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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 alkynylaiton of benzhydrazides was accomplished with terminal alkynes. Thus, a hetero-aromatic removable *N*-2-

pyridylhydrazide allowed for domino C–H/N–H functionalization. The approach featured remarkable functional group compatibility and ample substrates scope. Thereby, highly functionalized aromatic and hetero-aromatic isoindolin-1-ones were accessed with high efficacy with rate-limiting C–H cleavage.

Keywords

copper; benzhydrazides; 3-methyleneisoindolin-1-one; removable directing group

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 molecular due to its natural abundance and versatile reactivity. Early examples of copper-promoted C−H activation of 2-arylpyridines were disclosed by Yu [12] and Chatani [13] independently. Inspired by these studies, various copper-induced C−H functionalizations, such as arylations, alkynylations, cynations, aminations, nitrations, oxygenations, thiolations, halogenations and phosphorylations among others, were accomplished [14-19].

The 3-methyleneisoindolin-1-one moiety represents key structure motif in natural products [20-23] or important pharmacophores [24]. In this context, You [25], Huang [26], Liu [27] and Jack Li [28] elegantly disclosed copper-mediated/catalyzed cascade C−H alkynylation and annulation with terminal alkyne to afford 3-methyleneisoindolinone derivatives, through the assistance of 8-aminoquinoline [29] or 2-aminophnyl-1*H*-pyrazole [30] auxiliaries (Figure 1a). Besides, the cobalt(II) [31] or nickel(II) [32, 33] catalyzed, pyridine oxide (PyO) directed tandem alkynylaiton/annulation were realized by Niu and Song, which also provided the 3-

methyleneisoindolin-1-one scaffolds (Figure 1b). Notably, a sustainable cupraelectro-catalyzed alkyne annulation was very recently achieved by Ackermann, which gave rapid access to synthetically meaningful isoindolones (Figure 1c) [34]. In spite of these indisputable advances, the successful removal of the directing groups to deliver the NH-free 3-methyleneisoindolin-1-one has thus far unfortunately proven elusive [35].

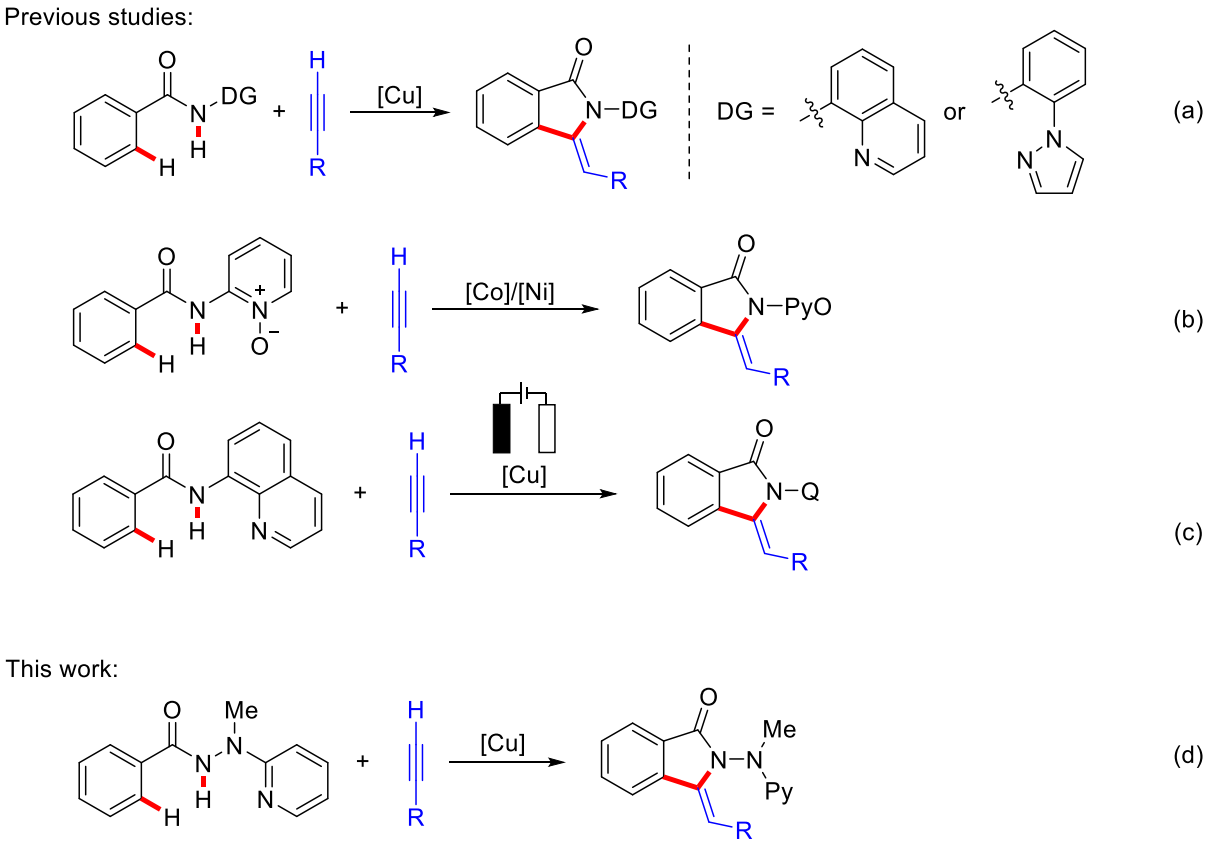


Figure 1: Assembly of 3-methyleneisoindolin-1-one *via* 3d transition metal-mediated/catalyzed oxidative C−H/N−H activation.

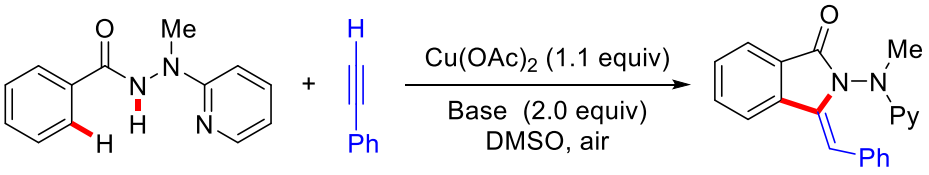
2-(1-Methylhydrazinyl)pyridine (MHP) [36], was identified as a powerful removable bidentate directing group, which found widespread application in various cobalt catalyzed C−H activations [37-40]. Thus, our group also accomplished a set of electrochemical cobalt-catalyzed C−H activations with the MHP 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 includes: 1) removable *N*-2-pyridylhydrazides (MHP) auxiliary used for copper-mediated oxidative C–H activations, 2) excellent functional group tolerance, 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 stoichiometric amount of $Cu(OAc)_2$ in DMSO (entries 1-3). Reaction optimization revealed that the most appropriate temperature was 90 ℃ (entries 3-6). An evaluation of bases showed that Na_2CO_3 was optimal (entries 7-11). The best result was obtained when $Cu(OAc)_2$ (1.3 equiv) was utilized in DMSO (6.0 mL) (entries 12-14). A similar result was abtained when $Cu(OAc)_2 \cdot H_2O$ was used instead of $Cu(OAc)_2$ (entry 15). Only trace amount of product **3aa** was observed in the absence of either $Cu(OAc)_2$ or Na_2CO_3 (entries 16-17). When the reaction was performed under a nitrogen atmosphere, the efficacy was significantly decreased (entry 18).

Table 1: Optimization of copper-mediated C−H/N−H functionalization with terminal alkynes **2a**.[a]



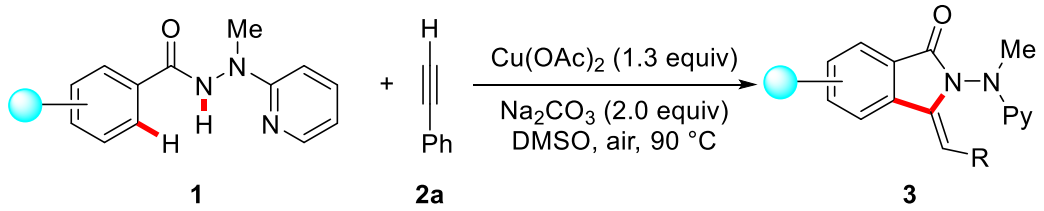
1a **2a** **3aa**

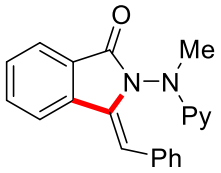
entry	solvent	base	temp. (ºC)	Z/E	yield (%)
1	DMF	Na_2CO_3	90	---	trace
2	NMP	Na_2CO_3	90	---	trace
3	DMSO	Na_2CO_3	90	12/1	67
4	DMSO	Na_2CO_3	110	8/1	57
5	DMSO	Na_2CO_3	80	15/1	41
6	DMSO	Na_2CO_3	60	---	27
7	DMSO	NaOAc	90	---	25
8	DMSO	NaOPiv	90	---	30
9	DMSO	K_2CO_3	90	18/1	58
10	DMSO	Cs_2CO_3	90	20/1	44
11	DMSO	DBU	90	---	13
12[b]	DMSO	Na_2CO_3	90	12/1	42
13[c]	DMSO	Na_2CO_3	90	9/1	83
14[c,d]	DMSO	Na_2CO_3	90	13/1	89
15 [c,d,e]	DMSO	Na_2CO_3	90	12/1	86
16	DMSO	---	90	---	trace
17[f]	DMSO	Na_2CO_3	90	---	trace
18[g]	DMSO	Na_2CO_3	90	---	37

[a] Reaction 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. [b] $Cu(OAc)_2$ (0.8 equiv). [c] $Cu(OAc)_2$ (1.3

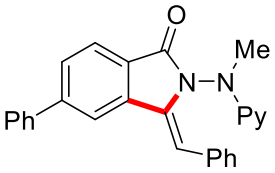
equiv). [d] DMSO (6.0 mL). [e] $Cu(OAc)_2 \cdot H_2O$ (1.3 equiv). [f] Without $Cu(OAc)_2$. g Under N_2.

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 delight, hydrazides **1** with electron-donating or electron-withdrawing substituents were efficiently converted within 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, were well compatible, which should prove instrumental for the further diversification of the thus-obtained 3-methyleneisoindolin-1-one **3da-3ka**. For substrates bearing two potential reactive sites, the annulation selectively took place at the less congested *ortho*-C−H bond (**3la**, **3ma**). Moreover, the challenging isonicotinic acid hydrazide **1n** was also amenable to this protocol and delivered the desired product **3na** with high regio-selectivity.

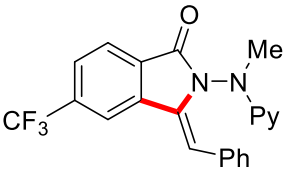




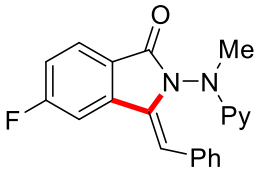
3aa, 89% (Z/E = 13/1)



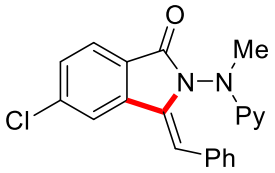
3ba, 54% (Z/E = 29/1)



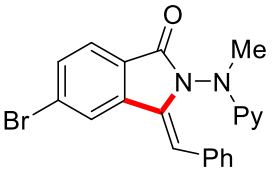
3ca, 99% (Z/E = 43/1)



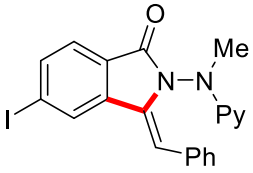
3da, 88% (Z/E = 8/1)



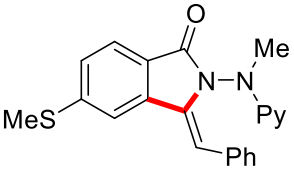
3ea, 90% (Z/E = 19/1)



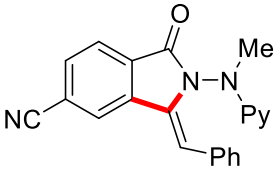
3fa, 89% (Z/E = 25/1)



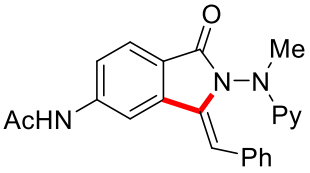
3ga, 60% (Z/E = 9/1)



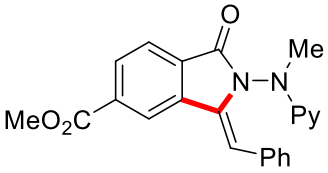
3ha, 79% (Z/E = 14/1)



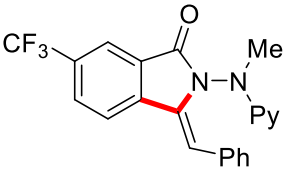
3ia, 95% (Z/E = 19/1)



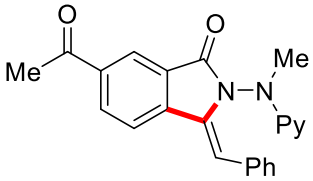
3ja, 85% (Z/E = 9/1)



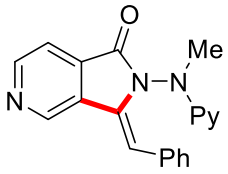
3ka, 70% (Z/E = 14/1)



3la, 98% (Z/E = 13/1)



3ma, 64% (Z/E = 15/1)



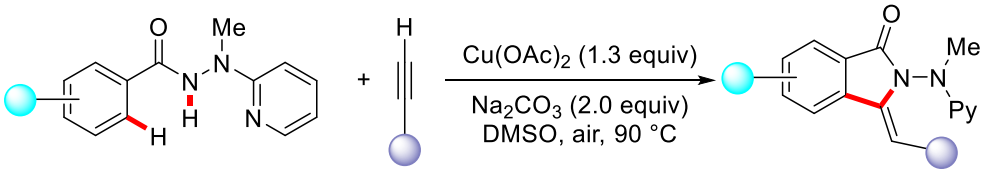
3na, 69% (Z/E = 27/1)

Scheme 1. Copper-mediated oxidative C−H/N−H functionalization of hydrazides **1** with ethynylbenzene **2a**.

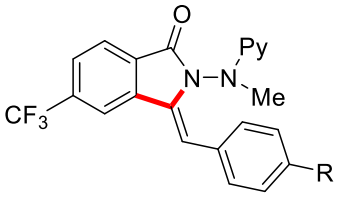
We further investigated the viable scope of differently substituted terminal alkynes **2** as the general coupling partners for this transformation. As showed in Scheme 2, a

variety of valuable electrophilic substitutes were well tolerated. Moreover, substrate 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 (**2p**-**2r**).

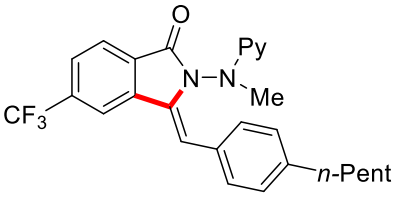
Our copper-promoted C−H annulation protocol was not restricted to terminal alkynes. Under identical reaction conditions, commercially available alkynyl carboxylic acids **4** also proved to be a viable substrate. Thus, the corresponding isoindolone **3aa** was assembled *via* a tandem decarboxylative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



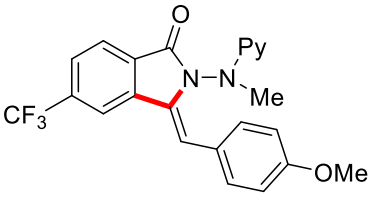
1 **2a** **3**



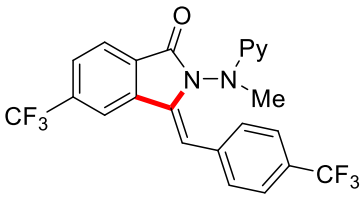
R = Me: **3cb**, 89%
R = Et: **3cd**, 91%



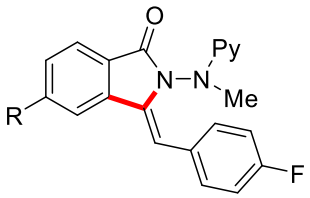
3ce, 97%



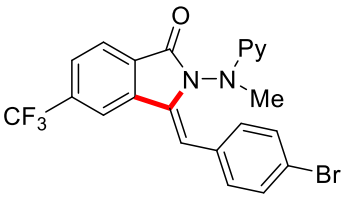
3cf, 99% (Z/E = 10/1)



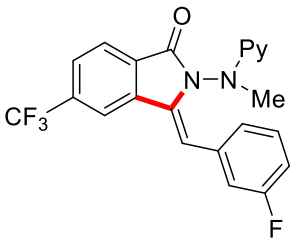
3cg, 52%



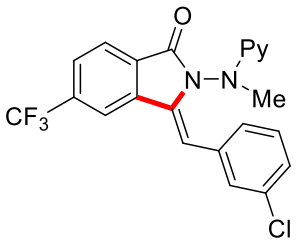
R = H: **3ah**, 86% (Z/E = 14/1)
R = CF_3: **3ch**, 27%



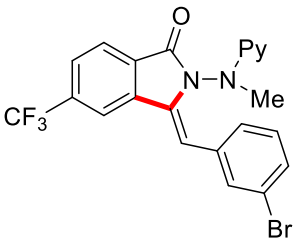
3ci, 31%



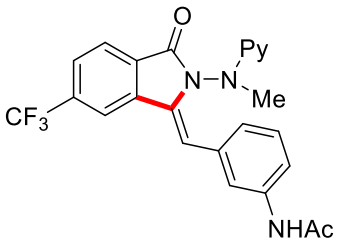
3cj, 56%



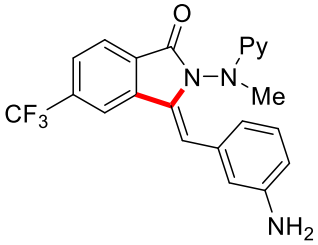
3ck, 89%



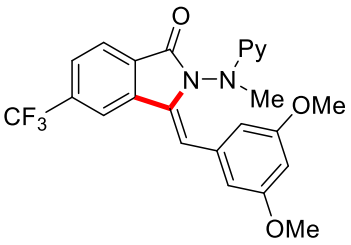
3cl, 69%



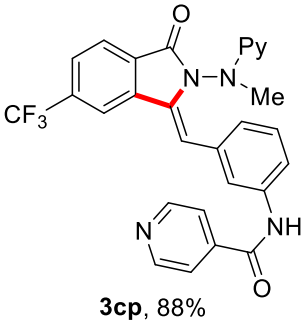
3cm, 73%



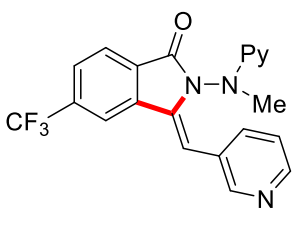
3cn, 74%



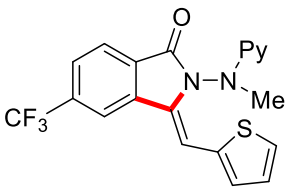
3co, 94% (Z/E = 12/1)



3cp, 88%

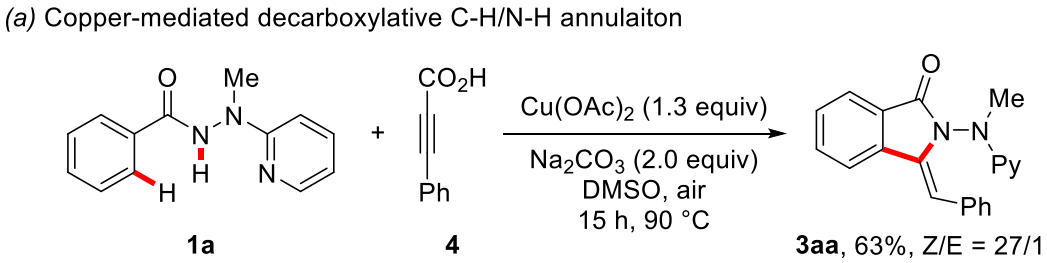


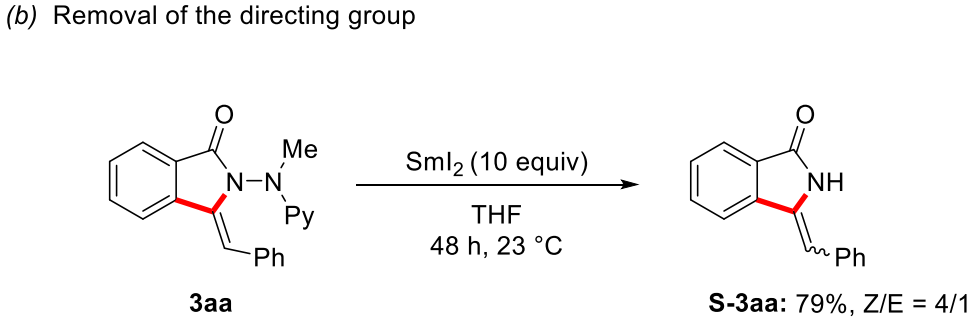
3cq, 89%



3cr, 88%

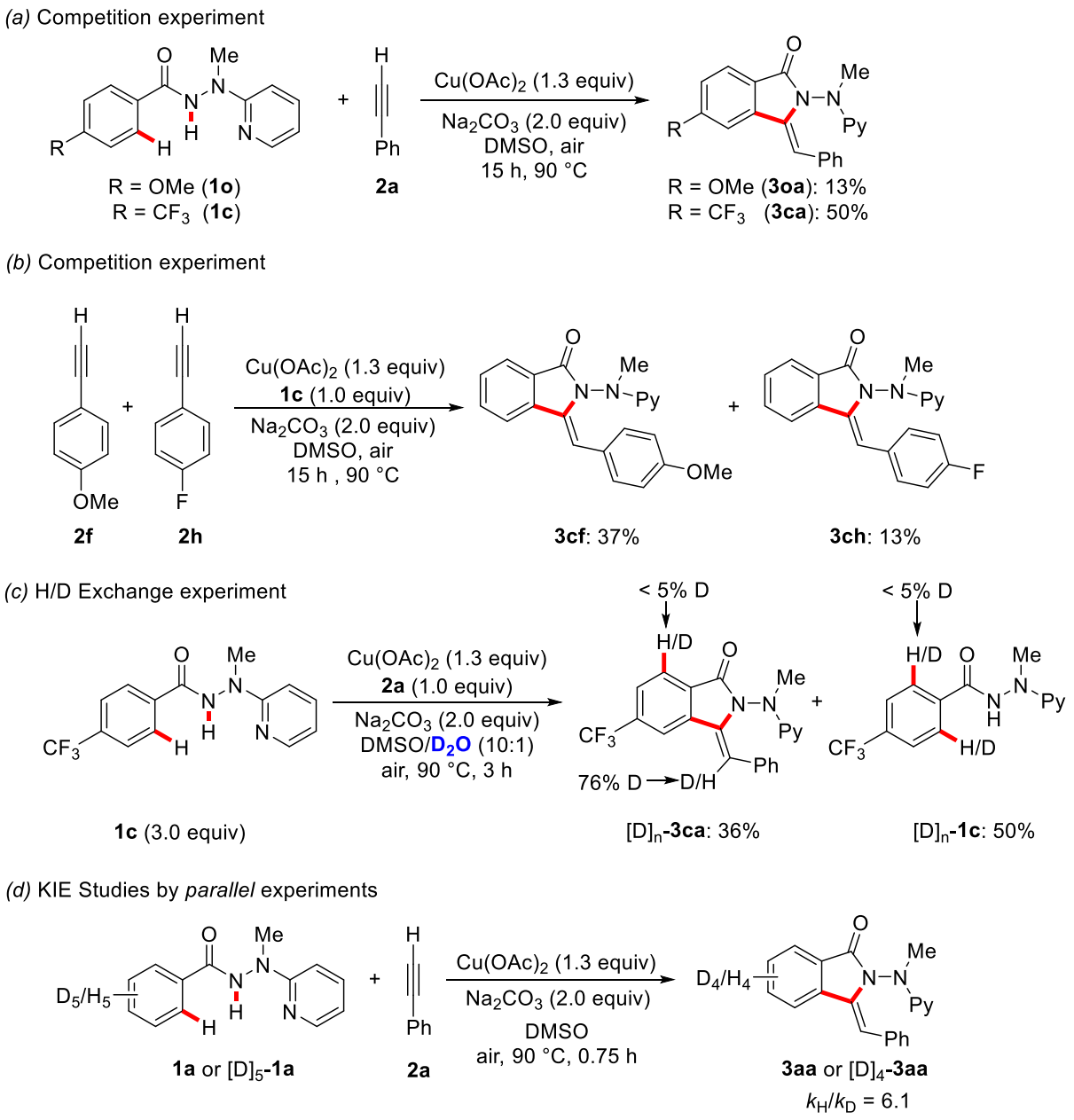
Scheme 2: Copper-mediated oxidative C−H/N−H functionalization of with alkynes **2**





Scheme 3: Decaboxylative C−H/N−H activation and cleavage of the directing group

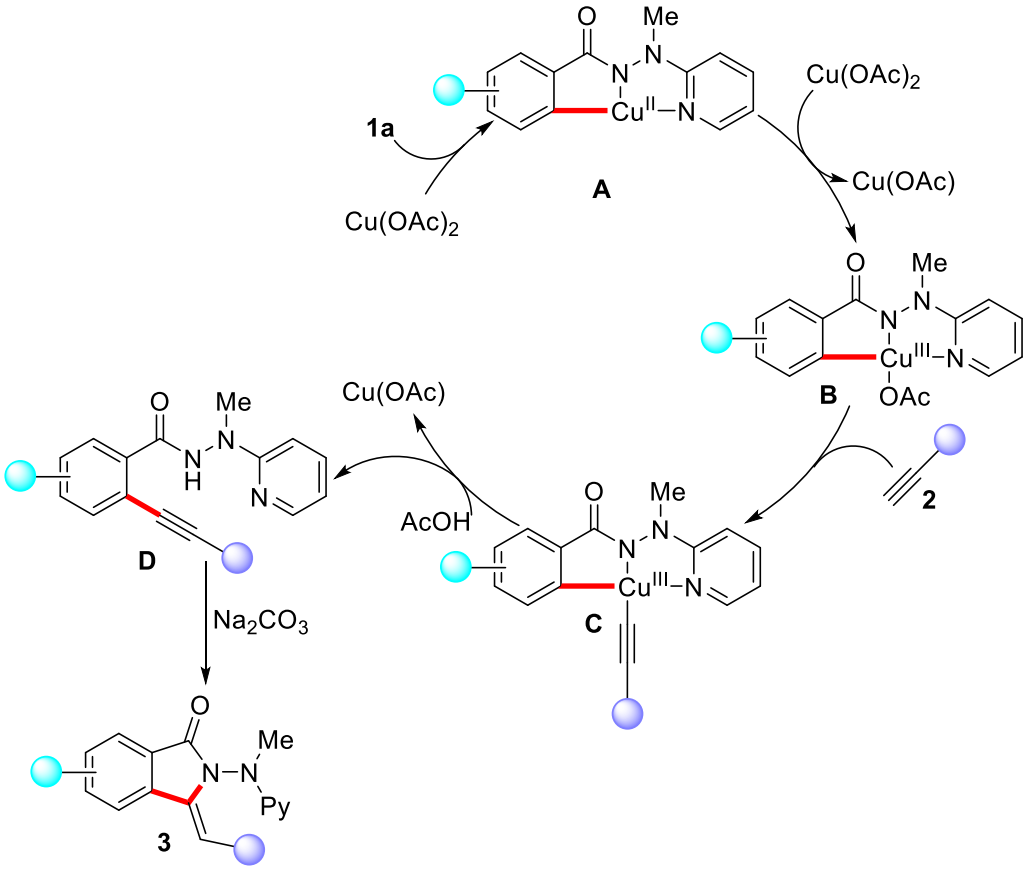
Inspired by the remarkable robustness of the copper-promoted C−H activations with alkynes, we became interested to explore its working mode by a set of experiments. To this end, electron-poor arenes inherently reacted preferentially in intermolecular competition experiments (Scheme 4a). This observation 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 their electron-poor analog (Scheme 4b). A significant H/D scrambling was not detected in the *ortho*-position of the re-isolated benzhydrazide **1c** and product **3ca**, when the reaction was conducted with the isotopically labelled D_2O as co-solvent (Scheme 4c). This observation indicated the C−H cleavage is irreversible. In accordance with this finding, a kinetic isotope effect (KIE) of $k_H/k_D \approx$ 6.1 was observed by parallel experiments, again suggesting that the C–H activation is kinetically relevant (Scheme 4d).



Scheme 4: Summary of key mechanistic findings

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 which was followed by reductive

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



Scheme 5: Proposed reaction pathway.

Conclusion

In conclusion, we have reported on the chelation-assisted oxidative copper-promoted cascade C−H alkynylation 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 ^{1}H-NMR. Chromatography separations were 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 Thermo-DFS mass spectrometer. NMR spectra were recorded on JEOL 600 NMR (^{1}H 600 MHz; ^{13}C 150 MHz; ^{19}F 565 MHz) in $CDCl_3$. If not otherwise specified, chemical shifts (δ) are given in ppm.

Materials

Reactions were carried out under an Argon atmosphere using pre–dried 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 was added benzhydrazide **1** (0.30 mmol, 1.00 equiv), alkyne (0.90 mmol, 3.0 equiv), $Cu(OAc)_2$ (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), 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) yielded 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% Et_3N) yielded **3aa** (87.4 mg, 89%, Z/E = 13:1) as a light yellow solid. M. p.: 67–68 °C. ^{1}H NMR (600 MHz, $CDCl_3$) 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). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) 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 (CH_3). HR-MS (ESI) *m/z* calcd for $C_{21}H_{18}N_3O$ [M+H$^+$] 328.1444, found 328.1439.

Supporting Information

Supporting Information File 1:

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

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