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Manganese-Catalyzed α-Alkylation of Ketones, Esters, and Amides Using Alcohols

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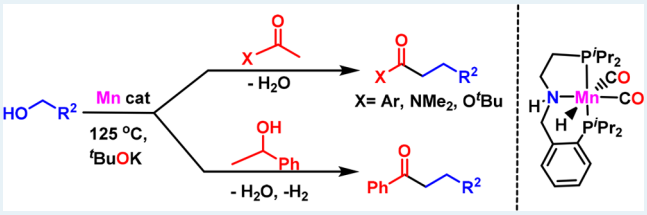
Supporting Information

ABSTRACT: Herein we report the manganese-catalyzed C−C bond-forming reactions via α-alkylation of ketones, amides, and esters, using primary alcohols. β-Alkylation of secondary alcohols by primary alcohols to obtain α-alkylated ketones is also reported. The reactions are catalyzed by a (^{i}Pr-PNP)Mn(H)(CO)$_2$ pincer complex under mild conditions in the presence of (catalytic) base liberating water (and H_2 in the case of secondary alcohol alkylation) as the sole byproduct.



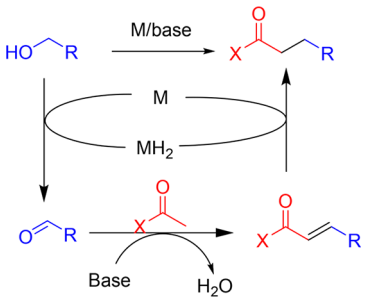
KEYWORDS: *alkylation, ketones, secondary alcohol, amides, esters, manganese, pincer*

Carbon−carbon bond formation represents one of the most important synthetic methodologies in organic chemistry. A classical route of carbon−carbon bond formation involves nucleophilic substitution reactions using an organometallic reagent and an organic electrophile. Transition-metal-catalyzed cross-coupling reactions have made great progress in C−C bond formation. However, traditional alkylations usually require environmentally unfriendly organic or organometallic coupling partners and large amounts of bases, and they generate copious waste.[1]

Recent catalysis is aimed at cheaper, greener, and sustainable methodologies. Therefore, development of a practical, green, and atom-economical alkylation process for the formation of C−C bonds is highly desirable. In recent years, transition-metal complexes have been developed as catalysts for dehydrogenation of alcohols to the corresponding carbonyl compounds, which subsequently undergo condensation with a CH-acidic compound followed by hydrogen autotransfer to form α-alkylated products.[2,3] This so-called redox neutral "hydrogen borrowing methodology" has attracted increasing attention for C−C bond formation reactions because of its atom-economy (Scheme 1).[2,4] Only water is released in these reactions, rendering them green or sustainable.

Moreover, use of alcohols as starting materials for C−C bond formation processes is attractive, because they are cheap, easy to handle and store, and are a renewable alternative to petroleum-based compounds. In the past few years, there has been a growing interest in replacing homogeneous catalysts based on noble metals by earth-abundant base metal complexes.[5,6] This is due to the higher cost of precious metals, lower abundance, and potential higher toxicity. In this respect, application of manganese complexes in (de)-hydrogenation reactions is an attractive goal;[7] manganese is the third most earth-abundant transition metal on earth crust after iron and titanium.[7b] Indeed, hydrogenation of ketones,[7h−q] nitriles,[8] esters,[9] CO_2,[10] and amides[11] catalyzed by manganese complexes has been reported in recent years by several groups including ours.

Scheme 1. Transition-Metal-Catalyzed C-Alkylation via Borrowing Hydrogen Methodology



Substantial efforts are also made in manganese-catalyzed dehydrogenation reactions. We reported dehydrogenative coupling of alcohols and amines to give imines,[12a] catalyzed by a pincer Mn-PNP complex **2** (Figure 1). Several other reports on Mn-catalyzed dehydrogenation reactions appeared

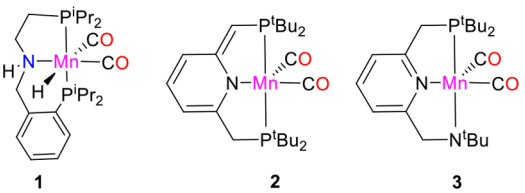


Figure 1. Manganese pincer complexes employed in this work.

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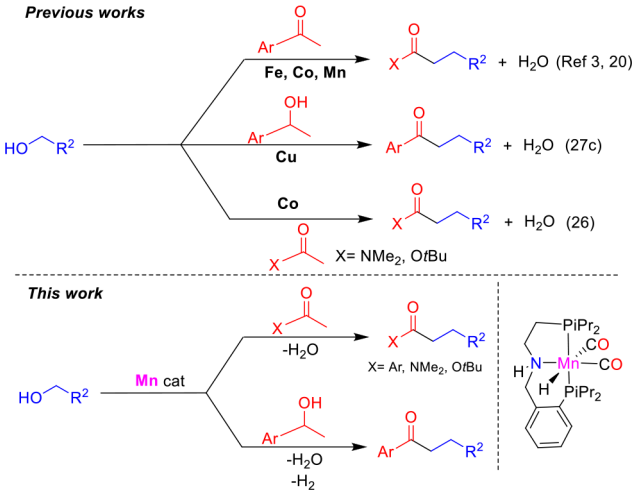
subsequently.[12b,c,13] Recently, N-alkylation of amines using alcohols,[14a−c] and catalytic upgrading of ethanol to 1-butanol[14d,e] via "borrowing hydrogen" were reported.

We reported the Mn-catalyzed N-formylation of amines using methanol,[15a] and deoxygenation of alcohols,[15b] catalyzed by MnPNP pincer complex **1** (Figure 1). Very recently, we demonstrated Mn-catalyzed synthesis of N-substituted hydrazones by dehydrogenative coupling of alcohols and hydrazines catalyzed by a MnPNN pincer complex,[16] as well as dehydrogenative coupling of alcohols and amines to form amides,[17] and that of diols and amines to form cyclic imides using complex **3**.[18] We also reported the unprecedented α-olefination of nitriles using alcohols catalyzed by the manganese complex **1**.[19]

Mn-pincer complex catalyzed α-alkylation reactions of ketones was reported by Beller[20] using primary alcohols (140 °C, 2 mol % catalyst, 5 mol % base). Very recently, while this paper was in preparation, Maji reported a limited scope α-alkylation of arylketones by benzyl alcohol derivatives under similar conditions, catalyzed by an undefined Mn complex generated in situ.[21] We now report that complex **1** is an effective catalyst for α-alkylation of ketones, nonactivated amides, and esters by primary alcohols. Complex **1** also catalyzes β-alkylation of secondary alcohols by primary alcohols to obtain α-alkylated ketones (Scheme 2).

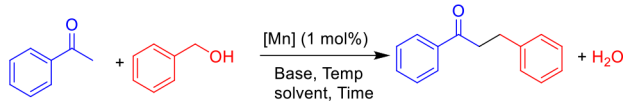
Scheme 2. Base-Metal-Catalyzed C−C Bond-Forming Reactions by α and β Alkylation



To the best of our knowledge, α-alkylation of activated[22] and nonactivated[23] esters and of activated[24] and unactivated[25] amides was reported using Ir and Ru complexes. The only base-metal-catalyzed C-alkylation of esters and nonactivated amides was reported by Kempe using a Co complex.[26]

At the outset, we explored the reaction of acetophenone and benzyl alcohol as model substrates. Reaction of benzyl alcohol (1 mmol) with acetophenone (1 mmol) using ^{t}BuOK (3 mol %) and the Mn complex **1** (1 mol %) in THF in a closed system resulted in the formation of 1,3-diphenylpropan-1-one in 75% yield at 125 °C after 20 h (Table 1, entry 1). However, in the absence of base, only 8% yield of the corresponding product was obtained (Table 1, entry 2). Changing the solvent to 1,4-dioxane or toluene furnished the desired product in excellent yields (96 and 98%, respectively; Table 1, entries 3 and 4). Exploring the effect of bases, NaOEt, KH, NaOH, and

Table 1. Optimization of the Reaction Conditions for the C-Alkylation of Acetophenone Using Benzyl Alcohol Catalyzed by 1−3



entry[a]	cat.	solvent	base (mol %)	time (h)	temp (°C)	conv. (%)[b]	yield (%)[b]
1	**1**	THF	^{t}BuOK(3)	20	125	95	75
2	**1**	THF	-	20	125	8	8
3	**1**	dioxane	^{t}BuOK (3)	20	125	98	96
4	**1**	toluene	^{t}BuOK (3)	18	125	>99	98
5	**1**	toluene	KH(3)	20	125	>99	97
6	**1**	toluene	NaOEt(3)	20	125	97	80
7	**1**	toluene	NaOH(3)	20	125	95	92
8	**1**	toluene	Na_2CO_3(3)	20	125	97	52
9	**1**	toluene	^{t}BuOK(3)	20	110	93	90
10	**1**	toluene	^{t}BuOK (3)	5	125	92	80
11	**2**	toluene	^{t}BuOK (3)	20	125	96	92
12	**3**	toluene	^{t}BuOK (3)	20	125	97	90

[a]Conditions: benzyl alcohol (1 mmol), acetophenone (1 mmol), cat (0.01 mmol), base (3 mol %), and solvent (2 mL), heated in a 25 mL Schlenk tube for given time at 125 °C. [b]yields and conversions determined by GC-MS analysis using m-xylene as internal standard.

Na_2CO_3 was employed under similar reaction conditions giving decent yields of propiophenone (NaOEt, 80%; KH, 97%, NaOH, 92%, Na_2CO_3, 52%) (Table 1, entries 5−8). Our previously reported dearomatized Mn-PNP^{t}Bu complex **2** and the deprotonated Mn-PNN complex **3** (Figure 1) were then screened, affording 1,3-diphenylpropan-1-one in 92 and 90% yields, respectively (Table 1, entries 11 and 12). Decreasing the reaction time to 5 h resulted in only a slight drop in conversion of the alcohol (92%) forming the corresponding ketone product in 80% yield (Table 1, entry 10). Temperature does not play crucial role, as lowering the temperature to 110 °C yielded 90% of the corresponding product (Table 1, entry 9).

Under the optimized reaction conditions (toluene, 125 °C, 3 mol % ^{t}BuOK and 1 mol % **1**), the scope of the manganese-catalyzed C-alkylation of ketones was explored. As shown in Table 2, reactions of benzyl alcohols bearing electron-donating substituents, including 4-methoxybenzyl alcohol, 4-methylbenzyl alcohol, 3-*N*,*N*-dimethylbenzyl alcohol, 2-methoxybenzyl alcohol, and 3,4-dimethoxy benzyl alcohol with acetophenone, produced substituted 1,3-diphenylpropan-1-one derivatives in excellent yields (Table 2, entries A−E). Under similar conditions, benzyl alcohols bearing electron-withdrawing substituents at the para positions, including 4-fluorobenzyl alcohol, 4-trifluoromethyl benzyl alcohol, and 4-bromobenzyl alcohol also afforded selectively the corresponding C-alkylated products with good to moderate yields (Table 2, entries F−H). 4-Cyanobenzyl alcohol afforded 68% of corresponding product in addition to a minute amount the α,β-unsaturated carbonyl product; no products of hydrogenation of the cyano group were observed (Table 2, entry I). Hex-5-en-1-ol as substrate afforded 61% of the target product without any hydrogenation of the olefin functionality (Table 2 entry J). 2-Naphthalene-methanol was also used as alkylating substrate with acetophenone, yielding the corresponding product in 88% yield (entry K). The scope of the reaction was further probed by employing the heterocyclic ketones 2-acetylpyridine and 2-

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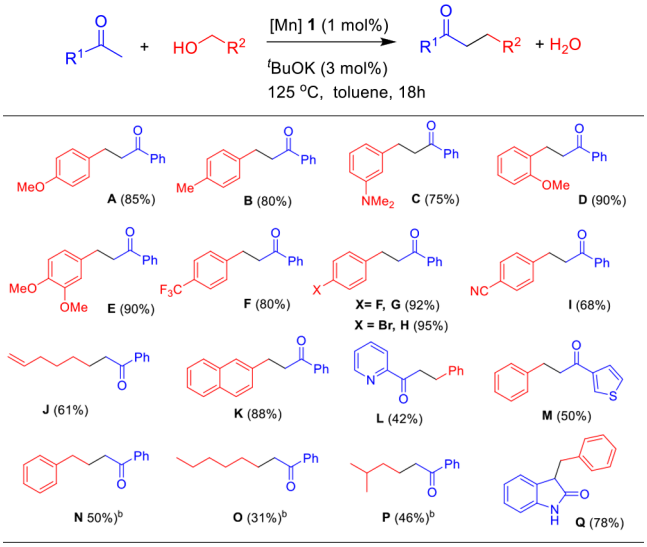
Table 2. C-Alkylation of Ketones with Alcohols Catalyzed by 1[a]

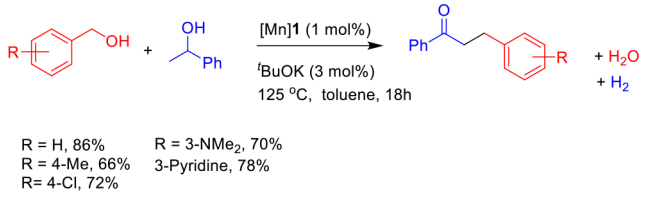


[a]Conditions: ketone (1 mmol), alcohol (1 mmol), **1** (0.01 mmol), ^{t}BuOK (3 equiv relative to **1**), and 2 mL of toluene heated in a 25 mL Schlenk tube at 125 °C in a closed system. Isolated yield in parentheses. [b]yields are based on NMR or GC.

acetylthiophene with benyzl alcohol, furnishing the corresponding product in moderate 42% and 50% yields, respectively (entries L and M). Aliphatic alcohols were also used under the optimized reaction conditions. 2-Phenylethanol, 2-phenyl-1-propanol, 1-hexanol, and 3-methyl-1-pentanol dehydrogenatively coupled with an equivalent amount of acetophenone, affording the corresponding C-alkylated product in good to moderate yields (entries N–P). C-Alkylation of the activated amide 2-oxindole with benzyl alcohol yielded 78% of the deisred product (entry Q). Employing the low-boiling methanol and ethanol resulted in poor yields of the targeted α-alkylated product (see details in SI). The branched carbonyl substrate propiophenone also afforded poor yield under the optimized condition, whereas cyclohexanone was completely inactive toward alkylation with alcohols.

Interestingly, it is possible to employ a secondary alcohol instead of a ketone. Thus, reaction of 1-phenyl ethanol (1 mmol) and benzyl alcohol (1 mmol) in the presence of 1 mol % cat **1** and 3 mol % ^{t}BuOK at 125 °C resulted in the corresponding ketone product in 86% yield (Scheme 3) with the liberation of water and dihydrogen. Analysis of the gas phase by gas chromatography shows the formation of H_2 (see Figure S1 in SI). Reaction of 4-methyl-, 4-chloro-, and 3-*N*,*N*-dimethylamino-benzyl alcohols provide 66%, 72%, and 70% of

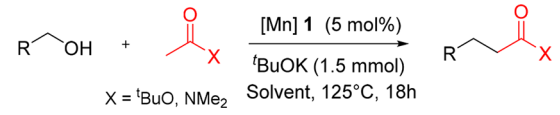
Scheme 3. Direct Synthesis of Ketones by Dehydrogenative Coupling of Secondary Alcohol with Primary Alcohol

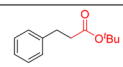
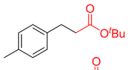
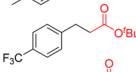
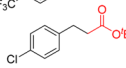
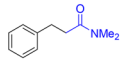
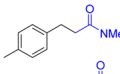
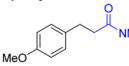
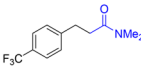
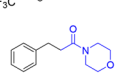


the corresponding α-alkylated ketones as the major product with hydrogenated alcohol as the other product. 3-Pyridinemethanol as substrate formed 78% of the corresponding ketone product under the optimized conditions. β-Alkylation of secondary alcohols to give α-alkylated ketones was previously reported using Ir, Ru, and Cu complexes.[27] Recently, β-alkylation of secondary alcohols to give β-alkylated alcohols catalyzed by Mn was reported.[28]

Carboxylic acid derivatives, such as esters and amides, are valuable intermediates and products in industry and academia. A useful approach to modify amides and esters is α-alkylation by alcohols. However, alkylations of these compounds have proved to be challenging. Amides have a relatively low CH-acidic nature due to resonance stabilization, while esters are amenable to side reactions. Taking note of the good performance of the Mn catalysts for C-alkylation of acetophenone, we explored the possibility to use an ester as the coupling partner (Table 3). The reaction between benzyl

Table 3. C-Alkylation of Esters and Amides Derivatives with Alcohols Catalyzed by 1[a]



Entry	Alcohol	Product	Conv (%)[b]	Yield (%)[b]
1			99	65
2			95	68
3			99	32
4			76	75
5			86	86
6			92	92
7			96	96
8			52	20
9			98	94

[a]Conditions: for esters: alcohol (1 mmol), *t*-butyl acetate (4 mmol), **1** (0.05 mmol), ^{t}BuOK (1.5 equiv. relative to alcohol), and *tert*-butanol (2 mL), heated in a 25 mL Schlenk tube. For amides: alcohol (1 mmol), *N*,*N*-dimethylacetamide (2 mmol), **1** (0.05 mmol), ^{t}BuOK (1.5 equiv relative to alcohol), and toluene (2 mL), heated in a 25 mL Schlenk tube. [b]conv. and yields determined by GC and difference between conversion and yield indicate formation of α,β-unsaturated products.

alcohol and *tert*-butyl acetate was investigated to find suitable reaction conditions. We found out that in order to obtain optimum product yields, the amount of *t*-butyl acetate needed to be increased to 4 equiv at 125 °C using 1.5 equiv of ^{t}BuOK and complex **1** (5 mol %). The reactions were carried out in ^{t}BuOH as solvent in order to shift the equilibrium toward the product. Thus, dehydrogenative coupling of benzyl- and 4-

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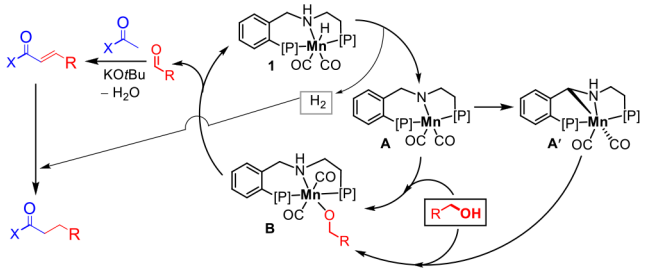
methylbenzyl alcohol with *t*-butylacetate gave the corresponding ester alkylation products in 65% and 68% yields, respectively (Table 3, entries1 and 2). However, in the former case, formation of the α,β-unsaturated *t*-butylcinnamate was also observed. The use of the electron-deficient 4-chloro- and 4-trifluoromethyl benzyl alcohols furnished the corresponding products in moderate yields with the formation of α,β-unsaturated esters as major products (Table 3, entries 3 and 4). Moreover, we also explored the possibility of C-alkylation of nonactivated amides with alcohols.

The reaction between benzyl alcohol and *N*,*N*-dimethylacetamide to give the C-alkylation of amide product was optimized in toluene at 125 °C using 1.5 equiv of ^{t}BuOK, 2 equiv of *N*,*N*-dimethylacetamide, benzyl alcohol derivatives (1 equiv), and complex **1** (5 mol %). Benzyl alcohol, 4-methylbenzyl alcohol, and 4-methoxybenzyl alcohol afforded the corresponding C-alkylated products with very good yields (86, 92, 96%, respectively) (entries 5−7). The dehydrogenative coupling of the electron deficient 4-trifluoromethylbenzyl alcohol with *N*,*N* dimethyacetamide gave the desired product in 20% yield only (Table 3, entry 8). However, employing 4-acetylmorpholine afforded 94% of the C-alkylated product upon treatment with benzyl alcohol under the optimized condition. (Table 3, entry 9).

On the basis of our experimental findings, and on recent mechanistic investigations of Mn-catalyzed dehydrogenative coupling of amines and methanol,[15a] as well as on deoxygenation of primary alcohols catalyzed by **1**,[15b] we propose the plausible catalytic cycle depicted in Scheme 4.

Scheme 4. Plausible Mechanism for the α-Alkylation Reactions with Primary Alcohols Catalyzed by Manganese



Dihydrogen liberation from complex **1** leads to the amido complex **A**, which undergoes intramolecular C−H activation to form the thermodynamically more stable C-metalated complex **A′**.[15a] O−H activation of the alcohol by complex **A** or **A′** via proton transfer, to either the amido nitrogen or benzylic carbon, results in the formation of the alkoxo complex **B**. The following β-hydride elimination step[29] releases the aldehyde. Nucleophilic attack of the deprotonated methyl group of the carbonyl functionality (ketone, ester, and amide) on the released aldehyde followed by water elimination leads to the α,β-unsaturated compound. The deprotonation of the methyl groups requires catalytic (for ketones) or stoichiometric base (for amides and esters). It should be mentioned at this stage that we previously reported that the same catalyst **1** is active for the dehydrogenative coupling of alcohols with nitriles in the absence of base to give substituted acrylonitriles, in which the formed olefinic double bond is completely inert toward hydrogenation by the evolved hydrogen.[19] However, in the current case, the intermediate α,β-unsaturated ketones (or esters, amides) undergo hydrogenation by the evolved hydrogen generating the final C-alkylated product. The hydrogenation is most likely mediated by some Mn species assisted by base, although it is not clear how this hydrogenation occurs.

In conclusion, we have developed a manganese pincer catalyst for the efficient α-alkylation of ketones using primary alcohols, generating water, via a hydrogen borrowing strategy. Formation of α-alkylated ketones by dehydrogenative coupling of secondary alcohols with primary alcohols was also achieved. Moreover, manganese-catalyzed C-alkylations of nonactivated amides and esters was achieved for the first time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b03720.

Experimental procedure, GCMS, and NMR data of products (PDF)

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Notes

The authors declare no competing financial interest.

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