This article can be cited before page numbers have been issued, to do this please use: P. Natho, Z. Yang, L. Allen, J. Rey, A. J. P. White and P. Parsons, *Org. Biomol. Chem.*, 2021, DOI: 10.1039/D1OB00430A.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
COMMUNICATION

An entry to 2-(cyclobut-1-en-1-yl)-1H-indoles through a
cyclobutenylation/deprotection cascade

Philipp Natho, a Zeyu Yang, a Lewis A. T. Allen, a Juliette Rey, a Andrew J. P. White, a Philip J. Parsons* a

A transition-metal-free strategy for the synthesis of 2-(cyclobut-1-en-1-yl)-1H-indoles under mild conditions is described herein. A series of substituted 2-(cyclobut-1-en-1-yl)-1H-indoles are accessed by a one-pot cyclobutenylation/deprotection cascade from N-Boc protected indoles. Preliminary experimental and density functional theory calculations suggest that a Boc-group transfer is involved in the underlying mechanism.

Introduction

The indole moiety is a privileged structural motif found in a wide range of natural products, active pharmaceutical agents, agrochemical products, and even functional materials. 1-3 Based on its versatile applications and properties, the invention of protocols for the regioselective direct functionalisation of indoles has been a long-standing goal in organic synthesis. 4-11 and C-H alkenylation is among the effective strategies for the introduction of molecular complexity that received particular attention. 12 Classically, alkenylation of indoles has been achieved by the hydroarylation of alkynes or an oxidative Heck reaction between aryl C(sp²)-H bonds and alkynes. 13,14

In contrast with functionalisation of the electron-rich C3-position of indole, alkenylation of the significantly less activated C2-position is a more challenging task, and as such, new methods to overcome this intrinsic selectivity are highly desirable. Although other tactics have been reported, 15-18 the use of metal-chelating directing groups on the indole nitrogen has been established as a general and broadly adopted strategy. To this end, a variety of different directing groups, such as N-carbamoyl, 19-22 N-acyl, 23-25 N-pyridyl sulfonyl, 26-28 N-pyrimidyl, 29-35 and others, 36-40 have successfully enabled the metal-catalysed C2-selective oxidative Heck reaction between alkenes and indole (Scheme 1, a). Similarly, C2-alkenylation of indole can also be effected by a transition-metal-catalysed C-H addition across alkynes when guided by an appropriate directing group, such as N-carbamoyl, 41,42 N-pyridyl, 43,44 or N-pyrimidyl 45-51 (Scheme 1, a).

Although these elegant C-H functionalisation protocols enable the regioselective C2-alkenylation of indole, removal of the directing group poses significant drawbacks when it is no longer desired in the target molecule. For example, deprotection strategies can limit functional group compatibility, as harsh reaction conditions are often required, or lead to dead ends in multi-step syntheses when the directing group proves to be non-removable. To avoid the aforementioned shortcomings, the development of one-pot C2-alkenylation/directing group-removal cascades is highly desirable, and seminal studies by Kim, 52,53 Zeng, 54 Matsunaga, 55 and Zhao 56 have recently established the viability of this approach (Scheme 1, a).

Despite these advances, the direct C2-alkenylation of indole is still largely limited to the installation of acyclic alkenes. Strained cyclic alkenes are inaccessible hitherto, and a direct route to 2-(cyclobut-1-en-1-yl)-1H-indoles remains unprecedented. 57,58 This is surprising given that 2-(cyclobut-1-en-1-yl)-1H-indole analogues and their saturated counterparts have shown promising biological activity, such as the reduction of pain by selective dual iNOS/nNOS inhibition, 59 or anticaner activity by tubulin polymerisation inhibition (Scheme 1, b). 60

The use of four-membered ring building blocks in medicinal chemistry remains relatively underdeveloped as chemists depend on a small number of viable protocols towards these moieties. 61,62 Given our laboratory’s interest in the use of four-membered rings to access biologically relevant scaffolds, 53-68 we questioned if we could expand the scope of 2-alkenylation protocols to hitherto virtually inaccessible 2-(cyclobut-1-en-1-yl)-1H-indole analogues through a transition-metal-free cyclobutenylation/deprotection cascade (Scheme 1, c). Our implementation of these design criteria and computational studies on the mechanistic details are described herein.

---

a Department of Chemistry, Imperial College London, Molecular Sciences Research Hub, W12 0BZ London, UK. E-mail: p.parsons@imperial.ac.uk
b Electronic Supplementary Information (ESI) available: [Detailed experimental procedures, NMR spectra and computational methods]. See DOI: 10.1039/x0xx00000x
Results and discussion

We discovered that treatment of representative N-Boc protected indole 1a with an equimolar amount of n-butyllithium in diethyl ether at −78 °C for one hour, followed by one equivalent of cyclobutanone at the same temperature, furnished cyclobutene 2a in 20% yield (Table 1, entry 1). Investigation into the composition of the crude reaction mixture revealed the presence of trace quantities of indole and approximately 50% starting material.

On the basis of these results, we initially chose to adjust the ratio of 1a and cyclobutanone. Pleasingly, using a two-fold excess of N-Boc protected indole and n-butyllithium with respect to cyclobutanone led to a significant improvement and provided the cyclobutene 2a in 47% yield (Table 1, entry 2).

Encouraged by this result, we next turned our attention to a screen of additional factors influencing the outcome of the reaction. First, the choice of base and reaction temperature were investigated. When n-butyllithium was substituted with sec-butyllithium, tert-butyllithium, lithium diisopropylamide, or a Turbo-Hauser base (TMPMg.LiCl), the reaction proceeded with inferior outcome or was shut down completely (Table 1, entries 3-6). Equally, raising the temperature during deprotonation to −40 °C or room temperature did not improve the outcome of the reaction, which we attributed to the instability of the protecting group under these reaction conditions (Table 1, entries 7-8). Next, we decided to screen solvents with different dielectric constants. The use of polar methyl tert-butyl ether led to a significant reduction of the reaction yield, whereas apolar solvents, including toluene and pentane, proved to be unsuitable reaction mediums, leading to complete cessation of the reaction (Table 1, entries 9-11).

Finally, we questioned whether other common protecting groups would be compatible with this tandem reaction. Of the additional protecting groups that we screened, including sulfonyl- and alkyl-based moieties, none were suitable for this tandem reaction and no cyclobutene 2a was formed (Table 1, entries 12-15). In the case of N-tosyl indole and N-methyl indole, we obtained the corresponding cyclobutanol addition product, whereas the reaction of N-Cbz indole and N-ethyloxycarbonyl indole mainly afforded starting material. This underscored the unique effectiveness of the Boc-protecting group to engage in this tandem reaction. Full disclosure of our optimisation studies is available in the Supplementary Information.
With optimal reaction conditions in hand (Table 1, entry 2), we sought to define the scope and limitations of our cyclobutenylation/deprotection cascade using a variety of differently substituted Boc-protected indoles 1a-o. These substrates were readily synthesised by treatment of commercially available indoles with di-tert-butyl dicarbonate and 4-dimethylaminopyridine in dichloromethane at room temperature (see Supplementary Information). As shown in Scheme 2, our choice of substituted indoles was determined by the ambition to cover a range of electronic properties, while avoiding substrates that are incompatible with \( \text{Boc} \)-lithium.

In the event, we were pleased to find that weakly activated 5-halogenated indoles 1b and 1c underwent the tandem alkenylation/deprotection sequence in up to 35% isolated yield. Gratifyingly, more strongly activated substances containing methoxy- or benzyloxy substituents 1d and 1e successfully participated in the desired cyclobutenylation/deprotection cascade to afford indoles 2d and 2e in 28% and 29% yield, respectively. The structure of the 5-methoxylated cyclobutenyl indole 2d was confirmed by x-ray crystallography. It is worth noting that in the crystalline form, the cyclobutene moiety resides in-plane with the indole system to extend the conjugated system. Next, we turned our attention to studying the effect of positional isomerism of weakly activated methyl-substituted indole. Indoles containing a methyl substituent in the C4-, C5-, C6-, and C7-position (1f-1i) all afforded the corresponding cyclobutenes 2f-2i in 20-51% yield under our standard reaction conditions. Notably, the best isolated yield was achieved for the 5-methoxylated substrate 2g, which furnished the corresponding cyclobutenyl in nearly double the yield compared with the other positional isomers. This positional isomer effect was even more pronounced for strongly electron-donating methoxy-substituted indole, for which the 4-methoxylated analogue 2j was afforded in significantly reduced 12% yield in comparison with 32% yield obtained for the 5-methoxylated analogue 2d. In contrast, electron-deficient 4-fluorinated indole 1k furnished the desired cyclobutene 2k in improved 34% yield compared with the 5-fluorinated derivative 2c. Moreover, we were pleased to find that the reaction of \( \text{N-Boc} \) protected benzimidazole, a privileged pharmacophore, delivered the expected cyclobutene 2l in 27% yield. Highly electron-deficient Boc-protected 4,6-difluoroindole 1m, on the other hand, afforded the corresponding cyclobutene 2m in measurable, but low 8% yield, which we attributed in part to its rapid decomposition during work-up and isolation. In contrast with other analogues, indole 2m was found to be unstable even at low temperatures under an atmosphere of nitrogen.

**Scheme 2. Substrate scope of the cyclobutenylation/deprotection cascade.**

---

**Table 1. Optimisation of Reaction Conditions.**

| Entry | Variation from above conditions\(^a\) | Yield [%]\(^b\) |
|-------|--------------------------------------|---------------|
| 1     | none                                 | 20            |
| 2     | Two equivalents of N-Boc indole and n-BuLi with respect to cyclobutanone | 53 (47)\(^c\) |
| 3\(^d\) | sec-BuLi instead of n-BuLi | 23          |
| 4\(^d\) | tert-BuLi instead of n-BuLi | 15          |
| 5\(^d\) | LDA instead of n-BuLi | --          |
| 6\(^d\) | TMPMg.LiCl instead of n-BuLi | --          |
| 7\(^d\) | Deprotonation at \(-40^\circ\) C instead of \(-78\) C | 16          |
| 8\(^d\) | Deprotonation at rt instead of \(-78\) C | --          |
| 9\(^d\) | Toluene instead of diethyl ether | --          |
| 10\(^d\) | Pentane instead of diethyl ether | --          |
| 11\(^d\) | Methyl tert-butyl ether instead of diethyl ether | 22          |
| 12\(^d\) | N-Tosyl instead of N-Boc | --          |
| 13\(^d\) | N-Methyl instead of N-Boc | --          |
| 14\(^d\) | N-Cbz instead of N-Boc | --          |
| 15\(^d\) | N-Ethoxycarbonyl instead of N-Boc | --          |

\(^a\) Initial conditions: 1a (1.0 mmol), \(-\text{Boc}\)lithium (1.1 mmol), \(\text{Et}_2\text{O}\) (4 mL), \(-78^\circ\) C, 1 hr, then cyclobutanone (1.0 mmol), \(-78^\circ\) C to rt, 17 hrs.  
\(^b\) \(\text{H-NMR}\) yields based on 1,4-dinitrobenzene as internal standard.  
\(^c\) Number in parentheses refers to isolated yield.  
\(^d\) Reagent stoichiometry was changed to: 1a (1.0 mmol), \(-\text{Boc}\)lithium (1.1 mmol), cyclobutanone (0.5 mmol).
Nevertheless, there are limitations to the current cyclobutenylation/deprotection cascade. We discovered that the successful conversion of Boc-protected indoles to cyclobutenes hinged on the presence of an unsubstituted 3-position. For example, when 3-methylated indole 1n was subjected to our standard conditions, a mixture of starting material and 3-methylindole was isolated, which we initially attributed to the facile deprotonation of the methyl group. Consequently, we hypothesised that 3-trifluoromethylated cyclobutenes hinged on the presence of an unsubstituted 3-position. In the event, however, we found that also this analogue was ineffective at delivering the desired cycloalkenylation/deprotection cascade when subjected to our standard conditions. In the event, however, we found that also this analogue was ineffective at delivering the desired cycloalkenylation/deprotection cascade when subjected to our standard conditions. In the event, however, we found that also this analogue was ineffective at delivering the desired cycloalkenylation/deprotection cascade when subjected to our standard conditions. Hence, in order to differentiate between the two proposed elimination pathways, we conducted experiments in deuterium-labeled solvents and compared the kinetic isotope effect. The results of these experiments are shown in Scheme 3, path b). We found that the isotope effect was 11.4 kcal mol\(^{-1}\) for the 2-cyclobutylidene-2H-indole D (path b), which is lower than the nucleophilic addition step. This lower isotope effect suggests that the elimination step is rate-determining for the 2-cyclobutylidene-2H-indole D (path b). The calculated transition state energy barrier for TS1 is 11.4 kcal mol\(^{-1}\) and for TS2 is 12.9 kcal mol\(^{-1}\). Next, an intramolecular nucleophilic addition step follows, which is energetically favourable. The resulting carbonate C was found to be 11.6 kcal mol\(^{-1}\) lower in energy than carbamate B, which supported our hypothesis that an in situ Boc-group transfer is indeed energetically favourable. Finally, in order to differentiate between the two proposed elimination pathways, we compared the relative acidities of the intermediates C and D by quantum mechanical methods. The pK\(_a\) values of the β-hydrogen of carbonate C and the allylic hydrogen of D were calculated to be 50.3 and 40.5, respectively (see Supplementary Information). Therefore, the allylic hydrogen of D is more readily deprotonated. We proposed that the most likely fate of the carbonate group was then to undergo an elimination, which was thermodynamically driven by the release of carbon dioxide and tert-butanol. Two plausible pathways are thus proposed for the conversion of carbonate C to the final product: (i) an intramolecular elimination pathway in which C3-substituted indoles also failed to deliver the desired products. Moreover, we found that other ketones, including linear ketones and other cycloalkanones, do not undergo the desired cycloalkenylation/deprotection cascade under these reaction conditions.

To conclude our study, we sought to elucidate a plausible mechanism for the one-pot cyclobutenylation/deprotection cascade. We found the role of the N-protecting group of particular interest and again turned to deuterium studies to investigate its stability (Scheme 3, A and Supplementary Information). To our surprise, these experiments revealed that the N-Boc group was tolerant to treatment with n-butyllithium even after extended reaction durations, which to us indicated that the observed deprotection of the Boc-group occurred after the introduction of cyclobutane to the reaction mixture. We postulated that the unique effectiveness of the Boc-protecting group for this tandem reaction stems from its ideal compromise between stability to tolerate treatment with n-butyllithium and susceptibility to subsequent deprotection. On this basis, a plausible reaction mechanism for the described cascade is presented in Scheme 3, B. We hypothesised that in situ generated organolithium A underwent nucleophilic addition to cyclobutane to reveal alkoide B, which, facilitated by its spatial proximity to the Boc-group, added to the carbamate to furnish carbonate C. We postulated that the most likely fate of the carbonate group was then to undergo an elimination, which was thermodynamically driven by the release of carbon dioxide and tert-butanol. Two plausible pathways are thus proposed for the conversion of carbonate C to the final product: (i) an intramolecular elimination pathway via 2-cyclobutylidene-2H-indole D (red, path a); or (ii) an intermolecular process by deprotonation of the neighbouring hydrogen atom (blue, path b).

Given the ambiguity of the elimination step, we further probed the underlying mechanism with a computational study. All calculations were performed at the B3LYP/6-311+G(d,p)/B3LYP/6-31G(d,p) level in diethyl ether with the IEF-PCM solvation model and N-Boc-protected indole 1a as a representative example (Figure 1). In line with our experimental results, the C2-deprotonated indole A undergoes nucleophilic addition to cyclobutanone to form alkoxide B, in which the anionic charge is mainly located on the oxygen. The calculated transition state energy barrier to TS1 is 11.4 kcal mol\(^{-1}\) and formation of alkoxide B is exothermic by 12.9 kcal mol\(^{-1}\). Next, an intramolecular Boc-group transfer from indole to the alkoxide takes place to yield carbonate C via a late transition state TS2 with a relative low energy barrier of 5.4 kcal mol\(^{-1}\). The resulting carbonate C was found to be 11.6 kcal mol\(^{-1}\) lower in energy than carbamate B, which supported our hypothesis that an in situ Boc-group transfer is indeed energetically favourable.

Finally, in order to differentiate between the two proposed elimination pathways (Scheme 3, path a vs path b), we compared the relative acidities of intermediates C and D by quantum mechanical methods. The pK\(_a\) values of the β-hydrogen of carbonate C and the allylic hydrogen of D were calculated to be 50.3 and 40.5, respectively (see Supplementary Information). Therefore, the allylic hydrogen of D is more readily deprotonated than C, and as such, we concluded that an intramolecular elimination/isomerisation pathway (path a) is possible. We located the transition state TS3 and our calculations suggest that this elimination step is plausible as it is exothermic overall (3.2 kcal mol\(^{-1}\)) and not rate-determining (ΔG\(^f\) = 10.3 kcal mol\(^{-1}\); 1.1 kcal mol\(^{-1}\) lower than the intramolecular nucleophilic addition step). Based on our combined experimental results and computational calculations, we suggest that a mechanism consisting of intramolecular Boc-group transfer followed by intramolecular carbonate elimination/isomerisation (path b) is in operation for the formation of the desired 2-(cyclobut-1-en-1-yl)-1H-indoles.
Figure 1. Free energy profile for the transformation from A to 2-cyclobutylidene-2H-indole D (path a in Scheme 3).

Conclusions
In summary, we report the first synthesis of 2-(cyclobut-1-en-1-yl)-1H-indoles through a one-pot cyclobutenylation/deprotection cascade. A series of substituted 2-(cyclobut-1-en-1-yl)-1H-indoles was obtained in up to 51% yield in one step from readily accessible N-Boc protected indoles by treatment with n-butyllithium, followed by the addition of cyclobutanone. Furthermore, DFT calculations confirmed that a plausible reaction mechanism involved the transfer of the Boc-group from indole to the intermediate alkoxide.

Conflicts of interest
There are no conflicts to declare.

Acknowledgements
The authors gratefully acknowledge an EPSRC Imperial College President’s Scholarship (to P.N.) and additional funding from Dr Isabel Bader and her late husband Dr Alfred Bader (to P.J.P.) and Oxana Bennett (to P.J.P.). The authors thank Pete Haycock, Corey Fülöp and Dr Lisa Haigh for NMR and mass spectrometric analysis at Imperial College London. The authors also acknowledge the service and support from Imperial College Research Computing Service (DOI: 10.14469/hpc/2232). JChem for Excel was used for producing and handling structure data files (SDF), JChem for Excel 21.3.0.817, ChemAxon (https://www.chemaxon.com).

Notes and references
1. J. A. Leitch, Y. Bhonoah and C. G. Frost, ACS Catal., 2017, 7, 5618–5627.
2. A. H. Sandtorv, Adv. Synth. Catal., 2015, 357, 2403–2435.
3. D. A. Horton, G. T. Bourne and M. L. Smythe, Chem. Rev., 2003, 103, 893–930.
4. S. Cacchi and G. Fabrizi, Chem. Rev., 2005, 105, 2873–2920.
5. G. R. Humphrey and J. T. Kuether, Chem. Rev., 2006, 106, 2875–2911.
6. M. Bandini and A. Eichholzer, Angew. Chem. Int. Ed., 2009, 48, 9608–9644.
7. L. Joucla and L. Djakovitch, Adv. Synth. Catal., 2009, 351, 673–714.
8. G. W. Gribble, J. Chem. Soc. Perkin Trans. 1, 2000, 1045–1075.
9. G. W. Gribble, Pure Appl. Chem., 2003, 75, 1417–1432.
10. S. Agarwal, S. Cammerer, S. Filali, P. Frohner, J. Knoll, M. Krahl, K. Reddy and H.-J. Knolker,Curr. Org. Chem., 2005, 9, 1601–1614.
11. M. Inman and C. J. Moody, Chem. Sci., 2013, 4, 29–41.
12. F. Zhang and D. R. Spring, Chem. Soc. Rev., 2014, 43, 6906–6919.
13. I. Moritani and Y. Fujiwara, Tetrahedron Lett., 1967, 8, 1119–1122.
14. Y. Fujiwara, I. Moritani, M. Matsuda and S. Teranishi, Tetrahedron Lett., 1968, 9, 633–636.
15. N. P. Grimster, C. Gauntlett, C. R. A. Godfrey and M. J. Gaunt, Angew. Chem. Int. Ed., 2005, 44, 3125–3129.
16. Y. Nakao, K. S. Kanyiva, S. Oda and T. Hiyama, J. Am. Chem. Soc., 2006, 128, 8146–8147.
17. A. Maehara, H. Tsurugi, T. Satoh and M. Miura, Org. Lett.,
2020, 151695.

69 J.-P. Wu, S. Sanyal, Z.-H. Lu and C. H. Senanayake, *Tetrahedron Lett.*, 2009, 50, 5667–5669.

70 H. Ila, J. Markiewicz, V. Malakhov and P. Knochel, *Synthesis*, 2013, 45, 2343–2371.

71 C. Agami and F. Couty, *Tetrahedron*, 2002, 58, 2701–2724.

72 A. D. Becke, *J. Chem. Phys.*, 1993, 98, 5648–5652.

73 C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, 37, 785–789.

74 T. H. Dunning, *J. Chem. Phys.*, 1989, 90, 1007–1023.

75 S. Miertuš, E. Scrocco and J. Tomasi, *Chem. Phys.*, 1981, 55, 117–129.

76 Q. Zeng, M. R. Jones and B. R. Brooks, *J. Comput. Aided. Mol. Des.*, 2018, 32, 1179–1189.