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A sustainable C–H functionalization of indoles, pyrroles and furans under a blue LED with iodonium ylides†

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Pyrrole and indole derivatives are functionalized *via* a green initiative with the dimethyl malonate derived phenyl iodonium ylide **4a** in the presence of a blue LED *via* C–H functionalization of the respective heterocycles in methanol to generate the desired compounds **5–7** in moderate to good yields. Control experiments provide insight into the probable reaction mechanism. Finally, the strategy is successfully applied in the generation of azepino[4,5-*b*]indole **12a**/**b**.

Introduction

Due to their presence in natural products and pharmaceutical drug candidates, heteroarenes hold an important position in organic and medicinal chemistry.[3,1] Typically, they can be functionalized either by halogenation followed by cross-coupling reactions or by their direct C–H activation.[4,2] In recent years, direct C–H bond functionalization of heterocycles has become an extremely significant strategy in organic synthesis. Compared to the C–H bond functionalization of arenes, the same for heteroarenes containing basic nitrogen is more challenging. Various transition metal catalysed strategies have been reported for the C–H bond functionalization of heteroarenes. Reactions like arylation, alkenylation, borylation, trifluoromethylation, *etc*. have been reported.[3–10] However, the application of metal hypervalent iodine (HVI) reagents in the direct C–H bond functionalization of heteroarenes is limited. HVI reagents address the concept of sustainability which in the last few decades has evolved as a crucial requirement in organic synthesis because it is important that novel reactions are successfully transferred from the laboratory to a commercial scale without endangering human lives and the environment.

Hypervalent iodine compounds were introduced in organic synthesis at the beginning of this century.[11] These non-toxic reagents are environmentally sustainable alternatives to transition metals in their chemical properties. They are utilized abundantly in various organic transformations which also include the ones accomplished by transition metals.[12] Iodonium ylides are an interesting class of HVI reagents involved in C–H functionalization of arenes and heteroarenes.[13] Fosu *et al.* reported site selective C–H functionalization of benzene and pyridine rings mediated by transient iodanes with chloro (Cl^-), bromo (Br^-), triflate (OTf^-), mesylate (OMs^-) and tosylate (OTs^-) ions.[14] In the recent past, numerous reports have been published wherein cyclopropanation and C–H functionalisation of olefins and heteroarenes are achieved respectively with dialkyl malonate derived iodonium ylides (Scheme 1a).[15] For example, Charette and co-workers reported an HVI mediated rhodium catalysed cyclopropanation of olefins.[15a] Murphy *et al.* reported a seminal work involving cyclopropanation of olefins *via* blue LED mediated reactions of hypervalent iodines (HVIs) (generated from dialkyl malonates). It included the detailed mechanism, principles and applications of this photolytic transformation (Scheme 1a).[15b] Additionally, $BF_3{\cdot}OEt_2$ mediated alkyl insertion of pyrroles (3 examples) and thiophenes (2 examples) from dialkyl malonate derived iodonium ylides is also reported (Scheme 1a).[15c,d] Inspired by Murphy's work, we explored the concept of the safe and sustainable C–H functionalization of indoles and pyrroles with iodonium ylides in the presence of methanol as a green solvent under mild reaction conditions. Herein, we have reported a dialkyl malonate derived iodonium ylide mediated hitherto novel alkylation of substituted pyrroles and indoles under a blue LED (Schemes 2 and 3). Finally, the strategy was harnessed to afford a library of azepino[4,5-*b*]indoles from tryptamine derivatives (Scheme 1).

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†Electronic supplementary information (ESI) available: Supplemental experimental procedures, Fig. S1–S8 and NMR spectra of the C2/C3 functionalized as well as azepino indoles. See DOI: 10.1039/d1ob01219c

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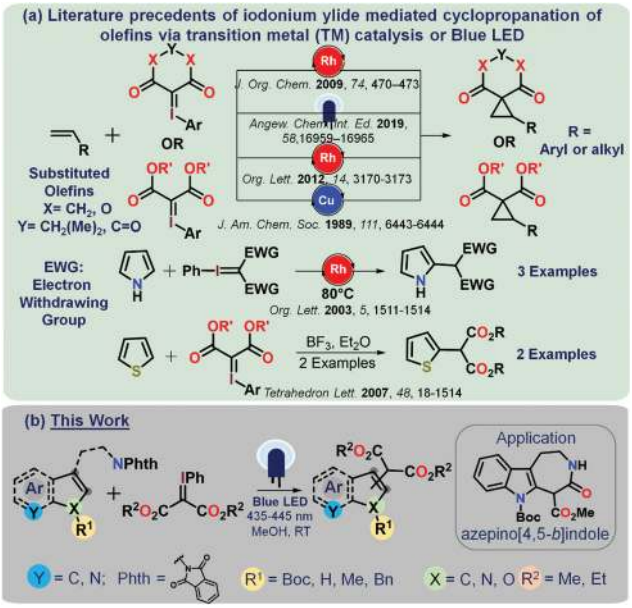
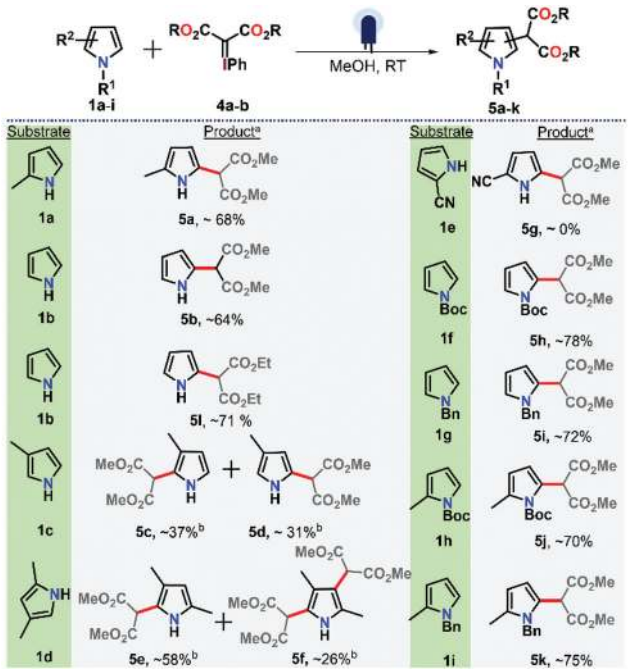
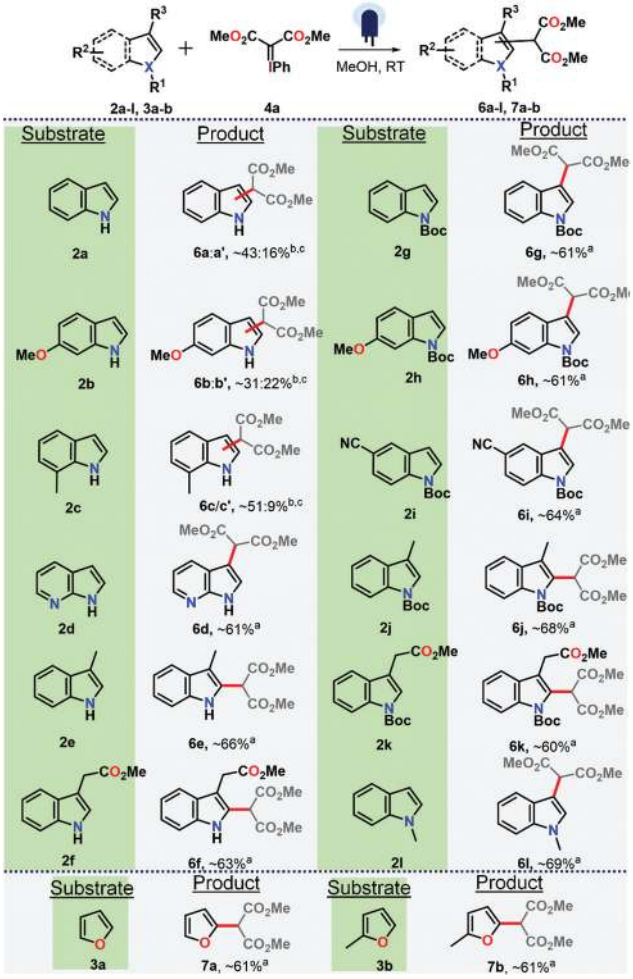


Scheme 1 (a) Literature precedents of cyclopropanation of olefins and alkylation of heteroarenes with iodonium ylides. (b) The blue LED mediated C2–H functionalization of pyrroles/indoles/furans with iodonium ylides.



Scheme 2 Library of C2 substituted pyrroles. [a] Isolated yield; [b] separated by chromatography.



Scheme 3 Library of substituted indoles and furans. [a] Isolated yield; [b] inseparable mixture; and [c] yields calculated from ^{1}H NMR spectra.

Results and discussion

Optimization studies

To begin with, the preliminary solvent screening for the iodonium ylide mediated C–H functionalization of pyrrole, 2-methyl pyrrole **1a** and dimethyl malonate derived iodonium ylides **4a** and **4c** (in 1 : 1 equivalent) involved the use of a variety of solvents such as methanol (MeOH), dichloromethane (DCM), acetonitrile and diethyl ether (DEE) under a blue LED (5–6 W Micro Photochemical Reactor [ALDKIT001] with a blue LED light [435–445 nm] source) (only the reactions in DCM and MeOH are shown in Table 1, entries 1–4).[16] The temperature for the optimization process was maintained at 25 °C (RT). Compound **5a** was expected to be the desired product (Table 1). Among all the reactions, the ones in DCM and methanol (MeOH) were the best to provide **5a** in 30 and 34% yields, respectively (Table 1, entries 1 and 2). Diethyl ether (Et_2O) was the next best solvent. Since MeOH is a greener and safer reaction medium than DCM or Et_2O, it was used as the solvent for the remaining reactions in this optimization study. It is also noteworthy that there was almost no difference in reactivity between the iodonium ylides **4a** and **4c**; hence, due to better yield, **4a** was used as the reaction partner for the remainder of the project. To improve the yield, next, the reactions were performed with a gradual increase in the equiv. of

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Table 1 Reaction optimization for the alkylation of pyrrole with the dimethyl malonate derived iodonium ylide

Entry	Iodonium ylide **4**	Energy source	Ratio of the amount of **1a : 4**	Solvent	Temperature (°C)	% Yield[b]
1	**4a**	Blue LED	1 : 1	DCM	RT[a]	30
2	**4a**	Blue LED	1 : 1	MeOH	RT	34
3	**4a**	Blue LED	1 : 1	ACN	RT	26
4	**4a**	Blue LED	1 : 1	DEE	RT	31
3	**4c**	Blue LED	1 : 1	DCM	RT	25
5	**4c**	Blue LED	1 : 1	MeOH	RT	30
6	**4a**	Blue LED	1.5 : 1	MeOH	RT	61
7	**4a**	Blue LED	2 : 1	MeOH	RT	68
8	**4a**	Blue LED	2.5 : 1	MeOH	RT	68
9	**4a**	Dark	2.5 : 1	DCM	RT	N.R.[c]
10	**4a**	Thermal	2.5 : 1	MeOH	40	27

[a] RT ~ 25 °C. [b] Isolated yield. [c] N.R. = no reaction.

1a from 1→1.5→2.0 equiv. (Table 1, entries 2, 6 and 7). Subsequently, the yield of **5a** improved from 34% to 68%, respectively (Table 1, entries 2, 5 and 6). Interestingly, with 2.5 equiv. of **1a**, the reactions in MeOH could not be improved further and provided **5a** in nearly the same yield as it was with 2 equiv. of **1a** (Table 1, entry 8). It is noteworthy that the reaction in the dark could not afford any product (Table 1, entry 10), and under thermal heating at 40 °C, the desired compound **5a** was obtained in only 27% yield along with the formation of a substantial amount of impurities (Table 1, entry 10). Hence, entry 7 (Table 1) depicts the optimized conditions for the alkylation of pyrrole **1a** with the dimethyl malonate derived iodonium ylide **4a**. The average reaction time for all the reactions was ~6 h.

Substitution of pyrroles, indoles and furans

With the optimized conditions in hand, various pyrroles **1a–i** were alkylated with dimethyl- and diethyl-malonate derived iodonium ylides **4a** and **4b** to provide mono- and di-substituted pyrroles **5a–k** as products in moderate to good yields (Scheme 2). Unsubstituted 2-methyl pyrrole and pyrrole **1a** and **1b**, when reacted with **4a** and **4b**, provided the C2 substituted products **5a**, **5b** and **5l** in 64 to 71% yields as the exclusive products (Scheme 2). On the other hand, 3-methyl pyrrole **1c** afforded an equimolar mixture of C2 and C5 substituted products **5c** and **5d** (Scheme 2). The electron rich 2,4-dimethyl pyrrole **1d** provided a mixture of mono- and di-substituted products **5e/f** in an equimolar amount (Scheme 2). These compounds were separately isolated from their equimolar mixture by column chromatography. Unfortunately, the electron poor 2-cyano pyrrole **1e** failed to afford the desired compound **5g** (Scheme 2) as it remained completely unreacted during the reaction. The *N*-Boc and *N*-benzyl, pyrrole and 2-methyl pyrrole, **1f–i**, afforded the C2 substituted compounds **5h–k** as the exclusive products (Scheme 2). Overall regioisomeric mixtures of products were obtained with C3 methyl substituted pyrroles, *i.e.*, **1c** and **1d**. This could occur due to the inductive effect exerted by the methyl moiety and also because of the fact that both the C2 and C5 positions were available for occupying.

The optimized reaction conditions were not limited to pyrroles and were extended in the reaction of diverse indoles **2a–l** with **4a** (Scheme 3). A variety of *N*-free indoles *viz.* **2a–f** afforded either exclusive or mixtures of C2 and C3 substituted products, depending on the substitution on the indoles. For example, indole **2a**, 6-methoxy indole **2b** and 7-methyl indole **2c** provided inseparable mixtures of C2 and C3 substituted compounds **6a/a′**, **6b/b′** and **6c/c′** with overall yields of 54–61% (Scheme 3). However, only C3 substituted product **5d** was isolated with 7-azaindole **2d** in 61% yield, and 3-methyl indole **2e** and indole-3-methyl acetate **2f** afforded exclusively C2 substituted products **6e** and **6f** in 66% and 63% yields, respectively (Scheme 3). Similarly, the *N*-Boc indole derivatives **2g–k** afforded C3 alkylated products **6g–k** exclusively with 61–64% yields, irrespective of the nature of the substituents on the indole aromatic ring. *N*-Methyl indole **2l** provided the C2 substituted product **6l** in 69% yield (Scheme 3). This difference in the generation of mixtures and exclusive products between **2a–c** and **2d–l**, respectively, could arise from the substitution at the nitrogen or on the pyrrole ring of the indole nucleus. The NH^- free indoles **2a–c** could provide an equal opportunity of the formation of either C2 or C3 substituted products. However, *N*- or C3-substituted indoles afforded a single product as a result of the substituent effect. In addition to pyrrole and indole derivatives, when furans **3a** and **3b** reacted with **4a** in the presence of a blue LED, we observed exclusively C2-substitued alkylated furans **7a** and **7b** in decent yields of 61% and 64%, respectively.

Control reactions

To understand the reaction mechanism of the blue LED induced C–H functionalization of indoles and pyrroles with

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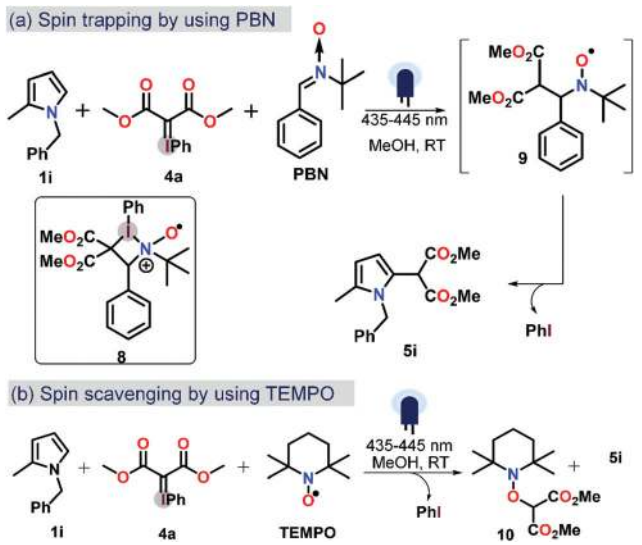
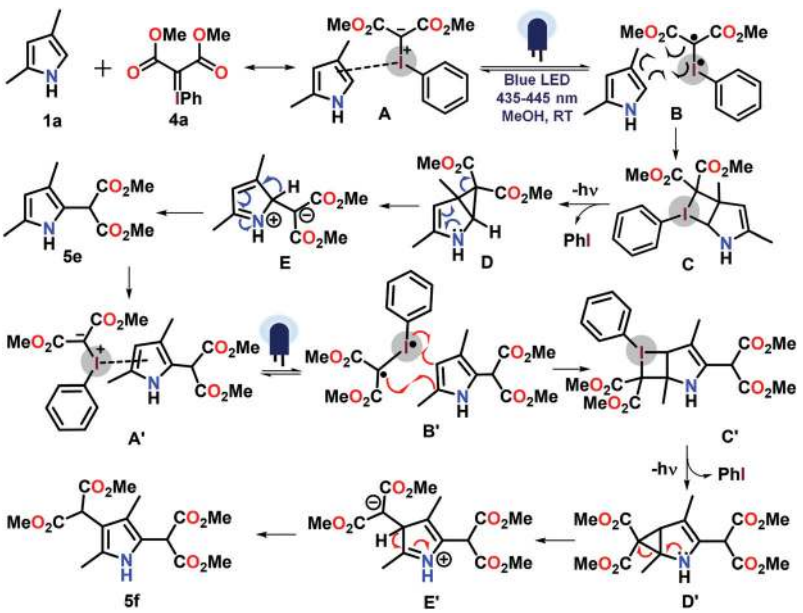
4a, control experiments were conducted. Literature precedents made us believe that this C–H functionalization protocol works through a radical pathway. Hence, a blue LED mediated reaction without pyrrole (**1i**) was performed in the presence of the radical trapping reagent phenyl *N*-*t*-butylnitrone (PBN) with **4a** in MeOH and was monitored by ESI-HRMS (see ESI-I, Fig. S6–S8†) (Scheme 4a). In ESI-HRMS analysis, the presence of intermediate **9** (see ESI-I, Fig. S6–S8†) was observed which could have been formed by the elimination of iodobenzene (PhI) from the speculated azaiodocyclobutane intermediate **8** (inspired by an earlier report by Murphy *et al.*).[15b] Interestingly, when the same reaction was carried out in the presence of **1i** (Scheme 4a), the spin intermediate **9** was detected along with the desired product **5i** (Scheme 4a). In both reactions, the reactions (see ESI-I, Fig. S6–S8† and Scheme 4b) and the existence of **9** were further confirmed by the targeted LC/MS/MS analysis (Fig. S8†). Next, the reaction in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine N-oxide (TEMPO) showed significant inhibition in the formation of **5i** (Scheme 4b and Fig. S8†). Furthermore, the kinetic isotope effect (KIE) study of **1i** and its deuterated analogue (**1i–D**) was performed under optimized conditions by reacting with compound **4a** to provide a KIE (k_H/k_D) of 0.94 (ESI-I, Fig. S1–S5†). This indicated that there is no direct involvement of the C2–H bond in the rate determining step of the reaction. Hence, all these observations strongly suggested the involvement of a radical pathway in our blue LED mediated C–H functionalization reaction with the iodonium ylide **4a**.



Scheme 4 Control experiments.

From the control experiments and literature reports, the probable mechanism of the reaction between the dialkyl malonate derived iodonium ylides **4a**/**b** and the pyrroles, indoles and furans (**1**–**3**) under a blue LED is depicted in Scheme 5. The reaction of 2,4-dimethyl pyrrole **1d** and **4a** was used for illustrating the mechanism as it generated both the C2 and C4 alkylated products **5e**/**f** (Scheme 2). It is expected that the photoexcitation of **4a** with the blue LED will provide the diradical intermediate **B**, which could react with **1d** at either the C2–C3 or C4–C5 bond, to undergo a ring closure *via* concerted or sequential bond formation to generate the iodocyclobutanes **C** and **C′** (as depicted by Murphy and co-workers)[16b] followed by reductive elimination to afford the cyclopropane intermediates **D** and **D′** along with iodobenzene as the by-product. The cyclopropane ring on **D** and **D′** opens up at C4 and C2, respectively, followed by rearomatization of the pyrrole ring at **E** and **E′** to afford the desired products **5e** and **5f** (Scheme 5).



Scheme 5 Putative mechanism of alkylation of pyrroles and indoles.

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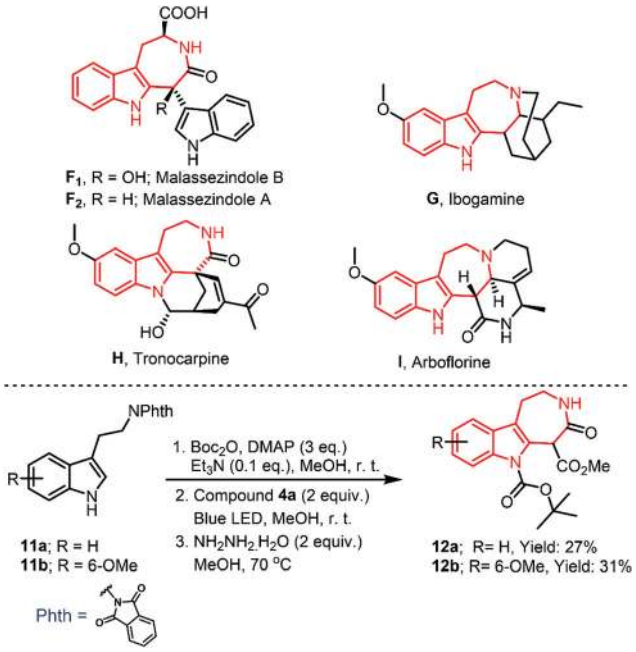

Scheme 6 One pot indole protection, C–H activation and deprotection of tryptamine derivatives to afford azepino[4,5-*b*]indoles.

Applications: synthesis of azepino[4,5-*b*]indoles 12

Among a myriad of indole fused polycyclic motifs that occur naturally as alkaloids, biologically active compounds and various active pharmaceutical ingredients, azepino[4,5-*b*] indole structures have gained elevated attention due to their ubiquitous presence in natural products such as malassezindole **F**, ibogamine **G**, tronocarpine **H**, arboflorine **I** (Scheme 6) and many more.[17] These compounds have shown therapeutic effects against cancer as cyclin dependent kinase (CDK) and glycogen synthase kinase (GSK) inhibitors.[18] Hence, facile synthetic strategies to access these scaffolds are desirable. Herein, to demonstrate the utility of our blue LED mediated hypervalent iodine based heterocyclic functionalization methodology, tryptamine derivatives **11** were transformed into azepino[4,5-*b*] indoles **12** (Scheme 6). Very recently, a one-pot three-step procedure was reported by our group for the synthesis of γ-carbolines.[19] Herein, a similar approach was applied for the synthesis of **12**. Hence, a one-pot *N*-Boc protection of **11a**/**b** (purchased commercially), subsequent C2 alkylation with **4a** (using the optimized conditions for C–H activation shown in Table 1) and finally phthalimide deprotection to facilitate the cyclization afforded the azepino[4,5-*b*] indoles **12a**/**b** in 27 and 34% overall yields (Scheme 6). The one-pot reaction sequence occurred smoothly in the presence of methanol, and the final product was purified by column chromatography.

Conclusion

Herein, we have demonstrated a sustainable C2–H bond functionalization of pyrroles, indoles and furans with the dialkyl malonate derived iodonium ylide **4a** under a blue LED in methanol. The desired alkylated products are obtained in moderate to good yields. The green nature of such HVI reagents used in this approach makes this transformation extremely interesting and provides an opportunity to scale it up from the laboratory to a production scale. The application of this methodology is demonstrated to generate compounds with the azepino[4,5-*b*] indole framework. This is particularly interesting because this motif is present in various natural products. Control reactions provided insight into the mechanism of the reaction.

Experimental procedures

Full experimental procedures are provided in the ESI.†

Author contributions

S. B. S. designed the strategy. S. S., R. D., D. B., S. G. and P. L. performed and analysed all chemical experiments. R. D. designed the control experiments. All authors contributed to writing this manuscript.

Conflicts of interest

The authors declare no competing interests.

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