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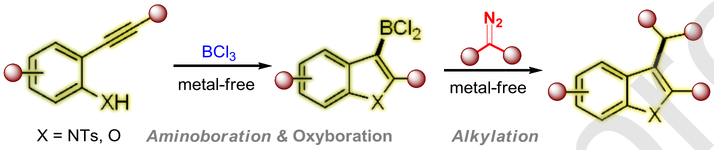
# Metal-free cascade boron–heteroatom addition and alkylation with diazo compounds

Jiahang Lv[a,b+], Binlin Zhao[+c], Ying Han[a]*, Yu Yuan[a], Zhuangzhi Shi[a,b*]

[a] *College of Chemistry and Chemical Engineering Yangzhou University, Yangzhou 225002, China*
[b] *State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China*
[c]*Department of Chemistry and Materials Science, College of Science, NanjingForestry University, Nanjing 210037, China*

* Corresponding authors.
*E-mail addresses*: hanying@yzu.edu.cn (Y. Han); shiz@nju.edu.cn (Z. Shi)
[+]*These authors contributed equally to this work.*

## Graphical Abstract



An efficient method on cascade boron–heteroatom addition and alkylation with diazo compounds to build substituted indoles and benzofurans has been uncovered undercatalyst- and metal-free conditions.

ABSTRACT

Transition metal-catalyzed carbene transfer reaction is one of the most notable advances for C−C bond formation reactionsduring the past decade, which has been widely employed in the preparation of C3-substituted indoles. Here, we described an efficient example of catalyst- and metal-free aminoboration of alkynes and C-C bond formation with diazo compounds to produce C3-substituted indoles. Diverse alkynylanilines and diazo compounds can be utilized for this tandem transformation under mild reaction conditions, resulting in broad functional group compatibility.Additionally, this metal-free strategy can be extended to construct substituted benzofurans.

Keywords: Indoles, Aminoboration, Metal-free, $BCl_3$, Diazo Compounds

The indole unit exists ubiquitously in biologically active molecules, natural products, pharmaceuticals, and agrochemicals [1]. Therefore, the development of new methods for the synthesis of functionalized indole derivatives has been a topic of great importance [2]. C3-Substituted indoles are the core structure of various drugs and medicinally important agents [3], transitionmetal-catalyzed functionalization of indoles by carbene transfer provides an attractive route to produce these compounds (Fig. 1a). Many groups have achieved the C−H functionalization of indoles with diazo compounds to build C−C bonds at C3-position [4]. More recently, other transition-metals like Au [5], Pd [6], Cu [7], Fe [8] and Mb [9] have also been employed to enable these transformations. Due to economic and toxicity concerns of transition-metals, there is a significant interest in the development of metal-free variant to mimic such conversions.

The generation of C–C bonds is at the heart of synthetic organic chemistry and the development of new method to build carbon–carbon bonds under metal-free conditions is attracting increasing attention [10]. In 2010, Barluenga and Valdés first developed an efficient method on C–C bond couplings between tosylhydrazones and boronic acids without any transition metals and catalysts (Fig. 1b) [11]. In 2016, Ley group also uncovered the *in situ* preparation of reactive allylic and benzylic boronic acids, obtained by reacting flow-generated diazo compounds with boronic acids, and their application in controlled iterative C–C bond forming reactions (Fig. 1c) [12]. Boron halides such as $BCl_3$ and $BBr_3$, are attractive borylation agents because they are commercially available in multigram to kilogram quantities and are cheaper than most common boron reagents. In 2018, we described an efficient metal-free aminoboration of alkynes to access C3-borylated indoles with $BCl_3$ [13]. Very recently, our group also reported a general method on construction of (hetero)aryl boronates by $BBr_3$-mediated directed C-H borylation [14], in which one example was showcased on metal-free C7-alkylation betweenan *in-situ* formed 7-borylatedindole and a tosylhydrazone. Here, we report a general strategy on tandem

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* Corresponding authors.

aminoboration of alkynes and alkylation with diazo compounds to access C3-substituted indoles avoiding the use of any metals (Fig. 1d). Replacing the transition metal-catalyzed carbene transfer reactions by tandem metal-free process offers an alternative pathway for construction of substituted indoles with exciting possibilities due to its superior practicality, low cost, and environmental friendliness.

We initiated our study by investigating the cyclization of *o*-alkynylaniline **1a** with $BCl_3$ (Scheme 1). As a result, we discovered that the use of 1.0 equiv. of **1a** with 2.0 equiv. of $BCl_3$ in DCM at room temperature for 2.5 h led to the full conversion of the precursors and formation of boron complex **2a**. Then, the solvent was removed in vacuo and diazo compound **3a** (3.0 equiv.) and dry $Et_3N$ (3.0 equiv.) in dry DCE was added slowly to the above system under argon atmosphere. The solution was then slowly warmed to room temperature and continued to stirr for another 2 h. Subsequently the temperature increased to 60 °C slowly, and then stirred for another 6 h. The desired indole product **4aa** was isolated with 50% yield in this cascade reaction. When the reaction was carried out without the base, we did not observe any alkylation product. Other bases such as pyridine were also efficient for this reaction, but with much lower reactivity. Lowering the reaction temperature to room temperature led to form product **4aa** in 25% yield. In addition, the use of DCM for the second step reaction was found slightly inferior than that of DCE.

With the optimized reaction conditions in hand, we first investigated the scope ofdiazo compounds **3** with *o*-alkynylaniline **1a** (Scheme 2). Diazoacetate **2a** bearing a COOBn substituent also underwent facile cyclization and alkylation to generate the corresponding product **4ab** in 47% yield. Diazo-phenylacetates containing COOMe (**3c**) and COO$^{i}$Pr (**3d**) worked well under the reaction conditions, affording the corresponding products **4ac** and **4ad** in 52% and 56% yields. Other diazo-arylacetates including methyl (**3e**), methoxy (**3f**), Cl (**3g**), and Br (**3h**) groups at aryl motifwere compatible under the reaction conditions (**4ae−4ah**). Next, we turned our attention toexplore the sequential C–C bond formation using different alkynylanilines with diazo compound **3a**. Aromatic groups with diverse substitution patterns like **4ba** and **4ca** could be transferred effectively from the corresponding *o*-alkynyl groups. The naphthalene and thiophene-containing products **4da-4ea** were also formed in 43%-48% yields. It was noteworthy that *ortho*-enynyl substituted amines including **1f** and **1g** were tolerable with the reaction system, and the products **4fa** and **4ga** were isolated in 55% and 52% yields. In addition, the developed system was also tolerant of alkyl substituent, and the compound **4ha** was produced in a 40% yield.

A major benefit of this metal-free and cascade strategy is that other substituted heteroaromatic compounds could also be formed. For example, C3-substituted benzofurans **7** and **8** resulted from $BCl_3$-induced annulation oxoborationand C-C coupling with diazo compounds could be produced in 43% and 48% yields, respectively (Scheme 3) [15].

Finally, we proposed a mechanism of this tandem process in Fig. 2. Based on the previously reported results [13], the reaction of alkynylanilines **1** and $BCl_3$ can form dichloro(indolyl)borane **2** first. Once it formed, the nucleophilic diazo carbon can attract to the $BCl_2$ group *via* intermediate **A** to form boron species **B**. The 1,2-indolyl migration occurs to produce another borane species **C**. According to reported work [11], compound **C** can further convert into product **4a** by protodeboronation in the presence of base and water.

In summary, we have put forward an efficient $BCl_3$-mediated strategy for the cascade cyclization of varieties of o-alkynylanilines and C-C coupling with diazo compounds under metal-free conditions. Although the modest total yields were provided for this two-step cascade transformation, the use of this method for the preparation of substituted indoles under mild conditions avoiding the use of transition metals would still be of great importance.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### References

[1] (a) D.G. Batt, J.X. Qiao, D.P. Modi, et al., Biorg. Med. Chem. Lett. 14 (2004) 5269-5273;
(b) T. Kawasaki, K. Higuchi, Nat. Prod. Rep. 22 (2005) 761-793;
(c) A.J. Kochanowska-Karamyan, M.T. Hamann, Chem. Rev. 110 (2010) 4489-4497;
(d) M. Ishikura, T. Abe, T. Choshi, S. Hibin, S, Hibino, Nat. Prod. Rep. 30 (2013) 694-752;

(e)A.J. Kochanowaska-Karamyan, M.T. Hamann, Chem. Rev. 110 (2010) 4489-4497;
(f) S.A. Patil, R. Patil, D.D. Miller, Future Med. Chem. 4 (2012) 2085-2099;
(g) N.K. Kaushik, N. Kaushik, P. Attri, et al., Molecules 18 (2013) 6620-6662;
(h) M.Z. Zhang, Q. Chen, G.F. Yang, Eur. J. Med. Chem. 89 (2015) 421-441.
[2] (a) B.E. Maryano, H.C. Zhang, J.H.Cohen, I.J.Turchi, C.A. Maryano, Chem. Rev. 104 (2004) 1431-1628;
(b) S. Cacchi, G. Fabrizi, Chem. Rev.105 (2005) 2873-2920;
(c) G.R. Humphrey, J.T. Kuethe, Chem. Rev. 106 (2006) 2875-2911;
(d) B.J. Stokes, H. Dong, B.E. Leslie, A.L. Pumphrey, T.G. Driver, J. Am. Chem. Soc. 129 (2007) 7500-7501;
(e) M. Ganesh, D. Seidel, J. Am. Chem. Soc. 130 (2008) 16464-16465;
(f) M. Bandini, A. Eichholzer, Angew. Chem. Int. Ed. 48 (2009) 9608–9644;
(g) C. Guo, J. Song, S. Luo, L. Gong, Angew. Chem. Int. Ed. 49 (2010) 5558-5564;
(h) T.P. Pathak, K.M. Gligorich, B.E. Welm, M.S Sigman, J. Am. Chem. Soc. 132 (2010) 7870-7871;
(i) J.B. Chen, Y.X. Jia, Org. Biomol. Chem. 15 (2017) 3550–3567;
(j) S. Patil, R. Patil, Curr. Org. Synth. 4 (2007) 201-222;
(k) Y.Y. Liu, X.Y. Yu, J.R. Chen, et al., Angew. Chem. Int. Ed. 56 (2017) 9527−9531.
[3] (a) C. Schultz, A. Link, M. Leost, et al., J. Med. Chem. 42 (1999) 2909-2919;
(b) B.W. Trotter, A.G. Quigley, W.C. Lumma, et al. Bioorg. Med. Chem. Lett. 11 (2001) 865-869;
(c) D.E. Williams, J. Davies, B.O. Patrick, et al., Org. Lett. 10 (2008) 3501-3504;
(d) F.R. de S. Alves, E.J. Barreiro, C.A.M. Fraga, Mini-Rev. Med. Chem. 9 (2009) 782-793.
[4] (a) R. Gibe, M.A. Kerr, J. Org. Chem. 67 (2002) 6247–6249;
(b) Y.J. Lian, H.M.L. Davies, J. Am. Chem. Soc. 132 (2010) 440–441;
(c)A. De Angelis, V.W. Shurtleff, O. Dmitrenko, J.M. Fox, J. Am. Chem. Soc. 133 (2011) 1650–1653;
(d) Y. Lian, H.M.L. Davies, Org. Lett. 14 (2012) 1934–1937;
(e) F. Ye, Z.X. Wang, J.Wang, etal., J. Am. Chem. Soc. 137 (2015) 4435–4444;
(f) D.T. Boruta, O. Dmitrenko, J.M. Fox, et al., Chem. Sci. 3 (2012) 1589-1593;
(g) H.M.L. Davies, S.J. Hedley, Chem. Soc. Rev. 36 (2007) 1109-1119;
(h) D.R. Stuart, P. Alsabeh, M. Kuhnand, K. Fagnou, J. Am. Chem. Soc. 132 (2010) 18326-18339;
[5] (a) Z. Yu, B. Ma, M. Chen, et al., J. Am. Chem. Soc. 136 (2014) 6904-6907;
(b) Y. Xi, Y. Su, Z. Yu, et al., Angew. Chem. Int. Ed. 53 (2014) 9817-9821;
(c) R.R. Singh, R.S. Liu, Chem. Commun. 53 (2017) 4593-4596.
[6] (a) X. Gao, B. Wu, W.X. Huang, M.W. Chen, Y.G. Zhou, Angew. Chem. Int. Ed. 54 (2015) 11956-11960;
(b) S. Cacchi, G. Fabrizi, Chem. Rev. 105 (2005) 2873-2920;
(c) Z. Hu, S. Luo, Q. Zhu, Adv. Synth. Catal. 357 (2015) 1060-1064.
(d) S. Wurtz, S. Rakshit, F. Glorius,et al., Angew. Chem. Int. Ed. 47(2008) 7230-7233;
(e) Z. Shi, C. Zhang. N. Jiao, et al., Angew. Chem. Int. Ed. 48 (2009) 4572-4576.
[7] (a) M. Delgado-Rebollo, A. Prieto, P.J. Perez, ChemCatChem 6 (2014) 2047–2052;
(b) X. Gao, B. Wu, Z. Yan, Y.G. Zhou, Org. Biomol. Chem. 14 (2016) 8237-8240;
(c) M.B. Johansen, M.A. Kerr, Org. Lett. 12 (2010) 4956-4959;
(d) A. Mark, A.A. Jaworski, K.A. Scheidt, et al., Angew. Chem. Int. Ed. 57 (2018) 17225-17229;
(d) Y.Z. Cheng, Q.R. Zhao, X. Zhang, et al., Angew. Chem. Int. Ed. 58 (2019) 18069-18074;
(e) J.M. Fraile, K.L. Jeune, J.A. Mayoral, et al., Org. Biomol. Chem. 11 (2013) 4327-4332.
[8] Y. Cai, S.F. Zhu, G.P. Wang, Q.L. Zhou, Adv. Synth. Catal. 353 (2011) 2939–2944
[9] D.A. Vargas, A. Tinoco, V. Tyagi, R. Fasan, Angew. Chem. Int. Ed. 57 (2018) 9911–9915.
[10] (a) S. Nakagawa, K.A. Bainbridge, K. Butcher, et al., ChemMedChem 7 (2012) 233–236;
(b) L. Kupracz, A. Kirschning, J. Flow Chem. 3 (2013) 11–16;
(c) D.M. Allwood, D.C. Blakemore, A.D. Brown, S.V. Ley, J. Org. Chem. 79 (2014) 328–338;
(d) C.L. Sun, Z.J. Shi, Chem. Rev. 114 (2014) 9219-9280;
(e) W. Liu, C.J. Li, Synlett 28 (2017) 2714−2754;
(f) W. Liu, J. Li, P. Querard, C.J. Li, J. Am. Chem. Soc. 141 (2019) 6755−6764;
(f) J. Chen, D. Chang, F. Xiao, G.J. Deng, J. Org. Chem. 84 (2019) 568−578
[11] J. Barluenga, M. Tomas-Gamasa, F. Aznar, C. Valde´s, Nat. Chem. 1 (2009) 494–499.
[12] C. Battilocchio, F. Feist, A. Hafner, S.V. Ley, et al., Nat. Chem. 8 (2016) 360-367.
[13] J. Lv, B. Zhao, L. Liu, et al., Adv. Synth. Catal. 360 (2018) 4054–4059.
[14] (a) J. Lv, X. Chen, K.N. Houk, Z. Shi, et al., Nature 575 (2019) 336-340;
(b) J. Lv, B. Zhao, Y. Yuan, Y. Han, Z. Shi, Nat. Commun. 11 (2020) 1316.
[15] A.J. Warner, A. Churn. J.S. McGough, M.J. Ingleson, Angew. Chem. Int. Ed. 56 (2017) 354–358.

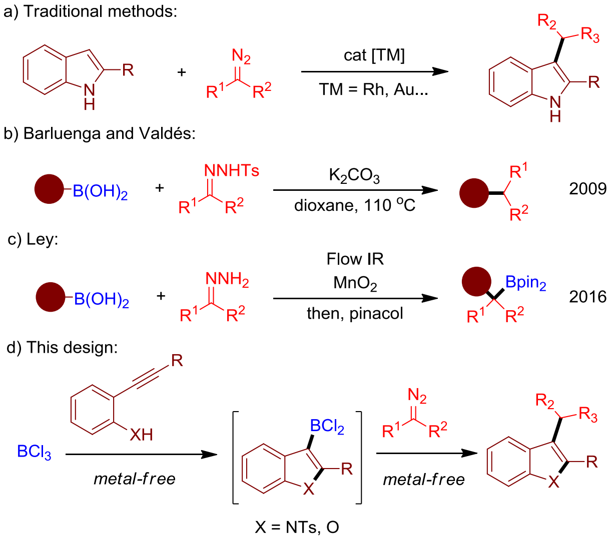


**Fig. 1.** Reaction design.

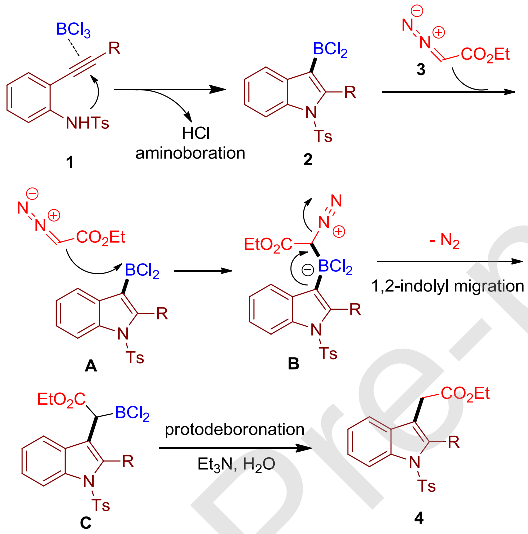
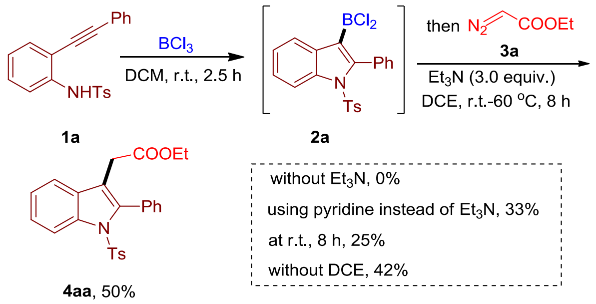
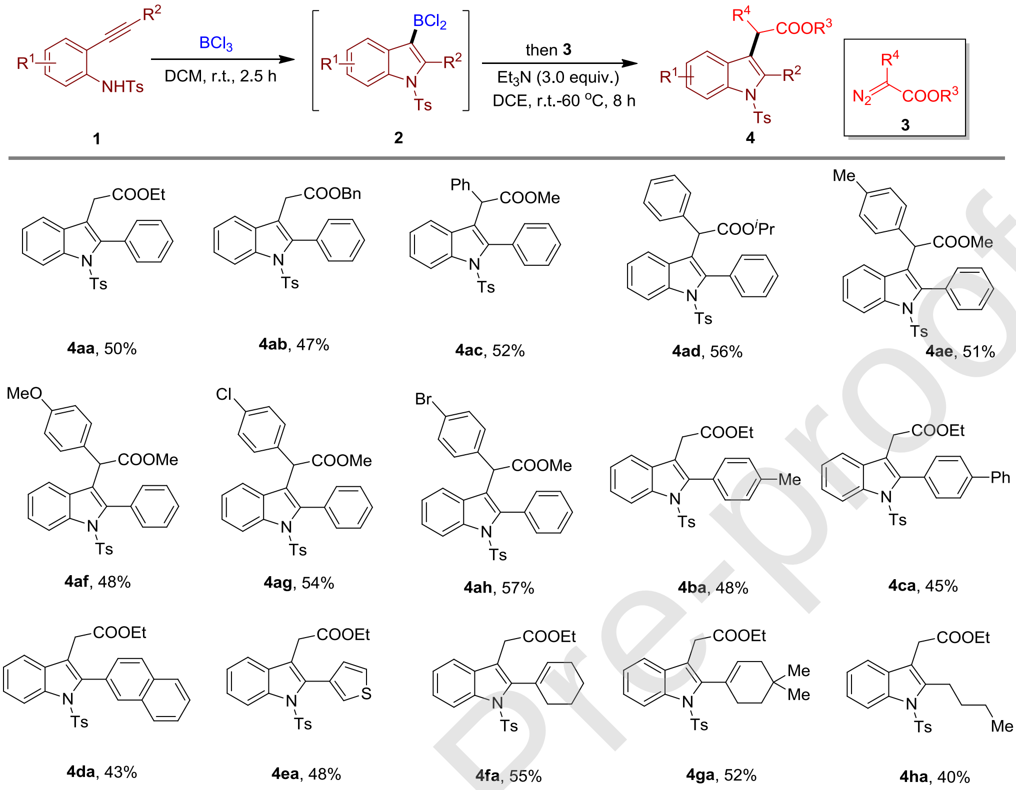


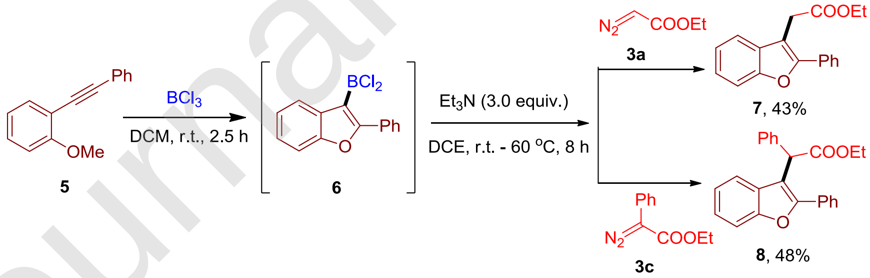
**Fig. 2**. Proposed mechanism.



**Scheme 1.** Reaction development.



**Scheme 2.** Metal-free cyclization and subsequent C-C bond formation. Reaction conditions: **1** (0.20 mmol), $BCl_3$ (0.4 mL, 1.0 mol/L in DCM), in DCM (1.0 mL), 2.5 h, r.t., under Ar; then diazo compound **3** (0.60 mmol), dry $Et_3N$ (0.60 mmol), in dry DCE (1 mL), r.t. to 60 °C, 8 h, under Ar.



**Scheme 3.** Cascade oxoboration and reaction with ethyl diazoacetate.