



Cite this: *RSC Adv.*, 2017, 7, 15176

Received 9th January 2017  
 Accepted 27th February 2017

DOI: 10.1039/c7ra00352h

[rsc.li/rsc-advances](http://rsc.li/rsc-advances)

# TBHP-promoted direct oxidation reaction of benzylic C<sub>sp</sub><sup>3</sup>–H bonds to ketones†

Jiajing Tan,<sup>\*a</sup> Tianyu Zheng,<sup>a</sup> Yuqi Yu<sup>c</sup> and Kun Xu<sup>\*b</sup>

A metal-free oxidation system employing *tert*-butyl hydroperoxide (TBHP) has been developed for selective oxidation of structurally diverse benzylic sp<sup>3</sup> C–H bonds. This low-cost methodology allows for rapid generation of synthetically and biologically valued arylketones in good to excellent yields from readily available alkylarenes and diarylmethanes.

C–H bond activation reactions have become one of the most important classes of reactions in organic synthesis, the synthetic scope and utility of which has advanced considerably during the past decade.<sup>1</sup> Undoubtedly, there are fundamental benefits for integrating such a strategy in organic synthesis, especially from the vantage point of environmental benignity and high atom/step economy. Furthermore, the construction of complex organic molecules nowadays can be designed in a more direct and effective fashion as these C–H functionalization transformations are an established piece in synthetic organic chemists' toolbox.<sup>1</sup> Among this progress, the direct oxidation of C–H bonds for the synthesis of functionalized molecules has been of great interest in both academic and industrial settings.<sup>2</sup> Many C–H oxidation methods have thus been developed to date.

Aryl ketones are widely recognized as key functional and structural motifs in a large plethora of significant molecules, including natural products, active pharmaceutical ingredients, agrochemicals and advanced materials (Fig. 1). Also, they frequently serve as useful precursors for the synthesis of complicated organic molecules.<sup>3</sup> The classical methods to assemble such motifs involve the Friedel–Crafts acylation<sup>4</sup> and transition metal catalyzed coupling reactions,<sup>5</sup> which often suffer from poor selectivity and require harsh reaction conditions as well as toxic or expensive metal salts. In this way, direct benzylic C<sub>sp</sub><sup>3</sup>–H oxidation reactions, as we proposed, could be a more ideal synthetic pathway.<sup>6</sup> However, the literature survey suggested that most of the existing methods relied on less sustainable oxidants, such as potassium permanganate or chromium acid derivatives.<sup>7</sup> The resulting vast metal residue not only caused operational challenges upon scale-up, but were

also known as potential carcinogens, and long-term exposure to those hazardous metals might lead to central nervous system disorders.<sup>8</sup> Consequently, less toxic, cost-effective and sustainable oxidants like peroxides or molecular oxygen, have drawn increasing research interest.

In recent years, considerable progress has been made in this field.<sup>9</sup> The group of Pandey and Lei independently reported a C–H aerobic oxidation approaches *via* photo-redox chemistry to synthesize aryl ketones.<sup>10</sup> In addition, Li and Wang's group achieved the benzylic C–H oxidation by developing a recyclable TEMPO catalyst.<sup>11</sup> Moreover, in 2016, Stahl *et al.* employed the electrochemical *N*-hydroxyphthalimide (NHPI) system to achieve benzylic oxygenation reaction to prepare (hetero)aryl ketones.<sup>12</sup> Very recently, our group also reported a simple and efficient potassium *tert*-butoxide promoted (hetero)benzylic C–H oxidation reaction using oxygen as oxidant.<sup>13</sup> Our approach provided a ready access to versatile diarylketones under mild conditions. While similar to most of other benzylic oxidation protocols, alkylbenzenes were unfortunately not amenable substrates in that report.<sup>14</sup> Therefore, further research is highly necessary, as direct oxidative C–H functionalization of diverse substrates are still challenging and reported examples are limited in terms of substrate types. Since one of our lab's long-term goal is to

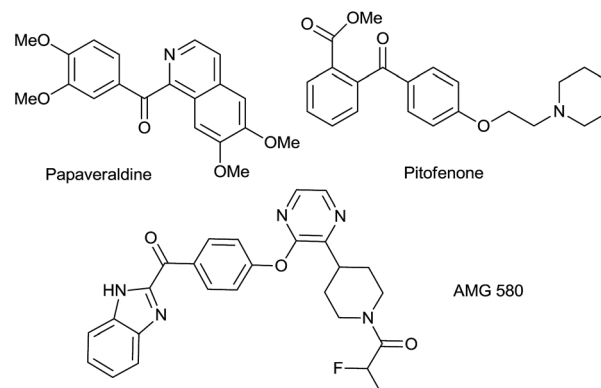


Fig. 1 Selected aryl ketones.

<sup>a</sup>Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, China. E-mail: [tanjj@mail.buct.edu.cn](mailto:tanjj@mail.buct.edu.cn)

<sup>b</sup>College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, Henan 473061, P. R. China. E-mail: [xukun@nynu.edu.cn](mailto:xukun@nynu.edu.cn)

<sup>c</sup>China Academy of Engineering Physics, P. O. Box 919, Mianyang, Sichuan, 621900, China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra00352h





ketone **2g** and **2o** in good yields. Noteworthy, these pyridine-containing substrates often showed poor reactivity under metal-mediated benzylic oxidation reaction, which is probably due to the product inhibition *via* chelation.<sup>12</sup> Finally, these optimized reaction conditions were examined for the oxygenation of pharmaceutically relevant imidazole substrates. 2-Benzoyl-1*H*-benzimidazole (**2p**), the core structural motif of potent phosphodiesterase inhibitor AMG 580, could be directly prepared in 70% yield.<sup>3f</sup>

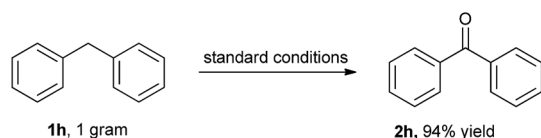
To expand the synthetic utility of this oxidative protocol, we then tested other benzylic sp<sup>3</sup> C–H compounds as substrates. Under the identical reaction conditions, 2-phenylacetophenone (**2q**) underwent the oxidation reaction to give the benzoic acid (**3q**) instead of the desired benzyl product in 70% isolated yields (Scheme 2).<sup>10b</sup>

The scale-up synthesis of **2h** also highlighted the utility and operational simplicity of this procedure. When the reaction was run at one-gram scale with diphenylmethane (**1h**), the product (**2h**) could still be obtained in a comparable 94% isolated yield (Scheme 3).

To gain insight into this oxidative reaction, control experiments were employed as shown in Scheme 4. Firstly, the reaction



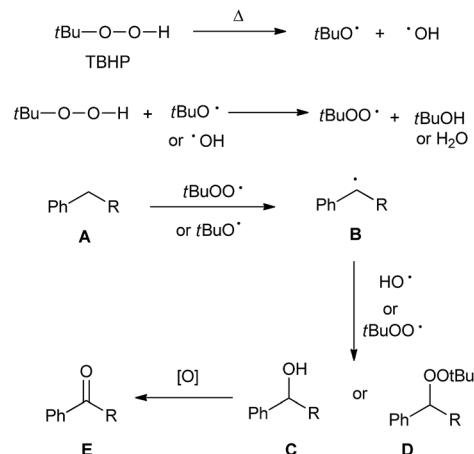
Scheme 2 Oxidative reaction of 2-phenylacetophenone.



Scheme 3 Scale-up synthesis.



Scheme 4 Control experiments.



Scheme 5 Proposed mechanism.

was stopped after 5 hours, the oxidation product **2h** and radical adducts **4** were both observed in 66% and 30% yields respectively. When intermediate **4** was subjected to the standard reaction conditions, the corresponding product **2h** was also obtained in 91% yield. When the diphenylmethanol (**5**) was subjected to the standard reaction conditions, the desired ketone product **2h** was also obtained with 95% yield. These results indicated that this transformation might involve benzylic peroxides and/or benzylic alcohols as the reaction intermediates.

On the basis of the above-mentioned experimental results and previous reports,<sup>17</sup> a plausible reaction mechanism was proposed in Scheme 5. First, the decomposition of TBHP generated the oxygen-based radicals, which then underwent hydrogen abstraction of substrate **A** to generate intermediate **B**. The radical intermediate **B** can either react with  $^\bullet\text{OH}$  or  $^\bullet\text{OO}t\text{Bu}$  to form the oxygenated intermediate **C** or **D**. The intermediate **D** either eliminated one molecule of  $t\text{BuOH}$  to directly form ketone **E**, or transformed into the benzylic alcohol **C**, which then underwent further oxidation to give final aryl ketone product **E**.

## Conclusions

In summary, a simple metal-free TBHP system has been identified for direct oxidation of benzylic methylene groups to the corresponding aryl ketones. The radical-based reaction pathway tolerates a large variety of benzylic C–H bonds, giving the desired product in good to excellent yields. More importantly, the methodology is amenable to challenging heterocyclic substrates, such as pyridines and imidazoles. The synthetic utility of this protocol was further showcased in the gram-scale synthesis of diphenylketone. Further studies on both reaction scope and reaction mechanism are currently under investigation in our group.

## Acknowledgements

We are grateful to Fundamental Research Funds for the Central Universities in Beijing University of Chemical Technology, and the Natural Science Foundation of China (21602119, U1504208),



the financial support from He'nan Provincial Department of Science and Technology (152300410117).

## Notes and references

- For selected recent reviews, see: (a) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (b) C.-L. Sun, B.-J. Li and Z. J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (c) T. Brueckl, R. D. Baxter, Y. Ishihara and P. S. Baran, *Acc. Chem. Res.*, 2012, **45**, 826; (d) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (e) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (f) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936, and reference therein.
- For selected recent reviews, see: (a) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976; (b) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362; (c) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (d) A. N. Campbell and S. S. Stahl, *Acc. Chem. Res.*, 2012, **45**, 851, and reference therein.
- (a) H. G. Franck and J. W. Stadelhofer, *Industrial Aromatic Chemistry*, Springer-Verlag, Berlin, 1988; (b) N. J. Lawrence, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1739; (c) R. K. Dieter, *Tetrahedron*, 1999, **55**, 4177; (d) H. Surburg and J. Panten, *Common Fragrance and Flavor Materials*, Wiley-VCH, Weinheim, Germany, 5th edn, 2006; (e) M. Mizuno, A. Inagaki, M. Yamashita, N. Soma, Y. Maeda and H. Nakatani, *Tetrahedron*, 2006, **62**, 4065; (f) A. J. Whitehead, R. A. Ward and M. F. Jones, *Tetrahedron Lett.*, 2007, **48**, 911; (g) H. B. Yang, K. Ghosh, Y. Zhao, B. H. Northrop, M. M. Lyndon, D. C. Muddiman, H. S. White and P. J. Stang, *J. Am. Chem. Soc.*, 2008, **130**, 839; (h) S. K. Vooturi, C. M. Cheung, M. J. Rybak and S. M. Firestine, *J. Med. Chem.*, 2009, **52**, 5020; (i) J. R. Luque-Ortega, P. Reuther, L. Rivas and C. Dardonville, *J. Med. Chem.*, 2010, **53**, 1788; (j) A. Shimada, I. Takahashi, T. Kawano and Y. Kimura, *Z. Naturforsch., B: J. Chem. Sci.*, 2011, **56**, 797; (k) Q.-F. Hu, B. Zhou, J.-M. Huang, X.-M. Gao, L.-D. Shu, G.-Y. Yang and C.-T. Che, *J. Nat. Prod.*, 2013, **76**, 292; (l) H. Chen, D. Lester-Zeiner, J. Shi, S. Miller, C. Glaus, E. Hu, N. Chen, J. Able, C. Biorn, J. Wong, J. Ma, K. Michelsen, G. Hill Della Puppa, T. Kazules, H. Dou, S. Talreja, X. Zhao, A. Chen, S. Rumpf, R. K. Kunz, H. Ye, O. R. Thiel, T. Williamson, C. Davis, A. Porter, D. Immke, J. R. Allen and J. Treanor, *J. Pharmacol. Exp. Ther.*, 2015, **352**, 327.
- (a) A. Furstner, D. Voigtlander, W. Schrader, D. Giebel and M. T. Reetz, *Org. Lett.*, 2001, **3**, 417; (b) S. Gmouh, H. L. Yang and M. Vaultier, *Org. Lett.*, 2003, **5**, 2219; (c) G. Sartori and R. Maggi, *Advances in Friedel-Crafts Acylation Reactions*, CRC Press, Boca Raton, FL, 2010; (d) P. H. Tran, P. E. Hansen, H. T. Nguyen and T. N. Le, *Tetrahedron Lett.*, 2015, **56**, 612.
- For a most recent review, see: (a) X.-F. Wu, *Chem.-Eur. J.*, 2015, **21**, 12252; For selected transition-metal-catalyzed reactions, see: (b) S. Ma and Z. Gu, *Angew. Chem., Int. Ed.*, 2005, **44**, 7512; (c) X. Jia, S. Zhang, W. Wang, F. Luo and J. Cheng, *Org. Lett.*, 2009, **11**, 3120; (d) C. W. Chan, Z. Zhou, A. S. C. Chan and W. Y. Yu, *Org. Lett.*, 2010, **12**, 3926; (e) Y. Lu, D. Leow, X. Wang, K. M. Engle and J.-Q. Yu, *Chem. Sci.*, 2011, **2**, 967; (f) M. Z. Li, C. Wang and H. B. Ge, *Org. Lett.*, 2011, **13**, 2062; (g) Z. Yin and P. Sun, *J. Org. Chem.*, 2012, **77**, 11339; (h) Q. Zhang, F. Yang and Y. Wu, *Chem. Commun.*, 2013, **49**, 6837; (i) P. Mamone, G. Danoun and L. J. Gooßen, *Angew. Chem., Int. Ed.*, 2013, **52**, 6704; (j) C. Pi, X. Cui, X. Liu, M. Guo, H. Zhang and Y. Wu, *Org. Lett.*, 2014, **16**, 5164; (k) S. D. Ramgren and N. K. Garg, *Org. Lett.*, 2014, **16**, 824, and reference therein.
- For selected recent reports, see: (a) X. Fan, Y. He, X. Zhang, S. Guo and Y. Wang, *Tetrahedron*, 2011, **67**, 6369; (b) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 11088; (c) X. Fan, Y. He, Y. Wang, Z. Xue, X. Zhang and J. Wang, *Tetrahedron Lett.*, 2011, **52**, 899; (d) J. De Houwer, K. Abbaspour Tehrani and B. U. W. Maes, *Angew. Chem., Int. Ed.*, 2012, **51**, 2745; (e) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Tetrahedron*, 2012, **68**, 5258; (f) Y.-F. Wang, F.-L. Zhang and S. Chiba, *Synthesis*, 2012, **44**, 1526; (g) C. Menendez, S. Gau, S. Ladeira, C. Lherbet and M. Baltas, *Eur. J. Org. Chem.*, 2012, 409; (h) Z. Xu, C. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 11367; (i) C. Zhang, L. Zhang and N. Jiao, *Adv. Synth. Catal.*, 2012, **354**, 1293; (j) S. Cacchi, G. Fabrizi, A. Goggiani, A. Iazzetti and R. Verdiglione, *Synthesis*, 2013, **45**, 1701; (k) B. Pieber and C. O. Kappe, *Green Chem.*, 2013, **15**, 320; (l) A. Dos Santos, L. El Kaïm and L. Grimaud, *Org. Biomol. Chem.*, 2013, **11**, 3282; (m) Q. Li, Y. Huang, T. Chen, Y. Zhou, Q. Xu, S.-F. Yin and L.-B. Han, *Org. Lett.*, 2014, **16**, 3672; (n) J.-W. Yu, S. Mao and Y.-Q. Wang, *Tetrahedron Lett.*, 2015, **56**, 1575; (o) Y. Huang, T. Chen, Q. Li, Y. Zhou and S.-F. Yin, *Org. Biomol. Chem.*, 2015, **13**, 7289; (p) H. Xie, Y. Liao, S. Chen, Y. Chen and G.-J. Deng, *Org. Biomol. Chem.*, 2015, **13**, 6944; (q) L. Ren, L. Wang, Y. Lv, G. Li and S. Gao, *Org. Lett.*, 2015, **17**, 2078; (r) Y. Jeong, Y. Moon and S. Hong, *Org. Lett.*, 2015, **17**, 3252; (s) H. Sterckx, J. DeHouwer, C. Mensch, I. Caretti, K. A. Tehrani, W. A. Herrebout, S. Van Doorslaer and B. U. W. Maes, *Chem. Sci.*, 2016, **7**, 346, and reference therein.
- P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301.
- (a) A. Wells, M. Teria and T. Eve, *Biochem. Soc. Trans.*, 2006, **34**, 304; (b) D. Avila, R. Puntel and M. Aschner, *Interrelations Between Essential Metal Ions and Human Diseases*, ed. A. Sigel, H. Sigel and R. K. O. Sigel, Springer, Netherlands, 2013, vol. 13, pp. 199–227.
- (a) A. M. Khenkin and R. Neumann, *J. Am. Chem. Soc.*, 2002, **124**, 4198; (b) L. Gonsalvi, I. W. C. E. Arends, P. Moilanen and R. A. Sheldon, *Adv. Synth. Catal.*, 2003, **345**, 1321; (c) A. J. Catino, J. M. Nichols, H. Choi, S. Gottipamula and M. P. Doyle, *Org. Lett.*, 2005, **7**, 5167; (d) C. Pavan, J. Legros and C. Bolm, *Adv. Synth. Catal.*, 2005, **347**, 703; (e) Y. Bonvin, E. Callens, L. Larrosa, D. A. Henderson, J. Oldham, A. J. Burton and A. G. M. Barrett, *Org. Lett.*, 2005, **7**, 4549; (f) M. Nakanishi and C. Bolm, *Adv. Synth. Catal.*, 2007, **349**, 861; (g) C. S. Yi, K. H. Kwon and D. W. Lee, *Org. Lett.*, 2009, **11**, 1567; (h) J. Zhang, Z. Wang, Y. Wang, C. Wan, X. Zheng and Z. Wang, *Green Chem.*,



- 2009, **11**, 1973; (i) H. Li, Z. Li and Z. Shi, *Tetrahedron*, 2009, **65**, 1856; (j) R. A. Kumar, C. U. Maheswari, S. Ghantasala, C. Jyothi and K. R. Reddy, *Adv. Synth. Catal.*, 2011, **353**, 401; (k) K. Moriyama, M. Takemura and H. Togo, *Org. Lett.*, 2012, **14**, 2414; (l) Y. J. Xie, Y. Z. Yang, L. H. Huang, X. B. Zhang and Y. H. Zhang, *Org. Lett.*, 2012, **14**, 1238; (m) A. V. Biradar and T. Asefa, *Appl. Catal., A*, 2012, **19**; (n) H. Peng, A. Lin, Y. Zhang, H. Jiang, J. Zhou, Y. Cheng, C. Zhu and H. Hu, *ACS Catal.*, 2012, **2**, 163; (o) X. F. Wu, *Tetrahedron Lett.*, 2012, **53**, 6123; (p) L. Meng, J. Su, Z. Zha, L. Zhang, Z. Zhang and Z. Wang, *Chem.–Eur. J.*, 2013, **19**, 5542; (q) C. He, X. H. Zhang, R. F. Huang, J. Pan, J. Q. Li, X. G. Ling, Y. Xiong and X. M. Zhu, *Tetrahedron Lett.*, 2014, **55**, 4458; (r) D. Shen, C. Miao, S. Wang, C. Xia and W. Sun, *Org. Lett.*, 2014, **16**, 1108; (s) W. J. Ang and Y. L. Lam, *Org. Biomol. Chem.*, 2015, **13**, 1048, and reference therein.
- 10 (a) G. Pandey, S. Pal and R. Laha, *Angew. Chem., Int. Ed.*, 2013, **52**, 5146; (b) H. Yi, C. Bian, X. Hu, L. Niu and A. Lei, *Chem. Commun.*, 2015, **51**, 14046.
- 11 Z. Zhang, Y. Gao, Y. Liu, J. Li, H. Xie, H. Li and W. Wang, *Org. Lett.*, 2015, **17**, 5492.
- 12 (a) D. P. Hruszkewycz, K. C. Miles, O. R. Thiel and S. S. Stahl, *Chem. Sci.*, 2017, **8**, 1282. For selected reviews on oxidation reaction mediated by NHPI, see: (b) F. Recupero and C. Punta, *Chem. Rev.*, 2007, **107**, 3800; (c) L. Melone and C. Punta, *Beilstein J. Org. Chem.*, 2013, **9**, 1296.
- 13 H.-Q. Wang, Z. Wang, H.-C. Huang, J.-J. Tan and K. Xu, *Org. Lett.*, 2016, **18**, 5680.
- 14 For selected examples on the oxidation of alkylarenes to Ketones by TBHP, see: (a) H. He, B.-J. Pei and A. W. M. Lee, *Green Chem.*, 2009, **11**, 1857; (b) J. T. Zhang, Z. T. Wang, Y. Wang, C. F. Wan, X. Q. Zheng and Z. Y. Wang, *Green Chem.*, 2009, **11**, 1973, and reference therein.
- 15 For examples on oxidation reactions of benzylic C<sub>sp<sup>3</sup></sub>-H bond to ketones under metal-free conditions, see: K. X. Chen, P. F. Zhang, Y. Wang and H. R. Li, *Green Chem.*, 2014, **16**, 2344, and references cited therein.
- 16 J. Y. Koo, C. H. Heo, Y.-H. Shin, D. Kim, C. S. Lim, B. R. Cho, H. M. Kim and S. B. Park, *Chem.–Eur. J.*, 2016, **22**, 14166.
- 17 (a) J. Muzart, *Tetrahedron Lett.*, 1986, **27**, 3139; (b) J. Muzart, *Synth. Commun.*, 1989, **19**, 2061; (c) A. A. Tarlani, A. Riahi, M. Abedini, M. Mohammadpour Amini and J. Muzart, *Appl. Catal., A*, 2006, **315**, 150; (d) J. A. S. Coelho, A. F. Trindade, R. Wanke, B. G. M. Rocha, L. F. Veiros, P. M. P. Gois, A. J. L. Pombeiro and C. A. M. Afonso, *Eur. J. Org. Chem.*, 2013, 1471.

