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Bromonium salts: diaryl-λ^3-bromanes as halogen-bonding organocatalysts†

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Bromonium salts have been typically but infrequently used in various reactions as good leaving groups or as aryl or vinyl transfer reagents owing to their extremely high nucleofugality. Herein, we report the synthesis of novel, stable bromonium salts and their first catalytic application to the Michael reaction, with excellent product yield (up to 96%).

Because of their high and unique reactivities, hypervalent halogen compounds have been widely investigated in organic chemistry.[1] The most familiar examples of this class are the hypervalent iodine reagents, which have been developed over the last few decades for many reactions, including chiral transformations.[2,3] These compounds have mainly been employed in the asymmetric oxidation of phenol derivatives,[2a,c,d,3c,e,i] oxidative functionalization of C–C multiple bonds,[2b,3b,j] and the construction of quaternary carbon centres.[3a] Iodonium salts, which comprise one species of hypervalent iodine reagents, have been widely used as strong arylating reagents due to their extremely high electron-withdrawing ability and nucleofugality.[4] In 2009, Gaunt and co-workers reported the copper-catalysed meta-selective C–H arylation of pivanilides with diaryliodonium salts, which provided the corresponding products in up to 93% yield (Fig. 1).[4e] In contrast to the iodonium salt motif, the research on bromonium salts, *i.e.*, hypervalent bromine reagents, is limited.[1a,5] In 1952, Sandin and Hay reported the first preparation of a bromonium salt through intramolecular nucleophilic bromine attack on an aryldiazonium salt.[1a] A bromonium salt possesses greater leaving group ability than an iodonium salt because of its higher electron-withdrawing ability and ionization potential.[6] Therefore, several elegant synthetic transformations employing bromonium salts have been described. In 2006, Ochiai and co-workers reported the first synthesis of bromonium ylides and demonstrated their applications as aryl or vinyl transfer reagents to nitrogen-containing heterocycles (Fig. 1).[5b] Subsequently, drawing on their extremely high nucleofugality, these compounds have been applied in fascinating reactions such as the metal-free amination of unactivated alkanes,[5f] thermal solvolysis,[5d] and the amination of ethers.[5g] Despite their unique structures and reactivities, only limited examples demonstrating the utility of bromonium salts have been reported due to their instability.

Halogen bonding[7] has been a focus in organic chemistry as a versatile interaction that is complementary to hydrogen bonding, which is employed as a major substrate-activation motif in organocatalysis.[8] Halogen-bonding organocatalysts have been developed as non-covalent Lewis-acidic activators.[9,10] In recent years, halonium salts have been utilized as catalysts by Wan *et al.* (bromine-containing cationic catalysts),[10a] Han, Liu, and Zhang (Lewis-acidic iodonium salt catalysts, Fig. 1),[10b] and Weiss, Huber and colleagues (halogen-bonding cyclic iodonium salt catalysts, Fig. 1).[10c] In 2020, Mayer, Legault, and co-workers constructed a Lewis acidity scale for diaryliodonium salts, which revealed that

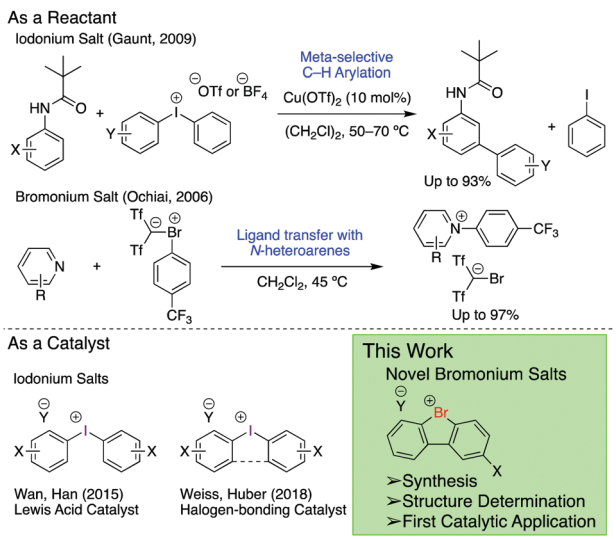

Fig. 1 Selected applications of halonium salts.

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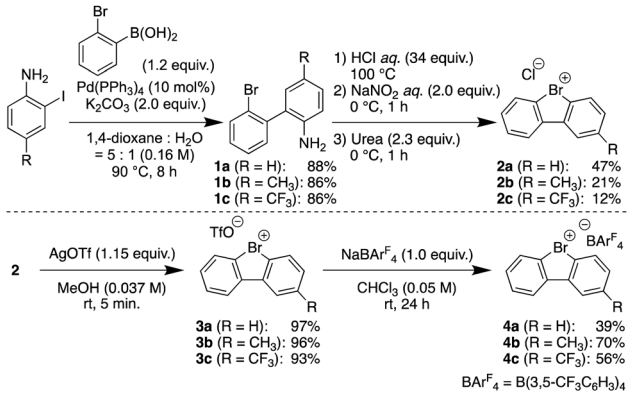


Scheme 1 Synthesis of λ^3-bromanes.

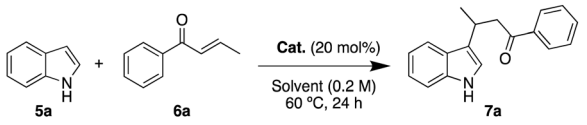
cyclic diaryliodonium salts possess higher acidities than acyclic ones.[10d] Herein, we report the synthesis and structure determination of novel, stable cyclic diarylbromonium salts and their first halogen-bonding-driven catalytic applications to the Michael reaction, which provided the corresponding products in up to 96% yield.

First, haloarenes **1** and bromonium salts **2** were synthesized using the reported procedure[5h] with slight modification (Scheme 1). Functionalised substrates **1**, obtained through palladium-catalysed coupling reactions, were successfully cyclised *via* the corresponding diazonium salts to afford novel bromonium salts **2**. To check the effect of counteranion on catalytic activity, bromonium salts **3** and **4** were prepared in good yields by the respective treatment of **2** with silver triflate and $NaB(3,5\text{-}CF_3C_6H_3)_4$ ($NaBAr^F{}_4$). Because **2a** could be isolated as a fine single crystal, X-ray crystallographic analysis was carried out. From the ORTEP diagram, **2a** exists in an ion pair rather than covalently bonded form.[11]

Next, the conditions for the Michael reaction of indole **5a** with *trans*-crotonophenone **6a** were optimised (Table 1).[9i] Solvent screening with **2b** revealed that the reaction in chloroform provided **7a**, whereas other polar or non-polar solvents gave no reaction (Table 1, entries 1–5). With this promising result in hand, catalyst screening was conducted (Table 1, entries 6–14). Although λ^3-bromanes **2** provided Michael adduct **7a** in moderate conversion, the bromonium salts with the triflate anion (**3**) and $BAr^F{}_4$ anion (**4**) gave **7a** in >99% conversion (Table 1, entries 6–13). Finally, the reaction without a λ^3-bromane additive failed to afford the desired product (Table 1, entry 14), which confirmed the effective and high catalytic activity of bromonium salts **2–4** for the present transformation.

To determine the best catalyst, further reaction optimizations were performed (Table 2). When the reactions were conducted for 1.5 h with 10 mol% catalyst loading of **3a** and **3b**, the desired product was obtained with >99% conversion; the other catalysts provided inferior results, even with higher catalyst loads or extended reaction times (Table 2, entries 2, 5, and 8–11). When the reactions were stopped after 0.5 h, **7a** was obtained in 58% conversion with **3a** and 59% conversion with **3b**, which revealed that the best catalyst was **3b** (Table 2, entries 1 and 4). When the

Table 1 Optimisation of conditions for the Michael reaction of indole (**5a**) with *trans*-crotonophenone (**6a**)[a]

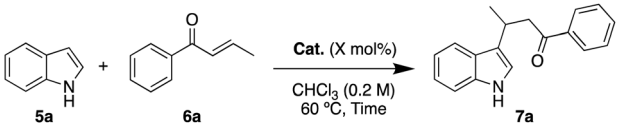


5a 6a 7a

Entry	Cat.	Solvent	Conv.[b] (%)
1	**2b**	$CHCl_3$	12
2	**2b**	^{t}AmylOH	0
3	**2b**	MeCN	0
4	**2b**	THF	0
5	**2b**	Toluene	0
6	**2a**	$CHCl_3$	36
7	**2c**	$CHCl_3$	26
8	**3a**	$CHCl_3$	>99
9	**3b**	$CHCl_3$	>99
10	**3c**	$CHCl_3$	>99
11	**4a**	$CHCl_3$	>99
12	**4b**	$CHCl_3$	>99
13	**4c**	$CHCl_3$	>99
14	—	$CHCl_3$	0

[a] Unless noted, reactions were performed with **5a** (1.0 equiv.), **6a** (1.0 equiv.), and Cat. (20 mol%) in appropriate solvent (0.2 M) at 60 °C. [b] All conversions were determined by ^{1}H NMR analysis.

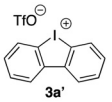
Table 2 Catalyst optimisation for the Michael reaction of indole (**5a**) with *trans*-crotonophenone (**6a**)[a]



5a 6a 7a

Entry	Cat.	X	Time (h)	Conv.[b] (%)
1	**3a**	10	0.5	58
2	**3a**	10	1.5	>99
3	**3a′**	10	1.5	Trace
4	**3b**	10	0.5	59
5	**3b**	10	1.5	>99
6	**3b**	5	4	>99 (92)
7[c]	**3b**	5	8	27
8	**3c**	10	1.5	76
9	**4a**	20	6	60
10	**4b**	20	6	21
11	**4c**	10	1.5	84

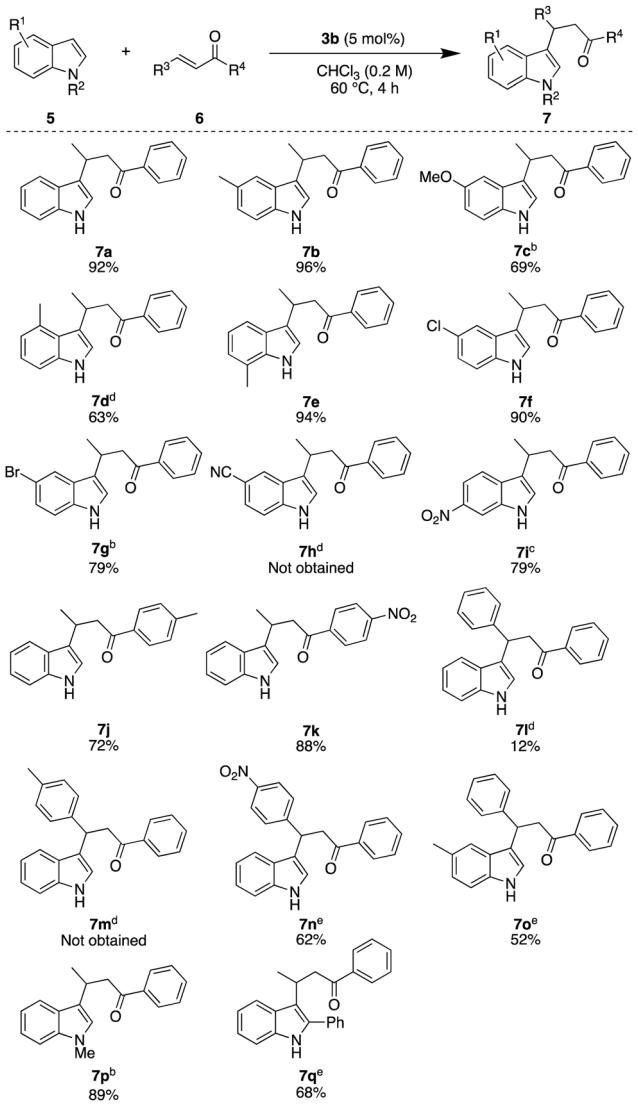
[a]Unless noted, reactions were performed with **5a** (1.0 equiv.), **6a** (1.0 equiv.), and Cat. (10 mol%) in $CHCl_3$ (0.2 M) at 60 °C.
[b]All conversions were determined by ^{1}H NMR analysis. The parenthetical value is the yield of isolated **7a**.
[c]The reaction was carried out at 25 °C.



3a′

reaction with **3b** was conducted at 25 °C, the conversion of **5a** was only 27% even after prolonged reaction (Table 2, entry 7). Remarkably, the λ^3-iodane analogue **3a′** exhibited significantly lower catalytic activity than the λ^3-bromane (Table 2, entry 3).

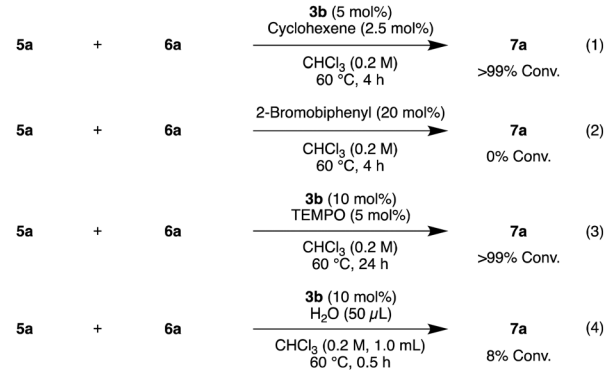
Next, the scope and limitations of the present reaction were explored (Scheme 2). Screening of the indole reactant revealed that, in every case, the corresponding products **7a–7i** could be isolated in high yields irrespective of their steric or electronic



Scheme 2 Scope and limitations for Michael reactions catalysed by λ^3-bromane **3b**.[a] [a] Unless noted, reactions were performed with **5** (1.0 equiv.), **6** (1.0 equiv.), and **3b** (5 mol%) in $CHCl_3$ (0.2 M) at 60 °C for 4 h. Yields of isolated products are shown. [b] Reactions were conducted for 6 h. [c] Reaction was conducted for 8 h. [d] Reactions were conducted for 12 h. [e] Reactions were conducted for 24 h.

nature, although strongly electron-withdrawing 5-cyano-substituted **7h** was not obtained, and only the substrate was recovered. The investigation of substituted *trans*-crotonophenones showed that electron-rich and -deficient aromatic substituents were well tolerated, giving products **7j** and **7k** in good yields. In the case of chalcone derivatives as Michael acceptors, **7m** was not obtained, even after 12 h, although products **7l**, **7n**, and **7o** were isolated in moderate yields. Finally, *N*-methyl indole and 2-phenyl indole were found to be well tolerated in the present reaction.[12]

To gain more insight into the reaction mechanism, control experiments were carried out (Scheme 3). Conducting the reaction in the presence of 2.5 mol% cyclohexene provided **7a** in almost the same yield as that under the standard conditions (Scheme 3(1)).[13] The reaction did not proceed when employing



Scheme 3 Mechanistic studies.

2-bromobiphenyl as a catalyst in place of **3b** (Scheme 3(2)).[5g] These results eliminate the possibility of catalytically active species of Br_2 or a bromoarene derived from decomposition of the λ^3-bromane. Additionally, the reaction in the presence of TEMPO proceeded smoothly, which excludes a radical-mediated mechanism (Scheme 3(3)).[14] Finally, the present reaction was conducted in the presence of water to accelerate the formation of TfOH through the decomposition of **3b**. The production of **7a** in only 8% yield indicates that *in situ*-generated TfOH is not the catalytically active species (Scheme 3(4)).[9i]

A plausible reaction mechanism is shown in Fig. 2. *trans*-Crotonophenone coordinates to **3b**, and the nucleophilic addition of indole to **II** takes place to form **III**. Then, intramolecular proton transfer provides **IV**, after which product **7a** is eliminated together with the regeneration of catalyst **3b**. Under this catalytic cycle, the triflate counteranion on **3b** is beneficial for the activation of **6** by increasing the halogen bonding strength, depending on the non-coordinating nature of the anion.[10c] Based on this effect and the substrate scope of the reaction, the indole addition step appears to be the rate-determining step.

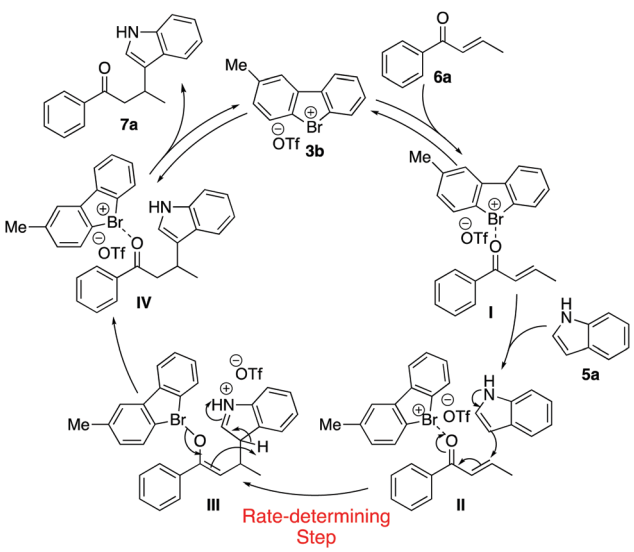


Fig. 2 Plausible reaction mechanism.

In conclusion, the first halogen-bonding λ^3-bromane catalyst was developed and characterised by X-ray crystallographic analysis. Its performance in the catalysis of the Michael reaction was evaluated, and its wide substrate scope suggests broad applicability. Mechanistic studies disclosed that the intact λ^3-bromane, rather than the decomposition products, functioned as the active catalyst in the reaction. Further investigations to develop chiral versions of these catalysts are ongoing.

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Conflicts of interest

There are no conflicts to declare.

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