, TEMPO and 1,4-dinitrobenzene, gave only minor impact on the reaction efficiency (maximum 36% decrease of the yield), thus indicating that a single electron transfer (SET) mechanism is unlikely (Scheme 8).

On the basis of literature information and our findings, we propose the reaction mechanism as shown in Scheme 9. The benzamide **1** initially reacts with the $Cu(OR)_2$ with the

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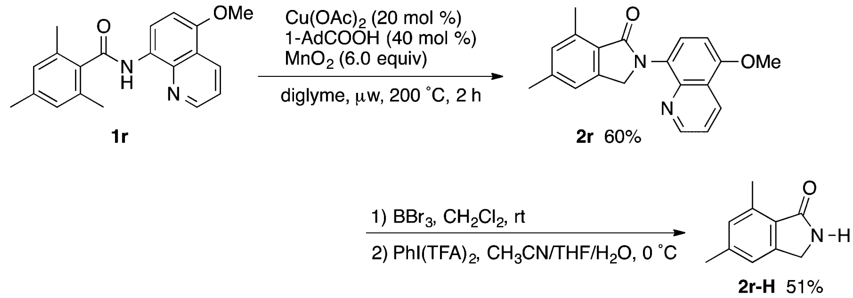
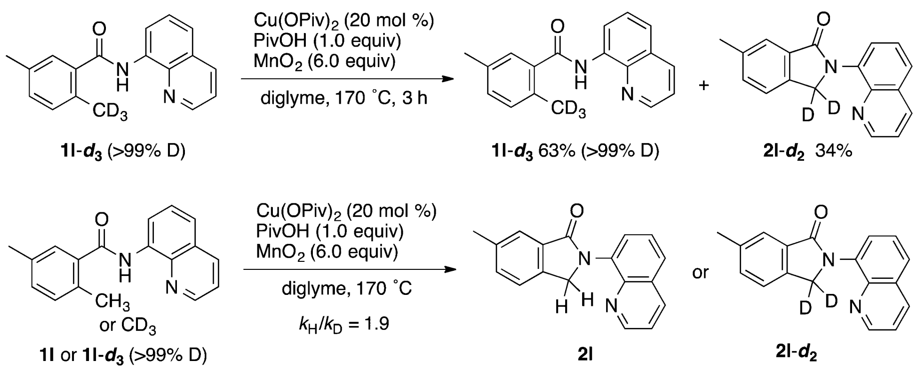
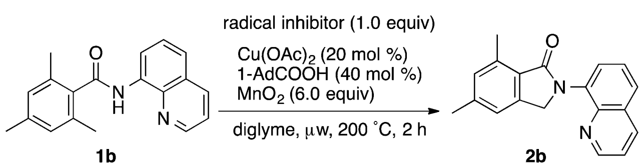
Scheme 6. Copper-Catalyzed Intramolecular Benzylic C−H Amination of 1r Followed by Deprotection



Scheme 7. Deuterium-Labeling Experiments

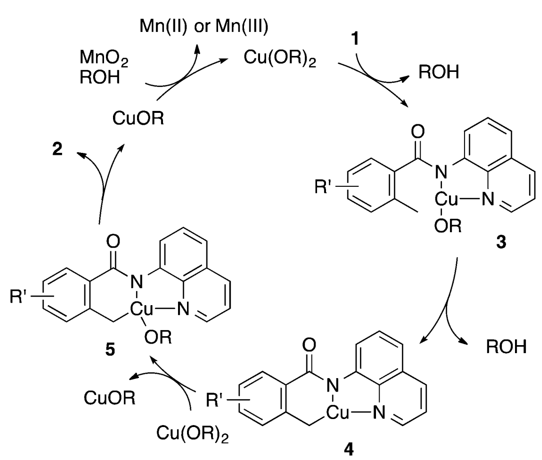


Scheme 8. Effects of Radical Inhibitors for 1b



radical inhibitor	GC yield of **2b**
none	83%
TEMPO	68%
1,4-dinitrobenzene	53%

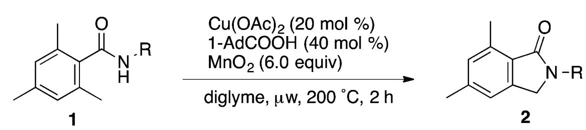
Scheme 9. Plausible Mechanism for 1. R = Ac, 1-AdCO, or Piv



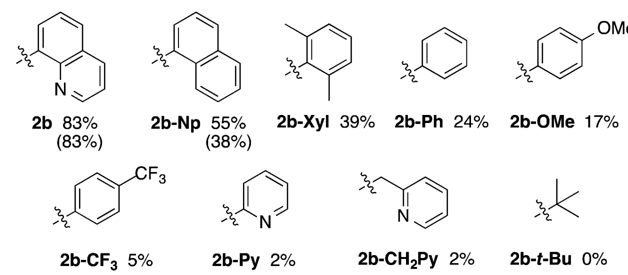
liberation of ROH to form a N,N-bidentately coordinated Cu species **3**. Subsequent irreversible and rate-limiting C−H cleavage at the proximal benzylic position generates the cyclometalated complex **4**. The one-electron oxidation (disproportionation)-induced reductive elimination then occurs via a Cu(III) intermediate **5**[19] to furnish the observed isoindolinone **2** along with the CuOR. The catalytic cycle is closed by the reoxidation of CuOR into $Cu(OR)_2$ with MnO_2 and ROH.[20] Although the exact role of acidic additives, 1-AdCOOH and PivOH, is not clear at present, they can accelerate the C−H cleavage step through an acetate-ligand-assisted concerted metalation−deprotonation.[21]

We finally investigated the effect of substituents on the nitrogen of benzamide substrate **1** (Scheme 10). Surprisingly, albeit with lower efficiency, the naphthyl-substituted **1b-Np** also underwent the reaction under conditions of entry 13 in Table 1, which contrasts with other 8-aminoquinoline-directed, copper-mediated C−H transformations.[22] Inspired by this

Scheme 10. Effects of Substituents on Nitrogen of Benzamide Substrates



substituent R and GC yield of **2** (yield given in parentheses)



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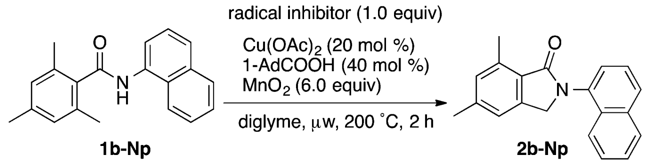
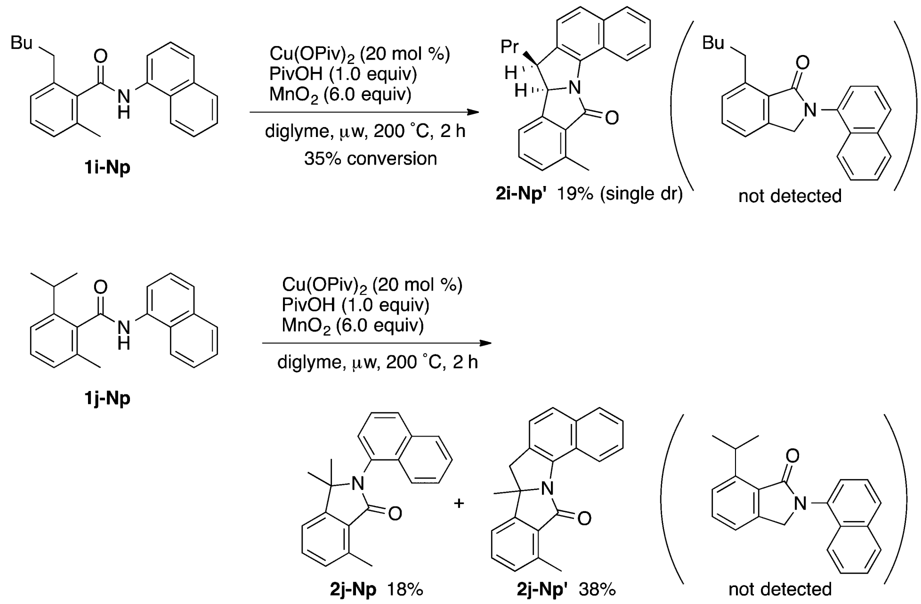
Scheme 11. Effects of Radical Inhibitors for 1b-Np



radical inhibitor	GC yield of **2b-Np**
none	55%
TEMPO	12%
1,4-dinitrobenzene	13%

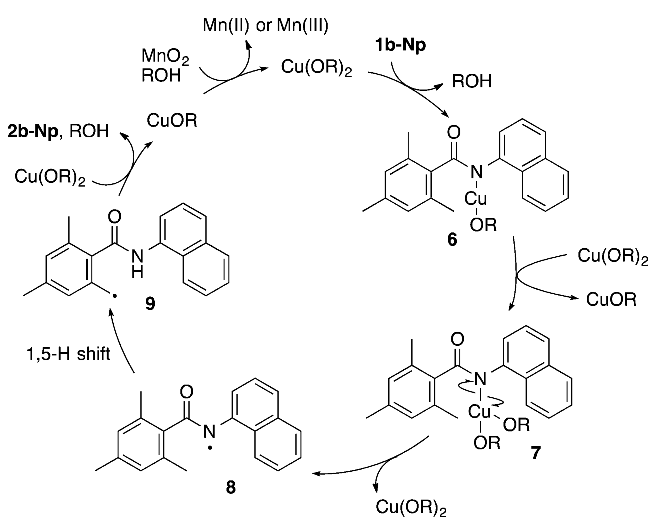
Scheme 12. Reactions of Naphthyl-Containing Unsymmetrical 2-Methyl-6-pentylbenzamide 1i-Np and 2-Isopropyl-6-methylbenzamide 1j-Np



outcome, we prepared a series of N-substituted benzamides and tested their reactivity. As a general trend, the sterically more demanding aryl group gave better yields and **1b-Np** and **1b-Xyl** formed the corresponding isoindolinones **2b-Np** and **2b-Xyl** in 55 and 39% GC yields, respectively, while simple phenyl and para-substituted phenyl groups largely dropped the yield regardless of their electronic property (**2b-Ph**, **2b-OMe**, and **2b-CF$_3$**). Potentially doubly coordinated *N*-pyridyl and *N*-(pyridyl)methyl as well as aliphatic *t*-butyl substituents delivered only trace amount of the cyclized products (**2b-Py**, **2b-CH$_2$Py**, and **2b-*t*-Bu**). Although the exact reason is not clear yet, the dihedral angle between the amide CON and aryl (on nitrogen) planes may play a pivotal role in these cases. The acidity of the amide NH can also be important, but it gave secondary effects on the reaction efficiency.[23]

Notably, in contrast to the quinoline-containing **1b**, the reaction of **1b-Np** was relatively largely inhibited by the radical inhibitors (maximum 76% decrease of the yield; Scheme 11 vs Scheme 8). Moreover, the unsymmetrical 2-methyl-6-pentylbenzamide derivative **1i-Np** showed the different reactivity from the original **1i**: the unique pentacyclic compound **2i-Np′** was formed as a single syn diastereomer (the relative stereochemistry was assigned by the coupling constant of vicinal protons; $J = 12.0$ Hz), via preferable cyclization at more sterically congested methylene benzylic C−H of **1i-Np** albeit with lower conversion. The **1j-Np**, which is naphthyl analogue to **1j**, was also predominantly converted to the more sterically demanding methine C−H aminated product **2j-Np** with concomitant formation of the pentacyclic **2j-Np′** (Scheme 12). Although the details remain to be elucidated, these results suggest that a distinct mechanism, namely, an aminyl-radical−mediated Hofmann−Loffler−Freytag (HLF)-type mechanism,[24] can be operative in the case of **1b-Np** (Scheme 13).

Scheme 13. Plausible Mechanism for 1b-Np. R = Ac or 1-AdCO



Initial binding of **1b-Np** to Cu(OR)$_2$ and oxidation (disproportionation) with additional Cu(OR)$_2$ generates a Cu(III)-amide intermediate **7**. The homolysis of the Cu(III)−N bond of **7** is followed by a 1,5-H shift of an aminyl radical **8** to form a benzyl radical **9**. Subsequent one-electron oxidation with Cu(OR)$_2$ and ring closure by an intramolecular nucleophilic attack of the amide nitrogen furnish the

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isoindolinone **2b-Np** together with CuOR.[25] Final oxidation with MnO_2/ROH regenerates the starting $Cu(OR)_2$ to complete the catalytic cycle. The proposed Cu-modified HLF-type pathway can explain phenomena observed in Schemes 11 and 12: radical scavengers such as TEMPO and 1,4-dinitrobenzene are detrimental to radical intermediates **8** and **9** (Scheme 11), and the 1,5-H shift predominantly gives more stable secondary carbon-centered radicals than primary ones (Scheme 12).[26]

■ CONCLUSION

We have developed a copper-catalyzed intramolecular benzylic sp^3 C−H amination of ortho-methylbenzamides for the synthesis of isoindolinones, which are of potent interest in medicinal chemistry. The cheap, safe, and abundant MnO_2 works well as a terminal oxidant, and the process does not necessitate potentially explosive organic peroxides, which are indispensable in related precedents.[10] Additionally, the directing-group-dependent divergent mechanism is proposed: the 8-aminoquinoline-containing substrates include a Cu(I)/(II)/(III) organometallic pathway while a Cu-modified, aminyl radical-mediated HLF-type mechanism is operative in the case of benzamide that bears simpler aryl group on the nitrogen. Although the substrate scope is still somewhat narrow,[27] the results obtained herein can provide useful information for the design of new and more efficient C−H activation catalysis based on copper.

■ EXPERIMENTAL SECTION

Instrumentation and Chemicals. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by APCI using TOF. GC analysis was carried out using a silicon OV-17 column (2.6 mm i.d. × 1.5 m) or a CBP-1 capillary column (0.5 mm i.d. × 25 m). TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck silica gel $60F_{254}$. Silica gel was used for column chromatography. Gel permeation chromatography (GPC) was performed with a $CHCl_3$ or an ethyl acetate eluent (UV detector). Microwave irradiation was conducted with Initiator$^+$ (Biotage), and the reaction temperature was measured by an internal probe. Unless otherwise noted, materials obtained from commercial suppliers were used as received. Diglyme was freshly distilled from CaH_2 prior to use. $Cu(OPiv)_2$ was prepared according to the literature.[28]

Preparation of Benzamides 1. ***Synthesis of 1b.***[29] 8-Aminoquinoline (2.3 g, 16 mmol) and *N,N*-dimethy-4-aminopyridine (DMAP; 550 mg, 4.5 mmol) were placed in a 50 mL two-necked reaction flask, and the flask was flushed with nitrogen. Anhydrous dichloromethane (20 mL) and Et_3N (3.0 mL, 18 mmol) were added, and the resulting solution was cooled to 0 °C. 2,4,6-Trimethylbenzoyl chloride (2.5 mL, 15 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 4 h. The mixture was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Combined organic phase was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (5/1, v/v) afforded 2,4,6-trimethyl-*N*-(quinolin-8-yl)benzamide (**1b**; 3.0 g, 10 mmol) in 68% yield. Other benzamides **1b-Np**, **1c**, and **1r** were prepared by the same procedure.

Synthesis of 1e.[30] To a 20 mL microwave vessel, 4-methoxy-*N*-(8-quinolinyl)benzamide (840 mg, 3.0 mmol), which was synthesized from the corresponding benzoyl chloride and 8-aminoquinoline by the same procedure as that for **1b**, methyl *p*-toluenesulfonate (1,8 mL, 12 mmol), $Ni(OTf)_2$ (210 mg, 0.6 mmol), PPh_3 (310 mg, 1.2 mmol), Na_2CO_3 (1.3 g, 12 mmol), NaI (1.8 g, 12 mmol), and toluene (10 mL) were added in a glovebox. The vessel was sealed with a cap and then taken out of the glovebox. The mixture was stirred for 24 h at 160 °C. The resulting mixture was then filtered through a short pad of Celite. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (5/1, v/v) followed by GPC (chloroform) afforded 4-methoxy-2,6-dimethyl-*N*-(quinolin-8-yl)-benzamide (**1e**; 670 mg, 2.3 mmol) in 76% yield as a white solid. Other benzamides **1d**, **1f**, **1g**, **1h**, and **1j** were prepared by the same procedure.

Synthesis of 1i.[10c] To a 100 mL two-necked reaction flask which was filled with nitrogen, diisopropylamine (3.5 mL, 25 mmol), anhydrous THF (25 mL), and *n*BuLi (1.6 M in hexane, 16 mL, 25 mmol) were added dropwise at 0 °C. The solution was stirred at the same temperature for 1 h to prepare a LDA solution. To another round-bottom flask which was flushed with nitrogen, a solution of 2,6-dimethylbenzoic acid (1.5 g, 10 mmol) in THF (15 mL) was added and cooled to 0 °C. The LDA solution prepared in advance was transferred via a syringe to the reaction mixture. After stirring the solution for 1.5 h at 0 °C, *n*-butyl bromide (3.2 mL, 30 mmol) was added dropwise. The solution was warmed to room temperature and stirred overnight. The reaction was quenched with 10% HCl aq. (30 mL), and the reaction mixture was extracted with Et_2O (3 × 60 mL). The combined organic phase was concentrated under vacuum. The crude product was redissolved in Et_2O (20 mL) and extracted with aqueous 20% KOH (3 × 30 mL) solution. The combined aqueous phase was diluted with ether (30 mL × 3) and acidified with 2.0 M HCl aq. to pH = 1. The aqueous phase was extracted with Et_2O (60 mL × 3). The combined organic phase was washed with water (60 mL) and brine (100 mL) and then dried over Na_2SO_4. After the filtration and evaporation, a mixture of mono- and dialkylated benzoic acids was obtained, which was used for the next step without further purifications. The obtained crude benzoic acid was then dissolved in $SOCl_2$ (8.0 mL) and heated at 100 °C overnight. After excess $SOCl_2$ was removed under reduced pressure at 80 °C, the residual oil was dissolved in CH_2Cl_2 (16 mL). 8-Aminoquinoline (1.2 g, 8.0 mmol), *N,N*-dimethy-4-aminopyridine (DMAP; 293 mg, 2.4 mmol), and Et_3N (1.3 mL, 9.6 mmol) were sequentially added at 0 °C, and the solution was stirred for 4 h at room temperature. The resulting mixture was quenched with NH_4Cl aq. (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Combined organic phase was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (5/1, v/v) followed by GPC (chloroform) afforded 6-methyl-2-pentyl-*N*-(quinolin-8-yl)benzamide (**1i**; 898 mg, 2.7 mmol) in 27% overall yield. The **1i-Np** was also prepared under similar conditions.

Synthesis of 1p.[10c] To a 100 mL two-necked reaction flask which was filled with nitrogen, diisopropylamine (2.8 mL, 20 mmol), anhydrous THF (20 mL), and *n*BuLi (1.6 M in hexane, 13 mL, 20 mmol) were added dropwise at 0 °C. The solution was stirred at the same temperature for 1 h to prepare a LDA solution. To another round-bottom flask which was flushed with nitrogen, a solution of 2,5-dimethylbenzoic acid (1.5 g, 10 mmol) in THF (15 mL) was added and cooled to 0 °C. The LDA solution prepared in advance was transferred via a syringe to the reaction mixture. After stirring the solution for 1.5 h at 0 °C, *n*-butyl bromide (2.2 mL, 20 mmol) was added dropwise. The solution was warmed to room temperature and stirred overnight. The reaction was quenched with 10% HCl aq. (30 mL), and the reaction mixture was extracted with Et_2O (3 × 60 mL). The combined organic phase was concentrated under vacuum. The crude product was redissolved in Et_2O (20 mL) and extracted with aqueous 20% KOH (3 × 30 mL) solution. The combined aqueous phase was diluted with ether (30 mL × 3) and acidified with 2.0 M HCl aq. to pH = 1. The aqueous phase was extracted with Et_2O (60 mL × 3). The combined organic phase was washed with water (60 mL) and brine (100 mL) and then dried over Na_2SO_4. After the filtration and evaporation, a mixture of mono- and dialkylated benzoic acids was obtained, which was used for the next step without further purifications. The residual solid, 8-aminoquinoline (650 mg, 4.5 mmol), *N,N*-dimethy-4-aminopyridine (DMAP; 550 mg, 4.5 mmol), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl; 1.3 g, 6.8 mmol) were placed in a 50 mL two-necked reaction flask, and the flask was flushed with nitrogen. Anhydrous

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CH_2Cl_2 (9.0 mL) was added. The resulting solution was cooled to 0 °C, and Et_3N (1.3 mL, 9.0 mmol) was added. The reaction mixture was stirred at room temperature for 18 h. The mixture was quenched with NH_4Cl aq. (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Combined organic phase was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (5/1, v/v) followed by GPC (chloroform) afforded 5-methyl-2-pentyl-*N*-(quinolin-8-yl)benzamide (**1p**; 860 mg, 2.6 mmol) in 26% overall yield.

*Synthesis of **1l**.*[29] 2,5-Dimethylbenzoic acid (2.3 g, 15 mmol), 8-aminoquinoline (2.4 g, 17 mmol), *N*,*N*-dimethy-4-aminopyridine (DMAP; 1.8 g, 15 mmol), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl; 4.3 g, 23 mmol) were placed in a 50 mL two-necked reaction flask, and the flask was flushed with nitrogen. Anhydrous dichloromethane (20 mL) was added to the solution. The resulting solution was cooled to 0 °C, and Et_3N (4.2 mL, 30 mmol) was added. The reaction mixture was stirred at room temperature for 18 h. The mixture was quenched with NH_4Cl aq. (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Combined organic phase was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (5/1, v/v) afforded 2,5-dimethyl-*N*-(quinolin-8-yl)benzamide (**1l**; 3.7 g, 13 mmol) in 89% yield. Other benzamides **1n** and **1o** were prepared by the same procedure.

*Synthesis of **1m**.* To a 100 mL two-necked reaction flask charged with 3-bromo-4-methylanisole (1.5 mL, 10 mmol) and anhydrous Et_2O (61 mL), *n*BuLi (1.6 M in hexanes, 6.1 mL, 10 mmol) was added dropwise at 0 °C. After the solution was stirred for 1.5 h, solid dry ice was added slowly. The reaction mixture was warmed up to room temperature and stirred for an additional 30 min. The reaction was quenched with 10% HCl aq. (60 mL) and washed with Et_2O (20 mL × 3). The aqueous layer was then acidified with conc. HCl to pH = 1 and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual solid, 8-aminoquinoline (720 mg, 5.0 mmol), *N*,*N*-dimethy-4-aminopyridine (DMAP; 610 mg, 5.0 mmol), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl; 1.4 g, 7.5 mmol) were placed in a 50 mL two-necked reaction flask, and the flask was flushed with nitrogen. Anhydrous CH_2Cl_2 (10 mL) was added to this solution. The resulting solution was cooled to 0 °C, and Et_3N (1.4 mL, 10 mmol) was added. The reaction mixture was stirred at room temperature for 18 h. The mixture was quenched with NH_4Cl aq. (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Combined organic phase was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (5/1, v/v) followed by GPC (chloroform) afforded 5-methoxy-2-methyl-*N*-(quinolin-8-yl)benzamide (**1m**; 910 mg, 3.1 mmol) in 31% overall yield.

*Synthesis of **1j-Np**.* A suspension of 2-isopropyl-6-methyl-*N*-(quinolin-8-yl)benzamide (**1j**; 365 mg, 1.2 mmol) in aq. H_2SO_4 (40%, 2.5 mL) was heated at 120 °C for 24 h. After being cooled to room temperature, the mixture was extracted with Et_2O, and the combined organic layer was dried over anhydrous Na_2SO_4. Subsequent filtration and evaporation formed 2-isopropyl-6-methylbenzoic acid (205 mg, 1.2 mmol) in 96% yield. The crude 2-isopropyl-6-methylbenzoic acid (303 mg, 1.7 mmol) was then dissolved in $SOCl_2$ (2.0 mL) and heated at 100 °C overnight. After excess $SOCl_2$ was removed under reduced pressure at 80 °C, the residual oil was dissolved in CH_2Cl_2 (3.5 mL). 1-Aminonaphthalene (243 mg, 1.7 mmol), *N*,*N*-dimethy-4-aminopyridine (DMAP; 62 mg, 0.51 mmol), and Et_3N (0.28 mL, 2.0 mmol) were sequentially added at 0 °C, and the solution was stirred for 4 h at room temperature. The resulting mixture was quenched with NH_4Cl aq. (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Combined organic phase was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (5/1, v/v) followed by GPC (chloroform) afforded 2-isopropyl-6-methyl-*N*-(naphthalen-1-yl)benzamide (**1j-Np**; 181 mg, 0.60 mmol) in 35% yield.

*Synthesis of **1l-d_3**.* To a solution of *p*-toluenesulfonyl chloride (TsCl; 1.5 g, 8.0 mmol) in THF (5.8 mL), CD_3OD (580 mg, 16 mmol) and 20% NaOH aq. (4.0 mL) were added at 0 °C. After 4 h, the mixture was diluted with water and extracted with ether. The combined organic phase was washed with saturated NH_4Cl aq. and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give $TsOCD_3$ (1.5 g, 7.7 mmol, 96%, > 99% D) as a colorless oil.[31] To a 20 mL microwave vessel, 3-methyl-*N*-(quinolin-8-yl)benzamide (700 mg, 2.7 mmol), $TsOCD_3$ (1.0 g, 5.3 mmol), $Ni(OTf)_2$ (95 mg, 0.27 mmol), PPh_3 (140 mg, 0.53 mmol), Na_2CO_3 (560 mg, 5.3 mmol), NaI (790 mg, 5.3 mmol), and toluene (9.0 mL) were added in a glovebox. The vessel was sealed with a cap and then taken out of the glovebox. The mixture was stirred for 24 h at 140 °C. The resulting mixture was then filtered through a short pad of Celite. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (5/1, v/v) followed by GPC (chloroform) afforded 5-methyl-2-(methyl-d_3)-*N*-(quinolin-8-yl)-benzamide (**1l-d_3**; 380 mg, 1.4 mmol, > 99% D) in 51% yield.

*Typical Procedure for Copper-Catalyzed Intramolecular Benzylic C–H Amination of 2,6-Disubstituted Benzamides **1**.* The synthesis of **2b** is representative (Scheme 4). $Cu(OAc)_2$ (9.1 mg, 0.050 mmol), 2,4,6-trimethyl-*N*-(quinolin-8-yl)benzamide (**1b**; 73 mg, 0.25 mmol), 1-adamantanecarboxylic acid (18 mg, 0.10 mmol), and MnO_2 (130 mg, 1.5 mmol) were placed in a 2.0 mL microwave vessel, and the vessel was flushed with nitrogen. Diethylene glycol dimethyl ether (diglyme, 1.5 mL) was sequentially injected via a syringe. The mixture was irradiated under microwave reactor conditions at 200 °C for 2 h. The resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate three times, and the combined organic layer was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (2/1, v/v) afforded 5,7-dimethyl-2-(quinolin-8-yl)isoindolin-1-one (**2b**; 60 mg, 0.21 mmol) in 83% yield.

*5,7-Dimethyl-2-(quinolin-8-yl)isoindolin-1-one (**2b**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (2:1, v/v) as an eluent; 60 mg (83%); yellow solid; mp 178.5–180.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.75(s, 3H), 5.18 (s, 2H), 7.06 (s, 1H), 7.13 (s, 1H), 7.41 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.61 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.81 (dd, *J* = 1.2. 8.2 Hz, 1H), 7.91 (dd, *J* = 1.4, 7.4 Hz, 1H), 8.20 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.87 (dd, *J* = 1.7, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 21.8, 53.1, 120.7, 121.3, 126.4, 127.1, 127.3, 128.9, 129.5, 130.9, 135.9, 136.4, 138.0, 141.8, 143.5, 144.5, 150.0, 169.7; HRMS (APCI) *m*/*z* ($[M + H]^+$) calcd for $C_{19}H_{17}N_2O$: 289.1335, found: 289.1336. X-ray quality crystals were grown from dichloromethane/heptane.

*7-Methyl-2-(quinolin-8-yl)isoindolin-1-one (**2c**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (2:1, v/v) as an eluent; 55 mg (80%); yellow solid; mp 172.3–173.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 3H), 5.23 (s, 2H), 7.25 (d, *J* = 6.4 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.42 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.63 (dd, *J* = 7.5, 8.1 Hz, 1H), 7.82 (dd, *J* = 1.3, 8.2 Hz, 1H), 7.92 (dd, *J* = 1.4, 7.4 Hz, 1H), 8.21 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.88 (dd, *J* = 1.8, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 53.2, 120.1, 121.4, 126.4, 127.4, 128.9, 129.5, 129.6, 129.9, 131.3, 135.7, 136.4, 138.3, 143.1, 144.5, 150.0, 169.6; HRMS (APCI) *m*/*z* ($[M + H]^+$) calcd for $C_{18}H_{15}N_2O$: 275.1179, found: 275.1184.

*5-(t-Butyl)-7-methyl-2-(quinolin-8-yl)isoindolin-1-one (**2d**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 66 mg (80%), yellow solid; mp 65.3–67.1 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.78 (s, 3H), 5.21 (s, 2H), 7.27 (s, 1H), 7.34 (s, 1H), 7.40 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.80 (dd, *J* = 1.3, 8.2 Hz, 1H), 7.90 (dd, *J* = 1.4. 7.4 Hz, 1H), 8.18 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.86 (dd, *J* = 1.7, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 31.4, 35.1, 53.3, 117.0, 121.3, 126.4, 127.2, 127.3 (2C), 128.9, 129.5, 135.9, 136.3, 137.6, 143.2, 144.6, 150.0, 155.2, 169.6; HRMS (APCI) *m*/*z* ($[M + H]^+$) calcd for $C_{22}H_{23}N_2O$: 331.1805, found: 331,1809.

*5-Methoxy-7-methyl-2-(quinolin-8-yl)isoindolin-1-one (**2e**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (2:1, v/v) as an eluent; 56 mg (73%); yellow solid; mp 202.6–204.3

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°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 3H), 3.87 (s, 3H), 5.19 (s, 2H), 6.78 (s, 1H), 6.82 (s, 1H), 7.40 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.61 (dd, *J* = 7.5 Hz, 1H), 7.79 (dd, *J* = 1.3, 8.2 Hz, 1H), 7.91 (dd, *J* = 1.4, 7.4 Hz, 1H), 8.19 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.87 (dd, *J* = 1.8, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 53.1, 55.6, 104.9, 116.3, 121.3, 122.6, 126.4, 127.2, 128.8, 129.5, 135.9, 136.4, 140.0, 144.5, 145.5, 149.9, 162.5, 169.4; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{19}H_{17}N_2O_2$: 305.1285, found: 305.1284.

*5-Chloro-7-methyl-2-(quinolin-8-yl)isoindolin-1-one (**2f**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 46 mg (59%), yellow solid; mp 182.5−184.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (s, 3H), 5.20 (s, 2H), 7.25 (s, 1H), 7.32 (s, 1H), 7.42 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.82 (dd, *J* = 1.3, 8.2 Hz, 1H), 7.90 (dd, *J* = 1.3. 7.4 Hz, 1H), 8.20 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.90 (dd, *J* = 1.7, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 52.8, 120.5, 121.4, 126.4, 127.6, 128.2, 128.8, 129.5, 130.1, 135.3, 136.4, 137.4, 140.0, 144.3, 144.6, 150.1, 168.7; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{18}H_{14}ClN_2O$: 309.0789, found: 309.0785.

*5-Bromo-7-methyl-2-(quinolin-8-yl)isoindolin-1-one (**2g**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 41 mg (46%), yellow solid; mp 207.3−208.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (s, 3H), 5.21 (s, 2H), 7.41−7.42 (m, 1H), 7.44 (d, *J* = 4.2 Hz, 1H), 7.49 (s, 1H), 7.62 (dd, *J* = 7.5, 8.2 Hz, 1H), 7.83 (dd, *J* = 1.3, 8.2 Hz, 1H), 7.90 (dd, *J* = 1.4. 7.4 Hz, 1H), 8.21 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.87 (dd, *J* = 1.7, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 52.7, 121.4, 123.5, 125.8, 126.4, 127.6, 128.7, 128.8, 129.5, 132.9, 135.3, 136.4, 140.2, 144.3, 144.8, 150.1, 168.8; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{18}H_{14}BrN_2O$: 353.0284, found: 353.0286.

*5-Iodo-7-methyl-2-(quinolin-8-yl)isoindolin-1-one (**2h**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 39 mg (39%), yellow solid; mp 231.9−233.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (s, 3H), 5.19 (s, 2H), 7.43 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.60−7.64 (m, 2H), 7.71 (s, 1H), 7.83 (dd, *J* = 1.3, 8.2 Hz, 1H), 7.90 (dd, *J* = 1.4, 8.4 Hz, 1H), 8.21 (dd, *J* = 1.7. 8.3 Hz, 1H), 8.87 (dd, *J* = 1.7, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 52.5, 98.3, 121.4, 126.4, 127.6, 128.9, 129.3, 129.4, 129.5, 135.2, 136.4, 138.8, 140.2, 144.3, 144.8, 150.1, 168.9; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{18}H_{14}IN_2O$: 401.0145, found: 401.0147.

*7-Pentyl-2-(quinolin-8-yl)isoindolin-1-one (**2i**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent; 45 mg (55%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0, 3H), 1.31−1.43 (m, 4H), 1.68−1.75 (m, 2H), 3.21 (t, *J* = 7.8 Hz, 2H), 5.24 (s, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.42 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.62 (dd, *J* = 7.6, 8.0 Hz, 1H), 7.81 (dd, *J* = 1.4, 8.2 Hz, 1H), 7.93 (dd, *J* = 1.4, 7.4 Hz, 1H), 8.20 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.88 (dd, *J* = 1.7, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 31.1, 31.3, 31.9 53.2, 120.2, 121.4, 126.4, 127.3, 128.9, 129.0, 129.1, 129.5, 131.3, 135.7, 136.4, 143.3, 143.6, 144.4, 150.0, 169.3; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{22}H_{23}N_2O$: 331.1805, found: 331.1804.

*7-Isopropyl-2-(quinolin-8-yl)isoindolin-1-one (**2j**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent; 36 mg (48%); yellow solid; mp 164.9−166.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.9 Hz, 6H), 4.48 (septet, *J* = 6.9 Hz, 1H), 5.23 (s, 2H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.40−7.44 (m, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.82 (dd, *J* = 1.0, 8.3 Hz, 1H), 7.93 (dd, *J* = 1.3, 7.4 Hz, 1H), 8.20 (dd, *J* = 1.1, 8.2 Hz, 1H), 8.88 (dd, *J* = 1.7, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 26.8, 53.0, 120.1, 121.4, 124.7, 126.4, 127.3, 128.2, 128.9, 129.5, 131.7, 135.8, 136.4, 143.1, 144.5, 149.7, 150.0, 169.3; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{20}H_{19}N_2O$: 303.1492, found: 303.1489.

*2-(5-Methoxyquinolin-8-yl)-5,7-dimethylisoindolin-1-one (**2r**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (2:1, v/v) as an eluent; 48 mg (60%); yellow solid; mp 218.9−220.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 2.74 (s, 3H), 4.04 (s, 3H), 5.06 (s, 2H), 6.91 (d, *J* = 8.3 Hz, 1H), 7.05 (s, 1H), 7.12 (s, 1H), 7.38 (dd, *J* = 4.2, 8.5 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 8.60 (dd, *J* = 1.8, 8.5 Hz, 1H), 8.85 (dd, *J* = 1.8, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 21.7, 53.1, 55.9, 103.9, 120.4, 120.6, 121.6, 127.3, 128.4, 129.2, 130.8, 131.1, 137.8, 141.6, 143.5, 145.2, 150.4, 154.6, 169.9; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{20}H_{19}N_2O_2$: 319.1441, found: 319.1441.

*5,7-Dimethyl-2-(naphthalen-1-yl)isoindolin-1-one (**2b-Np**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (2:1, v/v) followed by GPC with ethyl acetate as an eluent; 27 mg (38%); yellow solid; mp 164.2−165.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.75 (s, 3H), 4.78 (s, 2H), 7.13 (d, *J* = 10.6 Hz, 2H), 7.45−7.55 (m, 4H), 7.72−7.74 (m, 1H), 7.87−7.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 21.8, 53.4, 120.8, 123.1, 125.6, 125.7, 126.3, 126.8, 126.9, 128.4, 128.5, 130.7, 131.4, 134.6, 135.5, 138.2, 142.0, 142.8, 169.5; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{20}H_{18}NO$: 288.1383, found: 288.1382.

*Typical Procedure for Copper-Catalyzed Intramolecular Benzylic C−H Amination of 2,5-Disubstituted Benzamides 1 and 2,6-Disubstituted Benzamides **1i-Np** and **1j-Np**.* The synthesis of **2l** is representative. $Cu(OPiv)_2$ (13 mg, 0.050 mmol), 2,5-dimethyl-*N*-(quinolin-8-yl)benzamide (**1l**; 69 mg, 0.25 mmol), pivalic acid (26 mg, 0.25 mmol), and MnO_2 (130 mg, 1.5 mmol) were placed in a 2.0 mL microwave vessel, and the vessel was flushed with nitrogen. Diethylene glycol dimethyl ether (diglyme, 1.5 mL) was sequentially injected via a syringe. The mixture was irradiated under microwave reactor conditions at 200 °C for 1 h. The resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate three times, and the combined organic layer was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (1/1, v/v) afforded 6-methyl-2-(quinolin-8-yl)isoindolin-1-one (**2l**; 45 mg, 0.16 mmol) in 65% yield.

*6-Methyl-2-(quinolin-8-yl)isoindolin-1-one (**2l**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (1:1, v/v) as an eluent; 45 mg (65%); yellow solid; mp 167.6−168.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 5.25 (s, 2H), 7.40−7.45 (m, 3H), 7.64 (dd, *J* = 7.5, 8.1 Hz, 1H), 7.83 (dd, *J* = 1.3, 8.3 Hz, 2H), 7.93 (dd, *J* = 1.4, 7.4 Hz, 1H), 8.21 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.89 (dd, *J* = 1.8, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 53.7, 121.4, 122.4, 124.5, 126.5, 127.5, 128.7, 129.5, 132.7, 132.8, 135.7, 136.4, 137.9, 139.7, 144.3, 150.0, 169.0; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{18}H_{15}N_2O$: 275.1179, found: 275.1177.

*6-Methoxy-2-(quinolin-8-yl)isoindolin-1-one (**2m**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (5/1, v/v) as an eluent; 38 mg (53%), pale yellow solid; mp 163.8−165.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 5.21 (s, 2H), 7.18 (dd, *J* = 2.5, 8.3 Hz, 1H), 7.40−7.44 (m, 2H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.83 (dd, *J* = 1.3, 8.2 Hz, 1H), 7.93 (dd, *J* = 1.4, 7.4 Hz, 1H), 8.21 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.88 (dd, *J* = 1.8, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.5, 55.8, 106.8, 120.4, 121.4, 123.6, 126.5, 127.5, 128.6, 129.5, 133.9, 134.8, 135.7, 136.4, 144.3, 150.0, 159.9, 168.9; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{18}H_{15}N_2O_2$: 291.1128, found: 291.1124.

*6-Chloro-2-(quinolin-8-yl)isoindolin-1-one (**2n**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (1:1, v/v) as an eluent; 48 mg (65%); yellow solid; mp 159.6−161.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (s, 2H), 7.43−7.48 (m, 2H), 7.58 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.64 (dd, *J* = 7.5, 8.1 Hz, 1H), 7.85 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.93 (d, *J* = 1.4 Hz, 1H), 7.97 (d, *J* = 1.8 Hz, 1H), 8.22 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.88 (dd, *J* = 1.8, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.5, 121.5, 124.0, 124.5, 126.4, 127.8, 128.7, 129.5, 131.9, 134.2, 134.4, 135.2, 136.4, 140.6, 144.1, 150.1, 167.5; HRMS (APCI) *m*/*z* ([M + H]$^+$) calcd for $C_{17}H_{12}ClN_2O$: 295.0633, found: 295.0630.

*6-Bromo-2-(quinolin-8-yl)isoindolin-1-one (**2o**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (1:1, v/v) as an eluent; 38 mg (45%); yellow solid; mp 160.9−162.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 2H), 7.40−7.46 (m, 2H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.73 (dd, *J* = 1.8, 8.0 Hz, 1H), 7.85 (dd, *J* = 1.2, 8.2 Hz, 1H), 7.93 (dd, *J* = 1.3, 7.4 Hz, 1H), 8.13 (d, *J* = 1.7 Hz, 1H), 8.22 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.88 (dd, *J* = 1.7, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.6, 121.5, 121.9, 124.4, 126.4, 127.5, 127.8, 128.7, 129.5, 134.7 (2C), 135.1, 136.4, 141.1, 144.1, 150.1, 167.4;

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HRMS (APCI) m/z ([M + H]$^+$) calcd for $C_{17}H_{12}BrN_2O$: 339.0128, found: 339.0127.

(7R,7aS*)-11-Methyl-7-propyl-7,7a-dihydro-12H-benzo[g]-isoindolo[2,1-a]indol-12-one (**2i-Np′**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (10:1, v/v) followed by GPC with chloroform as an eluent; 15.7 mg (19%); yellow solid; mp 142.0−143.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J = 7.3 Hz, 3H), 1.60−1.74 (m, 2H), 2.34−2.50 (m, 2H), 2.84 (s, 3H), 3.11−3.13 (dt, J = 12.0, 3.6 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.46−7.57 (m, 5 H), 7.65 (dd, J = 0.9, 8.2 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 8.43 (dd, J = 1.0, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 16.8, 17.8, 29.5, 43.3, 59.1, 116.1, 121.3, 121.9, 123.7, 123.8, 125.9, 126.2, 126.7, 130.4, 130.9, 131.3, 133.1, 133.3, 134.0, 138.9, 144.2, 166.6; HRMS (APCI) m/z ([M + H]$^+$) calcd for $C_{23}H_{22}NO$: 328.1696, found: 328.1703.

*3,3,7-Trimethyl-2-(naphthalen-1-yl)isoindolin-1-one (**2j-Np**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (9:1 to 5:1, v/v) as an eluent; 14 mg (18%); white solid; mp 203.2−204.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.68 (s, 3H), 2.78 (s, 3H), 7.26−7.27 (m, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.42−7.57 (m, 5H), 7.74−7.77 (m, 1H), 7.90−7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 26.1, 28.0, 64.4, 118.4, 124.0, 125.4, 126.2, 126.7, 127.3, 128.0, 128.4, 129.1, 130.2, 131.6, 132.1, 132.7, 134.8, 138.6, 153.0, 168.7; HRMS (APCI) m/z ([M + H]$^+$) calcd for $C_{21}H_{20}NO$: 302.1539, found: 302.1540.

*7a,11-Dimethyl-7,7a-dihydro-12H-benzo[g]isoindolo[2,1-a]-indol-12-one (**2j-Np′**).* Purified by column chromatography on silica gel with hexane/ethyl acetate (9:1, v/v) followed by GPC with ethyl acetate as an eluent; 29 mg (38%); white solid; mp 177.9−179.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 2.83 (s, 3H), 3.16 (d, J = 15.0 Hz, 1H), 3.46 (d, J = 15.0 Hz, 1H), 7.26−7.31 (m, 2H), 7.39 (d, J = 7.5 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 8.43 (dd, J = 1.1, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 23.8, 40.8, 60.7, 117.5, 118.3, 122.8, 123.8, 125.6, 125.9, 126.5, 126.8, 128.3, 129.3, 130.6, 131.5, 131.9, 133.6, 138.8, 151.2, 166.4; HRMS (APCI) m/z ([M + H]$^+$) calcd for $C_{21}H_{18}NO$: 300.1383, found: 300.1384.

*Procedure for Deprotection of **2r**.* 2-(5-Methoxyquinolin-8-yl)-5,7-dimethylisoindolin-1-one (**2r**; 48 mg, 0.15 mmol) was placed in a 20 mL two-necked reaction flask, and the flask was flushed with nitrogen. Anhydrous dichloromethane (1.7 mL) was added to the solution. The resulting solution was cooled to 0 °C, and BBr_3 (1.0 M dichloromethane solution, 0.60 mL, 0.60 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was quenched with H_2O at 0 °C (20 mL) and extracted with chloroform (3 × 20 mL). Combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual solid and PhI(TFA)$_2$ (97 mg, 0.23 mmol) were placed in another 20 mL two-necked reaction flask, and the flask was flushed with nitrogen. Acetonitrile (6.0 mL), THF (1.9 mL), and H_2O (5.3 mL) were sequentially added at 0 °C. The reaction mixture was stirred at the same temperature for 4 h. The mixture was quenched with H_2O at 0 °C (20 mL) and extracted with chloroform/2-PrOH (3/1) (3 × 20 mL). Combined organic phase was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, purification by GPC (chloroform) afforded 5,7-dimethylisoindolin-1-one (**2r-H**; 12 mg, 0.077 mmol) in 51% overall yield.

*5,7-Dimethylisoindolin-1-one (**2r-H**).* Purified by GPC with chloroform as an eluent; 12 mg (51%); yellow solid; mp 164.2−165.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.68 (s, 3H), 4.34 (s, 2H), 6.62 (bs, 1H), 7.01 (s, 1H), 7.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 21.7, 44.7, 121.1, 126.6,130.9, 137.6, 142.0, 144.8, 172.6; HRMS (APCI) m/z ([M + H]$^+$) calcd for $C_{10}H_{12}NO$: 162.0913, found: 162.0914.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01393.

Detailed kinetic profiles for the reaction of **1l** and **1l-*d*$_3$**, ^{1}H and ^{13}C{^{1}H} NMR spectra for products, an ORTEP drawing of **2b**, and detailed pathways leading to **2i-Np′** and **2j-Np**/**2j-Np′** (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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(16) Crystallographic data for the structure of **2b** has been deposited with the Cambridge Crystallographic Data Center (CCDC 1483551). See the Supporting Information for details.

(17) The yields of **2b** with other copper salts under conditions of entry 5 are shown as follows: Cu(eh) (50%), $Cu(OBz)_2$ (38%), CuOAc (45%), $Cu(OTf)_2$ (24%), CuI (23%), and $CuCl_2$ (18%).

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