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Manganese-catalyzed allylation *via* sequential C–H and C–C/C–Het bond activation†

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Manganese-catalyzed sequential C–H and C–C/C–Het bond activation to synthesize allylic alcohols, allylated arenes, functionalized cyclopentenes and skipped dienes is reported. This protocol can be readily scaled up and various coupling partners are applied in manganese catalysis for the first time. Moreover, manganese-catalyzed alkenyl C(sp²)–H activation is also shown. Complimentary to the standard solution-based protocols, these reactions also proceed efficiently under neat conditions, which is unprecedented for abundant metal catalyzed C–H activation reactions.

Complimentary to the noble fifth- and sixth-row metals, direct C–H activation¹ using 3d-transition metal catalysis has fascinated chemists owing to their abundance, low price and low toxicity, as well as to their potential to promote novel reactivity.² Over the past years, the goal of achieving sustainability in organic synthesis has propelled important research in this field and significant progress has been made. Base-metals with flexible redox ability, such as Fe,³ Co,⁴ Ni,⁵ and Cu⁶ are extensively used in organometallic C–H activation today. In contrast to being the third most abundant transition metal, manganese is comparatively underutilized.⁷

Manganese-mediated stoichiometric C–H activation has been explored since the 1970s, however, catalytic variants of these reactions have proved challenging.⁷ Recently, the groups of Kuninobu and Takai, Wang, Ackermann and others have significantly advanced this field of research.⁸ Manganese catalysts have been found to be versatile as they can display unique reactivity and enable C–H functionalization with a variety of coupling partners containing polar multiple bonds.⁸ Mechanistically, these reactions mainly involve the formal addition of a metallacycle to an unsaturated reaction partner or a substitution reaction.⁸ In recent years, considerable efforts have been made to develop processes that can merge C–H activation with challenging C–C/C–Het cleavage reactions, which could allow for the efficient introduction of two different functional groups into one molecule in a single step.⁹ However, most of the examples reported to date suffer from the requirement for precious transition metal catalysts and stoichiometric activators. Very recently, a manganese-catalyzed substitutive C–H allylation through highly selective C–H/C–O functionalization was achieved by Ackermann *et al.*^{8k}

Owing to our continuous interest in 3d-transition metal catalysis, we questioned whether manganese catalysis can serve as an alternative route to integrating C–H activation with β -carbon/hetero atom elimination, which is largely unexplored in this field.

To date, cyclometalation has been the most straightforward and common method for the activation of C–H bonds. Such processes rely mainly on solvent-based techniques. From a sustainability perspective, solvent-free C–H activation processes are highly desirable. Recently, rhodium(III) and iridium(III) catalyzed C–H functionalizations under solvent-free conditions using a ball mill have been reported by Bolm and co-workers.¹⁰ However, to the best of our knowledge, first-row transition metal catalyzed C–H activation under neat conditions has not been developed thus far. Herein, our manganese catalyzed coupling offers an environmentally friendly, operationally simple alternative to the more traditional solvent-based protocols, featuring a cheap catalytic system. In this report, various coupling partners, including vinyl-1,3-dioxolan-2-one, 2-vinylloxirane, vinylcyclopropane and diazabicyclo, are applied in manganese catalysis for the first time, leading to the convenient synthesis of allylic alcohols, allylated arenes, functionalized cyclopentenes and skipped dienes (Scheme 1).

We started our investigation by reacting *N*-(2-pyridyl)-indole (1a) with vinyl-1,3-dioxolan-2-one (2aa) under [Mn₂(CO)₁₀]

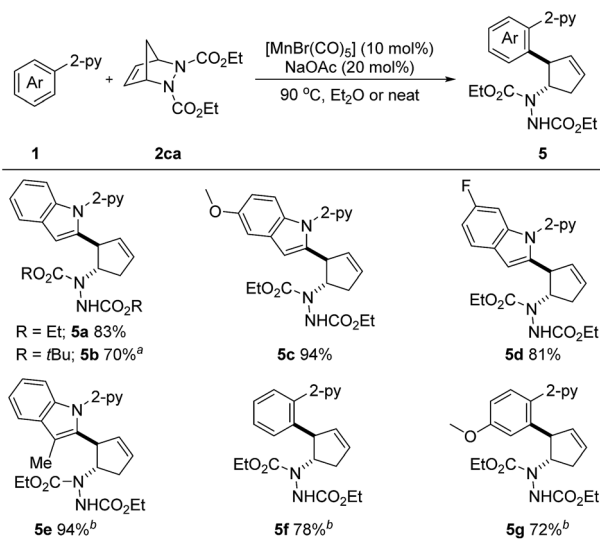


Scheme 1 Mn-catalyzed sequential C–H and C–C/C–Het activation.

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Scheme 4 Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol), **2** (0.3 mmol), $[\text{MnBr}(\text{CO})_5]$ (10 mol%) and NaOAc (20 mol%) in Et_2O (1.0 mL) at 90 °C under argon for 10 h, isolated yield. ^a 37 h. ^b $[\text{MnBr}(\text{CO})_5]$ (20 mol%) and NaOAc (40 mol%) were used under neat conditions at 100 °C for 37 h.

phenylpyridines were suitable substrates. It is important to note that this reaction also proved to be efficient under neat conditions. Arguably, this is the first example of a first-row transition metal catalyzed C–H activation/six-membered ring scission sequence.

Olefinic C–H activation could also be achieved under these conditions. For example, 2-(prop-1-en-2-yl)pyridine (**1m**) performed well in this transformation and the desired products **3m** and **5h**, a skipped diene with a valuable handle for further derivatization, were obtained in 75% and 62% yield respectively (Scheme 5).

This transformation is presumed to proceed through an organometallic C–H activation process, as was supported by radical trapping experiments (for details, see Scheme S1 in the ESI†). The reaction of **1a** and **2aa** under standard conditions was found to be compatible with radical scavengers 2,4-di-*tert*-butyl-4-methylphenol (BHT) and 1,1-diphenylethylene.

To gain more insight into the reaction mechanism, H/D scrambling experiments were next conducted (for details, see the ESI†). No H/D exchange at the 2-position of **1a** was observed when **1a** was simply mixed with CD_3OD and sodium acetate. Approximately 71% deuterium was incorporated into



Scheme 5 Manganese-catalyzed alkenyl C–H activation.



Scheme 6 Intramolecular C–H competition experiment.

the 2-position of recovered **1a** when sodium acetate was replaced with $[\text{MnBr}(\text{CO})_5]$. Furthermore, a larger deuterium incorporation (85%) at the 2-position of **1a** was observed when **1a** was treated with CD_3OD in the presence of both $[\text{MnBr}(\text{CO})_5]$ and sodium acetate. These results suggest that the C–H activation step is reversible and might occur *via* a base-assisted cyclometalation process. In addition, a $k_{\text{H}}/k_{\text{D}} = 1.0$ was observed from parallel reactions of **1a** and $[\text{D}]-\mathbf{1a}$ with **2aa**, respectively, which suggests that the cleavage of the C–H bond is not involved in the rate-determining step. Furthermore, when (3-pyridyl)-thiophene was utilized, the reaction occurred exclusively at the more electron rich 2-position (Scheme 6). On the basis of the above-mentioned results, we may draw the conclusion that the olefin coordination and insertion step is the rate-determining step, and that β -elimination is a facile process.¹¹

To acquire a better understanding of the observed reaction selectivity, a series of experiments were performed. As shown in Table 1, no obvious isomerization of the C=C bond was observed regardless of prolonged reaction time or decreased reaction temperature (entries 1–3, Table 1). On the contrary, solvent was found to have a dramatic effect on the *E/Z* selectivity (entries 3–5, Table 1). Compared to the neat reaction, DMF had a negative effect on the final *E/Z* selectivity, while diethyl ether had a positive effect. From these results, we inferred that the involvement of the π -allyl-manganese intermediate in the reaction mechanism might be excluded and that the solvent imparts selectivity during this transformation.

Table 1 Exploration of the influencing factor for the reaction selectivity^a

Entry	Temp./°C	Time/h	Solvent	Yield	Ratio <i>E/Z</i>
1	90	5	Et_2O	89	7.0
2	90	10	Et_2O	89	6.9
3	60	10	Et_2O	57	6.8
4	90	10	DMF	55	3.4
5	90	5	—	92	4.0

^a All reactions were carried out using **1a** (0.2 mmol), **2aa** (0.3 mmol), $[\text{MnBr}(\text{CO})_5]$ (10 mol%) and NaOAc (20 mol%) under different conditions, isolated yield, *E/Z* ratio is determined by ¹H NMR.



Conclusions

In conclusion, we have developed a general strategy to synthesize allylic alcohols, allylated arenes, functionalized cyclopentenes and skipped dienes, in which earth abundant manganese was utilized as the catalyst.¹² This protocol represents a combination of C–H and C–C/C–Het bond activation. Both aromatic and olefinic substrates are functionalized in this reaction. This work broadens the scope of manganese catalysis to include a series of new coupling partners. Additionally, this reaction can occur efficiently under neat conditions yet does not require the use of a large excess of a coupling partner as the solvent, which is unprecedented in abundant metal catalysis. Finally, β -carbon and β -nitrogen elimination were shown to be feasible under low-valent manganese catalysis for the first time.

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Notes and references

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- 11 A mechanism was proposed in Scheme S3 in the ESI.†
- 12 Only a trace amount of the desired products can be detected when 4-(hex-1-en-2-yl)-1,3-dioxolan-2-one or dimethyl 2-(prop-1-en-2-yl)cyclopropane-1,1-dicarboxylate was utilized under the optimized conditions.

