ACS Catalysis

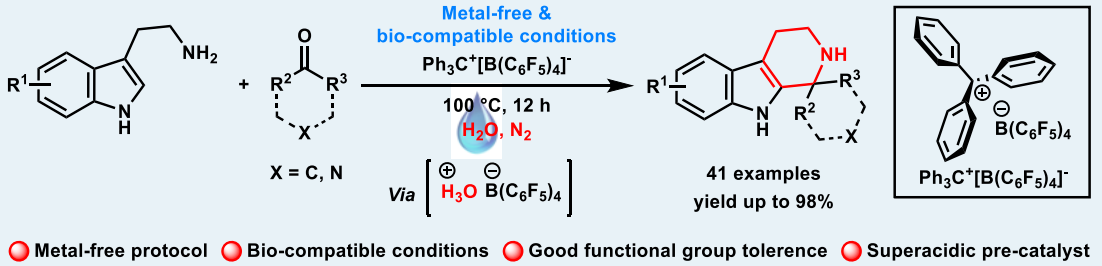
pubs.acs.org/acscatalysis Letter

Metal-Free Access to (*Spirocyclic*)Tetrahydro-*β*-carbolines in Water Using an Ion-Pair as a Superacidic Precatalyst

Zhenguo Zhang, Xiaoxiao Liu, Liang Ji, Ting Zhang, Zhenhua Jia,* and Teck-Peng Loh*

Cite This: https://doi.org/10.1021/acscatal.1c05546 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: The unprecedented triarylcarbonium ion-pair-catalyzed Pictet−Spengler reaction of tryptamines with aromatic aldehydes and cyclic ketones in water was disclosed. Under metal-free conditions, diverse tetrahydro-*β*-carbolines and *spirocyclic* tetrahydro-*β*-carbolines were obtained in good yields with excellent functional group tolerance, including late-stage modification of natural products and small molecular drugs. The practicability of this protocol is also characterized in the gram-scale synthesis of Komavine and several other functional compounds. Preliminary mechanistic studies indicated that in aqueous media the *in situ*-generated superacidic species from the carbonium ion pair with water was crucial to promote the Pictet−Spengler reaction.

KEYWORDS: *metal-free, (spirocyclic)tetrahydro-β-carboline, biocompatible, ion-pair, superacidic species*

Tetrahydro-*β*-carbolines moieties exist in a wide variety of drugs and natural products and exhibit a wide spectrum of biological activities, such as *anti*-tumor, *anti*-Alzheimer, *anti*-HIV, and so on.[1] Examples include the marketed drug Tadalafil, pharmaceutical agent AZD-9496 in clinical research and a series of compounds reported with potential antitumor activity, as well as the natural product Komavine (Figure 1).[2]

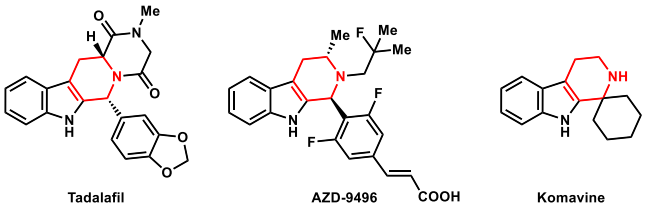


Figure 1. Presentative drugs and natural products containing tetrahydro-*β*-carbolines moieties.

Traditionally, this skeleton of tetrahydro-*β*-carboline is achieved through the Pictet−Spengler reaction mediated by stoichiometric amounts of acids.[3] Alternatively, the Li group reported a "Two-in-One" strategy of Pd-catalyzed C−H functionalization of tryptamines for the synthesis of (*spirocyclic*) tetrahydro-*β*-carbolines in water (Figure 2a).[4] However, the utilization of acids inevitably produced chemical waste, and processes involving transition metals potentially

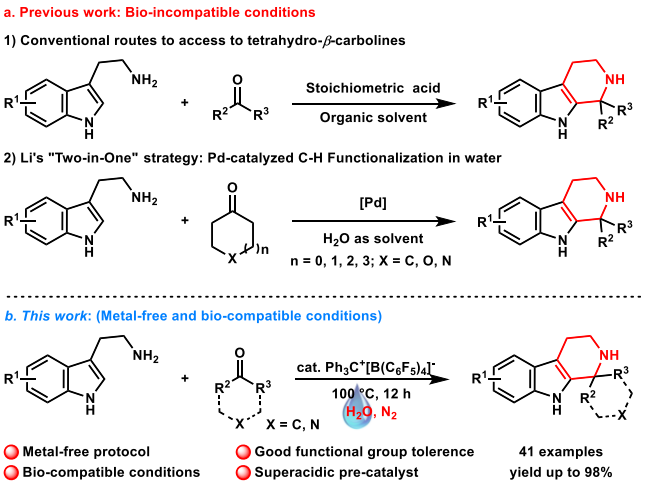


Figure 2. (A) Previous strategies to access the skeleton. (B) This work: Ion-pair-catalyzed protocol.

Received: December 2, 2021
Revised: January 18, 2022

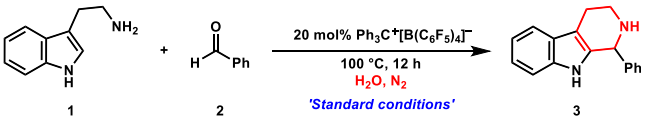
introduced toxic residues into the target compounds, which need to be avoided in the sustainable process.

Since the discovery of trityl cation ($Ar_3C^+X^-$) by Norris, Kehrman, and Wentzel in 1901, the applications of triarylcarbenium ion pairs as catalysts in organic synthesis have attracted tremendous attention.[5] This is probably due to their many attractive features such as high catalytic reactivities, metal-free nature as well as the possibilities of introducing chiral moieties to either the cationic or the anionic component for asymmetric catalysis. Accordingly, there has been much work directed toward the design of new organic ion pair species for various transformations including the design of chiral versions for asymmetric catalysis. Pioneering work using a triarylcarbonium ion to catalyze the aldol reactions was first reported by Mukaiyama.[6] The asymmetric version first studied by Chen and co-workers further spurred research in the direction of designing chiral ion catalysts.[7] Luo and Lv et al. presented that carbonium ion pair could catalyze Friedel–Crafts reaction, Diels–Alder reaction and 1,2-hydydride Migration process.[8] Stokes, Yao, and Hashmi respectively reported the intramolecular hydroarylation, intermolecular hydroarylation, and [2 + 2+1] cycloaddition with trityl tetrakis(pentafluorophenyl)-borate.[9] Oestreich and Johan Franzén et al. disclosed the novel carbenium-pair catalyzed cycloaddition.[10] Hou et al. utilized trityl tetrakis-(pentafluorophenyl)-borate as the cocatalyst with transition metals in the fields of polymerization, asymmetric catalysis, and so on.[11] Our group has been interested in the development of green and sustainable organic synthesis methodologies.[12] In this paper, we explore the use of the carbonium ion-pair as a water-tolerant precatalyst, probably producing the superacidic species, to promote the Pictet-Spengler reaction under biocompatible conditions.

We started our investigation with tryptamine **1** and benzaldehyde **2** as model substrates, and the influence of all reaction parameters were systematically evaluated (see Supporting Information for details). After intensive investigations, we found that the desired tetrahydro-β-carboline product **3** can be isolated in 86% yield when trityl tetrakis(pentafluorophenyl)-borate (ion-pair-2) was used as the catalyst and water as solvent at 100 °C under N_2 atmosphere was applied (Table 1, entry 1). A control experiment indicated that ion-pair-2 was essential for the success of this transformation (Table 1, entry 2). In the testing of various ion-pairs, trityl tetrakis(pentafluorophenyl)-borate was also found to be superior to the other tested ion pairs (Table 1, entries 3–9), which indicated that the matching pair of an anion and a cation may be necessary for the catalytic process. With the lower catalytic loading of trityl tetrakis-(pentafluorophenyl)-borate, the efficiency of the reaction was decreased down to 81% yield (Table 1, entry 10). Using an organic solvent instead of water, such as in dioxane, only a 10% yield of the target product was obtained, which showed that water was a significant biocompatible reaction medium (Table 1, entry 11). Notably, a 65% yield of **3** was afforded in air (Table 1, entry 12). When the temperature was adjusted to 90 °C, **3** was obtained in 67% yield (Table 1, entry 13). The remaining parameters were also screened and summarized in Supporting Information (Table S1–S4).

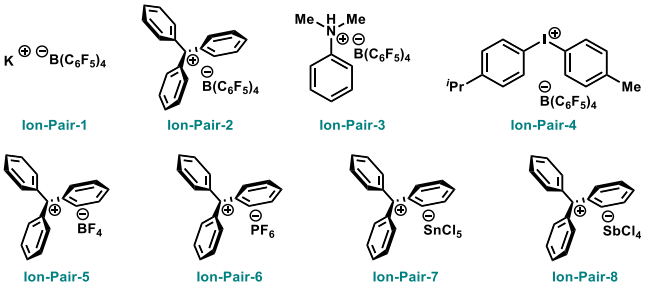
With optimal conditions in hand, we subsequently explored the scope of ion-pair-catalyzed Pictet–Spengler reaction in water. As illustrated in Scheme 1, a broad range of aromatic aldehydes were accommodated with tryptamine **1** to form the

Table 1. Investigation of the Reaction Conditions[§,a]



1 2 3

entry	change from the "standard conditions"	yield of **3**
1	none	88 (86[b])
2	without ion-pair-2	n.d.
3	ion-pair-1 instead of ion-pair-2	58
4	ion-pair-3 instead of ion-pair-2	62
5	ion-pair-4 instead of ion-pair-2	61
6	ion-pair-5 instead of ion-pair-2	trace
7	ion-pair-6 instead of ion-pair-2	trace
8	ion-pair-7 instead of ion-pair-2	trace
9	ion-pair-8 instead of ion-pair-2	trace
10	15 mol % catalytic loading	81
11	dioxane instead of water	10
12	in air	65
13	90 °C instead of 100 °C	67

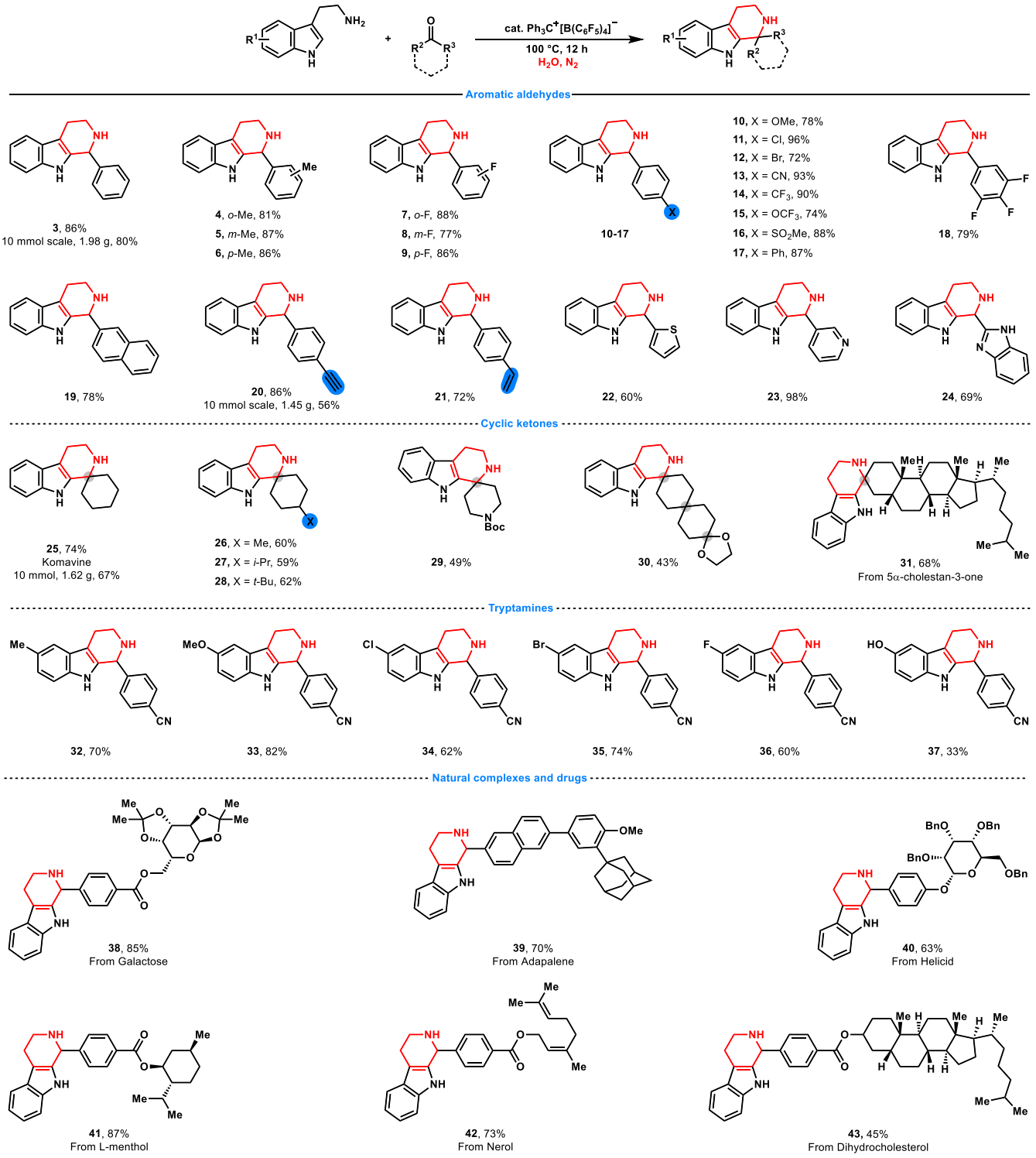


[§]Standard conditions were carried out on a scale of 0.2 mmol of **1** and 0.3 mmol of **2** in the presence of 0.04 mmol $Ph_3C^+[(C_6F_5)_4]^-$ in 1 mL H_2O under N_2 atmosphere at 100 °C for 12 h. [a]Yield is based on **1** and was determined by ^1H NMR analysis by using CH_3NO_2 as an internal standard. [b]Isolated yield.

corresponding products in good to excellent yields (**3**–**24**). In addition, the aldehydes bearing alkene, alkyne, halogen atoms, and cyano groups were well tolerated. These functional groups would provide avenues for further transformations of products. The heterocyclic aromatic aldehydes were suitable substrates, introducing thiophene, pyridine, and benzoimidazole moieties into tetrahydro-β-carbolines (**22**–**24**). It is noteworthy that cyclohexanone was also competent component to prepare the natural product Komavine in 74% yield under metal-free conditions in water, which was characterized with a spiro ring and was generally synthesized involving transition metals (**25**). Various para-substituted cyclohexanones were endured to deliver the site-specific corresponding products (**26**–**28**). Gratifyingly, Boc-protected piperidinone performed well in this newly developed procedure, without any cleavage of the Boc group (**29**). The consecutive spiro rings were successfully constructed in 43% yield, while a potentially sensitive protecting group was also compatible with this dehydration process (**30**). Considering that the cyclohexanone motifs are ubiquitous in natural complexes, the derivatization of cholestanone with tryptamine at the late-stage demonstrated the potential application in pharmaceutical field (**31**). Subsequently, we investigated the scope of tryptamines bearing diverse substitutes at specific positions with 4-cyano benzaldehyde under identified conditions (**32**–**37**). When electron-donating groups substituted at the 5 position of the phenyl ring, the Pictet–Spengler reaction in water could

https://doi.org/10.1021/acscatal.1c05546
ACS Catal. XXXX, XXX, XXX–XXX

Scheme 1. Reaction Scope of Tetrahydro-β-Carboline[a]



[a]General reaction conditions: tryptamine substrate (0.2 mmol), carbonyl substrate (0.2 mmol), $Ph_3C^+[B(C_6F_5)_4]^-$ (0.04 mmol), H_2O (1 mL), 100 °C, N_2, 12 h. All yields are isolated yields.

proceed smoothly to give the corresponding products (**32**, **33**). The halogen groups, such as chloride (**34**), bromide (**35**) and fluoride (**36**) were tolerated, which would preinstalled with handles for further manipulation of products. The serotonin with unprotected hydroxyl group afforded the desired product, albeit in low yield due to unidentified side reactions (**37**). Furthermore, to evaluate the prospective utilization of this protocol, the modification of natural complexes and small molecular drugs were examined with tryptamine, affording the corresponding derivatives in good to excellent yields (**38**−**43**). To showcase the industrial potential of this metal-free protocol, the synthesis of **3**, **20** bearing a versatile alkynyl functional group and natural product Komavine **25** was

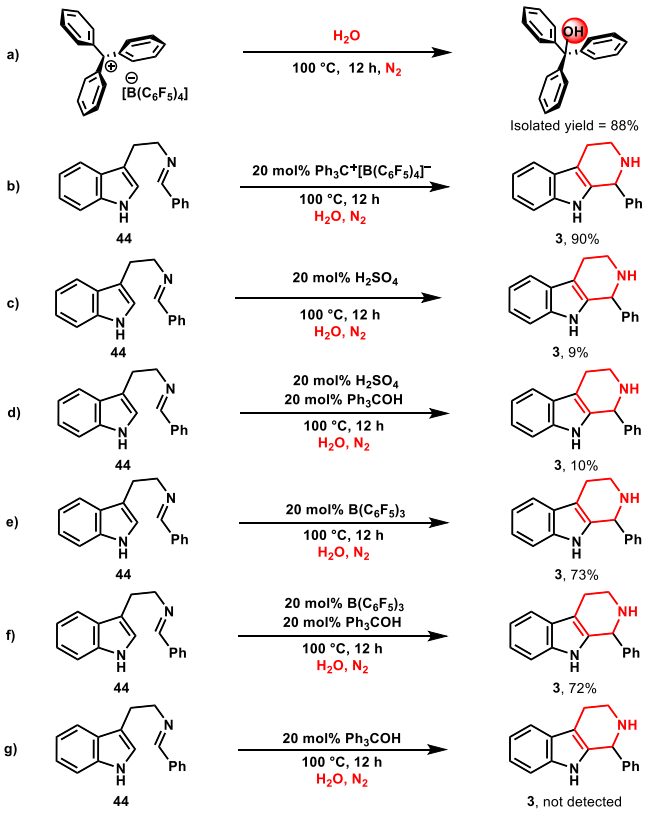
https://doi.org/10.1021/acscatal.1c05546
ACS Catal. XXXX, XXX, XXX−XXX

selected to scale up at the gram level without obvious drop of yields.

To gain insight into the mechanism of the metal-free Pictet–Spengler in water, we carried out preliminary mechanistic studies (Scheme 2 and Figure 3). Despite the results shown in Table 1, the anion was shown to be crucial to the desired transformation. When the stoichiometric trityl tetrakis(pentafluorophenyl)-borate was immersed in water under 100 °C, the triphenylmethanol was isolated in 88% yield after 12 h (Scheme 2a). Meanwhile, the target product **3** was obtained in 90% yield under standard conditions with the imine **44** as the starting material (Scheme 2b). Compared with conventional inorganic acids as the catalyst, such as sulfuric acid (H_2SO_4), only a 9% yield of **3** was generated from **44** (Scheme 2c, for details, see the Supporting Information). Even employing the combination of triphenylmethanol and H_2SO_4, **3** was formed in 10% yield (Scheme 2d). One possibility was that the boron Lewis acid $B(C_6F_5)_3$ dissociated from the anion of $Ph_3C^+[B(C_6F_5)_4]^-$ was treated as the catalytic species. Interestingly, using 20 mol % $B(C_6F_5)_3$ in water, **44** was converted into **3** in 73% yield (Scheme 2e). Additionally, **3** was still afforded in 72% yield using the combination of triphenylmethanol and $B(C_6F_5)_3$ (Scheme 2f). However, the desired product **3** was not detected when only triphenylmethanol was employed as the catalyst (Scheme 2g). To further elucidate the probable catalytic species, we conducted detailed NMR studies and found that the ^{11}B-NMR and ^{19}F-NMR spectra of the reaction crude sample using trityl tetrakis(pentafluorophenyl)-borate as the catalyst did not change before and after the reaction at 22 °C, whereas an obvious change was observed in both ^{11}B-NMR and ^{19}F-NMR spectra of the reaction crude sample using $B(C_6F_5)_3$ as the catalyst before and after the reaction at 22 °C (Figure 3 and Figure 4), indicating that $B(C_6F_5)_3$ was not likely the real species (for details, see the Supporting Information).[13] All the experimental evidence indicated the catalytic species was probably from the anion of trityl tetrakis(pentafluorophenyl)-borate and water.

On the basis of both precedent literatures and our preliminary investigations, we assumed that the superacidic species (H_3O^+ $[B(C_6F_5)_4]^-$) was probably involved, although this type of superacid could be unstable under ambient conditions or could not be isolated.[14] As shown in Scheme 3, the mechanism for the ion-pair-catalyzed Pictet–Spengler reaction in water was proposed. The hydrolysis of trityl tetrakis(pentafluorophenyl)-borate occurred in the presence of water to form the superacidic species, which could activate the carbonyl groups to generate the corresponding iminium ion (I) with tryptamines. Subsequently, the intermediate (II) was formed, which might tautomerize with the intermediate (III). Finally, the tetrahydro-β-carboline products were achieved via the deprotonation process.[15]

Scheme 2. Preliminary Mechanistic studies



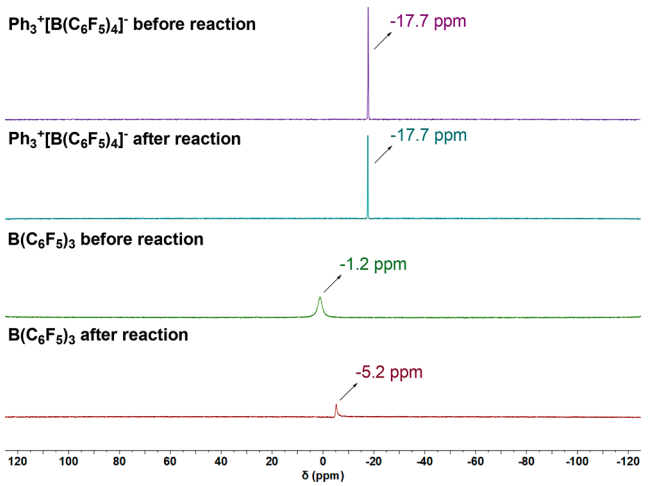


Figure 3. ^{11}B-NMR ($CDCl_3$) spectra of the reaction crude sample using $Ph_3C^+[B(C_6F_5)_4]^-$ and $B(C_6F_5)_3$ as the catalyst, respectively, before and after the reaction at 22 °C.

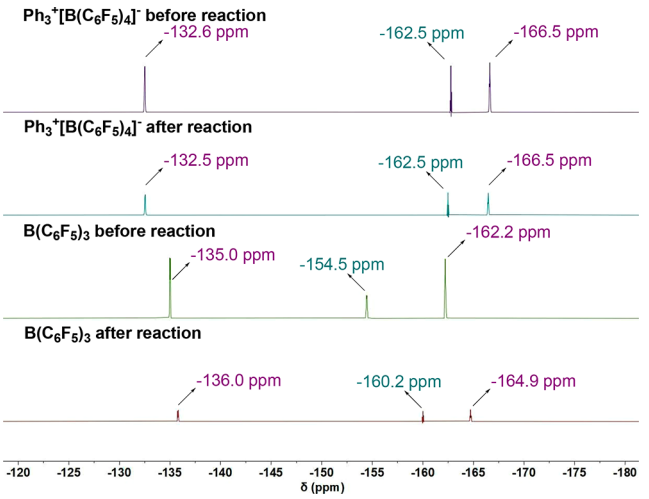
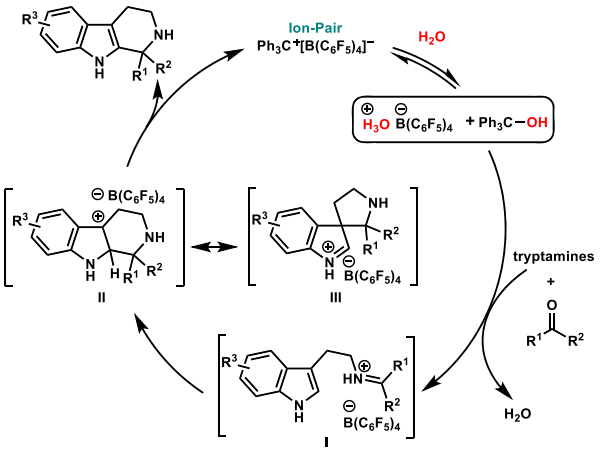


Figure 4. ^{19}F-NMR ($CDCl_3$) spectra of the reaction sample using $Ph_3C^+[B(C_6F_5)_4]^-$ and $B(C_6F_5)_3$ as the catalyst, respectively, before and after reaction at 22 °C.

https://doi.org/10.1021/acscatal.1c05546
ACS Catal. XXXX, XXX, XXX–XXX

Scheme 3. Proposed Mechanism



In summary, we have developed an efficient protocol using tetrakis(pentafluorophenyl)-borate to catalyze the Pictet−Spengler reaction under biocompatible conditions. The tetrahydro-β-carbolines have diverse functional groups, and their scope is broad, including modifying natural products and small molecular drugs by our metal-free strategy. Trityl tetrakis(pentafluorophenyl)borate was employed as the pre-catalyst of the superacidic species that catalyzed the desired transformation. Further application and the detailed mechanism study are underway in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c05546.

Materials and chemicals, full experiments and characterization data including ^1H and ^{13}C NMR spectra for the synthesized products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Zhenhua Jia − *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China;* orcid.org/0000-0002-5154-4839; Email: iaszhjia@njtech.edu.cn

Teck-Peng Loh − *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China; Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore;* orcid.org/0000-0002-2936-337X; Email: teckpeng@ntu.edu.sg

Authors

Zhenguo Zhang − *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China*

Xiaoxiao Liu − *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China*

Liang Ji − *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China;* orcid.org/0000-0001-8127-9215

Ting Zhang − *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.1c05546

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the financial support from the Start-up Grant of Nanjing Tech University (No. 38274017103, 38037037). T.P.L. thanks Nanyang Technological University Tier-1 grant support. We also acknowledge the Donors of the Science and Technology Innovation Research Fellowship in Nanjing for partial support of this research (No. 51237024) and the Postgraduate Research & Practice Innovation Program of Jiangsu Province (No. KYCX20_1031).

■ REFERENCES

(1) (a) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. The Pictet-Spengler Reaction in Nature and in Organic Chemistry. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538−8564. (b) Foley, C. A.; Al-Issa, Y. A.; Hiller, K. P.; Mulcahy, S. P. Synthesis and Structure-Activity Relationships of 1-Aryl-β-carbolines as Affinity Probes for the 5-Hydroxytryptamine Receptor. *ACS Omega* **2019**, *4*, 9807−9812. (c) Chen, J.; Peng, F.; Zhang, Y.; Li, B.; She, J.; Jie, X.; Zou, Z.; Chen, M.; Chen, L. Synthesis, characterization, cellular uptake and apoptosis-inducing properties of two highly cytotoxic cyclometalated ruthenium(II) β-carboline complexes. *Eur. J. Med. Chem.* **2017**, *140*, 104−117. (d) Aaghaz, S.; Sharma, K.; Jain, R.; Kamal, A. β-Carbolines as potential anticancer agents. *Eur. J. Med. Chem.* **2021**, *216*, 113321. (e) Son, J. H.; Phuan, P. W.; Zhu, J. S.; Lipman, E.; Cheung, A.; Tsui, K. Y.; Tantillo, D. J.; Verkman, A. S.; Haggie, P. M.; Kurth, M. J. 1-Benzylspiro[piperidine-4,1′-pyrido[3,4-b]*indole*] 'co-potentiators' for minimal function CFTR mutants. *Eur. J. Med. Chem.* **2021**, *209*, 112888.

(2) (a) Nge, C. E.; Gan, C. Y.; Low, Y. Y.; Thomas, N. F.; Kam, T. S. Voatinggine and Tabertinggine, Pentacyclic Indole Alkaloids Derived from an Iboga Precursor *via* a Common Cleavamine-Type Intermediate. *Org. Lett.* **2013**, *15*, 4774−4777. (b) Tulyaganov, T. S.; Nazarov, O. M.; Levkovich, M. G.; Abdullaev, N. D. Alkaloids of the Nitraria Genus. Komavine and Acetylkomavine. *Chem. Nat. Compd.* **2001**, *37*, 61−64.

(3) (a) Saha, B.; Sharma, S.; Sawant, D.; Kundu, B. Water as an efficient medium for the synthesis of tetrahydro-β-carbolines *via* Pictet-Spengler reactions. *Tetrahedron Lett.* **2007**, *48*, 1379−1383. (b) Li, S.; Yang, B.; Zhang, Q.; Zhang, J.; Wang, J.-R.; Wu, W. Synthesis and bioactivity of β-carboline derivatives. *Nat. Prod. Commun.* **2010**, *5*, 1591−1596. (c) Gholamzadeh, P. The Pictet-Spengler Reaction: A Powerful Strategy for the Synthesis of Heterocycles. *Adv. Heterocycl. Chem.* **2019**, *127*, 153−226. (d) Maity, P.; Adhikari, D.; Jana, A. K. An overview on synthetic entries to tetrahydro-β-carbolines. *Tetrahedron* **2019**, *75*, 965−1028.

(4) (a) Zeng, H.; Wang, Z.; Li, C.-J. Two-in-One Strategy for Palladium-Catalyzed C-H Functionalization in Water. *Angew. Chem., Int. Ed.* **2019**, *58*, 2859−2863. (b) Wang, Z.; Niu, J.; Zeng, H.; Li, C.-J. Construction of Spirocyclic Tetrahydro-β-carbolines *via* Cross-Annulation of Phenols with Tryptamines in Water. *Org. Lett.* **2019**, *21*, 7033−7037.

(5) (a) Norris, J. F. On the nonexistence of trivalent carbon. *Am. Chem. J.* **1901**, *25*, 117−122. (b) Kehrmann, F.; Wentzel, F. Die basischen eigenschaften des kohlenstoffs und die constitution des sogennanten tr phenylmeths. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3815−3819.

(6) (a) Mukaiyama, T.; Kobayashi, S.; Shoda, S.-i. A facile synthesis of α-glucosides and α-ribosides from the corresponding 1-O-acyl sugars and alcohols in the presence of trityl perchlorate. *Chem. Lett.* **1984**, *13*, 907−910. (b) Mukaiyama, T.; Kobayashi, S.; Shoda, S.-i. A facile synthesis of α-C-ribofuranosides from 1-O-acetylribose in the presence of trityl perchlorate. *Chem. Lett.* **1984**, *13*, 1529−1530. (c) Mukaiyama, T.; Kobayashi, S.; Murakami, M. Trityl perchlorate as an efficient catalyst in the aldol-type re-action. *Chem. Lett.* **1984**, *13*, 1759−1762. (d) Mukaiyama, T.; Kobayashi, S.; Murakami, M. An efficient method for the preparation of threo cross-aldols from silyl enol ethers and aldehydes using trityl perchlorate as a catalyst. *Chem. Lett.* **1985**, *14*, 447−450. (e) Kobayashi, S.; Murakami, M.; Mukaiyama, T. The trityl perchlorate catalyzed Michael reaction. *Chem. Lett.* **1985**, *14*, 953−956. (f) Mukaiyama, T.; Nagaoka, H.; Murakami, M.; Ohshima, M. A facile synthesis of homoallyl ethers. The reaction of acetals with allyltrimethylsilanes promoted by trityl perchlorate or diphenylboryl triflate. *Chem. Lett.* **1985**, *14*, 977−980. (g) Kobayashi, S.; Murakami, M.; Mukaiyama, T. Trityl salts as efficient catalysts in the aldol reaction. *Chem. Lett.* **1985**, *14*, 1535−1538. (h) Ohshima, M.; Murakami, M.; Mukaiyama, T. A convenient method for the preparation of γ-keto sulfides from thioacetals. *Chem. Lett.* **1985**, *14*, 1871−1874. (i) Kobayashi, S.; Matsui, S.; Mukaiyama, T. Trityl salt catalyzed aldol reaction between α,β-acetylenic ketones and silyl enol ethers. *Chem. Lett.* **1988**, *17*, 1491−1494. (j) Yanagisawa, M.; Mukaiyama, T. Catalytic and stereoselective glycosylation with glycosyl fluoride using active carbocationic species paired with tetrakis(pentafluorophenyl)borate or trifluoromethanesulfonate. *Chem. Lett.* **2001**, *30*, 224−225.

(7) Chen, C.-T.; Chao, S. D.; Yen, K.-C.; Chen, C.-H.; Chou, I.-C.; Hon, S.-W. Chiral Triarylcarbenium Ions in Asymmetric Mukaiyama Aldol Additions. *J. Am. Chem. Soc.* **1997**, *119*, 11341−11342.

(8) (a) Lv, J.; Zhang, Q.; Zhong, X.; Luo, S. Asymmetric Latent Carbocation Catalysis with Chiral Trityl Phosphate. *J. Am. Chem. Soc.* **2015**, *137*, 15576−15583. (b) Zhang, Q.; Lv, J.; Li, S.; Luo, S. Carbocation Lewis Acid Catalyzed Diels-Alder Reactions of Anthracene Derivatives. *Org. Lett.* **2018**, *20*, 2269−2272. (c) Shang, W.; Duan, D.; Liu, Y.; Lv, J. Carbocation Lewis Acid $TrBF_4$-Catalyzed 1,2-Hydride Migration: Approaches to (*Z*)-α,β-Unsaturated Esters and α-Branched β-Ketocarbonyls. *Org. Lett.* **2019**, *21*, 8013−8017.

(9) (a) Cai, X.; Keshavarz, A.; Omaque, J. D.; Stokes, B. J. Brønsted Acid-Catalyzed Intramolecular Hydroarylation of β-Benzylstyrenes. *Org. Lett.* **2017**, *19*, 2626−2629. (b) Zhu, W.; Sun, Q.; Wang, Y.; Yuan, D.; Yao, Y. Chemo- and Regioselective Hydroarylation of Alkenes with Aromatic Amines Catalyzed by $[Ph_3C][B(C_6F_5)_4]$. *Org. Lett.* **2018**, *20*, 3101−3104. (c) Jin, H.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. The Carbocation-Catalyzed Intermolecular Formal [2 + 2 + 1] Cycloaddition of Ynamides with Quinoxaline *N*-Oxides. *ACS Catal.* **2019**, *9*, 11663−11668.

(10) (a) He, T.; Wang, G.; Bonetti, V.; Klare, H. F. T.; Oestreich, M. Silylium-Ion-Promoted (5 + 1) Cycloaddition of Aryl-Substituted Vinylcyclopropanes and Hydrosilanes Involving Aryl Migration. *Angew. Chem., Int. Ed.* **2020**, *59*, 12186−12191. (b) Ni, S.; Franzén, J. Carbocation catalyzed ring closing aldehyde-olefin metathesis. *Chem. Commun.* **2018**, *54*, 12982−12985. (c) Bah, J.; Naidu, V. R.; Teske, J.; Franzén, J. Carbocations as Lewis Acid Catalysts: Reactivity and Scope. *Adv. Synth. Catal.* **2015**, *357*, 148−158.

(11) (a) Song, G.; Luo, G.; Oyamada, J.; Luo, Y.; Hou, Z. *ortho*-Selective C-H addition of *N,N*-dimethyl anilines to alkenes by a yttrium catalyst. *Chem. Sci.* **2016**, *7*, 5265−5270. (b) Shi, X.; Nishiura, M.; Hou, Z. Simultaneous Chain-Growth and Step-Growth Polymerization of Methoxystyrenes by Rare-Earth Catalysts. *Angew. Chem., Int. Ed.* **2016**, *55*, 14812−14817. (c) Nako, A. E.; Oyamada, J.; Nishiura, M.; Hou, Z. Scandium-catalyzed intermolecular hydroaminoalkylation of olefins with aliphatic tertiary amines. *Chem. Sci.* **2016**, *7*, 6429−6434. (d) Luo, Y.; Teng, H.; Nishiura, M.; Hou, Z. Asymmetric Yttrium-Catalyzed C(sp^3)-H Addition of 2-Methyl Azaarenes to Cyclopropenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 9207−9210. (e) Guo, F.; Jiao, N.; Jiang, L.; Li, Y.; Hou, Z. Scandium-Catalyzed Syndiospecific Polymerization of HalideSubstituted Styrenes and Their Copolymerization with Styrene. *Macromolecules* **2017**, *50*, 8398−8405. (f) Luo, Y.; Ma, Y.; Hou, Z. α-C-H Alkylation of Methyl Sulfides with Alkenes by a Scandium Catalyst. *J. Am. Chem. Soc.* **2018**, *140*, 114−117. (g) Wang, H.; Zhao, Y.; Nishiura, M.; Yang, Y.; Luo, G.; Luo, Y.; Hou, Z. Scandium-Catalyzed Regio- and Stereoselective Cyclopolymerization of Functionalized α,ω-Dienes and Copolymerization with Ethylene. *J. Am. Chem. Soc.* **2019**, *141*, 12624−12633. (h) Wang, H.; Wu, X.; Yang, Y.; Nishiura, M.; Hou, Z. Co-syndiospecific Alternating Copolymerization of Functionalized Propylenes and Styrene by Rare-Earth Catalysts. *Angew. Chem., Int. Ed.* **2020**, *59*, 7173−7177. (i) Guo, F.; Jiang, L.; Diao, K.; Hou, Z. Stereoselective copolymerization of 4-(*N,N*-diphenylamino)styrene and isoprene by a C_5H_5-ligated scandium catalyst: synthesis of amino-functionalized crystalline styrenic thermoplastic elastomers. *Polym. Chem.* **2020**, *11*, 1314−1320. (j) Nishii, K.; Zhou, G.; Saito, Y.; Yamamoto, A.; Nishiura, M.; Luo, Y.; Hou, Z. Synthesis of Thermoplastic Elastomers by Yttrium-Catalyzed Isospecific *Trans*-1,4-Polymerization of (*E*)-1,3-Pentadiene. *Bull. Chem. Soc. Jpn.* **2021**, *94*, 1285−1291. (k) Ma, Y.; Lou, S.; Hou, Z. Electron-deficient boron-based catalysts for C-H bond functionalization. *Chem. Soc. Rev.* **2021**, *50*, 1945−1967.

(12) (a) Shen, Z. L.; Ji, S. J.; Loh, T.-P. An Enviromentally friendly procedure for Mukaiyama aldol and Mukaiyama-Michael reactions using a catalytic amount of DBU under solvent- and metal-free conditions. *Tetrahedron Lett.* **2005**, *46*, 507−508. (b) Jiang, Y.; Park, C.-M.; Loh, T.-P. Transition-Metal-Free Synthesis of Substituted Pyridines *via* Ring Expansion of 2-Allyl-2H-azirines. *Org. Lett.* **2014**, *16*, 3432−3435. (c) Shen, Z.-L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. Organoindium Reagents: The Preparation and Application in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 271−401. (d) Zhao, K.; Shen, L.; Shen, Z.-L.; Loh, T.-P. Transition metal-catalyzed cross-coupling reactions using organoindium reagents. *Chem. Soc. Rev.* **2017**, *46*, 586−602.

(13) (a) Danopoulos, A. A.; Galsworthy, J. R.; Green, M. L. H.; Doerrer, L. H.; Cafferkey, S.; Hursthouse, M. B. Equilibria in the $B(C_6F_5)_3$-H_2O system: synthesis and crystal structures of $H_2O{\cdot}B(C_6F_5)_3$ and the anions $[HOB(C_6F_5)_3]^-$ and $[(F_5C_6)_3B(\mu\text{-}OH)B(C_6F_5)_3]^-$. *Chem. Commun.* **1998**, 2529−2560. (b) Beringhelli, T.; Maggioni, D.; D'Alfonso, G. ^1H and ^{19}F NMR Investigation of the Reaction of $B(C_6F_5)_3$ with Water in Toluene Solution. *Organometallics* **2001**, *20*, 4927−4938. (c) Hill, G. S.; Manojlovic-Muir, L.; Muir, K. W.; Puddephatt, R. J. Electrophilic Methylplatinum Complexes: First Structure of a Hydroxytris(pentafluorophenyl)-borate Complex. *Organometallics* **1997**, *16*, 525−530. (d) Fasano, V.; Radcliffe, J. E.; Ingleson, M. J. $B(C_6F_5)_3$-Catalyzed Reductive Amination using Hydrosilanes. *ACS Catal.* **2016**, *6*, 1793−1798.

(14) (a) Reed, C. A.; Fackler, N. L. P.; Kim, K.-C.; Stasko, D.; Evans, D. R.; Boyd, P. D. W.; Rickard, C. E. F. Isolation of Protonated Arenes (Wheland Intermediates) with BAr^F and Carborane Anions. A Novel Crystalline Superacid. *J. Am. Chem. Soc.* **1999**, *121*, 6314−6315. (b) Jutzi, P.; Müller, C.; Stammler, A.; Stammler, H.-G. Synthesis, Crystal Structure, and Application of the Oxonium Acid $[H(OEt_2)_2]^+[B(C_6F_5)_4]^-$. *Organometallics* **2000**, *19*, 1442−1444. (c) Krossing, I. In *Comprehensive Inorganic Chemistry II*, 2nd ed., Vol. *1*; Reedijk, J., Poeppelmeier, K. R., Eds.; Elsevier: Amsterdam, 2013; pp 681−705. (d) Wiesner, A.; Gries, T. W.; Steinhauer, S.; Beckers, H.; Riedel, S. Superacids Based on Pentafluoroorthotellurate Derivatives of Aluminum. *Angew. Chem., Int. Ed.* **2017**, *56*, 8263−8266. (e) Klare, H.; Oestreich, M. The Power of the Proton: From Superacidic Media to Superelectrophile Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 15490−15507.

(15) (a) Zheng, C.; Xia, Z.; You, S.-L. Unified Mechanistic Understandings of Pictet-Spengler Reactions. *Chem.* **2018**, *4*, 1952−1966. (b) Zheng, C.; You, S.-L. Exploring the Chemistry of Spiroindolenines by Mechanistically-Driven Reaction Development: Asymmetric Pictet-Spengler-type Reactions and Beyond. *Acc. Chem. Res.* **2020**, *53*, 974−987.

https://doi.org/10.1021/acscatal.1c05546
ACS Catal. XXXX, XXX, XXX−XXX