

Manganese catalyzed C-H functionalizations involving an unexpected heteroaryl-shift

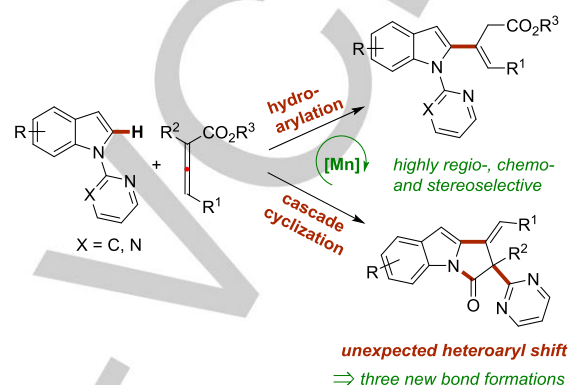
Chengming Wang,^[a] Ai Wang,^[b] and Magnus Rueping^{*[a]}

Abstract: A manganese catalyzed regio- and stereoselective hydroarylation of allenes is reported. The C-H functionalization protocol offers access to various alkenylated indoles with excellent yields. Moreover, a hydroarylation/cyclization cascade involving an unexpected C-N bond cleavage and aryl shift has been developed which provides a new synthetic approach to substituted pyrroloindolones.

During the past decades, transition-metal catalyzed C-H bond functionalizations have become a fundamental and powerful tool for assembling key structures essential in biochemistry, medicinal chemistry, agrochemicals and materials science.¹ Significant breakthroughs in C-H activation have been made using noble transition metals (e.g. Pd, Rh, Ru and Ir). However, their high price limits their large-scale application in industry. With the advantages of natural abundance, low cost and low toxicity, and relative stability to both air and moisture, the first-row transition metals (e.g. Mn, Fe, Co, Ni, Cu) have gained chemist's attention.^{2,3} In particular, the application of manganese in C-H functionalization reactions has recently started to attract interest.⁴

Based on our research into the development of ecologically and economically valuable transformations, as well as the synthesis of heterocycles, we became interested in developing a selective C-H functionalization of indoles with allenes. Although the chemistry of allenes has been greatly developed during the past years,⁵ there are only few examples for the use of allenes in C-H functionalizations.⁶⁻⁷

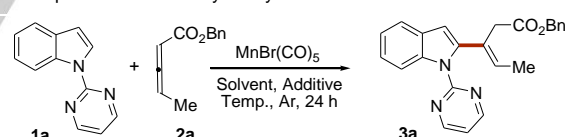
Herein, we report a first manganese-catalyzed allene hydroarylation and hydroarylation/cyclization cascade reaction (Scheme 1). The method features: (i) a readily available manganese catalyst; (ii) high stereo- and regioselectivity for the hydroarylation; (iii) good functional group tolerance; (iv) scalability and mild reaction conditions and (v) an unexpected heteroaryl shift in the redox neutral synthesis of pyrroloindolones. We began our investigations with the evaluation of different manganese catalysts for the reaction between *N*-pyrimidinyl indole **1a** and racemic allene **2a**. Among the different catalyst tested [MnBr(CO)₅] provided the product with 16% yield if the reaction was carried out in toluene (Table 1, entry 1).



Scheme 1. Mn catalyzed C-H functionalization of indoles with allenes.

The yield drastically increased by adding NaOAc as additive (Table 1, entry 2). While THF gives similar results to toluene, DMF inhibited the reaction (Table 1, entries 5, 6). It is worth noting that a slightly higher yield is obtained if the reaction temperature was lowered to 50 °C (Table 1, entry 7).

Table 1: Optimization of the hydroarylation.^[a]



Entry	Solvent	Additive (x equiv.)	Temp (°C)	Yield (%)
1	Toluene	-	80	16
2	Toluene	NaOAc (2.0)	80	97
3 ^[b]	Toluene	NaOAc (2.0)	80	97
4	Toluene	AgOAc (0.1)	80	97
5	THF	NaOAc (2.0)	80	97
6	DMF	NaOAc (2.0)	80	42
7 ^[b]	Toluene	NaOAc (2.0)	50	98
8 ^[b]	Toluene	NaOAc (2.0)	rt	86
9 ^[b,c]	Toluene	NaOAc (2.0)	80	87
10 ^[d]	Toluene	NaOAc (2.0)	80	-

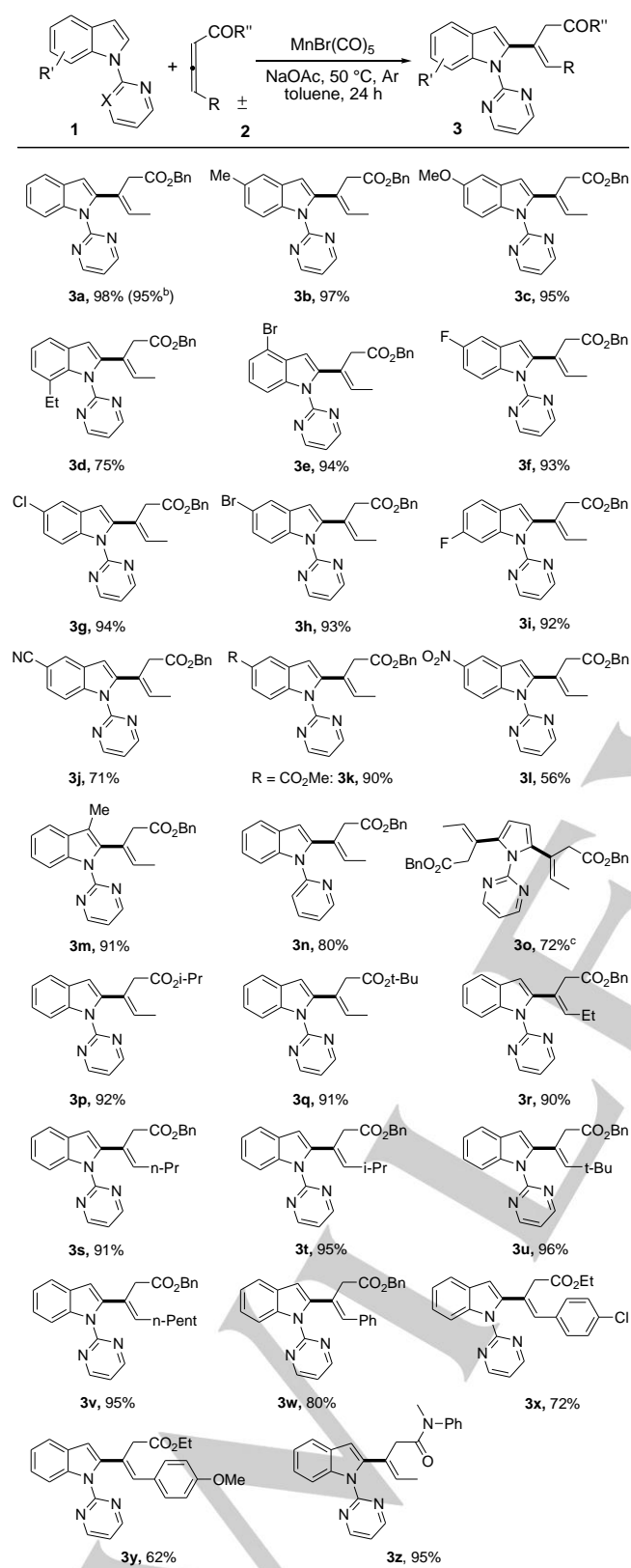
[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.3 mmol, 1.5 equiv.), MnBr(CO)₅ (10 mol%), solvent (1.0 mL), 80 °C, Ar, 24 h; [b] 5 mol% [Mn] was used; [c] under air; [d] without [Mn].

Moreover, the reaction proceeds smoothly even at room temperature or under air (Table 1, entries 8 and 9). Finally, the best conditions were defined as: indole (1.0 equiv.), allene (1.5 equiv.), Mn catalyst (5 mol%) in toluene at 50 °C.

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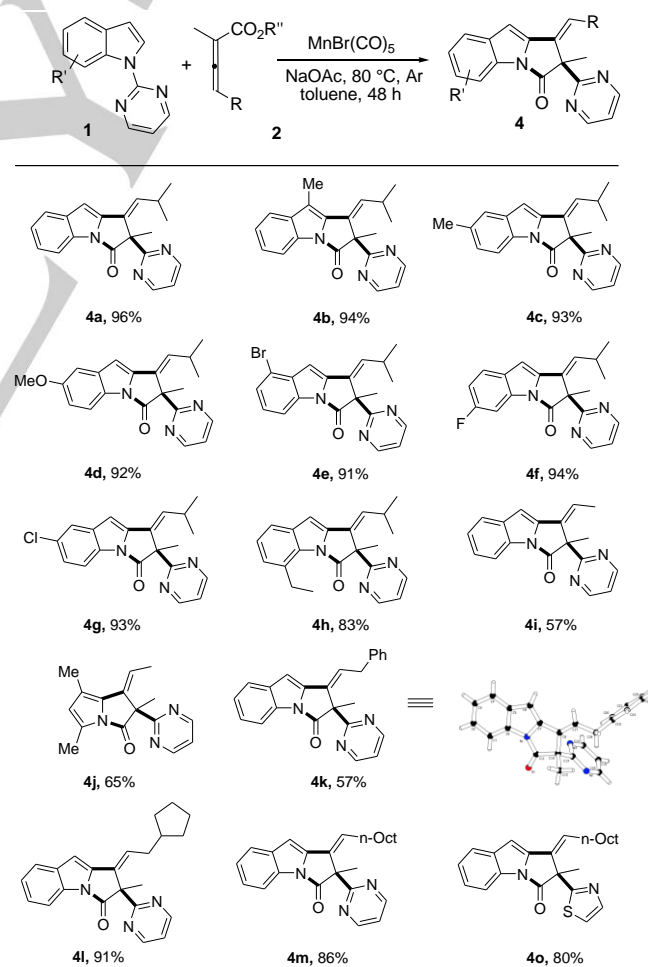
[+] X-ray crystal structure analysis.

Table 2: Substrate scope for the hydroarylation of allenes.^[a]

[a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.5 equiv.), MnBr(CO)₅ (5 mol%), NaOAc (0.4 mmol, 2.0 equiv.), toluene (1.0 mL), 50 °C, 24 h; [b] 1 mmol scale, rt, 72 h, [c] 3.0 equiv. allene were used.

With the optimized conditions in hand, we next focused on examining the substrate scope for this transformation. As shown in Table 2, this reaction has a good functional group tolerance and an acceptable substrate scope. Various indoles **1a-n** bearing electron-donating and electron-withdrawing groups can be applied. Substrates **1e-i** bearing halogen atoms are compatible in this transformation, which provides the possibility for further modifications. Even sterically hindered substrates **1d** and **1m** reacted smoothly, affording the desired products in high yields. Use of other heterocycles, such as pyrrole derivative **1o** also yielded the desired product (Table 2, **3o**). Furthermore, reaction of various aliphatic substituted allenes provided the products with excellent yields (Table 2, **3p-v**). Aryl allenes also undergo this reaction with acceptable yields (Table 2, **3w-y**). In addition, reaction with allene bearing an amide group furnished the corresponding product **3z** in 95% yield. Furthermore, the hydroarylation process is scalable and can be performed at room temperature, affording product **3a** in high yield (95%).

When tri-substituted allenes were applied in the above reaction, unexpectedly products **4** were obtained, as confirmed by NMR and single crystal X-ray analysis. Notably, this transformation provides a useful and efficient route to pyrroloindolone scaffolds.

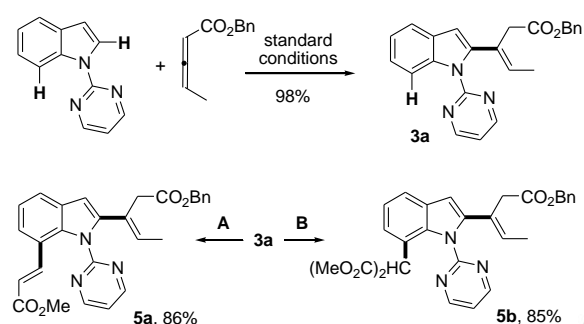
Table 3: Substrate scope for the cyclization reaction.^[a]

[a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.5 equiv.), MnBr(CO)₅ (10 mol%), NaOAc (0.4 mmol, 2.0 equiv.), toluene (1.0 mL), 80 °C, 48 h.

As depicted in Table 3, various indoles could be applied in this reaction to afford the products **4a-h**. A pyrrole derivative also gave in the corresponding product **4j**. However, use of benzyl and methyl substituted allenes resulted in lower yields (Table 3, **4i**, **4k**) while cyclopentyl and long carbon chain substituted allenes afforded products **4m-o** in high yields.

The products can be further modified via a sequential C-H activation strategy. Selective C2-alkenylation, followed by C-H activation at C7-position and subsequent reaction with methyl acrylate or dimethyl 2-diazomalonate affords the related olefination and alkylation products (Scheme 2a). Hydrogenation of the C=C double bond and amide hydrolysis provided the appropriate products **5c** and **5d** in 87% and 47% yield respectively (Scheme 2b, c)

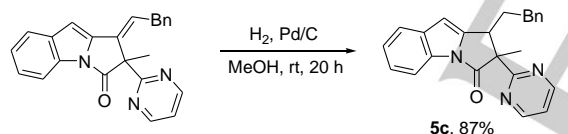
(a) Sequential C-H activation



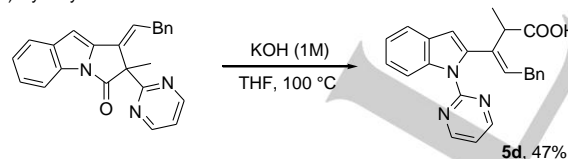
A: $[\text{Cp}^*\text{RhCl}_2]_2$, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, methyl acrylate, DMF, 80 °C, air, 20 h

B: $[\text{Cp}^*\text{RhCl}_2]_2$, AgSbF_6 , dimethyl 2-diazomalonate, MeOH, rt, 23 h

(b) Hydrogenation



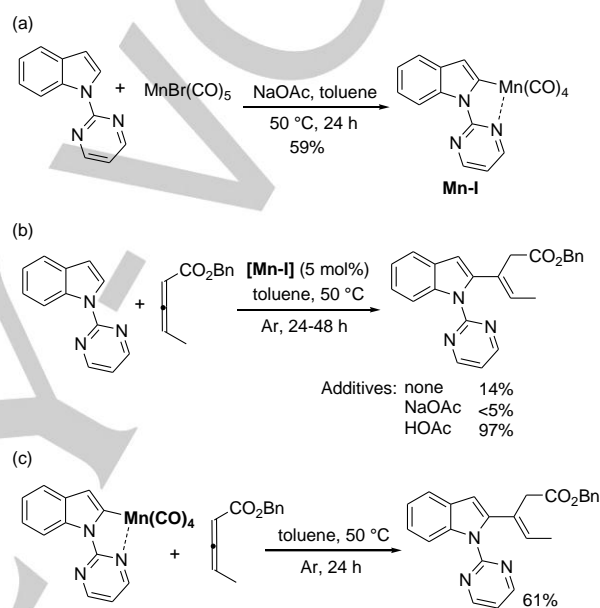
(c) Hydrolysis



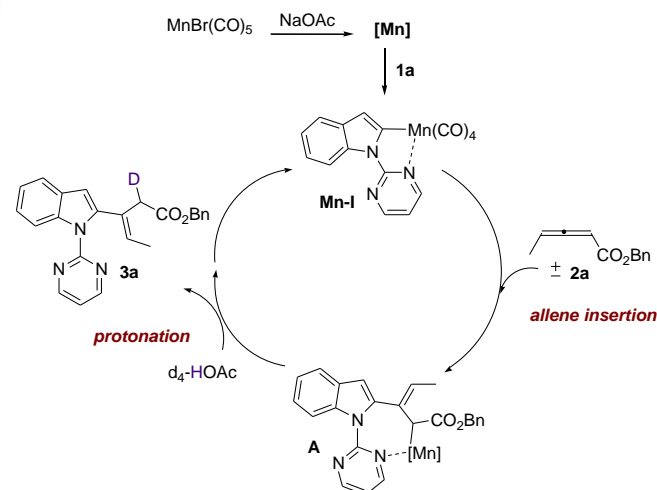
Scheme 2. Diversification of the products.

Next, a series of experiments were performed in order to shed light on the mechanism of this reaction. Firstly, manganese complex **Mn-I** was prepared (Scheme 3a). When **Mn-I** was applied in the catalytic reaction with HOAc as additive, the product was isolated in 97% yield. Only a low yield was obtained without additive or with NaOAc (Scheme 3b). The reaction with stoichiometric amounts of the cyclometalated **Mn-I** complex also provided the desired product (Scheme 3c). These experiments indicate that complex **Mn-I** may be involved in the catalytic cycle.

Based on the results above as well as literature reports we propose a mechanism for the hydroarylation process (Scheme 4). Initially, $\text{MnBr}(\text{CO})_5$ reacts with NaOAc to generate an active $[\text{Mn}]$ species. The following C-H cleavage affords cyclometalated intermediate **Mn-I**. The subsequent allene insertion and protonation produces the hydroarylation product **3a**. Formation of the unexpected cyclization product **4** can be explained by formation of the intermediate **A** or the corresponding Mn-enolate, followed by an aryl shift to give the arylated ester and free indole. The subsequent cyclization provides the pyrroloindolones comprising both, an olefinic as well as quaternary carbon atom substitution pattern.



Scheme 3. Mn-complexes involved in the C-H functionalization reaction.



Scheme 4. Proposed mechanism for the hydroarylation of allenes.

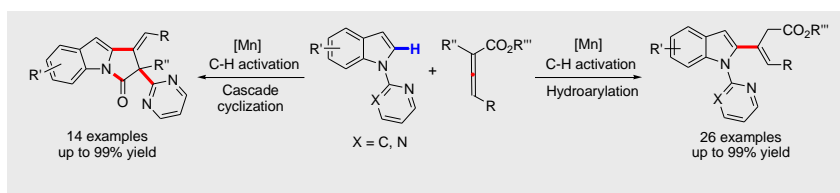
In conclusion, we report a new manganese-catalyzed C-H functionalization protocol. The redox-neutral catalysis protocol provides alkylated indoles as well as pyrroloindolones in high yields with excellent regio- and stereoselectivity. Mechanistic studies suggest formation of a cyclo-metalated manganese complex which reacts with an allene via a manganacycle to provide the alkylated product. The use of tri-substituted allenes resulted in an unexpected heteroaryl shift via a C-H functionalization/C-N bond cleavage/ cyclization sequence to provide a new synthetic approach to valuable pyrroloindolone scaffolds. Further applications of this new method in organic synthesis are currently under investigation and will be reported in due course.

Keywords: Manganese • hydroarylation • indole • allene • cascade cyclization

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Layout 2:

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Manganese catalyzed C-H functionalizations involving an unexpected heteroaryl-shift

A highly efficient, scalable, regio- and stereoselective Mn-catalyzed C-H arylation of allene is reported. When tri-substituted allenes are used, a C-H functionalization/C-N bond cleavage/cyclization cascade was developed affording indole fused pyrrole heterocycles. Detailed mechanistic studies suggest that a cyclo-Mn complex is formed during the catalytic cycle.