



Copper-mediated oxidative C–H/N–H activations with alkynes by removable hydrazides

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Abstract

The efficient copper-mediated oxidative C–H alkynylation of benzhydrazides was accomplished with terminal alkynes. Thus, a heteroaromatic removable *N*-2-pyridylhydrazide allowed for domino C–H/N–H functionalization. The approach featured remarkable functional group compatibility and ample substrate scope. Thereby, highly functionalized aromatic and heteroaromatic isindolin-1-ones were accessed with high efficacy with rate-limiting C–H cleavage.

Introduction

Inexpensive copper-promoted oxidative C–H activations [1–11] have been recognized as competent tools for the efficient assembly and late-stage functionalization of organic molecules due to the natural abundance and versatile reactivity. Early examples of copper-promoted C–H activation of 2-arylpyridines were disclosed by Yu et al. [12] and Chatami et al. [13] independently. Inspired by these studies, various copper-induced

C–H functionalizations, such as arylations, alkynylations, cyanations, aminations, nitrations, oxygenations, thiolations, halogenations, and phosphorylations, among others, were accomplished [14–19].

The 3-methyleneisindolin-1-one moiety represents a key structure motif in natural products [20–23] or important pharma-

cophores [24]. In this context, You [25], Huang [26], Liu [27], Li [28], and co-workers elegantly disclosed copper-mediated/catalyzed cascade C–H alkylation and annulation with terminal alkynes to afford 3-methyleneisindolinone derivatives, through the assistance of 8-aminoquinoline [29] or 2-aminophenyl-1*H*-pyrazole [30] auxiliaries (Figure 1a). Besides, the cobalt(II)- [31] or nickel(II)-catalyzed [32,33], pyridine oxide (PyO)-directed tandem alkylation/annulation was realized by Niu and Song et al., which also provided the 3-methyleneisindolin-1-one scaffolds (Figure 1b). Notably, a sustainable cupraelectro-catalyzed alkyne annulation was very recently achieved by Ackermann et al., which gave rapid access to synthetically meaningful isindolones (Figure 1c) [34]. In spite of these indisputable advances, the successful removal of the directing groups to deliver the free-NH 3-methyleneisindolin-1-one has thus far unfortunately proven elusive [35].

2-(1-Methylhydrazinyl)pyridine (MHP) [36] was identified as a powerful removable bidentate directing group, which found widespread application in various cobalt-catalyzed C–H activations [37–40]. Thus, our group also accomplished a set of electrochemical cobalt-catalyzed C–H activations with the MHP auxiliary [41–44]. In continuation of studies on sustainable 3d transition metal-catalyzed C–H activation [41–49], we have now discovered a robust copper-promoted oxidative C–H/N–H functionalization with terminal alkynes (Figure 1d). Notable advantages of our protocol include: 1) removable MHP auxiliary used

for copper-mediated oxidative C–H activations, 2) excellent functional group tolerance and compatibility with valuable heterocycles, and 3) mechanistic studies toward copper-mediated oxidative C–H alkynylations.

Results and Discussion

We initiated our investigation by utilizing benzhydrazide **1a** and ethynylbenzene (**2a**) as the standard substrates (Table 1). After preliminary solvent optimization, we discovered that the desired *ortho*-selective C–H activation occurred efficiently by the treatment of hydrazide **1a** with terminal alkyne **2a** and a stoichiometric amount of Cu(OAc)₂ in DMSO (Table 1, entries 1–3). Reaction optimization revealed that the most appropriate temperature was 90 °C (Table 1, entries 3–6). An evaluation of bases showed that Na₂CO₃ was optimal (Table 1, entries 7–11). The best result was obtained when Cu(OAc)₂ (1.3 equiv) was utilized in DMSO (6.0 mL, Table 1, entries 12–14). A similar result was obtained when Cu(OAc)₂·H₂O was used instead of Cu(OAc)₂ (Table 1, entry 15). Only a trace amount of product **3aa** was observed in the absence of either Cu(OAc)₂ or Na₂CO₃ (Table 1, entries 16 and 17). When the reaction was performed under a nitrogen atmosphere, the efficacy was significantly decreased (Table 1, entry 18).

We next examined the versatility of the copper-promoted ethynylbenzene (**2a**) annulation with various benzhydrazides **1** under the optimized reaction conditions (Scheme 1). To our

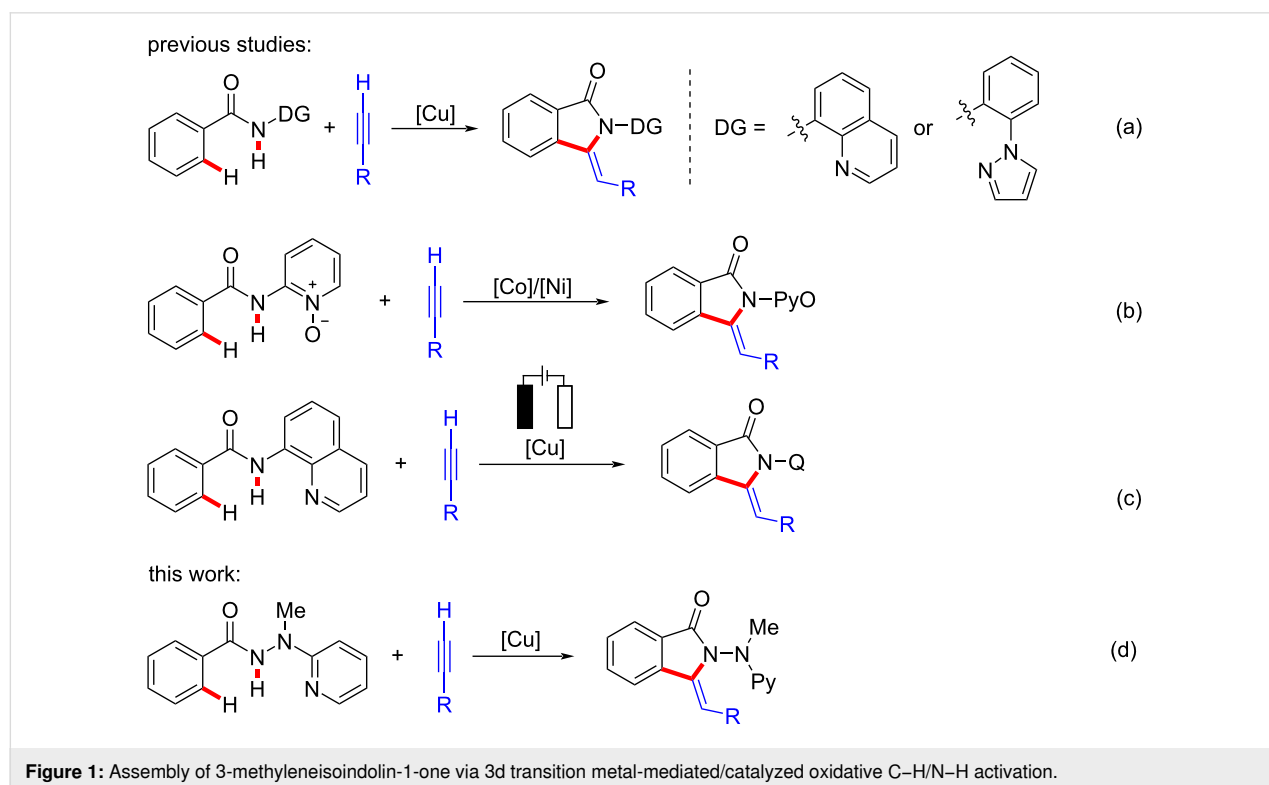
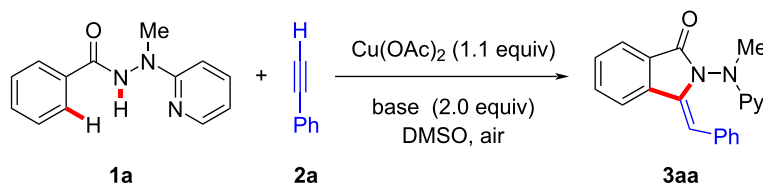


Table 1: Optimization of the copper-mediated C–H/N–H functionalization with terminal alkyne **2a**.^a

entry	solvent	base	<i>T</i> (°C)	<i>Z/E</i>	yield (%)
1	DMF	Na ₂ CO ₃	90	—	trace
2	NMP	Na ₂ CO ₃	90	—	trace
3	DMSO	Na ₂ CO ₃	90	12:1	67
4	DMSO	Na ₂ CO ₃	110	8:1	57
5	DMSO	Na ₂ CO ₃	80	15:1	41
6	DMSO	Na ₂ CO ₃	60	—	27
7	DMSO	NaOAc	90	—	25
8	DMSO	NaOPiv	90	—	30
9	DMSO	K ₂ CO ₃	90	18:1	58
10	DMSO	Cs ₂ CO ₃	90	20:1	44
11	DMSO	DBU	90	—	13
12 ^b	DMSO	Na ₂ CO ₃	90	12:1	42
13 ^c	DMSO	Na ₂ CO ₃	90	9:1	83
14 ^{c,d}	DMSO	Na ₂ CO ₃	90	13:1	89
15 ^{d,e}	DMSO	Na ₂ CO ₃	90	12:1	86
16	DMSO	—	90	—	trace
17 ^f	DMSO	Na ₂ CO ₃	90	—	trace
18 ^g	DMSO	Na ₂ CO ₃	90	—	37

^aReaction conditions: **1a** (0.30 mmol), **2a** (0.90 mmol), Cu(OAc)₂ (1.1 equiv), base (2.0 equiv), solvent (3.0 mL), 15 h, under air. ^bCu(OAc)₂ (0.8 equiv). ^cCu(OAc)₂ (1.3 equiv). ^dDMSO (6.0 mL). ^eCu(OAc)₂·H₂O (1.3 equiv). ^fWithout Cu(OAc)₂. ^gUnder N₂.

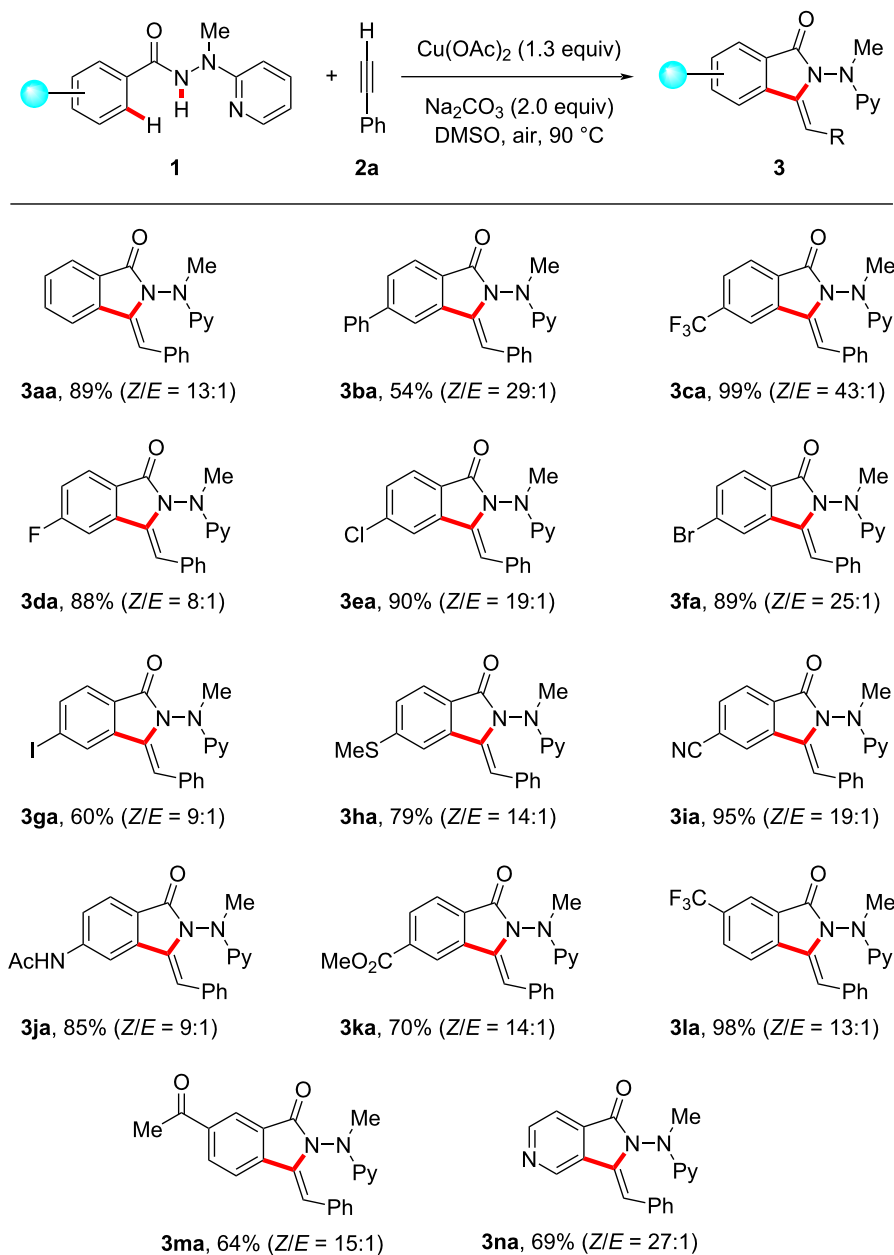
delight, hydrazides **1** with electron-donating or electron-withdrawing substituents were efficiently converted in the C–H/N–H activation annulation process. Notably, a wide range of valuable electrophilic functional groups, such as halogen, methylthio, cyano, amino, and ester groups, were well compatible, which should prove instrumental for the further diversification of the thus obtained 3-methyleneisindolin-1-ones **3da–ka**. For substrates bearing two potential reactive sites, the annulation selectively took place at the less congested *ortho*-C–H bond (see **3la** and **3ma**). Moreover, the challenging isonicotinic acid hydrazide **1n** was also amenable to this protocol and delivered the desired product **3na** with high regioselectivity.

We further investigated the viable scope of differently substituted terminal alkynes **2** as the general coupling partners for this transformation. As shown in Scheme 2, a variety of valuable electrophilic substituents were well tolerated. Moreover, substrates with a highly reactive unprotected amino group also delivered the corresponding product **3cn** with good yield. The

robustness of this protocol was further highlighted by the excellent reactivity of heterocyclic acetylenes (see **2p–r**). However, a complex mixture was observed when an aliphatic terminal alkyne was used, and no annulation product was detected for internal alkynes.

Our copper-promoted C–H annulation protocol was not restricted to terminal alkynes. Under identical reaction conditions, commercially available alkynylcarboxylic acid **4** also proved to be a viable substrate. Thus, the corresponding isindolone **3aa** was assembled via a tandem decarboxylative C–H/C–C sequence (Scheme 3a). The practical relevance of our approach was reflected by the cleavage of the *N*-2-pyridylhydrazide group, yielding **S-3aa** (Scheme 3b).

Inspired by the remarkable robustness of the copper-promoted C–H activations with alkynes, we became interested to explore the working mode by a set of experiments. To this end, electron-poor arenes inherently reacted preferentially in intermolecular competition experiments (Scheme 4a). This observation

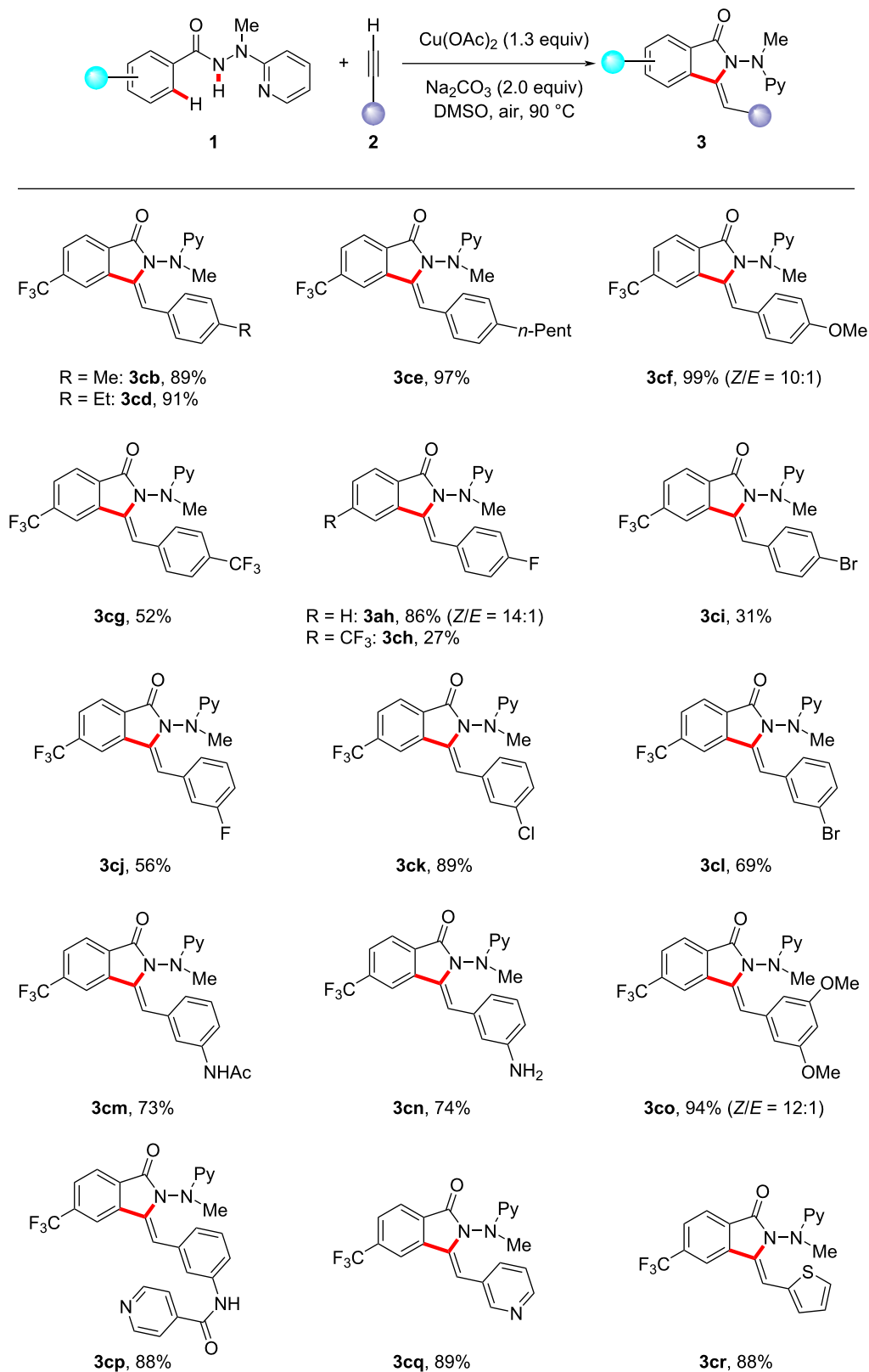


Scheme 1: Copper-mediated oxidative C–H/N–H functionalization of hydrazides **1** with ethynylbenzene (**2a**).

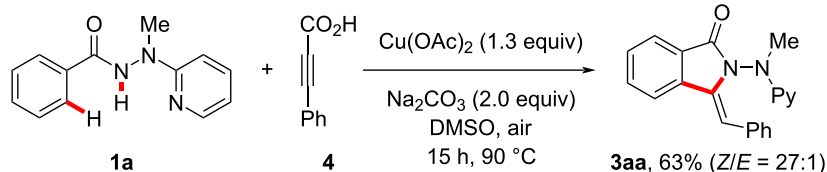
could be explained in terms of a concerted metalation deprotonation (CMD) mechanism [50]. Interestingly, electron-rich alkyne **2f** displayed a higher reactivity in the copper-promoted C–H activations as compared to the electron-poor analog **2h** (Scheme 4b). A significant H/D scrambling was not detected in the *ortho*-position of the reisolated benzhydrazide **1c** and product **3ca** when the reaction was conducted with the isotopically labeled D_2O as cosolvent (Scheme 4c). This observation indicated that the C–H cleavage is irreversible. In accordance with this finding, a kinetic isotope effect (KIE) of $k_{\text{H}}/k_{\text{D}} \approx 6.1$ was

observed by parallel experiments, again suggesting that the C–H activation is kinetically relevant (Scheme 4d).

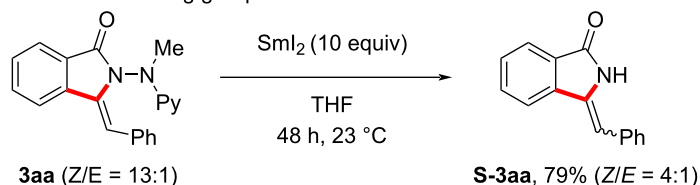
Based on our mechanistic findings and previous studies, we propose a tentative plausible reaction pathway in Scheme 5. The transformation commences with substrate coordination and subsequent carboxylate-assisted C–H cleavage to deliver copper(II) intermediate **A**. Next, the copper(III) carboxylate species **B** is generated. Thereafter, a facile base-assisted ligand exchange is followed by reductive elimination to afford the

Scheme 2: Copper-mediated oxidative C–H/N–H functionalization of **1** with alkynes **2**.

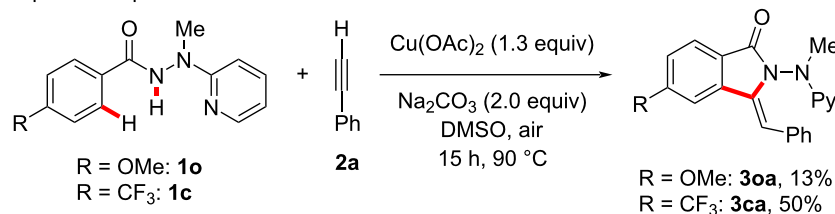
(a) copper-mediated decarboxylative C–H/N–H annulation



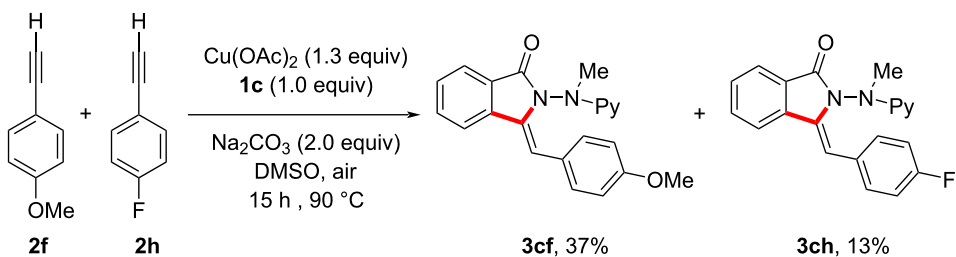
(b) removal of the directing group

**Scheme 3:** Decarboxylative C–H/N–H activation and cleavage of the directing group.

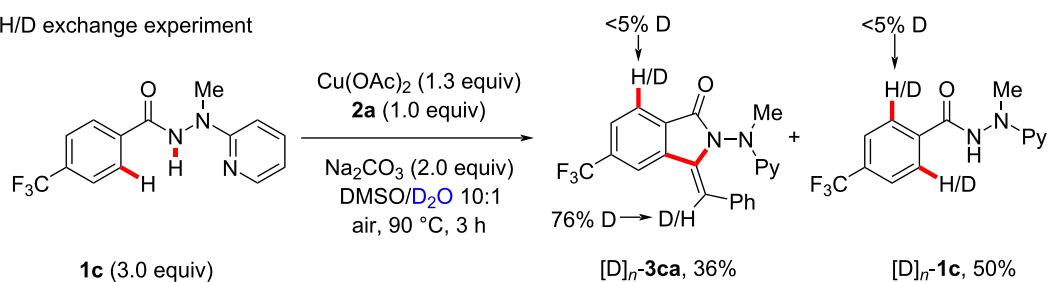
(a) competition experiment



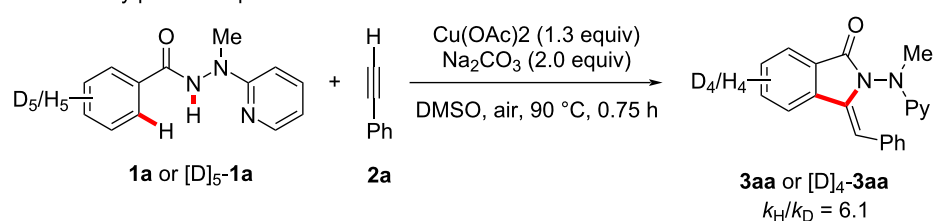
(b) competition experiment

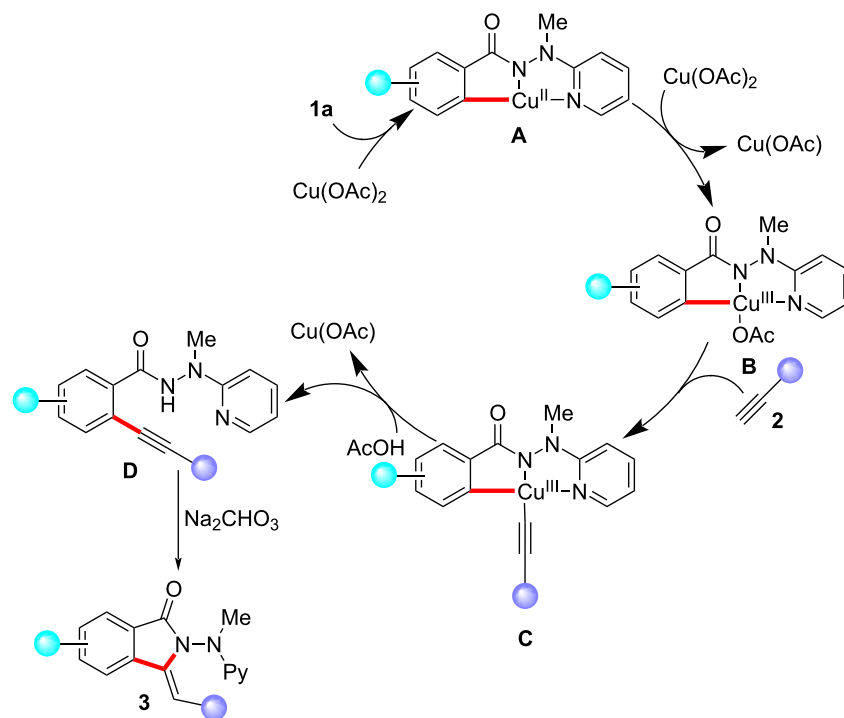


(c) H/D exchange experiment



(d) KIE studies by parallel experiments

**Scheme 4:** Summary of key mechanistic findings.



Scheme 5: Proposed reaction pathway.

alkynylated benzamide **D**. Finally, the desired isoindolone **3** is formed via an intramolecular hydroamination in the presence of base.

Conclusion

In conclusion, we have reported on the chelation-assisted oxidative copper-promoted cascade C–H alkylation and intramolecular annulation. The removable *N*-2-pyridylhydrazide was utilized to facilitate copper(II)-promoted C–H activations. Thus, the robust copper-mediated C–H activation featured remarkable compatibility of synthetically meaningful functional groups, giving facile access to valuable 3-methyleneisoindolin-1-one scaffolds.

Experimental

General information

Yields refer to isolated compounds, estimated to be >95% pure as determined by ^1H NMR spectroscopy. Chromatographic separation was carried out on silica gel 60H (200–300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China). High-resolution mass spectrometry (HRMS) was measured on a Thermo-DPS mass spectrometer. NMR spectra were recorded on a JEOL 600 NMR device (^1H : 600 MHz; ^{13}C : 150 MHz; ^{19}F : 565 MHz) in CDCl_3 . If not otherwise specified, the chemical shift (δ) is given in ppm.

Materials

Reactions were carried out under an argon atmosphere using predried glassware, if not noted otherwise. Benzhydrazides **1** were synthesized according to a previously described method [36,44]. Other chemicals were obtained from commercial sources and were used without further purification.

General procedure for the copper-promoted oxidative C–H/N–H activation with alkynes

To a 25 mL Schlenk tube were added benzhydrazide **1** (0.30 mmol, 1.00 equiv), the alkyne (0.90 mmol, 3.0 equiv), $\text{Cu}(\text{OAc})_2$ (71 mg, 0.39 mmol, 1.30 equiv), and Na_2CO_3 (64 mg, 0.60 mmol, 2.00 equiv) under an air atmosphere. The mixture was stirred at 90 °C for 15 h. At ambient temperature, H_2O (15 mL) and Et_3N (0.5 mL) were added, and a suspension was formed immediately. After filtrated through a Celite[®] pad, the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over Na_2SO_4 . Then, Et_3N (0.5 mL) and silica gel (0.8 g) were added, and the combined solvent was removed under reduced pressure. The residue solid sample was purified by column chromatography on silica gel (petroleum/ EtOAc 5:1 to 2:1, with 1% Et_3N), yielding the desired product **3**.

(Z)-3-Benzylidene-2-(methyl[pyridin-2-yl]amino)isoindolin-1-one (**3aa**)

The general procedure was followed using hydrazide **1a** (68.2 mg, 0.30 mmol) and alkyne **2a** (91.9 mg, 0.90 mmol). Purification by column chromatography on silica gel (petroleum/EtOAc 20:1, with 1% Et₃N) yielded **3aa** (87.4 mg, 89%, Z/E = 13:1) as a light yellow solid. mp 67–68 °C; ¹H NMR (CDCl₃, 600 MHz) δ 8.13 (ddd, *J* = 5.0; 1.9; 0.9 Hz, 1H), 7.90 (dd, *J* = 7.6; 1.0 Hz, 1H), 7.85–7.82 (m, 1H), 7.70 (d, *J* = 1.2 Hz, 1H), 7.56 (dd, *J* = 7.6; 0.9 Hz, 1H), 7.44 (ddd, *J* = 8.8; 7.1; 1.9 Hz, 1H), 7.17–7.05 (m, 5H), 6.85 (d, *J* = 0.9 Hz, 1H), 6.67 (ddd, *J* = 7.2; 5.0; 0.9 Hz, 1H), 6.44–6.41 (m, 1H), 3.01 (s, 3H); ¹³C{¹H} NMR (CDCl₃, 150 MHz) δ 165.7 (C_q), 157.6 (C_q), 147.7 (CH), 137.4 (CH), 136.2 (C_q), 133.2 (C_q), 132.8 (CH), 132.1 (C_q), 129.3 (CH), 128.7 (CH), 127.3 (CH), 127.3 (CH), 126.5 (C_q), 123.8 (CH), 119.8 (CH), 114.3 (CH), 107.8 (CH), 106.4 (CH), 36.7 (CH₃); HRESIMS (*m/z*): [M + H]⁺ calcd for C₂₁H₁₈N₃O, 328.1444; found, 328.1439.

Supporting Information

Supporting Information File 1

Characterization data for **3** and copies of ¹H, ¹³C, and ¹⁹F NMR spectra.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-113-S1.pdf>]

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