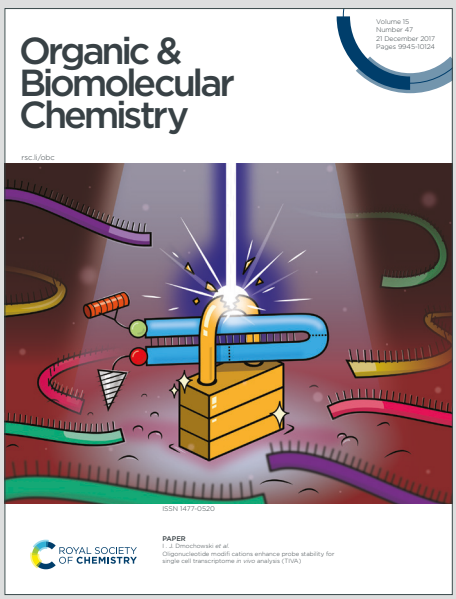
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: H. Liu, F. Han, H. Li, J. Liu and Q. Xu, *Org. Biomol. Chem.*, 2020, DOI: 10.1039/D0OB01549K.



ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/D0OB01549K

Journal Name

COMMUNICATION

Selective Construction of Alkaloid Scaffolds by Alcohol-Based Direct and Mild Aerobic Oxidative Pictet–Spengler Reactions†

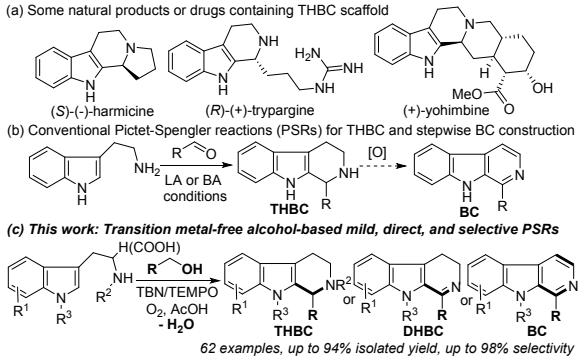
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Haicheng Liu,[a] Feng Han,[a] Huan Li,[a] Jianping Liu,[a]* and Qing Xu[a,b]*

Employing TBN/TEMPO as the catalysts and oxygen the oxidant, the biologically and pharmaceutically significant tetrahydro-*β*-carboline and *β*-carboline alkaloid scaffolds that used to be obtained by multi-step processes, can now be selectively obtained in only one-step *via* direct aerobic oxidative Pictet–Spengler reactions of tryptamines with alcohols under mild conditions, with water generated as the byproduct. In this reaction, TBN/TEMPO was interestingly found able to facilitate the cylization step of the whole reaction. This method tolerates a variety of C- and N-substituted tryptamines, and both the more reactive benzylic and allylic alcohols and the less reactive aliphatic alcohols. This method can also be extended to dihydro-*β*-carboline synthesis and applied to the more available and more economic tryptophan for *β*-carboline synthesis, revealing its broad substrate scopes and potential in synthetic applications.

Alkaloid scaffolds are abundant in numerous natural products and biologically active compounds. For exhibiting various remarkable and interesting biological and pharmacological activities, a plethora of alkaloids have been extracted from plants, which clearly cannot meet the tremendous demands in modern society. Therefore, their synthesis has also attracted extensive attention among the synthetic and bio-organic chemists.[1] Tetrahydro-*β*-carboline (THBC) derivatives, one of the alkaloid scaffolds, are also frequently used as drugs or drug candidates for having various significant biological and pharmaceutical activities (Scheme 1a).[1-10] Among the methods reported, THBCs were largely obtained by the famous Pictet–Spengler reaction (PSR) of tryptamines and aldehydes[1] using Brønsted acids,[2,3] Lewis acids,[4] iodine,[5] heterogeneous,[6] or enzyme catalysts,[7] or under microwave-irradiated[8] and even catalyst-free[9] conditions (Scheme 1b). In recent years, asymmetric PSRs have also been well-developed to obtain enantio-enriched THBCs for further synthesis of natural products or drugs.[1,3,7,10] However, using aldehydes is a disadvantage as they are more odor, more toxic, not stable, and not easy to store and handle. Thus, using the greener alcohols[11] as the substrate to replace the aldehydes for one-step construction of THBCs may be a useful and practical project in the field.



Scheme 1. Tetrahydro-*β*-carboline derivatives and their synthetic methods.

We have previously focused on alcohol-based dehydrative alkylation[12] and imination reactions,[13] as well as construction of heterocycle compounds.[14] Herein we report the first transition metal-free alcohol-based aerobic oxidative Pictet–Spengler reaction (PSR),[15] which can provide direct methods for selective construction of THBC, dihydro-*β*-carboline (DHBC) and *β*-carboline (BC) skeletons under mild conditions (Scheme 1c). This protocol can also be extended to the more available and more economic tryptophan for BC construction.

Referring to our previous findings,[12-14] we initially investigated the reaction of tryptamine (**1a**) and benzyl alcohol (**2a**) under air using alkali hydroxides as the catalyst (Table 1). However, no target PSR products were observed under a variety of conditions, with observation of the imine intermediate only (entry 1). Realizing that base catalysis may not be a good choice, other catalysts frequently used in alcohol oxidation (such as DDQ, HCl, HBr, HNO_3, $NaNO_2$, TBN, TEMPO, Cu salts/ligands, Pd salts/ligands, NMI, etc.) were then investigated.[13,16] This extensive catalyst screening showed that the transition metal-free combination of *tert*-butyl nitrite (TBN) and 2,2,6,6-tetramethylpiperidyl-1-oxy (TEMPO) was more effective, which led to a higher conversion of **1a** with

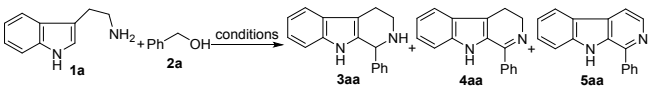
[a] College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang 325035, China. E-mail: qing-xu@wzu.edu.cn, 518liujianping@163.com; Fax: (+)-86-577-86689302; Tel: (+)-86-138-57745327.
[b] School of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou, Jiangsu 225002, China.

† Electronic Supplementary Information (ESI) available: Experimental details, condition screening tables, mechanistic studies, and characterization and copies of the ^{1}H and ^{13}C NMR spectra of the products. See DOI:10.1039/x0xx00000x

View Article Online
DOI: 10.1039/D0OB01549K

observation of PSR products **3aa**/**4aa**/**5aa** if acetic acid was used as the solvent (entry 2). Further condition screening showed that reduced temperature (entry 3) and higher catalyst loadings could enhance the selectivity for **3aa** (entries 4-5). Employing pure oxygen as the oxidant also led to a higher selectivity (88%) and a higher yield of **3aa** (entry 6). As observed, TBN, TEMPO, and acetic acid are all crucial for this reaction (entries 7-9).

Table 1. Condition Screening for aerobic oxidative PSR of tryptamine with benzyl alcohol.[a]

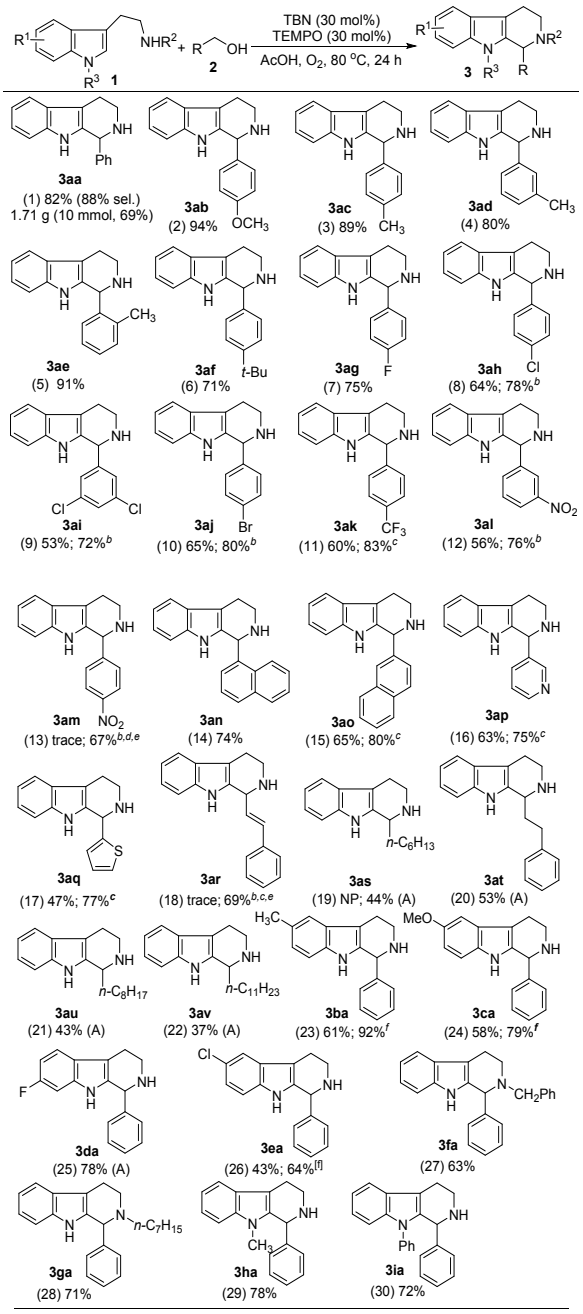


entry	cat. (mol%)	sol., atm., T	con.% (**3**/**4**/**5**)[b]	**3aa**%[c]
1	MOH (50)[d]	DCE, air, 100 °C	-	NP
2	TBN (10) TEMPO (10)	AcOH, air, 100 °C	94 (26/61/14)	24
3	TBN (10) TEMPO (10)	AcOH, air, 80 °C	65 (69/23/5)	45
4	TBN (20), TEMPO (20)	AcOH, air, 80 °C	85 (52/38/8)	44 (30)
5	TBN (30) TEMPO (30)	AcOH, air, 80 °C	92 (62/29/9)	57 (51)
6	***TBN (30) TEMPO (30)***	***AcOH, O_2, 80 °C***	***>99 (88/9/3)***	***88 (82)***
7	TBN (30)	AcOH, air, 80 °C	-	-
8	TEMPO (30)	AcOH, air, 80 °C	30 (47/53/0)	14
9	TBN (30) TEMPO (30)	AcOH,[e] O_2, 80 °C	98 (8/55/36)	trace

[a] Unless otherwise noted, the mixtures of **1a** (0.5 mmol), **2a** (1.2 equiv.), catalyst, and solvent (0.5 mL) in a 100 mL Schlenk tube was heated and then monitored by TLC/GCMS. [b]Conversion of **1a** and **3**/**4**/**5** ratios are based on GCMS analysis. [c]GC yields (isolated yields in parenthesis) based on **1a**. [d]MOH: LiOH, NaOH, KOH, CsOH. [e]With only 1.5 equiv. AcOH.

Various substituted alcohols and tryptamines were then investigated to extend the scope of the method (Table 2). Like the model reaction (Table 2, entry 1), electron-rich benzylic alcohols, including the sterically more bulky *ortho*-substituted ones, all afforded good to high yields of the THBCs (entry 2-6). The reactions of electron-deficient alcohols were less efficient (entries 7-13), but the yields could be improved by adding more catalysts or the alcohols (entries 8-12). For *p*-nitrobenzyl alcohol (entry 13), a satisfactory yield of the product could be obtained by using excess **1a** and more catalysts at a milder temperature of 40 °C. Similar to benzylic alcohols, the more bulky 1- and 2-napththylmethanols and heteroarylmethols (3-pyridylmethanol and 2-thienylmethanol) also afforded the target products in moderated to good yields (entries 14-17). The products' yields could also be enhanced using more alcohols (entries 15-17). Possibly due to the high activity and low stability of the generated cinnamyl aldehyde, only trace product was observed in the reaction of cinnamyl alcohol (entry 18). Thus, by adding more catalysts and the cinnamyl alcohol, a satisfactory yield of the product could be obtained at a lower temperature of 40 °C.

Table 2. Scopes of substrates for construction of THBC scaffold.[a]



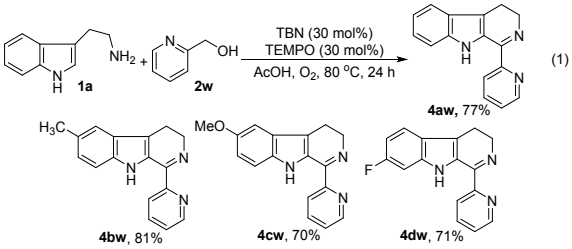
[a] See entry 6 of Table 1 for detailed conditions. For alternative conditions (A) for aliphatic alcohols, solvent AcOH was replaced by 1.5 equiv. TFA and 0.5 mL of the corresponding alcohol (100 °C). [b]TEMPO (0.5 equiv.), TBN (0.5 equiv.). [c]2.0 equiv. of **2**. [d]0.5 mmol **2**, 2.0 equiv. of **1**. [e]40 °C. [f]TEMPO (0.15 equiv.), TBN (0.15 equiv.), 60 °C.

Aliphatic alcohols were then investigated, but no product was initially observed, which may be due to their low reactivities in aerobic oxidation reactions. Condition modification revealed that heating **1a** at 100 °C using **2s** as the solvent and 1.5 equiv. trifluoroacetic acid the additive could

successfully afford the target product **3as** (Table 2, entry 19). These conditions were then applied to 2-phenylethanol, longer- and shorter-chained aliphatic alcohols, all affording the target products successfully (entry 20-22).

For Ar-substituted tryptamines with electron-donating or –withdrawing groups, all gave slightly lower yields of the products than the model reaction (Table 2, entries 23-26). Then, it was found that reducing both the catalyst loadings and the temperature could enhance the yields of the products. This may be due to the activation of tryptamine by the substituents. For N-substituted tryptamines, it seemed N-substitution at either the indole or the amino moiety does not affect the reaction at all. Thus, good yields of the products were easily obtained with either N-benzyl, -alkyl, or -phenyl substituents (entries 27-30). Moreover, a 10 mmol scale reaction of **1a** and **2a** was performed to test the synthetic practicality of the present method. The reaction afforded 1.71 gram of **3aa** (69% isolated yield, entry 1), revealing that the method is indeed synthetically practical.

Besides, unlike 3-pyridylmethanol (**1p**) that gave THBC **3ap** as the product (Table 2, entry 16), the reaction of 2-pyridylmethanol (**2w**) selectively afforded dihydro-*β*-carbolines (DHBC) **4aw** in 77% isolated yield under the same conditions (eq. 1). Thus, a series of DHBC **4bw**-**4dw** could be obtained in good yields starting from **2w**.

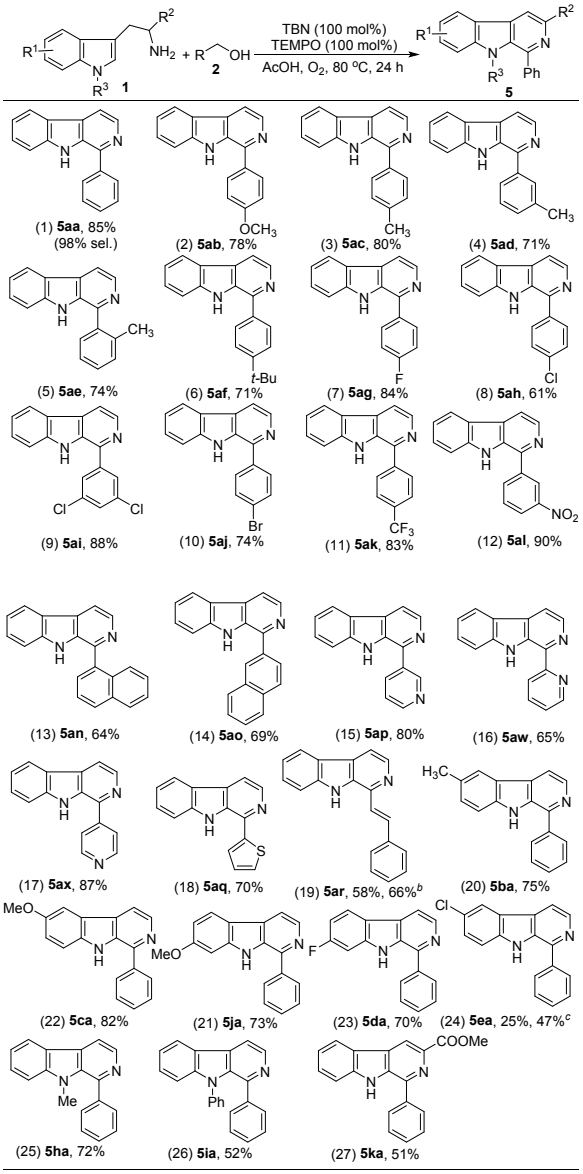


(1)

We then turned our attention to *β*-carbolines (BCs), another class of biologically and pharmacologically active alkaloids[17] that were mostly obtained by dehydrogenation[18] or oxidation[19] of THBCs. To date, examples for direct preparation of BCs from aldehydes and tryptamines, even via one-pot stepwise dehydrogenation[20] or oxidation[21] methods, were still very limited. Therefore, direct construction of BCs from alcohols may be a challenging task, but it may also be a meaningful and practical advance in the field if a one-pot straight method can be successfully developed.

In initial screening of the reaction conditions (Table 1), the observed selectivities for **5aa** suggested that BC construction may be promising but modification is still necessary.[22] Hence, at higher temperatures, the reaction of **1a** and **2a** got tarred and gave only moderate yields of **5aa** (130 °C, 53-69%). Additives were also found not helpful to the reaction. Then, by keeping the reaction at 80 °C to avoid getting tarred, the yield of **5aa** could be improved by adding more catalysts. Thus, with 100 mol% catalysts being the best condition, the reaction afforded **5aa** in 98% selectivity and 85% isolated yield (Table 3, entry 1). Like **2a**, both electron-rich and -deficient benzylic alcohols including the more bulky *ortho*-substituted ones (entries 5, 13) all gave good to high yields of the BC products (entries 2-14). Similarly, heteroarylmethanols (2-, 3-, and 4-pyridylmethols and 2-thienylmethanol) also afforded good to high yields of the products (entries 15-18). Under the present conditions, cinnamyl alcohol also afforded a satisfactory yield of the target **5ar** (entry 19), which could be enhanced at a lower temperature. In addition, most substituted tryptamines afforded moderate to good yields of the target products (entries 20-26). Moreover, tryptophan methyl ester that was not suitable for THBC construction under prior conditions also afforded the target BC **5ka** in a moderate yield (entry 27).

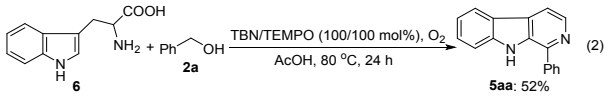
Table 3. Scopes of substrates for construction of BC scaffold.[a]



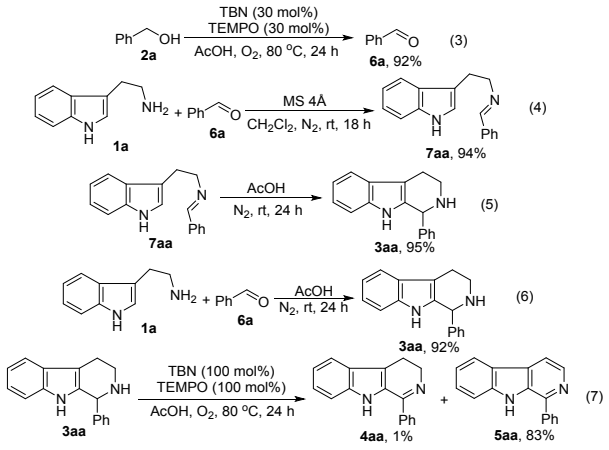
[a] The mixtures of **1a** (0.5 mmol), **2a** (1.2 equiv.), TBN (100 mol%), and TEMPO (100 mol%) in AcOH (0.5 mL) in a 100 mL Schlenk tube was sealed under O_2 and heated at 80 °C fro 24 h. [b]2.0 equiv. of **2**, 40 °C, 24 h. [c]TEMPO (50 mol%), TBN (50 mol%).

Based on above results, this alcohol-based PSR method was also applied to tryptophan as it's more stable, more

available, and more economic, and the potential decarboxylation is also a green process. To our knowledge, not to mention the reaction of tryptophan with alcohols, even the one-pot decarboxylative PSR of tryptophan with aldehydes was not known yet; whereas, only stepwise methods have been described in the literature so far.[23] Therefore, as shown in eq. 2, although the reaction of tryptophan (**6**) and **2a** may require further condition optimization, preliminary investigation showed that a moderate yield of **5aa** could be obtained under similar conditions. This result revealed the potential application of this alcohol-based PSR to tryptophan-type substrates.

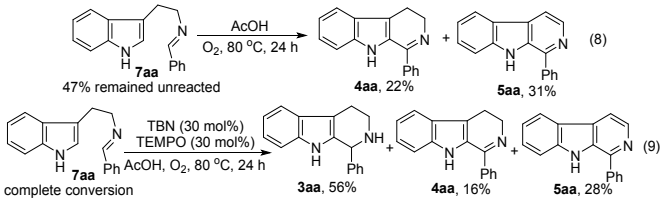


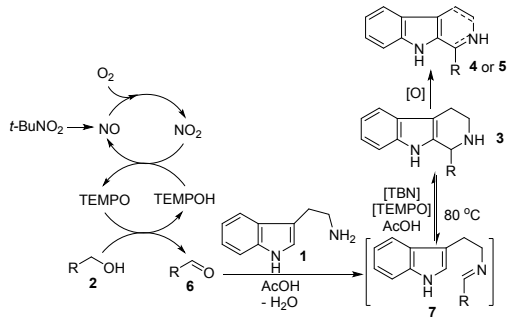
As to the mechanism of the present PSRs, firstly, it was observed that a high yield of PhCHO (**6a**) could be generated from $PhCH_2OH$ (**2a**) under the standard conditions (eq. 3).[22] Besides, no reaction occurred without TEMPO (Table 1, entry 7) and using TEMPO alone led to only low yields of the product (Table 1, entry 8). Therefore, TEMPO may work as the direct oxidant to oxidize the alcohols to the aldehyde intermediates, and TBN (the NO source) may serve as the catalyst for TEMPOH re-oxidation to TEMPO via generation of NO and NO_2 in the presence of O_2. The above findings are consistent with those observed in NO equivalents/TEMPO-catalyzed aerobic alcohol oxidation reactions.[16]



Moreover, the reaction of tryptamine (**1a**) and benzaldehyde (**6a**) in a neutral solvent CH_2Cl_2 could lead to isolation of imine intermediate **7aa** in a high yield (eq. 4),[22,24] which could further cyclize to give a high yield of **3aa** in the standard solvent AcOH at room temperature (eq. 5), without detecting other possible products **4aa** and **5aa**.[22] Similarly, the reaction of **1a** and **6a** in AcOH at room temperature could directly lead to **3aa** in a high yield without detecting **4aa** and **5aa**, either (eq. 6).[22] Then, aerobic oxidation of **3aa** under the standard conditions for BC construction (see Table 3) afforded 1% yield of **4aa** and 83% yield of **5aa** as detected by GC (eq. 7),[22] revealing that DHBCs and BCs are indeed the oxidation products of the THBCs as documented in the literature.[18,19]

On the other hand, although exposing **7aa** (or the mixture of **1a** and **6a**) to O_2 in AcOH could lead to a good yield of **3aa** along with lower yields of **4aa** and **5aa** at room temperature (eqs. 5-6), no **3aa** was observed when the same reaction was performed at 80 °C, with detection of considerable amounts of unreacted **7aa** along with **4aa** and **5aa** (eq. 8).[22] These results not only confirmed again that **4aa** and **5aa** should be the aerobic oxidation products of **3aa**, but may also support that the conversion of **7aa** to **3aa** is an equilibrium.[1-9] That is, in the absence of any facilitating reagents, **3aa** may convert back into **7aa** at elevated temperatures. Interestingly, addition of standard loadings of TBN and TEMPO to the above reaction could lead to complete conversion of **7aa**, a good yield of **3aa**, along with low yields of **4aa** and **5aa** (eq. 9).[22] This means that TBN/TEMPO or their derivatives may work as the facilitating reagent to promote the cyclization of **7** to **3**, thus providing high selectivities and high yields of THBC **3** and BC **5**, respectively, under the corresponding optimized conditions (vide supra). However, although we also tried more control reactions and as rather complicated results were obtained, it is still unclear at present how TBN/TEMPO facilitated these alcohol-based PS reactions.





Scheme 2. Proposed reaction paths for the alcohol-based PSRs: [TBN] and [TEMPO] means their derivatives or active facilitating reagents generated from TBN and TEMPO.

Based on above findings and the literature knowledge,[1-9,16] as shown in Scheme 2, TEMPO may work to directly oxidize the alcohols (**2**) to aldehydes (**6**) with itself being transformed into TEMPOH. Meanwhile, TBN (the NO source) may firstly generate NO, which is oxidized by O_2 to give NO_2. NO_2 then oxidizes TEMPOH to regenerate TEMPO. On the other hand, tryptamines (**1**) may condense with **6** to firstly give imine intermediates **7**, which quickly cyclizes to THBC **3** in AcOH. As can be implied by the control reactions (eq. 8),[22] this step may be an equilibrium, so that the absence of a facilitating reagent may convert **3** back into **7** at higher temperatures; while facilitated by the presence of TBN/TEMPO or their derivatives, **7** can readily convert into **3**. Upon formation of **3**, under the

corresponding optimized controlled conditions, this alcohol-based PSRs can selectively afford THBC **3** as well as DHBC **4** or BC **5** via further aerobic oxidation by O_2.

Conclusions

In conclusion, the biologically and pharmaceutically significant tetrahydro-*β*-carboline and *β*-carboline scaffolds can now be selectively obtained by a mild and direct aerobic oxidative Pictet–Spengler reaction of tryptamines with alcohols in only one step using TBN/TEMPO as the catalyst, oxygen the oxidant, and acetic acid a green solvent. This new method is more advantageous than the known methods for tetrahydro-*β*-carboline and *β*-carboline construction from aldehdyes, not only because the greener alcohols, transition metal-free catalyst, and waste-free oxidant O_2 can be used, but because the synthetic and purification processes can be greatly shortened and simplified, i.e., overall efficiency for construction of *β*-carboline scaffolds is greatly enhanced. Moreover, this method has a relatively broad scope of substrates, and can be extended to dihydro-*β*-carboline synthesis and applied to the more available and more economic tryptophan. Interestingly, TBN and TEMPO are not only the oxidation catalyst for the reaction, they are also found to be capable of facilitating the cyclization of imine intermediates into the THBC products though the reason was still remained to be clarified. Further extension and applications of the TBN/TEMPO-catalyzed aerobic oxidative cyclocondensation method in construction of other heterocycle compounds are still in progress in this group.

Acknowledgements

We thank National Natural Science Foundation of China (21672163) and Natural Science Foundation of Zhejiang Province for Distinguished Young Scholars (LR14B020002) for financial support.

Notes and references

1 (*a*) E. D. Cox and J. M. Cook, *Chem. Rev*., 1995, **95**, 1797-1842; (*b*) J. Stöckigt, A. P. Antonchick, F. Wu and H. Waldmann, *Angew. Chem. Int. Ed*., 2011, **50**, 8538-8564; (*c*) M. Chrzanowska, A. Grajewska and M. D. Rozwadowska, *Chem. Rev*., 2016, **116**, 12369-12465; (*d*) R. Dalpozzo, *Molecules* 2016, **21**, 699-716; (*e*) N. Glinsky-Olivier and X. Guinchard, *Synthesis,* 2017, **49**, 2605-2620; (*f*) R. N. Rao, B. Maiti and K. Chanda, *ACS Comb. Sci.,* 2017, **19**, 199-228; (*g*) M. M. Heravi, V. Zadsirjan and M. Malmir, *Molecules,* 2018, **23**, 943-990.

2 (*a*) K. Narayanan, L. Schindler and J. M. Cook, *J. Org. Chem*., 1991, **56**, 359-365; (*b*) A. Saito, J. Numaguchi and Y. Hanzawa, *Tetrahedron Lett*., 2007, **48**, 835-839; (*c*) F. Hadjaz, S. Yous, N. Lebegue, P. Berthelot and P. Carato, *Tetrahedron,* 2008, **64**, 10004-10008; (*d*) M. Barbero, S. Bazzi, S. Cadamuro and S. Dughera, *Tetrahedron Lett*., 2010, **51**, 6356-6359; (*e*) A. E. Wendlandt and S. S. Stahl, *J. Am. Chem. Soc*., 2014, **136**, 506-512; (*f*) V. Gobe', V. Gandon and X. Guincharda, *Adv. Synth. Catal*., 2018, **360**, 1280-1288.

3 (*a*) M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc*., 2004, **126**, 10558-10559; (*b*) J. Seayad, A. M. Seayad and B. List, *J. Am. Chem. Soc*., 2006, **128**, 1086-1087; (*c*) M. J. Wanner, R. N. S. vander Haas, K. R. de Cuba, J. H. van Maarseveen and H. Hiemstra, *Angew. Chem. Int. Ed*., 2007, **46**, 7485-7487; (*d*) R. S. Klausen and E. N. Jacobsen, *Org. Lett*., 2009, **11**, 887-890; (*e*) D. Huang, F. Xu, X. Lin and Y. Wang, *Chem. Eur. J*., 2012, **18**, 3148-3152.

4 (*a*) H. A. Dondas, J. Duraisingham, R. Grigg, W. S. MacLachlan, D. T. MacPherson, M. Thornton-Pett, V. Sridharan and S. Suganthan, *Tetrahedron,* 2000, 56, 4063-4070; (*b*) N. Srinivasan and A. Ganesan, *Chem. Commun*., 2003, 916-917; (*c*) A. S. Karpov, T. Oeser and T. J. J. Mueller, *Chem. Commun*., 2004, 1502-1503; (*d*) S. V. Ryabukhin, D. M. Panov, A. S. Plaskon, A. A. Tolmachev and R. V. Smaliy, *Monatsh Chem*., 2012, **143**, 1507-1517.

5 Y. Lingam, D. M. Rao, D. R. Bhowmik, P. S. Santu, K. R. Raoa and A. Islam, *Tetrahedron Lett.,* 2007, **48**, 7243-7245.

6 (*a*) Y. F. Wang, Z. B. Song, C. X. Chen and J. S. Peng, *Sci. China Chem.,* 2010, **53**, 562-568; (*b*) M. Izumi, T. Kido, M. Murakami, S. Nakajima and A. Ganesan, *Biosci. Biotechnol. Biochem*., 2011, **75**, 391–392.

7 (*a*) P. Bernhardt, A. R. Usera and S. E. O'Connor, *Tetrahedron Lett.,* 2010, **51**, 4400-4402; (*b*) D. Pressnitz, E.-M. Fischereder, J. Pletz, C. Kofler, L. Hammerer, K. Hiebler, H. Lechner, N. Richter, E. Eger and W. Kroutil, *Angew. Chem. Int. Ed*., 2018, **57**, 10683-10687.

8 (*a*) F.–M. Kuo, M.–C. Tseng, Y.–H. Yen and Y.–H. Chu, *Tetrahedron,* 2004, **60**, 12075-12084; (*b*) S. Eagon and M. O. Anderson, *Eur. J. Org. Chem*., 2014, **2014**, 1653-1665.

9 (*a*) L.–N. Wang, S.–L. Shen and J. Qu, *RSC Adv*., 2014, **4**, 30733-30741; (*b*) S. Handy and M. Wright, *Tetrahedron Lett*., 2014, **55**, 3440-3442; (*c*) S. Hati and S. Sen, *Tetrahedron Lett*., 2016, **57**, 1040-1043.

10 (*a*) Z. Sui, J. Guan, M. J. Macielag, W. Jiang, Y. Qiu, P. Kraft, S. Bhattacharjee, T. MatthewJohn, E. Craig, D. Haynes-Johnson and J. Clancy, *Bioorg. Med. Chem. Lett.,* 2003, **13**, 761-765; (*b*) J. Zheng, Z. Zhang, L. Zhao, X. Sha, X. Dong and R. Wen, *Phar. Biology*, 2008, **46**, 273-278; (*c*) F. Liu, L.–Q. Yu, C. Jiang, L. Y, W.–T. Wu and Q.–D. You, *Bioorg. Med. Chem*., 2010, **18**, 4167-4177; (*d*) H. Song, Y. Liu, Y. Liu, L. Wang and Q. Wang, *J. Agric. Food Chem*., 2014, **62**, 1010-1018; (*e*) N. Sudžukovic`, J. Schinnerl and L. Brecker, *Bioorg. Med. Chem*., 2016, **24**, 588-595; (*f*) A. Spindler, K. Stefan and M. Wiese, *J. Med. Chem*., 2016, **59**, 6121−6135.

11 (*a*) J. A. Watson and J. M. J. Williams, *Science,* 2010, **329**, 635-636; (*b*) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.,* 2010, **110**, 681-703; (*c*) G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.,* 2010, **110**, 1611-1641; (*d*) S.-Y. Zhang, F.-M. Zhang and Y.-Q. Tu, *Chem. Soc. Rev.,* 2011, **40**, 1937-1949; (*e*) E. Emer, R. Sinisi, M. G. Capdevila, D. Petruzziello, F. De Vincentiis and P. G. Cozzi, *Eur. J. Org. Chem.,* 2011, 647; (*f*) J. Muzart, *Tetrahedron,* 2005, **61**, 4179-4212; (*g*) X. Ma, C. Su and Q. Xu, *N-Alkylation by hydrogen autotransfer reactions,* in: *Hydrogen transfer reactions: reductions and beyond* (Eds.: G. Guillena, D. J. Ramón), *Topics in Current Chemistry*, Vol. 374, Springer, Berlin, Heidelberg, 2016, pp 1–74; (*h*) Q. Xu and Q. Li, *Chin. J. Org. Chem.,* 2013, **33**, 18-35; (*i*) H. Liu, J. Liu, X. Cheng, X. Jia, L. Yu and Q. Xu, *ChemSusChem*, 2019, **12**, 2994-2998.

12 (a) Q. Xu, J. Chen, H. Tian, X. Yuan, S. Li, C. Zhou and J. Liu, *Angew. Chem. Int. Ed.,* 2014, *53*, 225-229; (*b*) Q. Xu, Q. Li, X. Zhu and J. Chen, *Adv. Synth. Catal.,* 2013, **355**, 73-80; (*c*) Q. Xu, J. Chen and Q. Liu. *Adv. Synth. Catal*., 2013, **355**, 697-704; (*d*) Q. Xu, H. Xie, P. Chen, L. Yu, J. Chen and X. Hu, *Green Chem.,* 2015, **17**, 2774-2779; (*e*) Q. Xu, H. Xie, E.-L. Zhang, X. Ma, J. Chen, X.-C. Yu and H. Li, *Green Chem.,* 2016, **18**, 3940-3944; (*f*) X. Ma, L. Yu, C. Su, Y. Yang, H. Li and Q. Xu, *Adv. Synth. Catal.,* 2017, **359**, 1649-1655; (*g*) J. Chen, Y. Li, S. Li, J. Liu, F. Zheng, Z. Zhang and Q. Xu, *Green Chem.,* 2017, **19**,

623-628; (*h*) Y. Yang, Z. Ye, X. Zhang, Y. Zhou, X. Ma, H. Cao, J. Bao, H. Li, L. Yu and Q. Xu, *Org. Biomol. Chem*., 2017, **15**, 9638-9642; (*i*) X. Ma, Q. Xu, H. Li, C. Su, L. Yu, X. Zhang, H. Cao and L.–B. Han, *Green Chem*., 2018, **20**, 3408-3413; (*j*) X. Ma, J. Yu, R. Yan, M. Yan and Q. Xu, *J. Org. Chem.,* 2019, **84**, 11294-11300.

13 (a) L. Jiang, L. Jin, H. Tian, X. Yuan, X. Yu and Q. Xu, *Chem. Commun.,* 2011, **47**, 10833-10835; (*b*) H. Tian, X. Yu, Q. Li, J. Wang and Q. Xu, *Adv. Synth. Catal,.* 2012, **354**, 2671-2677; (*c*) B. Huang, H. Tian, S. Lin, M. Xie, X. Yu and Q. Xu. *Tetrahedron Lett.,* 2013, **54***,* 2861-2864; (*d*) E. Zhang, H. Tian, S. Xu, X. Yu and Q. Xu, *Org. Lett.,* 2013, **15***,* 2704-2707.

14 (a) Q. Wang, M. Lv, J. Liu, Y. Li, H. Cao, X. Zhang and Q. Xu, *ChemSusChem,* 2019, 12*,* 3043-3048; (*b*) S. Yao, K. Zhou, J. Wang, H. Cao, L. Yu, J. Wu, P. Qiu and Q. Xu, *Green Chem*., 2017, **19**, 2945-2951; (*c*) X. Shi, J. Guo, J. Liu, M. Ye and Q. Xu, *Chem. Eur. J.,* 2015, **21**, 9988-9993; (*d*) J. Liu, C. Wang, X. Ma, X. Shi, X. Wang, H. Li and Q. Xu, *Catal. Lett.,* 2016, **146**, 2139-2148; (*e*) Q. Li, Y. Huang, T. Chen, Y. Zhou, Q. Xu, S.-F. Yin and L.-B. Han, *Org. Lett.,* 2014, **16**, 3672-3675; (*f*) Q. Xu, X. Huang and J. Yuan, *J. Org. Chem*., 2005, **70**, 6948-6951.

15 During the submission processes of this work, Tang and co-wokers dscribed a Ni-catalyzed alcohol-based anaerobic dehydrogentative Pictet–Spengler reaction: P. Yang, C. Zhang, W.-C. Gao, Y. Ma, X. Wang, L. Zhang, J. Yue and B. Tang, *Chem. Commun.,* 2019, **55**, 7844-7847.

16 (*a*) R. Liu, X. Liang, C. Dong and X. Hu, *J. Am. Chem. Soc.,* 2004, **126**, 4112-4113; (*b*) X. Wang, R. Liu, Y. Jin and X. Liang, *Chem. Eur. J.,* 2008, **14**, 2679-2685; (*c*) X. He, Z. Shen, W. Mo, N. Sun, B. Hu and X. Hu, *Adv. Synth. Catal.,* 2009, **351**, 89-92; (*d*) Y. B. Kuang, H. Rokubuichi, Y. Nabae, T. Hayakawa and M. Kakimoto, *Adv. Synth. Catal.,* 2010, **352**, 2635-2642; (*e*) B. Karimi and E. Badreh, *Org. Biomol. Chem.,* 2011, **9**, 4194-4198; (*f*) M. Shibuya, Y. Osada, Y. Sasano, M. Tomizawa and Y. Iwabuchi, *J. Am. Chem. Soc.,* 2011, **133**, 6497-6500; *g*) A. Rahimi, A. Azarpira, H. Kim, J. Ralph and S. S. Stahl, *J. Am. Chem. Soc.,* 2013, **135**, 6415-6418.

17 (*a*) J. Reniers, S. Robert, R. Frederick, B. Masereel, S. Vincent and J. Wouters, *Bioorg. Med. Chem*., 2011, **19**, 134-144; (*b*) T. Takeuchi, S. Oishi, T. Watanabe, H. Ohno, J.–I. Sawada, K. Matsuno, A. Asai, N. Asada, K. Kitaura and N. Fujii, *J. Med. Chem*., 2011, **54**, 4839-4846; (*c*) L. He, S.–Y. Liao, C.–P. Tan, R.–R. Ye, Y.–W. Xu, M. Zhao, L.–N. Ji and Z.–W. Mao, *Chem. Eur. J*., 2013, **19**, 12152-12160; (*d*) H. Du, H. Gu, N. Li and J. Wang, *Med. Chem. Commun.,* 2016, **7**, 636-645; (*e*) J. Chen, F. Pengc, Y. Zhang, B. Li, J. She, X. Jie, Z. Zou, M. Chen and L. Chen, *Eur. J. Med. Chem*., 2017, **140**, 104-117.

18 (a) J. Wu, D. Talwar, S. Johnston, M. Yan, and J. Xiao, *Angew. Chem. Int. Ed*., 2013, **52**, 6983-6987; (*b*) S. Eagon and M. O. Anderson, *Eur. J. Org. Chem*., 2014, **2014**, 1653-1665; (*c*) K. C. Nicolaou, Z. Lu, R. Li, J. R. Woods and T.–I. Sohn, *J. Am. Chem. Soc.,* 2015, **137**, 8716-8719; (*d*) Q. Wang, H. Chai and Z. Yu, *Organometallics,* 2018, **37**, 584-591.

19 (*a*) J. D. Panarese and S. P. Waters, *Org. Lett.,* 2010, **12**, 4086-4089; b) B. Xin, W. Tang, Y. Wang, G. Lin, H. Liu, Y. Jiao, Y. Zhu, H. Yuan, Y. Chen and T. Lu, *Bioorg. Med. Chem. Lett*., 2012, **22**, 4783-4786; (*c*) L. P. P. Liewa, J. M. Fleming, A. Longeon, E. Mouray, I. Florent, M.-L. Bourguet-Kondracki and B. R. Copp, *Tetrahedron,* 2014, **70**, 4910-4920; (*d*) A. Kamal, Y. Tangella, K. L. Manasa, M. Sathish, V. Srinivasulu, J. Chetnac and A. Alarifi, *Org. Biomol. Chem*., 2015, **13**, 8652-8662; (*e*) S. Hati and S. Sen, *Tetrahedron Lett*., 2016, **57**, 1040-1043; (*f*) Y.-Q. Huang, H.-J. Song, Y.-X. Liu and Q.-M. Wang, *Chem. Eur. J.,* 2018, **24**, 2065-2069; (*g*) L. Guo, W. Chen, R. Cao, W. Fan, Q. Ma, J. Zhang and B. Dai, *Eur. J. Med. Chem*., 2018, **147**, 253-265.

20 (*a*) A. Kulkarni, M. Abid, B. Török and X. Huang, *Tetrahedron Lett*., 2009, **50**, 1791-1794; (*b*) W. Horton, A. Sood, S. Peerannawar, N. Kugyela, A. Kulkarni, R. Tulsan, C. D. Tran, J. Soule, H. LeVine III, B. Török and M. Török, *Bioorg. Med. Chem. Lett.,* 2017, **27**, 232-236.

21 B. Drung, C. Scholz, V. A. Barbosa, A. Nazari, M. H. Sarragiotto and B. Schmidt, *Bioorg. Med. Chem. Lett*., 2014, **24**, 4854-4860.

22 See the †ESI for details.

23 (*a*) A. Kamal, M. Sathish, A. V. G. Prasanthi, J. Chetna, Y. Tangella, V. Srinivasulu, N. Shankaraiah and A. Alarifi, *RSC Adv*., 2015, **5**, 90121-90126; (*b*) A. Kamal, Y. Tangella, K. L. Manasa, M. Sathish, V. Srinivasulu, J. Chetna and A. Alarifi, *Org. Biomol. Chem.,* 2015, **13**, 8652-8662; (*c*) R. Meesala, A. S. M. Arshad, M. N. Mordi and S. M. Mansor, *Tetrahedron,* 2016, **72**, 8537-8541.

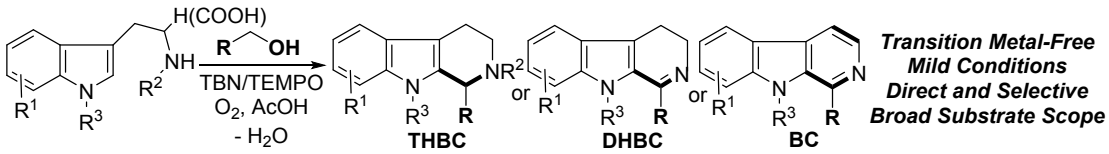
24 S. W. Youn, *J. Org. Chem*., 2006, **71**, 2521-2523.

Table of Contents

View Article Online
DOI: 10.1039/D0OB01549K

Selective Construction of Alkaloid Scaffolds by Alcohol-Based Direct and Mild Aerobic Oxidative Pictet–Spengler Reactions

Haicheng Liu, F. Han, Huan Li, Jianping Liu* and Qing Xu*



62 examples, up to 94% isolated yield, up to 98% selectivity

Biologically and pharmaceutically significant tetrahydro-*β*-carboline, dihydro-*β*-carboline, and *β*-carboline alkaloid scaffolds can be selectively obtained by direct aerobic oxidative Pictet–Spengler reactions of tryptamines with alcohols in one step using TBN/TEMPO as the catalyst and oxygen the oxidant under mild conditions. This method has a relatively broad scope of substrates and may have potentially practical applications in synthesis.