



# Bifunctional Iodoazolium Salts: Searching for Cooperation Between Halogen Bonding and Hydrogen Bonding

David Givaudan, Bohdan Biletskyi, Antonio Recupido, Virginie Hérán, Thierry Constantieux, Jean-luc Parrain, Xavier Bugaut, Olivier Chuzel

## ► To cite this version:

David Givaudan, Bohdan Biletskyi, Antonio Recupido, Virginie Hérán, Thierry Constantieux, et al.. Bifunctional Iodoazolium Salts: Searching for Cooperation Between Halogen Bonding and Hydrogen Bonding. European Journal of Organic Chemistry, 2024, 27 (15), pp.e202300261. 10.1002/ejoc.202300261 . hal-04701581

**HAL Id: hal-04701581**

**<https://hal.science/hal-04701581v1>**

Submitted on 18 Sep 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Bifunctional Iodoazolum Salts: Searching for Cooperation Between Halogen Bonding and Hydrogen Bonding

David Givaudan<sup>+, [a]</sup>, Bohdan Biletskyi<sup>+, [a]</sup>, Antonio Recupido<sup>+, [a]</sup>, Virginie Hérán,<sup>[a]</sup>  
Olivier Chuzel,<sup>[a]</sup> Thierry Constantieux,<sup>\*, [a]</sup> Jean-Luc Parrain,<sup>\*, [a]</sup> and Xavier Bugaut<sup>\*, [a, b, c]</sup>

Non-covalent interactions play an important role in all sub-fields of chemistry, including catalysis, where interactions of different natures can work together to improve reactivity and selectivity. Several families of molecules that incorporate both hydrogen bond (HB) and halogen bonding (XB) donors have already been studied. However, there is a lack of data on how grafting HB donors to iodoazolum salts could impact their association and reactivity properties. Herein, we disclose the synthesis of a library of iodoazolum salts bearing varied HB

donors, along with a study of their physico-chemical properties using different techniques (X-ray diffraction, <sup>31</sup>P NMR, ITC) and their behavior in catalysis. Even though no clear-cut evidence of cooperation between XB and HB could be obtained through physico-chemical evaluations, a iodoazolum salt bearing a urea function displayed better conversion and product selectivity in a Ritter reaction than all other activators lacking one or the other function.

## Introduction

Attractive non-covalent interactions play an essential role in all fields of chemistry, and have received strong attention for the development of catalysts.<sup>[1]</sup> In this context, the most studied non-covalent interaction is the hydrogen bond (HB),<sup>[2]</sup> but many others such as pi–pi,<sup>[3]</sup> anion–pi,<sup>[4]</sup> or cation–pi<sup>[5]</sup> interactions have also gained popularity. Among non-covalent interactions, the halogen bond (XB) has long received less attention, probably because of earlier difficulties in its precise identification.<sup>[6]</sup> However, the recent years have seen tremendous developments, so that XB is now applied in fields of chemistry,<sup>[7]</sup> including organocatalysis.<sup>[8]</sup>

An interesting aspect of non-covalent interactions is that they can easily cooperate to increase both the rate and the stereoselectivity of the reaction.<sup>[9]</sup> Examples of cooperation between XB and HB are known in biological systems,<sup>[10]</sup> and have also found applications in synthetic chemistry, with four different scenarios (Figure 1):<sup>[11]</sup>

- (i) *Parallel cooperation of XB and HB* that separately interact with the same molecule of substrate or different ones: it is the case for urea-(polyfluoro)iodoarene such as **1** or **2**,<sup>[12]</sup>

and in catenane and rotaxane systems developed by Beer and co-workers or in diaryliodonium salts (not shown).<sup>[13]</sup>

- (ii) *HB-preorganized XB*: as reported by the group of Schubert, intramolecular HB within the structure of a bis-(iodoazole-phenol) containing structure **3** helps preorganizing this scaffold for improved XB properties.<sup>[14]</sup>
- (iii) *HB-assisted XB*: for example, DFT calculations provided evidence that hydrogen-bond-assisted halogen bonding could exist between inorganic species: Br<sub>2</sub> and HF can create a complex network **4** when combined with the Lewis-basic NH<sub>3</sub>.<sup>[15]</sup> For organic molecules, Berryman (iodopyridinium ions bearing amine or amide functions **5** and **6**) and others have disclosed structures including external (to the backbone) or internal (to the iodine atom lone pairs) HB-assistance, respectively.<sup>[16]</sup> In both cases, HB-assistance resulted in much stronger XB and improved catalytic activities.
- (iv) *XB-assisted HB*: recently, the group of Takemoto showed that the sulfur atom of Schreiner thiourea can interact as a Lewis base with an iodobenzimidazolium ring.<sup>[17]</sup> The supramolecular assembly **7** becomes a very efficient catalyst for *N*-glycofunctionalization, whereas the two separated species are unable to perform the reaction.

[a] Dr. D. Givaudan,<sup>+</sup> Dr. B. Biletskyi,<sup>+</sup> Dr. A. Recupido,<sup>+</sup> Dr. V. Hérán,  
Dr. O. Chuzel, Prof. Dr. T. Constantieux, Dr. J.-L. Parrain, Prof. Dr. X. Bugaut  
Aix Marseille Univ, CNRS  
Centrale Marseille, iSm2  
Marseille (France)  
E-mail: jl.parrain@univ-amu.fr  
xavier.bugaut@univ-amu.fr

[b] Prof. Dr. X. Bugaut  
Université de Strasbourg  
Université de Haute-Alsace  
CNRS, LIMA, UMR 7042  
67000 Strasbourg (France)  
E-mail: xbugaut@unistra.fr

[c] Prof. Dr. X. Bugaut  
Institut Universitaire de France  
1 rue Descartes  
75231 Paris (France)

[\*] These authors contributed equally to this work.

Supporting information for this article is available on the WWW under  
https://doi.org/10.1002/ejoc.202300261

© 2023 The Authors. European Journal of Organic Chemistry published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

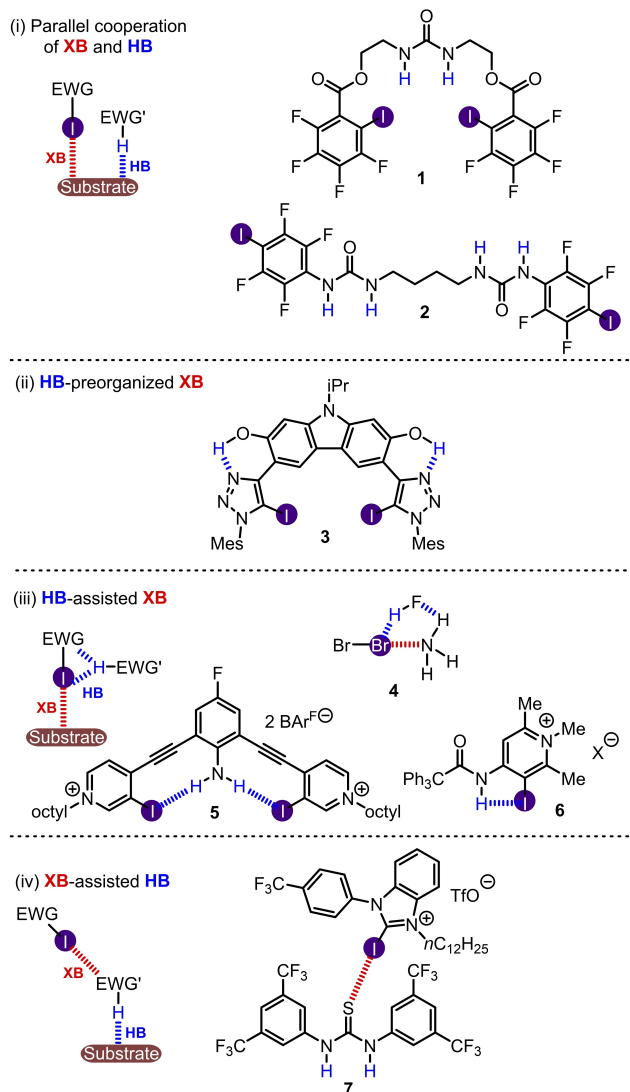


Figure 1. Four different scenarios for the cooperation between XB and HB.

Haloazolum ions represent a very interesting family of halogen-bond donors since they exhibit strong interaction with Lewis bases and a comparative reluctance to transfer their halogen atom.<sup>[18]</sup> Much to our surprise, studies on the possibility to prepare haloazolum ions that incorporate a HB donor are extremely scarce,<sup>[19]</sup> and the effect of their potential collaboration on association constants of catalytic efficiency is not documented. Herein, we wish to disclose our first attempts at preparing a family of bifunctional iodoazolum salts bearing a variety of HB donors, along with the study of their properties using physico-chemical methods and preliminary catalytic attempts.

## Results and Discussion

### Synthesis and Structure of Iodoazolum Salts Bearing Diverse HB Donors

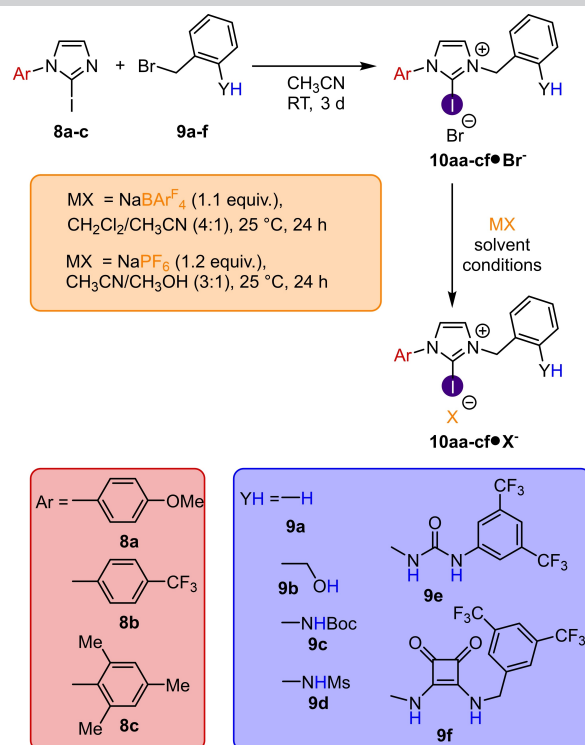
Our experimental studies started with the design of a simple and flexible synthesis of original iodoazolum salts **10aa–cf·Br<sup>−</sup>** bearing diversified HB donors (Table 1). The key step consisted in a nucleophilic substitution between easily accessible 2-iodo-1-arylimidazole **8a–c** and functionalized benzyl bromides **9a–f**.<sup>[20]</sup> The reaction proceeded smoothly at room temperature, delivering the expected products in reasonable yields and purities. Long reaction times (3 days) were required and heating could not help as it resulted in extensive degradation, notably deiodination and protonation. The aromatic substituent of **8a–c** incorporated either an electron-donating (–OMe) or an electron-withdrawing (–CF<sub>3</sub>) group at position 4, or consisted of a mesityl ring to evaluate the effect of steric hindrance on XB.<sup>[21]</sup> Benzylic bromides included the parent compound **9a** as a reference and other ones incorporating HB candidates such as a benzylic alcohol (**9b**), a carbamate (**9c**), a sulfonamide (**9d**), an urea (**9e**) and a squaramide (**9f**). Products were obtained in moderate to good purities after simple filtration, which could sometimes be improved by crystallization, but not by flash chromatography which caused extensive degradation.

To avoid the interference of the bromide anion in the evaluation of the association between XB and HB, ion metathesis was performed with different counterions including  $\text{BAR}_4^{\text{F}_4-}$  and  $\text{PF}_6^-$ , to deliver the corresponding iodoazolum salts **10aa–cf·BAR<sub>4</sub><sup>F\_4-</sup>** and **10aa–cf·PF<sub>6</sub><sup>−</sup>**. An interesting feature of ion metathesis is that it increased product stabilities, allowing purification of the iodoazolum salts by flash chromatography to obtain pure materials.

Among all the prepared XB donors, monocrystals suitable for X-ray diffraction could be grown for three of them: **10aa·Br<sup>−</sup>**, **10ac·Br<sup>−</sup>** and **10ab·PF<sub>6</sub><sup>−</sup>** (Figure 2).<sup>[20]</sup> The structure of **10aa·Br<sup>−</sup>** clearly establishes the existence of XB with a I–Br distance of 3.105 Å (81% of the sum of the van der Waals radii) with a C–I–B angle of 175.6°. The presence of a HB donor (NHBoc) in the structure of **10ac·Br<sup>−</sup>** did not seem to have a strong influence on its behavior in the solid state since no HB could be observed. XB remained largely unchanged with a I–Br distance of 3.041 Å (81% of the sum of the van der Waals radii) and a nearly perfect alignment between the three atoms involved in the interaction (178.7°). Lastly, the inertness of the weakly coordinating  $\text{PF}_6^-$  anion towards XB was confirmed by the structure of **10ab·PF<sub>6</sub><sup>−</sup>**, where the anion lies away from the iodine atom, with a non-directional electrostatic interaction with the cation.

### Physico-Chemical Studies

Even though solid state analysis failed to provide any insight about the potential cooperation between XB and HB in our bifunctional iodoazolum salts, we wanted to evaluate their properties in solution, which might be very different. In order to

Table 1. Synthesis of iodoazolium salts **10aa–cf**·Br<sup>−</sup> and counter-anion exchange to prepare **10aa–cf**·BAR<sub>4</sub><sup>F</sup><sup>−</sup> and **10aa–cf**·PF<sub>6</sub><sup>−</sup>.

Entry	Product <sup>[a]</sup>	Yield for 1 <sup>st</sup> step (%) <sup>[b]</sup>	Yield for 2 <sup>nd</sup> step (%) <sup>[b]</sup>
1	10 aa · BAr <sub>4</sub> <sup>F −</sup>	80	79
2	10 aa · PF <sub>6</sub> <sup>−</sup>		93
3	10 ab · BAr <sub>4</sub> <sup>F −</sup>	76	85
4	10 ab · PF <sub>6</sub> <sup>−</sup>		90
5	10 ac · BAr <sub>4</sub> <sup>F −</sup>	84	93
6	10 ad · BAr <sub>4</sub> <sup>F −</sup>	58	81
7	10 ae · BAr <sub>4</sub> <sup>F −</sup>	58	98
8	10 af · BAr <sub>4</sub> <sup>F −</sup>	43	99
9	10 ba · BAr <sub>4</sub> <sup>F −</sup>	71	86
10	10 bb · BAr <sub>4</sub> <sup>F −</sup>	80	88
11	10 bc · BAr <sub>4</sub> <sup>F −</sup>	62	89
12	10 ca · BAr <sub>4</sub> <sup>F −</sup>	64	73
13	10 cb · BAr <sub>4</sub> <sup>F −</sup>	91	72
14	10 cc · BAr <sub>4</sub> <sup>F −</sup>	78	81

[a] Elucidation of product numbering: **10<sub>xy</sub>** is prepared from **8<sub>x</sub>** and **9<sub>y</sub>**. [b] See SI for experimental details.

collect rapidly data for all the prepared compounds, we selected the Gutmann-Beckett method consisting in the saturation of a solution of triethylphosphine oxide (TEPO, **11**) in  $\text{CD}_2\text{Cl}_2$  and  $\text{CH}_2\text{Cl}_2$  with a large excess of the XB/HB donor to measure the influence on the chemical shift in  $^{31}\text{P}$  NMR (Table 2).<sup>[22]</sup> This method seemed especially appealing because of its easy implementation and since it has been recently applied for the separate evaluation of both HB<sup>[23]</sup> and XB,<sup>[24]</sup> with higher  $\Delta\delta(^{31}\text{P})$  values correlating with stronger attractive interactions. For comparison purposes, TEPO analysis was applied to bifunctional iodoazolium salts **10aa–cf**. $\text{X}^-$  but also

to the corresponding azolium salts **12ae–af**·**BAR**<sup>F<sub>4</sub>−</sup> and hydrogen bond donors **13ae–af**.<sup>[20]</sup> Reference compound **10aa**·**BAR**<sup>F<sub>4</sub>−</sup> without HB donor showed a  $\Delta\delta(^{31}\text{P})$  value of 6.70 ppm, in accordance with the literature data for other iodoazolium salts (5.68–6.25 ppm).<sup>[24b]</sup> Placing a benzylic alcohol in the structure of **10ab**·**BAR**<sup>F<sub>4</sub>−</sup> had no significant impact on  $\Delta\delta(^{31}\text{P})$ , in accordance with its relatively weak HB donor ability. Quite surprisingly, the NHBoc moiety of **10ac**·**BAR**<sup>F<sub>4</sub>−</sup> decreased  $\Delta\delta(^{31}\text{P})$  to 6.06 ppm. However, it is documented that NHBoc carbamates behave as stronger HB acceptors on the oxygen atom than HB donors.<sup>[25]</sup> Therefore, we can imagine that they

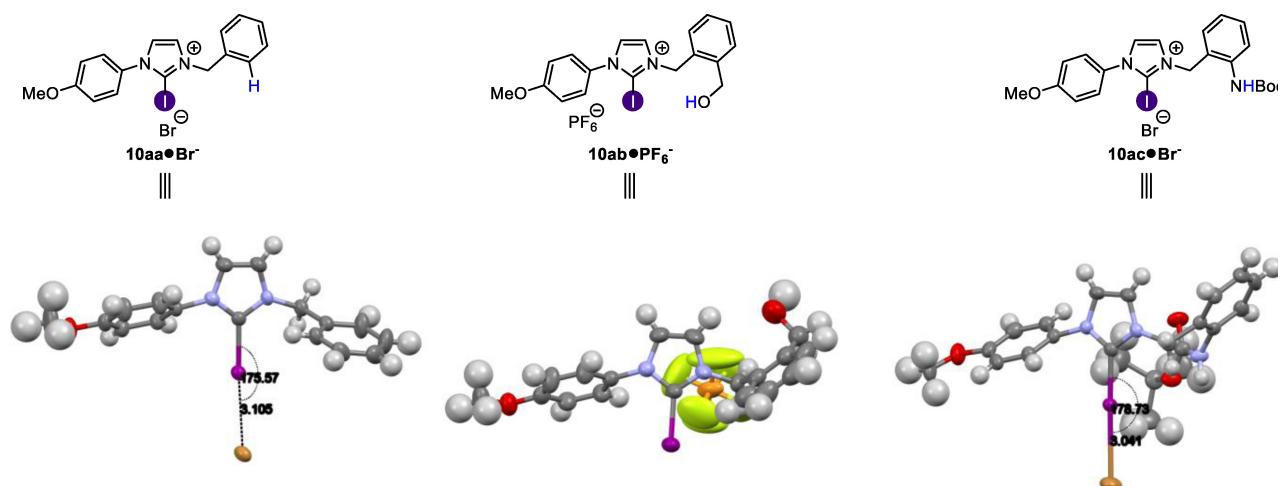


Figure 2. X-ray diffraction on monocrystals of several iodoazolum salts.

Table 2. TEPO analyses of bifunctional iodoazolum salts.

$\text{Et}_3\text{P}=\text{O} + \text{X-B/HB donor (10 equiv)} \xrightarrow{\text{CD}_2\text{Cl}_2, \text{CH}_2\text{Cl}_2} \text{complex of TEPO with X-B/HB donor (10 equiv)}$   
 $\delta(^{31}\text{P}) = 50.55 \text{ ppm}$        $\Delta\delta(^{31}\text{P}) = ? \text{ ppm}^{[a]} / \text{AN}^{[b]}$

**Evaluation of HB-donor**

<p><b>10aa•BARF<sub>4</sub><sup>−</sup></b>: 6.70 / 35.9</p>	<p><b>10ab•BARF<sub>4</sub><sup>−</sup></b>: 6.71 / 35.9</p>	<p><b>10ac•BARF<sub>4</sub><sup>−</sup></b>: 6.05 / 34.5</p>	<p><b>10ad•BARF<sub>4</sub><sup>−</sup></b>: 6.16 / 34.7</p>
<p><b>10ae•BARF<sub>4</sub><sup>−</sup></b>: 7.95 / 38.7</p>	<p><b>12ae•BARF<sub>4</sub><sup>−</sup></b>: 8.37 / 39.6</p>	<p><b>13ae</b>: 6.64 / 35.8<sup>[c]</sup></p>	<p><b>14ae•BARF<sub>4</sub><sup>−</sup></b>: 7.98 / 38.7</p>
<p><b>10af•BARF<sub>4</sub><sup>−</sup></b>: 10.10 / 43.4</p>	<p><b>12af•BARF<sub>4</sub><sup>−</sup></b>: 10.52 / 44.4</p>	<p><b>13af</b>: - / -<sup>[d]</sup></p>	

**Electronic and steric effects**

<p><b>10ba•BARF<sub>4</sub><sup>−</sup></b>: 6.60 / 35.7</p>	<p><b>10bb•BARF<sub>4</sub><sup>−</sup></b>: 6.40 / 35.2</p>	<p><b>10bc•BARF<sub>4</sub><sup>−</sup></b>: 6.42 / 35.3</p>
<p><b>10ca•BARF<sub>4</sub><sup>−</sup></b>: 5.80 / 33.9</p>	<p><b>10cb•BARF<sub>4</sub><sup>−</sup></b>: 5.90 / 34.1</p>	<p><b>10cc•BARF<sub>4</sub><sup>−</sup></b>: 5.76 / 33.8</p>

**Counterions**

<p><b>10aa•PF<sub>6</sub><sup>−</sup></b>: 4.53 / 31.1</p>
<p><b>10ab•PF<sub>6</sub><sup>−</sup></b>: 3.67 / 29.2</p>

[a] A stock solution of TEPO (11, 83 mM) was prepared in  $\text{CH}_2\text{Cl}_2$ . The compound to analyze (0.083 mmol, 10 equiv) was dissolved in a mixture of  $\text{CH}_2\text{Cl}_2$  (250  $\mu\text{L}$ ) and  $\text{CD}_2\text{Cl}_2$  (200  $\mu\text{L}$ ), and transferred into an NMR tube, followed by the addition of the suitable amount of TEPO solution (100  $\mu\text{L}$ , 0.0083 mmol, 1 equiv). The sample was analyzed by  $^{31}\text{P}$  NMR (300 MHz) and  $\Delta\delta(^{31}\text{P}) = \delta(^{31}\text{P})_{\text{sample}} - \delta(^{31}\text{P})_{\text{TEPO}}$  with  $\Delta\delta(^{31}\text{P})_{\text{TEPO}} = 50.55 \text{ ppm}$ . [b] Acceptor number  $\text{AN} = 2.21 * (\delta(^{31}\text{P}))_{\text{sample}} - 41.0$  [c] Only 3 equiv. of compound to analyze, because of low solubility. [d] Solubility of **13 af** was not sufficient to obtain a reliable result. [e] 300  $\mu\text{L}$  of TEPO solution were added.



could rather compete with TEPO as XB acceptors than being HB donors. The same tendency was observed for the NHMs group of  $10\text{ad} \cdot \text{BAR}_4^{\text{F}-}$ .

To outcompete these unwanted interactions, we turned our attention towards better HB donors such as ureas<sup>[26]</sup> and squaramides.<sup>[27]</sup> Urea-containing iodoazolum salt  $10\text{ae} \cdot \text{BAR}_4^{\text{F}-}$  indeed exhibited a stronger  $\Delta\delta(^{31}\text{P})$  than the parent compound, but it was even higher for the corresponding azolum salt  $12\text{ae} \cdot \text{BAR}_4^{\text{F}-}$  (8.37 ppm against 7.95 ppm). To verify the role of the urea function, compound  $13\text{ae}$  lacking the (iodo)azolum unit was prepared.<sup>[20]</sup> When it was submitted to TEPO analysis, a  $\Delta\delta(^{31}\text{P})$  value of 6.64 ppm was obtained,<sup>[28]</sup> which is matching literature precedents.<sup>[23a]</sup> These results lead us to elaborate two distinct scenarios to explain the observed high  $\Delta\delta(^{31}\text{P})$  value for  $10\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ :

- (i) either it acts only as a strong double HB donor thanks to its urea function, whose ability is heightened by the electron-withdrawing effects of the cationic (iodo)azolum rings, with stronger intensity for the more electron-deficient azolum ring of  $12\text{ae} \cdot \text{BAR}_4^{\text{F}-}$  than for the iodoazolum ring of  $10\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ ;
- (ii) or  $10\text{ae} \cdot \text{BAR}_4^{\text{F}-}$  actually exhibits XB/HB cooperation, but with a geometry that is less favored than the HB/HB cooperation of  $12\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ .

To discriminate between those two scenarios, ureido 2-methylazolum  $14\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ , which lacks a strong interaction point at position 2 of the azolum ring (hydrogen bonding to the hydrogen atoms of the methyl group or to the positions 4 and 5 of the imidazolium ring cannot be ruled out), was also prepared.<sup>[20]</sup> Its  $\Delta\delta(^{31}\text{P})$  value of 7.98 ppm similar to  $12\text{ae} \cdot \text{BAR}_4^{\text{F}-}$  seems to be in favor of the first scenario of electrostatic activation of the urea HB donor properties, and to rule out that an efficient XB/HB cooperation occurs for  $10\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ .

The same trend was observed in the squaramide series, with once again a stronger  $\Delta\delta(^{31}\text{P})$  for the non-iodinated  $12\text{af} \cdot \text{BAR}_4^{\text{F}-}$  than for  $10\text{af} \cdot \text{BAR}_4^{\text{F}-}$  (10.52 ppm against 10.10 ppm). The squaramide  $13\text{af}$  with no (iodo)azolum ring could not be compared because of its too low solubility.

We also wanted to evaluate whether the electronic and steric properties could have an impact on the XB and HB strengths. The iodoazolum salts bearing the trifluoromethyl substituent exhibited  $\Delta\delta(^{31}\text{P})$  similar to the ones with the methoxy group, showing no evidence for an impact of this electron-withdrawing substituent. These values were reduced by a little bit less than 1 ppm in the mesityl series. Moreover, no strong positive influence of the alcohol or NHBoc HB donors could be observed, with only a slightly higher  $\Delta\delta(^{31}\text{P})$  for  $10\text{cb} \cdot \text{BAR}_4^{\text{F}-}$  compared to  $10\text{ca} \cdot \text{BAR}_4^{\text{F}-}$  (5.90 ppm against 5.80 ppm). To finish, two compounds bearing a  $\text{PF}_6^-$  instead of  $\text{BAR}_4^{\text{F}-}$  as anion were evaluated. A  $\Delta\delta(^{31}\text{P})$  reduced by 2 ppm was observed for  $10\text{aa} \cdot \text{PF}_6^-$ , in accordance with the more coordinating nature of  $\text{PF}_6^-$ , with 1 additional ppm reduction for compound  $10\text{ab} \cdot \text{PF}_6^-$  with the alcohol function.<sup>[24b]</sup>

To complete the TEPO analyses, we also wanted to evaluate several of our compounds using a titration method.<sup>[30]</sup> For about a decade, isothermal titration calorimetry (ITC) has established itself as the most powerful method to characterize the

association between XB donors and Lewis bases in solution.<sup>[31]</sup> It notably has the advantage to be a global method (compared to NMR techniques which rely on local modifications, such as changes in the chemical shift of one selected proton). Moreover, ITC can give an access to all thermodynamic parameters of the equilibrium (stoichiometry  $N$ , dissociation constant  $K_D$  and its inverse, association constant  $K_A$ , variations of Gibbs free energy  $\Delta G$ , enthalpy  $\Delta H$  and entropy  $\Delta S$ ) in only one experiment. ITC analyses have been conducted on the three compounds  $10\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ ,  $12\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ ,  $13\text{ae}$  and  $14\text{ae} \cdot \text{BAR}_4^{\text{F}-}$  that bear an urea function, which were combined with tetrabutylammonium bromide (TBABr) in  $\text{CH}_3\text{CN}$  (Table 3). The experiments were carried out at 1.00 mM of studied compound in the cell and 10.0 mM of TBABr in the syringe, delivering good quality titration curves.<sup>[20]</sup> For the three compounds, only the fitting model with one set of sites allowed the regression to converge and furnish the thermodynamic parameters, pointing towards a scenario where the urea function is mostly responsible for ion sensing. The monofunctional urea  $13\text{ae}$  exhibited an association constant of  $1.38 \cdot 10^3 \text{ M}^{-1}$  consistent with the literature value ( $1.49 \cdot 10^3 \text{ M}^{-1}$ ) for Schreiner thiourea in related experimental conditions (Entry 3).<sup>[31]</sup> The association constants of the three cationic compounds are about 10 times higher, with the iodinated compound being slightly less efficient:  $1.55 \cdot 10^4 \text{ M}^{-1}$  for  $10\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ , to be compared with  $2.15 \cdot 10^4 \text{ M}^{-1}$  for  $12\text{ae} \cdot \text{BAR}_4^{\text{F}-}$  and  $2.00 \cdot 10^4 \text{ M}^{-1}$  for  $14\text{ae} \cdot \text{BAR}_4^{\text{F}-}$  (Entries 1 to 3). It should also be noted that the interactions of the cationic compounds display similar profiles with strong entropic contributions, whereas the interaction with  $13\text{ae}$  seems to be more dominated by enthalpic factors. Last but not least, even though the two methods are completely different in their physico-chemical principles and nature of the Lewis bases, the ITC measured association constants and the TEPO  $\Delta\delta(^{31}\text{P})$  values follow remarkably similar trends for these four ureas.

Table 3. ITC analyses in the urea series<sup>[a]</sup>.

Entry	Results
1	$10\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ $N = 0.926^{[b]}$ $K_D = 6.44 \cdot 10^{-5} \pm 8.39 \cdot 10^{-6} \text{ M}$ $K_A = 1.55 \cdot 10^4 \text{ M}^{-1}$ $\Delta G = -23.9 \text{ kJ} \cdot \text{mol}^{-1}$ $\Delta H = -7.28 \pm 0.22 \text{ kJ} \cdot \text{mol}^{-1}$ $-\Delta S = -16.7 \text{ kJ} \cdot \text{mol}^{-1}$
2	$12\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ $N = 0.895^{[b]}$ $K_D = 4.66 \cdot 10^{-5} \pm 9.99 \cdot 10^{-7} \text{ M}$ $K_A = 2.15 \cdot 10^4 \text{ M}^{-1}$ $\Delta G = -24.7 \text{ kJ} \cdot \text{mol}^{-1}$ $\Delta H = -7.03 \pm 0.03 \text{ kJ} \cdot \text{mol}^{-1}$ $-\Delta S = -17.7 \text{ kJ} \cdot \text{mol}^{-1}$
3	$13\text{ae}$ $N = 0.995^{[b]}$ $K_D = 7.23 \cdot 10^{-4} \pm 1.12 \cdot 10^{-4} \text{ M}$ $K_A = 1.38 \cdot 10^3 \text{ M}^{-1}$ $\Delta G = -18.0 \text{ kJ} \cdot \text{mol}^{-1}$ $\Delta H = -10.9 \pm 0.98 \text{ kJ} \cdot \text{mol}^{-1}$ $-\Delta S = -7.1 \text{ kJ} \cdot \text{mol}^{-1}$
4	$14\text{ae} \cdot \text{BAR}_4^{\text{F}-}$ $N = 0.778^{[b]}$ $K_D = 5.01 \cdot 10^{-5} \pm 8.25 \cdot 10^{-7} \text{ M}$ $K_A = 2.00 \cdot 10^4 \text{ M}^{-1}$ $\Delta G = -24.6 \text{ kJ} \cdot \text{mol}^{-1}$ $\Delta H = -7.56 \pm 0.03 \text{ kJ} \cdot \text{mol}^{-1}$ $-\Delta S = -17.0 \text{ kJ} \cdot \text{mol}^{-1}$

[a] Parameters: cell:  $\text{C}(10\text{ae} \cdot \text{BAR}_4^{\text{F}-}, 12\text{ae} \cdot \text{BAR}_4^{\text{F}-}, 13\text{ae}$  or  $14\text{ae} \cdot \text{BAR}_4^{\text{F}-}) = 1.00 \text{ mM}$ ; syringe:  $\text{C}(\text{TBABr}) = 10.0 \text{ mM}$ ; solvent:  $\text{CH}_3\text{CN}$ ;  $T = 25.1\text{--}25.2^\circ\text{C}$ ; fitting model: one set of sites. Several fitting models were evaluated, with the one accounting for a 1:1 interaction providing the best correlation.  
[b] Stoichiometry of the complex.

## Reactivity Attempts

Despite physico-chemical studies that do not seem to show positive impact of the HB donors on the properties of the iodoazolum salts, we carried out some catalytic attempts. Indeed, catalytic processes are much more complex than the simple association with a Lewis base since they involve several consecutive steps that might be sensitive to very slight differences in the catalyst structure. Especially, stronger interactions from the catalyst are sometimes deleterious to the overall reaction as they might result in inhibition by the product.

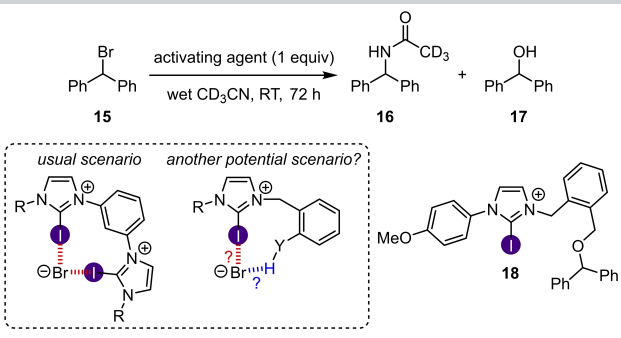
Initially, efforts to perform a hetero-Diels–Alder reaction between imines and dienes, which had already been promoted by other mono-iodoazolum salts,<sup>[21,32]</sup> were not conclusive. Imines possess only one lone pair on the nitrogen atom, so that concomitant XB and HB activation of this substrate is hard to conceive, leaving only the HB-activated XB scenario as possible. To test the scenario of parallel activation by XB and HB, we wanted to evaluate our bifunctional iodoazolum salts in a reaction where the Lewis base possesses several lone pairs.

For this, we retained the Ritter-type solvolysis of bromodiphenylmethane (**15**) in CD<sub>3</sub>CN, which affords amide **16** in the presence of trace amounts of water (Table 4).<sup>[33]</sup> This reaction is usually promoted by stoichiometric or sub-stoichiometric amounts of double XB-donors, and we wanted to assess the

possibility for the HB-donor to replace the second XB-donor. At first, the substrate was placed in CD<sub>3</sub>CN, containing traces of water, at room temperature. After 72 h, 7 % conversion to the final product **17** was observed (Entry 1). Using non-bifunctional iodoazolum salts **12aa**·**BAr**<sup>F</sup><sub>4</sub><sup>−</sup> increased the conversion to 41 %, with a product distribution of 80:20 between the Ritter product **16** and the product of direct hydrolysis **17** (Entry 2). Placing an alcohol function as HB donor in **10ab**·**BAr**<sup>F</sup><sub>4</sub><sup>−</sup> had a positive impact on the conversion (52 %) but also complicated the product distribution. Indeed, a third product **18** resulting from the trapping of the substrate by the alcohol function was also present (Entry 3).<sup>[34]</sup>

Since urea- and squaramide-containing XB donors were more promising in terms of physico-chemical properties, we also evaluated them in the Ritter-type solvolysis. Pleasingly, **10ae**·**BAr**<sup>F</sup><sub>4</sub><sup>−</sup> afforded a better conversion than all other compounds, with also a high ratio between the Ritter product **16** and benzhydryl alcohol **17** (Entry 4). Both the compound lacking the iodine atom **12ae**·**BAr**<sup>F</sup><sub>4</sub><sup>−</sup> and the one without the azolum unit **13ae** were not as efficient (Entries 5 and 6), pointing towards a positive impact of incorporating the iodoazolum and the urea motives within the structure of **10ae**·**BAr**<sup>F</sup><sub>4</sub><sup>−</sup>. Control experiment with the 2-methylazolum activator **14ae**·**BAr**<sup>F</sup><sub>4</sub><sup>−</sup> resulted in less convincing results (lower conversion and selectivity, Entry 7), letting the iodinated

Table 4. Reactivity attempts in Ritter-type solvolysis.

			
Entry	Activating agent <sup>[a]</sup>	Conversion of <b>15</b> (%) <sup>[b]</sup>	Product distribution <sup>[b]</sup>
1	no activating agent	7 %	Only <b>16</b>
2	<b>10aa</b> · <b>BAr</b> <sup>F</sup> <sub>4</sub> <sup>−</sup>	41 %	<b>16/17</b> = 80:20
3	<b>10ab</b> · <b>BAr</b> <sup>F</sup> <sub>4</sub> <sup>−</sup>	52 %	<b>16/17/18</b> = 57:7:35
4	<b>10ae</b> · <b>BAr</b> <sup>F</sup> <sub>4</sub> <sup>−</sup>	61 %	<b>16/17</b> = 96:4
5	<b>12ae</b> · <b>BAr</b> <sup>F</sup> <sub>4</sub> <sup>−</sup>	45 %	<b>16/17</b> = 85:15
6	<b>13ae</b>	28 %	<b>16/17</b> = 88:12
7	<b>14ae</b> · <b>BAr</b> <sup>F</sup> <sub>4</sub> <sup>−</sup>	39 %	<b>16/17</b> = 74:26
8	<b>10af</b> · <b>BAr</b> <sup>F</sup> <sub>4</sub> <sup>−</sup> <sup>[c]</sup>	61 %	<b>16/17</b> = 81:19
9	<b>12af</b> · <b>BAr</b> <sup>F</sup> <sub>4</sub> <sup>−</sup> <sup>[c]</sup>	68 %	<b>16/17</b> = 90:10
10	<b>13af</b> <sup>[c]</sup>	38 %	<b>16/17</b> = 67:33
11	<b>10ae</b> · <b>BAr</b> <sup>F</sup> <sub>4</sub> <sup>−</sup> <sup>[d]</sup>	40 %	<b>16/17</b> = 89:11

[a] Bromodiphenylmethane (**15**, 2.5 mg, 0.010 mmol, 1.0 equiv.), the activating agent (0.010 mmol, 1.0 equiv.) and CH<sub>2</sub>Br<sub>2</sub> (1.9 mg, 0.86 μL, 0.010 mmol, 1.0 equiv.) as internal standard were dissolved in CD<sub>3</sub>CN (0.50 mL), and the reaction mixture analyzed after 72 h at room temperature. [b] Conversions and product distributions were determined by <sup>1</sup>H NMR: substrate **15** (singlet at 6.44 ppm), expected product **16** (doublet at 6.23 ppm) and diphenylmethanol **17** (singlet at 5.78 ppm) and. [c] Reaction time: 96 h. [d] A sub-stoichiometric amount of activating agent **10ae**·**BAr**<sup>F</sup><sub>4</sub><sup>−</sup> (0.004 mmol, 0.4 equiv.) was used and TMSOH (0.030 mmol, 3.0 equiv.) was added.

compound **10ae**·**BAR**<sub>4</sub><sup>F<sup>-</sup></sup> as the clear best activating agent in the series. On the contrary, the results in the squaramide series were less interesting both in terms of yields and products distributions (Entries 8 to 10). At last, an attempt to achieve catalyst turnover was made (Entry 11), by adding an excess of TMSOH that could replace water as nucleophile and ensure catalyst regeneration by halide-induced desilylation.<sup>[35]</sup> Unfortunately, a conversion that matched the catalyst loading was observed, along with a slight decrease of the product selectivity.

## Conclusions

As a conclusion, we have developed the synthesis of a new family of bifunctional iodoazolum salts bearing diverse HB donors, in order to provide a first insight into the cooperation between XB and HB in the iodoazolum series. A convergent and efficient synthetic route consisting of the nucleophilic substitution of benzylic bromides was used to introduce alcohol, carbamate, sulfonamide, urea and squaramide functionalities. The bromide counterion could then be exchanged for less coordinating **BAR**<sub>4</sub><sup>F<sup>-</sup></sup> and **PF**<sub>6</sub><sup>-</sup> ions.

The bifunctional azolum salts were then submitted to different physico-chemical methods (X-ray diffraction, TEPO <sup>31</sup>P NMR analyses, ITC analyses) and reactivity attempts (aza-Diels–Alder reaction, Ritter-type solvolysis). No clear-cut evidence of the XB/HB cooperation could be detected by physico-chemical methods. Actually: (i) the alcohol function seems to be too weak a HB donor; (ii) the carbamate function is likely to behave rather as a HB acceptor on its oxygen atom than as a HB donor; (iii) the urea and the squaramide seem to be too strong double HB donors that outcompete the interaction at the iodine atom. In this case, the cationic azolum ring increases the HB donor properties of the urea or squaramide moiety thanks to its electron-withdrawing effect. Nevertheless, our physico-chemical studies provide the first evidence of similar tendencies between TEPO <sup>31</sup>P NMR and ITC analyses of XB donors.

On the contrary, reactivity studies were more encouraging, highlighting the fact that the stoichiometric or catalytic activation of a transformation is a much more complex process than a simple Lewis acid-base interaction. The bifunctional ureido iodoazolum salt **10ae**·**BAR**<sub>4</sub><sup>F<sup>-</sup></sup> proved to be a significantly better activating agent than the corresponding mono-functional structures in the Ritter-type reaction, both in terms of conversion and product selectivity.

To finish, based on a very recent competing study in the 3-iodopyridinium series,<sup>[16e]</sup> we feel like the linker between the XB and HB donors is likely to be too long and flexible to offer an efficient cooperation. Current studies are ongoing in our lab aiming at preparing other families of bifunctional iodoazolum salts with shorter linkers between the two active sites.

## Experimental Section

Only general procedures are presented here. The syntheses and analytical descriptions of all compounds are provided in the supporting information.

**General procedure A for the synthesis of (iodo)azolum bromides:** In an oven dried Schlenk tube were dissolved iodoimidazole or imidazole derivative (1.0 equiv) and benzylic bromide (1.0 equiv.) in anhydrous MeCN (0.06 M) under argon atmosphere. The reaction mixture was stirred at room temperature (25 °C) for 72 h. The product was then purified according to the specified procedure.

**General procedure B for Br<sup>-</sup>/**BAR**<sub>4</sub><sup>F<sup>-</sup></sup> exchange:** In an oven-dried Schlenk tube, iodoimidazolium or imidazolium bromide derivative (1.0 equiv.) and sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (1.1 equiv.) were dissolved under an argon atmosphere in a mixture of dry dichloromethane and dry acetonitrile (4:1, 0.05 M). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then concentrated under reduced pressure and the residue was purified by silica gel column chromatography (DCM/MeOH 98:2 to 95:5).

**General procedure C for Br<sup>-</sup>/**PF**<sub>6</sub><sup>-</sup> exchange:** In an oven dried Schlenk tube, iodoimidazolium bromide derivative (1.0 equiv.) and sodium hexafluorophosphate (1.2 equiv.) were dissolved under an argon atmosphere in a mixture of dry acetonitrile and dry methanol (3:1, 0.05 M). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then concentrated under reduced pressure and the residue was purified by silica gel column chromatography (DCM/MeOH 99:1 to 98:2).

**TEPO measurements:** According to the literature,<sup>[24b]</sup> all the NMR tubes were prepared and sealed in a glovebox. TEPO was solubilised with CH<sub>2</sub>Cl<sub>2</sub> to make a stock solution with concentration of 83 mM. The host compounds **10ac**–**af**·X<sup>-</sup>, **12ae**–**af**·**BAR**<sub>4</sub><sup>F<sup>-</sup></sup>, **13ae**–**af** and **14ae**·**BAR**<sub>4</sub><sup>F<sup>-</sup></sup> (0.083 mmol, 10 equiv, unless specified otherwise) were dissolved in of CH<sub>2</sub>Cl<sub>2</sub> (0.25 mL) and CD<sub>2</sub>Cl<sub>2</sub> (0.2 mL). The solution was transferred into an NMR tube followed by addition of TEPO stock solution (0.1 mL, 8.3 μmol, 1 equiv., unless specified otherwise). The <sup>31</sup>P NMR spectrum of each sample was immediately measured at room temperature with 32 scans and chemical shifts were compared to a standard (TEPO solution in CH<sub>2</sub>Cl<sub>2</sub>, 15 mM).

**ITC measurements** were performed on a MicroCal PEAQ-ITC (Malvern Instruments) with a 200-μL sample cell and a 40-μL titration syringe. The following parameters were used:

- host compounds **10ae**·**BAR**<sub>4</sub><sup>F<sup>-</sup></sup>, **12ae**·**BAR**<sub>4</sub><sup>F<sup>-</sup></sup>, **13ae** and **14ae**·**BAR**<sub>4</sub><sup>F<sup>-</sup></sup> (1.00 mM solution in dry CH<sub>3</sub>CN) in the cell;
- guest TBABr (10.0 mM solution in dry CH<sub>3</sub>CN) in the syringe;
- temperature of 25 °C;
- stirring speed of 750 rpm;
- reference power of 10 μcal.s<sup>-1</sup>;
- high-feedback mode;
- 1 injection of 0.4 μL over 4 s (which was not considered for correlation), followed by 18 injections of 2 μL over 4 s;
- intervals of 150 s between each injection;

Several fitting models were evaluated in the MicroCal PEAQ-ITC Panalytical software, with the single-site binding model accounting for a 1:1 interaction always providing the best correlation.

**General procedure D for Ritter-type reaction:** Bromodiphenylmethane (**15**, 2.5 mg, 0.010 mmol, 1.0 equiv.), the activating agent (0.010 mmol, 1.0 equiv.) and CH<sub>2</sub>Br<sub>2</sub> (1.9 mg, 0.86 μL, 0.010 mmol, 1.0 equiv.) as internal standard were dissolved in CD<sub>3</sub>CN (0.50 mL), and the reaction mixture analyzed after 72 h at room temperature. Conversions and product distributions were determined by <sup>1</sup>H NMR:



substrate **15** (singlet at 6.44 ppm), expected product **16** (doublet at 6.23 ppm) and diphenylmethanol **17** (singlet at 5.78 ppm).<sup>[33a]</sup> Even though this compound could not be isolated in its pure form, the presence of the cation **18** in the reaction depicted in Entry 3 was supported by HRMS analysis of the crude reaction mixture: HRMS (ESI): *m/z*: calcd for [C<sub>31</sub>H<sub>28</sub>IN<sub>2</sub>O<sub>2</sub>]<sup>+</sup> 587.1190; found 587.1189.

## Supporting Information

Additional references cited within the Supporting Information.<sup>[36–48]</sup>

## Acknowledgements

We warmly thank the whole team of the Spectropole for analytical work (www.spectropole.fr). Financial support from Aix Marseille Université, Centrale Marseille and the CNRS is acknowledged. The project leading to this publication has also received funding from Provepharm Life Solutions (funding for the PhD thesis of D.G.). Moreover, this work was supported by the ANR Bond-X-Bond project, grant ANR-19-CE07-0029 of the French Agence Nationale de la Recherche (scholarship for B. B. and A. R.). Dr. Yoann Coquerel is acknowledged for insightful discussions during manuscript preparation.

## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** cooperativity · halogen bond · hydrogen bond · organocatalysis · non-covalent interactions

- [1] a) C. A. Hunter, *Angew. Chem. Int. Ed.* **2004**, *43*, 5310; b) R. R. Knowles, E. N. Jacobsen, *Proc. Nat. Acad. Sci.* **2010**, *107*, 20678.
- [2] a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; b) T. Akiyama, Y. Arakawa, Y. C. Chen, H. L. Cui, L. Deng, J. Duschmalé, L. Z. Gong, Z. Y. Han, N. Haraguchi, T. Hashimoto, K. Hof, H. Imai, T. Inokuma, S. Itsuno, K. Izawa, H. B. Jang, M. Klussmann, K. M. Lippert, B. List, K. Maruoka, N. Momiyama, K. Nagasawa, T. Nishikawa, J. S. Oh, T. Ooi, I. Pápai, H. G. Park, P. R. Schreiner, S. Shirakawa, R. P. Singh, Y. Sohtome, C. E. Song, Y. Takemoto, M. Terada, T. Torii, D. Uruguchi, C. Wang, H. Wennemers, *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics*, Georg Thieme Verlag, Stuttgart, **2012**.
- [3] A. J. Neel, M. J. Hilton, M. S. Sigman, F. D. Toste, *Nature* **2017**, *543*, 637.
- [4] Y. Zhao, Y. Cotellet, L. Liu, J. López-Andarias, A.-B. Bornhof, M. Akamatsu, N. Sakai, S. Matile, *Acc. Chem. Res.* **2018**, *51*, 2255.
- [5] a) C. R. Kennedy, S. Lin, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2016**, *55*, 12596; b) S. Yamada, *Chem. Rev.* **2018**, *118*, 11353.
- [6] a) F. Guthrie, *J. Chem. Soc.* **1863**, *16*, 239; b) R. S. Mulliken, *J. Am. Chem. Soc.* **1950**, *72*, 600; c) O. Hassel, *Science* **1970**, *170*, 497; d) G. R. Desiraju, P. S. Ho, L. Kloo, A. C. Legon, R. Marquardt, P. Metrangolo, P. Politzer, G. Resnati, K. Rissanen, *Pure Appl. Chem.* **2013**, *85*, 1711.
- [7] a) P. Metrangolo, G. Resnati, *Halogen Bonding: Fundamentals and Applications*, Springer, Berlin, **2008**; b) T. M. Beale, M. G. Chudzinski, M. G. Sarwar, M. S. Taylor, *Chem. Soc. Rev.* **2013**, *42*, 1667; c) R. Wilcken, M. O. Zimmermann, A. Lange, A. C. Joerger, F. M. Boeckler, *J. Med. Chem.* **2013**, *56*, 1363; d) G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* **2016**, *116*, 2478; e) R. Tepper, U. S. Schubert, *Angew. Chem. Int. Ed.* **2018**, *57*, 6004; f) J. Y. C. Lim, P. D. Beer, *Chem* **2018**, *4*, 731; g) S. M. Huber, *Halogen Bonding in Solution*, Wiley-VCH, Weinheim, **2021**; h) R. Hein, P. D. Beer, *Chem. Sci.* **2022**, *13*, 7098.
- [8] a) D. Bulfield, S. M. Huber, *Chem. Eur. J.* **2016**, *22*, 14434; b) J. Bamberger, F. Ostler, O. G. Mancheño, *ChemCatChem* **2019**, *11*, 5198; c) R. L. Sutar, S. M. Huber, *ACS Catal.* **2019**, *9*, 9622; d) M. Kaasik, T. Kanger, *Front. Chem.* **2020**, *8*, DOI: 10.3389/fchem.2020.599064; e) H. Yang, M. W. Wong, *Molecules* **2020**, *25*, 1045; f) M. Breugst, J. J. Koenig, *Eur. J. Org. Chem.* **2020**, 5473.
- [9] A. S. Mahadevi, G. N. Sastry, *Chem. Rev.* **2016**, *116*, 2775.
- [10] Biological systems: R. K. Rowe, P. S. Ho, *Acta Crystallogr. Sect. B* **2017**, *73*, 255.
- [11] The competition between XB and HB has also been studied: a) C. C. Robertson, J. S. Wright, E. J. Carrington, R. N. Perutz, C. A. Hunter, L. Brammer, *Chem. Sci.* **2017**, *8*, 5392; b) J. C. Gamekkanda, A. S. Sinha, J. Desper, M. Đaković, C. B. Aakeröy, *New J. Chem.* **2018**, *42*, 10539.
- [12] a) M. G. Chudzinski, C. A. McClary, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 10559; b) L. Meazza, J. A. Foster, K. Fucke, P. Metrangolo, G. Resnati, J. W. Steed, *Nat. Chem.* **2013**, *5*, 42; c) R. Chutia, G. Das, *Dalton Trans.* **2014**, *43*, 15628; d) T. K. Ghosh, S. Mondal, S. Bej, M. Nandi, P. Ghosh, *Dalton Trans.* **2019**, *48*, 4538.
- [13] a) S. W. Robinson, C. L. Mustoe, N. G. White, A. Brown, A. L. Thompson, P. Kennepohl, P. D. Beer, *J. Am. Chem. Soc.* **2015**, *137*, 499; b) J. Y. C. Lim, I. Marques, V. Félix, P. D. Beer, *J. Am. Chem. Soc.* **2017**, *139*, 12228 and references included therein; c) M. V. Il'in, A. A. Sysoeva, A. S. Novikov, D. S. Bolotin, *J. Org. Chem.* **2022**, *87*, 4569.
- [14] R. Tepper, B. Schulze, H. Görls, P. Bellstedt, M. Jäger, U. S. Schubert, *Org. Lett.* **2015**, *17*, 5740.
- [15] P.-P. Zhou, W.-Y. Qiu, S. Liu, N.-Z. Jin, *Phys. Chem. Chem. Phys.* **2011**, *13*, 7408.
- [16] a) A. M. S. Riel, D. A. Decato, J. Sun, C. J. Massena, M. J. Jessop, O. B. Berryman, *Chem. Sci.* **2018**, *9*, 5828; b) J. Sun, A. M. S. Riel, O. B. Berryman, *New J. Chem.* **2018**, *42*, 10489; c) A. M. S. Riel, R. K. Rowe, E. N. Ho, A.-C. C. Carlsson, A. K. Rappé, O. B. Berryman, P. S. Ho, *Acc. Chem. Res.* **2019**, *52*, 2870; d) S. Kuwano, Y. Nishida, T. Suzuki, T. Arai, *Adv. Synth. Catal.* **2020**, *362*, 1674; e) D. A. Decato, A. M. S. Riel, J. H. May, V. S. Bryantsev, O. B. Berryman, *Angew. Chem. Int. Ed.* **2021**, *60*, 3685; f) S. Portela, I. Fernández, *Molecules* **2021**, *26*, 1885; g) M. Kaasik, J. Martónova, K. Erkmann, A. Metsala, I. Järving, T. Kanger, *Chem. Sci.* **2021**, *12*, 7561; h) A. M. S. Riel, D. A. Decato, J. Sun, O. B. Berryman, *Chem. Commun.* **2022**, *58*, 1378; i) D. A. Decato, J. Sun, M. R. Boller, O. B. Berryman, *Chem. Sci.* **2022**, *13*, 11156; j) O. Berryman, J. Sun, D. A. Decato, E. A. John, V. Bryantsev, *Chem. Sci.* **2023**, *10*, 1039/D3SC02348F.
- [17] Y. Kobayashi, Y. Nakatsuji, S. Li, S. Tsuzuki, Y. Takemoto, *Angew. Chem. Int. Ed.* **2018**, *57*, 3646.
- [18] N. Tsuji, Y. Kobayashi, Y. Takemoto, *Chem. Commun.* **2014**, *50*, 13691.
- [19] F. Zapata, A. Caballero, P. Molina, I. Alkorta, J. Elguero, *J. Org. Chem.* **2014**, *79*, 6959.
- [20] See supporting information for further details.
- [21] R. Haraguchi, S. Hoshino, M. Sakai, S.-G. Tanazawa, Y. Morita, T. Komatsu, S.-I. Fukuzawa, *Chem. Commun.* **2018**, *54*, 10320.
- [22] a) U. Mayer, V. Gutmann, W. Gerger, *Monatsh. Chem.* **1975**, *106*, 1235; b) M. A. Beckett, G. C. Strickland, J. R. Holland, K. Sukumar Varma, *Polymer* **1996**, *37*, 4629.
- [23] a) K. M. Diemoz, A. K. Franz, *J. Org. Chem.* **2019**, *84*, 1126; b) Preliminary studies for thioureas with tri-*n*-butylphosphine oxide: A. R. Nödling, G. Jakab, P. R. Schreiner, G. Hilt, *Eur. J. Org. Chem.* **2014**, 6394.
- [24] a) R. J. Mayer, A. R. Ofial, H. Mayr, C. Y. Legault, *J. Am. Chem. Soc.* **2020**, *142*, 5221; b) Y.-P. Chang, T. Tang, J. R. Jagannathan, N. Hirbawi, S. Sun, J. Brown, A. K. Franz, *Org. Lett.* **2020**, *22*, 6647.
- [25] R. Wechsel, M. Žabka, J. W. Ward, J. Clayden, *J. Am. Chem. Soc.* **2018**, *140*, 3528.
- [26] A. Shukla, E. D. Isaacs, D. R. Hamann, P. M. Platzman, *Phys. Rev. B* **2001**, *64*, 052101.
- [27] a) A. P. Davis, S. M. Draper, G. Dunne, P. Ashton, *Chem. Commun.* **1999**, 2265; b) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416; c) L. A. Marchetti, L. K. Kumawat, N. Mao, J. C. Stephens, R. B. P. Elmes, *Chem.* **2019**, *5*, 1398.

- [28] Value obtained with onyl 3 equivalents of **15ae** instead of 10 equivalents, because of its low solubility. Varying the amount of compound to study seemed to have a minimal impact on the experiment since similar  $\Delta\delta(^{31}\text{P})$  values were obtained with 10 and 3 equivalents of **14ae**·**BAr<sub>4</sub><sup>-</sup>** (8.37 ppm against 8.33 ppm, respectively). For this reason, we are confident that the  $\Delta\delta(^{31}\text{P})$  of 6.64 ppm for **15ae** can be compared with those of the other ureas.
- [29] Obtaining those results required the use of a tripled amount of TEPO so that its signal in  $^{31}\text{P}$  NMR remains intense enough compared to the one of  $\text{PF}_6^-$ .
- [30] P. Thordarson, *Chem. Soc. Rev.* **2011**, *40*, 1305.
- [31] S. M. Walter, F. Kniep, L. Rout, F. P. Schmidtchen, E. Herdtweck, S. M. Huber, *J. Am. Chem. Soc.* **2012**, *134*, 8507.
- [32] a) Y. Takeda, D. Hisakuni, C.-H. Lin, S. Minakata, *Org. Lett.* **2015**, *17*, 318; b) M. Kaasik, A. Metsala, S. Kaabel, K. Kriis, I. Järving, T. Kanger, *J. Org. Chem.* **2019**, *84*, 4294.
- [33] a) S. M. Walter, F. Kniep, E. Herdtweck, S. M. Huber, *Angew. Chem. Int. Ed.* **2011**, *50*, 7187; b) S. H. Jungbauer, S. M. Huber, *J. Am. Chem. Soc.* **2015**, *137*, 12110.
- [34] The presence of **18** was detected by HMRS analysis of the reaction mixture. However, it could not be independently prepared to fully ascertain its structure. See supporting information for further details.
- [35] For other selected examples of the use of silylated nucleophiles to ensure XB catalyst turnover, see: a) F. Kniep, S. H. Jungbauer, Q. Zhang, S. M. Walter, S. Schindler, I. Schnapperelle, E. Herdtweck, S. M. Huber, *Angew. Chem. Int. Ed.* **2013**, *52*, 7028; b) M. Saito, N. Tsuji, Y. Kobayashi, Y. Takemoto, *Org. Lett.* **2015**, *17*, 3000.
- [36] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press: Oxford, 3<sup>rd</sup> ed., **1988**.
- [37] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Golberg, *Organometallics* **2010**, *29*, 2176.
- [38] Y. Zhao, S. R. Gilbertson, *Org. Lett.* **2014**, *16*, 1033.
- [39] M. Sarmah, A. Dewan, P.-K. Boruah, M.-R. Das, U. Bora, *Appl. Organomet. Chem.* **2020**, *34*, e5554.
- [40] K. Nozawa-Kumada, S. Kurosu, M. Shigeno, Y. Kondo, *Asian J. Org. Chem.* **2019**, *8*, 1080.
- [41] F. Jahani, M. Tajbakhsh, H. Golchoubian, S. Khaksar, *Tetrahedron Lett.* **2011**, *52*, 1260.
- [42] C. Mukai, M. Kobayashi, S. Kubota, Y. Takahashi, S. Kitagaki, *J. Org. Chem.* **2004**, *69*, 2128.
- [43] R. Bernárdez, J. Suárez, M. Fañanás-Mastral, J. A. Varela, C. Saá, *Org. Lett.* **2016**, *18*, 642.
- [44] T. Ema, D. Tanida, T. Matsukawa, T. Sakai, *Chem. Commun.* **2008**, 957.
- [45] Monocationic aggregates consisting of two iodoazolium cations and one bromide anions have been observed.
- [46] H. Wu, Handoko, M. Raj, P. S. Arora, *Org. Lett.* **2017**, *19*, 5122.
- [47] M. Ryuichi, A. Keisuke, *Tetrahedron* **2021**, *97*, 132381.
- [48] P. Manesiotis, A. Riley, B. Bollen, *J. Mater. Chem. C* **2014**, *2*, 8990.

Manuscript received: March 21, 2023

Revised manuscript received: November 13, 2023

Accepted manuscript online: November 15, 2023

Version of record online: April 3, 2024