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Halogen bond-catalyzed Pictet–Spengler reaction†

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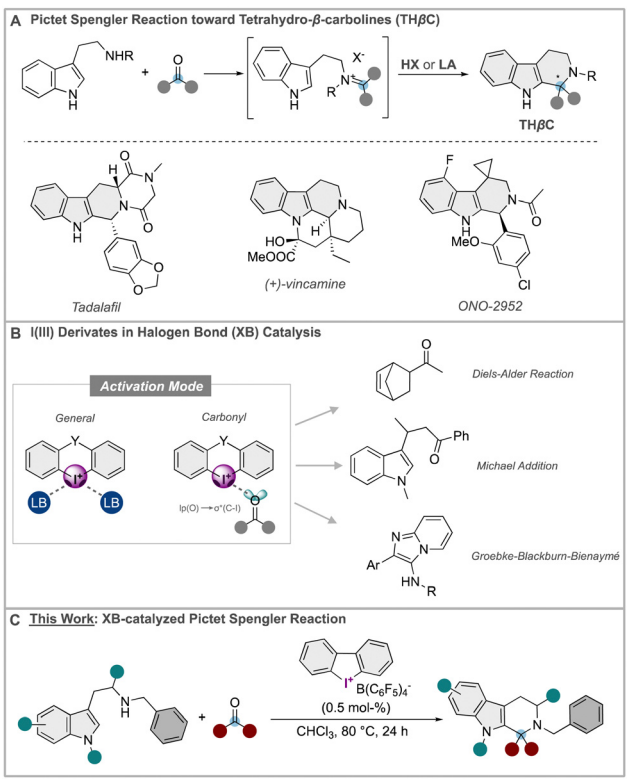
We report an efficient halogen bond-catalyzed Pictet–Spengler reaction using diaryliodonium salts as catalysts as a metal-free alternative to traditional acid catalysis. Through systematic optimization, exceptional catalytic activity was achieved with only 0.5 mol% of a simple dibenzoiodolium with a perfluorinated borate counterion. The protocol demonstrates a broad substrate scope, converting various *N*-protected tryptamines and diverse carbonyl compounds (aromatic, heteroaromatic, and aliphatic aldehydes) into the corresponding tetrahydro-β-carbolines (THβCs) 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 efficient reaction progress.

The tetrahydro-β-carboline (THβC) 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 THβCs 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 THβCs.

Besides its role in crystal engineering,[8] molecular recognition[9] and medicinal chemistry,[10] halogen bonding[11] (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] have been employed as more powerful XB donors compared to their iodine(I) analogs, particularly for the activation of neutral Lewis bases.[15] These strong Lewis acids were already described to efficiently activate carbonyl derivates, for example, in the Diels–Alder,[16] Michael[17] or Groebke–Blackburn–Bienaymé reaction.[18]



Scheme 1 (A) Overview of the Pictet–Spengler reaction and pharmacologically active THβBCs. (B) I(III) Derivates in halogen bond (XB) catalysis. (C) This work: XB-catalyzed Pictet–Spengler reaction.

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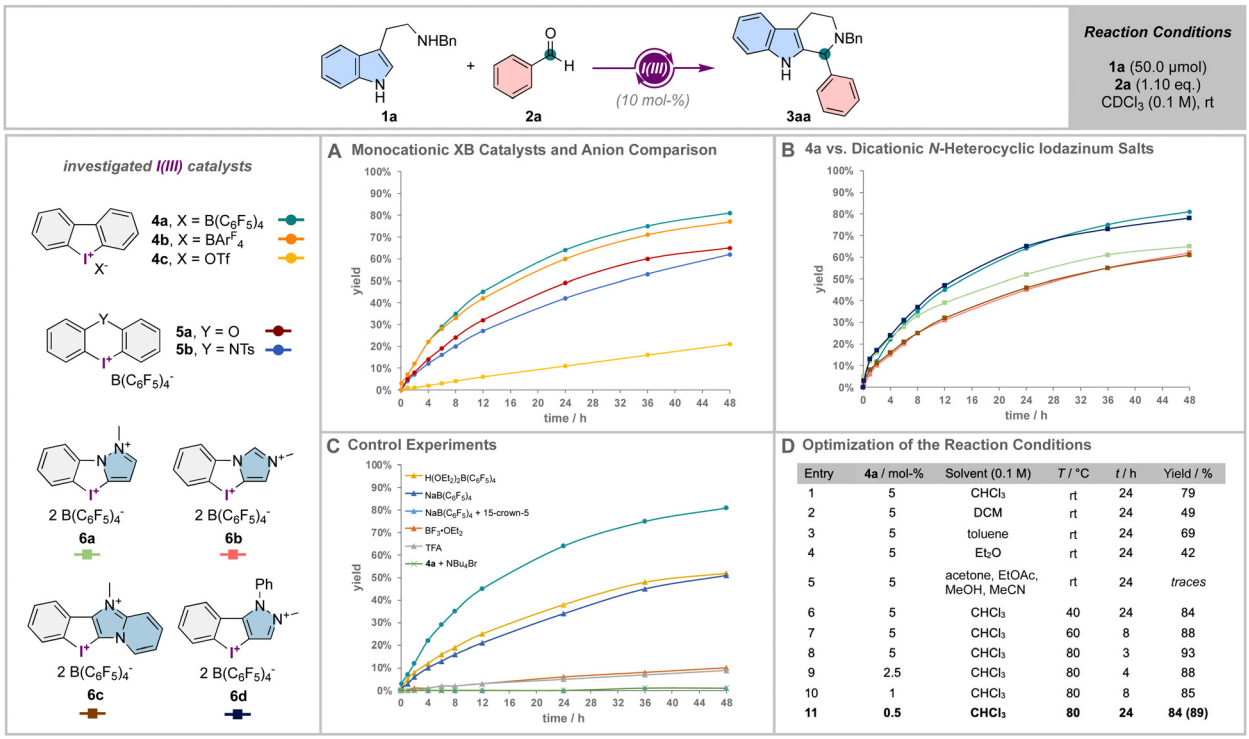
Herein, we report a successful deployment of diaryliodonium salt catalysts for the activation of carbonyls in an XB-catalyzed Pictet–Spengler reaction using *N*-protected tryptamines as the amine source to form THβCs (Scheme 1C).

We started our investigations by examining the Pictet–Spengler reaction of *N*-benzyl-protected tryptamine **1a** (Scheme 2A) and benzaldehyde (**2a**) to potentially yield THβC **3aa**. Using $CDCl_3$ as the solvent, we initially followed the reaction progress in an NMR tube *via* ^{1}H-NMR spectroscopy for various monocationic iodolium salts **4a–c** and their heteroatom-bridged six-membered analogs **5a,b**. By variation of the counteranion for iodolium salt **4**, we observed the following trend in reactivity: $B(C_6F_5)_4^- > BAr^F{}_4^- > OTf^-$, 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 dibenzoiodolium 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 h, 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.

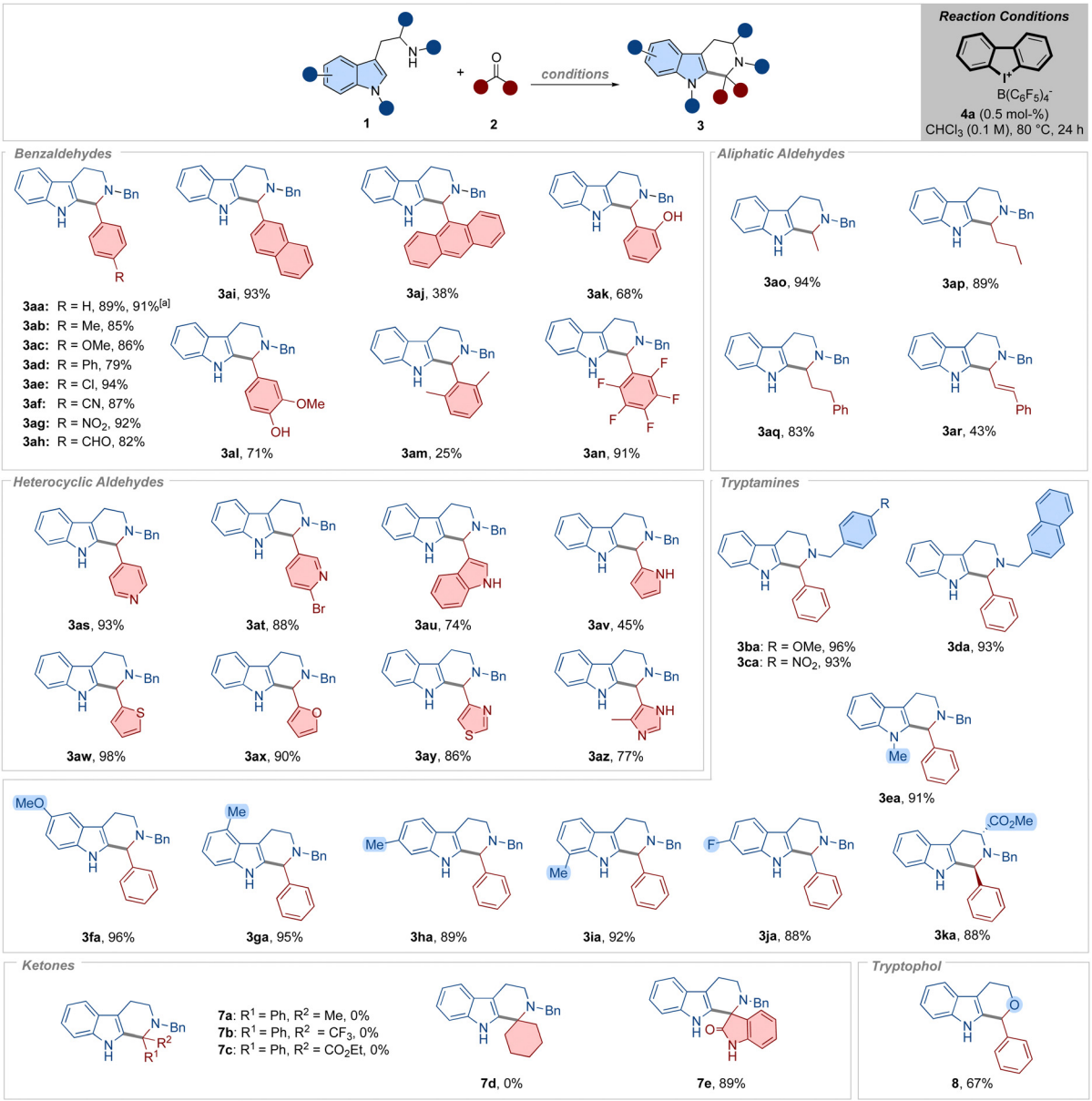
To validate the role of halogen bonding in this reaction, we performed several control experiments (Scheme 2C). Neither common Lewis acids ($BF_3{\cdot}OEt_2$) nor strong Brønsted acids (TFA) effectively catalyzed the reaction, with yields remaining below 10% after 48 h. The use of $NaB(C_6F_5)_4$ or $H(OEt_2)_2B(C_6F_5)_4$ as activators resulted in a reduced yield of 50% and 52%, respectively. Also, reactions of **4a** with NBu_4Br or $NaB(C_6F_5)_4$ and 15-crown-5 gave no product. These findings underscore the essential role of the iodolium 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 (entries 1–4), with $CHCl_3$ 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% (entries 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



Entry	4a / mol-%	Solvent (0.1 M)	T / °C	t / h	Yield / %
1	5	$CHCl_3$	rt	24	79
2	5	DCM	rt	24	49
3	5	toluene	rt	24	69
4	5	Et_2O	rt	24	42
5	5	acetone, EtOAc, MeOH, MeCN	rt	24	*traces*
6	5	$CHCl_3$	40	24	84
7	5	$CHCl_3$	60	8	88
8	5	$CHCl_3$	80	3	93
9	2.5	$CHCl_3$	80	4	88
10	1	$CHCl_3$	80	8	85
11	**0.5**	**$CHCl_3$**	**80**	**24**	**84 (89)**

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* ^{1}H-NMR spectroscopy with TES as the internal standard. Isolated yields are in parentheses.



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.

properties, delivering products **3ab–ah** in high yields (79–94%, Scheme 3). Extended π-systems, like the naphthyl-substituted product **3ai**, are suitable substrates as well, with a yield of 93%. With the anthracenyl derivate **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-carbolines **3ao–aq**. Only by using the cinnamaldehyde the yield significantly dropped to 43% for **3ar**, probably due to further unexplored side reactions of the contained double bond. We were further interested in the formation of heteroarene-substituted THβCs. 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. 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 dibenzoiodolium 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-carbolines 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.

Data availability

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

Conflicts of interest

There are no conflicts to declare.

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