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COMMUNICATION

Halogen Bond-catalyzed Pictet-Spengler Reaction

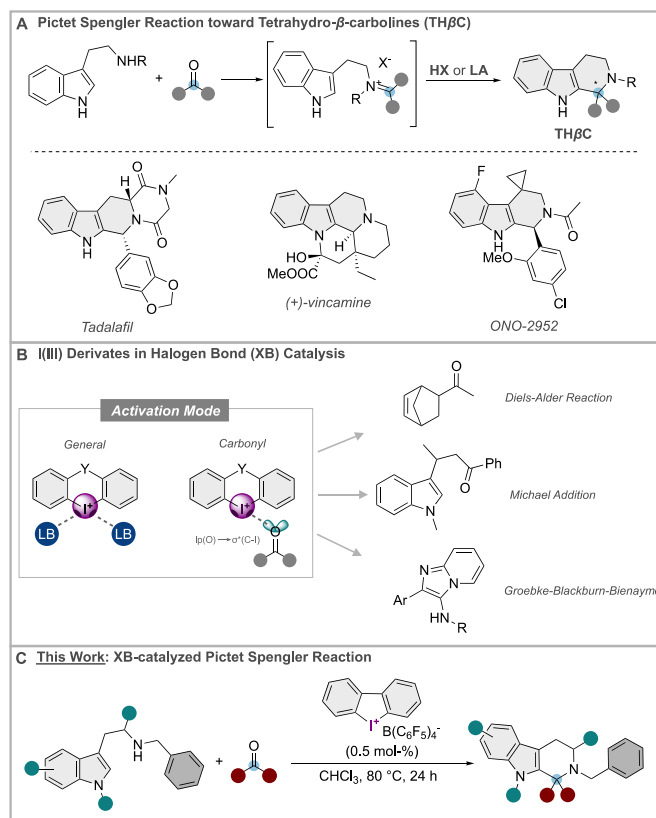
Received 00th January 20xx,
Accepted 00th January 20xxMattis Damrath^a, Alessandra Döring^a, Boris J. Nachtsheim^{*a}

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We report an efficient halogen bond-catalyzed Pictet-Spengler reaction using diaryliodonium salts as catalysts as a metal-free alternative to traditional acid catalysis. Through systematic optimization, exceptional catalytic activity was achieved with only 0.5 mol-% of a simple dibenziodolium with a perfluorinated borate counterion. The protocol demonstrates a broad substrate scope, converting various *N*-protected tryptamines and diverse carbonyl compounds (aromatic, heteroaromatic, and aliphatic aldehydes) to the corresponding tetrahydro- β -carbolines (TH β Cs) in up to 98% yield. The reaction versatility was further demonstrated by a successful oxa-variant using tryptophol. Control experiments revealed the crucial role of halogen bonding in ensuring an efficient reaction progress.

The tetrahydro- β -carboline (TH β C) skeleton represents a structural key element of thousands of naturally occurring and synthetically accessible indole alkaloids.¹ Due to their privileged potential as pharmacologically and biologically active motifs, such as Tadalafil (Scheme 1A) for male erectile dysfunction,² (+)-vincamine for the treatment of primary degenerative and vascular dementia,³ or as a novel and selective inhibitor of the translocator protein (ONO-2952),⁴ this structural framework has emerged as a key research target.⁵

Since the first synthetic approach of TH β Cs was introduced by Pictet and Spengler in 1911,⁶ various synthetic protocols have been well-documented utilizing Lewis- and Brønsted acids as well as organocatalysts and enzymes.⁷ In most cases, the reaction proceeds in a two-step manner: first, condensation of a carbonyl derivate with an amine followed by cyclization of the in situ formed iminium to the desired TH β Cs.



Scheme 1. A) Overview of the Pictet-Spengler reaction and pharmacologically active TH β Cs; B) (III) derivatives in halogen bond (XB) catalysis; C) This work: XB-catalyzed Pictet-Spengler reaction.

Besides its role in crystal engineering,⁸ molecular recognition⁹ and medicinal chemistry,¹⁰ halogen bonding¹¹ (XB) has recently been established as a novel mode of interaction in non-covalent organocatalysis (Scheme 1B).¹² Hypervalent iodine compounds,¹³ more precisely cyclic diaryliodonium salts,¹⁴ were employed as more powerful XB donors compared to their iodine(I) analogs, particularly for the activation of neutral Lewis

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† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (¹H-, ¹³C- and ¹⁹F-NMR-chemical shifts, IR-bands, melting points) including the corresponding NMR-spectra for unknown compounds can be found in the supporting information. For ESI see DOI: 10.1039/x0xx00000x



bases.¹⁵ These strong Lewis acids were already described to efficiently activate carbonyl derivatives, for example, in the Diels-Alder,¹⁶ Michael¹⁷ or Groebke-Blackburn-Bienaymé reaction.¹⁸

Herein, we report a successful deployment of diaryliodonium salt catalysts for the activation of carbonyls in an XB-catalyzed Pictet Spengler reaction using *N*-protected tryptamines as the amine source to form TH β Cs (Scheme 1C).

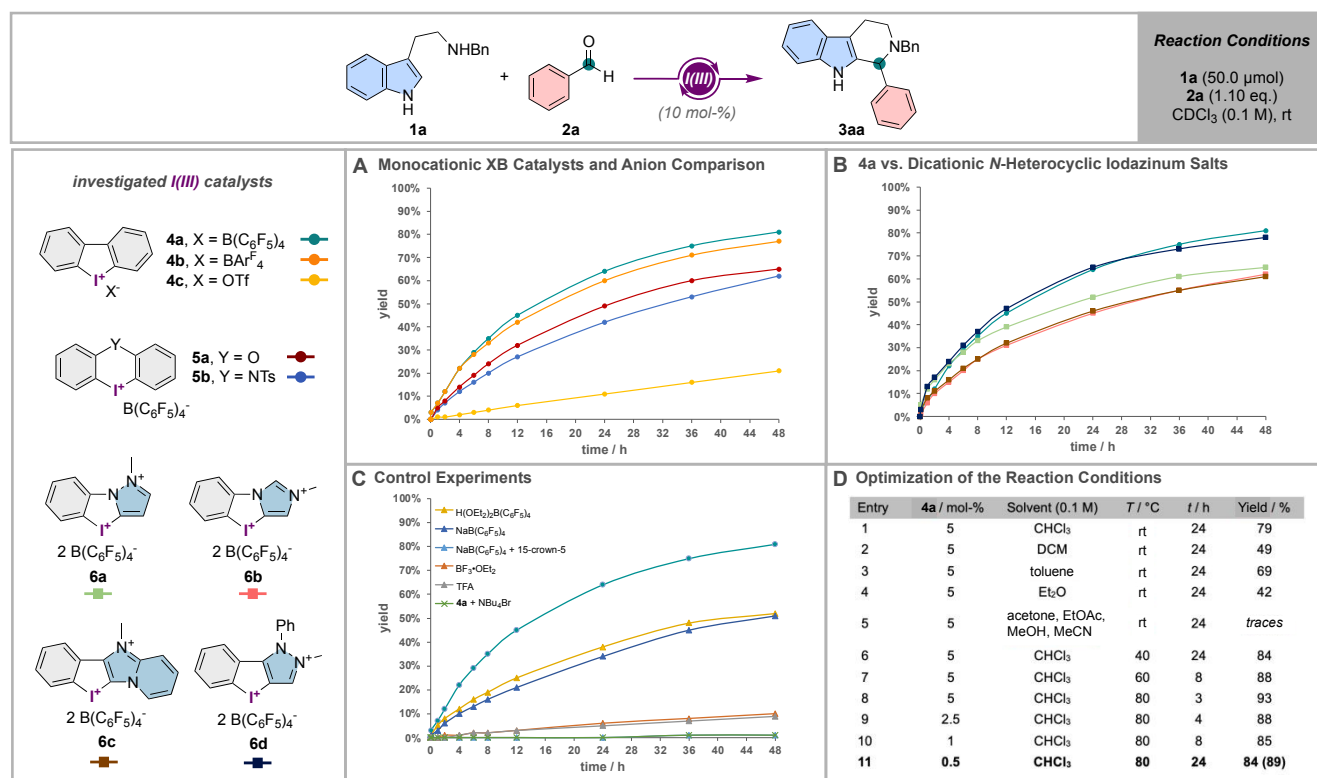
We started our investigations by examining the Pictet Spengler reaction of *N*-benzyl-protected tryptamine **1a** (Scheme 2A) and benzaldehyde (**2a**) to potentially yield TH β C **3aa**. Using CDCl₃ as the solvent, we initially followed the reaction progress in an NMR tube via ¹H-NMR spectroscopy for various monocationic iodonium salts **4a-c** and their heteroatom-bridged six-membered analogs **5a,b**. By variation of the counteranion for iodonium salt **4**, we observed the following trend in reactivity: B(C₆F₅)₄⁻ > BAr^F₄⁻ > OTf, with the perfluorinated borate as the superior counterion, yielding **3aa** in 81% after 48 h. In comparison, heteroatom-bridged iodonium salts **5a** and **5b** have shown diminished catalytic activity, which results in only moderate yields of up to 65% after the indicated time. In contrast to our previous studies about dicationic *N*-heterocyclic iodazolium salts **6a-d** in XB catalysis,^{17, 19} the more easily accessible dibenziodolium salt **4a** outperforms them in this reaction after 48 h (Scheme 2B). Only the C-bound pyrazole **6d** has shown a comparable conversion rate with 78% yield after the indicated time. In the initial 4 hours, catalysts **6a** and **6d** showed surprisingly higher activity than **4a** (see ESI for detailed analysis). While we are still investigating the mechanistic basis for this enhanced early-stage performance,

these findings demonstrate the value of accessing diverse diaryliodonium salts as catalysts, as their varying reactivity profiles can be optimized for specific applications.

To validate the role of halogen bonding in this reaction, we performed several control experiments (Scheme 2C). Neither common Lewis acids (BF₃•OEt₂) nor strong Brønsted acids (TFA) effectively catalyzed the reaction, with yields remaining below 10% after 48 h. The use of NaB(C₆F₅)₄ or H(OEt)₂B(C₆F₅)₄ as activators resulted in a reduced yield of 50% and 52%, respectively. Also, reactions of **4a** with NBu₄Br or NaB(C₆F₅)₄ and 15-crown-5 gave no product. These findings underscore the essential role of the iodonium for the activation

Next, we optimized the reaction under batch conditions (Scheme 2D) starting with 5 mol-% of **4a**. Screening of different solvents indicated the necessity of aprotic less polar solvents for a positive reaction outcome (entry 1-4), with CHCl₃ as the preferred one to give **3aa** in 79% yield after 24 h. Highly polar or protic solvents yielded the product only in traces (entry 5). Further optimization of the reaction temperature and the catalyst loading revealed, that the latter could be stepwise decreased to 0.5 mol-% at an elevated temperature of 80 °C in 24 h with an isolated yield of 89% (entry 6 - 11).

With these optimized conditions (scheme 2D, entry 11), we investigated the generality of our Pictet Spengler approach. First, we upscaled our method (5.00 mmol), which confirmed the scalability with a yield of 91%. We explored a range of para-substituted benzaldehydes (**2**) as coupling partners and found that the reaction performed well regardless of their electronic properties, delivering products **3ab-h** in high yields (79-94%,



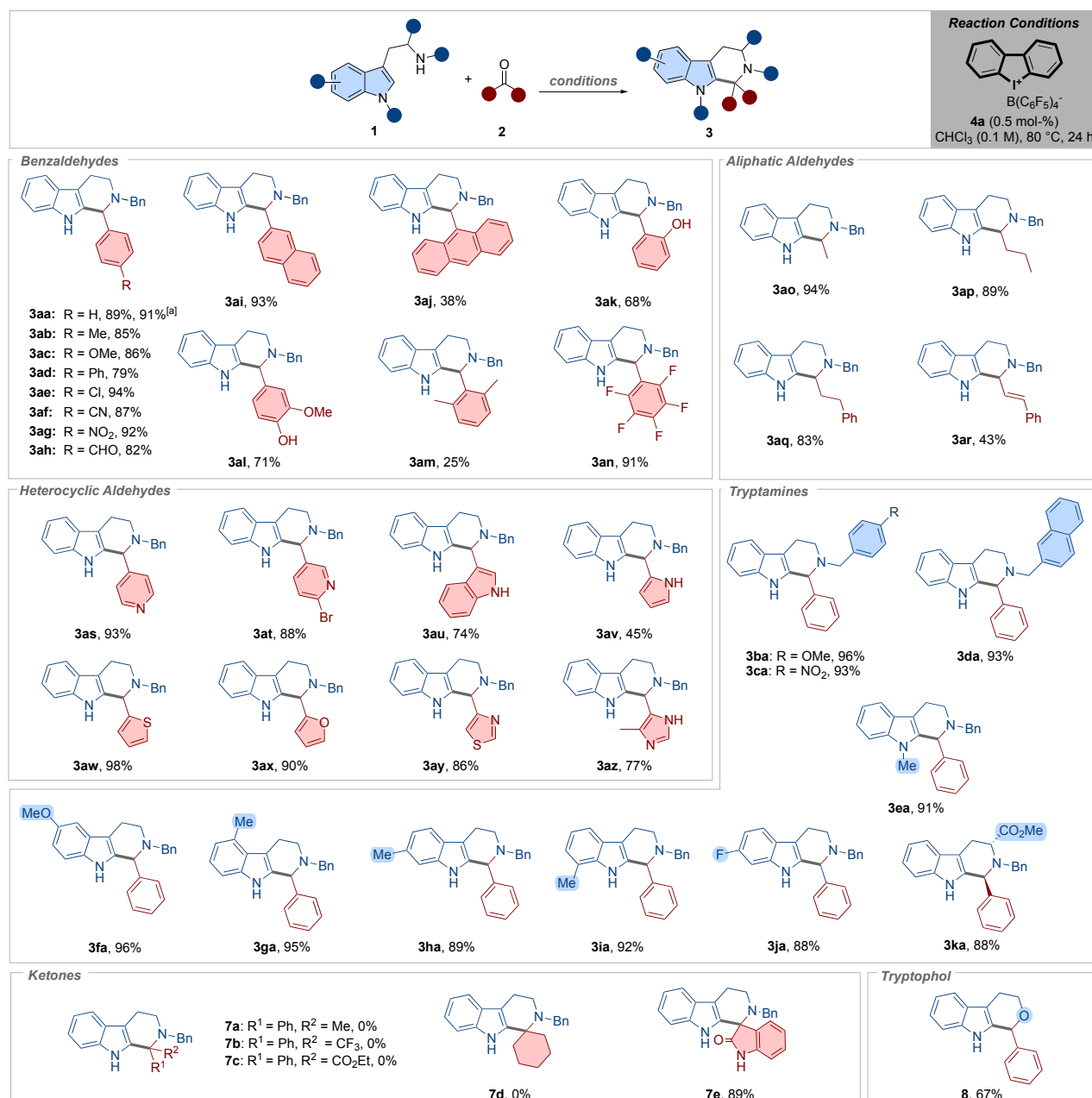
Scheme 2. Catalyst comparison and reaction optimization. A) Comparison of both monocationic XB catalysts **4** and **5** and various weakly coordinating anions. B) Comparison of **4a** and dicationic *N*-heterocyclic iodazolium salts **6**. C) Control experiments. D) Optimization of the reaction conditions under batch conditions (0.1 mmol scale) with additional stirring. Yields were determined via ¹H-NMR spectroscopy with TES as the internal standard. Isolated yields are in parentheses.



Scheme 3). Extended π -systems, like the naphthyl-substituted product **3ai**, are suitable substrates as well, with a yield of 93%. With the anthracenyl derivative **3aj**, the yield dropped to 38%, mainly due to the steric influence of the system in the ring closure step. This phenomenon was also observed for the sterically-hindered 2,6-dimethylbenzaldehyde, resulting in a low yield of 25% for **3am**. Hydroxy-substituted aldehydes could be successfully transformed into the Pictet Spengler products **3ak** and **3al** with yields of 68% and 71%.

The highly electron-deficient perfluorinated benzaldehyde gave **3an** in 91% yield. The reaction of tryptamine **1a** with aliphatic aldehydes was likewise suitable with yields of up to 94% for tetrahydro- β -carboline **3ao-aq**. Only by using the cinnamaldehyde the yield significantly dropped to 43% for **3ar**, probably due to further unexplored side reactions of the

containing double bond. We were further interested in the formation of heteroarene-substituted THBCs. While pyridinyl-substituted aldehydes yielded the desired products **3as** and **3at** in up to 93% yield, the five-membered *N*-heterocycles indole or pyrrole, resulted in slightly diminished yields of 74% and 45%, respectively. Furanyl- and thiophenyl-substituted analogs **3aw** and **3ax** as well as the bis-heteroatom-containing heterocycles **3ay** and **3az** were obtained in up to 98% yield. Different *N*-benzyl-protecting groups were tested further to expand the substrate scope of the developed method. Using electron-donating and electron-withdrawing groups or extended π -systems, the Pictet Spengler products **3ba-da** were obtained in yields of up to 96%. *N*-methylation of the indole proved compatible with the reaction conditions, furnishing **3ea** in 91% yield, indicating that a free NH is not required for reactivity.



Scheme 3. Substrate scope of the XB-catalyzed Pictet Spengler reaction. General reaction conditions: **1** (0.1 mmol), **2** (1.1 eq.), **4a** (0.5 mol-%), CHCl_3 (0.1 M), 80 °C, 24 h. ^[a] 5.00 mmol scale.



Further substitution of the indole moiety on the annulated aromatic ring indicates independence of the reaction mechanism from electronic or steric properties with yields from 88% to 96% for the desired products **3fa-ja**. With the protected D-tryptophan as the starting material, we exclusively observed the diastereoselective formation of **3ka** in 88% yield. This phenomenon has already been described and studied in the literature for various *N*-benzyl-protected tryptophans.²⁰ It is known that ketones instead of aldehydes are suitable reagents in Pictet Spengler reaction as well, however, mostly under harsher conditions.^{7a} We also investigated substituted acetophenones and cyclohexanone but observed no product formation. Among the tested ketones, only isatin provided the desired product **7e** in an unexpectedly high 89% yield. The methodology also proved effective for the oxa-Pictet-Spengler variant, converting tryptophol and benzaldehyde to product **8** in 67% yield.

We have developed an efficient halogen bond-catalyzed Pictet-Spengler reaction using dibenziodolium tetrakis-(pentafluorophenyl)borate, achieving high yields with only 0.5 mol-% catalyst loading. This metal-free protocol demonstrated exceptional scope, converting 38 different substrates to the corresponding tetrahydro- β -carboline in up to 98% yield. The reaction tolerates diverse functional groups and operates under mild conditions, offering advantages over traditional acid catalysis. Beyond methodology development, this study highlights the utility of readily accessible diaryliodonium salts as tunable halogen bond donors, expanding their potential in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Data availability

Experimental procedures and analytical data (¹H-, ¹³C- and ¹⁹F-NMR-chemical shifts, IR-bands, melting points) including the corresponding NMR-spectra for unknown compounds can be found in the supporting information.

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Data Availability Statement for the manuscript: „ Halogen Bond-catalyzed Pictet-Spengler Reaction “

The data supporting this study, including detailed experimental procedures, spectroscopic data, and additional information, are available in the submitted Electronic Supplementary Information (ESI).

Sincerely yours,



Boris J. Nachtsheim

