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Organocatalytic Friedel–Crafts arylation of aldehydes with indoles utilizing N-heterocyclic iod(az)olium salts as halogen-bonding catalysts†

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The Friedel–Crafts arylation is among the most known organic reactions, usually being promoted by a Lewis acid, that have been employed for the synthesis of bis-indolyl methanes. Herein, we report a mild, inexpensive, green and organocatalytic protocol for the promotion of a Friedel–Crafts-type reaction between indoles and aldehydes, where N-heterocyclic iod(az)olium salts are utilized as halogen-bonding catalysts, leading to the double addition of the indole motif. A variety of aliphatic and aromatic aldehydes were converted into diarylmethanes in good to high yields, while the scope of indoles was also investigated. Water was employed as the solvent, while the reaction time was short. The reaction mechanism was also studied.

Introduction

Among the most common reactions, taught in almost all undergraduate courses around the world, the Friedel–Crafts arylation has a prominent place. It was first introduced in the literature in 1877 by Friedel and Crafts,[1] presenting a new way, at the time, to attach substituents onto aromatic rings. Since then, the reaction has been thoroughly studied.[2] Bis-indolyl methanes (BIMs) and their analogues constitute an important class of compounds that exhibit various medicinal and pharmacological properties and are usually employed as anti-cancer, anti-oxidant, anti-bacterial, anti-inflammatory and anti-proliferative agents,[3] while one of the metabolites of indole-3-carbinol, its dimer 3,3′-bis-indolyl-methane (arundine or DIM), plays an important role in the prevention of breast cancer (Fig. 1).[4]

Since BIMs present so many different properties, a variety of synthetic routes have been devised for their synthesis, although the Friedel–Crafts-type reaction between aldehydes and indoles is the most common approach (Scheme 1). Most frequently, an acid, either Lewis or Brønsted, is employed, usually presenting major disadvantages, such as the use of high temperature or toxic reagents (Scheme 1A).[5] In order to provide greener approaches towards the synthesis of BIMs, green solvents, neat conditions, and sonochemistry or microwave chemistry have been employed.[6] In 2002, the use of a catalytic amount of NBS was proposed (Scheme 1B),[7] while attempts to anchor the acidic catalyst on a solid support, in order to recycle the catalyst, were also performed by other researchers.[8] In 2020, Bez and co-workers described the first aminocatalytic approach for the synthesis of BIMs, utilizing a prolinamide catalyst at elevated temperatures (Scheme 1C).[9] In the same year, Yuan and co-workers described an electrochemically promoted synthesis of BIMs,

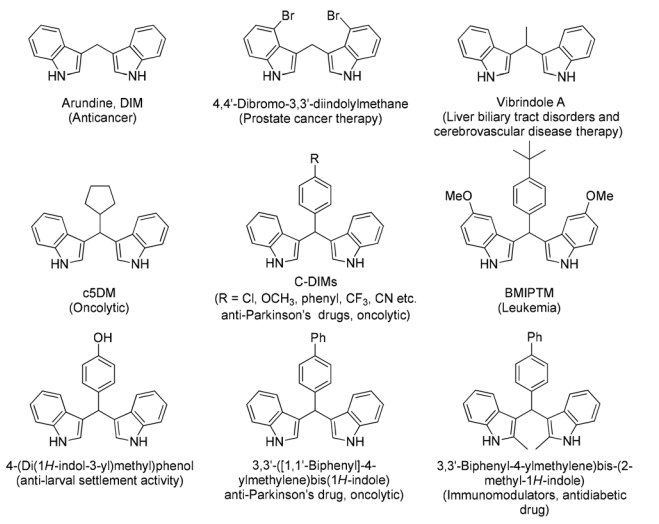

Fig. 1 Biologically active molecules containing the bis-indolyl methane moiety.

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†Electronic supplementary information (ESI) available: Full optimisation studies, experimental procedures and characterisation data of starting materials and products, mechanistic studies and NMR traces. See DOI: https://doi.org/10.1039/d3gc03687a

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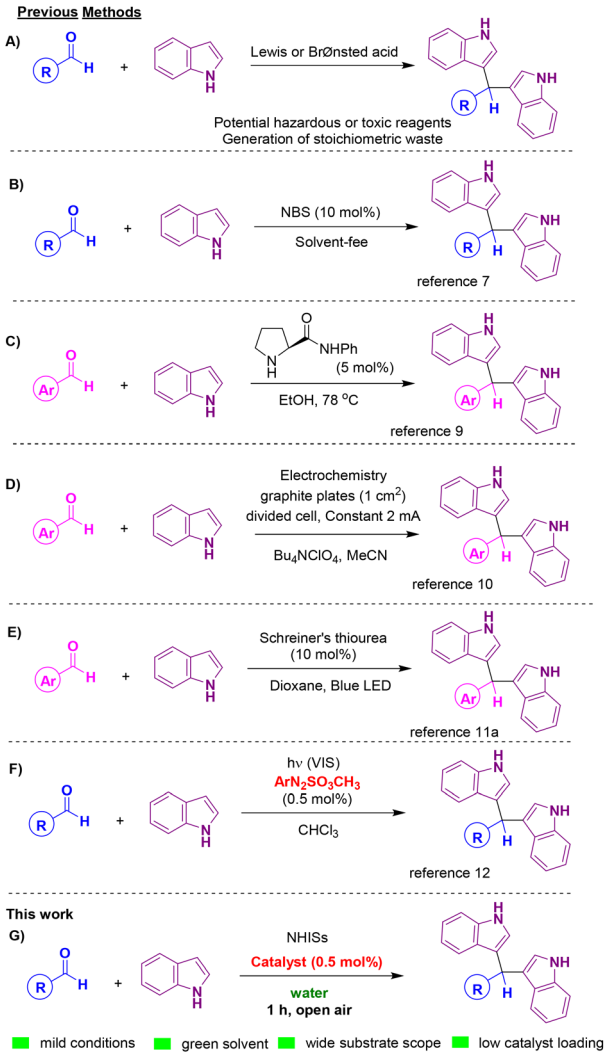

Scheme 1 Common synthetic pathways for the Friedel–Crafts-type reaction between indoles and aldehydes.

proposing an autocatalytic process (Scheme 1D).[10] In 2019, Badillo and co-workers described a very elegant photochemical protocol, where they employed the organocatalytic properties of Schreiner's thiourea, in order to promote a photo-acidic process using blue LED irradiation (Scheme 1E).[11] In 2023, the Kokotos' group, in collaboration with the research groups of Fagnoni and Protti, proposed a fast, versatile and efficient procedure for the visible-light-driven synthesis of diarylmethanes *via* Friedel–Crafts-type coupling of aldehydes and (hetero)arenes, utilising arylazo sulfones as photoacid generators (PAGs) (Scheme 1F).[12] Among the different applications of arylazo sulfones in synthesis and chemistry of materials, their use as non-ionic photoacid generators (PAGs) is able to generate methanesulfonic acid in oxygen-saturated or air equilibrated solutions.

Halogen bonding (XB) is the interaction of electrophilic halogen substituents with Lewis bases (LBs) and has been extensively studied in the past two decades.[13] Halogen bonding has been successfully applied in crystal engineering,[14] anion recognition,[15] organic synthesis[15] and organocatalysis.[16] Halogen-bond catalysis has attracted increasing attention, due to growing awareness of the problems associated with metal catalysts in recent years.[17] Among them, halogen-bond catalysis is largely led by iodine-derived catalysts. Since halogen bonding catalysts have the advantages of being relatively cheap, stable, green and easy-to-handle,[18] they have been gradually established in organocatalysis as an area of interest, receiving increased attention from 2008 and onwards, when Bolm and co-workers reported an example of using perfluoroiodoalkanes as halogen-bond catalysts.[19] It is known that iodine(I)-based halogen bond catalysts have been used in a variety of organic transformations, ranging from polyfluorinated arenes[20] to imidazolium salt[21] or triazolium salt derivatives.[22] The iodobenzimidazolium group is one of the most potent available iodine(I)-based halogen bond catalysts, and iodine(III)-based halogen bond catalysts were proven to exhibit high catalytic activity in halide abstractions, Diels–Alder reactions, Nazarov cyclizations and Michael addition reactions.[23] The research group of Nachtsheim has investigated in detail the application of N-heterocyclic iod(az)olium salts (NHISs) as halogen-bonding catalysts.[24] Thus, in 2019, Toy and co-workers proposed the use of a diiodine-based molecule as the potential catalyst for the Friedel–Crafts-type coupling of aldehydes with indoles.[25a] The authors employed a low catalyst loading of 1 mol%, but prolonged reaction times (up to 72 h), heating at 70 °C and MeCN as the solvent had to be applied. The reaction mechanism was recently studied by DFT calculations.[25b] Also, in 2020, Herrera and co-workers introduced the use of iodo-alkynes as potential catalysts for the same reaction.[25c] A high catalyst loading of 20 mol%, along with toluene as the solvent and a reaction time of 48 h, was necessary, while only aromatic aldehydes reacted successfully. In both cases, the products were purified by column chromatography.

We thus decided to merge the experience of Kokotos' group with that of Nachtsheim's group to investigate whether halogen bonding can be employed in introducing a fast, green and efficient procedure for the organocatalytic synthesis of diarylmethanes *via* Friedel–Crafts-type coupling of aldehydes with (hetero)arenes, utilizing NHISs as catalysts (Scheme 1G).

Results and discussion

We began our investigations by studying the reaction between 3-phenylpropanal (**1a**) and 1*H*-indole (**2a**) in CH_2Cl_2 at room temperature to form 3,3′-(3-phenylpropane-1,1-diyl)bis(1*H*-indole) (**4a**) (Scheme 2). The reaction in the absence of a catalyst does not lead to product formation. Then, we screened various substituted N-heterocyclic iod(az)olium salts (NHISs) (**3a–3e**).[24g] These compounds have decreased electron density at the N-heterocycle which strengthens the XB-bonding capability of the hypervalent iodine atom, through an increased electron-pull, which is initiated by the charged N-heterocycle. Among the compounds tested, catalyst **3e** afforded the most satisfactory yield (90%), when employed in a very low catalyst loading (0.5 mol%, Scheme 2). The catalysts with the highest

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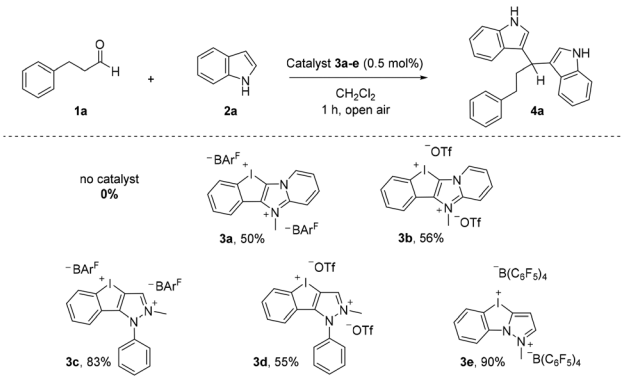
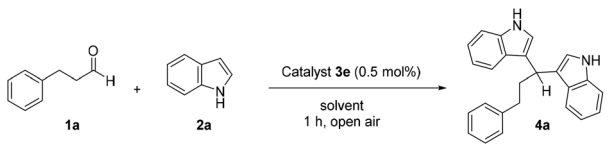


Scheme 2 N-heterocyclic iod(az)olium salts (NHISs) as catalysts for the Friedel–Crafts-type reaction between indole (**2a**) and 3-phenylpropanal (**1a**). $^{-}BAr^{F}$: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

yields were **3c** and **3e**, having a significant difference in terms of the counter anion (BAr^{F} instead of $B(C_6F_5)_4$), as well as an N- *vs.* C-bound heterocycle.

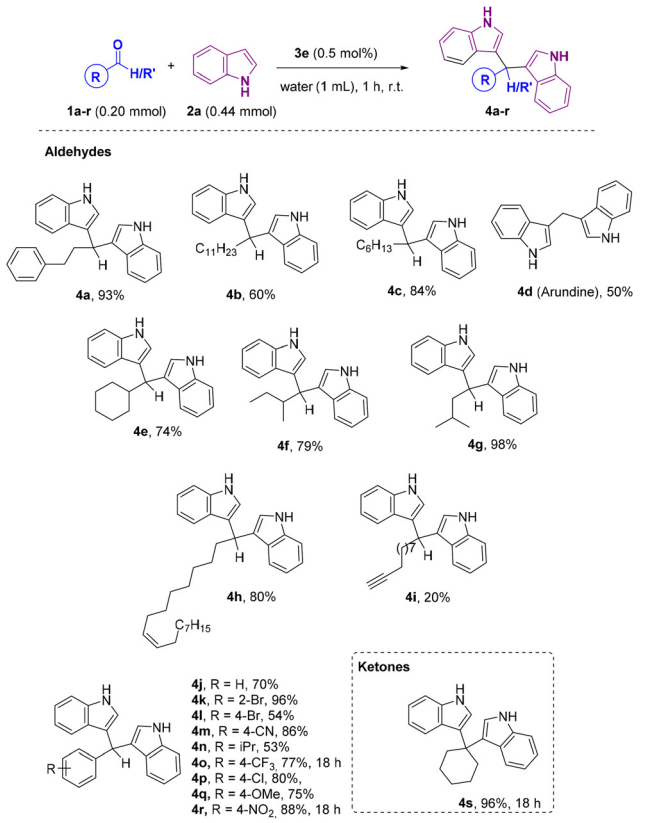
Next, we screened a number of common solvents (Table 1). Most organic solvents afforded moderate to excellent yields; however, water proved to be the best (Table 1, entry 9). In the case of water as the solvent, the desired product could be isolated by simple extraction from the reaction mixture, with high enough purity. In further investigation regarding the catalyst loading, using 0.1 mol% catalyst loading after 5 h led to the desired product in 79% yield. Thus, we concluded that when reducing the catalyst loading, the reaction time had to be increased. Taking this into account, we carried out reactions with 0.1, 0.01 and 0.005 mol% catalyst loading for 18 h and

Table 1 Optimization studies for the organocatalytic synthesis of diarylmethane **4a** from aldehyde **1a** and indole **2a**

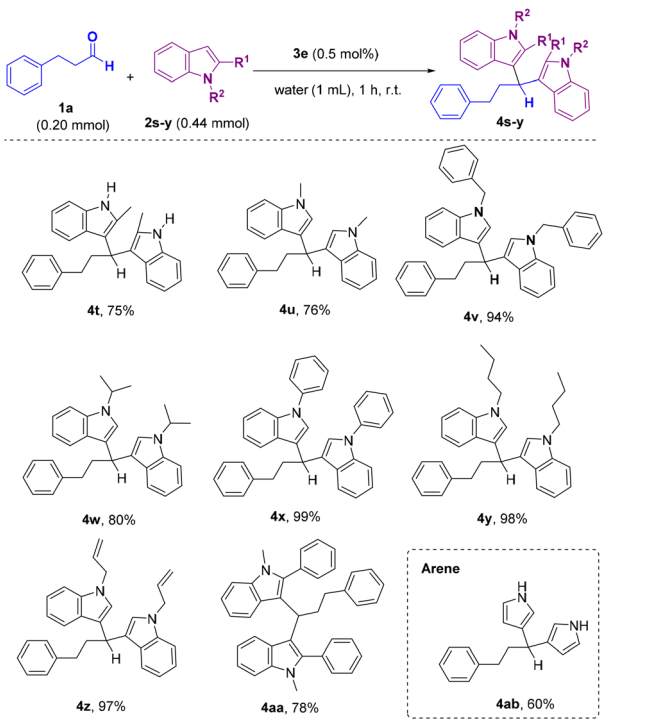


Entry	Solvent	Yield[a] (%)
1	CH_2Cl_2	93
2	$CHCl_3$	90
3	MeCN	93
4	EtOAc	89
5	DMSO	35
6	Toluene	96
7	Pet. Eth.	80
8	THF	50
9	**H_2O**	**97 (93)**
10	Et_2O	55
11	MeOH	53
12	Cyrene	—
13	2-Me-THF	76

[a] Yields determined by ^{1}H NMR using an internal standard. Yield of **4a** after isolation by column chromatography is given in parenthesis. The reaction was performed with 3-phenylpropanal (**1a**) (26 mg, 0.20 mmol), indole (**2a**) (52 mg, 0.44 mmol), and catalyst **3e** (0.5 mol%, 1.0 μmol) in solvent (0.5 mL) for 1 h.



Scheme 3 Substrate scope – substituted carbonyls.



Scheme 4 Substrate scope – substituted indoles.

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the product was obtained in 95%, 87% and 60% yields, respectively. In the framework of these experiments, a gram-scale reaction was also carried out with 0.01 mol% catalyst loading, affording the desired product in 79% yield.

Having in hand the optimum reaction conditions utilizing N-heterocyclic iod(az)olium salt **3e** as the organocatalyst and water as the solvent, we turned our attention to exploring the substrate scope (Schemes 3 and 4). Initially, we employed indole (**2a**) as a representative heterocycle, with a variety of aliphatic and aromatic aldehydes (Scheme 3). We began our investigations using aliphatic derivatives, isolating product **4a** in 93% yield. Moving to linear aliphatic aldehydes, bis-indoles **4b** and **4c**, as well as the anticancer bis-indole **4d** (arundine), were isolated in good to high yields. Also, we explored three different α,α-disubstituted aldehydes, and in all cases, the desired products **4e–4g** were obtained in very good yields (74–98%, Scheme 3). We then explored the scope of the aliphatic aldehydes having double or triple bonds. Oleyl aldehyde **1h** was employed successfully, leading to **4h** in 80% yield, whereas, in the case of aldehyde **1i** which contains a triple bond, the reaction was more problematic, leading to product **4i** in only 20% yield after 1 h or 18 h. Once we realized that the use of aliphatic aldehydes is possible, we explored the scope of aromatic aldehydes. Benzaldehyde provided the double addition product **4j** in a good yield. Substitution either at the *para*-position or the *ortho*-position of the aromatic ring was well tolerated, leading to products **4k** or **4l** in good to excellent yields. Both electron-withdrawing and electron-donating groups were well tolerated and products **4m–r** were isolated in good to excellent yields. CF_3- and NO_2-substituted aldehydes **1o** and **1r** required a prolonged reaction time (18 h). Cyclohexanone as a model ketone reacted as well, but for a prolonged reaction time of 18 h, affording **4s** in 96% yield. However, acetophenone did not react under the optimized conditions. Once the substrate scope of the aldehyde counterpart was investigated, we moved to testing the scope of substituted

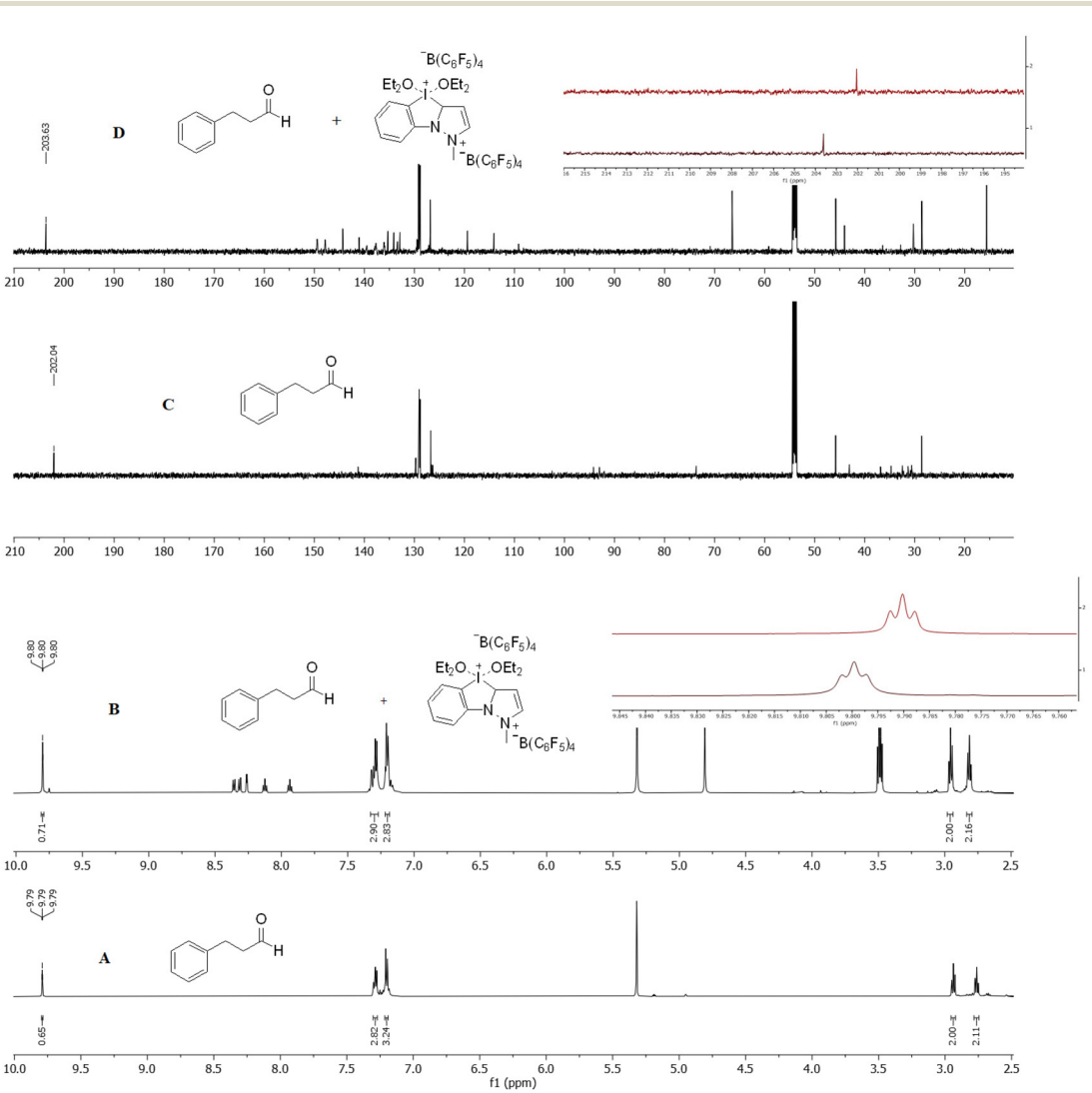

Fig. 2 ^{1}H NMR (600 MHz, DMSO-d_6) studies of (A) 3-phenylpropanal (**1a**) and (B) the mixture of **1a** with **3e**, and ^{13}C NMR (150 MHz, DMSO-d_6) studies of (C) 3-phenylpropanal (**1a**) and (D) the mixture of **1a** with **3e**.

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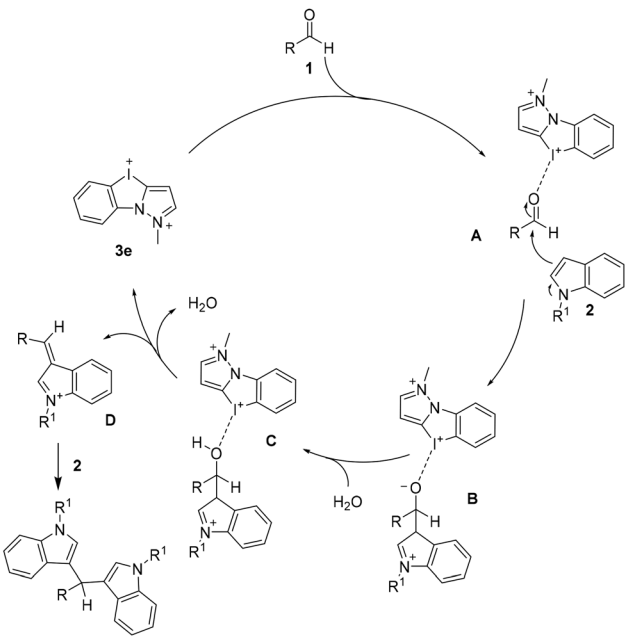
indoles (Scheme 4). By utilizing 3-phenylpropanal (**1a**) as a common starting material, a variety of *N*-substituted indoles were tested. Sterically hindered 2-methyl indole was a competent nucleophile, providing access to **4t** in 75% yield. Then, the substitution pattern on the nitrogen of the indole was probed. Simple alkyl substituents, such as methyl (**4u**), butyl (**4y**) or benzyl (**4v**), secondary alkyl substituents, such as isobutyl (**4w**), and aryl substituents, such as phenyl (**4x**) or allyl (**4z**), were well tolerated, leading to good to excellent yields. Substituted indoles at the 2-position, such as *N*-methyl-2-phenyl indole, afforded **4aa** in 78% yield. Also, we tested other arenes, such as pyrrole, thiophene, benzothiophene, thiazole or furan, but only pyrrole afforded product **4ab** in 60% yield.

Mechanistic studies

After studying the substrate scope, we turned our attention into studying the reaction mechanism. Having the literature as a strong inspiration[24] and in order to have a better understanding, we performed ^{1}H- and ^{13}C NMR mechanistic studies (Fig. 2). Initially, the ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of 3-phenyl-propanal (**1a**) was recorded (Fig. 2A). The triplet peak of the proton of the carbonyl group resonates at 9.79 ppm. The addition of 1.0 equiv. of catalyst **3e** to **1a** resulted in a slight shift in ^{1}H NMR from 9.79 ppm to 9.80 ppm (Fig. 2B). Moving to ^{13}C NMR (150 MHz, DMSO-d_6), the carbon of the carbonyl moiety of 3-phenyl-propanal (**1a**) resonates at 202.04 ppm (Fig. 2C). The mixture of **1a** to **3a** presents a significant shift for the carbon on the carbonyl moiety to 203.63 ppm (Fig. 2D). This low-field shift of 1.59 ppm is indicative of the halogen bonding between the oxygen of the carbonyl group of the aldehyde and the iodine of the iodonium catalyst **3e**, supporting the formation of an aldehyde–catalyst complex. We also performed similar NMR studies with indole and other NHIS catalysts **3a–d**.[26]

Taking all these data into account, the following mechanism is proposed (Scheme 5). Iodonium catalyst **3e** can enhance the electrophilicity of aldehyde **1**, through halogen bonding, leading to complex **A** (Scheme 5). This complexation facilitates the nucleophilic addition of indole to afford tetrahedral intermediate **B**. This, in turn, can collapse, losing a molecule of water *via* the protonated alcohol **C**, regenerating the organocatalyst and generating azafulvene intermediate **D**. This can react with another molecule of **2** in a conjugate addition, to afford the desired product **4**.



Scheme 5 Proposed reaction mechanism. The anions are omitted for better clarity.

Conclusions

In conclusion, a simple, green and efficient organocatalytic protocol was developed, activating aldehydes for their reaction with indoles, leading to diarylmethanes. This method relies on a small organic molecule activating efficiently both aliphatic and aromatic aldehydes, leading to diarylmethanes in good to high yields. Based on extensive mechanistic studies, the interaction between the iodonium catalysts and aldehydes by halogen bonding has been verified. Among the key features of this protocol are the extremely low catalyst loading (0.5 mol%), the use of water as the solvent and the quite fast reaction times (1 h).

Experimental

General procedure for the organocatalytic reaction between indoles and aldehydes

In a glass vial, catalyst (**3e**) (1.8 mg, 1.0 μmol) in H_2O (0.5 mL), aldehyde (0.20 mmol) and indole (0.44 mmol) were added consecutively. The reaction mixture was stirred for 1 h. After reaction completion, the reaction mixture was diluted with EtOAc (2 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo*. The desired product was isolated by column chromatography.

Author contributions

Conceptualization: C.G.K. and B.N.; reaction optimization, substrate scope and compound characterization: E.G.; synthesis of catalysts: T.K.; writing – original draft: E.G. and C.G.K.; writing, reviewing and editing: B.N. and C.G.K.; and supervision and project administration: C.G.K.

Conflicts of interest

There are no conflicts to declare.

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References

1 (*a*) C. Friedel and J. M. Crafts, *Compt. Rend.*, 1877, **84**, 1392–1395; (*b*) C. Friedel and J. M. Crafts, *Compt. Rend.*, 1877, **84**, 1450–1454.

2 For selected and recent reviews on the Friedel–Crafts reaction, see: (*a*) M. Rueping and B. J. Nachtsheim, *Beilstein J. Org. Chem.*, 2010, **6**, 6; (*b*) R. Sunke, S. B. Nallapati, J. S. Kumar, K. S. Kumar and M. Pal, *Org. Biomol. Chem.*, 2017, **17**, 4042–4057.

3 (*a*) M. Kobayashi, S. Aoki, K. Gato, K. Matsunami, M. Kurosu and I. Kitagawa, *Chem. Pharm. Bull.*, 1994, **42**, 2449–2451; (*b*) G. Sivaprasad, P. T. Perumal, V. R. Prabavathy and N. Mathivanan, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 6302–6305; (*c*) M. Damodiran, D. Muralidharan and P. T. Perumal, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3611–3614; (*d*) A. Kamal, M. N. A. Khan, K. S. Reddy, Y. V. V. Srikanth, S. K. Ahmed, K. P. Kumar and U. S. N. Murthy, *J. Enzyme Inhib. Med. Chem.*, 2009, **24**, 559–565; (*e*) K. Abdelbaqi, N. Lack, E. T. Guns, L. Kotha, S. Safe and T. Sanderson, *Prostate*, 2011, **71**, 1401–1412; (*f*) K. Yoon, S. Lee, S. Cho, K. Kim, S. Khan and S. Safe, *Carcinogenesis*, 2011, **32**, 836–842; (*g*) G. S. S. Kumar, S. Kumaresan, A. A. M. Prabhu, N. Bhuvanesh and P. G. Seethalakshmi, *Spectrochim. Acta, Part A*, 2013, **101**, 255–263.

4 (*a*) Y. S. Kim and J. A. Milner, *J. Nutr. Biochem.*, 2005, **16**, 65–73; (*b*) E. G. Rogan, *In Vivo*, 2006, **20**, 221–228.

5 For a review, see: (*a*) M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian, *Chem. Rev.*, 2010, **110**, 2250–2293. For selected examples, see: (*b*) J. S. Yadav, B. V. S. Reddy, C. V. S. R. Murthy, G. M. Kumar and C. Madan, *Synthesis*, 2001, 783–787; (*c*) R. Nagarajan and P. T. Perumal, *Tetrahedron*, 2002, **58**, 1229–1232; (*d*) G. Gupta, G. Chaudhari, P. Tomar, Y. Gaikwad, R. Azad, G. Pandya, G. Waghulde and K. Patil, *Eur. J. Chem.*, 2012, **3**, 475–479; (*e*) J. Beltrá, M. C. Gimeno and R. P. Herrera, *Beilstein J. Org. Chem.*, 2014, **10**, 2206–2214; (*f*) H. Veisi, B. Maleki, F. H. Eshbala, H. Veisi, R. Masti, S. S. Ashrafi and M. Baghayeri, *RSC Adv.*, 2014, **4**, 30683–30688.

6 For selected examples, see: (*a*) G. Penieres-Carrillo, J. G. García-Estrada, J. L. Gutiérrez-Ramirez and C. Alvarez-Toledano, *Green Chem.*, 2003, **5**, 337–339; (*b*) J. Li, H. Dai, W. Xu and T. Li, *Ultrason. Sonochem.*, 2006, **13**, 24–27; (*c*) N. Azizi, L. Torkian and M. R. Saidi, *J. Mol. Catal. A: Chem.*, 2007, **275**, 109–112; (*d*) M. Zahran, Y. Abdin and H. Salama, *ARKIVOC*, 2008, 256–265; (*e*) A. K. Chakraborti, S. R. Roy, D. Kumar and P. Chopra, *Green Chem.*, 2008, **10**, 1111–1118; (*f*) J. Li, M. Sun, G. He and X. Xu, *Ultrason. Sonochem.*, 2011, **18**, 412–414; (*g*) S. Handy and N. M. Westbrook, *Tetrahedron Lett.*, 2014, **55**, 4969–4971; (*h*) U. N. Yadav and G. S. Shankarling, *J. Mol. Liq.*, 2014, **191**, 137–141.

7 H. Koshima and W. Matsusaka, *J. Heterocycl. Chem.*, 2009, **39**, 1089–1091.

8 S. B. Kamble, R. K. Swami, S. S. Sakate and C. V. Rode, *ChemPlusChem*, 2013, **78**, 1393–1399.

9 G. Basumatary, R. Mohanta, S. D. Baruah, R. C. Deka and G. Bez, *Catal. Lett.*, 2020, **150**, 106–111.

10 C. Liu, Z. Xiao, S. Wu, Y. Shen, K. Yuan and Y. Ding, *ChemSusChem*, 2020, **13**, 1997–2001.

11 (*a*) Z. M. Salem, J. Saway and J. J. Badillo, *Org. Lett.*, 2019, **21**, 8528–8532. For a similar use of Schreiner's thiourea for acetalization of aldehydes, see: (*b*) N. Spiliopoulou, N. F. Nikitas and C. G. Kokotos, *Green Chem.*, 2020, **22**, 3539–3545.

12 E. M. Galathri, L. Di Terlizzi, M. Fagnoni, S. Protti and C. G. Kokotos, *Org. Biomol. Chem.*, 2023, **21**, 365–369.

13 G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati and G. Terraneo, *Chem. Rev.*, 2016, **116**, 2478–2601.

14 A. Mukherjee, S. Tothadi and G. R. Desiraju, *Acc. Chem. Res.*, 2014, **47**, 2514–2524.

15 M. S. Taylor, *Coord. Chem. Rev.*, 2020, **413**, 213270.

16 D. Bulfield and S. M. Huber, *Chem. – Eur. J.*, 2016, **22**, 14434–14450.

17 (*a*) A. Bauza, T. J. Mooibroek and A. Frontera, *ChemPhysChem*, 2015, **16**, 2496–2517; (*b*) M. Breugst and J. J. Koenig, *Eur. J. Org. Chem.*, 2020, 5473–5487; (*c*) J. Bamberger, F. Ostler and O. G. Mancheno, *ChemCatChem*, 2019, **11**, 5198–5211.

18 (*a*) R. L. Sutar and S. M. Huber, *ACS Catal.*, 2019, **9**, 9622–9639; (*b*) H. Yang and M. W. Wong, *Molecules*, 2020, **25**, 1045.

19 C. Bolm, A. Bruckmann and M. Pena, *Synlett*, 2008, 900–902.

20 (*a*) F. Heinen, D. L. Reinhard, E. Engelage and S. M. Huber, *Angew. Chem., Int. Ed.*, 2021, **60**, 5069–5073; (*b*) F. Kniep, S. H. Jungbauer, Q. Zhang, S. M. Walter, S. Schindler, I. Schnapperelle, E. Herdtweck and S. M. Huber, *Angew. Chem., Int. Ed.*, 2013, **52**, 7028–7032.

21 (*a*) C. W. Kee and M. W. Wong, *J. Org. Chem.*, 2016, **81**, 7459–7470; (*b*) S. H. Jungbauer, S. M. Walter, S. Schindler, L. Rout, F. Kniep and S. M. Huber, *Chem. Commun.*, 2014, **50**, 6281–6284; (*c*) S. H. Jungbauer and S. M. Huber, *J. Am. Chem. Soc.*, 2015, **137**, 12110–12120; (*d*) A. Dreger, P. Wonner, E. Engelage, S. M. Walter, R. Stoll and S. M. Huber, *Chem. Commun.*, 2019, **55**, 8262–8265; (*e*) Y. C. Chan and Y. Y. Yeung, *Org. Lett.*, 2019, **21**, 5665–5669; (*f*) V. P. N. Nziko and S. Scheiner, *J. Org. Chem.*, 2016, **81**, 2589–2597; (*g*) J. P. Gliese, S. H. Jungbauer and S. M. Huber, *Chem. Commun.*, 2017, **53**, 12052–12055.

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22 (*a*) M. Breugst, D. von der Heiden, E. Detmar and R. Kuchta, *Synlett*, 2017, **29**, 1307–1313; (*b*) R. Haraguchi, S. Hoshino, M. Sakai, S. G. Tanazawa, Y. Morita, T. Komatsu and S. I. Fukuzawa, *Chem. Commun.*, 2018, **54**, 10320–10323; (*c*) M. Kaasik, A. Metsala, S. Kaabel, K. Kriis, I. Jarving and T. Kanger, *J. Org. Chem.*, 2019, **84**, 4294–4303; (*d*) R. A. Squitieri, K. P. Fitzpatrick, A. A. Jaworski and K. A. Scheidt, *Chem. – Eur. J.*, 2019, **25**, 10069–10073.

23 (*a*) R. L. Sutar, E. Engelage, R. Stoll and S. M. Huber, *Angew. Chem., Int. Ed.*, 2020, **59**, 6806–6810; (*b*) A. J. To and G. K. Murphy, *New J. Chem.*, 2022, **46**, 15313–15320; (*c*) Y. Zhang, J. Han and Z.-J. Liu, *RSC Adv.*, 2015, **5**, 25485–25488; (*d*) F. Heinen, E. Engelage, A. Dreger, R. Weiss and S. M. Huber, *Angew. Chem., Int. Ed.*, 2018, **57**, 3830–3833; (*e*) A. Boelke, T. J. Kuczmera, E. Lork and B. J. Nachtsheim, *Chem. – Eur. J.*, 2021, **27**, 13128–13134; (*f*) R. Robidas, D. L. Reinhard, C. Y. Legault and S. M. Huber, *Chem. Rec.*, 2021, **21**, 1912–1927.

24 (*a*) A. Boelke, E. Lork and B. J. Nachtsheim, *Chem. – Eur. J.*, 2018, **24**, 18653–18657; (*b*) A. Boelke, Y. A. Vlasenko, M. S. Yusubov, B. J. Nachtsheim and P. S. Postnikov, *Beilstein J. Org. Chem.*, 2019, **15**, 2311–2318; (*c*) A. Boelke, T. J. Kuczmera, L. D. Caspers, E. Lork and B. J. Nachtsheim, *Org. Lett.*, 2020, **22**, 7261–7266; (*d*) A. Boelke and B. J. Nachtsheim, *Adv. Synth. Catal.*, 2020, **362**, 184–191; (*e*) A. H. Abazid and B. J. Nachtsheim, *Angew. Chem., Int. Ed.*, 2020, **59**, 1479–1484; (*f*) A. H. Abazid, N. Clamor and B. J. Nachtsheim, *ACS Catal.*, 2020, **10**, 8042–8048; (*g*) A. Boelke, T. J. Kuczmera, E. Lork and B. J. Nachtsheim, *Chem. – Eur. J.*, 2021, **27**, 13128–13134.

25 (*a*) X. Liu, S. Ma and P. H. Toy, *Org. Lett.*, 2019, **21**, 9212–9216; (*b*) C. Zhao, Y. Li, X. Li and Y. Zeng, *Phys. Chem. Chem. Phys.*, 2023, **25**, 21100–21108; (*c*) J. V. Alegre-Requena, A. Valero-Tena, I. G. Sonsona, S. Uriel and R. P. Herrera, *Org. Biomol. Chem.*, 2020, **18**, 1594–1601.

26 For more details, see the ESI.†