# *C*-Alkylation of Secondary Alcohols by Primary Alcohols via Manganese Catalyzed Double Hydrogen Autotransfer

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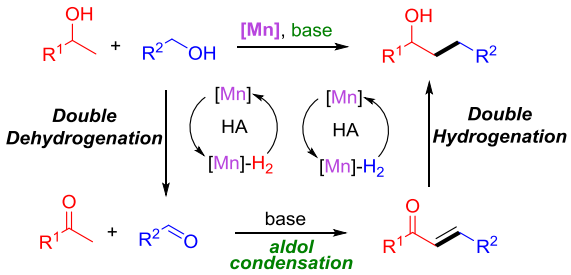
**Abstract:** A new manganese catalyzed alkylation of secondary alcohols with non-activated alcohols is presented. The use of a stable and well-defined manganese PNN complex together with catalytic amount of base enables the conversion of renewable alcohol feedstocks to a broad range of higher value alcohols in good yields while water is the sole by-product. The strategy eliminates the need for exogenous and detrimental alkyl halides as well as the use of noble metal catalysts, making the C-alkylation via double hydrogen autotransfer a highly sustainable and environmentally benign process. Mechanistic investigations support a hydrogen autotransfer mechanism in which a non-innocent ligand plays a crucial role.

β-Alkylation of alcohols is one of the most fundamental carbon-carbon bond forming reactions. The conventional route requires three chemical steps (i.e., stoichiometric oxidation, alkylation with alkyl halides and stoichiometric reduction), making the overall process environmentally unfriendly.[1] With aim to avoid the use of mutagenic and waste-forming reagents,[2] modern processes have emerged which are based on the hydrogen autotransfer strategy[3] utilizing biomass derived alcohols as alkylating agents.[4] Hence a strategy which comprises the dehydrogenation of both of the primary and secondary alcohols, followed by base catalyzed aldol condensation to produce α,β-unsaturated ketones and subsequent double hydrogenation can provide β-alkylated alcohols. Thus, the need of stoichiometric oxidation and reduction reagents as well as alkyl halides can be substituted by abundantly available alcohols.

So far, the vast majority of these approaches rely on the use of more expensive noble metal catalysts, such as iridium,[5] ruthenium,[6] rhodium [7] and palladium.[8] Replacement of the precious metal catalysis by earth abundant low-toxicity base metals is a topic of current interest.[9] Processes relaying on the use of iron[10] nickel[11] and copper[12] catalysts have been disclosed. More recently, cobalt catalysis has been successfully used. However, higher catalyst loading (5 mol%) along with super stoichiometric amounts of a more sensitive and expensive base (KHMDS) may be a drawback.[13]

Despite all these efforts, the alkylation of *sec*-alcohols with primary alcohols often leads to mixtures of the desired β-alkylated alcohols along with the corresponding undesired ketones, presenting a crucial selectivity issue. Therefore, the development of a base-metal catalyst for the selective alkylation of *sec*-alcohols would be highly desirable.




***Scheme 1.*** Manganese catalysed double hydrogen autotransfer

Based on our recent experience in manganese catalysis and its application in the reduction of carbonates,[14] we questioned if highly reactive Mn-catalysts may be suitable for the efficient hydrogenation of the intermediate α,β-unsaturated ketone, resulting exclusively in the desired alkylated alcohol products. However at the outset of this work, the alkylation of secondary alcohols by primary alcohols was not known by manganese catalysis. During the preparation of this manuscript a related parallel study was reported by Yu et al.[15] Herein, we demonstrate that the Mn-PNN complex **Mn-1** is remarkably active and selective catalyst for the alcohol alkylation reaction (Scheme 1).[16-17]

The cross-coupling between 1-phenylethanol (**1a**) and the benzyl alcohol (**2a**) was selected as test reaction (Table 1). Initially, we screened the catalytic properties of different manganese complexes (**Mn-1** to **Mn-4**) in combination with 10 mol% of $Cs_2CO_3$. To our delight, the use of 3 mol% of our PNN complex **Mn-1** led to promising results providing the desired product **3a** in 49% yield along with 8% of the corresponding ketone **3a'** (Table 1, entry 1). The application of the di-*tert*-butyl complex **Mn-2** showed similar dehydrogenation activity and slightly lower hydrogenation activity (Table 1, entry 2).[16f] In the presence of PNP complexes, such as **Mn-3** and **Mn-4**, excellent conversion was observed. However, the inefficient hydrogenation of the unsaturated intermediate provided considerable amount of the undesired ketone **3a'** (Table 1, entry 3, 4). Thus, we decided to further optimize the model reaction using **Mn-1** in combination with different bases and solvents. 1,4-Dioxane and 2-Me-THF proved to be unsuitable for this reaction. However, performing the reaction in toluene resulted in better results (table 1, entries 5-7). Additionally, we tested various bases such as KHMDS, KH, KOH and KO*t*Bu (Table 1, entries 8-11). From these experiments the reaction proceeds best when 25 mol% of KO*t*Bu are applied and the desired product was obtained in 92% yield (Table 1, entries 12-13).

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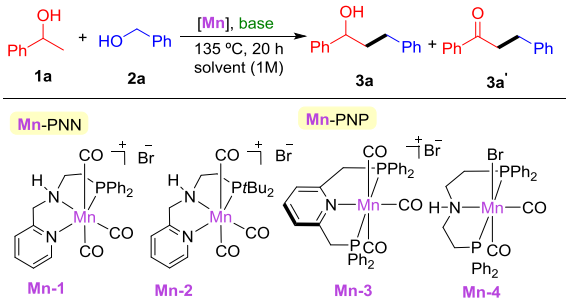
**Table 1.** Optimization of the reaction conditions.[a]




| Entry | [Mn] (mol%) | base (mol%) | solvent | conv. (%) | yield of **3a/3a'** (%) |
|---|---|---|---|---|---|
| 1 | **Mn-1** (3) | $Cs_2CO_3$ (10) | TAA | 57 | 49/08 |
| 2 | **Mn-2** (3) | $Cs_2CO_3$ (10) | TAA | 60 | 42/14 |
| 3 | **Mn-3** (3) | $Cs_2CO_3$ (10) | TAA | >99 | 69/30 |
| 4 | **Mn-4** (3) | $Cs_2CO_3$ (10) | TAA | 90 | 55/34 |
| 5 | **Mn-1** (3) | $Cs_2CO_3$ (10) | 1,4-dioxane | 62 | 20/03 |
| 6 | **Mn-1** (3) | $Cs_2CO_3$ (10) | 2-Me-THF | 60 | 30/04 |
| 7 | **Mn-1** (3) | $Cs_2CO_3$ (10) | Toluene | 73 | 50/22 |
| 8 | **Mn-1** (3) | KHMDS (10) | Toluene | 77 | 50/08 |
| 9 | **Mn-1** (3) | KH (10) | Toluene | 90 | 65/08 |
| 10 | **Mn-1** (3) | KOH (10) | Toluene | 93 | 76/05 |
| 11 | **Mn-1** (3) | KO*t*Bu (10) | Toluene | 88 | 81/05 |
| 12 | **Mn-1** (3) | KO*t*Bu (5) | Toluene | 85 | 57/17 |
| 13 | **Mn-1** (3) | KO*t*Bu (25) | Toluene | >99 | 92/08 |
| **14** | **Mn-1 (1)** | **KO*t*Bu (25)** | Toluene | **>99** | **92/08** |
| 15[b] | **Mn-1 (1)** | KO*t*Bu (25) | Toluene | >99 | 83/13 |

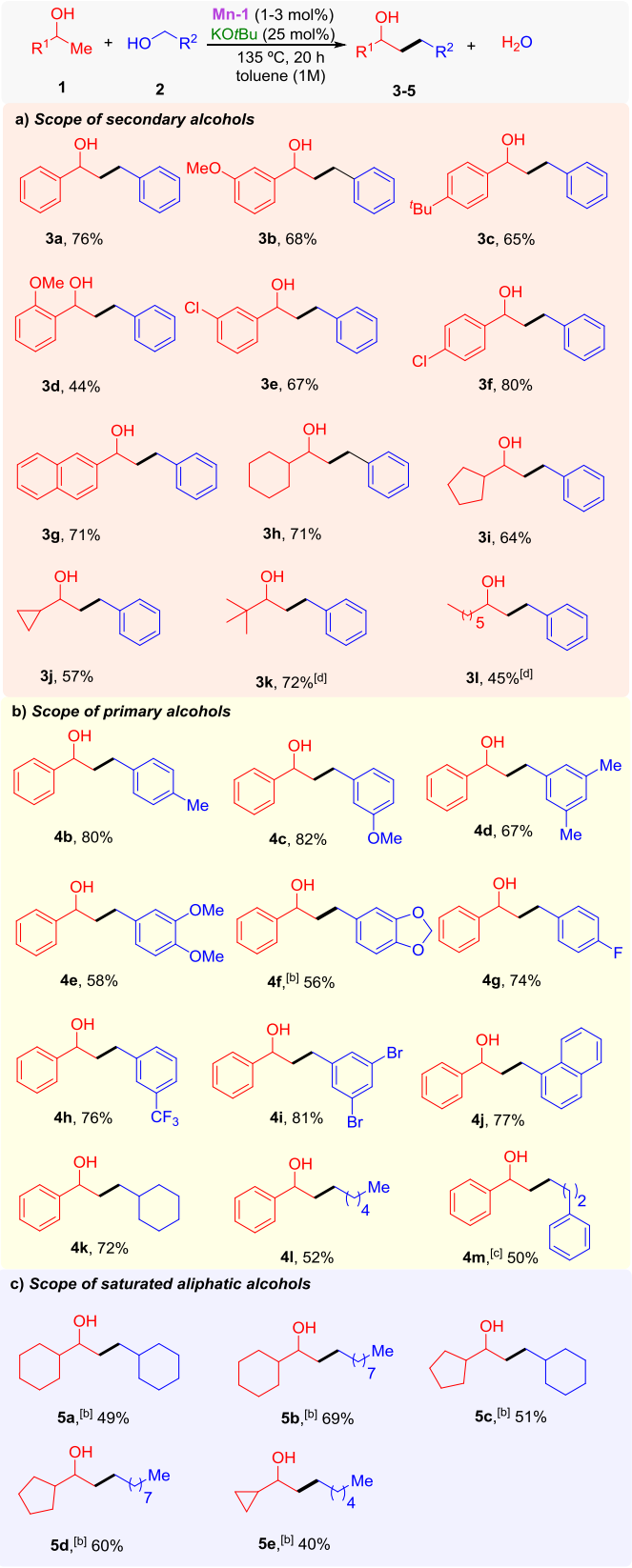
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), [**Mn**] and base in 0.5 mL of solvent at 135 °C in a glass tube under argon for 20 h. Conversions and yields were determined by the $H^1$ NMR analysis of the crude reaction mixture using mesytilene as an internal standard. TAA is *t*-amyl alcohol. [b] a drop of mercury was added

Pleasingly, we could reduce the catalyst loading to only 1 mol% while still obtaining excellent yield (Table 1, entry 14). Finally, full conversion was observed upon adding mercury to the reaction mixture, proving the homogenous nature of the manganese catalyst (Table 1, entry 15).

Next, the substrate scope of the β-alkylation of different *sec*-alcohols **1** with benzyl alcohol **2a** was conducted (Table 2a). 1-Phenylethanol derivatives **1b**-**1d** bearing electron-donating substituents in *ortho*, *meta* and *para* positions gave the desired products **3b**-**3d** in good yields. Similarly, the electron-deficient substrates **1e**-**1f** furnished the upgraded alcohols **3e**-**3f** in good yields. Furthermore, the alkylation of the naphthyl substrate **1g** afforded the expected product in 71% yield. Importantly, the substrate scope could be extended to the use of the less active aliphatic *sec*-alcohols **1h**-**1l** and the corresponding alcohols **3h**-**3l** were obtained in good to moderate yields. Noteworthy, even the sterically demanding alcohol **1k** is tolerated in this manganese catalyzed reaction.

After successfully varying the secondary alcohols, we became interested in studying the scope of the β-alkylation of 1-phenylethanol (**1a**) with different primary alcohols **2** (Table 2b).

**Table 2.** Manganese catalyzed C-alkylation of secondary alcohols by primary alcohols.[a]




[a] Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), **Mn-1** (0.005 mmol) and KO*t*Bu (0.125 mmol) in toluene (0.5 mL) were stirred at 135 °C for 20 h in a glass tube under an inert atmosphere. Yields after column chromatography. [b] **Mn-1** (0.015 mmol). [c] **Mn-1** (0.01 mmol).[d] NMR yield.

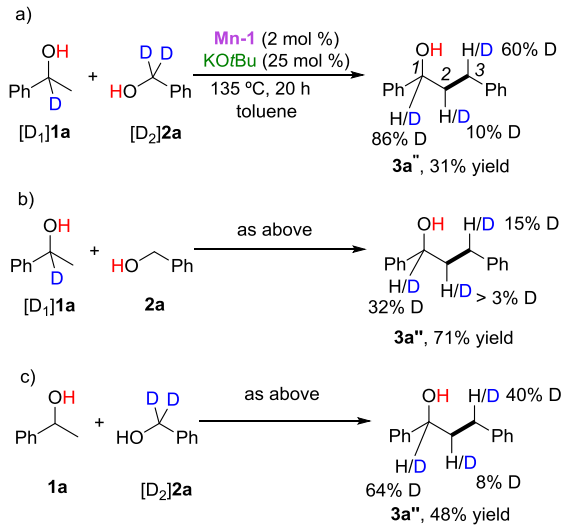
To our delight the alkylation of **1a** with the electron rich benzyl alcohols **2b**-**2f** as well as the electron poor substrates **2g**-**2i** resulted in the *sec*-alcohols **4b**-**4i** in good yields as well. Also the alcohol **4j** containing a naphthyl group was obtained in 77% yield. Additionally, various aliphatic primary alcohols could also be used as a coupling partner to afford the alcohols **4k**-**4m**.

Encouraged by these promising results, we decided to investigate the more challenging coupling reaction between saturated aliphatic primary and secondary alcohols (Table 2c).

Indeed, our catalytic system proved also to be suitable to couple the branched cyclohexanemethanol and unbranched 1-octanol with 1-cyclohexylethanol and the products **5a**-**5b** were isolated in good yields. Furthermore, 1-cyclopenylethanol and 1-cyclopropylethanol were alkylated with different linear and non-linear alcohols to produce the alcohols **5c**-**5e** in good yields .

In order to gain insight into the reaction mechanism, we performed deuterium labeled experiments (Scheme 2). When 1-phenylethanol-α-$d_1$ [$D_1$]**1a** was reacted with benzyl alcohol-α,α-$d_2$ [$D_2$]**2a**, a very strong kinetic isotope effect was observed and **3a''** was obtained in 31% yield with 86% deuteration in the α-position and 60% D incorporation at C3. No deuteration occurred at the OH and only 10% deuterium incorporation occurred at C2 position (Scheme 2a). Similarly, the reaction between [$D_1$]**1a** and **2a** gave the alkylated product with 32% D incorporation at C1, 15% D incorporation at C3, and > 3% deuterium incorporation at C2 (Scheme 2b). The presence of only 40% deuterium incorporation at C3 in the reaction between **1a** and [$D_2$]**2a**, indicates the reversibility of the primary alcohol dehydrogenation process and supports the hydrogen autotransfer pathway (Scheme 2c).

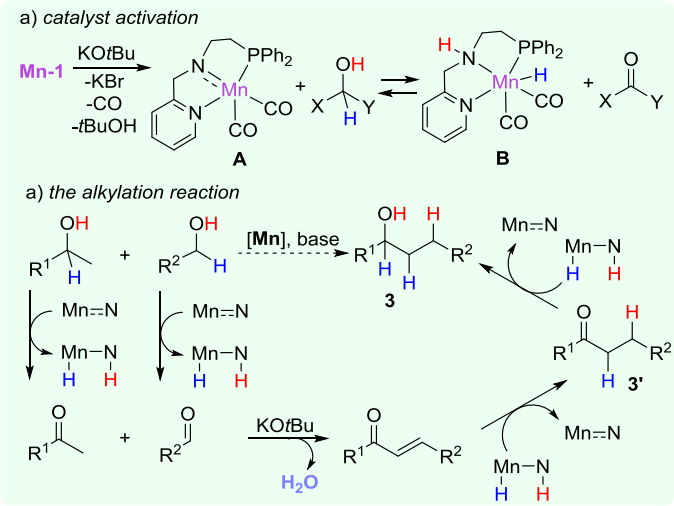
Interestingly, the high deuterium content at C1 and C3 and the low deuterium incorporation at C2 position are not in alignment with both, the classical dihydride mechanism and proposed amidate assisted pathway.[16e] The presented deuterium experiments support a monohydride mechanism and highlight the involvement of both, the metal and the non-innocent ligand in the transfer hydrogenation pathways. [18-20]




***Scheme 2.*** Deuterium-labelling experiments

The metal monohydride can be formed by the β-hydride elimination of the manganese alkoxide (inner sphere pathway).

Alternatively, the alcohol can be (de)hydrogenated through the outer sphere of the metal without coordination of the alcohol to the metal center.[20] Subsequently we investigated the progress of the model reaction between **1a** and **2a** as a function of time (see SI for details). The investigation indicates that the dehydrogenation of the alcohol substrates is most likely the rate limiting step. The proposed reaction mechanism is shown in scheme 3. Initially, the pre-catalyst **Mn-1** reacts with the base to form the 16e species **A**. This active species can reversibly react with an alcohol to form the corresponding ketone and the hydrogenated catalyst **B** (Scheme 3a). The alkylation reaction starts with the dehydrogenation of both of the alcohols to form carbonyl compounds and the hydrogenated catalyst **B**. Then, the base catalyzed aldol condensation leads to the irreversible formation of the α,β-unsaturated ketone intermediate. Based on the experimental results and the reaction profile, it is suggested that the hydrogenation of the α,β-unsaturated ketone to ketone takes place prior to the reduction of the ketone **3'** to the desired alcohol product **3** (Scheme 3b).




***Scheme 3.*** Proposed reaction mechanism

In conclusion, we herein report the synthesis of *C*-alkylated secondary alcohols via a hydrogen autotransfer strategy using a stable and well-defined manganese catalyst. The newly developed catalytic system distinguishes itself through the absence of noble metals, and stoichiometric amounts of base as well as external hydrogen acceptors or hydrogen donors are not required. The environmentally benign, atom-economical process operates under relatively mild conditions and water is the only by-product. The Mn-catalyzed reaction features a wide substrate scope and, importantly, the cross-coupling between two different aliphatic saturated alcohols is feasible resulting in the desired secondary aliphatic alcohols with excellent chemoselectivity.

## *Acknowledgements*

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**Keywords:** hydrogen autotransfer • manganese catalysis • alkylation • alcohols • base metals

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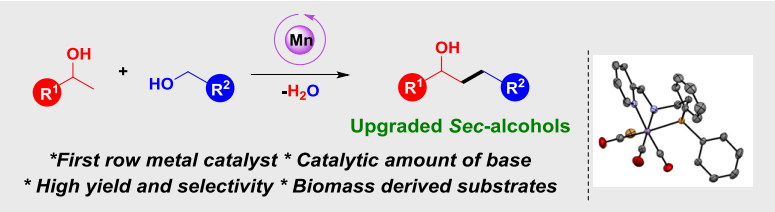
# COMMUNICATION

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