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Sustainable Alkylation of Unactivated Esters and Amides with Alcohols Enabled by Manganese Catalysis

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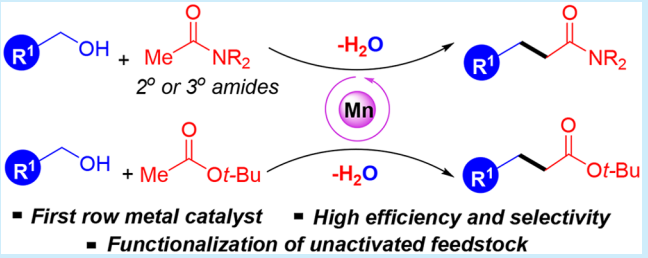
Supporting Information

ABSTRACT: The first example of manganese-catalyzed *C*-alkylation of the carboxylic acid derivatives is reported. The bench-stable homogeneous manganese complex enables the transformation of the renewable alcohol and carboxylic acid derivative feedstock to higher value esters and amides. The reaction operates via hydrogen autotransfer and ideally produces water as the only side product. Importantly, aliphatic-, benzylic-, and heterocyclic-containing alcohols can be used as alkylating reagents, eliminating the need for mutagenic alkyl halides.



The catalytic functionalization of the C−H bonds is a central challenge in modern chemistry.[1] Carboxylic acids and their derivatives are pervasive in nature. Accordingly, an elegant approach to utilize the readily available esters and amides is to convert them to more valuable intermediates upon α-alkylation reaction. Conventional noncatalytic methods for the α-alkylation of the carbonyl compounds involve the generation of the corresponding enolate nucleophile using superbase (such as organolithium or alkali metal amides) at very low temperature. In addition to the need for toxic alkyl halide electrophiles, such methods suffer from low atom economy and the generation of copious amounts of waste.[2]

Recently, alkylation of the carbonyl compounds with primary alcohols using a hydrogen autotransfer strategy has emerged as an environmentally friendly alternative for conventional alkylation methods.[3] The key features of this hydrogen-neutral process are the use of the alcohols as a green electrophile, and the only stoichiometric byproduct is water. Alcohols are renewably available from the lignocellulosic biomass and a variety of industrial processes.[4] In fact, progress has been made in the α-alkylation of ketones and β-alkylation of alcohols.[5,6] In contrast, the α-C−H bonds of the esters and amides exhibit comparably low Brønsted acidity owing to the resonance stabilization effect of the adjacent NR_2 group. Furthermore, esters typically undergo side reactions such as self-condensation and transesterification. Among the carboxylic acid derivatives, the functionalization of dimethylacetamide (DMA) and *tert*-butyl acetate is of particular interest because these compounds can be obtained in one step from acetic acid and are frequently used as solvents in synthetic chemistry. Only a few reports are known for the α-alkylation of esters and amides using iridium[7] and ruthenium[8] catalysis. Very recently, Kempe and co-workers have reported an elegant cobalt-catalyzed alkylation of esters and amides. However, the extensive need for a glovebox may complicate large-scale application.[9]

For sustainability reasons, the current key challenge is the development of efficient catalytic systems that rely on the use of widely abundant, inexpensive metals.[10] Manganese, the third most abundant transition metal, was recently recognized by several groups including ours as a potential alternative for the toxic noble metal in the hydrogenation of polar[11] and nonpolar bonds,[12] acceptorless dehydrogenation transformations,[13] and *C*- and *N*-alkylation with primary alcohols.[5e−j,6c,14] Despite recent advances,[15] alkylation of the esters and amides via a hydrogen autotransfer strategy remains an unsolved challenge. Herein, we report the first example of manganese-catalyzed α-alkylation of unactivated esters and amides with alcohols (Scheme 1). Our catalytic system features a bench-stable catalyst stabilized by an air-stable PNN ligand.

The *C*-alkylation of DMA with benzyl alcohol (**1a**) was selected as a model reaction for the optimization of the reaction conditions (Table 1). Initially, we tested the catalytic

Scheme 1. Unprecedented Manganese-Catalyzed C−H Functionalization of Esters and Amides

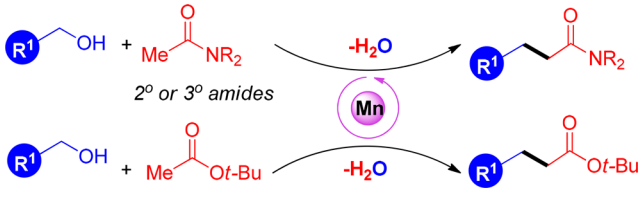


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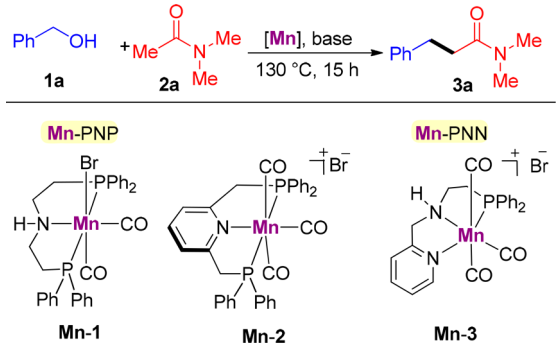
Table 1. Optimization of the Reaction Conditions[a]



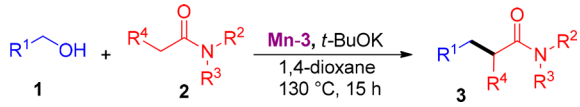
entry	[Mn]	base	solvent	yield (%)
1	**Mn-1**	*t*-BuOK	1,4-dioxane	22
2	**Mn-2**	*t*-BuOK	1,4-dioxane	15
3	**Mn-3**	*t*-BuOK	1,4-dioxane	91
4	**Mn-3**	*t*-BuOLi	1,4-dioxane	9
5	**Mn-3**	*t*-BuONa	1,4-dioxane	28
6	**Mn-3**	Cs_2CO_3	1,4-dioxane	0
7	**Mn-3**	Na_2CO_3	1,4-dioxane	0
8	**Mn-3**	NaOH	1,4-dioxane	0
9	**Mn-3**	KOH	1,4-dioxane	0
10	**Mn-3**	*t*-BuOK	2-Me-THF	57
11	**Mn-3**	*t*-BuOK	diglyme	9
12	**Mn-3**	*t*-BuOK	toluene	62

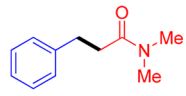
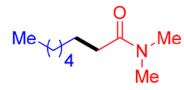
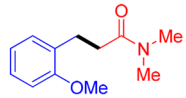
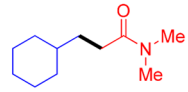
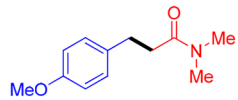
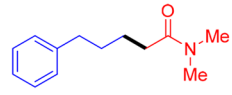
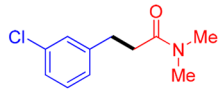
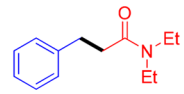
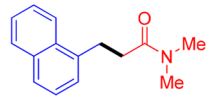
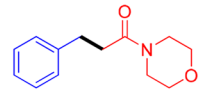
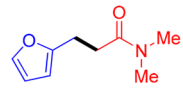
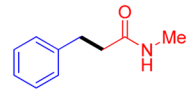
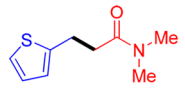
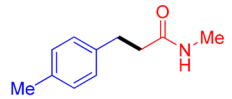
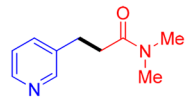
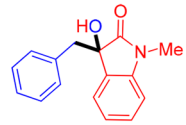
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), [**Mn**] (0.015 mmol), base (0.6 mmol), solvent (1 mL), 130 °C, 15 h. Yields determined by GC analysis using *m*-xylene as an internal standard.

activity of different manganese complexes (**Mn-1**–**Mn-3**)[16] in 1,4-dioxane using *t*-BuOK as a base. While the PNP–Mn complexes **Mn-1** and **Mn-2** gave unsatisfactory results, **Mn-3** bearing a PNN ligand afforded the desired alkylated amide **3a** in 91% yield (Table 1, entries 1–3). Thus, **Mn-3** was selected for the further optimization of the common reaction parameters such as base and solvent. It was found that efficiency of the reaction was reduced upon use of *t*-BuOLi and *t*-BuONa (Table 1, entries 4 and 5). Additionally, relatively weak bases such as Cs_2CO_3 and Na_2CO_3 were inert in this transformation (Table 1, entries 6 and 7). Similarly, NaOH and KOH proved unsuitable for this reaction (Table 1, entries 8 and 9). Next, we examined different solvents. The use of other polar aprotic solvents such as 2-Me-THF and diglyme resulted in the formation of the desired product in 57% and 9% yields, respectively (Table 1, entries 10 and 11). The application of the nonpolar toluene led to lower yield compared to that of 1,4-dioxane (Table 1, entry 12). In summary, the reaction works best using 3 mol % of **Mn-3** and 1.2 equiv of *t*-BuOK in 1,4-dioxane at 130 °C.

With the optimized conditions in hand, we explored the scope of the α-alkylation of amides with alcohols (Table 2). First, the scope of the alkylation of *N*,*N*-dimethylacetamide with alcohols was investigated. Benzylic alcohols bearing electron-donating or electron substituents in the *ortho*, *meta*, and *para* positions delivered the corresponding alkylated amide **3a**–**d** in good to excellent yield (Table 2, entries 1–4). Similarly, 1-naphthalenemethanol performed well in this transformation and gave **3e** in 72% yield (Table 2, entry 5). Importantly, alcohols bearing different heterocyclic moieties; furan, thiophene, and pyridine, were tolerated, and the high-value-added amides **3f**–**h** were obtained in good yield (Table 2, entries 6–8). Furthermore, long-chain and α-branched aliphatic alcohols could be used in this new method to produce the *C*-alkylated amide derivatives **3i**–**k** in good yields (Table 2, entries 9–11). Afterward, we investigated different types of amides. Pleasantly, when *N*,*N*-diethylacetamide and 4-acetylmorpholine **2b** and **2c** were subjected to the reaction, the alkylation products were obtained in moderate yields (Table 2, entries 12 and 13). Importantly, this catalytic system was not limited to the alkylation of the tertiary amide. Thus, the selective alkylation of *N*-methylacetamide resulted in the formation of the desired *C*-alkylated products **3n** and **3o** in

Table 2. Manganese Catalyzed Alkylation of Amides[a]



entry	**3**, yield	entry	**3**, yield
1	 **3a** (90%)	9	 **3i** (72%)
2	 **3b** (78%)	10	 **3j** (71%)[b]
3	 **3c** (92%)	11	 **3k** (52%)
4	 **3d** (62%)	12	 **3l** (56%)
5	 **3e** (72%)	13	 **3m** (59%)
6	 **3f** (61%)	14	 **3n** (53%)
7	 **3g** (80%)[c]	15	 **3o** (86%)
8	 **3h** (76%)	16	 **3p** (87%)[b]

[a]Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), **Mn-3** (0.015 mmol), *t*-BuOK (0.6 mmol), 1,4-dioxane (1.0 mL), 15 h, 130 °C. Isolated yields are shown. [b]**Mn-3** (0.02 mmol) and *t*-BuOK (1.0 mmol). [c]1 mmol scale.

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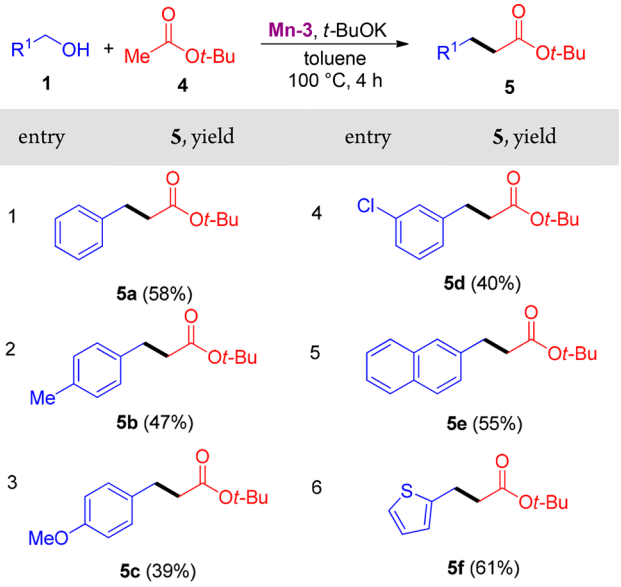
53% and 86% yields (Table 2, entries 14 and 15). It is worth noting that the conventional alkylation of secondary amides using alkyl halides often leads to the *N*-alkylation products.[2c] Afterward, we examined our catalytic system for the alkylation of the 2-oxindole derivative **2p**. Indeed, the alkylation reaction proceeds well followed by C−H hydroxylation to afford the C3-hydroxy-functionalized 2-oxoindole **3p** in 87% yield (Table 1, entry 16).

Encouraged by these results, we decided to further expand the scope to the alkylation of esters. Thus, the reaction conditions for the *tert*-butyl acetate alkylation with benzyl alcohol were investigated. In summary, the best conditions involve the use **Mn-3** and 2 equiv of *t*-BuOK in toluene at 100 °C for 4 h. We then focused on the substrate scope (Table 3).

Table 3. Manganese Catalyzed Alkylation of Esters[a]

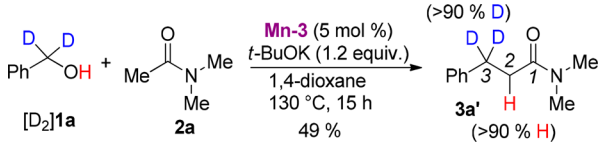


[a]Reaction conditions: **1** (0.5 mmol), **4** (2 mmol), **Mn-3** (0.025 mmol) and *t*-BuOK (1 mmol), toluene (1 mL), 100 °C, 4 h. Isolated yields are shown.

The application of the benzyl alcohol as a coupling partner gave the desired product **5a** in 58% yield (Table 3, entry 1). Benzylic alcohols containing *p*-methyl, *p*-methoxy, and *m*-chloro were compatible with the reaction conditions, and the *C*-alkylated esters **5b−d** were obtained in moderate yields (Table 3, entries 2−4). The application of 1-naphthaleneme-thanol led also to the desired product **5e** in moderate yield (Table 3, entry 5). Noteworthy, thiophene-containing substrate and products such as **5f** are tolerated in this alkylation reaction (Table 3, entry 6).

In order to gain more insight in the reaction mechanism, we carried out a deuterium-labeled experiment (Scheme 2). In more detail, [D_2]**1a** was used an alkylating reagent for the

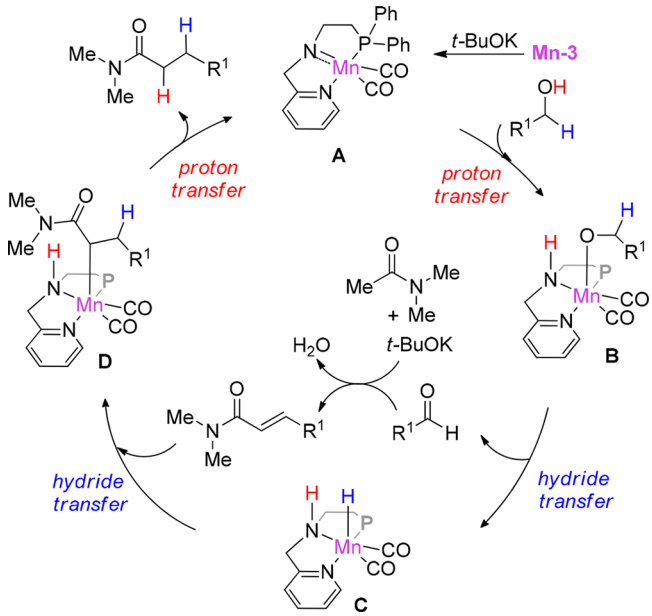
Scheme 2. Deuterium-Labeled Experiment



DMA. However, when the catalyst loading was increased to 5 mol %, only 49% yield was observed, which indicates a very strong kinetic isotope effect. Furthermore, the alkylated amide **3a′** was obtained with >90% deuterium incorporation at C3 and very low deuteration at C2. The deuterium experiment indicates that the hydrogen autotransfer reaction takes place via a monohydride mechanism with involvement of both the metal and the non innocent ligand in the dehydrogenation and hydrogenation steps.[17−19]

On the basis of our experimental observations, the proposed reaction mechanism is presented in Scheme 3. Initially, proton

Scheme 3. Proposed Reaction Mechanism



transfer from the alcohol to the 16e species **A** takes place to generate the manganese alkoxide intermediate **B**. Subsequently, *β*-hydride elimination leads to the formation of an aldehyde and the hydrogenated catalyst **C**, storing the abstracted hydrogen on the metal ligand catalyst. The base-catalyzed condensation between the in situ generated aldehyde and carboxylic acid derivative result in the formation of an unsaturated amide. The shuttled hydrogen on the hydrogenated catalyst **C** is then transferred to the C═C bond in two discrete steps. First, the the C═C bond is inserted into the Mn−H bond to produce the intermediate **D**. Second, the desired product is released upon proton transfer and the manganese species **A** is regenerated. The proton transfer may also occur by transferring a proton directly from an alcohol, producing the desired product and the intermediate **B** without the regeneration of the 16e species **A**.[20]

In conclusion, we have reported the first example of manganese-catalyzed environmentally benign *C*-alkylation of unactivated esters and amides with unactivated alcohols.[21] The reaction tolerates a wide range of functional groups and heterocyclic moieties, providing highly useful upgraded amides and esters in excellent efficiency. The presented sustainable alkylation reaction liberates water as the only side product.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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