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Received: May 03, 2023; Accepted: June 19, 2023

Highly efficient copper-catalyzed benzylic C–H alkoxylation with NFSI

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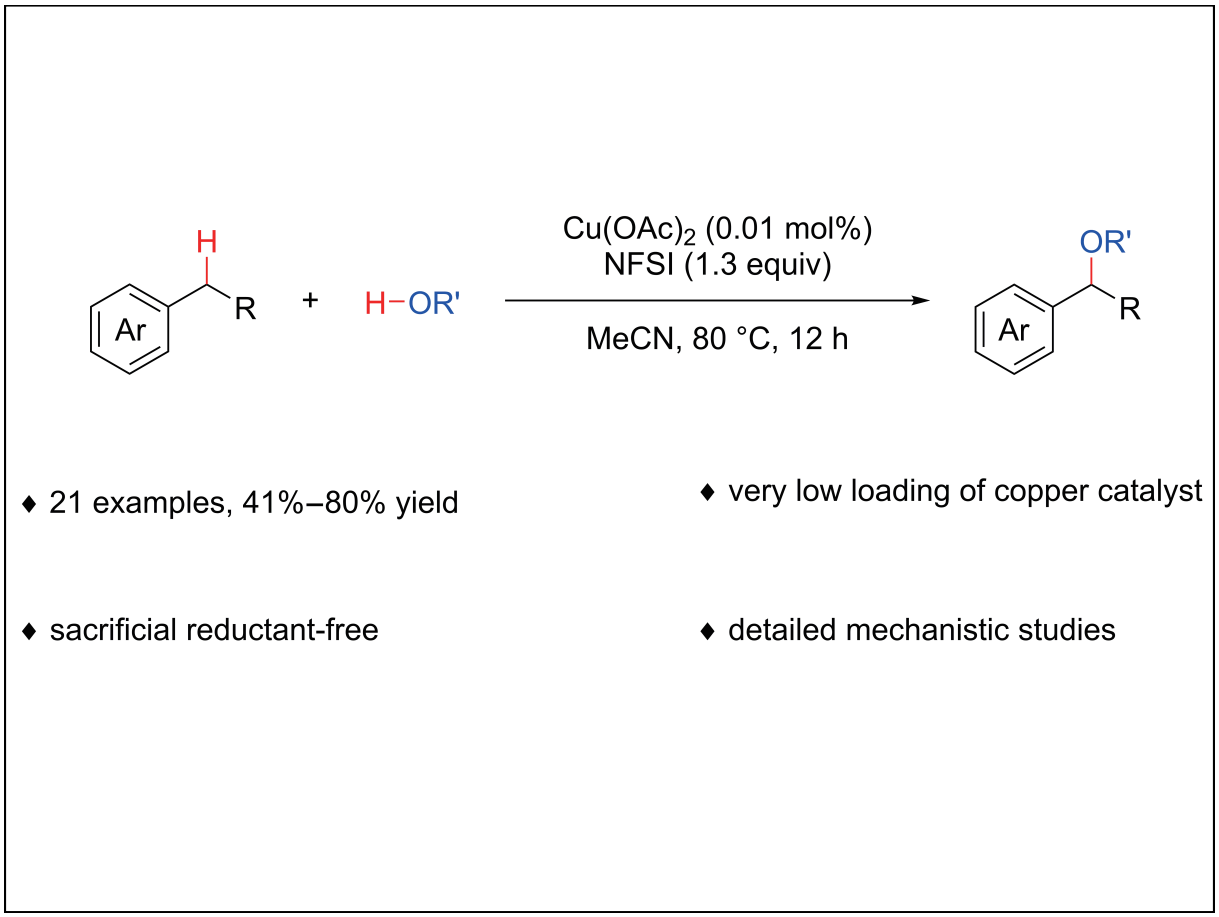
Graphical abstract



A copper-catalyzed benzylic C–H alkoxylation with NFSI without using an external sacrificial reductant.

Public summary

■ A sacrificial reductant-free copper-catalyzed benzylic C–H alkoxylation with NFSI is disclosed.

■ Mechanistic studies suggest a new pathway to generate Cu^{I} from Cu^{II}.

■ This reaction provides an attractive approach for the synthesis of benzyl ethers.

Citation: Zhang C, Wang P S. Highly efficient copper-catalyzed benzylic C–H alkoxylation with NFSI. *JUSTC*, **2023**, 53(12): 1202. DOI: 10.52396/JUSTC-2023-0080

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Cite This: *JUSTC*, **2023**, 53(12): 1202 (6pp) Read Online SI Supporting Information

Abstract: A sacrificial reductant-free copper-catalyzed benzylic C–H alkoxylation with N-Fluorobenzenesulfonimide (NFSI) was reported. Mechanistic studies suggested a novel pathway for the generation of active Cu^{I} species from $Cu(OAc)_2$, NFSI and MeOH. A proper loading amount of copper catalyst was found to balance the reaction rates of benzylic C–H alkoxylation and overoxidation of benzyl ether to exhibit the best performance.

Keywords: C–H activation; hydrogen atom transfer; alkoxylation; alcohol; copper; radical

CLC number: O621.3 **Document code:** A

1 Introduction

Benzyl ethers are frequently encountered building blocks in a range of pharmaceuticals and bioactive molecules owing to their fine stability and pharmacokinetic characteristics (Fig. 1a)[1–4]. The efficient synthesis of benzyl ethers has long received considerable attention from generations of researchers, ranging from conventional Williamson ether synthesis[5,6] to modern catalytic methods of oxidative cross-coupling of alcoholic O–H and benzylic C–H bonds[7,8]. Among them, direct benzylic C–H alkoxylation is an appealing, step- and pot-economic approach for the incorporation of oxygen-centered fragments at the benzylic position of molecules containing alkylarene moieties[9]. In recent years, a number of catalytic methods have been developed for benzylic C−H alkoxylation (Fig. 1b), for instance, light-induced transformations by Yoon

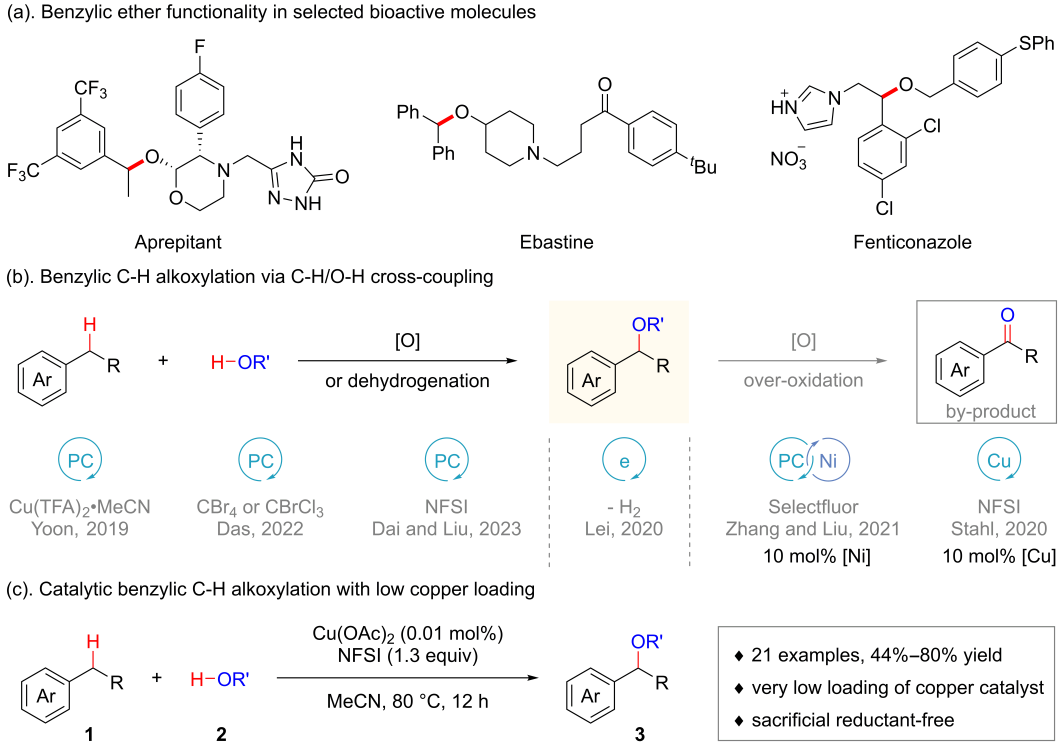

Fig. 1. Strategies toward benzylic C−H alkoxylation.

DOI: 10.52396/JUSTC-2023-0080
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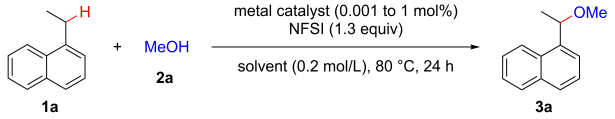
et al.[10], Das et al.[11], and Liu et al.[12], electrochemical transformations by Lei et al.[13], photoredox/nickel dual catalysis by Liu et al.[14], and Cu-catalyzed radical-relay C−H oxidation reactions by Stahl et al[15]. In particular, the radical-relay process[16] has emerged as an attractive catalytic pathway by providing the basis for efficient diversification of a broad scope of substrates. However, in Stahl et al.'s work[15], the presence of a sacrificial reductant (dimethyl phosphite, $(MeO)_2P(O)H$) was critical to maintain the catalytic efficiency of the copper catalyst, in which active Cu^I reacted rapidly with N-Fluorobenzenesulfonimide (NFSI) to generate resting-state Cu^{II} species and nitrogen-centered radical (•NSI) for benzylic C–H activation, and a sacrificial reductant was able to regenerate active Cu^I from Cu^{II}. In this work, we report a sacrificial reductant-free copper-catalyzed benzylic C–H alkoxylation with NFSI by finding an undisclosed pathway for the generation of Cu^I from Cu^{II} (Fig. 1c).

2 Results and discussion

As shown in Table 1, our initial investigation stemmed from the accidental discovery of a "catalyst-free" benzylic C–H alkoxylation of 1-ethylnaphthalene **1a** with methanol **2a** in a tap-water-cleaned Schlenk tube using NFSI as an oxidant at 80 °C, generating benzylic C−H alkoxylation product **3a** in 66% yield (entry 1). However, the use of a distilled-water-cleaned new Schlenk tube resulted in the generation of **3a** in trace amounts (entry 2). Given the residual trace metals in the Schlenk tube[17], a range of transition-metal salts at 0.01 mol% loading were examined (entries 3–9). Interestingly, in comparison with the results of Stahl et al.'s work[15], these reactions did not require a sacrificial reductant to sustain the activity of metal catalysts, and the copper salts were disclosed to be the most active catalyst system (65%–70% yield). The screening of the loading amount of copper catalyst (entries 10–12), methanol **2a** (entries 13–14) and NFSI (entries 15–16) revealed that the use of 0.01 mol% of $Cu(OAc)_2$, together with 5.0 equiv of methanol and 1.3 equiv of NFSI, was able to achieve superior performance in terms of yield. By screening solvents and reaction time (entries 17–19), we found that this catalytic system conducted in MeCN for 12 h was capable of affording **3a** in the best yield of 80%.

With the optimized reaction conditions in hand, the scope of both benzylic C–H and alcohol substrates was explored (Fig. 2). For benzylic C–H substrates, 4-ethylbiphenyl and its derivatives bearing electron-withdrawing substituents were nicely tolerated to give the desired products (**3b**–**3d**) in

Table 1. Optimization of reaction conditions.[a]



entry	metal catalyst	solvent	yield (%)[b]
1[c]	none	MeCN	66
2	none	MeCN	<5
3	$CoCl_2$ (0.01 mol%)	MeCN	<5
4	$FeCl_3$ (0.01 mol%)	MeCN	34
5	$Ni(OTf)_2$ (0.01 mol%)	MeCN	21
6	$Cu(OAc)_2$ (0.01 mol%)	MeCN	70
7	$Cu(OTf)_2$ (0.01 mol%)	MeCN	70
8	$CuCl_2$ (0.01 mol%)	MeCN	70
9	CuCl (0.01 mol%)	MeCN	65
10	$Cu(OAc)_2$ (1 mol%)	MeCN	58
11	$Cu(OAc)_2$ (0.1 mol%)	MeCN	66
12	$Cu(OAc)_2$ (0.001 mol%)	MeCN	55
13[d]	$Cu(OAc)_2$ (0.01 mol%)	MeCN	64
14[e]	$Cu(OAc)_2$ (0.01 mol%)	MeCN	70
15[f]	$Cu(OAc)_2$ (0.01 mol%)	MeCN	68
16[g]	$Cu(OAc)_2$ (0.01 mol%)	MeCN	58
17	$Cu(OAc)_2$ (0.01 mol%)	PhCl	26
18	$Cu(OAc)_2$ (0.01 mol%)	DCM	25
19[h]	$Cu(OAc)_2$ (0.01 mol%)	MeCN	80

[a]Reaction conditions: 1-ethylnaphthalene **1a** (0.10 mmol), methanol **2a** (0.50 mmol), NFSI (0.13 mmol), metal catalyst (0.001 to 1 mol%), solvent (0.5 mL), 80 °C, 24 h, under argon atmosphere, using distilled-water-cleaned new Schlenk tube. [b]Isolated yield. [c]Using tap-water-cleaned Schlenk tube. [d]Using 0.40 mmol **2a**. [e]Using 0.80 mmol **2a**. [f]Using 0.12 mmol NFSI. [g]Using 0.15 mmol NFSI. [h]12 h. NFSI = N-fluorobenzenesulfonimide.

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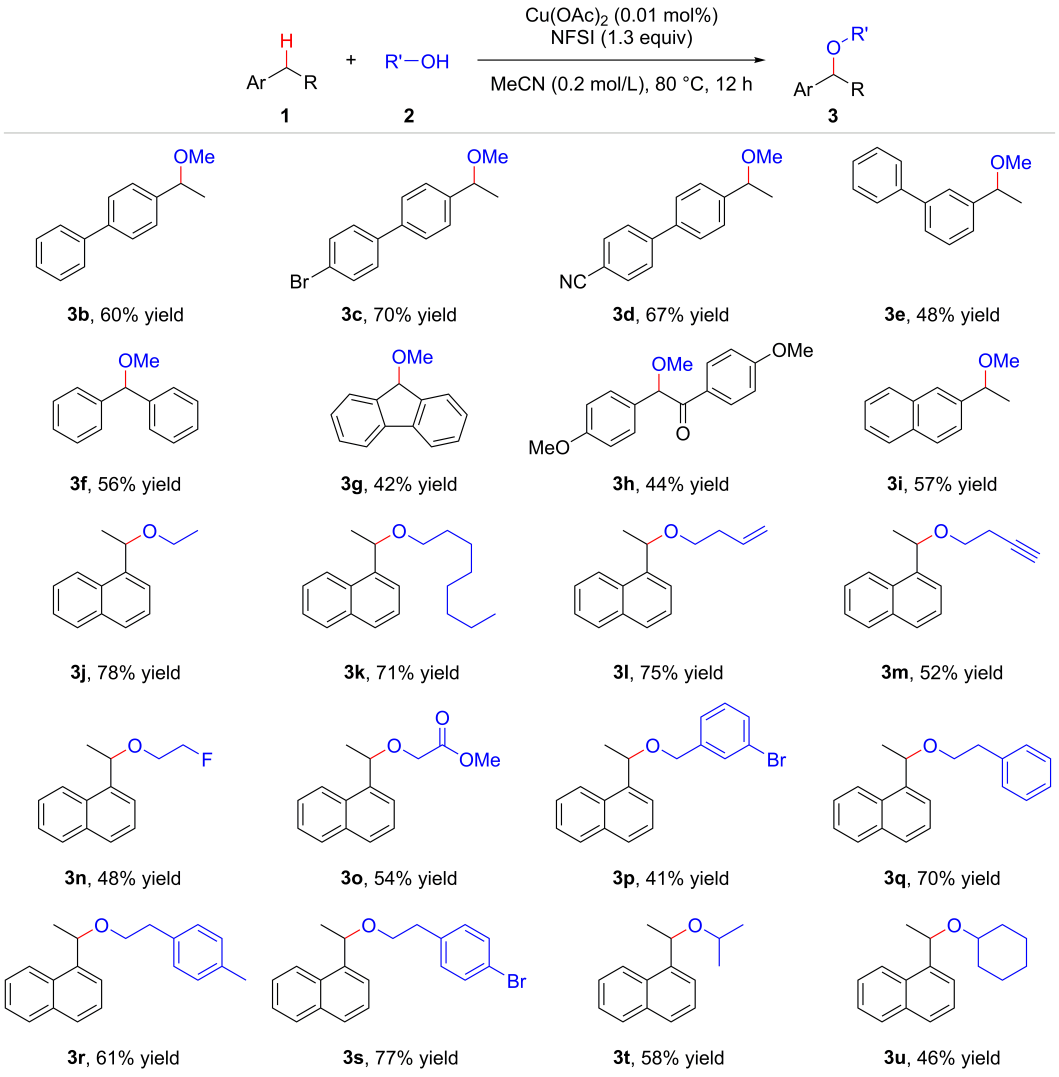

Fig. 2. Scope of substrates. Reaction conditions: alkylarene **1** (0.10 mmol), alcohol **2** (0.50 mmol), NFSI (0.13 mmol), $Cu(OAc)_2$ (0.01 mol%), MeCN (0.5 mL), 80 °C, 12 h, under argon atmosphere. Isolated yield.

60%–70% yield, but the installation of a phenyl group at the *meta*-position of ethylbenzene (**3e**) led to an obvious decrease in the yield. Substrates including benzhydryl, fluorene, phenylacetic ester derivative and 2-ethylnaphthalene could also participate in this oxidative cross-coupling with methanol to give structurally diverse methyl ethers (**3f**–**3i**) in synthetically acceptable yields. For alcohol substrates, the use of aliphatic primary alcohols afforded the desired products (**3j**–**3k**) in good yields, but a larger length of the aliphatic chain slightly decreased the yield. Functional groups such as alkenes, alkynes, alkyl fluoride and esters were well tolerated (48%–75%, **3l**–**3o**). Although benzyl alcohol as a coupling partner only gave a very low yield (see Supporting information), the use of 3-bromobenzyl alcohol smoothly furnished the desired product (**3p**) in 41% yield. Interestingly, 2-arylethanols bearing a longer carbon chain than benzyl alcohol were amenable to generating products (**3q**–**3s**) in 61%–77% yield. In addition, this protocol was also suitable for secondary alcohols to give moderate yields of the corresponding products (**3t**–**3u**).

To probe the kinetic behavior of the reaction, a series of mechanistic studies were carried out. First, monitoring the reaction (Fig. 3) with 0.01 mol% loading amount of $Cu(OAc)_2$ by ^{1}H NMR spectroscopy showed an approximately 30 min induction period for the conversion of **1c** and the appearance of byproduct **4** until 6 h later. Second, both the conversion rate of **1c** and the generation rate of **3c** showed a positive dependence on the loading amount of $Cu(OAc)_2$, while byproduct **4** had a minimal generation rate at a 0.01 mol% loading amount of $Cu(OAc)_2$. These results were in accordance with the experimental results in Table 1, entries 10–12, where the use of 0.01 mol% $Cu(OAc)_2$ exhibited the best catalytic performance. In addition, using *para*-substituted biphenyl benzylic C–H substrates (see Supporting information), comparing substituent effects on the rate of reaction showed that the electron-donating substituent was able to obviously accelerate the reaction[18], indicating that a positive charge might be built during the reaction. Third, control experiments (Fig. 4a) showed that the presence of a $Cu(OAc)_2$ catalyst could significantly accelerate the oxidation rate of ether product **3c** to acetophenone byproduct **4**. Furthermore, the treatment of $Cu(OAc)_2$ with NFSI resulted in an obvious decrease in the characteristic absorption of $Cu(OAc)_2$ in the

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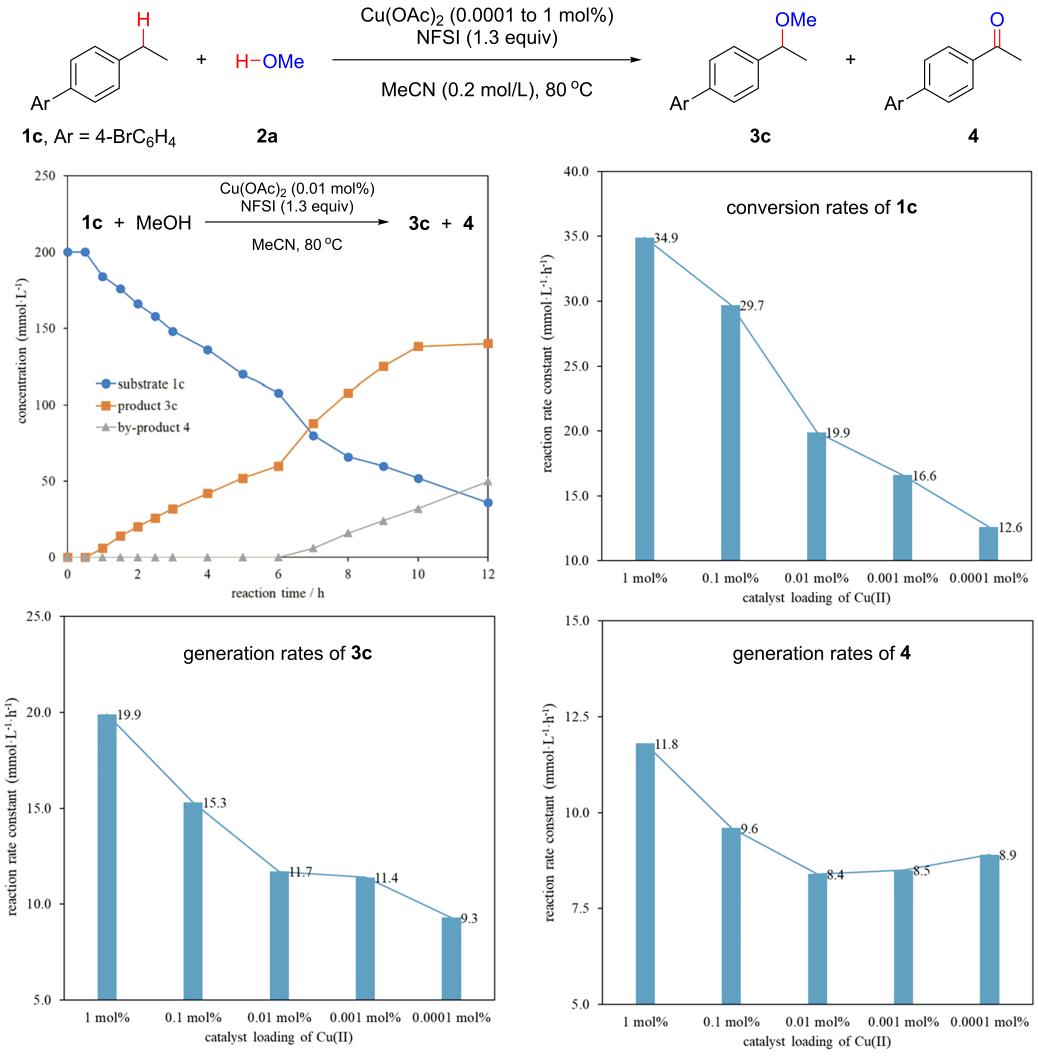

Fig. 3. Kinetic studies.

300–500 nm wavelength range (Fig. 4b) and a new peak of Cu^{II} species in the EPR signals[19], and the addition of NFSI and MeOH to $Cu(OAc)_2$ led to a large change in the peak strengthening of the EPR signals (Fig. 4c). Combining the obtained results and related literature[15,20], we suggested that the active Cu^{I} species might be generated from the sluggish reaction of $Cu(OAc)_2$, NFSI and MeOH, thereby leading to an obvious induction period, as shown in Fig. 3.

Based on the mechanistic investigations, a plausible reaction mechanism was proposed (Fig. 5). In the induction period, active Cu^{I} species were generated from $Cu(OAc)_2$, NFSI and MeOH. Cu^{I} species delivered a N-centered radical $\bullet N(PhSO_2)_2$ and Cu^{II} species after the reaction with NFSI. Then, $\bullet N(PhSO_2)_2$ underwent a productive reaction with the benzylic C–H bond to give a benzyl radical, which was oxidized by Cu^{II} species to provide benzyl cations and regenerate Cu^{I} species. The capture of benzyl cations with alcohol gave rise to the desired benzylic C–H alkoxylation product. Finally, the acetophenone byproduct was generated from a Cu-catalyst oxidation of the benzyl ether product with NFSI.

3 Conclusions

In summary, we have developed a copper-catalyzed benzylic C–H alkoxylation with NFSI without using an external sacrificial reductant by disclosing a novel pathway for the generation of Cu^{I} from Cu^{II}. Mechanistic studies suggest that the active Cu^{I} species can be generated from $Cu(OAc)_2$, NFSI and MeOH by heating, and a proper loading amount of copper catalyst can balance the reaction rates of benzylic C–H alkoxylation and overoxidation of benzyl ether to exhibit the best performance. The current catalytic system was compatible with various benzylic C–H and alcohol substrates, providing an attractive approach for the synthesis of benzyl ethers.

Supporting information

The supporting information for this article can be found online at https:// doi.org/10.52396/JUSTC-2023-0080.

Acknowledgements

This work was supported by USTC Research Funds of the Double First-Class Initiative (YD2060002024), Youth Innovation Promotion Association CAS (2020448), National Natur-

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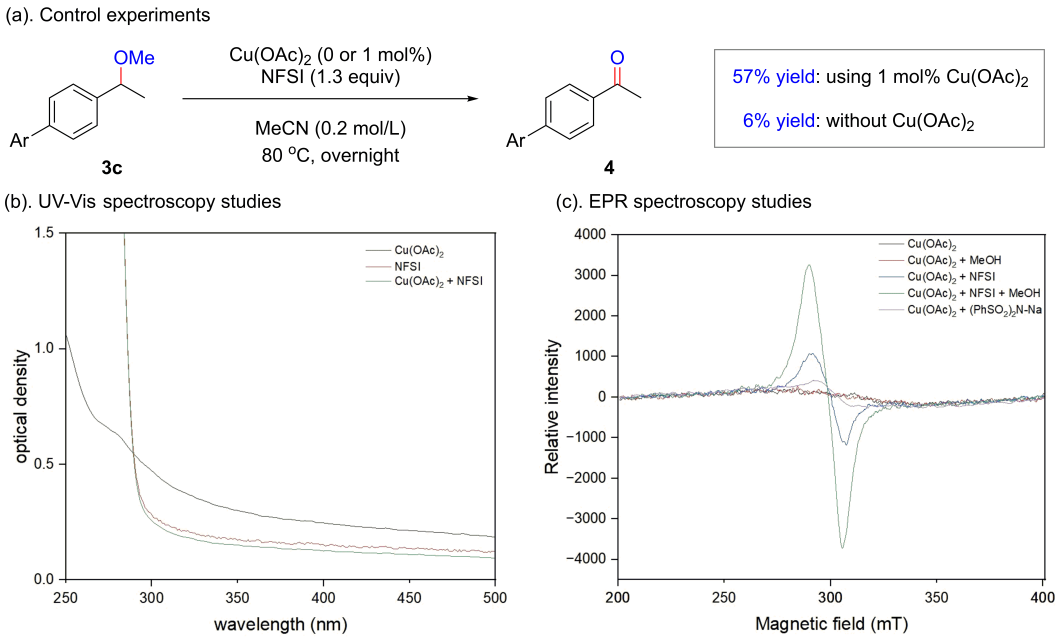

Fig. 4. Mechanistic studies.

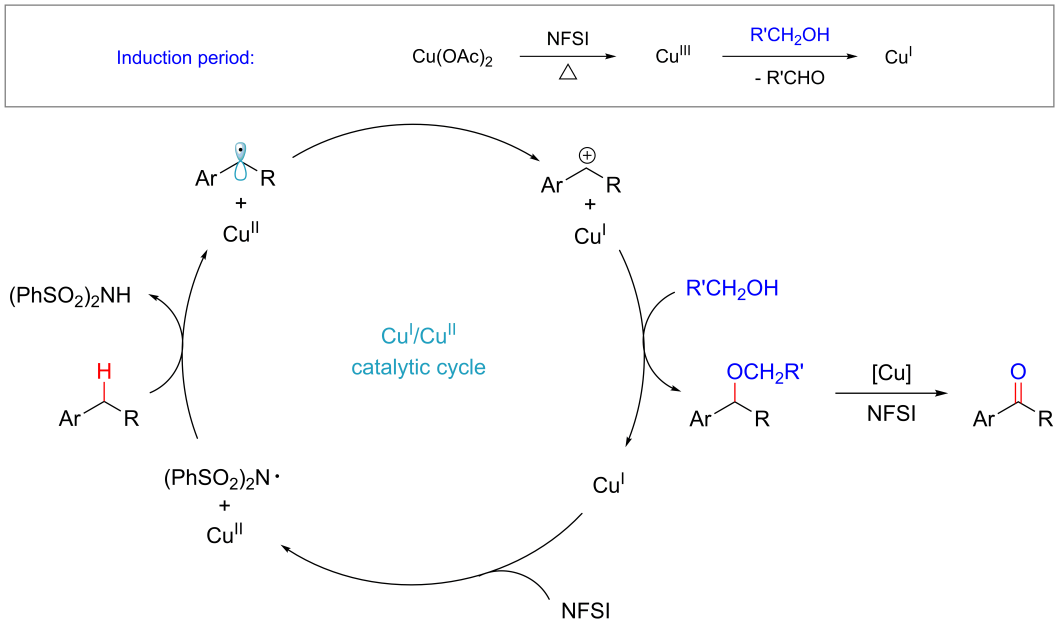

Fig. 5. Proposed catalytic cycle.

al Science Foundation of China (22171254), Anhui Provincial Natural Science Foundation (2108085MB58) and Start-up Research Fund from University of Science and Technology of China (KY2060000216).

Conflict of interest

The authors declare that they have no conflict of interest.

Biographies

Cheng Zhang received his master's degree from the University of Science and Technology of China, under the supervision of Prof. Liu-Zhu Gong. His research mainly focuses on green synthesis and catalysis.

Pu-Sheng Wang received his Ph.D. degree in Chemistry from the University of Science and Technology of China. He is currently an Associate Professor at the University of Science and Technology of China. His research interests include asymmetric catalysis and radical chemistry.

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