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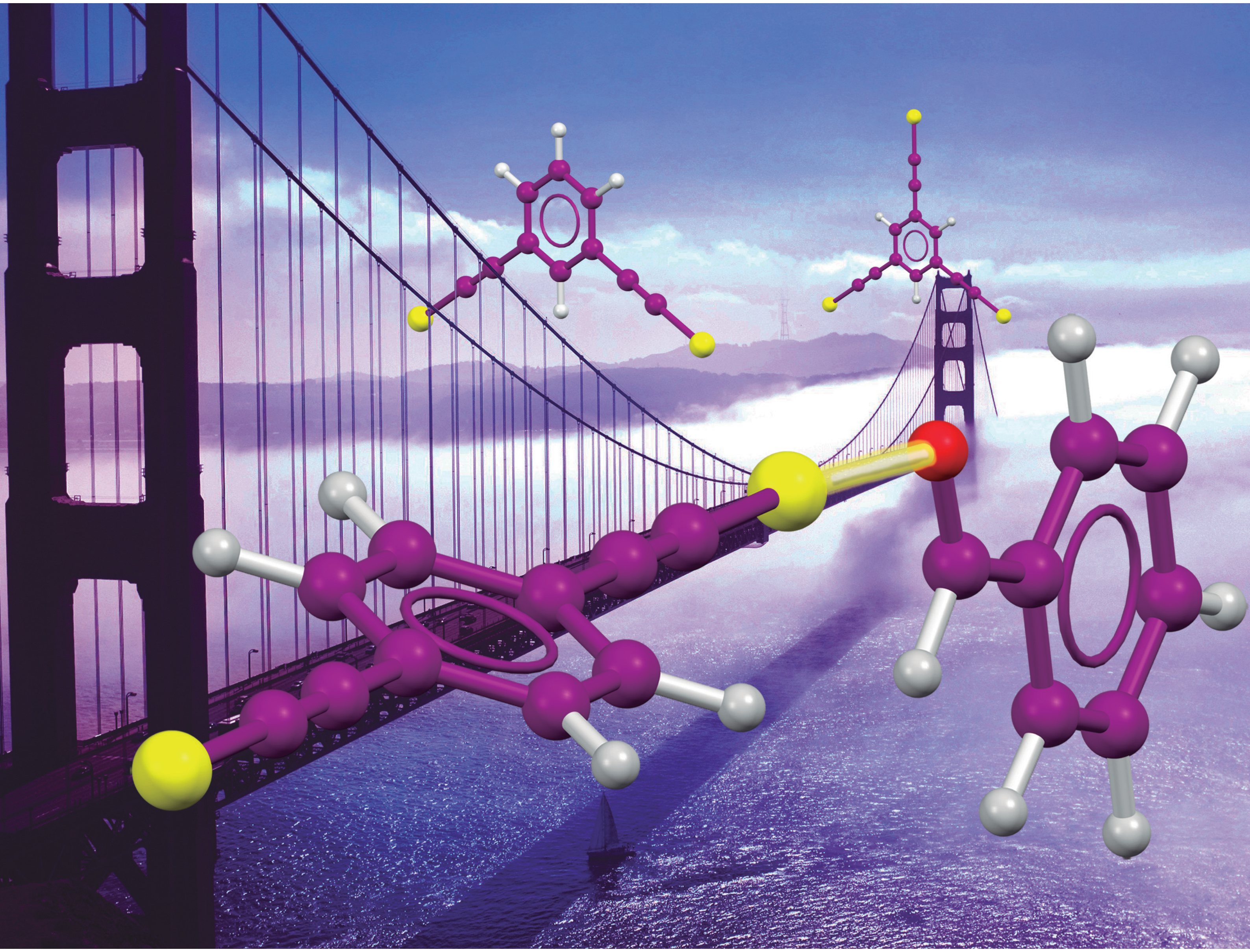

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Simple iodoalkyne-based organocatalysts for the activation of carbonyl compounds†

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A novel approach for the formation of bisindolylmethane derivatives (BIMs) is described as a proof of concept to evaluate the catalytic capacity of iodoalkynes. The use of these derivatives is reported as an example of simple halogen bond-based organocatalyst. This kind of activation has not been used before for the synthesis of bisindolylmethane derivatives **3**. Interestingly, the preparation of 3-(1*H*-indol-3-yl)-1-phenylbutan-1-one (**8**) has been also achieved for the first time with an iodoalkyne derivative. We prove the efficiency of this family of new catalysts by developing a simple and easy operational methodology, opening the door to the development of alternative catalysts in the area of halogen bond-based organocatalysts.

Introduction

Along the years, the search for new kinds of interactions or modes of activation has fascinated chemists and has been the focus of research of many scientific groups. Among the variety of non-covalent interactions, where normally hydrogen bonds occupy a privileged place,[1] more recently halogen bond (XB) interactions have been making space as an alternative tool.[2] Their use as Lewis acid activating Lewis bases has been recently explored in the literature.[3] In contrast, during the past two decades, many applications of halogen bonding in fields as diverse as crystal engineering, enantiomer separation, biology, and supramolecular architectures have been reported and reviewed.[4–6]

In comparison, the use of XB in organocatalysis remains underexplored. Since 2008 when Bolm reported an example of perfluoroiodoalkanes as an XB catalyst,[7] positively charged iodo heterocycles such as imidazolium,[8] 1,2,3-triazolium[8e,9] and pyridinium[9a,10] or neutral halogen bond donors have been used as catalysts in a variety of organic transformations. The most common neutral XB-donor scaffolds typically contain iodopolyfluoroaromatic moieties,[11] although *N*-iodosuccinimide, *N*-iodosaccharin,[12] and tetrabromomethane,[13] have also been used.

Halogen atoms bound to carbon, nitrogen or halide atoms show a positive electrostatic potential end-cap, *i.e.*, a σ-hole, that interacts with Lewis bases by halogen bonding.[14] Moreover, halogen atoms can be activated to participate in halogen bonding by introducing electron-withdrawing groups into the molecular backbone.

Haloalkynes have a well-established role in synthetic organic chemistry[15] but their application as halogen bond donors is less well developed despite their long history.[16] Theoretical, statistical and crystallographic studies demonstrate that the sp hybridization of the carbon atom adjacent to the halogen allows the ethynyl-based iodine atom to display a polar σ-hole.[17] The maximum positive value of calculated electrostatic potential ($V_{\mathrm{s,max}}$) of 1,4-bis(iodoethynyl)benzene is 25.2 kcal mol^{-1} and is similar to those of strong XB donors such as 1,4-diiodo-tetrafluorobenzene (25.9 kcal mol^{-1}), which is one of the most widely used halogen bonding donors. Therefore, haloalkynes can form strong, directional and selective halogen bonds, which makes them suitable for being used as organocatalysts.[18,19] Moreover, iodoalkynes are stable towards nucleophiles and elevated temperatures and easily accessible from terminal alkynes,[20] which allows to modify the number and arrangement of halogen bond donors, their solubility and their rigidity or flexibility among other characteristics. However, to the best of our knowledge, there is only one example where a perfluorinated iodoethynyl compound has been used as a catalyst.[20] Therefore, more contributions in this new field could be of great interest.

Indole is a privileged structural core present in many natural products and biological systems[21] and its use in drug discovery has grown over the past decades.[22] Consequently, considerable attention has been focused on the development of new synthetic[23] and catalytic[24] methods, leading to more complex indole structures. Moreover, indole is the structural unit of bisindolylmethane derivatives (BIMs), many of them

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isolated from marine natural sources.[25] This family of indoles discloses a range of biological properties such as antibacterial, antifungal, antimicrobial, anti-inflammatory or antitumor, among others.[26]

Inspired in our own experience in the field of organocatalysis[27] using hydrogen bond-based catalysts, we focused our attention on the activation of aldehydes for the production of bisindoles[28] using iodoalkyne derivatives (non-perfluorinated) as promising catalysts for the first time in the literature.

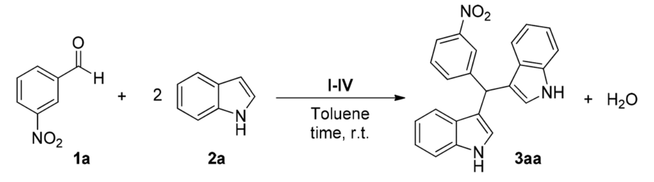
Results and discussion

Recently, several mild and convenient methods have been developed to prepare haloalkynes, most of them from terminal alkynes.[9a,15] Among them, we have used the electrophilic iodation of terminal alkynes with *N*-iodosuccinimide (NIS) and an Ag(I) catalyst[29] due to the mild reaction conditions required, high efficiency, and simple manipulation. Organocatalysts **I–IV** were obtained with yields in the range of 63 to 82% from the corresponding terminal alkynes (Scheme 1).[18] The precursors to synthesise **I** to **III** are commercially available and the precursor for **IV** was directly prepared through esterification reaction of 1,3,5-benzenecarbonyl trichloride with 2-propyn-1-ol.[30]

In order to further evaluate the viability of our work hypothesis, the efficiency of halogen bond-based organocatalysts **I–IV** was first tested in the model reaction between indole (**2a**) and 3-nitrobenzaldehyde (**1a**). Interestingly, the synthesis of bisindole **3aa** was successful in all cases. First, the activity of catalysts **I–IV** was evaluated in CH_2Cl_2. Although the reaction worked well in all cases (Table S1,† entries 1–4), it was noted that small loss of solvent through evaporation could be accelerating the reaction and the results could be misleading. Therefore, in order to prevent this problem, toluene was tested as a solvent. In this case, catalyst **I** successfully activated bisindole **3aa** formation better than the other three catalysts (Table 1, entry 1).

Although other more polar solvents were also tested, such as acetonitrile, THF, dioxane and ethyl acetate (Table S1,† entries 5–8), they led to reaction quenching or lower yields. This finding is not surprising since polar solvents typically disrupt the activating catalyst⋯substrate XB interactions easier than nonpolar solvents such as toluene. Using toluene and catalyst **I** in the model reaction, an optimization of different reaction conditions was carried out (Table 2).

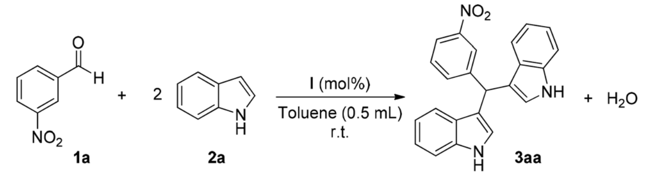
Table 1 Screening of catalysts **I–IV**[a]



Entry	Catalyst	Time (days)	Yield[b] (%)
1	**I**	2	98
2	**II**	3	89
3	**III**	5	92
4	**IV**	2	54

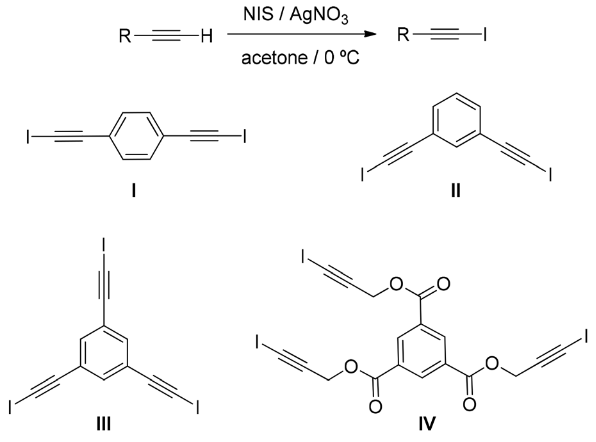
[a] Experimental conditions: To a mixture of catalyst **I–IV** (0.03 mmol) and aldehyde **1a** (0.1 mmol) in toluene (250 μL), indole (**2a**) (0.4 mmol, 2 equiv.) was further added at room temperature. After the reaction time, adduct **3aa** was isolated by column chromatography (hexane : AcOEt 8 : 2). [b] Isolated yield.

Table 2 Screening of the best reaction conditions using catalyst **I**[a]



Entry	**I** (mol%)	Indole **2a** (mmol)/equiv.	Time (days)	Yield[b] (%)
1	30	0.4/2	2	98
2	30	0.3/1.5	2	98
3	30	0.2/1	2	47
4	30[c]	0.2/1	2	74
5	20	0.4/2	2	98
6	20[c]	0.4/2	2	98
7	20[c]	0.3/1.5	2	98
8	20[c]	0.2/1	2	35
9	10	0.4/2	5	77
10	—	0.4/2	2	n.r.[d]

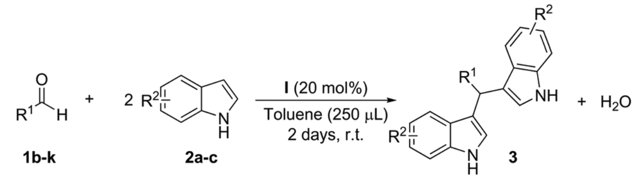
[a] Experimental conditions: to a mixture of catalyst **I** (30–0 mol%) and aldehyde **1a** (0.1 mmol) in toluene (0.5–0.25 mL), indole (**2a**) (0.4–0.2 mmol) was further added at room temperature. After the reaction time, adduct **3aa** was isolated by column chromatography (hexane : AcOEt 8 : 2). [b] Isolated yield. [c] 0.25 mL of toluene. [d] No reaction observed.



Scheme 1 Synthesis of iodoalkynes **I–IV**.

Reactions were stopped after two days to allow for a better comparison of the yields obtained; however, reactions using 2 and 1.5 equivalents of indole **2a** (0.4 mmol or 0.3 mmol) with 20–30 mol% of catalyst were probably completed before the reaction time employed (Table 2, entries 1, 2, 5, 6 and 7). The results showed that 20 and 30 mol% of catalyst lead to similar yields while 10 mol% of catalyst affords lower yields. Also,

Table 3 Scope of the reaction for the synthesis of bisindoles **3**[a]



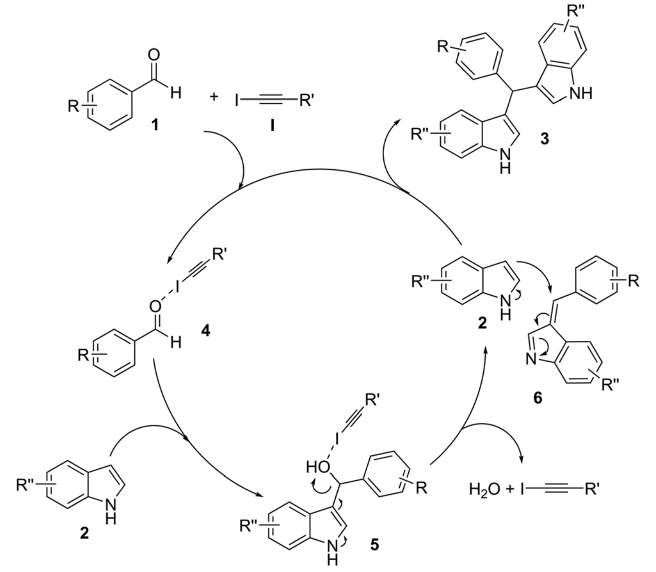
Entry	Aldehyde	Indole	Product	Yield[b] (%)
1	4-NO_2Ph (**1b**)	H (**2a**)	**3ba**	98
2	4-CNPh (**1c**)	H (**2a**)	**3ca**	95
3[c]	4-ClPh (**1d**)	H (**2a**)	**3da**	95
4[c]	4-BrPh (**1e**)	H (**2a**)	**3ea**	85
5	3-ClPh (**1f**)	H (**2a**)	**3fa**	89
6	3-BrPh (**1g**)	H (**2a**)	**3ga**	90
7[d]	Ph (**1h**)	H (**2a**)	**3ha**	98
8[d]	4-MePh (**1i**)	H (**2a**)	**3ia**	85
9	2-Phenylethyl (**1j**)	H (**2a**)	**3ja**	95
10[d]	2-Furyl (**1k**)	H (**2a**)	**3ka**	81
11[d]	Ph (**1h**)	2-Me (**2b**)	**3hb**	98
12[d]	Ph (**1h**)	5-OMe (**2c**)	**3hc**	54

[a] Experimental conditions: to a mixture of catalyst **I** (20 mol%) and aldehyde **1b–k** (0.1 mmol) in toluene (250 μL), indole **2a–c** (0.3 mmol) was further added at room temperature. After two days of reaction time, adducts **3** were isolated by column chromatography (hexane : AcOEt 8 : 2). [b] Isolated yield. [c] After 3 days of reaction. [d] 30 mol% of **I**.

raising the amount of indole **2a** from one to two equivalents (Table 2, entries 6 and 8) and increasing concentration (Table 2, entries 3 and 4) have great positive impacts on the yields obtained. The best conditions found included 1.5 equivalents of indole **2a** and 20 mol% of catalyst in 250 μL of toluene (Table 2, entry 7). It is worth noting that in the absence of catalyst **I** the reaction did not work (Table 2, entry 10), which supports the role of **I** as the catalyst of this process. In all cases, the crudes of the reactions are very clean and only the excess of indole and the final product appear in the NMR spectra.

Using the best reaction conditions, the scope of this methodology was evaluated employing diverse commercially available aldehydes and indoles. This methodology was successfully applied to produce a great number of substituted bisindoles **3** with very good results (Table 3).

As reported in Table 3, high yields were achieved in a reasonable reaction time using a representative spectrum of aldehydes **1b–k**. Non-activated aldehydes **1h,i** (without an electron withdrawing group in their skeleton, entries 7 and 8) or heteroaromatic aldehyde **1k** (entry 10) showed a lower reactivity and a 30 mol% of catalyst **I** was necessary to achieve high yields in the same reaction time. In contrast, activated aldehydes **1b–g** (entries 1–6) or aliphatic **1j** (entry 9) afforded good levels of reactivity in all cases. Surprisingly, aldehydes **1d,e** (entries 3 and 4) required longer reaction times (72 h), although with good yields. Activated indole **2b** (entry 11) showed high reactivity with aldehyde **1h** while indole **2c** only led to a moderate yield (entry 12).



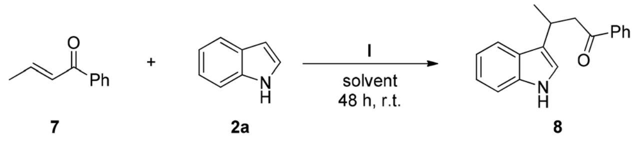
Scheme 2 Plausible reaction mechanism.

A plausible mechanism is proposed assuming the same route as that previously reported by us when using AgOTf as a Lewis acid (Scheme 2).[28] Hence, catalyst **I** would activate the first addition of one molecule of indole **2** to aldehyde **1** through halogen bonding (**4**).[31] Unstable intermediate **5** would promote the elimination of a molecule of H_2O to give azafulvene derivative **6**.[32] Finally, intermediate **6** would undergo a further addition of a second molecule of indole **2** to produce the final observed product **3**.

In order to expand the utility of catalyst **I**, an additional model reaction between *trans*-1-pheny-2-buten-1-one (**7**) and indole (**2a**) has been also explored as described in Table 4.[8c,33]

Interestingly, we have also observed reactivity using catalyst **I** in the Michael addition reaction depicted in Table 4 with MeOH as solvent at room temperature (entries 4 and 5). It is remarkable that the process did not work in other less polar

Table 4 Screening of the Michael addition between indole (**2a**) and trans-1-pheny-2-buten-1-one (**7**)[a]



Entry	**I** (mol%)	Solvent	Yield[b] (%)
1	—	MeOH	n.r.[c]
2	10	CH_3CN	n.r.[c]
3	10	Toluene	n.r.[c]
4	10	MeOH	37
5	20	MeOH	82

[a] Experimental conditions: to a mixture of catalyst **I** (0–20 mol%) and *trans*-crotonophenone (**7**) (0.1 mmol) in the corresponding solvent (0.25 mL), indole **2a** (0.2 mmol) was further added at room temperature. After 48 h of reaction, product **8** was isolated by column chromatography (hexane : AcOEt 8 : 2). [b] Isolated yield. [c] No reaction observed.

solvents such as toluene or in polar aprotic solvents such as acetonitrile (entries 2 and 3, respectively). Since it is remarkable that even with the presence of protic solvents, such as MeOH, the halogen–bond interaction is formed, in order to be sure that the reaction was not promoted by MeOH itself, the background of this Michael addition was also examined. In the absence of catalyst, the formation of the final product **8** was not observed at the same reaction time (entry 1). This reaction shows the importance of our catalyst promoting also this benchmark reaction with a simpler iodine-based catalyst in comparison with those catalysts previously used to promote this reaction.[8c,33] Moreover, Breugst and co-workers found that an iodoalkyne-based catalyst did not promote the latter reaction.[33d] Therefore, this proves that structural variations in the aromatic ring could be pivotal to promote the process. The efficiency of catalyst **I** to activate other α,β-unsaturated ketone derivatives is being explored in this moment in our lab.

Computational study of the I···O halogen bond

We have computationally analysed the impact that the I···O halogen bond created between catalyst **I** and the initial aldehydes has on the reaction. Initially, the I···O interaction is compared with the H···O interaction created by an analogous hydrogenated catalyst (**IH**) that does not contain iodine atoms (Fig. 1).[34]

The distance and angle of the calculated halogen bonding are in accordance with those determined in the crystal structure of **II**···acetone halogen bonding complex.[18] The results suggest that iodine atoms create stronger interactions with the O atom of benzaldehyde compared to H atoms (more negative BE when catalyst **I** is used). Analogous to the electron flow in hydrogen bonds, iodine atoms take electron density from O atoms in halogen bonds.[2] Therefore, this I···O interaction could activate the carbonyl group of the aldehyde molecule towards a subsequent indole attack. In order to verify this, we calculated the electrostatic potentials at nuclei (EPN) of the carbonyl C atom of benzaldehyde and complexes **I···1h** and **IH···1h** (Table 5).

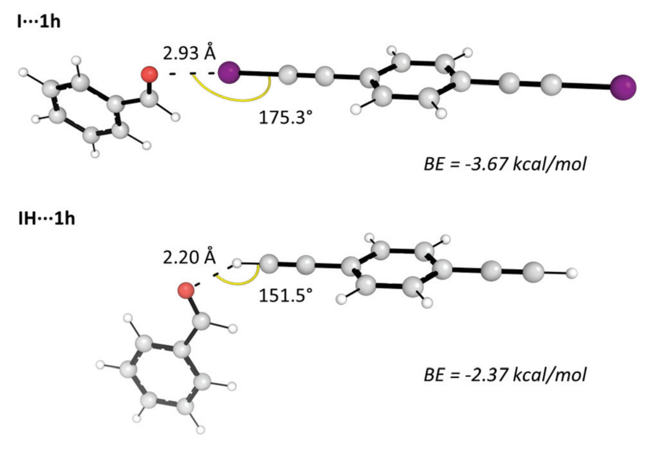


Fig. 1 Optimised complexes of benzaldehyde (**1h**) with catalyst **I** (**I···1h**) or **IH** (**H···1h**) along with the bonding energies (BE) created by the I···O and H···O interactions. Negative values in the BE values correspond to attractive interactions. Calculated at the ωB97X-D/Def2-QZVPP(SMD)//ωB97X-D/Def2-TZVP(SMD) level of theory.[35]

Table 5 EPN values of benzaldehyde (**1h**) and complexes **IH···1h** and **I···1h**

Entry	System	Relative EPN (kcal mol^{-1})	Experimental yield (%)
1	**1h**	0.0	0
2	**IH···1h**	4.5	0
3	**I···1h**	11.1	98

EPN values have previously been correlated to the reactivity of different functional groups, including carbonyl groups.[36] As the EPN value of the carbonyl C atom becomes higher, the electrophilicity and reactivity of the carbonyl group increases. As seen in Table 5, benzaldehyde **1h** shows the lowest EPN value of the three values calculated (Table 5, entry 1) and suggests that the carbonyl group of benzaldehyde is the least reactive carbonyl group of the carbonyl groups studied. The results also indicate that the I···O interaction created by catalyst **I** (Table 5, entry 3) activates the carbonyl group in a greater extent than the H···O interaction created by its hydrogenated analogous **IH** (Table 5, entry 2). As expected, the reaction was performed experimentally using catalyst **IH** and no reaction was observed after two days, while catalyst **I** showed a 98% yield after two days under the same reaction conditions (Table 3, entry 7).

Furthermore, in order to ensure that the I···O interaction was generated, NCIPLOT[37] was employed to analyse the noncovalent interactions (NCI) generated in the **I···1h** complex (Fig. 2). The results suggest that the I···O halogen is the only relevant intermolecular NCI created in the **I···1h** complex and, therefore, the only NCI that activates the carbonyl group towards the nucleophilic attack of indole.

Preliminary kinetic studies performed with the aim of knowing the order of reaction of the aldehyde seem to provide a more complex mechanism of reaction. These studies suggest that more than one molecule of aldehyde is involved in the process. Since at this stage the role of more than one molecule of aldehyde could not be clear, more computational calculations and experimental studies are ongoing in our lab in order to understand this interesting aspect.

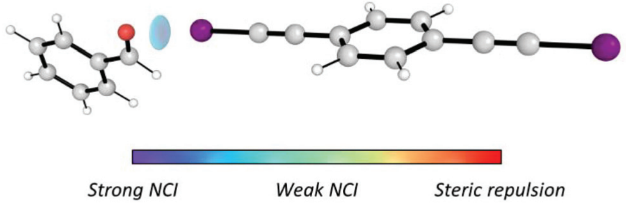


Fig. 2 I···O halogen bond created between catalyst **I** and benzaldehyde (**1h**). Only attractive NCI are shown.

Conclusions

A novel approach for the formation of bisindolylmethane derivatives (BIMs) is described as a proof of concept to evaluate the catalytic ability of iodoalkyne organocatalysts. The use of these derivatives is reported as an example of simple halogen bond-based organocatalyst. This kind of activation has not been used before for the synthesis of bisindolylmethane derivatives. We prove the efficiency of this family of new catalysts by developing a simple and easy operational methodology, opening the door to the development of alternative catalysts in the area of halogen bond-based catalysts. Additional kinetic studies and computational calculations are ongoing in our lab in order to shed light to the mechanism of this process.

Experimental section

General experimental methods and instrumentation

Purification of reaction products was carried out either by flash chromatography using silical-gel (0.063–0.200 mm). Analytical thin layer chromatography was performed on 0.25 mm silica-gel 60-F plates. ESI ionization method and mass analyser type MicroTof-Q were used for the ESI measurements. ^{1}H and ^{13}C{^{1}H}-APT NMR were recorded at room temperature on a BRUKER AVANCE 400 spectrometer (^{1}H, 300 or 400 MHz; ^{13}C, 75 or 100.6 MHz) in $CDCl_3$, CD_3COCD_3 or CD_3CN as solvent. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.28 ppm), CH_3COCH_3 (2.05 ppm) and CH_3CN (1.94 ppm) for ^{1}H NMR and to the central line of $CHCl_3$ (77.16 ppm), CH_3COCH_3 (29.84 ppm) and CH_3CN (1.32 ppm) for ^{13}C{^{1}H}-APT NMR. Tri(Prop-2-ynyl)benzene-1,3,5-tricarboxylate was synthesized according to the literature procedure.[30] All other reagents were obtained from commercial sources and used without prior purification.

All commercially available solvents and reagents were used as received. ^{1}H- and ^{13}C{^{1}H}-APT NMR spectra for compounds **3aa**,[38] **3ba**,[39] **3ca**,[40] **3da**,[41] **3ea**,[40] **3fa**,[38] **3ha**,[38] **3ia**,[38] **3ka**,[42] **3hb**,[43] **3hc**[44] and **8**[33d] are consistent with values previously reported in the literature.

General procedure for electrophilic iodation of terminal alkynes

2 mmol of the corresponding ethynyl derivative was dissolved in acetone (30 mL) followed by the addition of $AgNO_3$ (0.1 mol/mol C≡C–H). The reaction was kept for 30 min in an ice bath, in the dark, then *N*-iodosuccinimide (1.2 mol/mol C≡C–H) was added slowly. The reaction was stirred overnight at room temperature. The crude was filtered over Celite, the solvent was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 (30 mL) and washed with $NaHCO_3$ (10%) (3 × 20 mL). The organic fraction was dried over $MgSO_4$, filtered and the solvent was evaporated. The pure products were recovered as yellow solids (63–82%).

1,4-Bis(iodoethynyl)benzene (I).[18] Following the general procedure, compound **I** was obtained in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 132.3, 123.9, 93.7, 77.2, 9.1. HRMS calcd for $C_{10}H_4I_2$ 377.8397; found [M] 377.8410.

1,3-Bis(iodoethynyl)benzene (II).[18] Following the general procedure, compound **II** was obtained in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (t, J = 1.4 Hz, 1H), 7.41–7.33 (m, 2H), 7.29–7.20 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.3, 136.2, 132.6, 128.4, 123.8, 93.2, 7.8. HRMS calcd for $C_{10}H_4I_2$ 377.8397; found [M] 377.8395.

1,3,5-Tris(iodoethynyl)benzene (III).[9a] Following the general procedure, compound **III** was obtained in 63% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 124.1, 92.3, 9.1. HRMS calcd for $C_{12}H_3I_3$ 522.7363; found [M] 527.7369.

Tris(prop-2-ynyl)benzene-1,3,5-tricarboxylate (IV). Following the general procedure, compound **IV** was obtained in 76% yield. ^{1}H NMR (300 MHz, CD_3CN): δ 8.73 (s, 3H), 5.10 (s, 6H). ^{13}C-APT NMR (75 MHz, CD_3CN): δ 164.7, 135.3, 132.1, 88.5, 55.5, 8.9. HRMS (ESI+) calcd for $C_{18}H_9I_3NaO_6$ 724.7425; found [M + Na] 724.7401.

Representative procedure for synthesis of bis(indolyl) methanes (3)

To a mixture of catalyst **I** (20 mol%, 7.6 mg) and aldehyde **1a–k** (0.1 mmol) in toluene (250 μL), indole **2a–c** (0.3 mmol) was further added in a test tube at room temperature. After two days of reaction time, adducts **3** was isolated by column chromatography (hexane : AcOEt 8 : 2). The yields are given in Table 3.

3,3′-((3-Nitrophenyl)methylene)bis(1*H*-indole) (3aa).[38] Following the general procedure, compound **3aa** was obtained after 2 days of reaction at room temperature in 98% yield, as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (t, J = 2.0 Hz, 1H, Ar–H), 8.08 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H, Ar–H), 7.96 (br s, 2H, N–H), 7.69 (d, J = 7.7 Hz, 1H, Ar–H), 7.43 (d, J = 7.9 Hz, 1H, Ar–H), 7.40–7.34 (m, 4H, Ar–H), 7.23–7.18 (m, 2H, Ar–H), 7.04 (ddd, J = 8.1, 5.9, 0.9 Hz, 2H, Ar–H), 6.64 (d, J = 1.4 Hz, 2H, Ar–H), 6.00 (s, 1H, CH).

3,3′-((4-Nitrophenyl)methylene)bis(1*H*-indole) (3ba).[39] Following the general procedure, compound **3ba** was obtained after 2 days of reaction at room temperature in 98% yield, as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–8.12 (m, 2H, Ar–H), 8.01 (br s, 2H, N–H), 7.52–7.49 (m, 2H, Ar–H), 7.40–7.33 (m, 4H, Ar–H), 7.20 (ddd, J = 8.2, 7.1, 1.0 Hz, 2H, Ar–H), 7.03 (ddd, J = 8.0, 7.1, 1.0 Hz, 2H, Ar–H), 6.69 (d, J = 2.4, 0.8 Hz, 2H, Ar–H), 5.99 (s, 1H, CH).

4-(Di(1*H*-indol-3-yl)methyl)benzonitrile (3ca).[40] Following the general procedure, compound **3ca** was obtained after 2 days of reaction at room temperature in 95% yield, as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 2H, N–H), 7.58–7.55 (m, 2H, Ar–H), 7.46–7.44 (m, 2H, Ar–H), 7.39–7.32 (m, 4H, Ar–H), 7.20 (ddd, J = 8.2, 7.1, 1.1 Hz, 2H, Ar–H), 7.03 (ddd, J = 8.0, 7.1, 1.0 Hz, 2H, Ar–H), 6.66 (d, J = 2.4, 0.8 Hz, 2H, Ar–H), 5.94 (s, 1H, CH).

3,3′-((4-Chlorophenyl)methylene)bis(1*H*-indole) (3da).[41] Following the general procedure, compound **3da** was obtained after 3 days of reaction at room temperature in 95% yield, as a red solid. ^{1}H NMR (400 MHz, CD_3COCD_3) δ 10.04 (br s, 2H, N–H), 7.40 (d, *J* = 8.3 Hz, 4H, Ar–H), 7.36–7.29 (m, 4H, Ar–H), 7.08 (t, *J* = 7.6 Hz, 2H, Ar–H), 6.91 (t, *J* = 7.5 Hz, 2H, Ar–H), 6.83 (s, 2H, Ar–H), 5.94 (s, 1H, CH).

3,3′-((4-Bromophenyl)methylene)bis(1*H*-indole) (3ea).[40] Following the general procedure, compound **3ea** was obtained after 3 days of reaction at room temperature in 85% yield, as a red solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (br s, 2H, N–H), 7.42–7.34 (m, 6H, Ar–H), 7.24–7.16 (m, 4H, Ar–H), 7.02 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 2H, Ar–H), 6.63 (dd, *J* = 2.4, 0.9 Hz, 2H, Ar–H), 5.85 (s, 1H, CH).

3,3′-((3-Chlorophenyl)methylene)bis(1*H*-indole) (3fa).[38] Following the general procedure, compound **3fa** was obtained after 2 days of reaction at room temperature in 89% yield, as a red solid. ^{1}H NMR (400 MHz, CD_3COCD_3) δ 10.06 (br s, 2H, N–H), 7.42–7.21 (m, 8H, Ar–H), 7.08 (t, *J* = 7.6 Hz, 2H, Ar–H), 6.92 (t, *J* = 7.5 Hz, 2H, Ar–H), 6.86 (s, 2H, Ar–H), 5.97 (s, 1H, CH).

3,3′-((3-Bromophenyl)methylene)bis(1*H*-indole) (3ga). Following the general procedure, compound **3ga** was obtained after 2 days of reaction at room temperature in 90% yield, as a red solid. ^{1}H-NMR (400 MHz, CD_3COCD_3): δ 10.05 (br s, 2H, N–H), 7.58 (t, *J* = 1.8 Hz, 1H, Ar–H), 7.42–7.36 (m, 6H, Ar–H), 7.23 (t, *J* = 7.8 Hz, 1H, Ar–H), 7.09 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 2H, Ar–H), 6.93 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 2H, Ar–H), 6.86 (dd, *J* = 2.4, 0.8 Hz, 2H, Ar–H), 5.97 (s, 1H). ^{13}C NMR (100.6 MHz, CD_3COCD_3) δ 148.9, 138.1, 132.3, 130.9, 129.8, 128.5, 127.9, 124.7, 122.7, 122.3, 120.2, 119.5, 119.1, 112.3, 40.8. HRMS (ESI−) calcd for $C_{23}H_{16}BrN_2$ 399.0491; found 399.0508 [M − H].

3,3′-(Phenylmethylene)bis(1*H*-indole) (3ha).[38] Following the general procedure, compound **3ha** was obtained after 2 days of reaction at room temperature in 98% yield, as a red solid. ^{1}H NMR (400 MHz, CD_3COCD_3) δ 9.98 (br s, 2H, N–H), 7.43–7.36 (m, 6H, Ar–H), 7.29–7.26 (m, 2H, Ar–H), 7.20–7.18 (m, 1H, Ar–H), 7.07 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 2H, Ar–H), 6.90 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 2H, Ar–H), 6.82 (dd, *J* = 2.3, 0.8 Hz, 2H, Ar–H), 5.93 (s, 1H, CH).

3,3′-(*p*-Tolylmethylene)bis(1*H*-indole) (3ia).[38] Following the general procedure, compound **3ia** was obtained after 2 days of reaction at room temperature in 85% yield, as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br s, 2H, N–H), 7.40 (dd, *J* = 7.9, 1.0 Hz, 2H, Ar–H), 7.34 (dt, *J* = 8.2, 0.8 Hz, 2H, Ar–H), 7.24 (d, *J* = 8.1 Hz, 2H, Ar–H), 7.17 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 2H, Ar–H), 7.09 (d, *J* = 7.8 Hz, 2H, Ar–H), 7.01 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 2H, Ar–H), 6.65 (dd, *J* = 2.4, 1.0 Hz, 1H, Ar–H), 5.86 (s, 1H, CH), 2.33 5.86 (s, 3H, CH_3).

3,3′-(3-Phenylpropane-1,1-diyl)bis(1*H*-indole) (3ja). Following the general procedure, compound **3ja** was obtained after 2 days of reaction at room temperature in 95% yield, as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (br s, 2H, N–H), 7.56 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.34 (dt, *J* = 8.1, 0.9 Hz, 2H, Ar–H), 7.31–7.12 (m, 7H, Ar–H), 7.08–6.98 (m, 4H, Ar–H), 4.52 (t, *J* = 7.4 Hz, 1H, CH), 2.74 (dd, *J* = 9.2, 6.3 Hz, 2H, CH_2), 2.60–2.49 (m, 2H, CH_2). ^{13}C-APT NMR (100.6 MHz, $CDCl_3$) δ 142.7, 136.7, 128.7, 128.4, 127.2, 125.8, 121.9, 121.6, 120.2, 119.8, 119.2, 111.2, 37.5, 34.6, 33.6. HRMS (ESI−) calcd for $C_{25}H_{21}N_2$ 349.1699; found 349.1692 [M − H].

3,3′-(Furan-2-ylmethylene)bis(1*H*-indole) (3ka).[42] Following the general procedure, compound **3ka** was obtained after 2 days of reaction at room temperature in 81% yield, as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br s, 2H, N–H), 7.48 (dd, *J* = 4.2, 3.7 Hz, 2H, Ar–H), 7.38–7.34 (m, 3H, Ar–H), 7.18 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 2H, Ar–H), 7.04 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 2H, Ar–H), 6.88 (dd, *J* = 2.4, 0.8 Hz, 2H, Ar–H), 6.30 (dd, *J* = 3.0, 1.9 Hz, 1H, Ar–H), 6.06 (dt, *J* = 3.2, 0.8 Hz, 1H, Ar–H), 5.95 (s, 1H, CH).

3,3′-(Phenylmethylene)bis(2-methyl-1*H*-indole) (3hb).[43] Following the general procedure, compound **3hb** was obtained after 2 days of reaction at room temperature in 98% yield, as a red solid. ^{1}H NMR (400 MHz, CD_3COCD_3) δ 9.85 (br s, 2H, N–H), 7.30–7.18 (m, 7H, Ar–H), 6.95–6.90 (m, 4H, Ar–H), 6.71 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 2H, Ar–H), 6.05 (s, 1H, CH), 2.11 (s, 6H, 2 × CH_3).

3,3′-(Phenylmethylene)bis(5-methoxy-1*H*-indole) (3hc).[44] Following the general procedure, compound **3hc** was obtained after 2 days of reaction at room temperature in 54% yield, as a red solid. ^{1}H NMR (400 MHz, CD_3COCD_3) δ 9.84 (br s, 2H, N–H), 7.43–7.40 (m, 2H, Ar–H), 7.30–7.26 (m, 4H, Ar–H), 7.20–7.16 (m, 1H, Ar–H), 6.83 (dd, *J* = 8.2, 2.3 Hz, 4H, Ar–H), 6.73 (dd, *J* = 8.8, 2.5 Hz, 2H, Ar–H), 5.83 (s, 1H, CH), 3.62 (s, 6H, 2 × OCH_3).

Representative procedure for synthesis of 3-(1*H*-indol-3-yl)-1-phenylbutan-1-one (8)

To a mixture of catalyst **I** (20 mol%, 7.6 mg) and ketone **7** (0.1 mmol) in MeOH (250 μL), indole **2a** (0.2 mmol) was further added in a test tube at room temperature. After two days of reaction time, adduct **8** was isolated by chromatography (hexane : AcOEt 9 : 1).

3-(1*H*-indol-3-yl)-1-phenylbutan-1-one (8).[33d] Following the general procedure, compound **8** was obtained after 2 days of reaction at room temperature in 82% yield, as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.90 (m, 3H, 2Ar–H and N–H), 7.72–7.66 (m, 1H, Ar–H), 7.59–7.52 (m, 1H, Ar–H), 7.49–7.41 (m, 2H, Ar–H), 7.36–7.33 (m, 1H, Ar–H), 7.20 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, Ar–H), 7.13 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, Ar–H), 7.03 (d, *J* = 2.0 Hz, 1H, NHC*H*), 3.91–3.77 (m, 1H, CH_3C*H*), 3.49 (dd, *J* = 16.0, 4.0 Hz, 1H, C*H*H), 3.25 (dd, *J* = 16.0, 8.0 Hz, 1H, CH*H*), 1.46 (d, *J* = 6.9 Hz, 3H, CH_3).

Conflicts of interest

There are no conflicts to declare.

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