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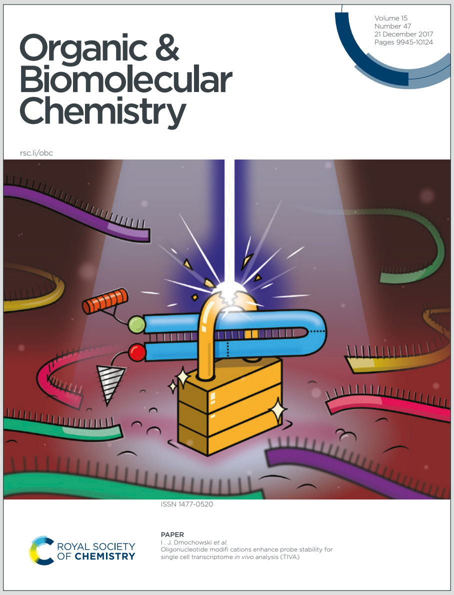
Organic & Biomolecular Chemistry
Volume 15
Number 47
21 December 2017
Pages 9945-10124
rsc.li/obc
ISSN 1477-0520
ROYAL SOCIETY OF CHEMISTRY
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DOI: 10.1039/D0OB01055C

Journal Name

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Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Copper(I)-Catalyzed Intermolecular Cyanoarylation of Alkenes: Convenient Access to α-Alkylated Arylacetonitriles

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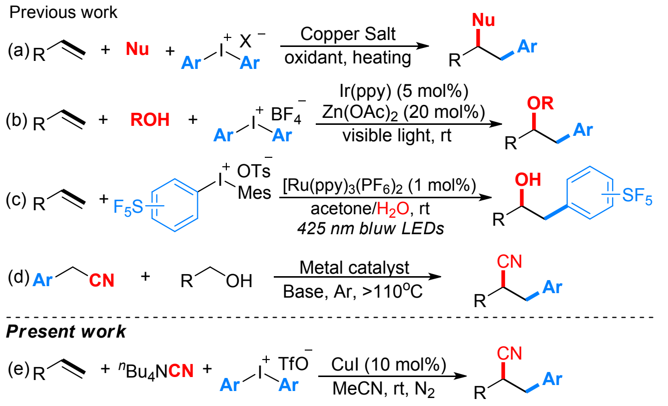
A novel Cu(I)-catalyzed intermolecular cyanoarylation of alkenes with diaryliodonium salts as radical arylating reagent and *tetra*-butylammonium cyanide as electrophilic cyanating reagent was established. A broad range of α-alkylated arylacetonitriles were efficiently constructed in good to excellent yields under base-, oxidant-free and mild conditions.

Introduction

Alkenes as cheap and abundant feedstocks are sourced from both petroleum and renewable resources. The dual functionalization of readily available alkenes is a special advantageous strategy that can be applied to construct multifunctional compounds with high added value.[1] For the functionalization reactions of alkenes, the hypervalent diaryliodonium salts have emerged as an ideal arylation reagent because of their unique properties such as good environmental friendliness, easy preparation and good functional group compatibility.[2] Diaryliodonium salts have been used in combination with copper catalyst as an effective strategy for electrophilic arylation reaction through a copper (III) aryl intermediate (Scheme 1a).[3] In 2013, Michael F. Greaney and coworkers reported a visible-light-induced arylation of alkenes using diaryliodonium salts as an aryl radical source (Scheme 1b).[4] Munetaka Akita and Takashi Koike disclosed the visible-light-driven phenylation of styrenes with pentafluorosulfanylphenyliodonium salts as the radical reagent (Scheme 1c).[5]

On the other hand, nitrile structures are found in a wide range of natural products, bioactive molecules, synthetic pharmaceuticals, and organic materials.[6] In particular, α-alkylated arylacetonitriles are one of the most important building blocks because they can be employed for the synthesis of various high-value chemicals.[7] The alkylation of arylacetonitriles is one of the most straightforward routes for their preparation (Scheme 1d).[8] However, these methods generally require the usage of some strong base and high reaction temperature, which resulted in the intolerance of base-sensitive functionalities, and/or limited substrate scope. Thus, it is highly demanded to develop a mild protocol for the synthesis of α-alkylated arylacetonitriles. Given the abundance and accessibility of alkene substrates, the direct cyanation of alkenes represents a highly attractive method for the preparation of ß-functionalized acetonitriles.[9] However, to the best of our knowledge, the synthesis of α-alkylated arylacetonitriles through radical cyanoarylation of alkenes is unprecedented and still remains a great challenge.

As part of our continuous efforts on the synthesis of multifunctional compounds,[10] we herein report an efficient and general method for the synthesis of a series of α-alkylated arylacetonitriles through Cu(I)-catalyzed[11] intermolecular cyanoarylation of unactivated alkenes with diaryliodonium salts and *tetra*-butylammonium cyanide ($^{n}Bu_4NCN$) at ambient temperature under base, oxidant-free and mild conditions (Scheme 1e).



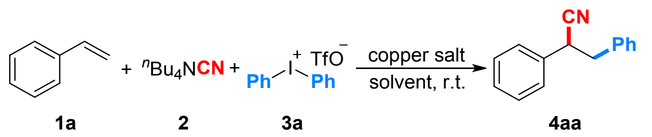
Scheme 1 Cu-catalyezd arylation of alkenes with diaryliodonium salts

Results and discussion

We started our studies on a multicomponent reaction by employing phenylethylene (**1a**), $^{n}Bu_4NCN$ (**2**), and $Ph_2I^+TfO^-$ (**3a**) as the template substrates. To our delight, the reaction occurred in MeCN at room temperature under nitrogen in the presence of 10 mol% of CuI as the catalyst, delivering the

2,3-diphenylpropanenitrile (**4aa**) in 89% NMR yield (entry 1). Subsequently, a series of copper salts were examined (entries 2 - 6) and CuI was revealed to be the optimum catalyst (entry 1) for the current reaction. Varying the loading of catalyst did not improve the reaction efficiency (entries 7 - 8). When other solvents were used instead of MeCN, lower yields of **4aa** were obtained (entries 9 - 13). Elevated reaction temperature (entry 14) and lower loading of **1a** (entry 15) caused the yield of **4aa** to descend. Control experiment revealed that the copper salt catalyst was essential for the transformation to occur (entry 16).

Table 1. Optimization of reaction conditions[a]

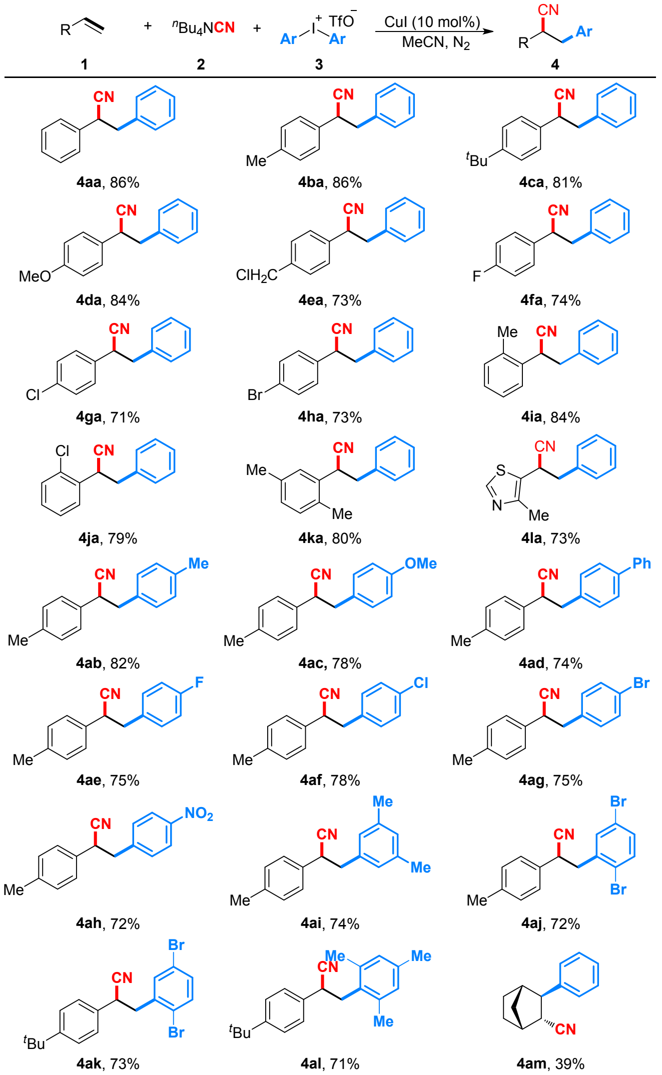


Entry	Catalyst(mol%)	Solvent	Yield (%)[b]
1	CuI (10)	MeCN	89
2	CuBr (10)	MeCN	50
3	CuCl (10)	MeCN	67
4	CuCN (10)	MeCN	45
5	[Cu(MeCN)$_4$]PF$_6$ (10)	MeCN	35
6	Cu(OTf)$_2$ (10)	MeCN	30
7	CuI (20)	MeCN	88
8	CuI (5)	MeCN	72
9	CuI (10)	DCE	51
10	CuI (10)	THF	40
11	CuI (10)	DMSO	38
12	CuI (10)	DMF	17
13	CuI (10)	Dioxane	19
14[c]	CuI (10)	MeCN	62
15[d]	CuI (10)	MeCN	67
16	--	MeCN	N.R.

[a]Conditions: **1a** (0.4 mmol), **2** (0.1 mmol), **3a** (0.1 mmol), catalyst, solvent (1 mL). [b]Estimated by ^{1}H NMR using diethyl phthalate as internal reference. [c] 60 ℃ [d]0.3 mmol **1a** was used. N.R: no reaction

Having the optimal reaction conditions in hand (Table 1, entry 1), we set out to investigate the substrate scope of alkene and diaryliodonium salts (Table 2). The substituted phenylethylene substrates, no matter the *para*-substituents are electron-neutral, electron-rich, or electron-poor, reacted smoothly to form the desired products (**4aa** – **4ha**) in good to excellent yields. In addition, sterically hindered *ortho*-substituted phenylethylenes were well-tolerated and delivered the targeted products in 84 - 79% yields (**4ia** – **4ja**). Both disubstituted phenylethylene and heteroaromatic ethylene were suitable reaction substrates for the transformation, providing the desired products **4ka** and **4la** in good yields. Subsequently, the reaction scope of this present reaction with respect to diaryliodonium salts was explored. Diaryliodonium salts with an array of functional groups on the phenyl ring produced the desired products (**4ab** – **4ah**) in good yields, even with a strong electron-withdrawing nitro group. Ditisubstituted diphenyliodonium salts could also give good yields under the optimal conditions (**4ai** – **4ak**). Delightfully, the sterically bulky 2,4,6-trisubstituted product (**4al**) was also generated in 71% yield, which was hardly obtained in precious reported protocols. The aliphatic alkenes, like norbornene, provided the target product **4am** in 39% yield, presumably due to the unstable free-radical intermediate in the reaction.

Table 2. Reaction scope[a]



[a]All reactions were carried out in a round-bottom flask in the presence of **1** (1.2 mmol), **2** (0.3 mmol), **3** (0. 3 mmol), CuI (0.03 mmol) and MeCN (3 mL), N$_2$, r.t.; isolated yields are reported.

In order to probe the possible reaction mechanism, some control experiments were carried out (Scheme 2). In the presence of 2 equiv. of radical scavenger (BHT or TEMPO), the present reaction was completely inhibited (Scheme 2a). These experimental results indicated that a free-radical process might be involved in this cyanoarylation reaction. When the diene **5a** was subjected to the standard reaction conditions, the cyclization product **5aa** was obtained in 42% NMR yield (Scheme 2b). Such reactivity and stereoselectivity are typical of the cyclization of the derived secondary alkyl radical.[12]

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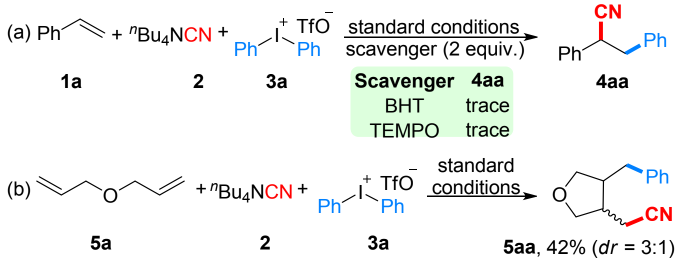
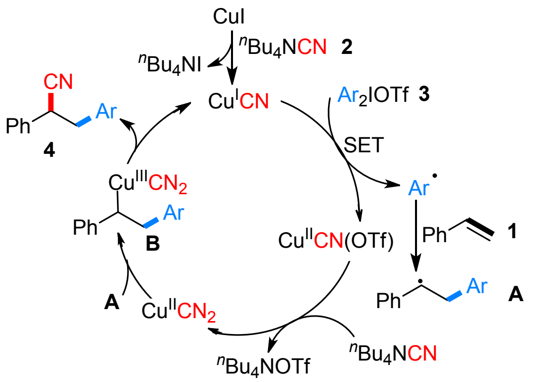


Scheme 2 Control experiments

On the basis of the above mechanistic studies and the literature reports,[12b, 13] a plausible reaction mechanism is proposed outlined in Scheme 3. The reasonable first step is the diaryliodonium salt **3** undergoes $Cu^I(CN)$ (*in-situ* generated from CuI and ⁿBu$_4$NCN **2**) assisted single-electron-transfer (SET) oxidation to generate the $Cu^{II}(CN)(OTf)$ specie along with an aryl radical. In step 2, addition of the aryl radical to styrene **1** takes place to generate the free radical intermediate **A**. In step 3, the radical **A** could be trapped by $Cu^{II}(CN)_2$ to deliver the Cu(III) species **B**. Finally, the reductive elimination of intermediate **B** would provide the target product **4** and regenerate the Cu(I) catalyst.



Scheme 3 Proposed mechanism

Conclusions

In conclusion, we have developed a oxidant-free Cu(I)-catalyzed intermolecular cyanoarylation of alkenes. The present reaction employed diaryliodonium salts as the radical arylating reagent and ⁿBu$_4$NCN as the electrophilic cyanating reagent, providing a broad range of α-alkylated arylacetonitriles in good to excellent yields at ambient temperature under base-free and mild conditions. Mechanistic studies revealed that the aryl radical was firstly generated from the diaryliodonium salts and then initiated the dual functionalization reaction, which is different from the previous reported Cu-catalyzed arylation reaction with diaryliodonium salts as electrophilic source of aryl. The developed multicomponent reaction not only extended the difunctionalization of alkenes but also expanded the application of diaryliodonium salts.

Acknowledgements

We are grateful for financial support from the Scientific Research Fund of Hunan Provincial Education Department (No. 18A192) and Hunan Provincial Natural Science Foundation of China (No. 2019JJ20008).

Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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