Dalton Transactions

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Dalton Trans.*, 2023, **52**, 5039

Received 10th March 2023,
Accepted 10th April 2023

DOI: 10.1039/d3dt00745f

rsc.li/dalton

$B(3,4,5\text{-}F_3H_2C_6)_3$ Lewis acid-catalysed C3-allylation of indoles†

Nusaybah Alotaibi, [a] Rasool Babaahmadi, [a] Milan Pramanik,[a] Tanja Kaehler,[a] Ayan Dasgupta,[a,b] Emma Richards, [a] Alireza Ariafard, [c] Thomas Wirth [d] and Rebecca L. Melen *[a]

Herein we report the $B(3,4,5\text{-}F_3H_2C_6)_3$-catalysed C3-allylation of indoles using allylic esters. 25 examples of C3-allylated products are presented in up to 97% yield. The mechanism for the reaction was explored using detailed Density Functional Theory (DFT) studies.

Indole is one of the most important nitrogen-containing heteroaromatic compounds not only as an essential building block for biologically active natural products and pharmaceuticals, but also for pigments and materials science.[1] Therefore, catalytic functionalisation of electron-rich indoles has been explored extensively,[2] especially at the nucleophilic C3-position through electrophilic substitution.[3] Typically metal catalysts are employed,[2] but the major disadvantages associated with these classical metal-catalyzed C3 functionalisation reactions are the post-reaction contamination, use of precious and toxic metals, high temperature, prolonged reaction time, unwanted by-products and several side selectivity issues. In this regard, the implementation of a metal-free catalyst as a sustainable reaction strategy is highly desired in the chemical community. Recently, the use of main group catalysts such as fluorinated triaryl boranes (*e.g.* $B(C_6F_5)_3$) has gained popularity due to their potentially lower toxicity and high selectivities (Fig. 1).[4] For example, Melen, Morrill, and Pulis *et al.* used catalytic amounts of $B(C_6F_5)_3$ for the direct C3 alkylation of indoles with amine-based alkylating reagents.[5] Under similar reaction conditions, Melen *et al.* reported the introduction of alkyl groups with diazoesters *via* C–H insertion.[6] The stereoselective *C*-glycosylation of indoles with $B(C_6F_5)_3$ and glycosyl trichloroacetimidates has also been achieved by Mandal *et al.*[7] The synthesis of bis(indolyl)alkanes by a $B(C_6F_5)_3$-catalysed Markovnikov addition of indoles to aryl alkynes as well as the $B(C_6F_5)_3$-catalysed dehydrogenative C–C bond formation of indoles with *N*-tosylhydrazones have also been reported.[8,9] An interesting new approach by Tang *et al.* was the use of $B(C_6F_5)_3$ as a single-electron oxidant.[10] Here, an electron donor–acceptor complex is formed between $B(C_6F_5)_3$ and the indole which promotes a photoinduced single electron transfer event resulting in an oxidative C–S cross-coupling reaction of indoles with thiophenols.[10]

The strong Brønsted acidity of the $H_2O{\cdot}B(C_6F_5)_3$ adduct is well known,[11] and has been used by Tang *et al.* to perform dehydrative Friedel–Crafts alkylations catalytically,[12] and for

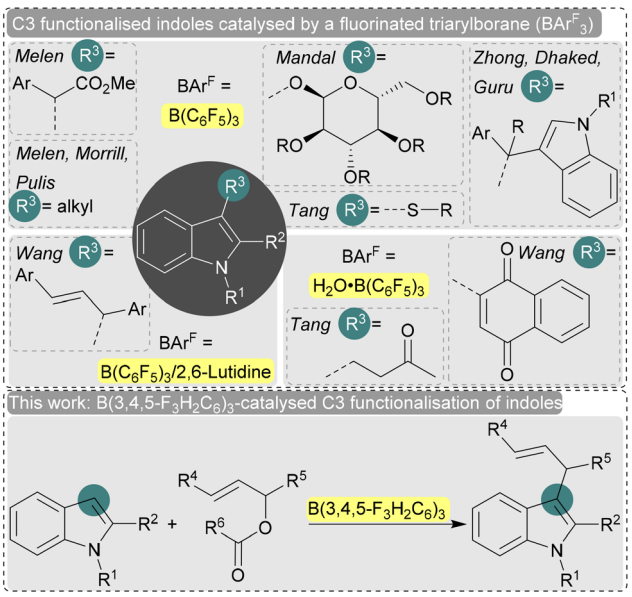


Fig. 1 Previous and current work.

[a]*Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Translational Research Hub, Maindy Road, Cathays, Cardiff, CF24 4HQ Cymru/Wales, UK. E-mail: MelenR@cardiff.ac.uk*
[b]*Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK*
[c]*School of Natural Sciences (Chemistry), University of Tasmania, Private Bag 75, Hobart, Tasmania, 7001 Australia*
[d]*School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT Cymru/Wales, UK*

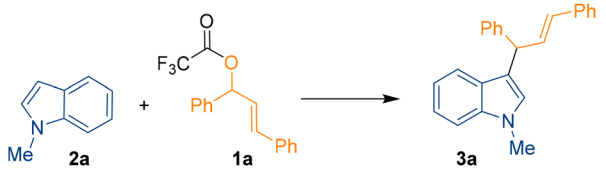
†Electronic supplementary information (ESI) available: Experimental procedures, optimisation tables, NMR spectra, DFT data. See DOI: https://doi.org/10.1039/d3dt00745f.

the C–C coupling of 1,4-naphthoquinones with indoles in water as reported by Wang *et al.*[13,14] The same group and others reported the allylation of indole in water catalysed by the $B(C_6F_5)_3$/2,6-lutidine frustrated Lewis pair.[15,16] The introduction of an allyl group yields highly functionable synthetic intermediates that are important for further manipulations.[17] However, the previous report with $B(C_6F_5)_3$/2,6-lutidine used high temperatures and no scope of the allyl reagent was explored.[15] We anticipate that a further investigation into this reaction to establish a mild catalytic reaction protocol might be of interest.

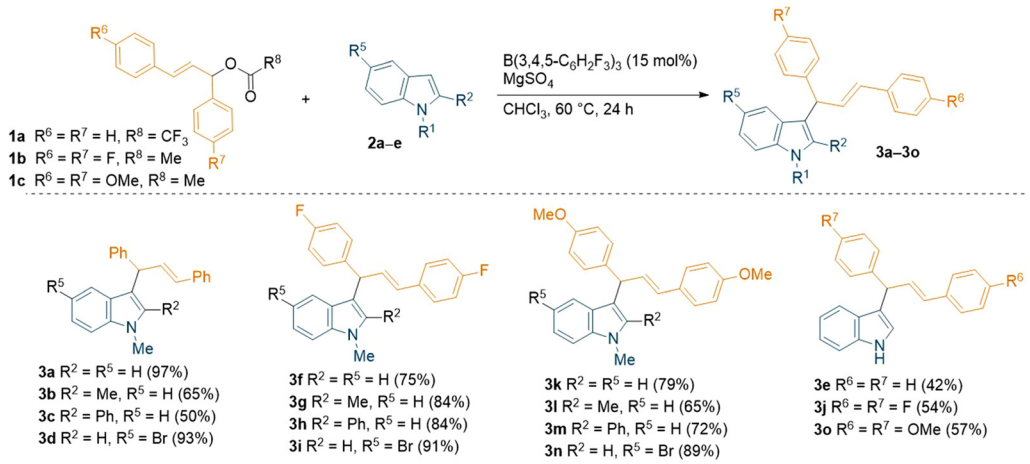
Herein we report the high yielding $B(3,4,5\text{-}F_3H_2C_6)_3$ Lewis acid-catalysed C3-allylation of indoles with allylic esters including a full DFT supported mechanistic investigation. We started our investigation by searching for the optimal reaction conditions for the C3-allylation of 1-methyl indole **2a** (1 equiv.) with allylic ester **1a** (1 equiv.) using a Lewis acid catalyst to give allylation product **3a** (Scheme 1).

A trifluoroacetic ester was used as the coupling partner since CF_3COO^- is a good leaving group. Following extensive optimisation studies (see ESI, Table S1†), we found that the optimum conditions for the reaction were 15 mol% $B(3,4,5\text{-}F_3H_2C_6)_3$ catalyst loading in chloroform for 24 h at 60 °C. Under these conditions, **3a** was formed in 97% yield. Other Lewis acids such as $B(C_6F_5)_3$, $B(2,4,6\text{-}F_3H_2C_6)_3$, $BF_3{\cdot}OEt_2$, BPh_3, and Brønsted acid trifluoroacetic acid (TFA) were screened as different catalysts but none of these produced higher yields than $B(3,4,5\text{-}F_3H_2C_6)_3$. Again, no product formation was observed in absence of the catalyst. In all reactions, $MgSO_4$ was added to ensure no residual water was helping to form $H_2O{\cdot}B(C_6F_5)_3$ or $H_2O{\cdot}B(3,4,5\text{-}F_3H_2C_6)_3$ and the reaction was not catalysed by a Brønsted acid. Following on from a previous publication from Wang *et al.*,[15] we also attempted the reaction of the alcohol derivative of **1a** with **2a** using 15 mol% $B(C_6F_5)_3$ as a catalyst in the presence of $MgSO_4$, which yielded **3a** in just 40%, confirming our choice for the ester **1a**. Other variables like catalyst loading, solvents, concentration, and stoichiometry of **1a** and **2a** were studied with $B(3,4,5\text{-}F_3H_2C_6)_3$ but did not help to improve the reactivity.

With the optimised conditions in hand, we explored the substrate scope using different commercially available indoles with diphenyl allylic ester **1a** (Scheme 2). The 5-bromo-1-methylindole afforded the desired allylated product **3d** in near-quantitative yield (93%). On the other hand, relatively lower yields (65% and 50%) were observed with more sterically hindered 1,2-dimethylindole and 1-methyl-2-phenylindole, (**2b** and **2c** respectively). Successful introduction of an allyl moiety to 1-methylindole derivatives was also achieved using allylic esters with symmetrical aryl rings bearing electron-donating group (OMe) or electron-withdrawing group (F) in *para*-position (**1c** and **1b**, Scheme 2). Regardless of the electronic effect of the substituents on **1**, the corresponding allylated products (**3f–3i**, **3k–3n**) were obtained in good to high yields (up to 91%). Interestingly, the unprotected indole also afforded the desired products (**3e**, **3j** and **3o**) in moderate yields (up to 57%). The relatively lower yields compared to the allylated 1-methylindole could be attributed to the coordination of the unprotected indole with the borane catalyst, forming a Lewis acid–base adduct. When using unsymmetrical esters **1e** or **1f** (Table 1), a mixture of two inseparable regio-isomers was formed (**3p–y**, **3p′–y′**, see ESI†) in good to high combined yields (up to 79%) possibly supporting the formation of an allylic carbocation. Despite the different electronic effect of the substituents on the aryl rings of the ester, the ratio of the two isomers determined by NMR spectroscopy was 1 : 1 in all

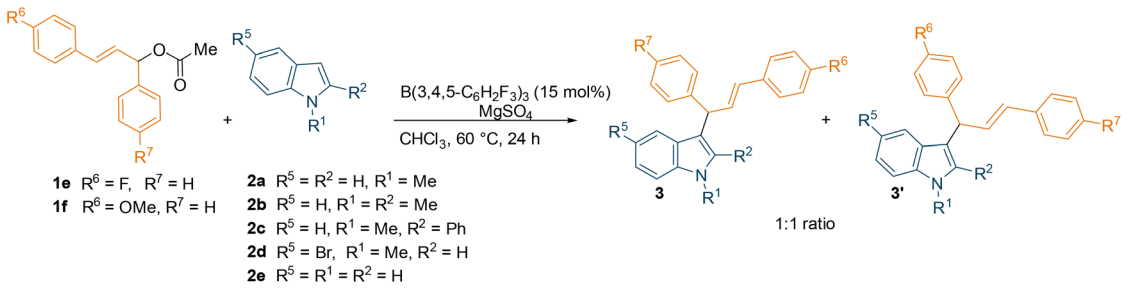


Scheme 1 C3-allylation of indoles catalysed by $B(3,4,5\text{-}F_3H_2C_6)_3$.



Scheme 2 $B(3,4,5\text{-}F_3H_2C_6)_3$-catalyzed C3-allylation of indoles using symmetrical diaryl allylic esters. All reactions were carried out on a 0.1 mmol scale; yields reported are isolated.

Table 1 $B(3,4,5\text{-}F_3H_2C_6)_3$-catalyzed C3-allylation of indoles using unsymmetrical diaryl allylic esters. All reactions were carried out on a 0.1 mmol scale; yields reported are isolated



1e R^6 = F, R^7 = H
1f R^6 = OMe, R^7 = H

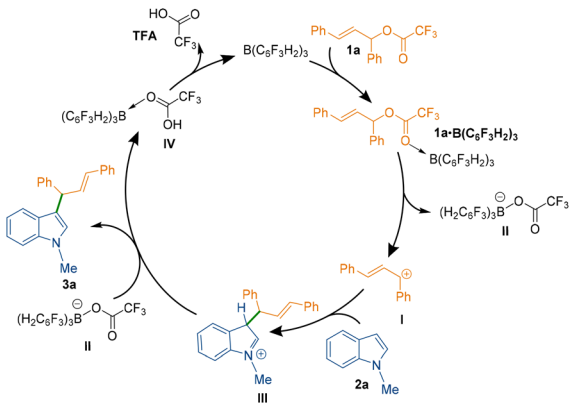
2a $R^5 = R^2$ = H, R^1 = Me
2b R^5 = H, $R^1 = R^2$ = Me
2c R^5 = H, R^1 = Me, R^2 = Ph
2d R^5 = Br, R^1 = Me, R^2 = H
2e $R^5 = R^1 = R^2$ = H

Entry	Ester	Indole	Combined yield (%)	Products	Entry	Ester	Indole	Combined yield (%)	Products
1	**1e**	**2a**	79	**3p, 3p′**	6	**1f**	**2a**	51	**3u, 3u′**
2	**1e**	**2b**	72	**3q, 3q′**	7	**1f**	**2b**	65	**3v, 3v′**
3	**1e**	**2c**	69	**3r, 3r′**	8	**1f**	**2c**	65	**3w, 3w′**
4	**1e**	**2d**	76	**3s, 3s′**	9	**1f**	**2d**	79	**3x, 3x′**
5	**1e**	**2e**	61	**3t, 3t′**	10	**1f**	**2e**	68	**3y, 3y′**

cases. However, we have tried the reaction with C3 methylated indole which did not respond under the standard reaction conditions to give the desired C2-allylation product.

To understand the mechanism of the C3-allylation of 1-methyl indole with allylic ester **1a** catalysed by $B(3,4,5\text{-}F_3H_2C_6)_3$, we performed density functional theory (DFT) calculations in chloroform at the SMD/M06-2X/def2-TZVP//SMD/M06-2X/6-31G(d) level of theory. According to the calculations, the reaction commences with the coordination of the borane catalyst to the carbonyl functionality of allylic ester **1a** to form adduct **1a·B($C_6F_3H_2$)$_3$**. This weakens the C–O bond, allowing it to be cleaved *via* transition structure **TS_2** to generate carbocation **I** and tetrahedral boron anion **II**. The indole then nucleophilically attacks the ensuing carbocation to form a new C–C bond. This attack is possible *via* two transition structures, **TS_3** and **$TS_{3'}$**. The transition structure **TS_3** has a lower energy than **$TS_{3'}$** by 7.4 kcal mol^{-1}, supporting the notion that the C3 position of indole is more nucleophilic than the C2 position.[18] Following the completion of the nucleophilic attack through **TS_3**, the iminium ion **III** is formed. **III** has a highly acidic proton and is therefore easily deprotonated by tetrahedral boron anion **II** to produce product **3a** and adduct **IV**. The TFA component of adduct **IV** is a weakly coordinating species, so it easily leaves the system and regenerates the borane catalyst in an exergonic fashion (Scheme 3 and Fig. 2, top). According to our calculations, the rate-determining step of the catalytic reaction is the nucleophilic attack of the indole on the *in situ* generated carbocation **I** *via* transition structure **TS_3** with a relative free energy of 21.5 kcal mol^{-1}. It is worth noting that dispersive interactions contribute significantly to the stability of this transition structure. This claim is verified by performing single-point calculations at the SMD/B3LYP/def2-TZVP and SMD/B3LYP-D3/def2-TZVP levels of theory on the structures optimised by SMD/M06-2X/6-31G(d).

Using B3LYP calculations, the overall activation barrier to the nucleophilic addition of the indole to the carbocation is



Scheme 3 Proposed reaction mechanism for the formation of **3a**.

calculated to be 33.8 kcal mol^{-1}, whereas it is reduced to 15.8 kcal mol^{-1} when dispersive interactions are considered using B3LYP-D3 calculations. The NCI analysis depicted in Fig. 3 confirms the presence of non-covalent interactions (NCIs) in transition structure **TS_3**, which originate primarily from π–π stacking interactions (Fig. 3). We then turned our attention to determining computationally why the replacement of ester derivative **1a** with alcohol derivative **1a_(al)** impedes the C3-allylation of 1-methyl indole. Fig. 2 (bottom) depicts the free energy profile for the C3-allylation of 1-methyl indole with allylic alcohol **1a_(al)**. As depicted, this replacement causes the activation barrier for the allylation reaction to increase to 29.3 kcal mol^{-1}. This increase in activation energy is because the key carbocation **I** in this instance has much higher energy (15.1 kcal mol^{-1} for the allylation reaction with alcohol substrate **1a_(al)** *versus* 7.3 kcal mol^{-1} for the allylation reaction with ester substrate **1**). Our calculation indicated that, although the borane catalyst binds more strongly to the alcohol substrate than to the ether substrate, the alcohol sub-

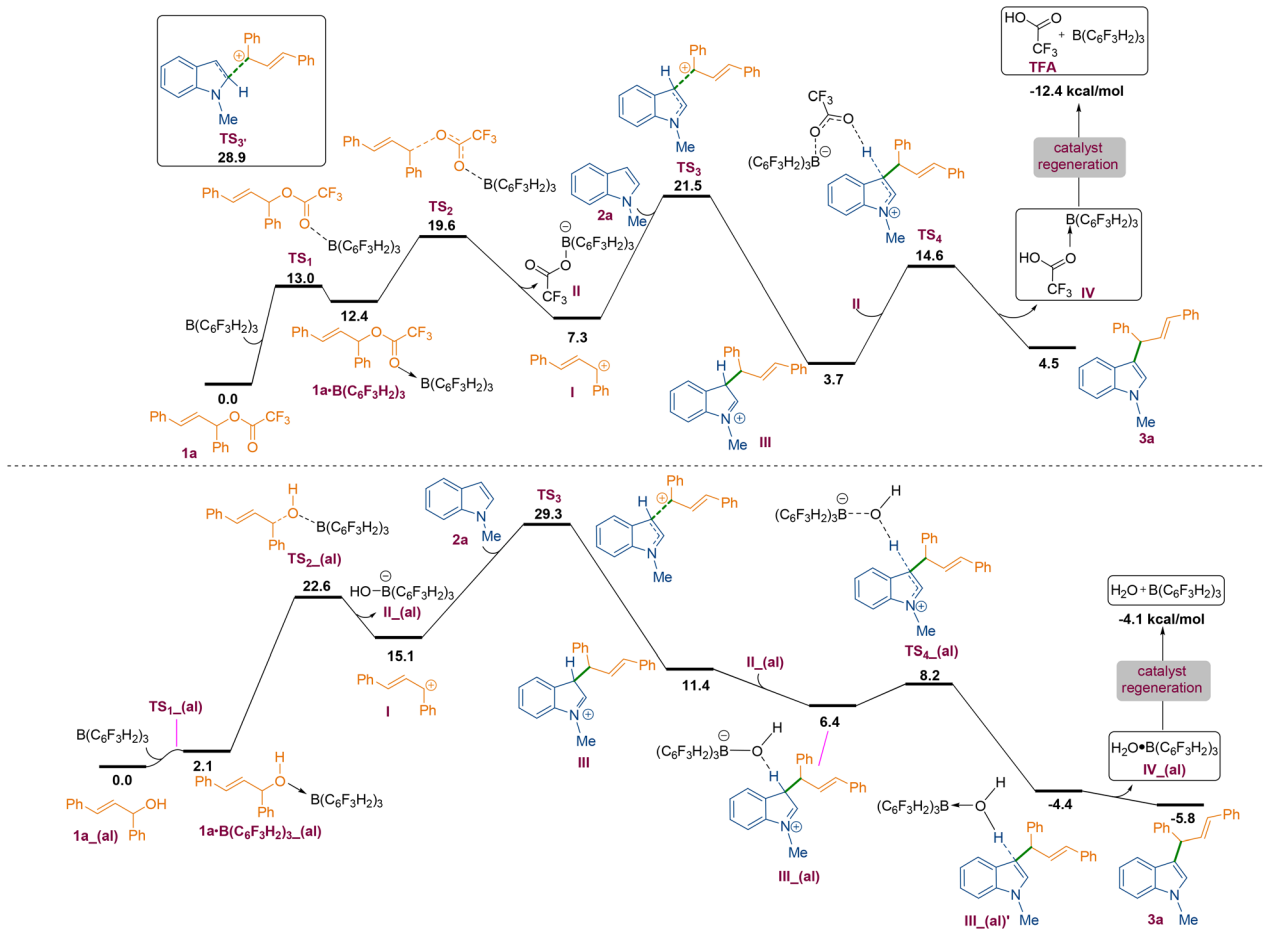


Fig. 2 DFT calculated reaction pathways for the formation of **3a** compound from the reaction of C3-allylation of 1-methyl indole with allylic ester **1a** (top) and alcohol derivative **1a_(al)** (bottom) in $CHCl_3$ using SMD/M06-2X/def2-TZVP//SMD/M06-2X/6-31G(d) level of theory. The relative free energies are given in kcal mol^{-1}.

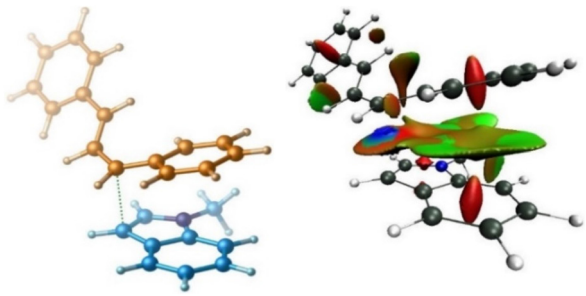


Fig. 3 The non-covalent interaction (NCI) analysis of transition structure TS_3.

strate is less reactive towards the formation of the key carbocation. Thus, the nature of the leaving group on the allylic substrate largely dictates the ease of such reactions.

In conclusion, we have demonstrated the $B(3,4,5\text{-}F_3H_2C_6)_3$ Lewis acid catalysed C3-allylation of indoles using allylic ester substrates giving 25 examples of allylated products in moderate to excellent yields. The mechanism for the reaction was fully explored by DFT studies which demonstrate that an ester substrate is crucial for the reaction to proceed. Other reactions using the $B(3,4,5\text{-}F_3H_2C_6)_3$ Lewis acid are ongoing in our group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

R.B. would like to thank the Royal Society for a Newton International Fellowship (NIF\R1\211330). A.D., E.R., and R.L.M. thank the Leverhulme Trust (RPG-2020-016)., and M.P.T.K. and R.L.M. thank the EPSRC (EP/R026912/1) for funding. R.B. and A.A. also thank the Australian National Computational Infrastructure Digital Research Services, IT Services at the University of Tasmania for the generous allocation of computing time. N.A. also acknowledges support from the Saudi Ministry of Education and the King Faisal

University, Saudi Arabia. Information about the data that underpins the results presented in this article can be found in the Cardiff University data catalogue at http://doi.org/10.17035/d.2023.0252049034.

References

1 (*a*) R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, 1970; (*b*) R. K. Brown, *Indoles Part I*, Wiley-Interscience, New York, 1972.
2 (*a*) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608; (*b*) R. Dalpozzo, *Chem. Soc. Rev.*, 2015, **44**, 742; (*c*) K. Urbina, D. Tresp, K. Sipps and M. Szostak, *Adv. Synth. Catal.*, 2021, **363**, 2723; (*d*) S. Pradhan, P. B. De, T. A. Shah and T. Punniyamurthy, *Chem. – Asian J.*, 2020, **15**, 4184.
3 S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial and H. Mayr, *J. Org. Chem.*, 2006, **71**, 8088.
4 For reviews see: (*a*) J. L. Carden, A. Dasgupta and R. L. Melen, *Chem. Soc. Rev.*, 2020, **49**, 1706; (*b*) S. Basak, L. Winfrey, B. A. Kustiana, R. L. Melen, L. C. Morrill and A. P. Pulis, *Chem. Soc. Rev.*, 2021, **50**, 3720. For selected examples see: (*c*) G. Kumar, S. Roy and I. Chatterjee, *Org. Biomol. Chem.*, 2021, **19**, 1230; (*d*) T. Hackel and N. A. McGrath, *Molecules*, 2019, **24**, 432; (*e*) V. Nori, F. Pesciaioli, A. Sinibaldi, G. Giorgianni and A. Carlone, *Catalysts*, 2022, **12**, 5.
5 S. Basak, A. Alvarez-Montoya, L. Winfrey, R. L. Melen, L. C. Morrill and A. P. Pulis, *ACS Catal.*, 2020, **10**, 4835.
6 A. Dasgupta, R. Babaahmadi, B. Slater, B. F. Yates, A. Ariafard and R. L. Melen, *Chem*, 2020, **6**, 2364.
7 A. Dubey, A. Tiwari and P. K. Mandal, *J. Org. Chem.*, 2021, **86**, 8516.
8 F. Ling, L. Xiao, L. Fang, C. Feng, Z. Xie, Y. Lv and W. Zhong, *Org. Biomol. Chem.*, 2018, **16**, 9274.
9 Dipika, Y. B. Sharma, S. Pant, D. K. Dhaked and M. M. Guru, *Org. Chem. Front.*, 2022, **9**, 3428.
10 W. Yuan, J. Huang, X. Xu, L. Wang and X.-Y. Tang, *Org. Lett.*, 2021, **23**, 7139.
11 (*a*) A. Di Saverio, F. Focante, I. Camurati, L. Resconi, T. Beringhelli, G. D'Alfonso, D. Donghi, D. Maggioni, P. Mercandelli and A. Sironi, *Inorg. Chem.*, 2005, **44**, 5030; (*b*) A. F. Schneider, Y. Chen and M. A. Brook, *Dalton Trans.*, 2019, **48**, 13599.
12 H. H. San, J. Huang, S. L. Aye and X.-Y. Tang, *Adv. Synth. Catal.*, 2021, **363**, 2386.
13 Y. Dong, H. Zhang, J. Yang, S. He, Z.-C. Shi, X.-M. Zhang and J.-Y. Wang, *ACS Omega*, 2019, **4**, 21567.
14 Also see: A. Das, K. Watanabe, H. Morimoto and T. Ohshima, *Org. Lett.*, 2017, **19**, 5794.
15 H. Zhang, X.-Y. Zhan, Y. Dong, J. Yang, S. He, Z.-C. Shi, X.-M. Zhang and J.-Y. Wang, *RSC Adv.*, 2020, **10**, 16942.
16 (*a*) M. Kimura, M. Futamata, R. Mukai and Y. Tamaru, *J. Am. Chem. Soc.*, 2005, **127**, 4592; (*b*) B. Mouhsine, A. Karim, C. Dumont, A. S. Pol, I. Suissse and M. Sauthier, *Eur. J. Org. Chem.*, 2022, e202200042. Examples for C2-allylation of indoles: (*c*) P. Ullrich, J. Schmauck, M. Brauns, M. Mantel, M. Breugst and J. Pietruszka, *J. Org. Chem.*, 2020, **85**, 1894; (*d*) A. A. Atia and M. Kimura, *Tetrahedron*, 2021, **90**, 132213.
17 (*a*) J. W. J. Kennedy and D. G. Hall, *Angew. Chem., Int. Ed.*, 2003, **42**, 4732; (*b*) S. Dutta, T. Bhattacharya, D. B. Werz and D. Maiti, *Chem*, 2021, **7**, 555.
18 A. Ariafard, *ACS Catal.*, 2014, **9**, 2896.