Catalytic C1-Alkylation with Methanol and Isotope Labelled Methanol

Jan Sklyaruk, Jannik C. Borghs, Osama El-Sepelgy* and Magnus Rueping*

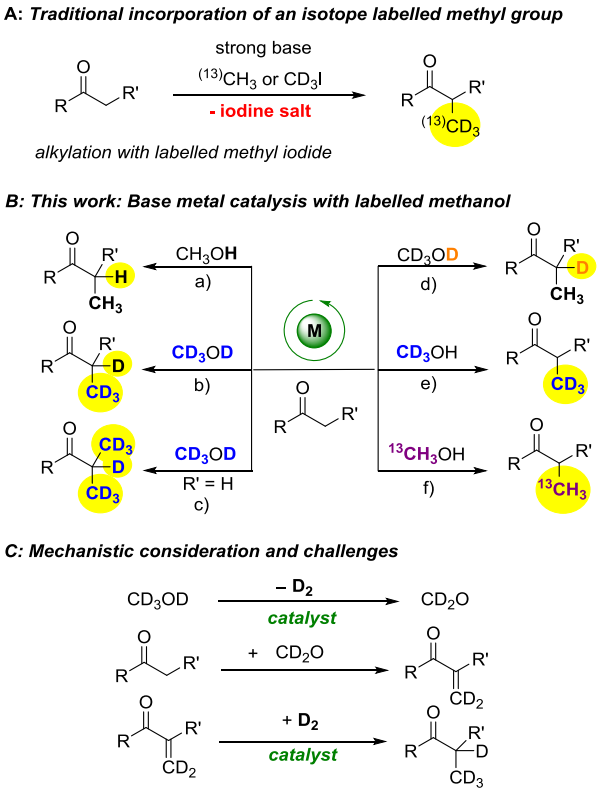
Abstract: A new metal catalyzed protocol for the C1-methylation has been developed. By employing an air and moisture stable catalyst together with isotopically labelled methanol a series of D-, CD_3- and ^{13}C-labelled products were obtained with good yields under mild reaction conditions with water as the only side product.

Isotope labelling is a very important topic in various fields of life sciences.[1] Deuterium labelled compounds are widely used as internal standards for spectroscopy and for biochemical applications.[2] Carbon deuterium bonds which are more stable than carbon hydrogen bonds may have a positive effect on the metabolic stability. Furthermore, the potency and selectivity of the deuterated compounds is still retained.[1c] As a consequence, deuterated drugs are intensively studied.[3] The incorporation of deuterium follows different strategies, either by heterogeneously and homogeneously catalysed H/D exchange, or by organic synthesis, using deuterium labelled building blocks.[4]

In general, the methyl group has an extraordinary significance, being one of the most common fragments in biologically active molecules.[5] Furthermore, many pharmaceuticals feature improved properties if methyl groups are incorporated.[5] However, the exchange of methyl groups by the corresponding labelled analogue is not always straightforward and is traditionally accomplished by the use of either the electrophilic or the nucleophilic CD_3 sources which may have drawbacks. Besides toxicity, carcinogenic properties and high cost, a further disadvantage is the waste production (Figure 1 A). In this regard, recent efforts focused on trideuteromethylation with deuterated dimethylsulfoxide[6] or the generation of aryl methyl ethers, aryl-OCD_3, with the aid of deuterated methanol.[7]

Given the importance of the methyl group in medicinal and pharmaceutical chemistry and the improved metabolic properties of deuterated analogues, together with the current synthetic limitations we decided to examine a new base metal catalyzed methylation of carbonyl groups using cheap and readily available isotope labelled methanol as the C1-building block.[8] The successful development of such a reaction would allow access to diverse labelled products in which water would be the only by-product (Scheme 1B).

Based on our interest in developing new sustainable reactions using inexpensive base metal catalysts we decided to investigate a new C1-alkylation reaction[9,10] with methanol following a dehydrogenation, aldol condensation, hydrogenation pathway (Scheme 1C).



Scheme 1. Comparison of different methods for the isotope labelling of ketones.

In order to develop this sustainable reaction we needed to address several challenges: i) a general restriction for the use of methanol is the high stability towards the dehydrogenation step and low stability of the intermediates which often leads to the formation of CO_2 and hydrogen,[11] ii) the aldol condensation with formaldehyde which can lead to by-products; iii) the following hydrogenation needs to be chemoselective towards the olefinic bond to avoid the carbonyl reduction and iv) the base metal catalyst needs to be reactive, readily available, stable and moisture tolerant as water is the by-product.

To the best of our knowledge a general and practical base metal catalyzed C1-alkyation of carbonyl compounds with isotope labelled methanol has not been reported. Manganese is the third most abundant metal in the earth crust and currently considered for the development of sustainable catalytic transformations,[12] including alkylations.[9a] Thus, we initiated our studies with the synthesis of different manganese complexes (Mn-**1** to Mn-**4**), starting from the corresponding ligands and the precursor $Mn(CO)_5Br$ (Table 1).[13] However, before directly applying isotope labelled methanol we decided to first develop the variant with non-labelled methanol. Hence, we applied different manganese complexes in the α-methylation of propiophenone **1a** with methanol (Table 1).[14] To our delight, the air-stable aromatic and cationic diphenyl phosphine based complex [Mn-**1**]

M.Sc. Jan Sklyaruk, M.Sc. Jannik C. Borghs, Dr. O. El-Sepelgy, Prof. Dr. M. Rueping
Institute of Organic Chemistry
RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: Osama.Elsepelgy@rwth-aachen.de
E-mail: magnus.rueping@rwth-aachen.de

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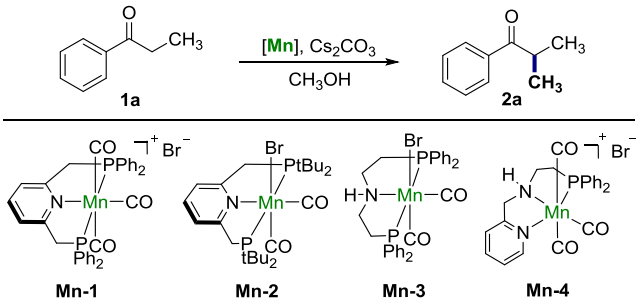
gave the desired product in quantitative yield (Table 1, entry 1). In contrast, the tert-butyl phosphine based complex Mn-**2** proved to be inactive (Table 1, entry 2). The use of the aliphatic, diphenyl phosphine based complex Mn-**3** provided the desired product in a lower yield of 22% (Table 1, entry 3). Furthermore, the pyridine and diphenyl phosphine containing complex Mn-**4**, which we recently applied in the hydrogenation of carbonates, was inactive under these reaction conditions (Table 1, entry 4). The catalyst screening showed that the presence of an aromatic pyridyl based backbone together with an aromatic phosphine is required for good activity and chemoselectivity.

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



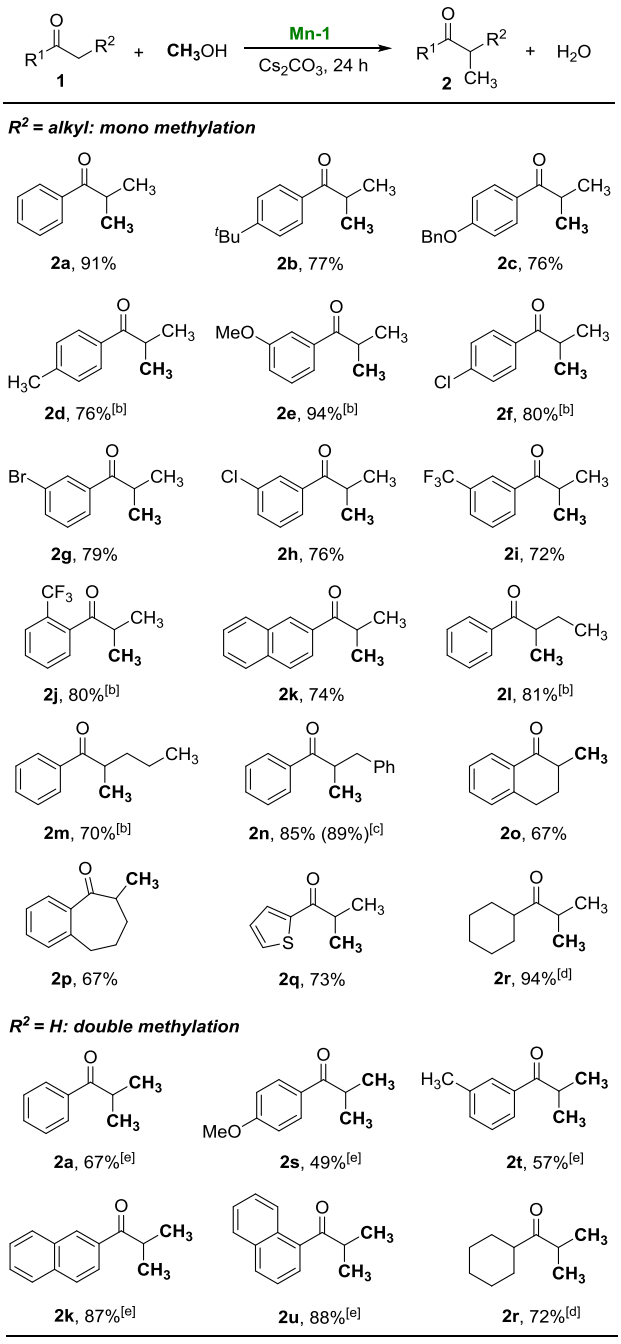
Entry	Cat. (mol%)	Base (equiv.)	Temp. [°C]	Yield (%)
1	**Mn-1** (5)	4	85	97
2	**Mn-2** (5)	4	85	0
3	**Mn-3** (5)	4	85	22
4	**Mn-4** (5)	4	85	0
5	$Mn(CO)_5Br$ (5)	4	85	0
6	-	4	85	0
7	**Mn-1** (5)	-	85	0
8	**Mn-1** (2.5)	4	85	94
9	**Mn-1** (1)	4	85	57
10	**Mn-1** (2.5)	4	70	36
11[b]	**Mn-1** (2.5)	2	85	99
12[b]	**Mn-1** (2.5)	0.2	105	80

[a] Reaction conditions: **1a** (0.2 mmol), [**Mn**], Cs_2CO_3, MeOH (2 mL), 24 h. Yields were determined by GC using ethylbenzene as internal standard. [b] MeOH (1 mL).

Control experiments using either the manganese precursor $Mn(CO)_5Br$, Mn-**1** without base, only Cs_2CO_3 or only ligand L1, did not provide the product (Table 1, entries 5-7). Since the subsequent base screening (see SI) did not result in improved reaction conditions, Cs_2CO_3 was used as base. Decreasing the catalyst loading to 2.5 mol% gave also almost quantitative conversion (Table 1, entry 8). However, when the catalyst loading was lowered to 1 mol%, the yield dropped to 57% (Table 1, entry 9). Lowering the temperature to 70 °C as well as decreasing the amount of base also resulted in diminished yield (Table 1, entries 10). However, when the concentration of **1a** was increased, a quantitative yield was obtained (Table 1, entry 11). Furthermore, at higher temperature the base can be used in catalytic amounts (Table 1, entries 12).

With the optimized conditions in hand we examined the scope of the newly developed manganese catalyzed C1-alkylation of carbonyl compounds (Table 2).

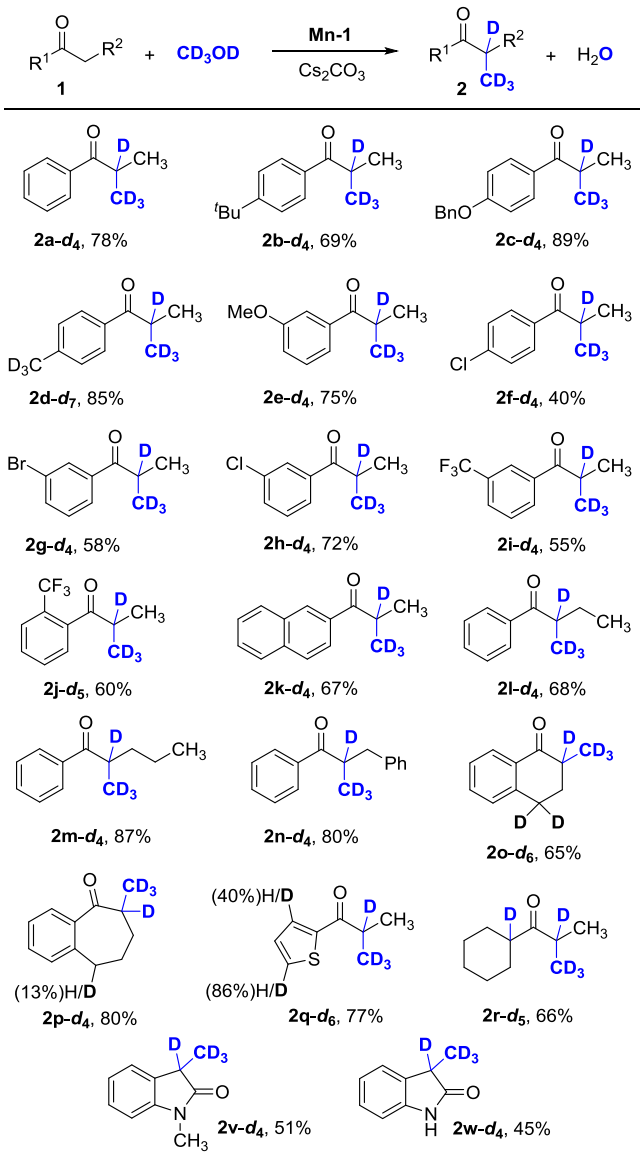
Table 2. Manganese catalyzed methylation of ketones[a]



[a] Reaction conditions: **1** (1 mmol), Cs_2CO_3 (2 mmol), **Mn-1** (2.5 mol%) in CH_3OH (5 mL) at 85 °C, [b] **Mn-1** (5 mol%), [c] **1n** (10 mmol), Cs_2CO_3 (2 mmol), CH_3OH (10 mL), 105 °C, 24 h. [d] **1** (1 mmol), Cs_2CO_3 (4 mmol), **Mn-1** (5 mol%), CH_3OH (2 mL) at 105 °C. [e] **1** (1 mmol), Cs_2CO_3 (4 mmol), **Mn-1** (5 mol%), CH_3OH (5 mL) at 85 °C.

In general, the reaction proceeded well and differently substituted propiophenone derivatives as well as cyclic, heteroaromatic and aliphatic ketones reacted to the corresponding α-methylated products **2a-r** in good yields. Furthermore, using acetophenone derivatives double alkylation was also achieved and the corresponding products were obtained in good yields (Table 2). The practical applicability of the **Mn-1** catalytic system was demonstrated by performing the α-methylation of **1n** on a 10 mmol scale using 2.5 mol% of the **Mn-1** and 20 mol% of Cs_2CO_3.

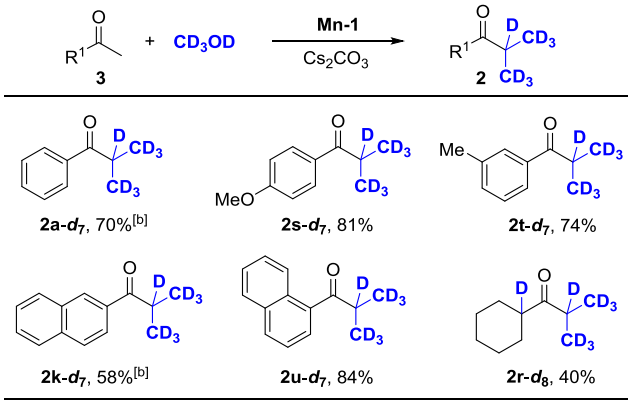
Table 3 Manganese catalyzed trideuteromethylation of ketones.[a]



[a] Reaction conditions: **1** (0.5 mmol), Cs_2CO_3 (2 mmol), catalyst **Mn-1** (5 mol%), CD_3OD (1 mL) at 105 °C.

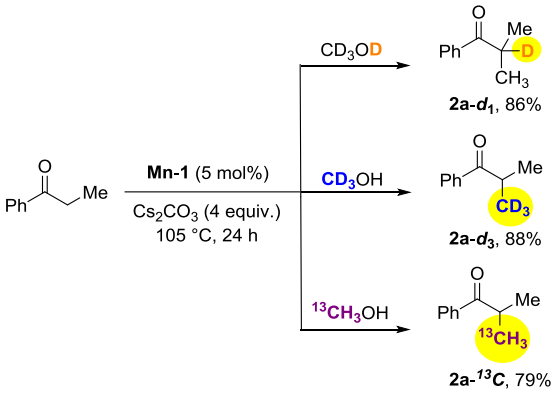
Following the successful development using methanol as alkylating reagent, we turned our attention to the D- and ^{13}C-labelled methanol. Due to the kinetic isotope effect (kCH_3OH/kCD_3OD = 2.4), we needed to adjust the reaction conditions. Again the manganese catalyzed C-1 alkylation proceeded well when fully deuterated CD_3OD was applied and the corresponding trideuteromethylated products **2-*d*$_4$** were obtained in good yields (Table 3). According to the proposed mechanism deuterium incorporation in the α-carbonyl position is observed. Overall the yields are comparable to the non-deuterated version (Table 2). Interestingly, we also observed an H/D exchange for substrates with benzylic positions (**2o**, **2p**) indicating that the manganese catalyst can be used beyond the C1-deuteromethylation. Subsequently, we also applied acetophenone and derivatives in the alkylation reaction and obtained the double deuteromethylated products **2-*d*$_7$** in good yields (Table 4).

Table 4. Manganese catalyzed double trideuteromethylation of ketones.[a]



[a] Reaction conditions for deuterium methylation: **1** (0.5 mmol), Cs_2CO_3 (2 mmol), catalyst **Mn-1** (5 mol%), CD_3OD (1 mL) at 105 °C. [b] 48 h.

To point out the regioselectivity of the deuterium incorporation and illustrate the different possibilities for highly selective isotope labelling, we applied three other isotope labelled methanol variants, CH_3OD, CD_3OH and $^{13}CH_3OH$ in the manganese catalyzed alkylation (Scheme 2). Ketone **2a-*d*$_1$** was isolated in 86% yield, giving almost exclusively the α-deuterated isotopomer. In the case of CD_3OH, **2a-*d*$_3$** was isolated in 88%, giving the desired β-trideuterated product. To prove the generality, we also applied ^{13}C-labelled methanol and pure **2a-*^{13}C*** was obtained in 79% yield.



Scheme 2. Selective isotope labelling of propiophenone **1a** using different methanol variants.

In summary, a new manganese catalyzed C1-alkylation with methanol as environmentally benign alkylating reagent has been developed which provides methylated products with good yields under mild reaction conditions whereby water is the only by-product. The new base metal catalyzed process has been extended to the use of differently isotope labelled methanol variants to selectively provide CD_3, $(CD_3)_2$, and ^{13}C-labelled products. Given the simplicity of the protocol, readily available substrates and catalysts as well as the inexpensive labelled reagents, both the newly developed methylation as well as labelling reaction should be of interest for the straightforward synthesis of methyl containing bioactive compounds.

Acknowledgements

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Keywords: C1-alkylation • trideuteromethylation • manganese •

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Layout 2:

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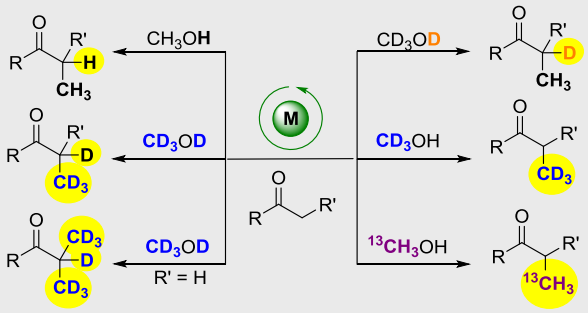

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