Check for updates

View Article Online
View Journal

Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: C. Pan, J. Zhu, R. Chen and J. Yu, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB01564J.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB01564J

Journal Name

COMMUNICATION

Direct arylation of unactivated benzene with aryl acyl peroxides toward biaryls

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

DOI: 10.1039/x0xx00000x

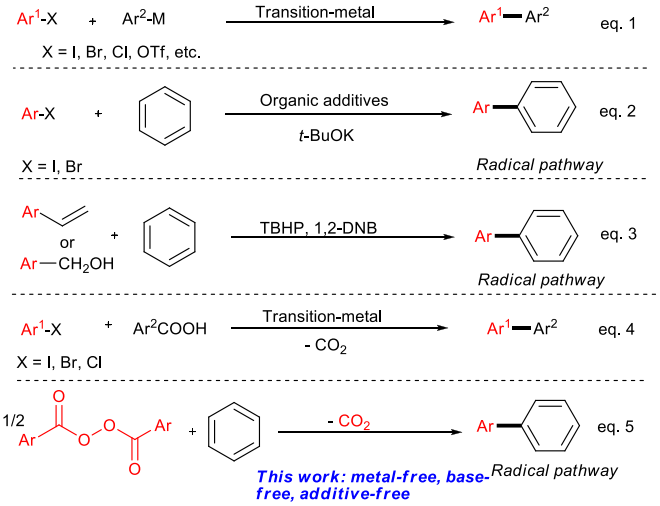
www.rsc.org/

Changduo Pan,*[a] Jiawei Zhu,[b] Rongzhen Chen[b] and Jin-Tao Yu*[b]

A direct arylation of unactivated benzene with acyl peroxides was developed, affording biaryls in good to excellent yields. The transformation underwent radical pathway under metal-free, base-free and additive-free conditions with good functional groups compatibility.

Biaryl scaffolds are abundant in a great many natural products, pharmaceuticals, agrochemicals and functional organic materials.[1] Undoubtedly, transition metal catalyzed cross coupling reactions including many classic name reactions like Suzuki, Negishi, Ullman, Hiyama, Stille, and Kumada couplings as well as the direct arylation of aromatic C-H bonds were demonstrated as efficient approaches for the synthesis of biaryls in the past decades (Scheme 1, eq. 1).[2] However, these methods suffered from some inevitable drawbacks such as the employment of noble metals or very sensitive organometallic reagents. Therefore, the development of efficient synthetic approaches performed under transition-metal-free conditions is highly desired.[3] In this regard, homolytic aromatic substitution (HAS) by an aryl radical and related processes was developed and provides as an alternative and promising strategy toward biaryl structures without the participation of metals.[4] For example, the coupling of aryl halides with benzene derivatives promoted by organic additives in the assistance of base through homolytic aromatic substitution has emerged as a transition-metal-free approach for the direct arylation toward biaryls (Scheme 1, eq. 2).[5] Except for aryl halide, styrenes and benzyl alcohols were also suitable coupling partners in the transition-metal-free direct arylation of benzene (Scheme 1, eq. 3).[6] Although those transition-metal-free approaches for the synthesis of biaryls have made remarkable progress, organic additive and base were needed in most cases.

Additionally, decarboxylative arylation of carboxylic acid and aryl halide catalyzed by transition-metals was also employed for the preparation of biaryls (Scheme 1, eq. 4).[7] However, those catalytic systems were complex and difficult to handle. Acylperoxide which usually used as oxidant was demonstrated as excellent aryl donor and successfully applied in the Pd-catalyzed arylation of aromatic C-H bond.[8] Zhu have developed a decarboxylation/cyclization of 2-isocyanobiphenyls with acylperoxides to 6-aryl phenanthridines under metal-free and base-free conditions.[9] With respect to the importance of decarboxylative arylation, herein we report a direct arylation of benzene with acyl peroxides toward biaryls under metal-free, base-free and additive-free conditions (Scheme 1, eq. 5).[10]



Scheme 1. The method toward biaryls.

In our previous work,[11] when benzoyl peroxide was used as aryl radical source, considerable amount of biphenyl was detected. We once thought it was formed by homocoupling of phenyl radicals. While, further elaborate study indicated that the biphenyl was generated from the reaction between phenyl

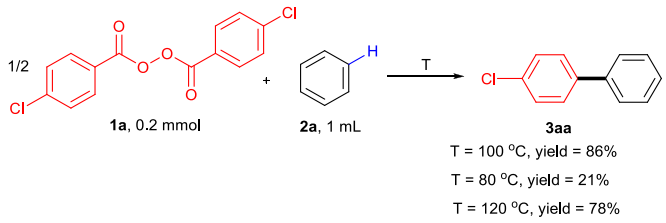
[a] School of Chemical and Environmental Engineering, Jiangsu University of Technology, Changzhou 213001, P. R. China
[b] School of Petrochemical Engineering, Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, Changzhou University, Changzhou 213164, P. R. China
E-mail: panchangduo@jsut.edu.cn; yujintao@cczu.edu.cn
Electronic Supplementary Information (ESI) available]. See DOI: 10.1039/x0xx00000x

Published on 18 July 2017. Downloaded by Cornell University Library on 18/07/2017 22:14:36.

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB01561J

radical and solvent benzene. The inert phenyl C-H bond was activated under such conditions. With this interesting result in hand, we begin our research on the direct arylation of benzene by utilizing 4-chlorobenzoic peroxyanhydride and benzene as the model reaction. To our delight, the reaction performed efficiently at 100 °C in the absence of metal, additive or base, giving the product **3aa** in 86% yield along with about 0.2 mmol of 4-chlorobenzoic acid. The yield of **3aa** was decreased to 21% at 80 °C, whereas no better yield was obtained at elevated temperature (Scheme 2). Additionally, the product **3aa** was isolated in 82% when the reaction was conducted in 2 mmol scale.

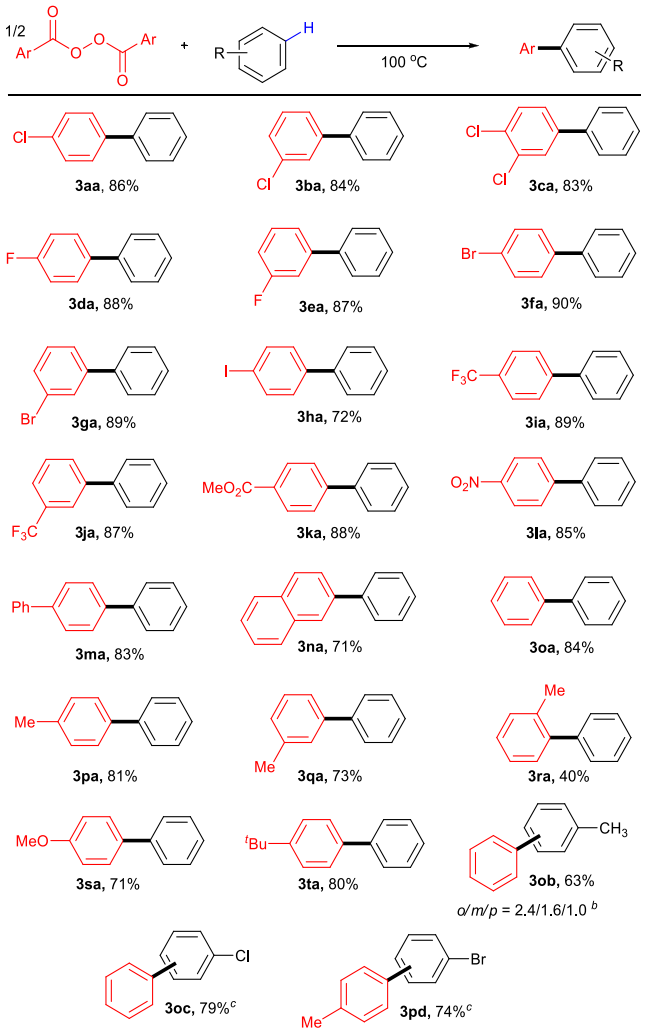


Scheme 2. Temperature effect

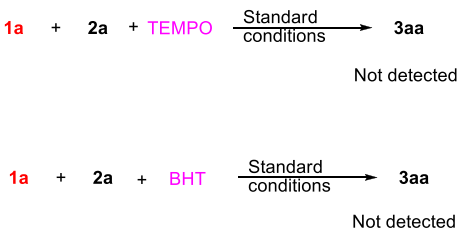
With the optimized conditions in hand, the scope of aryl acyl peroxides was investigated. The aryl acyl peroxides bearing electron-withdrawing or -donating substituents were reacted smoothly with benzene, providing the products in good to excellent yields (Figure 1). Various halogenated aryl acyl peroxides were suitable for the procedure and a range of substituted aryl acyl peroxides such as *m*- and *p*-chloro-, fluoro-, bromo-, and iodo-groups proceeded efficiently to give the products in excellent yields. These halogen groups (F, Cl, Br, I) were kept intact during the transformation, offering the potential for further functionalizations. Strong electron-withdrawing groups such as carbonyl, nitro and trifluoromethyl were also well tolerated. Generally, the aryl acyl peroxides **1a**-**1l** bearing electron-withdrawing groups delivered the product in higher yields than their electron-donating analogues **1p**-**1t**. Additionally, steric effect was obvious. For *ortho*-methyl aryl acyl peroxide resulted the corresponding product (**3ra**) in only 40% yield. Moreover, the arylation also occurred on mono substituted benzene as toluene with the isolation of regio-isomers **3ob** (*o*/*m*/*p* = 2.4/1.6/1.0) in moderate yield. The reaction of aryl acyl peroxides with chlorobenzene or bromobenzene also ran smoothly and gave the indistinguishable regio-isomers **3oc** or **3pd** in good yields.

Then, some experiments were conducted to investigate the reaction mechanism. Radical scavenger 2,2,6,6-tetramethyl-piperidine oxide (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were added into the reaction under standard conditions, respectively. As expected, the arylation was completely suppressed (Scheme 3). These results indicated this procedure undergoes a radical pathway. Moreover, kinetic isotope experiment was conducted and showed a low K_H/K_D value, which suggested that the cleavage of phenylic C–H bond is not the rate-determining step in this transformation (Scheme 4). Moreover, about 0.2 mmol 4-chlorobenzoic acid was isolated when the reaction of **2a** with **1a** was conducted in 0.2 mmol scale under standard conditions.

Figure 1. The substrate scope [a]



[a] Reaction conditions: **1** (0.2 mmol), benzene (1 mL), 100 °C, 12 h. [b] The ratio of isomers was determined by ^{1}H NMR. [c] The o/m/p ratio was difficult to identify by ^{1}H NMR.



Scheme 3. Radical trapping experiments

Based on these results, a plausible mechanism is proposed in Scheme 5. First, peroxide **1** is thermally decomposed and the following CO_2 releasing gives aryl radical **A**. Subsequently, the addition of radical **A** to benzene produces radical intermediate **B**, which is oxidized by peroxide **1** to form cation

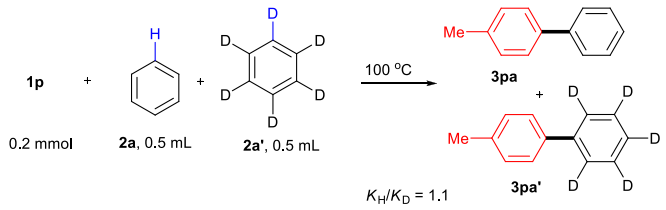
Published on 18 July 2017. Downloaded by Cornell University Library on 18/07/2017 22:14:36.

Organic & Biomolecular Chemistry Accepted Manuscript

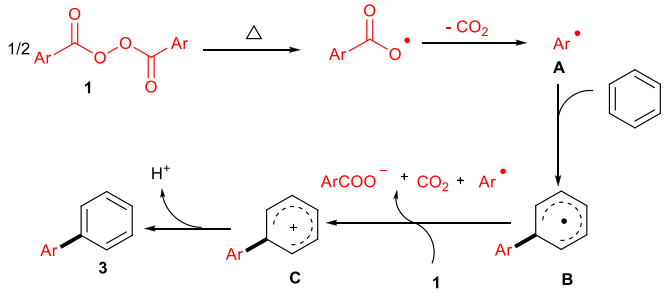
This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

intermediate **C**. Finally, the deprotonation of intermediate **C** gives the biaryl product **3**.



Scheme 4. Kinetic isotope experiment



Scheme 5. Proposed mechanism.

In conclusion, we have disclosed a direct arylation of unactivated benzene with acyl peroxides affording the biaryls in good to excellent yields. This transformation went through radical pathway under metal-free, base-free and additive-free conditions with good functional groups compatibility. Compared with previous methods toward biaryls, this procedure is more simple, mild and environment friendly.

We thank the National Natural Science Foundation of China (21602086 and 21672028), the Natural Science Foundation for Colleges and Universities of Jiangsu Province (16KJB150002) and Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology (BM2012110) for financial supports.

Notes and references

1 (a) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.,* 2002, **102**, 1359. (b) P. J. Hajduk, M. Bures, J. Praestgaard and S. W. Fesik, *J. Med. Chem.,* 2000, **43**, 3443.

2 (a) A. Suzuki, *Angew. Chem., Int. Ed.,* 2011, **50**, 6722. (b) E. Negishi, *Angew. Chem., Int. Ed.,* 2011, **50**, 6738. (c) Y. Nakao and T. Hiyama, *Chem. Soc. Rev.,* 2011, **40**, 4893. (d) J. K. Stille, *Angew. Chem., Int. Ed.*, 1986, **25**, 508. (e) C. E. I. Knappke and A. J. V. Wangelin, *Chem. Soc. Rev.,* 2011, **40**, 4948. (f) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.,* 2007, **107**, 174. (g) G. P. McGlacken and L. M. Batemana, *Chem. Soc. Rev.,* 2009, **38**, 2447. (h) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.,* 2009, **48**, 9792.

3 C.-L. Sun and Z.-J. Shi, *Chem. Rev.,* 2014, **114**, 9219.

4 (a) W. R. Bowman and J. M. D. Storey, *Chem. Soc. Rev.,* 2007, **36**, 1803. (b) S. Yanagisawa and K. Itami, *ChemCatChem,* 2011, **3**, 827. (c) A. Studer and D. P. Curran, *Angew. Chem. Int. Ed.,* 2011, **50**, 5018. (d) A. Studer and D. P. Curran, *Nat. Chem.,* 2014, **6**, 765.

5 (a) S. Yanagisawa, K. Ueda, T. Taniguchi and K. Itami, *Org. Lett.,* 2008, **10**, 4673. (b) C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nat. Chem.,* 2010, **2**, 1044. (c) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.,* 2010, **132**, 16737. (d) E. Shirakawa, K.-I. Itoh, T. Higashino and T. Hayashi, *J. Am. Chem. Soc.,* 2010, **132**, 15537. (e) J. Cuthbertson, V. J. Gray and J. D. Wilden, *Chem. Commun.,* 2014, **50**, 2575. (f) Y. Gao, P. Tang, H. Zhou, W. Zhang, H. Yang, N. Yan, G. Hu, D. Mei, J. Wang and D. Ma, *Angew. Chem., Int. Ed.,* 2016, **55**, 3124. (g) C.-L. Sun, Y.-F. Gu, W.-P. Huang and Z.-J. Shi, *Chem. Commun.,* 2011, **47**, 9813. (h) Z. Xu, L. Gao, L. Wang, M. Gong, W. Wang and R. Yuan, *ACS Catal.,* 2015, **5**, 45. (i) W.-C. Chen, Y.-C. Hsu, W.-C. Shih, C.-Y. Lee, W.-H. Chuang, Y.-F. Tsai, P. P.-Y. Chen and T.-G. Ong, *Chem. Commun.,* 2012, **48**, 6702. (j) A. Dewanji, S. Murarka, D. P. Curran and A. Studer, *Org. Lett.,* 2013, **15**, 6102. (k) Q. Song, D. Zhang, Q. Zhu and Y. Xu, *Org. Lett.,* 2014, **16**, 5272. (l) M. Patil, *J. Org. Chem.,* 2016, **81**, 632. (m) L. Zhang, H. Yang and L. Jiao, *J. Am. Chem. Soc.,* 2016, **138**, 7151. (n) J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.,* 2016, **138**, 7402. (o) H. Zhao, J. Shen, C. Ren, W. Zeng and H. Zeng, *Org. Lett.,* 2017, **19**, 2190.

6 A. Kumar and B. A. Shah, *Org. Lett.,* 2015, **17**, 5232.

7 Reviews: (a) O. Baudoin, *Angew. Chem., Int. Ed.,* 2007, **46**, 1373. (b) N. Rodrıguez and L. J. Gooßn, *Chem. Soc. Rev.*, 2011, **40**, 5030 (c) R. Shang and L. Liu, *Sci. China: Chem.,* 2011, **54**, 1670. (d) Y. Wei, P. Hu, M. Zhang and W. Su, *Chem. Rev.,* 2017, **117**, 8864.

8 (a) W. Y. Yu, W. N. Sit, Z. Zhou and A. S. C. Chan, *Org. Lett.,* 2009, **11**, 3174. (b) D. Li, N. Xu, Y. Zhang and L. Wang, *Chem. Commun.,* 2014, **50**, 14862. (c) M. Sun, Z. Wang, J. Wang, P. Guo, X. Chen and Y.-M. Li, *Org. Biomol. Chem.,* 2016, **14**, 10585. (d) C. Qian, D. Lin, Y. Deng, X.-Q. Zhang, H. Jiang, G. Miao, X. Tang and W. Zeng, *Org. Biomol. Chem.,* 2014, **12**, 5866. (e) K. R. Babu, N. Zhu and H. Bao, *Org. Lett.,* 2017, **19**, 46.

9 C. Pan, H. Zhang, J. Han, Y. Cheng and C. Zhu, *Chem. Commun.,* 2015, **51**, 3786.

10 The reaction of bis-3,4-dichlorobenzoyl peroxide with benzene utilizing *m*-dinitro-benzene as additive, see: D. H. Hey and M. J. Perkins, *Org. Synth.,* 1969, **49**, 44.

11 C. Pan, Y. Fu, Q. Ni and J.-T. Yu, *J. Org. Chem.,* 2017, **82**, 5005.

View Article Online DOI: 10.1039/C7OB01540

Published on 18 July 2017. Downloaded by Cornell University Library on 18/07/2017 22:14:36.

Organic & Biomolecular Chemistry Accepted Manuscript

Please do not adjust margins