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Copper-catalysed three-component carboiodination of arynes: expeditious synthesis of *o*-alkynyl aryl iodides[†]

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A copper-catalysed three-component iodoalkynylation reaction of arynes for the expeditious and versatile synthesis of o-alkynyl aryl iodides has been developed. Mechanism research shows that the reaction goes through two steps enabled by copper catalysis: the formation of 1-iodo-2-arylacetylene and the insertion of the aryne into a C(sp)–I bond.

As the core building blocks in modern organic synthesis, aromatic halides have been extensively utilized as precursors to manufacture organometallic reagents¹ and as electrophiles in cross-coupling reactions.² Typically, due to the combination of reactivity of aromatic halides and alkynes, ortho-alkynyl aryl iodides have become significant synthons for the rapid and efficient construction of fused carbo- or heterocyclic skeletons.^{3,4} Although numerous powerful methods toward formation of aromatic carbon-halogen bonds have been established,⁵⁻¹⁰ the expeditious routes to access ortho-alkynyl aryl iodides have still been limited. To our best knowledge, the strategies used currently to produce this class of compounds are Sonogashira coupling reactions¹¹ of *o*-iodoanilines or 1,2-dihaloarenes and subsequent transformations, such as Br-I exchange^{1,7} and Sandmeyer reaction⁶ (Fig. 1A). However, it is not easy to regulate the coupling reactions of 1,2-dihaloarenes to afford the monosubstituted products. Moreover, the procedures of a Br-I exchange and Sandmeyer reaction are not always compatible with many sensitive functional groups due to the harsh conditions. In addition, the indispensable sequential transformations reduce the step- and atom-economy of this strategy. Therefore, it is highly desirable yet still challenging to develop versatile protocols to achieve ortho-alkynyl aryl iodides through other strategies.

The rise of transition-metal-catalysed aryne chemistry has provided more opportunities for the efficient construction of 1,2-difunctionalized arenes in recent years.^{12–15} In this field,

Xu's group^{15*a*} and our group^{15*b*} separately developed coppercatalysed multicomponent reactions to produce *o*-alkynyl arylsulfides or *o*-alkynyl anilines (Fig. 1B). The fundamental mode of these reactions can be described as alkynyl-metalation of benzynes and successive electrophilic traps of the *in situ* generated *ortho*-alkynyl aryl copper species. We inferred that the scope of electrophilic capture reagents used in this transformation can be enlarged by carefully adjusting the catalytic system. Based on this, we designed and developed a copper-catalysed three-component reaction of *in situ* formed benzynes, terminal alkynes, and electrophilic iodinating reagents to access *o*-alkynyl aryl iodides. This facile strategy can be regarded as a complement to the Sonogashira coupling reaction (Fig. 1B).

Our initial attempts were aimed at optimizing the conditions of the model reaction of Kobayashi reagent **1a**, alkyne **2a**, and *N*-iodosuccinimide (NIS) **3a** (Table 1). The 10 mol% IMesCuCl catalysed process at 60 °C in acetonitrile in the presence of CsF and Cs_2CO_3 furnished *o*-alkynyl phenyl iodide **4a** in 83% GC yield (entry 1). Control experiments (entries 2 and 3) recognized



Fig. 1 Strategies to synthesize *ortho*-alkynyl aryl iodides.



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^{*a*} *n*-Tridecane as an internal standard, the GC yields were calculated from the standard curve of the product. ^{*b*} 0.2 mmol **1a**, 0.3 mmol **2a** and 0.3 mmol **3a** in 0.8 mL MeCN in the presence of 0.4 mmol Cs_2CO_3 , 0.4 mmol CsF, and 0.02 mmol IMesCuCl. ^{*c*} The isolated yield is in parentheses.

the importance of the fluorine resource and base in the system. Replacing the MeCN with 1,4-dioxane, THF or nonpolar toluene, the yield of **4a** decreased greatly (entry 4). The reaction was also enabled by the catalysis of more easily available cuprous halides, but in low yields (entry 5). An appropriate temperature and concentration of substrates were also necessary for the reaction (entries 6 and 7). When only one equivalent of each of the three components was used, the product can only be obtained in a moderate yield (entry 8).

Then, we investigated the range and limitations of the substrates (Fig. 2). Phenyl alkynes bearing either an electrondonating or electron-withdrawing group at the para-, meta-, and ortho-position of the benzene ring underwent the threecomponent reaction smoothly to provide the corresponding products in good to excellent yields (4b-4af). In addition, the reaction conditions were compatible with amino (4b, 4c), ether (4d, 4e, 4ae), thioether (4af), trifluoromethoxy (4h), bromide (4j, 4s, 4y), chloride (4k, 4t, 4z), fluoride (4u, 4aa), ester (4l, 4v, 4ab), carbonyl (4m), trifluoromethyl (4n), cyan (4o), and nitro (4p, 4ac) groups. Notably, the presence of various halogen substituents in the products provides an opportunity for later functionalization of the molecule through a stepwise crosscoupling strategy. Further exploration demonstrated that the reaction also proceeded successfully with a variety of polycyclic aromatic substrates (4ag-4ai). Besides, electron rich or poor heterocyclic alkynes can also participate in this transformation to afford the corresponding *o*-alkynyl phenyl iodides (4aj-4an). Terminal alkynes with alkenyl, alkyl and trialkylsilyl substitutions have also been investigated. Vinyl alkynes were proven to be useful starting materials for the construction of o-alkynyl phenyl iodides (4ao), although the reactions of alkyl alkynes cannot proceed under standard or adjusted conditions. Due to the presence of indispensable fluorine anions, trimethylsilyl ethyne and triisopropylsily ethyne were not compatible in this reaction. The strategy was not restricted to benzyne precursors; other aryne precursors were also viable substrates for the reaction (4ap-4at). Remarkably, o-alkynyl naphthyl iodides 4ar and 4as could be separately obtained from the corresponding silylnaphthyl triflates



Fig. 2 Scope of the three-component reaction of Kobayashi reagents, alkynes, and NIS. Isolated yields.

in good yields. Additionally, only one regioisomer (**4at**) could be efficiently generated from 3-methoxyl substituted silylphenyl triflate.

Moreover, the downstream transformations of *o*-alkynyl aryl iodides produced by our methodology can be effortlessly realized. For instance, the Suzuki–Miyaura coupling product 5 and the Sonagashira reaction product 6 were successfully achieved in good yields under conventional conditions (Fig. 3a and b). The product 4a can be competently converted into 2-phenyl benzo[*b*]-thiophene 7 using inexpensive sodium sulfide as the sulfur source enabled by copper catalysis (Fig. 3c). To further demonstrate the synthetic utility of our strategy, we applied it to the synthesis of the fused heterocyclic compound 11 that can be utilized as a potential block for the construction of organic light-emitting materials.¹⁶ Through the expeditious Cu(1)-catalysed *ortho*-iodo arylation of 1,4-diethynylbenzene, Suzuki–Miyaura coupling, and Larock electrophilic cyclization¹⁷ in sequence, the symmetrical large π conjugated molecule can be easily obtained (Fig. 3d).

Finally, a preliminary investigation into the mechanism of the reaction was made (Scheme 1). Experiments A, B and D indicate that phenylacetylene **2a** reacts with NIS **3a** faster than it does with Kobayashi reagent **1a** under the standard conditions. Experiments C and E reveal that the *in situ* generated **13** reacts with **1a** smoothly to afford the target product **4a**. Experiments E and F show that the formation of alkynyl iodine compound¹⁸ and the insertion of benzyne into C(sp)–I bond are both enabled by copper catalysis. Based on these facts, we prefer the reaction to be realized through the catalytic Cycle B (Scheme **1J**). It is a



Fig. 3 Derivatives of products and application of our strategy for the efficient construction of polycyclic aromatics.



Scheme 1 Control experiments and proposed catalytic cycle.

completely different mechanism from what we originally envisioned (Cycle A) and the relative reports,¹⁵ albeit the details of the C–I σ -bond insertion process are not quite clear. We speculate that there are two possible paths to produce **4a** from

compound **13**: Path I: formation of **int-IV** *via* oxidative addition, generation of **int-III** *via* benzyne insertion, and production of **4a** *via* reductive elimination; and Path II: **13** as a nucleophile attacks benzyne¹⁹ to form **int-V**, then leading to **4a** through 1,3 migration of an alkynyl group. On the other hand, NIS has not been replaced by *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) in our transformation until now (Scheme 1G). It can also be rationally explained by the plausible mechanism. Although the corresponding alkynyl bromide can also be formed under the standard conditions, the reaction rate is significantly slower than that of alkynyl iodide (Scheme 1B, H). And the C(sp)–Br bond of 1-bromo-2-phenylacetylene **16a** cannot be inserted by benzyne under the standard conditions (Scheme 1I).^{20–22}

In conclusion, we have disclosed a copper-catalysed threecomponent reaction of arvne precursors, terminal alkynes, and electrophilic iodinating reagents, affording an expeditious and versatile approach to o-alkynyl aryl iodides which are valuable synthetic blocks and otherwise difficult to prepare. From the perspective of the reaction mechanism, the transformation can be described as two steps enabled by copper catalysis: the formation of 1-iodo-2-arylacetylene and the insertion of aryne into the C(sp)-I bond. To our best knowledge, the Cu-catalysed insertion of aryne into C-I bonds has not been reported before.²³ Although the exact mechanism of the insertion process is not yet known, we believed that more transition-metal catalysed carbon-hetero bond insertion reactions with arynes can be continuously developed inspired by this work and the catalytic image of this novel reaction model will gradually become clearer in further research.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 (a) Handbook of Functionalized Organometallics, ed. P. Knochel, Wiley-VCH, Weinheim, 2005; (b) Handbook of Grignard Reagents, ed. G. S. Silverman and P. E. Rakita, Dekker, New York, 1996.
- 2 *Metal Catalysed Cross Coupling Reactions and More*, ed. A. de Meijere, S. Bräse and M. Oestreich, Wiley, Weinheim, 2013.
- (a) D. J. C. Prasad and G. Sekar, Org. Biomol. Chem., 2013, 11, 1659;
 (b) J. Shen, D. Yuan, Y. Qiao, X. Shen, Z. Zhang, Y. Zhong, Y. Yi and X. Zhu, Org. Lett., 2014, 16, 4924; (c) J. Jin, Y. Luo, C. Zhou, X. Chen, Q. Wen, P. Lu and Y. Wang, J. Org. Chem., 2012, 77, 11368;
 (d) A. K. Verma, T. Kesharwani, J. Singh, V. Tandon and R. C. Larock, Argew. Chem., Int. Ed., 2009, 48, 1138; (e) L. Ackermann, W. Song and R. Sandmann, J. Organomet. Chem., 2011, 696, 195.
- 4 (a) J. Meesin, M. Pohmakotr, V. Reutrakul, D. Soorukram, P. Leowanawat, S. Saithong and C. Kuhakarn, Org. Lett., 2017, **19**, 6546; (b) R.-H. Li, C.-K. Ding, Y.-N. Jiang, Z.-C. Ding, X.-M. An, H.-T. Tang, Q.-W. Jing and Z.-P. Zhan, Org. Lett., 2016, **18**, 1666; (c) T. Yao, M. A. Campo and R. C. Larock, J. Org. Chem., 2005, **70**, 3511; (d) P. M. Byers and I. V. Alabugin, J. Am. Chem. Soc., 2012, **134**, 9609.
- 5 Friedel-Crafts-type Electrophilic Halogenation: *Electrophilic Halogenation: Reaction Pathways Involving Attach by Electrophilic Halogens on Unsaturated Compounds*, ed. P. B. D. de la Mare, Cambridge, New York, 1976.

- 6 Sandmeyer-type reactions of diazonium salts: H. H. Hodgson, *Chem. Rev.*, 1947, **40**, 251.
- 7 Halogenations of preformed organometallic reagents: V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
- 8 Transition-metal catalysed C-X bond formation, for a review: (a) D. A. Petrone, J. Ye and M. Lautens, Chem. Rev., 2016, 116, 8003; For recent examples: (b) Y. Kommagalla and N. Chatani, Org. Lett., 2019, 21, 5971; (c) Y. H. Lee and B. Morandi, Nat. Chem., 2018, 10, 1016; (d) M. D. L. H. Macias and B. A. Arndtsen, J. Am. Chem. Soc., 2018, 140, 10140; (e) E. Erbing, A. Sanz-Marco, A. Vázquez-Romero, J. Malmberg, M. J. Johansson, E. Gomez-Bengoa and B. Martin-Matute, ACS Catal., 2018, 8, 920; (f) X.-Q. Ning, S.-J. Lou, Y.-J. Mao, Z.-Y. Xu and D.-Q. Xu, Org. Lett., 2018, 20, 2445; (g) X.-H. Liu, H. Park, J.-H. Hu, Y. Hu, Q.-L. Zhang, B.-L. Wang, B. Sun, K.-S. Yeung, F.-L. Zhang and J.-Q. Yu, J. Am. Chem. Soc., 2017, 139, 888; (h) J. B. Diccianni, C. Hu and T. Diao, Angew. Chem., Int. Ed., 2017, 56, 3635; (i) S. Warratz, D. J. Burns, C. Zhu, K. Korvorapun, T. Rogge, J. Scholz, C. Jooss, D. Gelman and L. Ackermann, Angew. Chem., Int. Ed., 2017, 56, 1557; (j) A. Goitia, E. Gomez-Bengoa and A. Correa, Org. Lett., 2017, 19, 952; (k) F. Lied, A. Lerchen, T. Knecht, C. Mück-Lichtenfeld and F. Glorius, ACS Catal., 2016, 6, 7839; (l) N. Schröder, F. Lied and F. Glorius, J. Am. Chem. Soc., 2015, 137, 1448; (m) C. J. Teskey, A. Y. W. Lui and M. F. Greaney, Angew. Chem., Int. Ed., 2015, 54, 11677.
- 9 Morden metal-free C-X bond formation: (a) Y. Liang, F. Lin, Y. Adeli, R. Jin and N. Jiao, Angew. Chem., Int. Ed., 2019, 58, 4566; (b) Y. Yuan, A. Yao, Y. Zheng, M. Gao, Z. Zhou, J. Qiao, J. Hu, B. Ye, J. Zhao, H. Wen and A. Lei, *iScience*, 2019, 12, 293; (c) D. A. Rogers, A. T. Bensalah, A. T. Espinosa, J. L. Hoerr, F. H. Refai, A. K. Pitzel, J. J. Alvarado and A. A. Lamar, Org. Lett., 2019, 21, 4229; (d) G. J. P. Perry, J. M. Quibell, A. Panigrahi and I. Larrosa, J. Am. Chem. Soc., 2017, 139, 11527; (e) B. Huang, Y. Zhao, C. Yang, Y. Gao and W. Xia, Org. Lett., 2017, 19, 3799; (f) S. Song, X. Sun, X. Li, Y. Yuan and N. Jiao, Org. Lett., 2015, 17, 2886; (g) R. A. Rodriguez, C.-M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate and P. S. Baran, J. Am. Chem. Soc., 2014, 136, 6908.
- 10 Halogenase catalysed site-selective C-H bond halogenation: J. Latham, E. Brandenburger, S. A. Shepherd, B. R. K. Menon and J. Micklefield, *Chem. Rev.*, 2018, **118**, 232.
- 11 Recent reviews on Sonogashira coupling: (a) A. Biffis, P. Centomo, A. Del Zotto and M. Zecca, *Chem. Rev.*, 2018, **118**, 2249; (b) R. Chinchilla and C. Nájera, *Chem. Soc. Rev.*, 2011, **40**, 5084.
- 12 Recent reviews on aryne chemistry: (a) H. Takikawa, A. Nishii, T. Sakai and K. Suzuki, Chem. Soc. Rev., 2018, 47, 8030; (b) J. Shi, Y. Li and Y. Li, Chem. Soc. Rev., 2017, 46, 1707; (c) F. I. M. Idris and C. R. Jones, Org. Biomol. Chem., 2017, 15, 9044; (d) J.-A. Garcia-Lopez and M. F. Greaney, Chem. Soc. Rev., 2016, 45, 6766; (e) E. Goetz, T. K. Shah and N. K. Garg, Chem. Commun., 2015, 51, 34; (f) A. Bhunia, S. R. Yetra and A. T. Biju, Chem. Soc. Rev., 2012, 41, 3140; (g) C. M. Gampe and E. M. Carreira, Angew. Chem., Int. Ed., 2012, 51, 3766; (h) P. M. Tadross and B. M. Stoltz, Chem. Rev., 2012, 112, 3550.
- 13 Recent reviews on aryne chemistry involving metal catalysis: (a) I. Pozo, E. Guitián, D. Pérez and D. Peña, Acc. Chem. Res., 2019, **52**, 2472; (b) R. A. Dhokale and S. B. Mhaske, Synthesis, 2018, 1; (c) M. Feng and X. Jiang, Synthesis, 2017, 4414; (d) O. J.

Diamond and T. B. Marder, Org. Chem. Front., 2017, 4, 891; (e) R. Karmakar and D. Lee, Chem. Soc. Rev., 2016, 45, 4459.

- 14 Recent examples of transition-metal catalysed difunctionalization of arynes: (a) W.-J. Yoo, T. V. Q. Nguyen and S. Kobayashi, Angew. Chem., Int. Ed., 2014, 53, 10213; (b) L. K. B. Garve and D. B. Werz, Org. Lett., 2015, 17, 596; (c) M. Pareek, T. Fallon and M. Oestreich, Org. Lett., 2015, 17, 2082; (d) J.-A. García-López, M. Cetin and M. F. Greaney, Angew. Chem., Int. Ed., 2015, 54, 2156; (e) M. Feng, B. Tang, N. Wang, H.-X. Xu and X. Jiang, Angew. Chem., Int. Ed., 2015, 54, 14960; (f) T.-Y. Zhang, C. Liu, C. Chen, J.-X. Liu, H.-Y. Xiang, W. Jiang, T.-M. Ding and S.-Y. Zhang, Org. Lett., 2018, 20, 220; (g) X. Yang and G. C. Tsui, Org. Lett., 2018, 20, 1179; (h) H. Jia, Z. H. Liu, B. Mao, X. Shi and H. Guo, Chem. Commun., 2018, 54, 7050; (i) Z. Zuo, H. Wang, Y. Diao, Y. Ge, J. Liu and X. Luan, ACS Catal., 2018, 8, 11029; (j) J.-T. Hu, B. Zheng, Y.-C. Chen and Q. Xiao, Org. Chem. Front., 2018, 5, 2045; (k) R. O. Torres-Ochoa, T. Buyck, Q. Wang and J. Zhu, Angew. Chem., Int. Ed., 2018, 57, 5679; (1) Y.-Y. Meng, X.-J. Si, Y.-Y. Song, H.-M. Zhou and F. Xu, Chem. Commun., 2019, 55, 9507.
- (a) X. Peng, C. Ma, C.-H. Tung and Z. Xu, Org. Lett., 2016, 18, 4154;
 (b) S.-L. Niu, J. Hu, K. He, Y.-C. Chen and Q. Xiao, Org. Lett., 2019, 21, 4250.
- 16 Organic Light-Emitting Materials and Devices, ed. Z. R. Li, CRC Press, Boca Raton, 2nd edn, 2015.
- 17 T. Yao, M. A. Campo and R. C. Larock, J. Org. Chem., 2005, 70, 3511.
- 18 Stoichiometric KI/CuSO₄ mediated process: T. Ferris, L. Carroll, R. C. Mease, A. C. Spivey and E. O. Aboagye, *Tetrahedron Lett.*, 2019, **60**, 936.
- 19 Y. Zhang, W. Xiong, J. Cen, W. Yan, Y. Wu, C. Qi, W. Wu and H. Jiang, *Chem. Commun.*, 2019, 55, 12304. Unlike the conventional role played in organic synthesis as electrophiles, in this paper, ally bromides served as nucleophiles to benzyne intermediates with high electrophilicity. Iodine is less electronegative than bromine, and its electron cloud is more diffuse. Thus, 1-iodo-2-arylacetylenes may also play the roles of nucleophiles in our system.
- 20 CuBr₂ catalysed two molecules of aryne (generated by the Kobayashi protocol) insertion into a C(sp)-Br bond of bromoalkynes: T. Morishita, H. Yoshida and J. Ohshita, *Chem. Commun.*, 2010, **46**, 640.
- 21 CuBr₂ catalysed one molecule of aryne (generated via the hexadehydro-Diels-Alder cycloisomerization) insertion into a C(sp)-Br bond of bromoalkynes: X. Xiao, T. Wang, F. Xu and T. R. Hoye, *Angew. Chem., Int. Ed.*, 2018, 57, 16564.
- 22 Transition-metal free three-component coupling of arynes and organic bromides: H. Yoshida, Y. Asatsu, Y. Mimura, Y. Ito, J. Ohshita and K. Takaki, *Angew. Chem., Int. Ed.*, 2011, **50**, 9676.
- 23 Pd- or Ni-catalysed unsaturated compound insertions into aromatic C-I bonds have just been disclosed very recently. For intramolecular olefin insertion, see: (a) H. Yoon, A. D. Marchese and M. Lautens, J. Am. Chem. Soc., 2018, 140, 10950; (b) A. D. Marchese, F. Lind, Á. E. Mahon, H. Yoon and M. Lautens, Angew. Chem., Int. Ed., 2019, 58, 5095; (c) Z.-M. Zhang, B. Xu, L. Wu, L. Zhou, D. Ji, Y. Liu, Z. Li and J. Zhang, J. Am. Chem. Soc., 2019, 141, 8110; (d) A. D. Marchese, L. Kersting and M. Lautens, Org. Lett., 2019, 21, 7163; For intermolecular alkyne insertion, see: (e) T. Takahashi, D. Kuroda, T. Kuwano, Y. Yoshida, T. Kurahashi and S. Matsubara, Chem. Commun., 2018, 54, 12750; (f) Y. H. Lee and B. Morandi, Angew. Chem., Int. Ed., 2019, 58, 6444.