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A halogen-bonding-catalysed Nazarov cyclisation reaction†

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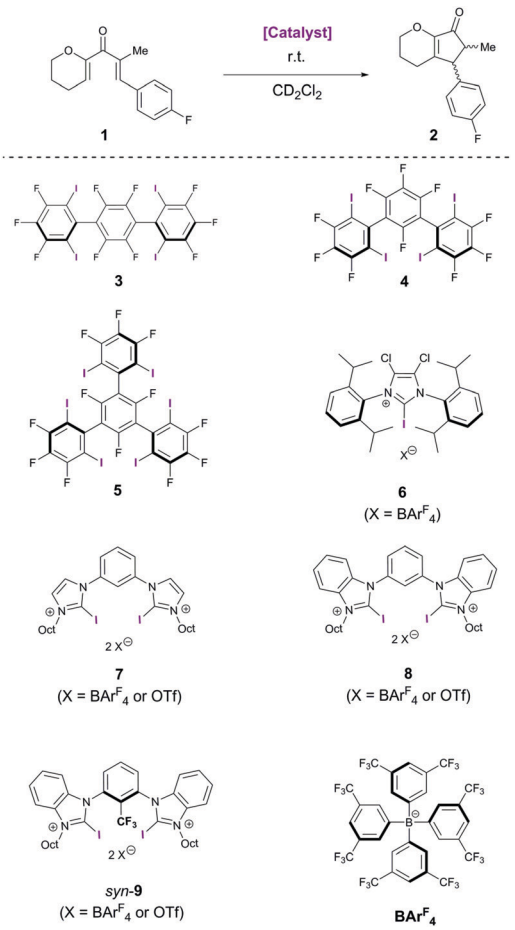
Various neutral, mono- and dicationic halogen bond donors were screened for their ability to act as catalysts in a Nazarov cyclisation reaction. Using a highly preorganized dicationic catalyst with a noncoordinating counterion proved essential for high activity.

The Nazarov cyclisation is a versatile method to obtain highly substituted cyclopentenones.[1] This carbon–carbon bond formation reaction, which involves 4π electrocyclization, is usually catalysed either by Brønsted or Lewis acids.[2] In recent years, several examples of organocatalysed Nazarov reactions have also been reported.[3–6] These cases include electrophilic phosphonium ions as non-metallic Lewis acids[3a] as well as enantioselective transformations with organoboron compounds,[3b] phosphoramide Brønsted acids[5] or bifunctional thiourea derivatives.[6] The latter represents, to the best of our knowledge, the only case of a hydrogen-bond-catalysed Nazarov reaction.

In recent years, halogen bonding[7] (XB) – the attraction between electrophilic halogen substituents and Lewis bases – has emerged as a promising noncovalent interaction for various applications in solution.[8] Its usage in organocatalysis is still relatively sparsely investigated.[8c,d,9] Next to several examples of XB-catalysed halide abstraction reactions, there are also a few cases involving the activation of neutral electrophiles by XB.[12–16] Most notably, imines/quinolines and carbonyl compounds have so far been addressed by XB donors in reduction,[12] Mukaiyama-aldol addition,[12c,16b] Michael addition[13b,14] and (aza) Diels–Alder reactions.[15,16] Still, however, these cases only include three examples of carbonyl activation, and thus the Nazarov cyclization represents a perfect further test reaction to study the intricacies of XB organocatalysis.

Herein, we investigate the catalytic activity of previously reported mono- and bidentate halogen bond donors, as well as of neutral polyfluorinated variants in the reaction depicted in Scheme 1. As the chemical shifts of the starting material (divinyl ketone **1**) and the product (cyclopentenone **2**) are clearly separated, the reaction can easily be monitored *via* ^{1}H-NMR spectroscopy.



Scheme 1 Nazarov cyclisation reaction and various XB donors as potential catalysts; Oct = *n*-octyl.

In the absence of any catalyst, no reaction occurs at room temperature. Similarly, no catalytic activity was observed even

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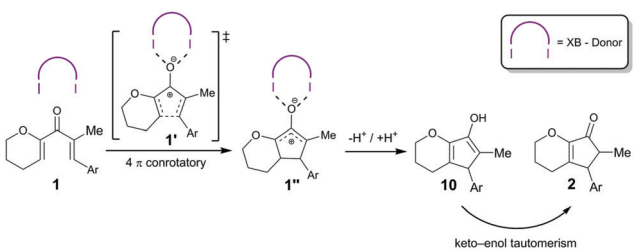
after a few weeks for the neutral multidentate polyfluorinated XB donors **3**, **4** and **5**, as well as for the monodentate cationic XB donor **6**. The inactivity of the former class of compounds, which are all active in halide abstraction reactions,[10] illustrates the additional challenges associated with the activation of neutral substrates like divinyl ketones. As the reaction seemed to require stronger Lewis acids as catalysts, bidentate cationic XB donors were studied next. These were successfully used in a Diels–Alder and a Michael addition reaction,[14,15] and in both cases a strong influence of the counterion was observed: satisfactory performance could only be achieved with noncoordinating anions like tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate ($\mathbf{BAr^F_4}$) but not with counterions like triflate. Somewhat surprisingly, however, the triflate as well as the $\mathbf{BAr^F_4}$ salt of bis(imidazolium) derivative **7** showed no catalytic activity in this reaction – despite their earlier mentioned success in carbonyl activation reactions. Apparently, the Lewis acidity of these compounds is too low to allow sufficient reduction of the activation barrier, and thus the more electrophilic bis(benzimidazolium) derivatives **8** and **9** were investigated. The triflate salt of the direct benzimidazolium analogue, **8/OTf**, leads to hardly noticeable formation of product **2** ($\leq$5%) after 5 hours (Table 1).[17]

The corresponding $\mathbf{BAr^F_4}$ salt, on the other hand, showed a markedly increased performance (full consumption of **1** after 2 h with 5 mol% catalyst), which is in line with the noncoordinating nature of this counterion. In the ^{1}H-NMR spectra of the reaction, next to the chemical shifts of starting material **1** and product **2**, an additional set of signals was observed over time, which likely correspond to enol **10** (see Scheme 2 and the ESI†). An example for such spectra (with compound ***syn*-9/OTf** as a catalyst) is depicted in Fig. 1.

Table 1 Performance of catalyst candidates

Cat. (mol%)	Yield of 10 (5 h)	Yield of 2 (5 h)[a]	*cis*/*trans* ratio of 2[a]
None	—	—	—
3–7 (5)	—	$\leq$5%	—
8/OTf (5)	<5%	$\leq$5%	—
8/BAr$^F_4$ (5)	71%	26%	3 : 1
***syn*-9/OTf** (5)	70%	23%	2.3 : 1
***syn*-9/BAr$^F_4$** (5)	20%	65%	2 : 1
11–13 (5)	—	—	—
HOTf (1)	—	$\geq$95%	6.5 : 1
I_2 (5)	—	$\geq$95%[b]	23 : 1[b]
***syn*-9/OTf** (5)[c]	6%[c]	90%[c] (80%)[d]	2.3 : 1

c(**1**) = 15.4 mM in CD_2Cl_2. [a] Determined by ^{1}H NMR. [b] After 1 h. [c] c_0(**1**) = 655.4 mM in CD_2Cl_2 and reaction time 12 h. [d] Isolated yields.



Scheme 2 Postulated mechanism of the halogen bond catalysed Nazarov reaction.

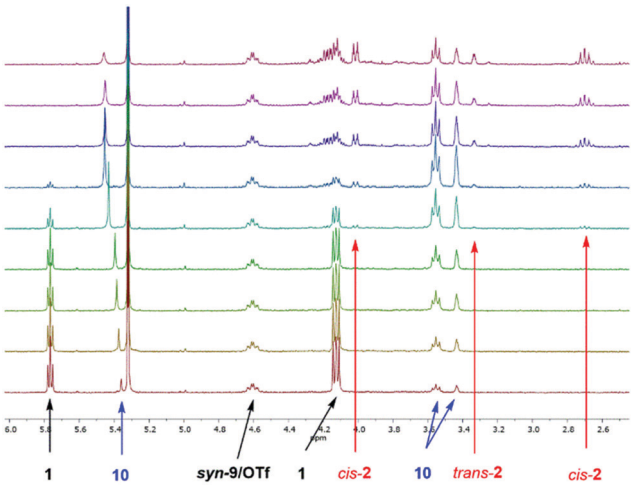


Fig. 1 Selected section of the ^{1}H-NMR kinetics in CD_2Cl_2 of the Nazarov reaction (c_0(**1**) = 15.4 mM) catalysed by XB Donor ***syn*-9/OTf** (10 mol%). The ^{1}H-NMR signals of the corresponding compounds **1**, **2**, ***syn*-9/OTf** and enol **10** are marked with arrows.

Since we postulate that halogen bonding will only influence the initial step (electrocyclization) of the overall reaction, but not the following keto–enol tautomerization (see Scheme 2), the analysis will first focus on the rate acceleration of the electrocyclization (which can be conveniently monitored *via* the consumption of starting material **1**). The kinetic profile of this step in the presence of catalysts **8** or **9** is shown in Fig. 2.

It becomes immediately apparent that the better performance of **8/BAr$^F_4$** *vs.* **8/OTf** in overall product formation is also observed in the electrocyclization step. The Lewis acidity of these bidentate XB donors can be further increased by the introduction of a trifluoromethyl group in the central benzene core,[11] which prevents rotation of the XB-donating moieties and allows the isolation of preorganized *syn*-atropisomer **9**. The superior performance of **9** *vs.* **7** in a halide abstraction case[11] and a Michael addition reaction has been demonstrated before.[14]

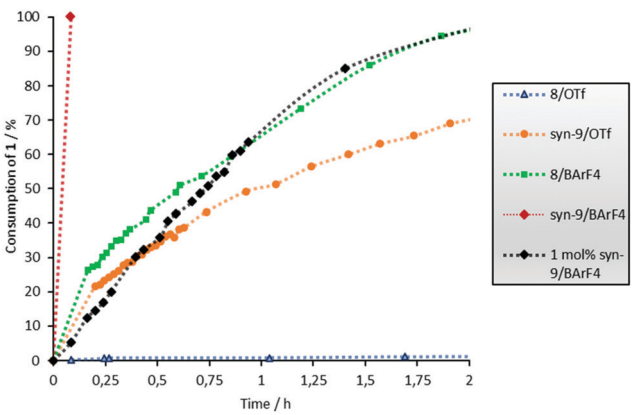


Fig. 2 Consumption of **1** *versus* the time profile of the Nazarov cyclisation with 5 mol% catalyst (unless noted otherwise) and c_0(**1**) = 15.4 mM. No reaction without a catalyst and with compounds **3–7** and **11–13**. The error is approximately 5%.

A strong effect of this preorganization was also found in the Nazarov reaction: triflate salt ***syn*-9/OTf** showed a markedly better performance compared to its almost inactive analogue **8/OTf** (70% *vs.* 2% consumption of **1** after 2 h, see Fig. 2). As expected, the highest catalytic activity was achieved with the $\mathbf{BAr^F_4}$ salt ***syn*-9/$\mathbf{BAr^F_4}$** – in less than 5 min, and the complete conversion of starting material **1** to enol **10** was observed with only 5 mol% of the catalyst. A reasonable kinetic profile of the electrocyclization step could only be obtained after reducing the amount of catalyst to 1 mol% (Fig. 2). In all cases mentioned so far, the *cis*/*trans* ratio of product **2** was in the range between 2 : 1 and 3 : 1 (Table 1).

Thus, the two key parameters to increase the performance of **8/OTf** are the change of the counterion to $\mathbf{BAr^F_4}$ and the introduction of preorganization. Closer inspection of Fig. 2 indicates that the former has a larger impact: exchanging the counterion provides a more active catalyst (**8/$\mathbf{BAr^F_4}$**, green line) compared to the more preorganized one with the same counterion (***syn*-9/OTf**, orange line).

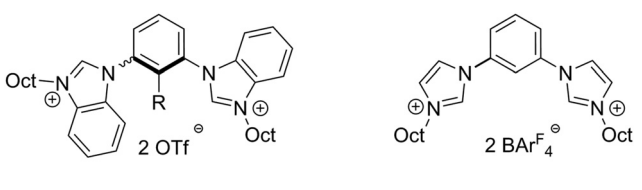
In order to establish whether the observed activity was in indeed due to halogen bonding, non-iodinated compounds **11**, **12** and **13** were also tested as catalysts (Fig. 3). Even though they share all structural features except the iodine substituents with catalysts **7–9**, none of them showed any activity. Consequently, activation by hydrogen bonding or electrostatic interactions can be ruled out.

Two possible catalytically active decomposition products of the XB donors are elemental iodine and acid traces. A comparison experiment with 5 mol% of elemental iodine showed that it indeed induces quantitative product formation after 30 minutes.[18] The exact origin of this activity is not entirely clear, as elemental iodine has several pathways (XB, hidden acid catalysis[19] or iodonium formation) to activate organic molecules.[20] It is, however, very unlikely that the observed activity of XB donors **8** and ***syn*-9** is due to the decomposition to elemental iodine, for various reasons: (a) no spectroscopic evidence of decomposition was obtained (only one ^{19}F signal was observed in the case of ***syn*-9** after the reaction); (b) the consumption of the starting material follows sigmoidal kinetics with 0.1 mol% of iodine (see Fig. S8 in the ESI† and compare Fig. 2 for **8** and **9**); and (c) a drastically different *cis*/*trans* ratio of product **2** (23 : 1) was found with elemental iodine.

Likewise, addition of 1 mol-% of HOTf triggered full conversion of compound **1** to product **2** within 1 hour. The kinetic profile of the acid-catalysed reaction, however, is entirely different from the ones observed for catalysts **8** and ***syn*-9**, in which the enol is accumulated (see the ESI†). In addition, the *cis*/*trans* ratio of product **2** is once again markedly different (6.5 : 1). As a consequence, catalysis by elemental iodine or acid traces – either as impurities or decomposition products – appears very unlikely and the mode of activation is most probably halogen bonding.

Even though the focus of this study was on the electrocyclization step, it is noteworthy that the rate of the keto–enol tautomerization was apparently not significantly influenced by the catalysts. Also, in some cases the rate of formation of cyclopentenone **2** decreases significantly after full consumption of starting material **1** (see Fig. 4).

Finally, the nature of XB catalysis in this reaction was also investigated by DFT calculations using the M06-2X functional,[21] Grimme D3 dispersion corrections[22] and the def2-TZVP(D) basis set.[23] The corresponding transition state of the Nazarov cyclisation of substrate **1** with a truncated version[24] of XB donor ***syn*-9** is shown in Fig. 5.



11 (R = H)
12 (R = CF_3)

13

Fig. 3 Structures of reference compounds.

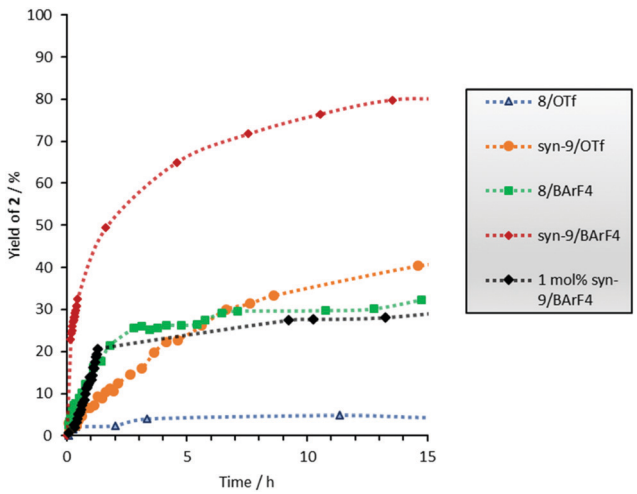


Fig. 4 ^{1}H-NMR yield *vs.* time profile for the formation of cyclopentenone **2**. The error is approximately 5%. c_0(**1**) = 15.4 mM.

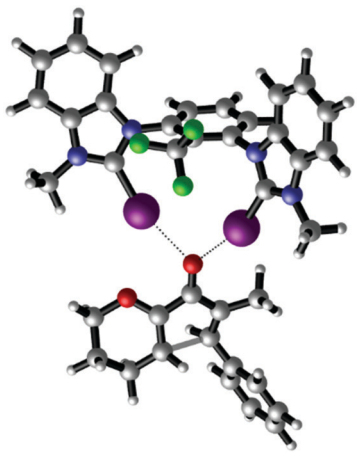


Fig. 5 DFT-calculated transition state structure of the Nazarov cyclisation catalysed by halogen bond-donor ***syn*-9** (M06-2X D3 def2-TZVP(D)).[25] Selected distances [Å] and angles [°]: I–O 2.68 and 2.69; C–I–O 162 and 164. Graphic generated using CYLview.[26]

The optimized geometry features a clear bidentate binding to the carbonyl oxygen with iodine–oxygen bond distances of 2.68 Å and 2.69 Å. The corresponding barrier of activation (corrected with the SMD18[25] intrinsic solvent model for dichloromethane) is 26.4 kcal mol^{-1}. This result is in good agreement with the experimental findings. The barrier for the uncatalysed Nazarov cyclisation (33.1 kcal mol^{-1}) is significantly higher.

In conclusion, the first halogen-bonding-catalysed Nazarov cyclisation reaction was reported, which is also just the 4th example of carbonyl activation by this interaction. The catalytic activity could be clearly traced back to halogen bonding *via* comparison experiments. The effect of counterion exchange and preorganization was investigated and compared, and strong performance could only be achieved by a combination of both. In fact, it seems that this reaction is the most challenging one activated by halogen bonding so far (as **7**/$\mathbf{BAr^F_4}$ did not show any effect in contrast to all examples reported earlier).

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Conflicts of interest

There are no conflicts to declare.

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18 Lower amounts of iodine lead to sigmoidal kinetics, see Fig. S8 in the ESI†.

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