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C-Alkylation of Secondary Alcohols by Primary Alcohols through Manganese-Catalyzed Double Hydrogen Autotransfer

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A new Mn-catalyzed alkylation of secondary alcohols with non-activated alcohols is presented. The use of a stable and well-defined manganese pincer complex, stabilized by a PNN ligand, together with a catalytic amount of base enabled the conversion of renewable alcohol feedstocks to a broad range of higher-value alcohols in good yields with water as the sole byproduct. The strategy eliminates the need for exogenous and detrimental alkyl halides as well as the use of noble metal catalysts, making the C-alkylation through 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 that 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, stoichiometric oxidation and reduction reagents as well as alkyl halides can be substituted by abundantly available alcohols.

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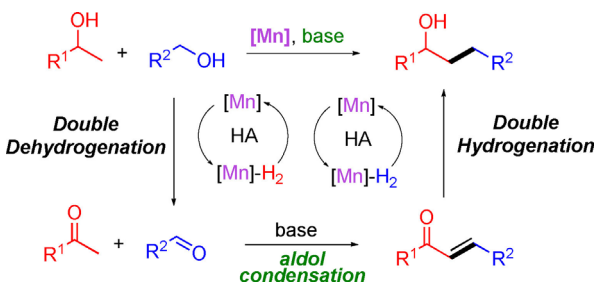
So far, the vast majority of these approaches rely on the use of more expensive noble-metal catalysts, such as Ir,[5] Ru,[6] Rh[7] and Pd.[8] Replacement of the precious-metal catalysts by earth-abundant low-toxicity base-metal catalysts is a topic of current interest.[9] Processes relying on the use of Fe[10] Ni[11] and Cu[12] catalysts have been disclosed. More recently, Co catalysis has been successfully used. However, higher catalyst loading (5 mol%) along with superstoichiometric amounts of a more sensitive and expensive base [potassium bis(trimethylsilyl)amide (KHMDS)] may be a drawback.[13]

Despite all these efforts, the alkylation of secondary 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 secondary alcohols would be highly desirable.

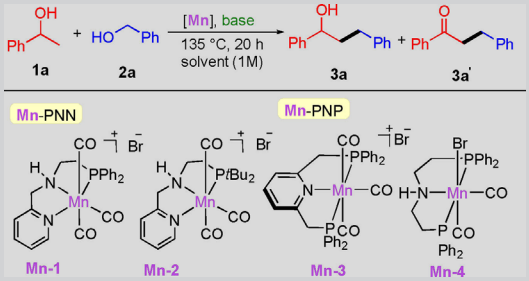
Based on our recent experience in Mn catalysis and its application in the reduction of alkynes and organic carbonates,[14] we questioned if highly reactive Mn catalysts may be suitable for the efficient hydrogenation of the intermediate α,β-unsaturated ketone, resulting exclusively in the desired alkylated alcohols. However, at the outset of this work, the alkylation of secondary alcohols using/from primary alcohols by Mn catalysis was not known to the best of our knowledge. During the preparation of this Communication a related parallel study was reported by Yu and co-workers.[15] Here, we demonstrate that the Mn–PNN pincer complex **Mn-1** is a remarkably active and selective catalyst for the alkylation reaction of alcohols (Scheme 1).[16,17]

The cross-coupling between 1-phenylethanol (**1a**) and benzyl alcohol (**2a**) was selected as a model reaction (Table 1). Initially, we screened the catalytic properties of different Mn complexes (**Mn-1** to **Mn-4**) in combination with 10 mol% of Cs_2CO_3 in *tert*-amyl alcohol (TAA) as solvent. The use of



Scheme 1. Mn-catalyzed double hydrogen autotransfer.

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



Entry	Catalyst ([mol%])	Base ([mol%])	Solvent	Conv. [%]	Yield of **3a**/**3a**′ [%]
1	**Mn-1** (3)	Cs_2CO_3 (10)	TAA	57	49/8
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	20/3
6	**Mn-1** (3)	Cs_2CO_3 (10)	2-Me-THF	60	30/4
7	**Mn-1** (3)	Cs_2CO_3 (10)	toluene	73	50/22
8	**Mn-1** (3)	KHMDS (10)	toluene	77	50/8
9	**Mn-1** (3)	KH (10)	toluene	90	65/8
10	**Mn-1** (3)	KOH (10)	toluene	93	76/5
11	**Mn-1** (3)	KO*t*Bu (10)	toluene	88	81/5
12	**Mn-1** (3)	KO*t*Bu (5)	toluene	85	57/17
13	**Mn-1** (3)	KO*t*Bu (25)	toluene	>99	92/8
14	**Mn-1 (1)**	**KO*t*Bu (25)**	toluene	>**99**	**92/8**
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 mesitylene as an internal standard. TAA = *tert*-amyl alcohol. [b] A drop of mercury was added.

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** resulted in 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, entries 3 and 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 8–13). From these experiments the reaction proceeded best when 25 mol% of KO*t*Bu were applied and the desired product was obtained in 92% yield (Table 1, entry 13). Interestingly, we could reduce the catalyst loading to 1 mol% while still obtaining excellent yield (Table 1, entry 14). Finally, full conversion was still observed upon adding Hg to the reaction mixture, proving the homogenous nature of the Mn catalyst (Table 1, entry 15).

Next, the substrate scope of the β-alkylation of different secondary alcohols **1** with benzyl alcohol **2a** was conducted (Scheme 2a). The 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** and **1f** furnished the upgraded alcohols **3e** and **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 secondary alcohols **1h**–**1l**; the corresponding alcohols **3h**–**3l** were obtained in good-to-moderate yields. Noteworthy, even the sterically demanding alcohol **1k** was tolerated in this Mn-catalyzed reaction.

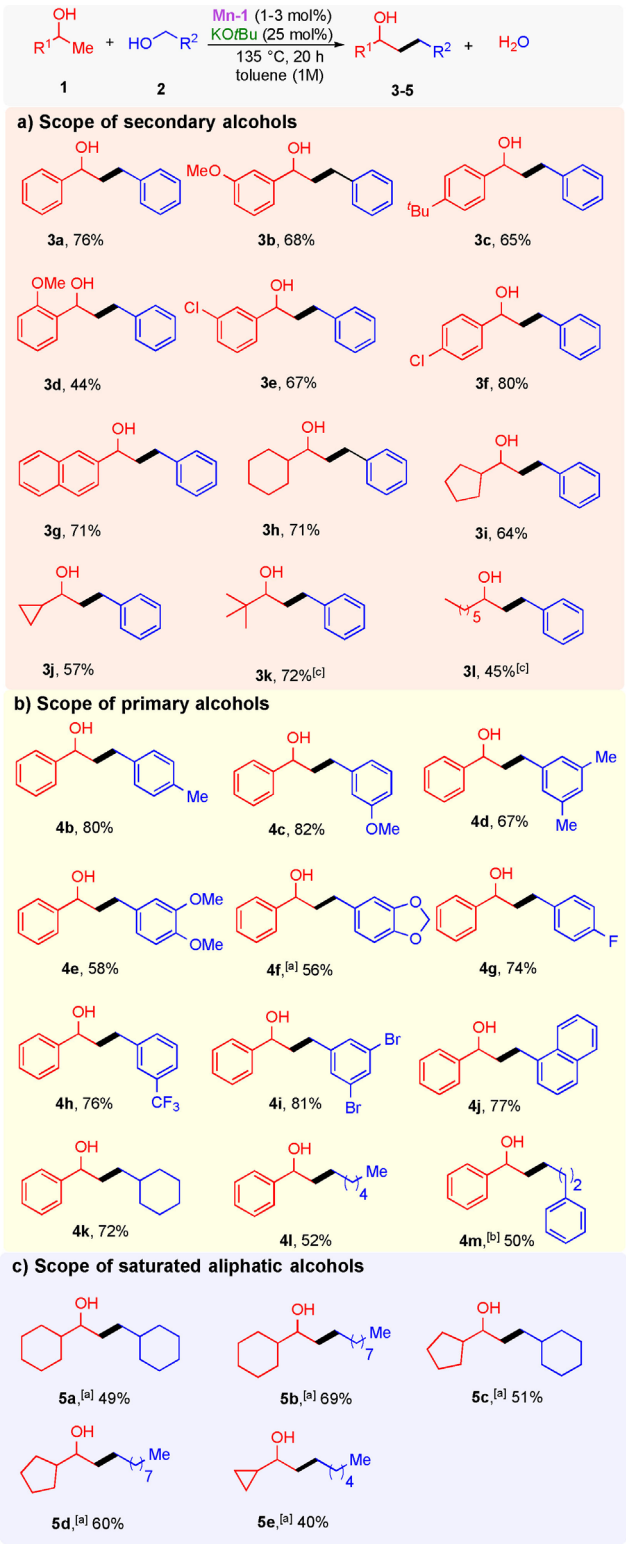
After successfully varying the secondary alcohols, we became interested in studying the scope of the β-alkylation of 1-phenylethanol (**1a**) with different primary alcohols **2** (Scheme 2b). The alkylation of **1a** with the electron-rich benzyl alcohols **2b**–**2f** as well as the electron-poor substrates **2g**–**2i** resulted in the secondary alcohols **4b**–**4i** in good yields. 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 (Scheme 2c). Indeed, our catalytic system also proved to be suitable to couple the branched cyclohexanemethanol and unbranched 1-octanol with 1-cyclohexylethanol and the products **5a** and **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.

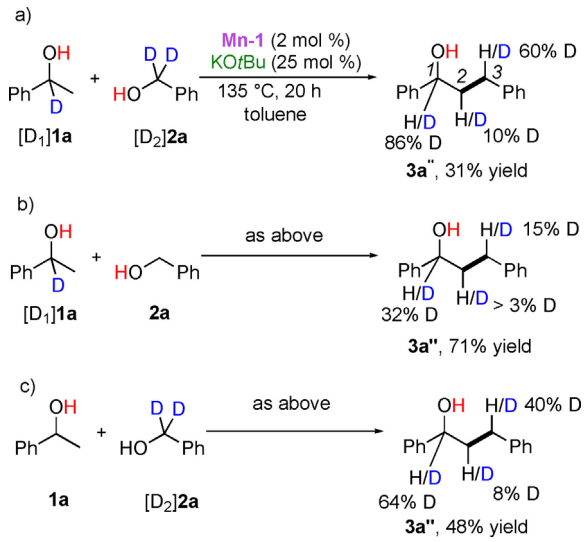
To gain insight into the reaction mechanism, we performed deuterium-labeling experiments (Scheme 3). When 1-phenylethanol-α-d_1 [D_1]**1a** was reacted with benzyl alcohol-α,α-d_2 [D_2]**2a**, a very strong kinetic isotope effect was observed and **3a**′′ was obtained in 31% yield with 86% deuteration in the α-position and 60% deuterium incorporation at C3. No deuteration occurred at the OH moiety and only 10% deuterium incorporation occurred at the C2 position (Scheme 3a). Similarly, the reaction between [D_1]**1a** and **2a** gave the alkylated product with deuterium incorporations of 32% at C1, 15% at C3, and >3% at C2 (Scheme 3b). 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 3c).

Interestingly, the high deuterium content at C1 and C3 and the low deuterium incorporation at C2 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]

The metal monohydride can be formed by the β-hydride elimination of the Mn alkoxide (inner sphere pathway). Alternatively, the alcohol can be (de)hydrogenated through the outer

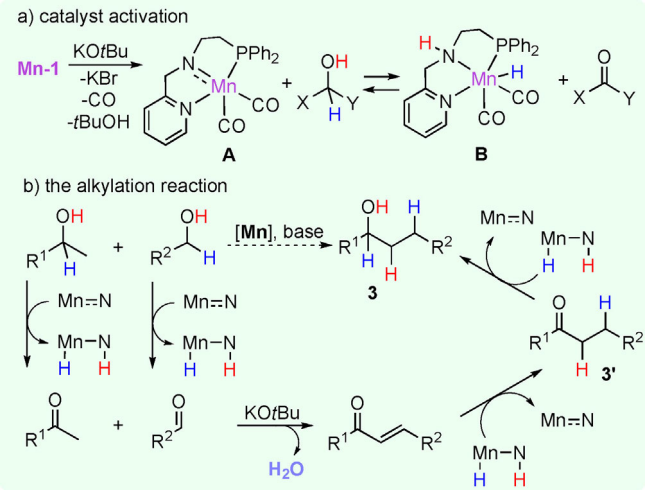


Scheme 2. Scope of Mn-catalyzed C-alkylation of secondary alcohols by primary alcohols. Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), **Mn-1** (0.005 mmol) and KO*t*Bu (0.125 mmol) in toluene (0.5 mL) were stirred at 135 °C for 20 h in a glass tube under an inert atmosphere. Yields after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



Scheme 3. Deuterium labeling experiments.

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 the Supporting Information 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 4. Initially, the precatalyst **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 4a). The alkylation reaction starts with the dehydrogenation of both 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 C=C double bond of the α,β-unsaturated ketone



Scheme 4. Proposed reaction mechanism.

takes place prior to the reduction of the ketone **3'** to the desired alcohol product **3** (Scheme 4b).

In conclusion, we report here the synthesis of C-alkylated secondary alcohols through a hydrogen autotransfer strategy using a stable and well-defined Mn 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 not being required. The environmentally benign, atom-economical process operates under relatively mild conditions and water is the only byproduct. 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.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alcohols · alkylation · base metals · hydrogen autotransfer · manganese catalysis

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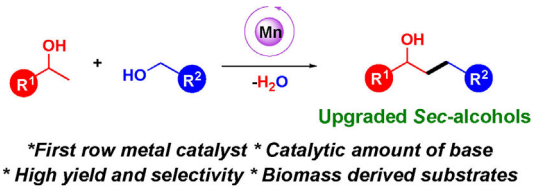

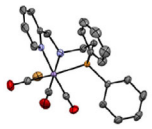

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C-Alkylation of Secondary Alcohols by Primary Alcohols through Manganese-Catalyzed Double Hydrogen Autotransfer

Alcohol upgrading: A well-defined Mn pincer complex, stabilized by a PNN ligand, catalyzes the β-alkylation of secondary alcohols with primary alcohols without the need for further stochiometric reagents. Almost equimolar ratios of substrates are sufficient to achieve good yields of the corresponding alkylated alcohols and water is liberated as the only byproduct in this sustainable reaction.