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Organocatalysis by a multidentate halogen-bond donor: an alternative to hydrogen-bond based catalysis†

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A charge neutral iodoethynyl-based multidentate halogen-bond donor was synthesized and successfully utilized as an organocatalyst in a benchmark Ritter-type solvolysis reaction. The catalytic activity was monitored using ^{1}H NMR spectroscopy and several control experiments were systematically carried out in order to rule out hidden catalysis based on other functional groups.

Introduction

In organocatalysis, small organic molecules are employed in order to facilitate covalent transformations, and the emergence of such processes has a played a significant role in chemical synthesis over the last two decades.[1,2] The activation of substrates and reactants through organocatalysis is often classified into[3,4] covalent and non-covalent catalysis.[5] In the latter category, hydrogen bonding is the most well-established interaction[3,4,6] and, furthermore, most reported hydrogen-bond (HB) based organocatalysts are bidentate. Halogen bonding can be considered a close kin of hydrogen bonding and there are many examples of structural similarities between hydrogen and halogen bonding in crystal engineering and supramolecular chemistry.[7–10] Despite the fundamental correspondences between the two interactions, there have been very few reports on the use of halogen-bond based systems in homogenous organocatalysis.[11–16] From a structural point of view, halogen bonds are marginally more directional than hydrogen bonds, which is due to the enhanced repulsion of halogen atom lone pairs with the Lewis base at obtuse angles. Also, halogen bonds are ostensibly very tunable[17] since three different atoms are capable of acting as donors (Cl, Br, and I).[15,18–20] Furthermore, by introducing electron-withdrawing groups (typically fluorine atoms), or by changing the hybridization of the carbon atom to which the halogen-bond (XB) donor is attached, it is possible to modify the magnitude of the σ-hole. In the context of catalysis, since polyfluorinated halogen-bond donors are relatively non-polar, they may be used for applications that rely on low polarity, whereas hydrogen-bond based systems may not be suitable in such situations.[21] Finally, since hydrogen and iodine atoms reside at opposite ends of the periodic table, there is a significant difference in size, orbital energy, polarizability and consequently hydrogen-bond and halogen-bond based systems can be deployed for different classes of Lewis bases in organocatalysis.[15]

Mono and multidentate halogen-bond donors can both be used as Lewis acidic activators of suitable substrates; however the latter are often advantageous as they tend to bind more strongly to the substrate and create a more stable activated complex. In the anion-bonding approach, halogen-bond donors interact with a leaving anion which is formed during an S_N1 reaction. With the removal of the anion, the reaction is accelerated but the liberated anion may bind so strongly to the halogen-bond donor that there is risk of catalyst inhibition; in short, catalytic transformation requires special reaction design.[15] Even though XB-based organocatalysis could offer new avenues for effective organic synthesis, only a small number of multidentate halogen-bond donors have been examined in this context. The synthesis and design remain challenging and therefore halogen-bond-based catalysis is still an emerging area. In some early studies, confirmation of activation of substrates through halogen bonding was not clearly established since hidden acid catalysis could not be ruled out and the exact mode of action was not properly understood.[22,23] However, Huber and co-workers have provided convincing evidence for catalysis purely based on halogen-bond donors, by successfully ruling out other possible substrate activations. They synthesized both cationic and neutral halogen-bond donors which were subsequently applied to many benchmark reactions in order to examine the catalytic effects of halogen-bond donors.[14,15,24,25]

Although the first steps in halogen-bond based catalysis have been taken, it is clear that many potentially useful molecular fragments have yet to be explored in this context. In the work reported herein, we have employed our knowledge on halogen-bond

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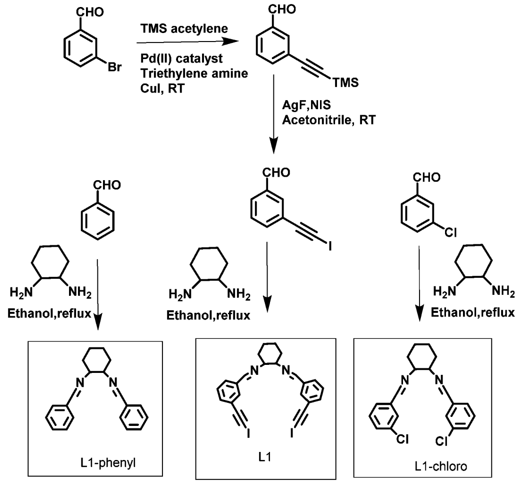


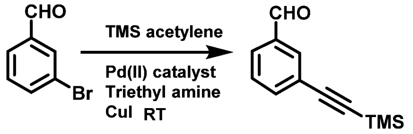
Fig. 1 Reaction scheme for the synthesis of the catalyst, **L1**, and the control molecules, **L1-phenyl** and **L1-chloro**. Experimental details for the synthesis are provided in the ESI.†

based supramolecular synthons in the design of a charge-neutral halogen-bond-based catalyst. Our goals were to develop a new catalytic system, examine its activity in a benchmark reaction through an anion recognition mechanism, and then to eliminate any possible hidden catalysis within the system. It has previously been demonstrated that the iodo ethynyl group is a very capable halogen-bond donor,[26–28] and the catalyst presented herein uses two such activated moieties. In order to give the catalyst the potential for acting in a bifunctional manner, the two XB-donors were attached to a 1,2-diaminocyclohexane backbone using simple Schiff-base chemistry, Fig. 1. In addition to the catalyst, we also prepared two control molecules which were required in order to establish the true origin of any catalytic activity.

Experimental

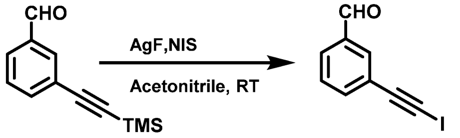
All chemicals were purchased from available commercial sources and used without further purification. ^{1}H NMR data were recorded using a Varian Unity plus 400 MHz spectrophotometer in CDCl$_3$. IR spectroscopy was carried out on a Nicolet 380 FT-IR. Melting points were measured on Fisher-Johns melting point apparatus. The synthesis of **L1** was achieved in three steps.

Synthesis of 3-((trimethylsilyl)ethynyl)benzaldehyde



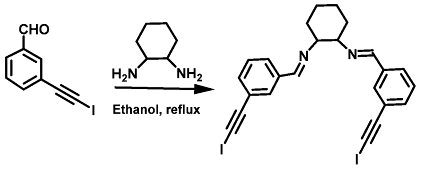
To a one-neck round-bottom flask equipped with a stir bar, 3-bromobenzaldehyde (1.89 mL, 0.0162 mmol) and 150 mL of triethyl amine were added and degassed with nitrogen gas for 20 min. To the reaction mixture bis(triphenylphosphine)palladium(II) dichloride (0.113 g, 0.162 mmol) and CuI (0.0600 g, 0.324 mmol) were added followed by the addition of trimethylsilyl acetylene (2.5 mL, 0.0178 mol). Nitrogen gas was bubbled through the mixture for an additional 30 min until the reaction medium was saturated and the reaction was stirred at room temperature for 24 hours. Upon the completion of the reaction (confirmed by TLC), the solvent was removed by rotary evaporator. The resulting solid was extracted in CHCl$_3$, washed with brine and dried over anhydrous MgSO$_4$. The organic layer was removed in a rotary evaporator and the pure product was obtained as a brown liquid (43%) after column chromatography with hexane. (^{1}H NMR, CDCl$_3$, δH) 9.98 (s 1H), 7.96 (s 1H), 7.81 (d 1H) 7.69 (d 1H) 7.47 (t 1H).

Synthesis of 3-(iodoethynyl)benzaldehyde



To a one-neck round-bottom flask equipped with a stir bar, 3-trimethylsilyl benzaldehyde (1.4 g, 6.9 mmol) and 0.87 g (6.9 mmol) of silverfluoride were added followed by the addition of 75 mL of acetonitrile. The flask was then wrapped with aluminium foil and the stirring was continued for 24 h. The reaction mixture was then passed through a silica plug using acetonitrile and concentrated using a rotary evaporator. The resulting solid was then extracted in diethyl ether and washed with water. After concentration, pure yellow color product was obtained in 88% yield. (1.50 g) m.p. 95–100 °C, (1H NMR, CDCl$_3$, δH) 9.99 (s 1H) 7.94 (d 1H) 7.82 (d 1H) 7.68 (9d 1H) 7.51 (t 1H).

Synthesis of *N*,*N*′-(cyclohexane-1,2-diyl)bis(1-(3-iodoethynyl)-phenylmethanimine) (L1)



To 0.068 g (0.60 mmol) of 1,2-diaminocyclohexane, 100 mL of ethanol was added and heated to 70 °C for 10 min. To this a solution of 3-(iodoethynyl)benzaldehyde (0.30 g, 1.2 mmol) was added and heated under reflux for 2 h. The reaction mixture was cooled, and the volume was reduced to half using a rotary evaporator. To the reaction 200 mL of water was then added to induce precipitation. The resulting solid was filtered and redissolved in 120 mL of methylene chloride, washed with distilled water and brine. The organic layer was evaporated and the resulting brown solid was collected in 60% yield. M.p 60–65 °C (^{1}H NMR, DMSO-d6 δH) 8.18 (s 1H) 7.62 (d 2H) 7.41(d 1H) 7.34 (t 1H) 3.18 (s 1H) 15–1.8 (m 5H).

Detailed synthesis of control molecules **L1-chloro** and **L1-phenyl** are listed in the ESI.†

Results and discussion

Once the catalyst and the control molecules were synthesized and fully characterized, catalytic activity was explored using a

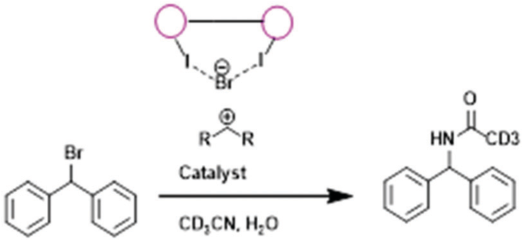


Fig. 2 Ritter type solvolysis reaction through halide abstraction.

benchmark Ritter-type solvolysis reaction. The choice of reaction was informed by the elegant work by Huber and co-workers, which demonstrated that solvolysis of benzhydryl bromide is ideally suited for identifying catalytic activity involving halide abstraction, Fig. 2.[15] In this reaction, acetonitrile is used both as a solvent and as a nucleophile and the intermediate nitrilium ion reacts with traces of water in the solvent to form *N*-benzhydryl acetamide.

Since no additional reagents are required, side reactions can be excluded, and this provides an optimal environment wherein to study halogen-bond based catalysis. However, during the reaction, weakening of the C–Br bond can take place as a result of a required C–I···Br$^-$ halogen bond, and in extreme situations this may lead to heterolytic cleavage. An additional driving force for the reaction would arise if the complex formed between the halogen-bond donor and the halide anion were insoluble. As a result, it is then possible that the halogen-bond donor (catalyst) is no longer available for further substrate activity and thus stoichiometric amounts of catalyst will be required. Catalytic activity and product formation was determined using ^{1}H NMR spectroscopy by measuring the ratio of the product peak (literature value appears around 6.15–6.30 ppm) to the peak of the starting material, (singlet at 6.45 ppm), however based on the specific catalyst–substrate interaction, the position of the product peak can vary slightly,[25,29] and in our experiment a new peak appeared around 5.77 ppm. No measurable amount of product was formed in the absence of a catalyst even after 96 h (ESI†). According to the NMR data, the addition of **L1** (100% loading) resulted in 90% conversion of starting material to the product after 96 h, and no side products or decomposition products of **L1** could be detected. When 10% of **L1** was added, the product conversion was 33% and with 20% addition this was increased to 63% conversion. This observation confirms the stoichiometric effect of the catalyst during the reaction progress, Fig. 3, and Table 1.

Analysis of the catalytic activity at different time intervals showed that activity reached its maximum after 96 h. Extending the reaction time did not increase the yield.

During the reaction progress, we noticed the formation of a precipitate and we surmised that the halogen-bond donor might not be available for further reactivity. This assumption was further supported by the stoichiometric usage of the catalysts and ^{1}H NMR analysis of the precipitate confirmed the presence of the peaks associated with the catalyst. These results were confirmed by three repetitive experiments.

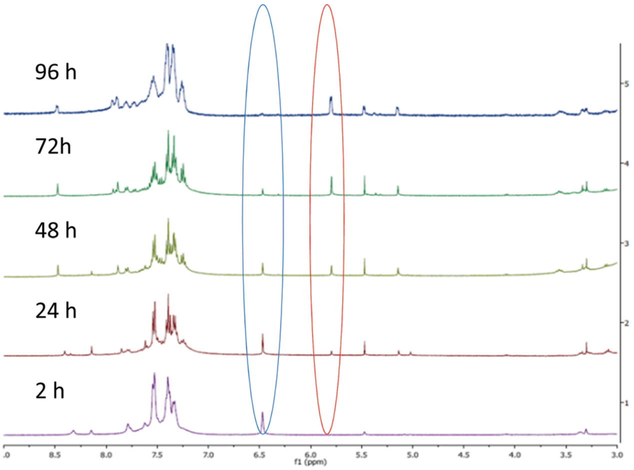


Fig. 3 Reaction progress of **L1** with change of time; and with 100% stoichiometric loading, blue circle represents the changes of the starting material and the red circle shows the product formation.

Table 1 Reaction progress over the time with changes of the catalytic amount

	^{1}H NMR yields (%)		
Amount of **L1**	24 h	48 h	96 h
10%	21.6 ± 0.9	32.5 ± 1	33 ± 1.7
20%	25.6 ± 1.8	38.3 ± 1.5	63 ± 2.8
100%	33 ± 2	66 ± 2.6	90 ± 3.4

Since **L1** possesses considerable torsional flexibility, there is obviously no guarantee that it exclusively engages with an anion in a 'chelating' manner, Fig. 4.

However, both of the two postulated arrangements produce two halogen bonds to the anion (in motif II), each anion would act as a halogen-bond acceptor for two different molecules. Despite extensive efforts using slow evaporation, vapour diffusion and solvent diffusion techniques we were unable to grow crystals suitable for single-crystal diffraction of an **L1**-anion containing solid. Motif I should be slightly favoured due to entropic effects, but it is more likely that **L1** acts as a bridge between anions.

Control experiments with (a) a non-halogenated and (b) an a very weak halogen-bond donor were also performed to confirm

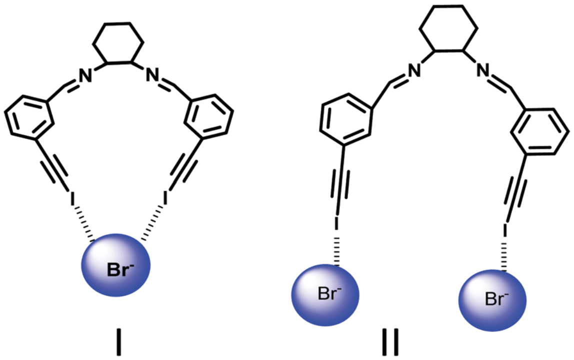


Fig. 4 Two postulated modes of interaction between **L1** and a bromide ion.

that the source of the catalytic activity is halogen bonding. When the reaction was carried out for 96 h in the presence of a stoichiometric amount of **L1-phenyl**, less than 5% of product was detected. Similar results were found when the reaction was performed in the presence of **L1-Chloro** using the same reaction conditions. The appearance of additional peaks suggests that both **L1-phenyl** and **L1-chloro** decompose during the reaction and have no effect on the catalytic activity (see ESI†). In theory, if acetonitrile was hydrolyzed in the presence of **L1**, it could generate acetamide which, over time, could react with benzhydryl bromide. However, this possibility was discounted since no acetamide was detected even when **L1** was kept in acetonitrile for several days. Since we used a Schiff base approach for synthesizing the catalyst, we could not use acids as a control to rule out any hidden acid catalysis in the reaction (imine bonds are susceptible hydrolysis). However, Huber and co-workers used 5% HOTf for Ritter-type solvolysis of benzhydryl bromide and confirmed that there is a very little effect ($<$25% yield) and therefore the catalytic activity can be attributed to halogen bonding. In the same study they confirmed that the HBr generated during the reaction is not active in an autocatalytic way.[25] Consequently we can confidently state that the results obtained with **L1** demonstrate that halogen bonding is responsible for the catalytic activity.

Conclusions

We have demonstrated that a charge-neutral ditopic iodo-ethynyl based halogen-bond donor molecule can act as a stoichiometric catalyst in a bench mark Ritter-type solvolysis reaction. Several control experiments have allowed us to rule out any possible hidden organo-catalytic mechanism. Once the reaction conditions were optimized, we were able to obtain a 90% yield of the desired product, whereas in the absence of catalyst, less than 5% of product was detected. Although the exact structure of any activated complexes is still unknown, we believe that this work represents an important first step towards a new molecular framework where structural rigidity and halogen-bond ability can be refined such that catalytic activity can be optimized for a range of different transformations.

Conflicts of interest

There are no conflicts to declare.

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