Reusable Manganese Catalyst for Site-Selective Pyridine C–H Arylations and Alkylations

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Abstract: Herein, we disclose a recyclable, hybrid manganese catalyst for site-selective azine C–H activation by weak amide assistance. The novel, reusable catalyst enabled C3–H arylation and C3–H alkylation with ample scope, and was characterized by detailed transmission electron microscopy analysis.

Azines are key structural motifs in a plethora of bio-relevant compounds, pharmaceuticals, and drugs.[1] Particularly, C3-H functionalized pyridine scaffolds broadly exhibit numerous biological activities (Figure 1).[2] Consequently, there is a continued strong demand for efficient C–H functionalizations in a sustainable manner.

During the past decades, the activation of inert C–H bonds has surfaced as an increasingly viable platform for molecular syntheses.[3] Notable progress was predominantly made with the aid of noble 4d and 5d transition metals, such as ruthenium,[4] rhodium,[5] palladium,[6] and iridium.[7] In sharp contrast, Earth-abundant 3d metal catalysts provide prospect for less-toxic metals in C–H activations[8] with notable advances in manganese-catalyzed[9] C–H activations[10] by Kuninobu/Takai,[11] Wang,[12] Glorius,[13] Rueping,[14] and Ackermann,[15] among others.[16] Despite the indisputable progress, manganese catalyzed-C–H functionalizations continue to be largely limited to homogeneous catalysis.[17]

Heterogeneous catalysis,[18] particularly hybrid catalysis,[19] has emerged as an increasingly potent tool for transition metal-catalyzed C–H activations[20] due to its easy catalyst recovery and improved controls of reactivity and selectivity.[21] More importantly, the simple separation of the catalysts significantly reduces the amount of trace metal impurities[22] in the pharmaceutical or agrochemical compounds,[23] which enables to avoid additional processes.[24]

Within our program on sustainable C–H activation,[25] we have now developed the first hybrid-manganese-catalyzed[26] C–H arylations and alkylations, which we report herein (Figure 2). The salient features of our strategy include a) the development of mesoporous SBA-15-based recyclable hybrid-manganese catalyst for azine C–H activations, b) robust site-selective C3–H arylations and alkylations of azines by weak coordination,[27] c) detailed electron microscopy analysis of the novel covalently anchored manganese catalyst.

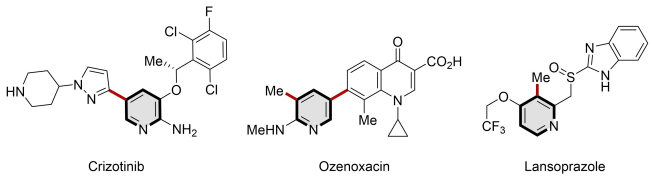

Figure 1. Selected medications containing C3-functionalized pyridine motifs.

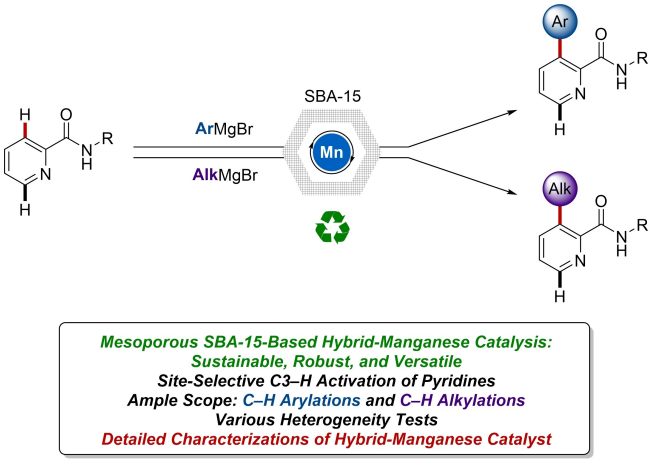

Figure 2. Reusable hybrid-manganese-catalyzed C–H activation.

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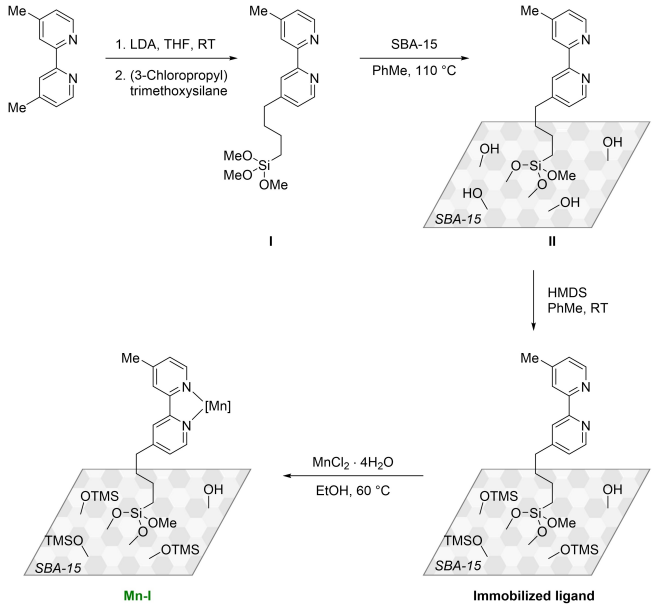
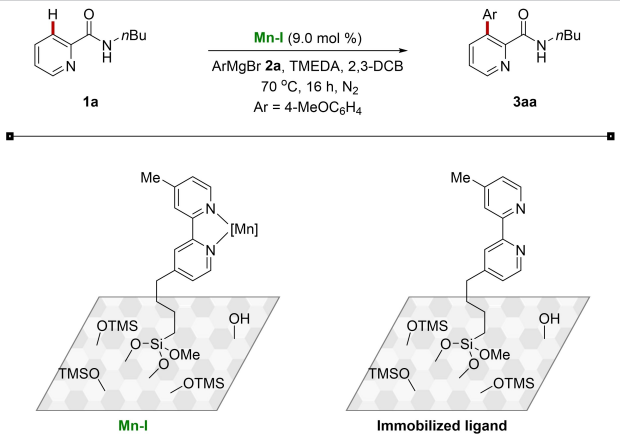
The novel hybrid-manganese catalyst was synthesized by anchoring the bipyridine ligand on the solid support (Scheme 1 and Supporting Information). Thus, the bipyridine moiety was tethered to zeolite SBA-15, of which the silanol group on the surface was capped by hexamethyldisilazane, providing the ligand attached on the surface. Afterwards, $MnCl_2 \cdot 4H_2O$ was heterogenized on the bipyridine ligand, affording the hybrid-manganese catalyst **Mn-I**.



Scheme 1. Preparation of the novel hybrid-manganese catalyst.

Table 1. Establishing C–H arylation by hybrid-manganese catalyst.



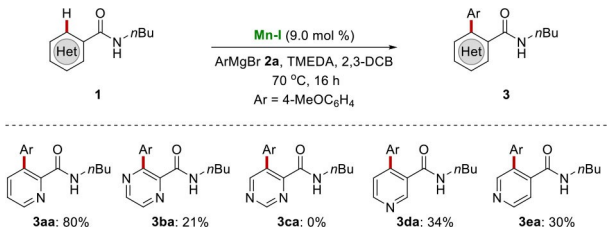
	Deviation from standard condition	Yield [%][a]
1	standard conditions	80
2	$MnCl_2$ as catalyst	17
3	immobilized ligand instead of **Mn-I**	NR
4	without **Mn-I**	NR
5	without TMEDA	43
6	without 2,3-DCB	5

[a] Reaction condtitions: **1a** (0.25 mmol), **2a** (1.0 mmol, 1.0 M in THF), **Mn-I** (9.0 mol%), TMEDA (0.5 mmol), 2,3-DCB (0.75 mmol), 70 °C, 16 h, under N_2 atmosphere, isolated yields. TMEDA = tetramethylethylenediamine. 2,3-DCB = 2,3-dichlorobutane. NR = no reaction.

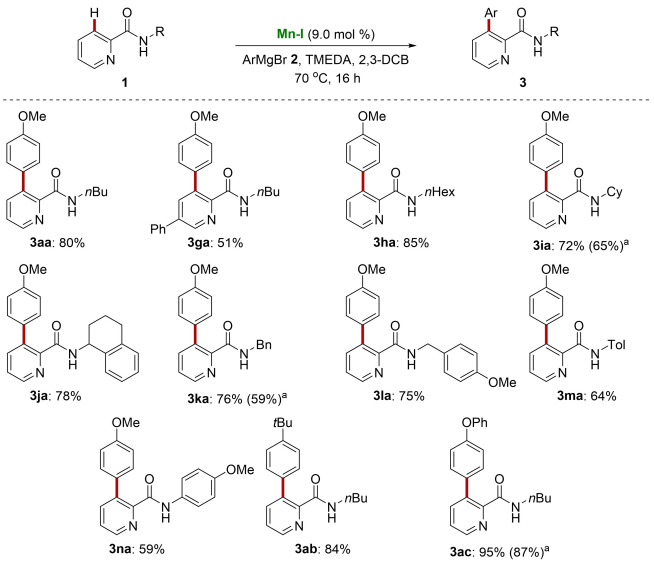
We initiated our studies by probing various reaction conditions for the envisioned C–H arylation of pyridines **1a** with the synthesized hybrid-manganese catalyst **Mn-I** (Table 1 and Table S1 in the Supporting Information). We were pleased to observe that the desired arylated product **3aa** was obtained under solvent-free reaction conditions (entry 1). It is noteworthy that the hybrid catalyst could be successfully recycled and reused (entry 2). In contrast, the use of simple $MnCl_2$ provided unsatisfactory results (entry 3). Control experiments verified the essential role of the hybrid-manganese catalyst, the ligand, and the DCB oxidant for C–H arylations (entries 4–7).

Thereafter, we probed the effect exerted by changing the substitution pattern on the azines **1** (Scheme 2). Differently decorated heteroarenes, such as structural isomeric azines or diazines were thus subjected to the optimized reaction conditions for the C–H arylation. Whereas the picolinic amide **1a** gave an effective transformation, other azines and diazines showed diminished reactivity likely due to less effective metal coordination.

With the optimized reaction conditions in hand, we set out to explore the catalytic performance in the C3-H arylations of azines (Scheme 3). Various pyridines **1** were efficiently converted to the desired C3-arylated product **3** by weak amide-



Scheme 2. Examination of heteroarenes' patterns.



[a] The yield in the parentheses was obtained from the 2nd run

Scheme 3. Scope of hybrid-manganese-catalyzed C–H arylations.

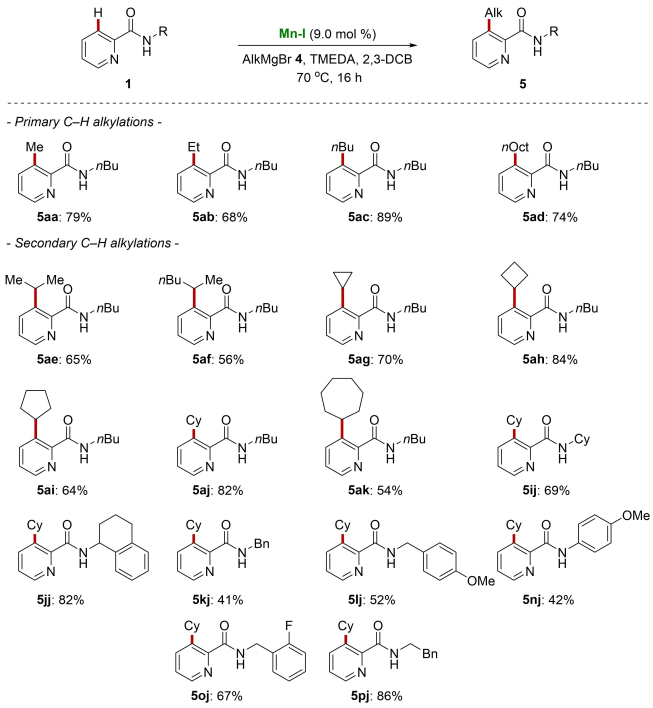
chelation assistance, whereas alkyl, benzyl and aryl substituted amides were fully tolerated.

Additionally, the versatility of the hybrid-manganese catalysis was highlighted by C–H alkylations, providing a broadly applicable strategy (Scheme 4). Therefore, the robust hybrid-manganese-catalyzed C–H functionalization enabled direct primary alkylations. It is noteworthy that the hybrid-manganese catalysis enabled the installation of the methyl group[28] onto azine (**5aa**). Furthermore, challenging secondary alkylations proved viable, including cyclopropylation (**5ag**) and cyclobutylation (**5ah**) and isomerizations were not observed.

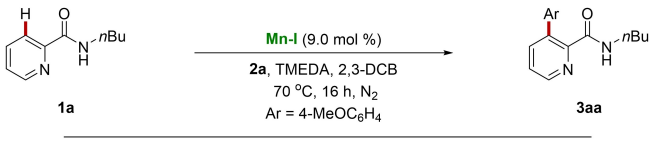
Given the robustness of our hybrid-manganese catalyst, we next tested the recyclability of the hybrid-manganese catalyst in further detail (Scheme 5). To this end, a reuse test for C–H arylation was performed, and we observed that the hybrid-manganese catalyst was recyclable and could be reused for at least three times. It is noteworthy that less than 1 ppm of manganese was detected by inductively coupled plasma optical emission spectrometry (ICP-OES) studies of the reaction mixture, reflecting negligible leaching of the transition metal during the course of catalysis. The decrease in the yield was attributed to a physical loss during the filtration or the deactivation of the catalyst.

The addition of mercury and a hot-filtration test were subsequently probed, showing that the hybrid-manganese-catalyzed C–H arylation was operating within a heterogeneous regime (Scheme 6).

Thereafter, the pristine ligand-support (Immobilized ligand), the hybrid-manganese catalyst (**Mn-I**), and reused **Mn-I** were in detail characterized by transmission electron microscopy (TEM) techniques to determine morphological properties (Figure 3

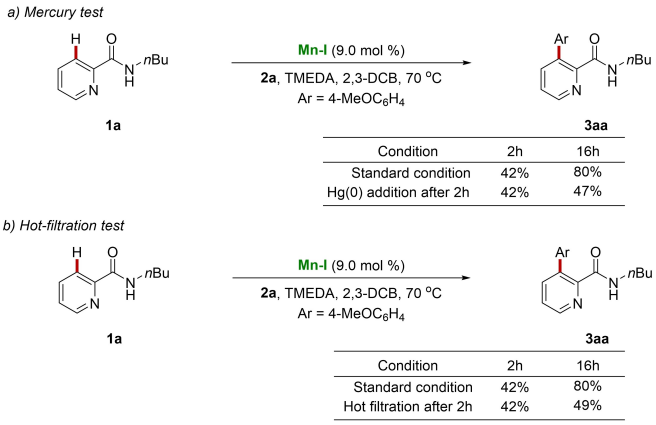


Scheme 4. Scope of C–H alkylations by hybrid-manganese catalysis.



Run	1st	2nd	3rd
Yield (%)	80	75	63
Leaching (ppm)	0.9	0.5	0.4

Scheme 5. Reuse tests for hybrid-manganese-catalyzed C–H arylation and ICP-OES analysis of trace metal impurities.



Condition	2h	16h
Standard condition	42%	80%
Hg(0) addition after 2h	42%	47%

Condition	2h	16h
Standard condition	42%	80%
Hot filtration after 2h	42%	49%

Scheme 6. Heterogeneity tests.

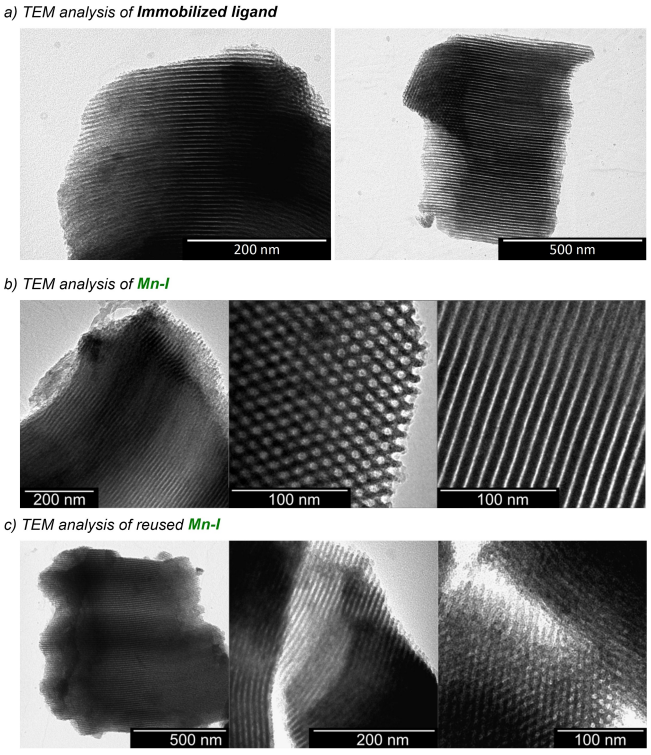


Figure 3. Transmission microscopy images of the mesoporous silica with a) the immobilized ligand, b) with **Mn-I**, and c) with **Mn-I** after reuse. All images are taken in bright field mode.

and Supporting Information). Thereby, we observed highly ordered one-dimensional mesoporous channels without morphological agglomeration or disorder during the process of end-capping or the binding of the manganese. Additionally, it was revealed that the pore distance between **Mn-I** and reused **Mn-I** showed 12.08 ± 0.91 and (11.87 ± 0.53) nm, respectively; hence remaining unmodified.[29]

In summary, we have reported a novel recyclable hybrid-manganese catalyst for C–H activation. The hybrid-manganese catalyst featured a remarkable catalytic performance towards site-selective C3-H arylations and C3-H alkylations of azines by weak amide-chelation assistance. Detailed heterogeneity investigations and characterization of the hybrid-manganese catalyst reflected its stability during the course of the C–H activation of azines.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: C–H alkylation · C–H arylation · hybrid catalysis · manganese catalysis · site-selectivity

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