Organic & Biomolecular Chemistry

Accepted Manuscript

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View Article Online
DOI: 10.1039/C9OB00572B

Journal Name

COMMUNICATION

Synthesis of Benzoxazoles via the Copper-Catalyzed Hydroamination of Alkynones with 2-Aminophenols

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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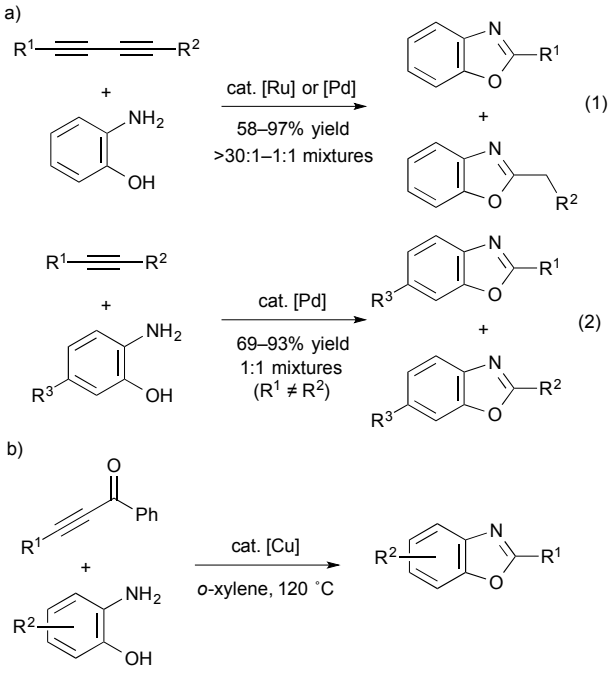
We describe herein the synthetic method of benzoxazole derivatives via the copper-catalyzed hydroamination of alkynones with 2-aminophenols. The method produced a wide variety of functionalized benzoxazole derivatives in good yields. Preliminary mechanistic experiments revealed that the reaction would proceed through the copper-catalyzed hydroamination of alkynones and the sequential intramolecular cyclization of β-iminoketones/elimination of acetophenone promoted by the copper catalyst.

Benzoxazoles have been proven to be important structural units that are found in pharmacologically active compounds[1] and fluorescent materials.[2] Therefore, considerable efforts have been devoted to the development of efficient methods for the synthesis of benzoxazoles.[3,4] The major strategies accessing to benzoxazoles are as follows: (1) condensation of carboxylic acids and its derivatives with 2-aminophenols,[5] (2) oxidative cyclization of a phenolic Schiff base intermediate,[6] (3) metal-catalyzed oxidative intramolecular C-O coupling of 2-haloanilides and their analogues,[7] (4) metal-catalyzed direct C-H arylation reaction.[8] However, these synthetic methods often require harsh reaction conditions (e.g. high reaction temperature,[5a,5b,5e,5g] the use of acidic activators[5b,5d,5e] and oxidants[6a–d,6f,6h–k,6m,6p]). Therefore, developing an efficient and versatile method for the synthesis of benzoxazoles is still a significant research subject in the field of synthetic organic chemistry.

The transition-metal-catalyzed hydroamination of carbon-carbon multiple bonds provides a straightforward method for the synthesis of a wide variety of functionalized amine derivatives.[9] In 2003, Yamamoto and co-workers revealed that the use of 2-aminophenols in the ruthenium- or palladium-catalyzed hydroamination of diynes led to the formation of two different benzoxazoles depending on the relative size of R^1 and R^2 (Scheme 1a, eq 1).[10] Later, Pan, Liang and co-workers achieved the synthesis of benzoxazoles via the palladium-catalyzed hydroamination of alkynes with 2-aminophenols (Scheme 1a, eq 2).[11] However, this method yields a mixture of two different benzoxazoles due to the low regioselectivity during the hydroamination reaction of unsymmetrical internal alkynes. On the other hand, we recently reported the copper-catalyzed intermolecular hydroamination of internal alkynes with anilines and amines, providing the corresponding hydroamination products in high yields.[12] During the course of this study, we have found that the reaction of alkynones with 2-aminophenols in the presence of a copper catalyst proceeded to give



Scheme 1 a) Examples for the synthesis of benzoxazoles via transition-metal-catalyzed hydroamination of alkynes with 2-aminophenols. b) This work

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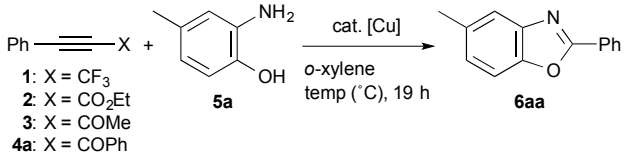
†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

the 2-substituted benzoxazoles in good yields.[13] Herein, we present a synthetic method of benzoxazoles via the copper-catalyzed hydroamination of alkynones with 2-aminophenols (Scheme 1b).

We initially examined the reaction of alkynes containing a trifluoromethyl group (**1**) or an ethyl ester group (**2**) with 2-amino-4-methylphenol (**5a**) in the presence of 10 mol% of $Cu(OTf)_2$ in *o*-xylene at 120 ˚C (Table 1, entries 1 and 2). We confirmed the formation of benzoxazole **6aa** in moderate yields. These results led us to investigate further optimization of the reaction conditions to establish an efficient synthetic method of the benzoxazoles. Replacement of the ester group by an acetyl group (**3**) did not affect the reaction efficiency (Entry 3). Fortunately, the reaction of alkynone **4a** bearing a benzoyl group with **5a** afforded the desired product **6aa** in 89% isolated yield (Entry 4). Furthermore, the loading amount of the catalyst could be decreased to 5 mol% without loss of the catalytic performance (Entry 5). Based on ^{1}H NMR analyses of the crude reaction mixture, we confirmed the formation of acetophenone (Mechanistic details, see: Scheme 3). We also tested the other copper species as the catalysts under the same reaction conditions (Entries 6–11). The catalytic activity of Cu(OTf)•toluene was comparable to that of $Cu(OTf)_2$, whereas the use of CuCl, CuI, CuTC, $CuCl_2$, and $CuBr_2$ led to the decreased yield of **6aa**. The reaction of **4a** with **5a** at 100 ˚C or 80 ˚C was sluggish, yielding benzoxazole **6aa** in low yields (Table 1, entries 12 and 13). When the reaction of **4a** with **5a** was carried out in the absence of $Cu(OTf)_2$, the yield of benzoxazole **6aa** decreased to 34% yield (Table 1, entry 14). We assume that the conjugate addition of **5a** to **4a**[14] followed by the intramolecular cyclization would occur to give **6aa**.

Table 1 Optimization of reaction conditions[a]



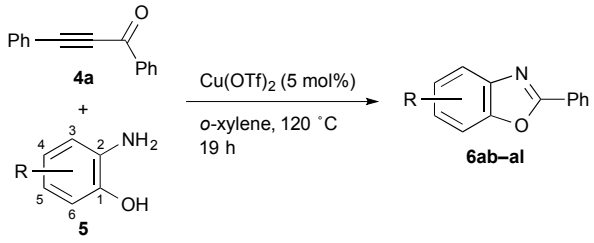
entry	X	[Cu]	yield of **6aa** (%)[b]
1	CF_3 (**1**)	$Cu(OTf)_2$ (10 mol%)	55[c]
2	CO_2Et (**2**)	$Cu(OTf)_2$ (10 mol%)	51[c]
3	COMe (**3**)	$Cu(OTf)_2$ (10 mol%)	54
4	COPh (**4a**)	$Cu(OTf)_2$ (10 mol%)	89
5	COPh (**4a**)	$Cu(OTf)_2$ (5 mol%)	91
6	COPh (**4a**)	CuOTf•tol (5 mol%)	87
7	COPh (**4a**)	CuCl (5 mol%)	82[c]
8	COPh (**4a**)	CuI (5 mol%)	80[c]
9	COPh (**4a**)	CuTC (5 mol%)	77[c]
10	COPh (**4a**)	$CuCl_2$ (5 mol%)	72[c]
11	COPh (**4a**)	$CuBr_2$ (5 mol%)	85[c]
12[d]	COPh (**4a**)	$Cu(OTf)_2$ (5 mol%)	26
13[e]	COPh (**4a**)	$Cu(OTf)_2$ (5 mol%)	7
14	COPh (**4a**)	–	34

[a]Reaction conditions: **1–4a** (0.3 mmol), **5a** (0.36 mmol), $Cu(OTf)_2$ (0.015 mmol) in *o*-xylene (0.6 mL) at 120 ˚C for 19 h. [b]Isolated yield. [c]NMR yield (CH_2Br_2 was used as an internal standard). [d]at 100 ˚C. [e]at 80 ˚C.

With the optimized reaction conditions in hand, several 2-aminophenol derivatives **5** were employed for the reaction with alkynone **4a** (Table 2). Acetophenone generated from the catalysis (See, Scheme 3 for details) was reduced with $NaBH_4$ in some cases, because the benzoxazoles **6** and acetophenone were inseparable by preparative tin-layer chromatography. 2-Aminophenol (**5b**) was reacted with alkynone **4a** under the optimized reaction conditions to give benzoxazole **6ab** in 82% yield, and the reaction could be scaled up without any loss of the catalytic performance (Table 2, entries 1 and 2). 2-Aminophenols having methyl groups at the 5, 3, or 6 position underwent the reaction to give the corresponding benzoxazoles **6ac–ae** in 67–95% yields (Entries 3–5). Electron-donating and -deficient substituents (OMe, CF_3) did not affect the reaction efficiency, furnishing **6af** and **6ag** in 84% and 76% yield, respectively (Entries 6 and 7). The reaction of alkynone **4a** with *o*-aminophenols **5h–k** bearing chloro and bromo atoms afforded **6ah–ak** in 74–83% yields (Entries 8–11). We observed a small amount of debrominated product **6ab** in the reactions of **5j** and **5k**.[15] When aminophenol **5l** having a phenyl substituent at the 4 position on the phenyl ring was used, desired product **6al** was obtained in 57% yield (Table 3, entry 12).

We next investigated the reaction of the alkynones **4** bearing various substituents with 2-amino-4-methylphenol (**5a**) using the copper catalyst system (Table 3). We obtained the desired benzoxazoles **6** as a mixture with

Table 2 Scope of 2-aminophenols **5**[a]



entry	**5**	R	**6**	yield (%)[c]
1[b]	**5b**	H	**6ab**	82
2[b,d]	**5b**	H	**6ab**	79
3[b]	**5c**	5-Me	**6ac**	73
4	**5d**	3-Me	**6ad**	95
5[b]	**5e**	6-Me	**6ae**	67
6	**5f**	4-CF_3	**6af**	84
7	**5g**	4-MeO	**6ag**	76
8[b]	**5h**	5-Cl	**6ah**	82
9[b]	**5i**	4-Cl	**6ai**	83
10[b]	**5j**	5-Br	**6aj**	76[e]
11[b]	**5k**	4-Br	**6ak**	74
12[b]	**5l**	4-Ph	**6al**	57

[a]Reaction conditions: **4a** (0.3 mmol), **5** (0.36 mmol), $Cu(OTf)_2$ (0.015 mmol) in *o*-xylene (0.6 mL) at 120 ˚C for 19 h. [b]Reaction conditions: **4a** (0.3 mmol), **5** (0.36 mmol), $Cu(OTf)_2$ (0.015 mmol) in *o*-xylene (0.6 mL) at 120 ˚C for 19 h, then $NaBH_4$ in MeOH was added to the resulting mixture at room temperature. [c]Isolated yield. [d]1 mmol of **4a** was used. [e]As a 90:10 mixture of **6aj**:**6ab**.

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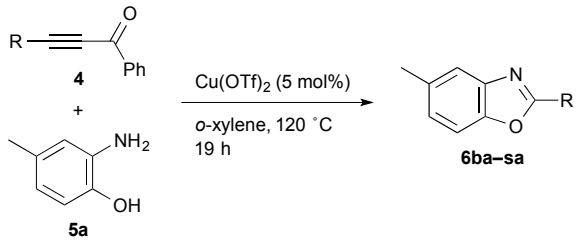
a small amount of **6aa** in some cases.[16] The effect of a wide variety of *para*-substituents on their phenyl rings was evaluated (Table 3, entries 1–9). The reaction of alkynones **4b–e** bearing electro-donating (Me, *t*-Bu, MeO) and -withdrawing (CF_3) substituents with **5a** proceeded to give the corresponding benzoxazoles **6ba–ea** in 50–76% yields (Entries 1–4). The reaction of alkynone **4g** bearing a fluoro substituent on the phenyl ring afforded benzoxazole **6ga** in 74% yield (Entry 6). When the reaction of alkynone **4h** having a bromo atom was conducted under the reaction conditions, the desired product **6ha** was obtained in 69% yield as a 86 : 14 mixture of **6ha** : **6aa** (Entry 7). The use of cyano, acetyl, and ester group-substituted alkynones **4f**, **4i**, and **4j** resulted in diminished yields (Entries 5, 8, 9). Various *meta*- and *ortho*-substituents on the phenyl ring were tolerated under the reaction conditions to give the benzoxazoles **6ka–na** in 65–82% yields (Entries 10–13). The reaction of alkynones **4o** and **4p** resulted in low yields (Entries 14 and 15). The present method could be applicable to the reaction of alkynones **4q** and **4r** having alkyl groups, furnishing the desired benzoxazoles **6qa** and **6ra** in 82% and 62% yield, respectively (Entries 16 and 17). Unfortunately, the desired product was not formed by the reaction of alkynone **4s** bearing a terminal alkyne group (Entry 18).

We examined the preliminary mechanistic experiments to elucidate the reaction mechanism of the present copper catalysis (Scheme 2). The reaction of alkynone **4a** with *o*-anisidine was conducted under the optimized reaction conditions to give hydroamination product **7** in 66% yield (Scheme 2a). On the other hand, the yield of **7** decreased to 7% without use of the copper catalyst. These results show that the hydroamination process would proceed by the copper catalysis. When hydroamination product **8** was subjected to the catalyst system, benzoxazole **6ab** was obtained in 69% yield (Scheme 2b). Although the transformation of **8** to **6ab** proceeded in the absence of the copper catalyst, **6ab** was formed in diminished yield. These results imply that the transformation of **8** to **6ab** may be promoted by the copper catalyst.

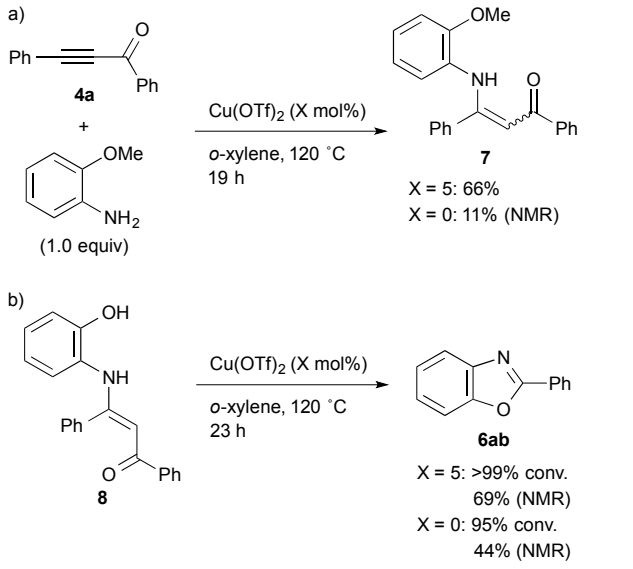
Based on the results of the preliminary mechanistic experiments and previously proposed mechanism for the synthesis of benzoxazoles via the transition-metal-catalyzed hydroamination of the alkynes,[10,11] we show the possible reaction pathway of the present copper catalysis in Scheme 3. Initially, the copper-catalyzed hydroamination of alkynone **4a** with 2-aminophenol **5b** occurs to give hydroamination product **A**. The subsequent tautomerization of **A** produces β-iminoketone **B**. The intramolecular cyclization of **B**, which seems to proceed via intermediate **C**, followed by the retro-Mannich-type reaction of intermediate **D** would occur to give benzoxazole **6ab** along with the formation of acetophenone.

Table 3 Scope of alkynones **4**[a]

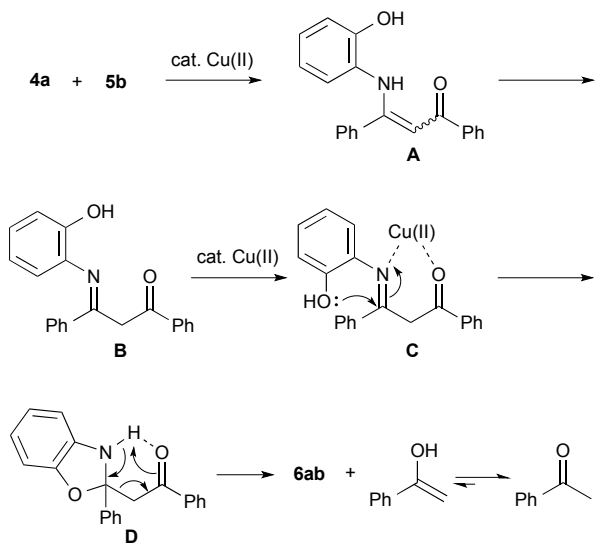


entry	**4**	R	**6**	yield (%)[c]
1[b]	**4b**	4-MeC_6H_4	**6ba**	76[d]
2[b]	**4c**	4-*t*-BuC_6H_4	**6ca**	56
3[b]	**4d**	4-$MeOC_6H_4$	**6da**	66
4[b]	**4e**	4-$CF_3C_6H_4$	**6ea**	50
5[b]	**4f**	4-CNC_6H_4	**6fa**	26
6	**4g**	4-FC_6H_4	**6ga**	74[e]
7[b]	**4h**	4-BrC_6H_4	**6ha**	69[f]
8	**4i**	4-AcC_6H_4	**6ia**	23
9[b]	**4j**	4-$CO_2EtC_6H_4$	**6ja**	19
10	**4k**	3-MeC_6H_4	**6ka**	82[g]
11[b]	**4l**	3-$MeOC_6H_4$	**6la**	68
12[b]	**4m**	3-$CF_3C_6H_4$	**6ma**	65[h]
13	**4n**	2-MeC_6H_4	**6na**	70
14	**4o**	1-Naphthyl	**6oa**	15
15[b]	**4p**	2-thienyl	**6pa**	30[i]
16	**4q**	Cyclohexyl	**6qa**	82[j]
17	**4r**	$PhCH_2CH_2$	**6ra**	62
18	**4s**	H	**6sa**	–

[a]Reaction conditions: **4** (0.3 mmol), **5a** (0.36 mmol), $Cu(OTf)_2$ (0.015 mmol) in *o*-xylene (0.6 mL) at 120 ˚C for 19 h. [b]Reaction conditions: **4a** (0.3 mmol), **5** (0.36 mmol), $Cu(OTf)_2$ (0.015 mmol) in *o*-xylene (0.6 mL) at 120 ˚C for 19 h, then $NaBH_4$ in MeOH was added to the resulting mixture at room temperature. [c]Isolated yield. [d]As a 90 : 10 mixture of **6ba** : **6aa**. [e]As a 74 : 26 mixture of **6ga** : **6aa** (determined by a GC-MS analysis). [f]As a 87 : 13 mixture of **6ha** : **6aa**. [g]As a 95 : 5 mixture of **6ka** : **6aa**. [h]As a 92 : 8 mixture of **6ma** : **6aa**. [i]As a 99 : 1 mixture of **6pa** : **6aa**. [j]As a 93 : 7 mixture of **6qa** : **6aa**.



Scheme 2 Preliminary mechanistic experiments



Scheme 3 Proposed reaction pathway

Conclusions

We have developed the synthetic method of benzoxazole derivatives via the copper-catalyzed hydroamination of alkynones with 2-aminophenols. The method can be applicable to the synthesis of a wide range of functionalized benzoxazole derivatives in good yields. Preliminary mechanistic experiments showed that the copper catalyst would be involved in the hydroamination of alkynones with 2-aminophenos and the sequential intramolecular cyclization of β-iminoketones/elimination of acetophenone processes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (17K05794). We thank Mr. Keisuke Hashimoto and Mr. Yoshiyuki Takahashi for their experimental supports.

References

1 For a recent review, see: S. Singh, G. Veeraswamy, D. Bhattarai, J.-l. Goo, K. Lee and Y. Choi, *Asian. J. Org. Chem.* 2015, **4**, 1338.

2 C. Carayon and S. Fery-Forgues, *Photochem. Photobiol. Sci.* 2017, **16**, 1020.

3 For recent reviews, see: (a) R. V. Kumar, *Asian. J. Chem.* 2004, **16**, 1241; (b) S. Rajasekhar, B. Maiti and K. Chanda, *Synlett* 2017, **28**, 521; (c) J. He, *Curr. Org. Chem.* 2017, **21**, 1991.

4 For a general overview, see: G. V. Boyd, In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations; E. Schaumann, Ed.; Thieme, Stuttgart,* 2002, **11**, 481.

5 For examples, see: (a) L. C. Galatis, *J. Am. Chem. Soc.* 1948, **70**, 1967; (b) D. W. Hein, R. J. Alheim and J. J. Leavitt, *J. Am. Chem. Soc.* 1957, **79**, 427; (c) Y. Kanaoka, T. Hamada and O. Yonemitsu, *Chem. Pharm. Bull.* 1970, **18**, 587; (d) M. Terashima and M. Ishii, *Synthesis* 1982, 484; (e) C. S. Cho, D. T. Kim, J. Q. Zhang, S.-L. Ho, T.-J. Kim and S. C. Shim, *J. Heterocyclic Chem.* 2002, **39**, 421; (f) R. Kumar, C. Selvam, G. Kaur and A. K. Chakraborti, *Synlett* 2005, 1401; (g) J. A. Seijas, M. P. Vázquez-Tato, M. R. Carballido-Reboredo, J. Crecente-Campo and L. Romar-López, *Synlett* 2007, 313; (h) G. Nieddu and G. Giacomelli, *Tetrahedron* 2013, **69**, 791.

6 For examples, see: (a) F. F. Stephens and J. D. Bower, *J. Chem. Soc.* 1949, 2971; (b) F. F. Stephens and J. D. Bower, *J. Chem. Soc.* 1950, 1722; (c) K. Nakagawa, H. Onoue and J. Sugita, *Chem. Pharm. Bull.* 1964, **12**, 1135; (d) S. K. Talapatra, P. Chaudhuri and B. Talapatra, *Heterocycles* 1980, **14**, 1279; (e) G. Speier, *J. Mol. Catal.* 1987, **41**, 253; (f) R. G. Srivastava and P. S. Venkataramani, *Synth. Commun.* 1988, **18**, 1537; (g) T. Kondo, S. Yang, K.-T. Huh, M. Kobayashi, S. Kotachi and Y. Watanabe, *Chem. Lett.* 1991, 1275; (h) K. H. Park, K. Jun, S. R. Shin and S. W. Oh, *Tetrahedron Lett.* 1996, **37**, 8869; (i) R. S. Varma, R. K. Saini and O. Prakash, *Tetrahedron Lett.* 1997, **38**, 2621; (j) R. S. Varma and D. Kumar, *J. Heterocyclic Chem.* 1998, **35**, 1539; (k) J. Chang, K. Zhao and S. Pan, *Tetrahedron Lett.* 2002, **43**, 951; (l) Y. Kawashita, N. Nakamichi, H. Kawabata and M. Hayashi, *Org. Lett.* 2003, **5**, 3713; (m) C. Praveen, K. H. Kumar, D. Muralidharan and P. T. Perumal, *Tetrahedron* 2008, **64**, 2369; (n) Y.-X. Chen, L.-F. Qian, W. Zhang and B. Han, *Angew. Chem. Int. Ed.* 2008, **47**, 9330; (o) A. J. Blacker, M. M. Farah, M. I. Hall, S. P. Marsden, O. Saidi and J. M. J. Williams, *Org. Lett.* 2009, **11**, 2039; (p) D. S. Bose and M. Idrees, *Synthesis* 2010, 398; (q) Y. H. Cho, C.-Y. Lee, D.-C. Ha and C.-H. Cheon, *Adv. Synth. Catal.* 2012, **354**, 2992; (r) M. Wu, X. Hu, J. Liu, Y. Liao and G.-J. Deng, *Org. Lett.* 2012, **14**, 2722; (s) Y. Endo and J.-E. Bäckvall, *Chem. Eur. J.* 2012, **18**, 13609.

7 For examples, see: (a) S. Ueda and H. Nagasawa, *Angew. Chem. Int. Ed.* 2008, **47**, 6411; (b) G. Altenhoff and F. Glorius, *Adv. Synth. Catal.* 2004, **346**, 1661; (c) G. Evindar and R. A. Batey, *J. Org. Chem.* 2006, **71**, 1802; (d) R. D. Viirre, G. Evindar and R. A. Batey, *J. Org. Chem.* 2008, **73**, 3452; (e) J. Bonnamour and C. Bolm, *Org. Lett.* 2008, **10**, 2665; (f) S. Ueda and H. Nagasawa, *J. Org. Chem.* 2009, **74**, 4272; (g) M. L. Kantam, G. T. Venkanna, K. B. S. Kumar, V. Balasubrahmanyam and S. Bhargava, *Synlett* 2009, **11**, 1753;(h) P. Saha, T, Ramana, N. Purkait, M. A. Ali, R. Paul and T. Punniyamurthy, *J. Org. Chem.* 2009, **74**, 8719; (i) A. B. Naidu and G. Sekar, *Synthesis* 2010, 579; (j) P. Saha, M. A. Ali, P. Ghosh and T. Punniyamurthy, *Org. Biomol. Chem.* 2010, **8**, 5692; (k) D. Suresh, A. Dhakshinamoorthy and K. Pitchumani, *Tetrahedron Lett.* 2013, **54**, 6415; (l) A. Ahmed, R. Singha and J. K. Ray, *Tetrahedron Lett.* 2015, **56**, 2167; (m) J. I. Urzúa, R. Contreras, C. O. Salas and R. A. Tapia, *RSC Adv.* 2016, **6**, 82401.

8 For examples, see: (a) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.* 2007, **129**, 12404; (b) F. Derridj, S. Djebbar, O. Benali-Baitich and H. Doucet, *J. Organomet. Chem.* 2008, **693**, 135; (c) L. Ackermann, A. Althammer and S. Fenner, *Angew. Chem. Int. Ed.* 2009, **48**, 201; (d) L. Ackermann, S. Barfüsser and J. Pospech, *Org. Lett.* 2010, **12**, 724; (e) C. M. So, C. P. Lau and F. Y. Kwong, *Chem. Eur. J.* 2011, **17**, 761; (f) S. Ranjit and X. Liu, *Chem. Eur. J.* 2011, **17**, 1105; (g) Y. C. Teo, S. N. Riduan and Y. Zhang, *Green Chem.* 2013, **15**, 2365; (h) S. Tabuchi, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.* 2014, **79**, 5401; (i) F. Zhu and Z.-X. Wang, *Org.*

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DOI: 10.1039/C9OB00572B

Lett. 2015, **17**, 1601; (j) F. Zhu, J.-L. Tao and Z.-X. Wang, *Org. Lett.* 2015, **17**, 4926; (k) J. C.-H. Yim, M. Nambo and C. M. Crudden, *Org. Lett.* 2017, **19**, 3715.

9 For reviews, see: (a) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo and M. Tada, *Chem. Rev.* 2008, **108**, 3795; (b) L. Huang, M. Arndt, K. Gooßen, H. Heydt and L. J. Gooßen, *Chem. Rev.* 2015, **115**, 2596.

10 T. Shimada and Y. Yamamoto, *J. Am. Chem. Soc.* 2003, **125**, 6646.

11 H.-Z. Xie, Q. Gao, Y. Liang, H.-S. Wang and Y.-M. Pan, *Green Chem.* 2014, **16**, 2132.

12 T. Ishikawa, T. Sonehara, M. Minakawa and M. Kawatsura, *Org. Lett.* 2016, **18**, 1422.

13 Shimada and Yamamoto reported the reaction of the alkynone with 2-aminophenols as the mechanistic experiment, affording benzoxazoles, see: ref. 10.

14 For examples, see: (a) V. K. Tripathi, P. S. Venkataramani and G. Mehta, *J. Chem. Soc. Perkin Trans. 1*, 1979, 36. (b) T. Sakamoto, T. Nagano, Y. Kondo and H. Yamanaka, *Synthesis* 1990, 215. (c) S. M. Bromidge, D. A. Entwistle, J. Goldstein and B. S. Orlek, *Synth. Commun.* 1993, **23**, 487. (d) W. Liu, C. Chen and Q. Zhang, *Org. Biomol. Chem.* 2011, **9**, 6484. (e) S. Roy, M. P. Davydova, R. Pal, K. Gilmore, G. A. Tolstikov, S. F. Vasilevsky and I. V. Alabugin, *J. Org. Chem.* 2011, **76**, 7482. (f) J. Shao, X. Huang, X. Hong, B. Liu and B. Xu, *Synthesis* 2012, **44**, 1798. (g) G. Cheng, X. Zeng, J. Shen, X. Wang and X. Cui, *Angew. Chem. Int. Ed.* 2013, **52**, 13265.

15 Selected examples for transition-metal-catalyzed deharogenation of aryl halides, see: (a) M. S. Viciu, G. A. Grasa and S. P. Nolan, *Organometallics* 2001, **20**, 3607; (b) K. Fujita, M. Owaki and R. Yamaguchi, *Chem. Commun.* 2002, 2964; (c) C. Desmarets, S. Kuhl, R. Schneider and Y. Fort, *Organometallics* 2002, **21**, 1554; (d) H. Guo, K. Kanno and T. Takahashi, *Chem. Lett.* 2004, **33**, 1356; (e) A. Bhattacharjya, P. Klumphu and B. H. Lipshutz, *Org. Lett.* 2015, **17**, 1122.

16 We speculate that the condensation of alkynones **4** with **5a** in the presence of the copper catalyst would afford the corresponding alkynyl ketimines, which undergo the sequential intramolecular cyclization/elimination of phenylacetylene to give **6aa**.