



Cite this: *Chem. Commun.*, 2020, **56**, 2202

Received 12th December 2019,
Accepted 17th January 2020

DOI: 10.1039/c9cc09657d

rsc.li/chemcomm

A general method for the synthesis of structurally diverse *N*-arylpypyrazoles from readily available cyclopropanols and aryl diazonium salts is disclosed. The reaction was conducted at room temperature within minutes with a broad substrate scope and excellent regioselectivity.

Pyrazole, a five-membered heterocycle with two adjacent nitrogen atoms used extensively in agrochemical and pharmaceutical applications, displays a broad spectrum of biological activities, such as anti-inflammatory, antimicrobial, antiobesity, antidepressant, antidiabetic, analgesic, and antiviral activities,¹ as exemplified by the presence of this core structure in several commercial drugs, including rimonabant, lonazolac and celecoxib, as well as the insecticide fipronil (Fig. 1).² In addition to their medicinal value, *N*-arylpypyrazoles have also been applied as ligands in transition-metal-catalyzed cross-coupling reactions,³ *N*-heterocyclic carbene (NHC) precursors⁴ and directing groups for C–H bond functionalizations.⁵

Due to the important applications of *N*-arylpypyrazole scaffolds, the construction of these useful compounds has attracted considerable attention during the past few decades.⁶ Conventional approaches for the preparation of *N*-arylpypyrazoles mainly focus on the condensation of arylhydrazines with 1,3-dicarbonyl or α,β -unsaturated carbonyl compounds.⁷ Alternatively, the 1,3-dipolar cycloaddition of diazo compounds or their surrogates with olefins or alkynes⁸ followed by transition-metal-catalyzed *N*-arylation represents another popular approach.⁹ Although these strategies can provide efficient routes to prepare *N*-arylpypyrazoles, some drawbacks, such as harsh reaction conditions, narrow substrate scope, and poor regioselectivity, limit their synthetic application to some extent. In order to overcome these problems, several alternative strategies involving transition metal catalyzed or mediated intermolecular coupling reactions have been developed.¹⁰

School of Chemistry and Chemical Engineering/Institute of Clean Energy and Materials/Guangzhou Key Laboratory for Clean Energy and Materials, Guangzhou University, Guangzhou, 510006, P. R. China. E-mail: jdl11@gzhu.edu.cn

† Electronic supplementary information (ESI) available. CCDC 1959009. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc09657d

Copper-mediated tandem ring-opening/cyclization reactions of cyclopropanols with aryl diazonium salts: synthesis of *N*-arylpypyrazoles†

Jidan Liu, * Erjie Xu, Jinyuan Jiang, Zeng Huang, Liyao Zheng and Zhao-Qing Liu

Albeit great achievements have been achieved, further exploration of convenient, efficient, and mild protocols to afford structurally diverse *N*-arylpypyrazoles from readily available starting materials is still highly desirable.

Cyclopropanols are important and useful synthetic intermediates in organic synthesis and can be readily prepared *via* Kulinkovich cyclopropanation of the corresponding esters in one step or Simmons–Smith cyclopropanation of silyl-enol ethers.¹¹ The tandem radical ring-opening couplings of cyclopropanols that proceed *via* single-electron oxidation can be easily realized owing to the intrinsic ring strain associated with the three-membered ring, and many efforts have been devoted to synthesizing β -functionalized carbonyl compounds with different single-electron oxidants.¹² In these transformations, the β -keto alkyl radical intermediates generated from the oxidative ring-opening of cyclopropanols were involved. However, despite progress in this area, the tandem radical ring-opening/coupling strategy for the construction of nitrogen-containing heterocycles *via* the cyclization with the C=O bond of β -functionalized carbonyl compounds is quite rare. In 2009, Chiba and co-workers reported

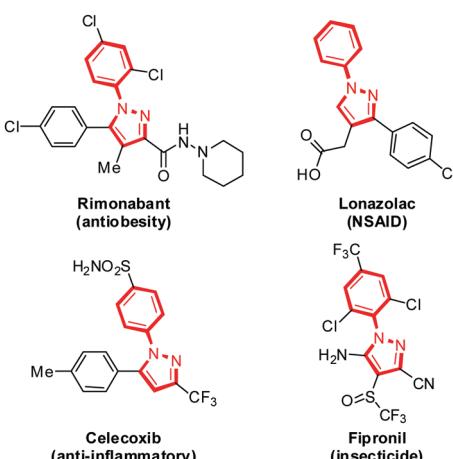
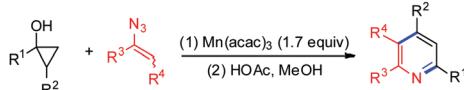


Fig. 1 Representative commercialized bioactive *N*-arylpypyrazoles.

a) Chiba's work: vinyl azides as radical receptors



b) This work: aryl diazonium salts as radical receptors



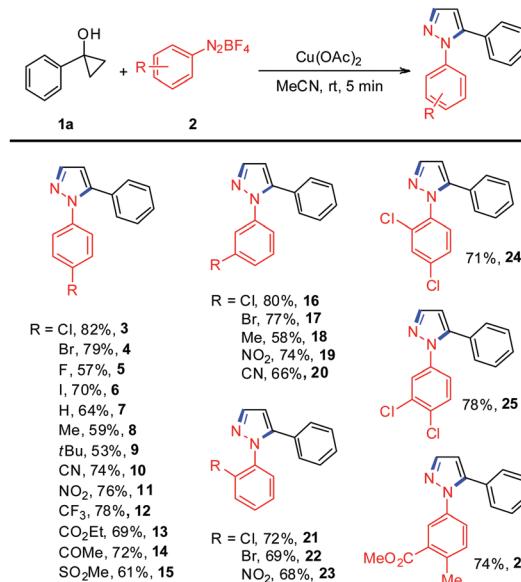
Scheme 1 Ring-opening coupling of cyclopropanols to construct N-heterocycles.

an efficient Mn(III)-mediated ring-opening coupling reaction of cyclopropanols with vinyl azides for the synthesis of substituted pyridines (Scheme 1a).¹³ Mechanistic studies revealed that this transformation was initiated with the generation of β -keto alkyl radical intermediates *via* the Mn(acac)₃-mediated oxidative radical ring-opening of cyclopropanols, followed by radical addition to vinyl azides and annulations. In light of our continuous interest in the chemistry of cyclopropanols and the synthesis of heterocycles,¹⁴ we envisioned that the β -keto alkyl radicals derived from cyclopropanols may be trapped by aryl diazonium salts followed by the cyclization with intramolecular carbonyl groups to afford important nitrogen-containing heterocycles. Herein, we described a copper-mediated tandem ring-opening/cyclization reaction of cyclopropanols with aryl diazonium salts for the construction of diversely substituted *N*-arylpypyrazoles (Scheme 1b). This procedure can be conducted at room temperature with high efficiency, excellent regioselectivity and broad substrate scope.

We began our investigations with the use of 1-phenylcyclopropanol **1a** and aryl diazonium tetrafluoroborate **2a** as model substrates to optimize the reaction conditions and these results are summarized in Table S1 (see the ESI†). Encouragingly, treating 1-phenylcyclopropanol **1a** with aryl diazonium tetrafluoroborate **2a** in the presence of 20 mol% Cu(OAc)₂ in MeCN at room temperature under N₂ gave the expected *N*-arylpypyrazole **3** in 18% yield (Table S1, ESI† entry 1). The yield of the desired product was dramatically improved (82%) by increasing the loading of Cu(OAc)₂ to 1.0 equiv. (Table S1, ESI† entry 4). Extensive solvent screening revealed that MeCN was important since reactions conducted in other solvents, such as DMSO, DMF, toluene, DCE, and 1,4-dioxane, generated the desired product in less than 5% yield (Table S1, ESI† entries 6–10). Among various copper salts tested, Cu(OAc)₂ gave the highest yield, whereas the others were far less effective (Table S1, ESI† entries 11–17), indicating that the counter ions of copper salts have a remarkable impact on the reaction yield. Subsequently, various other metal salts were also examined, and it was observed that only the acetate-type metal salts, such as Fe(OAc)₂, Mn(OAc)₂, and Mn(OAc)₃, could efficiently promote the reaction to deliver the desired product in moderate yields (Table S1, ESI† entries 18–26).

With the optimized reaction conditions in hand, we set out to investigate the scope and generality of the reaction between various aryl diazonium tetrafluoroborates and 1-phenylcyclopropanol **1a**. As shown in Table 1, aryl diazonium salts bearing either

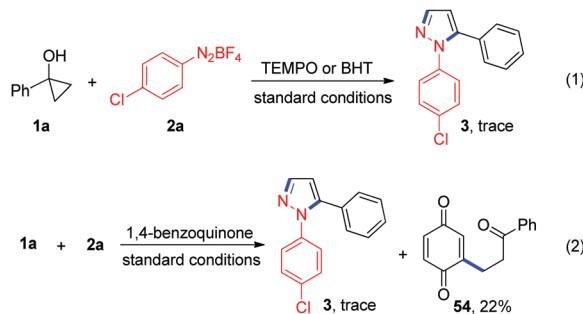
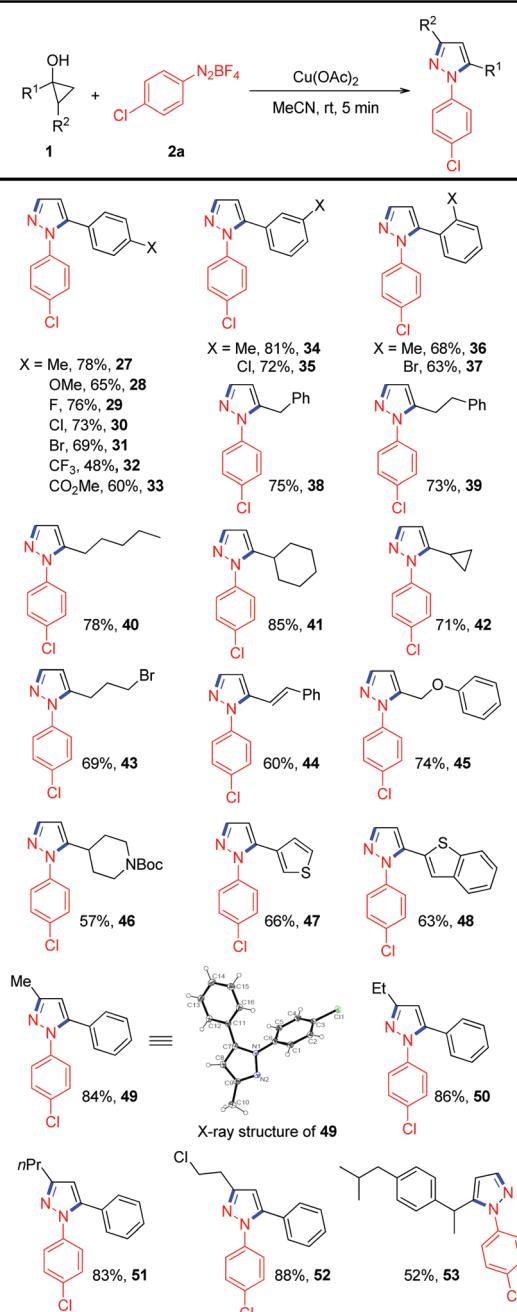
Table 1 Substrate scope with aryl diazonium tetrafluoroborates^{a,b}



^a Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), and Cu(OAc)₂ (0.2 mmol) were stirred in 1.0 mL MeCN at room temperature for 5 min under N₂. ^b Isolated yields.

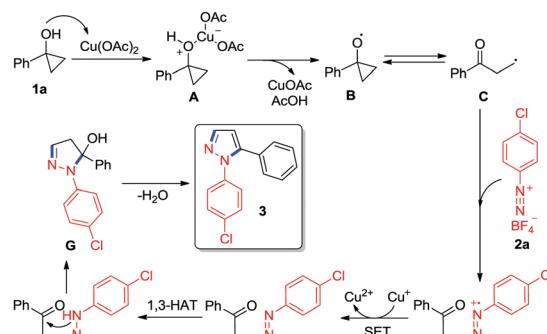
electron-withdrawing groups or electron-donating groups at the *para*-position of the benzene rings produced the corresponding *N*-arylpypyrazoles in moderate to good yields (Table 1, 3–15). It should be mentioned that the halogens in *N*-arylpypyrazoles 3–6 remained intact, offering new possibilities for cross-coupling-type manipulations. Similar yields could be achieved with *ortho*- and *meta*-substituted aryl diazonium salts, indicating that this transformation is not sensitive to steric effects (Table 1, 16–23). Disubstituted aryl diazonium salts were also compatible to generate the desired *N*-arylpypyrazole derivatives in yields ranging from 71% to 78% (Table 1, 24–26). Unfortunately, diazonium salts possessing other aromatic motifs such as 3-thienyl and 3-pyridyl were not suitable substrates for the reaction.

Next, the substrate scope with respect to cyclopropanol was also tested, and the results are summarized in Table 2. Phenylcyclopropanols with different substituents on the phenyl rings, such as *p*-Me, *p*-OMe, *p*-F, *p*-Cl, *p*-Br, *p*-CO₂Me, *m*-Me, *m*-Cl, *o*-Me, and *o*-Br, reacted smoothly with **2a** to give the desired *N*-arylpypyrazoles in moderate to good yields. A slightly decreased yield was observed for cyclopropanol with a strong electron-withdrawing CF₃ group (Table 2, 32). Alkyl substituted cyclopropanols were also viable for this reaction, generating the corresponding products 38–42 in 71% to 85% yields. Functional groups, such as alkyl bromide, alkene, aryl ether and alkylsulfonamide, were all well tolerated (Table 2, 43–46). In addition, thiophene- and benzothiophene-containing cyclopropanols were also compatible to deliver the expected *N*-arylpypyrazoles in 66% and 63% yields, respectively. It is worth mentioning that when 1,2-disubstituted cyclopropanols were employed, the desired 1,3,5-trisubstituted pyrazoles 49–52 could be obtained in better yields than those of 1-substituted cyclopropanols, which could be attributed to the formation of

Table 2 Substrate scope with cyclopropanols^{a,b}

with **2a** in the presence of 3.0 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) afforded only a trace amount of the desired product **3**, thus indicating that a radical pathway might be involved in this transformation (Scheme 2, eqn (1)). To trap the possibly formed β -keto alkyl radical in this reaction, 1,4-benzoquinone (3 equiv.) was subjected to the reaction and the expected coupling product **54** was observed (Scheme 2, eqn (2)). This result supports the generation of the β -keto alkyl radical during the reaction.

Based on the above control experiments and literature precedents,^{13,15} a plausible mechanism for copper-mediated tandem ring-opening/cyclization of cyclopropanols with aryl diazonium salts is proposed in Scheme 3. Initially, the coordination of the hydroxyl group of cyclopropanol **1a** to **Cu(OAc)₂** leads to the formation of a Lewis base-acid complex **A**, which undergoes an inner-sphere electron-transfer to produce the cyclopropoxy radical **B** with the elimination of **CuOAc** and **AcOH**.^{15a} Subsequently, the oxygen-centered radical **B** undergoes ring-opening to generate a β -keto alkyl radical **C**. The *in situ* generated β -keto alkyl radical **C** can be readily trapped by aryl diazonium salt **2a** to afford a radical cation **D**.^{15b,c} Next, the radical cation **D** is reduced to intermediate **E** *via* single-electron transfer,^{12j,15d,16} which is followed by a formal 1,3-hydrogen atom transfer (1,3-HAT) process to give a phenylhydrazone **F**. Finally, the intermolecular nucleophilic attack of the amino group on the ketone in intermediate **F** followed by the elimination of water from intermediate **G** yields the desired *N*-arylpypyrazole **3**.



Scheme 3 Plausible mechanism.

In conclusion, we have developed a general method for the synthesis of various *N*-arylpyrazoles from readily available cyclopropanols and aryldiazonium salts through a copper-mediated tandem ring-opening/cyclization reaction. This procedure can be conducted at room temperature with high efficiency, excellent regioselectivity and broad substrate scope with respect to cyclopropanol and the aryldiazonium salt substrate. Due to the importance of this structural motif as well as the easy availability of starting materials and the simplicity of the reaction conditions, we expect that the protocol will find broad applications in synthetic and medicinal chemistry.

We thank the National Natural Science Foundation of China (Grant No. 21875048 and 21576056), the Guangdong Natural Science Foundation (Grant No. 2017A030310620), and the Science and Technology Research Project of Guangzhou (Grant No. 201707010483) for financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 (a) G. Szabó, J. Fischer, Á. Kis-Varga and K. Gyires, *J. Med. Chem.*, 2008, **51**, 142–147; (b) J. B. Thomas, A. M. Giddings, R. W. Wiethe, S. Olepu, K. R. Warner, P. Sarret, L. Gendron, J.-M. Longpre, Y. Zhang, S. P. Runyon and B. P. Gilmour, *J. Med. Chem.*, 2014, **57**, 5318–5332; (c) J. V. Faria, P. F. Vegi, A. G. C. Miguila, M. S. dos Santos, N. Boechat and A. M. R. Bernardino, *Bioorg. Med. Chem.*, 2017, **25**, 5891–5903.
- 2 Ş. G. Küçükgüzel and S. Şenkardeş, *Eur. J. Med. Chem.*, 2015, **97**, 786–815.
- 3 (a) R. A. Singer, S. Caron, R. E. McDermott, P. Arpin and N. M. Do, *Synthesis*, 2003, 1727–1731; (b) R. A. Singer, M. Doré, J. E. Sieser and M. A. Berliner, *Tetrahedron Lett.*, 2006, **47**, 3727–3731.
- 4 A. Schmidt and A. Dreger, *Curr. Org. Chem.*, 2011, **15**, 2897–2970.
- 5 (a) T. Asaumi, N. Chatani, T. Matsuo, F. Kakiuchi and S. Murai, *J. Org. Chem.*, 2003, **68**, 7538–7540; (b) N. Umeda, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 7094–7099; (c) V. S. Thirunavukkarasu, K. Raghuvanshi and L. Ackermann, *Org. Lett.*, 2013, **15**, 3286–3289; (d) S.-S. Zhang, C.-Y. Jiang, J.-Q. Wu, X.-G. Liu, Q. Li, Z.-S. Huang, D. Li and H. Wang, *Chem. Commun.*, 2015, **51**, 10240–10243; (e) T.-J. Gong, M.-Y. Xu, S.-H. Yu, C.-G. Yu, W. Su, X. Lu, B. Xiao and Y. Fu, *Org. Lett.*, 2018, **20**, 570–573.
- 6 S. Fustero, M. Sánchez-Roselló, P. Barrio and A. Simón-Fuentes, *Chem. Rev.*, 2011, **111**, 6984–7034.
- 7 For selected examples, see: (a) B. C. Bishop, K. M. J. Brands, A. D. Gibb and D. J. Kennedy, *Synthesis*, 2004, 43–52; (b) S. Peruncheralathan, T. A. Khan, H. Ila and H. Junjappa, *J. Org. Chem.*, 2005, **70**, 10030–10035; (c) S. T. Heller and S. R. Natarajan, *Org. Lett.*, 2006, **8**, 2675–2678; (d) B. S. Gerstenberger, M. R. Rauckhorst and J. T. Starr, *Org. Lett.*, 2009, **11**, 2097–2100; (e) A. DeAngelis, D.-H. Wang and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 3434–3437; (f) Y. Tu, Z. Zhang, T. Wang, J. Ke and J. Zhao, *Org. Lett.*, 2017, **19**, 3466–3469; (g) R. S. Thombal and Y. R. Lee, *Org. Lett.*, 2018, **20**, 4681–4685.
- 8 For selected recent reviews, see: (a) T. V. Baiju and I. N. N. Namboothiri, *Chem. Rec.*, 2017, **17**, 939–955; (b) Y. Xia and J. Wang, *Chem. Soc. Rev.*, 2017, **46**, 2306–2362; For selected examples, see: (c) X. Qi and J. M. Ready, *Angew. Chem., Int. Ed.*, 2007, **46**, 3242–3244; (d) M. C. Pérez-Aguilar and C. Valdés, *Angew. Chem., Int. Ed.*, 2013, **52**, 7219–7223; (e) G. Zhang, H. Ni, W. Chen, J. Shao, H. Liu, B. Chen and Y. Yu, *Org. Lett.*, 2013, **15**, 5967–5969; (f) F.-G. Zhang, Y. Wei, Y.-P. Yi, J. Nie and J.-A. Ma, *Org. Lett.*, 2014, **16**, 3122–3125; (g) Z. Chen, Y. Zheng and J.-A. Ma, *Angew. Chem., Int. Ed.*, 2017, **56**, 4569–4574; (h) Y. Shao, H. Zheng, J. Qian and X. Wan, *Org. Lett.*, 2018, **20**, 2412–2415; (i) W. Wu, M. Li, J. Zheng, W. Hu, C. Li and H. Jiang, *Chem. Commun.*, 2018, **54**, 6855–6858; (j) X. Peng, X. Zhang, S. Li, Y. Lu, L. Lan and C. Yang, *Org. Chem. Front.*, 2019, **6**, 1775–1779.
- 9 (a) J. C. Antilla, J. M. Baskin, T. E. Bards and S. L. Buchwald, *J. Org. Chem.*, 2004, **69**, 5578–5587; (b) H. Kaddouri, V. Vicente, A. Ouali, F. Ouazzani and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 333–336; (c) S. Onodera, T. Kochi and F. Kakiuchi, *J. Org. Chem.*, 2019, **84**, 6508–6515.
- 10 (a) X. Li, L. He, H. Chen, W. Wu and H. Jiang, *J. Org. Chem.*, 2013, **78**, 3636–3646; (b) X. Tang, L. Huang, J. Yang, Y. Xu, W. Wu and H. Jiang, *Chem. Commun.*, 2014, **50**, 14793–14796; (c) D. Li, X. Mao, H. Chen, G. Chen and P. Liu, *Org. Lett.*, 2014, **16**, 3476–3479; (d) H. Guo, D. Zhang, C. Zhu, J. Li, G. Xu and J. Sun, *Org. Lett.*, 2014, **16**, 3110–3113; (e) J. J. Neumann, M. Suri and F. Glorius, *Angew. Chem., Int. Ed.*, 2010, **49**, 7790–7794.
- 11 For selected reviews, see: (a) O. G. Kulinkovich, *Chem. Rev.*, 2003, **103**, 2597–2632; (b) A. Nikolaev and A. Orellana, *Synthesis*, 2016, 1741–1768; (c) X. Cai, W. Liang and M. Dai, *Tetrahedron*, 2019, **75**, 193–208; (d) X. Wu and C. Zhu, *Chem. Commun.*, 2019, **55**, 9747–9756.
- 12 For selected examples, see: (a) N. Iwasawa, S. Hayakawa, M. Funahashi, K. Isobe and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 819–827; (b) S. Chiba, Z. Cao, S. A. A. E. Bialy and K. Narasaka, *Chem. Lett.*, 2006, **35**, 18–19; (c) A. Ilangovan, S. Saravanakumar and S. Malayappasamy, *Org. Lett.*, 2013, **15**, 4968–4971; (d) D. G. Kananovich, Y. A. Konik, D. M. Zubrytski, I. Järving and M. Lopp, *Chem. Commun.*, 2015, **51**, 8349–8352; (e) H. Zhao, X. Fan, J. Yu and C. Zhu, *J. Am. Chem. Soc.*, 2015, **137**, 3490–3493; (f) S. Wang, L.-N. Guo, H. Wang and X.-H. Duan, *Org. Lett.*, 2015, **17**, 4798–4801; (g) X. Fan, H. Zhao, J. Yu, X. Bao and C. Zhu, *Org. Chem. Front.*, 2016, **3**, 227–232; (h) K. Jia, F. Zhang, H. Huang and Y. Chen, *J. Am. Chem. Soc.*, 2016, **138**, 1514–1517; (i) Z. Ye, X. Cai, J. Li and M. Dai, *ACS Catal.*, 2018, **8**, 5907–5914; (j) Q. Tan, Z. Yang, D. Jiang, Y. Cheng, J. Yang, S. Xi and M. Zhang, *Angew. Chem., Int. Ed.*, 2019, **58**, 6420–6424.
- 13 (a) Y.-F. Wang and S. Chiba, *J. Am. Chem. Soc.*, 2009, **131**, 12570–12572; (b) Y.-F. Wang, K. K. Toh, E. P. J. Ng and S. Chiba, *J. Am. Chem. Soc.*, 2011, **133**, 6411–6421.
- 14 (a) J. Sheng, J. Liu, L. Chen, L. Zhang, L. Zheng and X. Wei, *Org. Chem. Front.*, 2019, **6**, 1471–1475; (b) J. Liu, J. Zou, J. Yao and G. Chen, *Adv. Synth. Catal.*, 2018, **360**, 659–663; (c) J. Sheng, J. Liu, H. Zhao, L. Zheng and X. Wei, *Org. Biomol. Chem.*, 2018, **16**, 5570–5574; (d) J. Liu, Z. Xue, Z. Zeng, Y. Chen and G. Chen, *Adv. Synth. Catal.*, 2016, **358**, 3694–3699.
- 15 (a) E. Hasegawa, M. Tateyama, R. Nagumo, E. Tayama and H. Iwamoto, *Beilstein J. Org. Chem.*, 2013, **9**, 1397–1406; (b) M. R. Heinrich, O. Blank and S. Wölfel, *Org. Lett.*, 2006, **8**, 3323–3325; (c) F. Liu, J.-Y. Wang, P. Zhou, G. Li, W.-J. Hao, S.-J. Tu and B. Jiang, *Angew. Chem., Int. Ed.*, 2017, **56**, 15570–15574; (d) S. E. Schaafsma, R. Jorritsma, H. Steinberg and T. J. de Boer, *Tetrahedron Lett.*, 1973, **14**, 827–830.
- 16 The need for a stoichiometric amount of $\text{Cu}(\text{OAc})_2$ in our reaction suggests that the $\text{Cu}(\text{II})$ which was re-generated from $\text{Cu}(\text{I})$ and intermediate **D** may not react again from **A** to **B**.