



Manganese-catalysed C₂ allylation and deuteration of indoles in water

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ABSTRACT

Mn-catalysed C–H activation has emerged as a useful sustainable methodology for the formation of new C–C bonds. To date most of the protocols are described in organic solvents. Water as solvent, on the other hand, would be highly advantageous, but is often incompatible with organometallic chemistry. Herein, we describe the C–H activation of indoles using an unmodified, commercially available manganese catalyst in water. Two types of valuable allyl groups can be added and a good substrate scope is described. Substitution at the C-3 group is tolerated, allowing access to medicinally important frameworks, and the reaction works on a gram scale. Finally, harnessing the tolerance of water as the reaction medium, D₂O can be used as an inexpensive source of deuterium for the C-2 labelling of indoles.

1. Introduction

The formation of carbon-carbon (C–C) bonds is a fundamental transformation in organic chemistry. The approach often takes the form of reacting a carbon electrophile with a carbon nucleophile [1]. Since the discovery of alkylzinc compounds by Frankland [2], the use of organometallic nucleophiles has developed through significant contributions from Reformatsky [3], Barbier [4], Grignard [5] and Gilman [6]. In the last few decades, catalytic palladium (Pd) cross-coupling has emerged as a critical tool in the organic chemists' toolbox [7–10] and has been widely applied in numerous industrial processes [11]. More recently, 'Earth Abundant Metals' (EAMs) have emerged as useful alternatives to precious metals. One particularly useful avenue to exploit is the EAM catalysed C–H functionalisation [12]. C–H Functionalisation involves the direct cleavage of an otherwise inert C–H bond. This approach avoids the installation of activating groups on both coupling partners, and the associated waste.

Manganese catalysed C–H activation has several advantages compared to precious metal (palladium, platinum, rhodium, iridium, or ruthenium) mediated catalysis [12] and has been reviewed by Ackermann [13] and McGlacken [14]. Manganese is the third most abundant transition metal, after iron and titanium, and the twelfth most abundant element in the Earth's crust, making bulk manganese quite affordable. The low toxicity and low cost of manganese renders it a particularly attractive alternative to the typically used transition-metal catalysts

[15]. Early work by Stone and Bruce in 1970 used Mn(Me)(CO)₅ for stoichiometric C–H activation [16] while in 2007, Kuninobu and Takai [17] reported a catalytic manganese-directed C–H activation. Following these seminal reports, a wide variety of Mn catalysed C–H activation reactions have been developed [13,14]. Despite the flurry of activity in this space, there remains significant interest in the development of manganese-based systems as more sustainable alternatives to precious metal catalysis.

Mn-catalysed C–H activation chemistry has, to date, been mainly conducted in organic solvents. This limitation will become more problematic with the increasing general concern over the use of fossil-derived organic solvents [18–20]. Water represents the greenest and most ideal solvent and is thus considered the logical reaction medium for the future of sustainable organic synthesis [21–24]. However, the challenge of carrying out organometallic transformations in water is multifaceted [25–27]. The two main challenges are **1**) insolubility of the substrates, reagents, and catalysts and **2**) incompatibility of the organometallic intermediates with water [28]. The former problem can be approached by structural modification to more water-soluble ligands, for example [29]. On occasion, the insolubility of substrates in water can actually improve reaction efficiency [25,30–33]. While recent efforts to undertake organometallic chemistry in aqueous medium have been impressive [34–39], these represent the exception rather than the rule. Most classical organometallic compounds, including manganese compounds, are strong bases and thus can potentially abstract a proton

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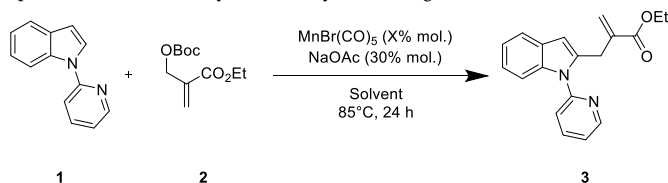
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Table 1
Optimisation of Mn-catalysed C–H allylation using MBH adduct 2.



Entry	Equiv. (2)	[Mn] mol%	Solvent	(% Conversion) ^a % Isolated Yield ^b
1 ^c	2	10	1,4-dioxane	79
2	2	10	DCE	(99)
3	1	10	Water	(70)
4	1.2	10	Water	(78)
5	2	10	Water	(96) 85
6	2	10	TPGS-750 M	(96) 80
7	2	7.5	Water	(100)
8	2	5	Water	(98) 81
9	2	2	Water	(70)
10 ^d	2	5	Water	(86) 68
11	2	0	Water	(0)
12 ^e	2	5	Water	(58)
13 ^f	2	5	Water	(64)
14 ^g	2	5	Water	(72)
15 ^h	2	5	Water	(88)
16 ⁱ	2	5	Water	(27)

^a Conversions indicated by parentheses. All conversions were determined by ¹H NMR by integration of the pyridin-indole peak at 8.57 ppm relative to the product peak at 8.63 ppm.

^b Isolated yield.

^c Solvent dried over 4 Å molecular sieves, reaction carried out at 80 °C for 16 h.

^d Carried out under microwave conditions.

^e Carried out without NaOAc.

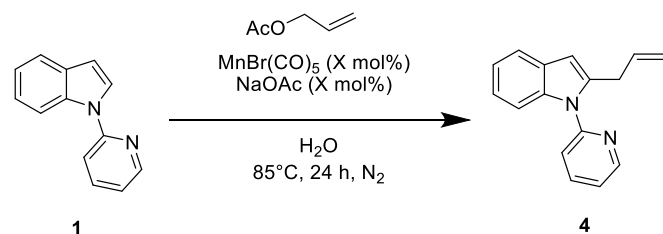
^f Reaction carried out for 8 h.

^g Reaction carried out for 16 h.

^h Reaction carried out at 70 °C.

ⁱ Reaction carried out at 55 °C.

Table 2
Optimisation of C2 allylation using allyl acetate.



Entry	NaOAc (mol%)	[Mn] mol%	(Conversion) ^a Isolated Yield ^b (%)
1	30	5	(22)
2	60	5	(22)
3	30	10	(35)
4	60	10	(80) 64

^a Conversions indicated by parentheses. All conversions were determined by ¹H NMR by integration of the pyridin-indole peak at 8.56 ppm relative to the product peak at 8.64 ppm.

easily from water. Even trace amounts of moisture can prove highly problematic, which has meant that much chemistry, underpinned by organometallic species, is carried out under Schlenk or glove-box conditions [40].

In this paper, we attempt to address this issue with the use of unmodified, phosphine free, manganese catalysts for C–H activation in aqueous media. To date, there is little literature precedent involving the use of MnBr(CO)₅ in aqueous media for C–H functionalisation although alkenylation, decarbonylation and amidations have been reported [41–43]. Herein we describe a Mn-catalysed C–H allylation of indoles [44–50], in aqueous medium, providing access to a number of useful products. Finally, the compatibility of the methodology with water allowed the use of D₂O as a deuterium source and installation of the label in excellent isotopic purity. This cheap source of deuterium for indole labelling is significant in the context of physical organic chemistry measurements, biological labelling studies and recent progress in the approval of deuterated drugs [51–55].

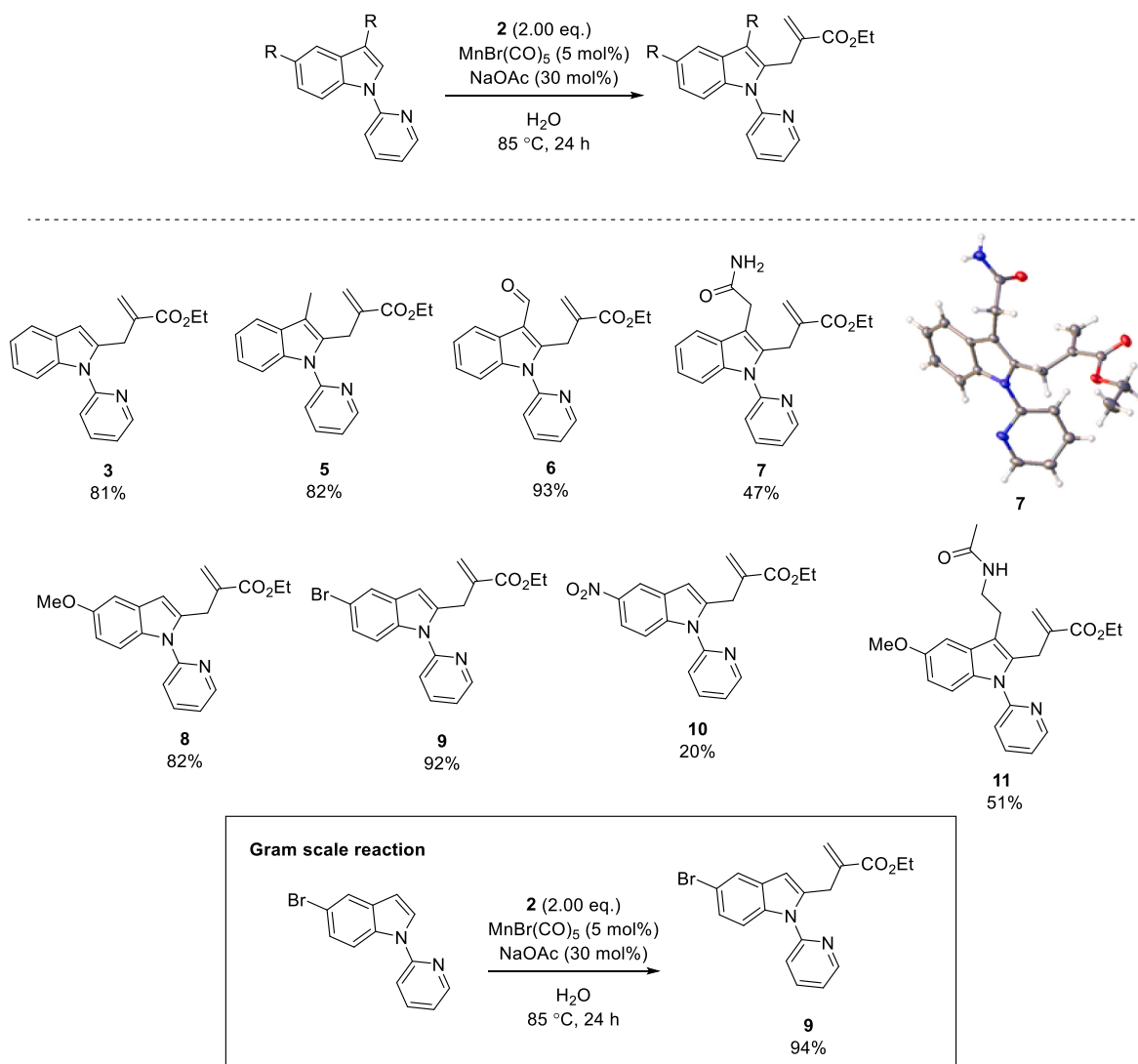
2. Results and discussion

Initial optimisation: The study initiated with the allylation of 1 with ester 2 using MnBr(CO)₅ (10 mol%) and NaOAc (30 mol%), in various solvents at 85 °C for 24 h under air (Table 1). Varying the ratios of 1 to 2 yielded different conversions to the allylated indole (3), with the highest observed at 96%, and an isolated yield of 85% (Entry 5). A test was carried out using a micellar solution of 5% TPGS-750 M (Entry 6), however, a similar conversion was observed. We then reduced the catalytic loading to 7.5, 5, 2.5 mol% (Entry 7, 8, 9). While the reaction worked well at 2.5 mol% (70% conversion), we chose 5 mol% as our loading for further studies (98% conversion/81% isolated yield). Microwave conditions (Entry 10) did not improve the reaction yield (86% conversion/68% isolated yield). Finally, the reaction did not progress without the catalyst (Entry 11) and performed poorly without base (58% conversion, Entry 12). In the absence of the pyridine directing group, no reaction was observed at C2 or C3 position of the indole. However, it is known that C3 functionalisation can occur with other methods in water [56–60]. A plausible mechanism for the C–H activation at the C2 position is published by Ackermann's group [48].

We then sought to explore whether a less reactive allylation reagent could be used to generate a useful 3-carbon terminal alkene moiety. Initially, we used similar conditions to that uncovered in Table 1, with ester 2 being replaced by allyl acetate (Table 2). We were disappointed to see the dramatic drop off in conversion to 22% (Entry 1 and 2) for allylated product 4 when 5 mol% catalyst loading was used. However, when we increased the catalytic loading to 10 mol%, the conversion improved to 35% (Entry 3) and finally to 80% conversion (with 60 mol% base), with an isolated yield of 64% (Entry 4). Conditions from entry 4 was used for the substrate scope reactions.

Substrate scope: With the optimised conditions in hand for coupling partner 2, the scope of potential indole partners was explored using the optimised condition from Table 1, entry 8 (Scheme 1). Considering the potential congestion at C2–C3, substitution at C3 of the indole was very well-tolerated and gave isolated yields of 82, 93 and 47% for compounds 5, 6 and 7. It is notable that the C3 aldehyde on compound 6 remains intact in this process. Substitution of the indole with electronically donating and withdrawing groups also gave the corresponding products (compounds 8–10) in mostly excellent yields (82 and 92% for 8 and 9), although the nitro derivative gave a poor yield (20% for compound 10). The medicinally relevant melatonin derivative was also allylated nicely in 51% isolated yield (to give compound 11). Importantly, we conducted a gram scale reaction and a 94% yield of product (9) was obtained.

A similar scope was investigated using allyl acetate as the alkylating agent (Scheme 2) using the conditions from Table 2, entry 4. C3-Substituted indoles were allylated to give 4, 12, 13 and 14 in 64, 54, 59 and 45% isolated yield respectively. Substitution of the indole (with an -OMe or -Br group) allowed access to the corresponding allylated products 15 and 16. Finally, melatonin derivative 17 could be formed in 48% isolated yield. Use of the nitroindole analogue with allyl acetate represented the limiting point of this study and only a trace of product 18 could be detected by ¹H NMR spectroscopy.



Scheme 1. – Scope of indole partners in the Mn-catalyzed allylation with ester 2.

3. Deuteration studies

Deuterium (D/²H), with an increased mass relative to protium (¹H), results in a lower vibrational frequency, and subsequently a higher C–H bond dissociation energy [61]. In the context of medicinal chemistry, deuterated molecules display superior metabolic stability, which, in practical terms, results in altered pharmacokinetics [62]. Direct hydrogen isotope exchange of aromatic C–H bonds using organometallic reagents is often challenging due to the instability of the active catalyst in D₂O (or DCl for example) [63]. A significant advantage of the methodology described herein, is the presumed compatibility of D₂O with the Mn catalytic cycle. Thus, we initiated a study using the previously optimised conditions for the allylation of indole 1. Initially, we achieved full deuteration at the C2 position (and 10% deuteration at C3) after 24 h. When we reduced the reaction time to only 1 h, we still achieved 90% deuteration in C2, but with a slightly reduced deuteration at C3 (8%) (Scheme 3[a]).

Using the same conditions, we then attempted to deuterate indole 20. However, only 23% deuterium incorporation was observed at C2. When the temperature was elevated to 120 °C, we observed an increase in deuteration of up to 77%. When we carried out the deuteration reaction in the absence of base, full deuterium incorporation at C2 was observed (Scheme 3[b]). This result implies that base is not necessary for the deuteration at C2 position. Finally, we note that in the absence of the

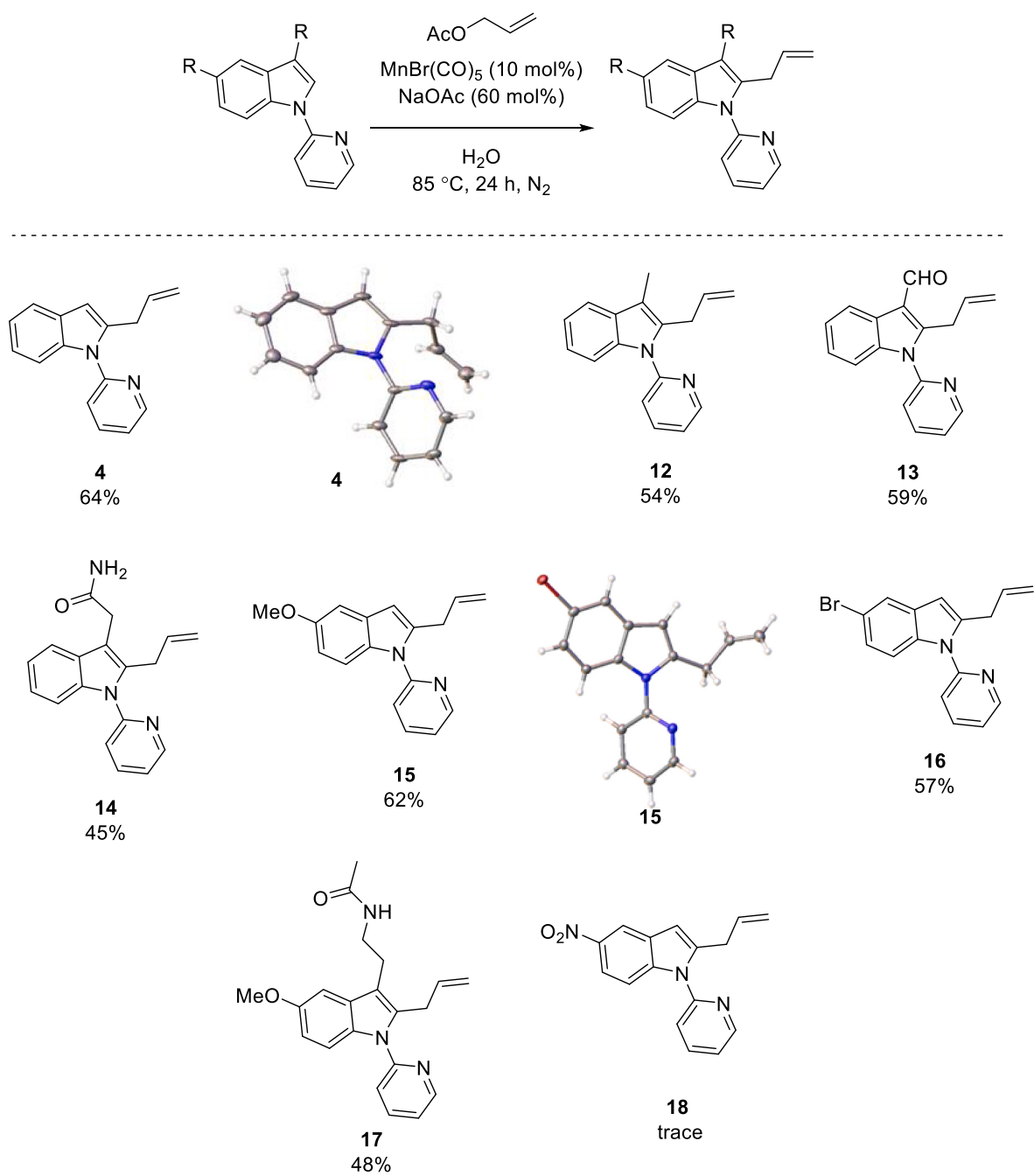
pyridine directing group [64], deuteration at the C2 position is not viable, and deuteration occurs exclusively at C3 (Scheme 3[c]). Finally, the removal of the pyridine directing group under mild conditions is well-established [65].

4. Conclusion

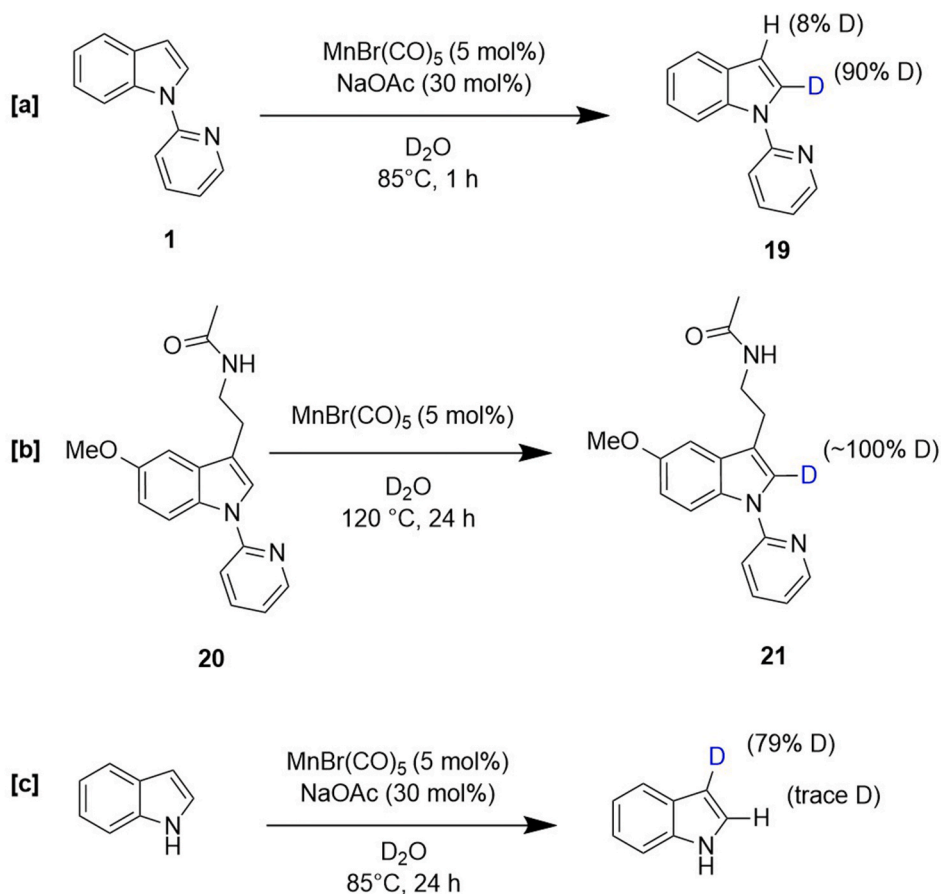
The application of earth abundant metals in transformations previously held within the domain of precious metals remains a priority in modern green chemistry research. The obligate use of organic solvents and high catalytic loadings in Mn(I) catalysis is a significant impediment in realising its significant potential in sustainable organic synthesis. In this report, we have developed an efficient methodology for the allylation of various indole substrates in water with catalyst loadings of 5–10 mol%. Various electron-withdrawing and electron-donating substituents are tolerated on the indole thus marking this as a potentially useful strategy in medicinal chemistry. The applicability of this approach in drug discovery is also demonstrated through the development of a gram scale variant and a base-free, C2 C–H deuteration reaction.

Declaration of competing interest

There are no conflicts to declare.



Scheme 2. – Scope of indole partners in the Mn-catalysed allylation with allyl acetate.



Scheme 3. – Deuteration experiments.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tgchem.2023.100019>.

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