COPPER-CATALYZED CYANOPROPYLATION OF ACTIVATED ALKENES

Shi Tang,1,2 Zhi-Hao Li,2 Dong Zhou,2 You-Lin Deng,2 Guo-Liang Ding,2 Qian Zhang,2 Li-Ya Liu,2 and Shu-Hua Li1

1College of Chemistry and Chemical Engineering, Central South University, Changsha, China
2College of Chemistry and Chemical Engineering, Jishou University, Jishou, China

GRAPHICAL ABSTRACT

Abstract A practical copper-catalyzed alkylarylation of activated alkenes with azobisisobutyronitrile (AIBN) and beyond has been developed, in which incorporation of 3° nitrile moiety into an oxindole scaffold proceeded smoothly through cascade radical addition=C(sp2)-H cyclization. The use of readily available AIBN as radical source and inexpensive CuI as catalyst, as well as broad substrate scope and the simplicity of operation and handling, make this protocol a highly attractive approach to oxindoles bearing 3° nitrile moiety.

Keywords 3° nitrile; AIBN; Cu catalysis; cyanopropylation; oxindole

INTRODUCTION

The efficient construction of multiple C-C bonds in a cascade process is a perennial topic of interest for organic chemists.[1] In this regards, inexpensive metal-catalyzed radical biscarbonation of alkenes to form a dual C-C bond simultaneously has attracted increasing attention, where various aryl=alkyl radical precursors, such as aryl diazonium salts, carbazates, diaryliodonium salts, CF3 reagents, C-H reactants, etc., were successfully utilized to initiate the tandem addition=interception process.[2]
Aliphatic azo compound (e.g., azobisisobutyronitrile [AIBN] and diethyl acetylenedicarboxylate [DEAD]), a type of widespread reagent in organic and polymer synthesis, decomposes softly to give radical species, which could be used for C-H functionalization [Fig. 1, Eq. (1)]. Therefore, we envisage that the difunctionalization of alkenes with AIBN, by judicious design, makes it possible to give oxindoles with a tertiary–alkyl nitrile moiety via a tandem radical addition/C(sp²)-H cyclization process [Fig. 1, Eq. (2)]. Remarkably, AIBN in combination with Bu₃SnH was commonly used as a initiator for radical addition of alkyl halide onto alkene, whereas direct addition of electrophilic radical produced by AIBN onto the double bond of an electron-poor alkene (e.g., acrylamides) was usually slow and thus less commonly encountered. Moreover, despite of significant advances in alkene difunctionalization research (including Heck-type and free radical reactions), the direct construction of α-functionalized quaternary carbon center via simple alkene biscarbonation step remains rare and challenging. It can be expected that this strategy would undoubtedly represent a highly interesting approach to oxindole scaffold with an α-cyano quaternary carbon center. Unfortunately, this alkylarylation of activated alkenes with AIBN, to our best knowledge, has not been reported.

It had been known that oxindoles are common structural motifs in pharmaceutical agents and natural products. Given that cyano-containing molecules exhibit important functions in materials, synthetic intermediates, and pharmaceuticals, the incorporation of cyano-containing group into oxindole scaffold via C-H activation of acetonitrile has attracted increasing interests recently. For example, Liu and coworkers reported a pioneering Pd-catalyzed oxidative alkylarylation of alkene with the aid of stoichiometric AgF in the early stage [Eq. (1)]. Just recently, You

Figure 1. Synthesis of cyano-substituted oxindole via cyclization of arylacrylamides. AIBN, azodiisobutyronitrile; DTBP, di-tert-butyl peroxide.
and coworkers\textsuperscript{[7b]} reported an elegant copper-catalyzed oxidative radical cyanomethylation of activated alkenes using a catalytic combination of CuCl and \textsuperscript{t}BuOO\textsuperscript{t}Bu [Eq. (2)]. Regardless of substantial achievements realized through the \(\alpha\)-C\textsubscript{sp3}-H activation of acetonitrile for this purpose, apparent limitation remains: (1) requirement of either the combination of expensive Pd/=Ligand combination with stoichiometric AgF or an elevated temperature (\(\geq 120\, ^\circ\text{C}\))\textsuperscript{[7c]} and (2) in general inefficiency for the introduction of 3\textsuperscript{o} nitrile moiety via \(\alpha\)-C(sp\textsuperscript{3})-H functionalization of 3\textsuperscript{o} alkyl nitrile (possibly due to steric hindrance or lower reactivity of \(\alpha\)-C\textsubscript{sp3}-H bond of 3\textsuperscript{o} nitriles).\textsuperscript{[7a]} Remarkably, oxindoles bearing an \(\alpha\)-cyano quaternary carbon center are important synthetic precursor for many pharmacologically interesting scaffolds.\textsuperscript{[8]} As a continuation of our interest in oxindole synthesis,\textsuperscript{[9]} we herein want to demonstrate an alternative AIBN-mediated cyanopropylation reaction of \(N\)-arylacrylamides by copper catalysis, which allows for the preparation of rare-reported oxindoles bearing 3\textsuperscript{o} nitrile moiety under rather mild conditions [Eq. (3)].

RESULTS AND DISCUSSION

Initially, the reaction between \(N\)-methyl-\(N\)-phenylacrylamide 1a and AIBN was employed as the model reaction to explore the optimal conditions to prepare oxindoles with 3\textsuperscript{o} alkyl nitrile moiety (Table 1, for more detail see the electrospray ionization [ESI]). Delightedly, we observed the formation of the desired cyclization product 3a in a 23\% yield when the reaction was conducted in the absence of metal catalyst (Table 1, entry 1). Encouraged by this result, various inexpensive copper(I) and iron(II) salts were subsequently used as the catalyst to enhance the yield (entries 2–8). Among the metals examined, CuI turned out to be the most effective one, and afforded 3a in a yield of 78\% when using di-tert-butyl peroxide (DTBP) as an oxidant (entry 4). In this process, adding an oxidant improved the reaction and using DTBP is optimal. Other oxidants, such as tert-butyl hydroperoxide (TBHP), \(K_2S_2O_8\), PhI (OAc)\textsubscript{2}, and PhI(OTF)\textsubscript{2}, resulted in unparalleled yields (entries 9–13). Sequential screening of solvents revealed CH\textsubscript{3}CN as the best choice (entries 14–16). The optimal temperature effect for the current reaction was 80\, ^\circ\text{C} (entries 17 and 18).

After the standard reaction conditions had been established, we set out to investigate the scope of \(N\)-arylacrylamides in the difunctionalization reaction using AIBN as \(\alpha\)-cyano alkyl radical source (Scheme 1). Initial screening revealed that \(N\)-substituents of acrylamides had obvious effects on the reaction. For example, N-arylacrylamides with a benzyl or ethyl group on the N-atom were found to be well compatible with the reaction conditions, whereas unprotected \(N\)-arylacrylamide (\(R^2=\text{H}\)) was less efficient in the cyclization (products 3b, 3c, and 3d). Next, we embarked upon investigating the substitution effect on the N-aryl moiety in the reaction. Gratifyingly, a wide array of substituents including Me, MeO, Cl, F, and CF\textsubscript{3} at the 4-, 3-, or 2-position of the aromatic ring displayed good reactivity, and the reactive order is poor electron-withdrawing and electron donating groups > strong electron-withdrawing groups (products 3e–o). Notably, the halo groups, such as Cl and F on the 3- or 4-position of the N-aryl moiety, were intact in the difunctionalization process, whereas bromo substituent at 2-position was very reactive and lead to many unidentified by-products. The reaction of \textit{meta}-methyl substituted \(N\)-arylacrylamide afforded a mixture of two regioselective products 3j and 3j'.

\textsuperscript{1233}
Ortho-substituted N-arylacrylamides were also tolerated, but the yield decreased to some extent owing to the steric hindrance (products 3k and 3i). Remarkably, a polycyclic oxindole derivative was successfully synthesized by this protocol (product 3p), and the N-containing ligand (1,10-phenanthroline) was found useful to achieve good yield. Sequential investigations revealed that several groups (Ph and CH2OAc) at the 2-position of the acrylamide moiety were compatible with the optimal conditions to afford 3q and 3s respectively, whereas hydroxymethyl (R3 = CH2OH) and mono-substituted olefins (R3 = H) were inefficient for the cyclization process (products 3r and 3t).

Next, the scope of α-cyano tertiary-alkyl azo compounds was investigated. Delightedly, beside AIBN, other α-cyano azo compounds could also involve the alkylarylation reaction to give desired oxindoles with various 3° nitrile moieties (Scheme 2). Notably, irrespective of electronic and steric character of the substituent groups on the aromatic ring of acrylamides, the α-cyano azo compounds bearing a cyclohexyl ring underwent the C-H cyclization to yield corresponding oxindole in

### Table 1. Optimization of reaction conditions

| Entry | Metal | Oxidant | Solvent | Yield (%) |
|-------|-------|---------|---------|-----------|
| 1     | None  | DTBP    | CH3CN   | 23        |
| 2     | CuCl  | DTBP    | CH3CN   | 53        |
| 3     | CuBr  | DTBP    | CH3CN   | 74        |
| 4     | CuI   | DTBP    | CH3CN   | 78        |
| 5     | CuCN  | DTBP    | CH3CN   | 65        |
| 6     | FeSO4·7H2O | DTBP | CH3CN | 45        |
| 7     | FeBr2 | DTBP    | CH3CN   | 57        |
| 8     | Fe(H2N)2(SO4)2·6H2O | DTBP | CH3CN | 46        |
| 9     | Cu    | TBHP    | CH3CN   | 61        |
| 10    | Cu    | K2S2O8  | CH3CN   | 51        |
| 11    | Cu    | Phl(OAc)2 | CH3CN | 46        |
| 12    | Cu    | Phl(OTFA)2 | CH3CN | 42        |
| 13    | Cu    | None    | CH3CN   | 14        |
| 14    | Cu    | DTBP    | Dioxane | 62        |
| 15    | Cu    | DTBP    | Toluene | 55        |
| 16    | Cu    | DTBP    | DCE     | 39        |
| 17a   | Cu    | DTBP    | CH3CN   | 42        |
| 18b   | Cu    | DTBP    | CH3CN   | 64        |

*a*Reaction conditions: 1a (0.5 mmol), AIBN (2 equiv.), oxidant (2 equiv.), metal (5 mol%), and solvent (2 mL) at 80 °C for 12 h. DTBP, di-tert-butyl peroxide; TBHP, tert-butyl hydrogenperoxide (70% aqueous solution); DCE, 1,2-dichloroethane.

*b*Yield of the isolated product.

*c*60 °C.

*d*100 °C.
good to excellent yield (products 3u–v). Notably, no reaction was observed when using the azo compounds bearing carboxylic group CO₂H (3y).

To investigate the mechanism of the cascade addition/C(sp³)-H cyclization process, the inter- and intramolecular kinetic isotope control experiments were performed (Scheme 3). Small kinetic isotopic effects (the intramolecular $K_H/K_D = 1.3$ and intermolecular $K_H/K_D = 1.0$) were observed, which suggested that either the S$_{E}$Ar mechanism or the free radical mechanism was involved in the reaction. Notably, the free radical mechanism was supported by the control experiment: a stoichiometric amount of 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO) (4 equiv.), a well-known radical inhibitor, was used in the reactions of 1a with AIBN, and the formation of the corresponding oxindoles was suppressed [Eq. (4)].

Based on the experimental results and previously reported mechanism, a possible mechanism is proposed as outlined in Scheme 4 for this alkylarylation.

**Scheme 1.** Scope of N-arylacrylamines. Reaction conditions: 1 (0.5 mmol), AIBN (2 equiv.), DTBP (2 equiv.), CuI (5 mol%), and CH₃CN (2 mL) at 80 °C for 12 h. Run on a 2-mmol scale. ¹1,10-Phenanthroline (10 mol%) was used.
process of N-arylacrylamides. First, the copper(II) alkoxide [Cu\textsuperscript{II}]-O\textsuperscript{t}Bu and \textit{t}-BuO\textsuperscript{•} were generated by the reaction of [Cu\textsuperscript{I}] with \textit{t}BuOO\textit{t}Bu.\textsuperscript{[11]} Then, AIBN decomposes to give the nitrile-stabilized radical \textit{A}, followed by its addition onto the carbon–carbon double bond of \textit{N}-methyl-\textit{N}-phenylacrylamide \textit{1a} generating an alkyl radical \textit{B}. Intramolecular cyclization of intermediate \textit{B} with a aryl ring forms radical intermediate \textit{C}, and then abstraction of an aryl hydrogen in the intermediate \textit{C} by [Cu\textsuperscript{II}]-species takes place to afford desired oxindole 3\textit{a}.

![Scheme 2. Scope of \textit{\alpha}-cyano azo compounds. Reaction conditions: 1 (0.5 mmol), 2 (2 equiv.), DTBP (2 equiv.), CuI (5 mol%), and CH\textsubscript{3}CN (2 mL) at 80 °C for 12 h. "Run on a 2-mmol scale.](image)

![Scheme 3. Control experiments of copper-catalyzed cyanopropylation of \textit{1a}.](image)
CONCLUSIONS

In summary, we have developed a practical copper-catalyzed oxidative cyanopropylation reaction of activated alkenes with AIBN, providing a rare access to oxindoles bearing 3° nitrile moiety. In addition, the use of safe and readily available AIBN, inexpensive copper as the catalyst- and ligand-free catalytic system, as well as the simplicity of operation and handling make this protocol a highly attractive complement for the construction of pharmaceutically interesting cyano-containing oxindoles. The detail mechanism and application of the novel reaction to more complex targets are currently under investigation in our laboratory.

EXPERIMENTAL

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Syringes used to transfer anhydrous solvents or reagents were purged with argon prior to use. NMR spectra were recorded on solutions in deuterated chloroform (CDCl₃) with residual chloroform (δ 7.26 ppm for ¹H NMR and δ 77.0 ppm for ¹³C NMR). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. Column chromatographical purifications were performed using SiO₂ (0.040–0.063 mm, 230–400 mesh) from Merck. Unless otherwise noted, commercial available starting materials were purchased from commercial sources and used without further purification. Preparation of N-arylacrylamides 1 were prepared according to literature procedures.[7a]

General Procedure for the Synthesis of Oxindoles with 3° Nitrile Moiety

¹BuOO'Bu (2.0 equiv.) was added dropwise to a mixture of N-arylacrylamide 1 (0.5 mmol), AIBN or its analogs (2.0 equiv.), and CuI (5 mol%) in CH₃CN (2.0 mL), and then the resulting solution was stirred at the indicated temperature for 12–15 h. The solvent was evaporated under reduced pressure and the resulted mixture was filtered through a Florisil pad, diluted with Et₂O, and washed with water and then brine. The organic layer was dried over anhydrous MgSO₄ and concentrated in
vacuo. The residue was purified by flash chromatography on silica gel to afford the corresponding oxindole with 3\(^o\) nitrile moiety in yields listed in Schemes 1 and 2.

**FUNDING**

We acknowledge financial support from China Postdoctoral Science Foundation Project (No. 2014M50649), the National Natural Science Foundation of China (No. 21462017), the Scientific Research Fund of Hunan Provincial - Education Department (No. 13B094), the Fund of Science and Technology Innovation and Entrepreneur for Hunan Young Talents, and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry.

**SUPPORTING INFORMATION**

Full experimental details, \(^1\)H and \(^{13}\)C NMR spectra, and x-ray data for product 3a for this article can be accessed on the publisher’s website.

**REFERENCES**

1. (a) Posner, G. H. *Chem. Rev.* 1986, *1*, 831; (b) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* 2013, *56*, 685.

2. For selected examples on the oxinole synthesis via radical mechanism, see (a) Fu, W.; Xu, F.; Fu, Y.; Zhu, M.; Yu, J.; Xu, C.; Zou, D. *J. Org. Chem.* 2013, *78*, 12202–12206; (b) Tang, S.; Zhou, D.; Deng, Y.; Yang, Y.; He, J.; Wang, Y. *Sci. China.* 2014, doi:10/1007/s11426–014-5158-z; (d) Xu, X.; Tang, Y.; Li, X.; Hong, G.; Fang, M.; Du, X. *J. Org. Chem.* 2014, *79*, 446–451; (e) Pan, C.; Han, J.; Zhang, H.; Zhu, C. *J. Org. Chem.* 2014, *79*, 5374–5378; (f) Zhou, B.; Hou, W.; Yang, Y.; Feng, H.; Li, Y. *Org. Lett.* 2014, *16*, 1322–1325; (g) Peng, J.; Chen, C.; Chen, J.; Xu, X.; Xi, C.; Chen, H. *Org. Lett.* 2014, *16*, 3776–3779; (h) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem.* 2013, *125*, 4092–4095; *Angew. Chem. Int. Ed.* 2013, *52*, 4000–4003; (i) Wang, J.; Zhang, X.; Bao, Y.; Yu, Y.; Cheng, X.; Wang, X. *Org. Biomol. Chem.* 2014, *12*, 5582–5585; (j) Kong, W.; Casimiro, M.; Merino, E.; Nevada, C. *J. Am. Chem. Soc.* 2013, *135*, 14480–14483; (k) Dai, Q.; Yu, J.; Jiang, Y.; Guo, S.; Yang, H.; Cheng, J. *Chem. Commun.* 2014, *50*, 3865–3867; (l) Xu, P.; Xie, J.; Xue, Q.; Pan, C.; Cheng, Y.; Zhu, C. *Chem.–Eur. J.* 2013, *19*, 14039–14042; (m) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Hu, M.; Xie, P.; Li, J.-H. *Angew. Chem.* 2013, *125*, 3725–3729; *Angew. Chem. Int. Ed.* 2013, *52*, 3638–3641; (n) Zhou, S.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem.–Eur. J.* 2013, *19*, 12970–12973; (o) Li, Z.; Zhang, Y.; Zhang, L.; Liu, Z. *Org. Lett.* 2014, *16*, 382–385.

3. For a rare example on C-H functionalization by using azo compounds, see Yu, W.; Sit, W. N.; Lai, K.; Zhou, Z.; Chan, A. S. C. *J. Am Chem. Soc.* 2008, *130*, 3304.

4. (a) Stork, G.; Sher, P. M.; Chen, H. L. *J. Am. Chem. Soc.* 1986, *108*, 6384; (b) Curran, D. P. In Comprehensive Organic Synthesis; B. M. Trost and I. Fleming(Eds.); Pergamon: Oxford, 1991; for reviews, see (c) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*, 2nd ed.; Oxford University Press: Oxford, 2012; p. 1047.

5. For a rare Heck-type example, see Fan, J.; Wei, W.; Zhou, M.; Song, R.; Li, J. *Angew. Chem. Int. Ed.*, 2014, *53*, 665.

6. For reviews, see (a) Trost, B. M.; Brennan, M. K. *Synthesis* 2009, 3003–3025; (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem.* 2007, *119*, 8902–8912; *Angew. Chem.*
7. (a) Wu, T.; Mu, X.; Liu, G.-S. Angew. Chem. 2011, 123, 12786–12789; Angew. Chem. Int. Ed. 2011, 50, 12578–12581. While this manuscript was in preparation, examples for the synthesis of cyano-substituted oxindoles via Cu-catalyzed cyanomethylation of alkene under elevated temperature conditions (>120 °C) were reported: (c) Wang, L. Z.; Wu, N.; Gao, G.; You, J. Chem. Commun. 2014, 50, 15049.

8. (a) Yu, Q.-S.; Luo, W.; Holloway, H. W.; Utsuki, T.; Perry, T.; Lahiri, D. K.; Greig, N. H.; Brosi, A. Heterocycles 2003, 61, 529; (b) Matsuura, T.; Overman, L. E.; Poon, D. J. Am. Chem. Soc. 1998, 120, 6500; (c) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. J. Am. Chem. Soc. 2008, 130, 12874.

9. (a) Tang, S.; Zhou, D.; Wang, Y. Eur. J. Org. Chem. 2014, 3565; (b) Tang, S.; Yu, Q.; Peng, P.; Li, J.-H.; Zhong, P.; Tang, R.-Y. Org. Lett. 2007, 9, 3413; (c) Tang, S.; Peng, P.; Zhong, P.; Pi, S.-F.; Li, J. J. Org. Chem. 2008, 73, 5476; (d) Tang, S.; Peng, P.; Wang, Z.; Deng, C.; Li, J.; Zhong, P.; Wang, N. Org. Lett. 2008, 10, 1875; (e) Tang, S.; Li, Q.; Zhou, D.; Tang, X.; Li, S. Synth. Commun. 2014, 44, 689; (f) Tang, S.; Li, Z.; Zhou, D.; Li, S.; Sheng, R. Tetrahedron Lett. 2015, 56, 1423.

10. (a) Jones, W. D. Acc. Chem. Res. 2003, 36, 140; (b) Pinto, A.; Neuvillle, L.; Retailleau, P.; Zhu, J. Org. Lett. 2006, 8, 4927–4930; (c) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. J. Am. Chem. Soc. 2006, 128, 6790–6791.

11. (a) Gephart, R. T.; McMullin III, C. L.; Sapiezynski, N. G.; Jang, E. S.; Aguila, M. J. B.; Cundari, T. R.; Warren, T. H. J. Am. Chem. Soc. 2012, 134, 17350–17353; (b) Kochi, J. K. J. Am. Chem. Soc. 1963, 85, 1958–1968.