Borrowing Hydrogen

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# Manganese-Catalyzed Hydrogen-Autotransfer C–C Bond Formation: α-Alkylation of Ketones with Primary Alcohols

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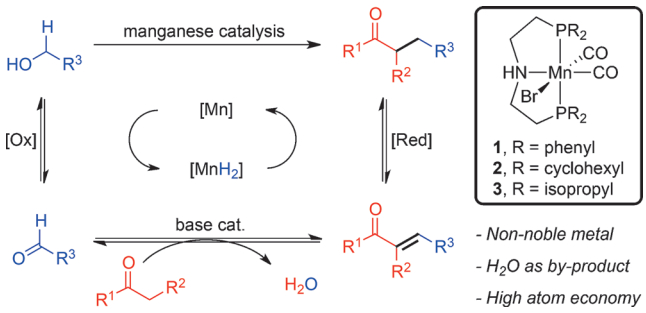
***Abstract:*** *A novel catalytic hydrogen-autotransfer protocol for the atom-efficient α-alkylation of ketones with readily available alcohols is presented. The use of manganese complexes bearing non-innocent PNP pincer ligands enabled the functionalization of a broad range of valuable ketones, including 2-oxindole, estrone 3-methyl ether, and testosterone. Mechanistic investigations suggest the participation of an intramolecular amidate-assisted alcohol-dehydrogenation process.*

Transition-metal-catalyzed hydrogen autotransfer—also called borrowing hydrogen—has become an important synthetic strategy in organic chemistry as a result of its efficiency, low cost, and versatility. It allows the formation of C–N and C–C bonds through the reaction of non-activated alcohols with amines or C-nucleophiles, respectively,[1] as well as the synthesis of valuable heterocycles by domino processes.[2] The availability of starting materials from renewable resources, the operational simplicity, and the generation of $H_2O$ as the only stoichiometric by-product make this process sustainable, atom-economical, and environmentally benign.

Applications of this methodology include the formation of new carbon–carbon bonds. More specifically, the α-functionalization of carbonyl compounds with simple alcohols as electrophiles provides several advantages as compared to classical procedures involving enolates. In the latter reactions, relevant amounts of waste are formed as a result of the use of stoichiometric bases and halides.[3] Hydrogen autotransfer, which is commonly performed with noble metals, such as ruthenium and iridium, constitutes a greener alternative.[4] Besides different reactivity, catalysis with nonprecious metals has economic and ecological benefits. In this regard, the report of a general iron-catalyzed α-alkylation of ketones with Knölker-type complexes is notable.[5]

Apart from iron, manganese is attracting increasing interest in synthesis, since it is cheap and toxicologically benign in comparison to most other transition metals. It is also an abundant element on Earth's crust and is capable of existing in several oxidation states. A wide variety of derivatives are readily available, and the number of manganese-catalyzed transformations has increased considerably during the last few years.[6] Despite all this progress, the use of manganese in dehydrogenative coupling processes is scarce,[7] and to the best of our knowledge no catalytic hydrogen-autotransfer C–C bond-forming processes in the presence of defined molecular manganese complexes have been described previously.[8]

On the basis of our recent study on the iron-catalyzed α-alkylation of ketones with alcohols,[5] we became interested in the catalytic application of manganese(I) pincer complexes for such transformations (Scheme 1). We therefore prepared precatalysts **1**–**3** by the treatment of the corresponding




***Scheme 1.*** Manganese-catalyzed α-alkylation of ketones with alcohols.

tridentate ligands with $[Mn(CO)_5Br]$ (see the Supporting Information for a general procedure). In accordance with the outer-sphere mechanism established for related processes with ruthenium-based complexes,[9] the active catalytic species would be formed through base-mediated dehydrobromination of the precatalyst. Then, the in situ dehydrogenation of the alcohol would afford the corresponding carbonyl compound. Subsequent aldol condensation with the starting ketone should provide the α,β-unsaturated intermediate, which would finally be reduced by the hydrogen extracted in the first step. Water would be formed as the only by-product in a reaction which avoids the use of stoichiometric reagents for both redox processes.

As a model system, the manganese-catalyzed alkylation of acetophenone (**4a**) with benzyl alcohol (**5a**) was optimized (Table 1). To our delight, the use of 3 mol% of pincer complexes **1**–**3** for the reaction of **4a** (1 mmol) with **5a** (1.2 mmol) in the presence of $Cs_2CO_3$ (10 mol%) in 1,4-dioxane at 150 °C allowed the alkylated ketone **6a** to be obtained selectively in good yields (77–90%; Table 1, entries 1–3). The diisopropylphosphine derivative **3** was the most effective precatalyst, whereas $[Mn(CO)_5Br]$, the precursor in the preparation of the pincer complexes, only

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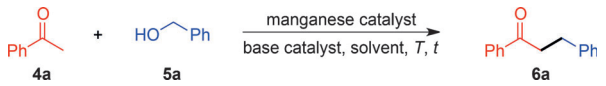
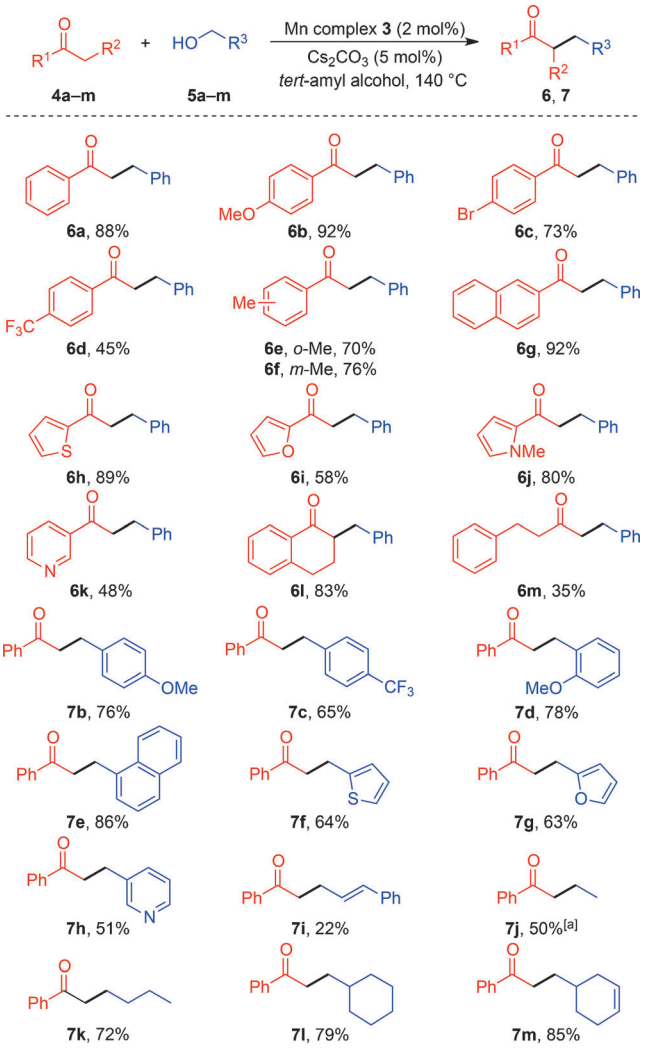
***Table 1:*** Optimization of the reaction conditions for the synthesis of 1,3-diphenylpropan-1-one (**6a**).[a]




| Entry | Mn catalyst | Base | Solvent | $T$ [°C] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | Mn complex **1** | $Cs_2CO_3$ | 1,4-dioxane | 150 | 83 |
| 2 | Mn complex **2** | $Cs_2CO_3$ | 1,4-dioxane | 150 | 77 |
| 3 | Mn complex **3** | $Cs_2CO_3$ | 1,4-dioxane | 150 | 90 |
| 4 | $[Mn(CO)_5Br]$ | $Cs_2CO_3$ | 1,4-dioxane | 150 | 6 |
| 5 | Mn complex **3** | KOH | 1,4-dioxane | 150 | 69 |
| 6 | Mn complex **3** | $K_2CO_3$ | 1,4-dioxane | 150 | 52 |
| 7 | Mn complex **3** | KO*t*Bu | 1,4-dioxane | 150 | 70 |
| 8[c] | Mn complex **3** | $Cs_2CO_3$ | 1,4-dioxane | 150 | 87 |
| 9[d] | Mn complex **3** | $Cs_2CO_3$ | 1,4-dioxane | 150 | 78 |
| 10[c] | Mn complex **3** | $Cs_2CO_3$ | 1,4-dioxane | 140 | 84 |
| 11[c] | Mn complex **3** | $Cs_2CO_3$ | 1,4-dioxane | 130 | 63 |
| 12[c] | Mn complex **3** | $Cs_2CO_3$ | toluene | 140 | 85 |
| 13[c] | Mn complex **3** | $Cs_2CO_3$ | *tert*-amyl alcohol | 140 | 86 |
| 14[c,e] | Mn complex **3** | $Cs_2CO_3$ | *tert*-amyl alcohol | 140 | 88 |
| 15[c,f] | Mn complex **3** | $Cs_2CO_3$ | *tert*-amyl alcohol | 140 | 64 |
| 16[c] | Mn complex **3** | – | *tert*-amyl alcohol | 140 | – |
| 17[c,e] | – | $Cs_2CO_3$ | *tert*-amyl alcohol | 140 | 20 |

[a] Unless otherwise specified, reactions were carried out with **4a** (1 mmol), **5a** (1.2 mmol), the Mn catalyst (0.03 mmol), and the base (0.10 mmol) in 1 mL of the solvent at the indicated temperature for 22 h. [b] Yield of the isolated product. [c] Catalyst loading: 2 mol%. [d] Catalyst loading: 1 mol%. [e] Base: 5 mol%. [f] Base: 2 mol%.




***Scheme 2.*** Manganese-catalyzed reaction of ketones **4** with primary alcohols **5**. Yields are for the isolated product. [a] EtOH (1 mL) was used as the solvent. The yield was determined by GC with hexadecane as an internal standard.

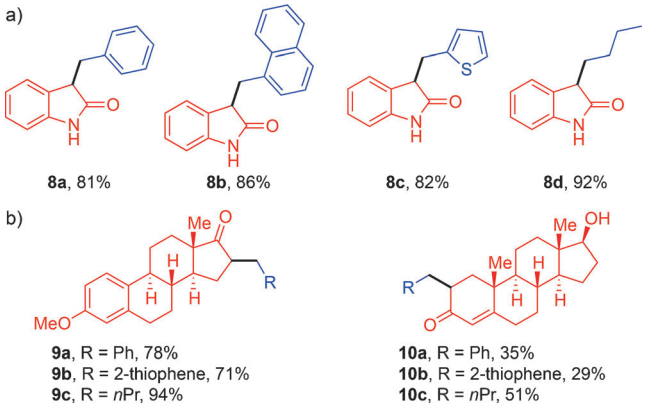
afforded the desired product in 6% yield (Table 1, entry 4). The relevance of the basic medium for both catalyst activation and aldol condensation led us to analyze different bases. We obtained the best result when using cesium carbonate (Table 1, entries 5–7). For further optimization, we examined other critical parameters, such as the catalyst loading, solvent, base concentration, and temperature (Table 1, entries 8–15). Finally, we selected the reaction of **4a** (1 mmol), **5a** (1.2 mmol), **3** (0.02 mmol), and $Cs_2CO_3$ (0.05 mmol) in *tert*-amyl alcohol at 140°C for 22 h as optimal conditions, which gave **6a** in 88% yield (Table 1, entry 14). An experiment without a base showed no conversion, and a reaction in the absence of a manganese complex led to the coupling product in 20% yield (Table 1, entries 16 and 17). As reported previously, such processes can be promoted in a basic medium under metal-free conditions.[10] The selectivity of the transformation is notable, since by-product formation is completely avoided.

Having developed a reliable procedure, we analyzed the reaction of benzyl alcohol (**5a**) with structurally diverse ketones **4a–l** (Scheme 2). An aryl ketone substituted with a methoxy group was converted into **6b** in excellent 92% yield, whereas the presence of electron-withdrawing substituents, such as Br and $CF_3$, led to a slight decrease in efficiency (products **6c**,**d**, 73 and 45%, respectively). This reaction could also be carried out with 2- and 3-acetyltoluene as well as 2-acetylnaphthalene as starting materials (products **6e–g**, 70–92%). Gratifyingly, heterocyclic ketones containing thiophene, furyl, pyrrole, and pyridine moieties were transformed into the desired products **6h–k** in moderate to good yields (48–89%). A cyclic substrate with a secondary α-carbon atom was also functionalized. Thus, the reaction of benzyl alcohol with **4l** afforded the product **6l** in 83% yield. Interestingly, the aliphatic ketone **4m** also showed reactivity, although in this case the alkylated compound **6m** was obtained in lower 35% yield.

We also studied the reaction of acetophenone (**4a**) with differently substituted primary alcohols **5a–m** (Scheme 2). The electron-rich derivative **5b** afforded ketone **7b** in good yield (76%), and the reaction with 4-(trifluoromethyl)benzyl alcohol (**5c**) took place in a similar manner (65%). An experiment with more hindered 2-methoxybenzyl alcohol gave rise to **7d** in 78% yield, and 1-naphthylmethanol reacted with **4a** to give the desired product **7e** in high yield (86%). Heteroaromatic substrates were also efficiently applied to the alkylation of **4a**, although in moderate yields (products **7f–h**, 51–64% yield). Moreover, the reaction with cinnamyl alcohol (**5i**) gave the desired ketone **7i** but in low 22% yield. Next, we studied the reactivity of aliphatic alcohols. The alkylation of acetophenone (**4a**) with ethanol, used as the solvent, pro-

vided **7j** in 50% yield (as determined by GC), whereas 1-butanol afforded the corresponding ketone **7k** in good 72% yield. Cyclohexanemethanol (**5l**) was also used effectively as the electrophile (79%). Interestingly, the reaction with cyclohex-3-en-1-ylmethanol (**5m**) provided **7m** in 85% yield. In this case, unlike in some ruthenium-catalyzed hydrogen-autotransfer applications,[11] reduction of the C–C double bond present in the starting alcohol did not take place.

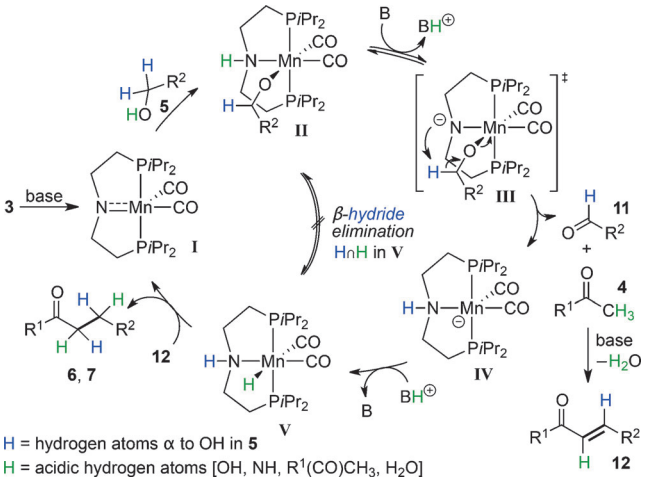
To increase the versatility of this catalytic protocol, we applied it to the functionalization of other interesting carbonyl compounds (Scheme 3). Initially, we studied the α-alkylation of 2-oxindole, a relevant heterocycle found in many biologically active molecules.[12] Such compounds often present substituents at the 3-position, which are normally introduced by the use of organic halides. Owing to the presence of a free amine in this cyclic amide, carbon–carbon bond formation by the method described herein must be performed selectively to avoid the amination reaction.[13] The manganese-catalyzed reaction of 2-oxindole with alcohols bearing aryl, heteroaryl, and alkyl groups under the previously optimized conditions provided the C–C coupled products **8a–d** in excellent yields (81–92%, Scheme 3a).




***Scheme 3.*** Manganese-catalyzed α-alkylation of a) 2-oxindole and b) estrone 3-methyl ether and testosterone with alcohols. Yields are for the isolated product.

The modification of natural products allows for structure–activity relationship (SAR) studies with the aim of exploring their full drug potential.[14] Along this line, we applied our catalytic strategy to the derivatization of hormones. Indeed, estrone and testosterone derivatives could be readily functionalized by using simple alcohols as starting materials (Scheme 3b). In this way, estrone 3-methyl ether was effectively alkylated at the carbon atom adjacent to the carbonyl group with benzyl alcohol, 2-thiophenemethanol, and 1-butanol to afford products **9a–c** in 71–94% yield. Despite the presence of a free secondary alcohol in the D ring of testosterone, the α-position of the six-membered cyclic ketone was smoothly substituted with the same alcohols. In this case, lower product yields were observed (products **10a–c**, 29–51%) owing to the formation of two main side products.[15]

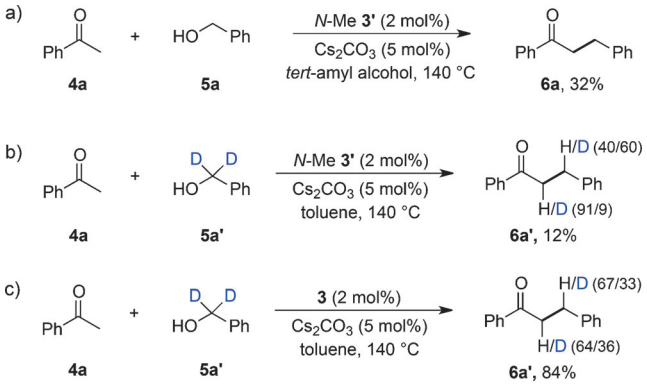
Finally, we propose a plausible mechanism depicted in Scheme 4 for this manganese-catalyzed transformation. Initially, the precatalyst **3** is activated by reaction with a base in a dehydrobromination reaction to give species **I**. In agreement with related complexes based on other transition metals,[16] coordination of the deprotonated alcohol **5** then provides an alkoxo-type complex **II**. At this point, a dehydrogenation reaction might take place by β-hydride elimination, despite the lack of free coordination sites at the metal center. However, we do not think that this option is very probable and instead propose that the basic medium promotes the formation of an amidate, which undergoes abstraction of the β-hydrogen atom, as shown in transition state **III**. Such an intramolecular ligand-assisted mechanism leads to aldehyde **11** and the intermediate **IV**, which is protonated to form the manganese hydride **V**. An aldol condensation between **11** and the enolate resulting from the starting ketone **4** affords the α,β-unsaturated compound **12** with the release of a molecule of $H_2O$. Finally, hydrogenation by species **V** yields the desired ketone **6/7** and regenerates the catalytic active species **I**. Previously, organometallic hydride complexes (e.g. Ru, Ir, as well as Fe) with pincer ligands have been shown to reduce polarized multiple bonds.[17] Thus, we assume that our reaction proceeds through Mn–H hydride transfer from complex **V** to the β-position in a Michael-type process followed by N–H proton transfer to the corresponding enolate.[4f]




***Scheme 4.*** Plausible mechanism for the manganese-catalyzed α-alkylation of ketones with alcohols.

To confirm the participation of the N–H moiety of the pincer ligand in this transformation, we performed the alkylation of acetophenone (**4a**) with benzyl alcohol (**5a**) in the presence of the corresponding N-methylated manganese complex **3′** (Scheme 5a). When the optimal conditions were applied, ketone **6a** was isolated in only 32% yield (88% yield was observed with **3** as the catalyst). This observation indicates the possibility of different pathways with the prevalence of an NH-assisted outer-sphere mechanism. Deuterium-labeling experiments were also carried out with [α,α-$D_2$]benzyl alcohol (**5a′**). In this case, the aprotic solvent toluene was used instead of *tert*-amyl alcohol to avoid additional H/D exchange. An experiment with the *N*-Me complex **3′** provided the desired ketone **6a′** in low yield




***Scheme 5.*** Control experiments. Yields are for the isolated product.

(12%) with 9% deuteration at the α-position and 60% at the β-position (Scheme 5b). The lower yield is caused by the absence of an alcoholic solvent (alkoxide formation in basic medium) or the different reactivity of **5a′**. Alternatively, the reaction of **4a** with **5a′** under the catalysis of the N–H complex **3** led to **6a′** in 84% yield with deuterium atoms equally distributed in the C2 and C3 positions (36 and 33% D, respectively, Scheme 5c). Deuterium incorporation at the α-position of **6a′** implies the formation of "$D^+$" from deuterated benzyl alcohol. As shown in Scheme 4, the amidate-assisted pathway offers the possibility of transforming the C–D bonds in the benzyloxy intermediate **II** to give an N-deuterated complex **IV**, which acts as a source of "$D^+$". On the other hand, with complex **3′** such transition state cannot be formed, thereby explaining the high incorporation of $H^+$ at the α-position in this experiment (91%). Notably, the observed H/D ratios in both reactions suggest the possibility of alternative pathways for this manganese-catalyzed transformation.

In conclusion, we have developed the first manganese-catalyzed alkylation of ketones and related compounds with primary alcohols. This straightforward transformation takes place with an air- and water-stable manganese(I) PNP pincer precatalyst. A low base concentration and broad applicability are notable features of this hydrogen-autotransfer methodology.

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**Keywords:** alcohols · atom economy · hydrogen transfer · ketones · manganese catalysis

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# Communications

**Borrowing Hydrogen**

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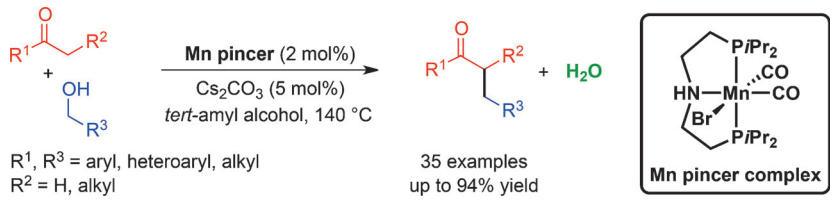
Manganese-Catalyzed Hydrogen-Autotransfer C–C Bond Formation: α-Alkylation of Ketones with Primary Alcohols




**Something borrowed, something new**: A hydrogen-autotransfer reaction catalyzed by manganese(I) PNP pincer complexes was developed for the α-alkylation of ketones with alcohols (see scheme). Structurally diverse primary alcohols were used to functionalize a wide range of ketones, including 2-oxindole, estrone 3-methyl ether, and testosterone, by this straightforward method.