Manganese catalyzed α-methylation of ketones with methanol as a C1 source

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Manganese Catalyzed α-methylation of ketones with methanol as C1 source

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The first direct α-methylation of ketones with methanol under hydrogen borrowing conditions using well-defined manganese PN³P complex as pre-catalyst was achieved. The reactions typically proceed at 120°C for 20h with 3 mol% pre-catalyst loading and in the presence of NaOtBu (50 mol%) as base. The scope of the reaction was extented to the α-methylation of esters.

α-Methylated carbonyl functions are often encountered in biological active molecules.[1] Characteristically, α-alkylation of ketones is achieved by reaction of the corresponding enolate with an alkyl halide, thus generating stoichiometric amounts of wastes. In the prospect of sustainable chemistry, new strategies to introduce a methyl group under catalytic conditions starting from renewable resources and in an atom economical manner are indeed highly desirable.[2] In this respect, alkylation at the α–position of carbonyl derivatives with alcohols under hydrogen borrowing conditions providing water as the sole by-product constitutes an inviting strategy.[3] Complementary, methanol, which is produced on industrial scale from a wide variety of sources including renewable ones,[4,5] represents a very attractive C1 source for an environmentally benign, inexpensive, and abundant alkylating agent.[6]

Yet, although alkylation of ketones with alcohols in the presence homogeneous catalysts based on precious metals,[3a, 3b] including Ru[7], Rh,[8] Ir,[9] or Re,[10] is well established, α-methylation using methanol still remains challenging[11] due to its higher activation barrier for the dehydrogenation step into aldehyde compared to heavier alcohols.[12] In this context, the implementation of an efficient system based on inexpensive and abundant base metals constitute an additional challenge,[13] some successes being recently reported by Liu[14] then Morril[15] using cobalt or iron-based catalysts, respectively.

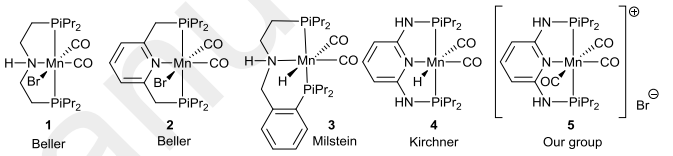
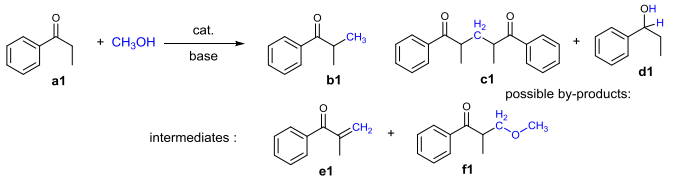


Chart 1: Manganese catalysts promoting reactions with methanol

The potential of manganese in (de)-hydrogenation reactions as an alternative to noble metals[16] has been demonstrated with the seminal works of Beller in hydrogenation[17] and Milstein in dehydrogenative coupling of amines with alcohols.[18] Since then, several reactions based on hydrogen borrowing processes involving alcohols have been developed[19] and a few well defined homogeneous manganese-based catalysts (Chart 1) proved their ability to promote complete dehydrogenation of methanol,[20] *N*-formylation,[21] aminomethylation[22] and *N*-methylation reactions[19a, 23] demonstrating that MeOH associated with manganese can be efficiently used as C1 source *via* a partial oxidation. In line with our interest in manganese organometallic catalysis,[24] we report hereafter the first α-methylation of carbonyl compounds using methanol as alkylating reagent.

The optimisation of the reaction conditions was carried out considering the methylation of propiophenone **a1** with methanol (Scheme 1) as the model reaction (Table 1). Initial assessments were performed in sealed ACE® pressure tubes at 120 °C for 20 h.



Scheme 1. Methylation of propiophenone **a1** with MeOH.

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Table 1. Optimization of the parameters of the α-methylation of **a1** catalysed by **5**.

Entry	*t*BuONa (mol%)	CH_3OH (mL)	Toluene (mL)	Conv. (%)	Yield [c] **b1**	**c1**
1[a]	20	1	1	93	55(55)	39(14)
2[a]	50	2	4	98	90	10
3	50	2	4	99	87(64)	13
4[b]	50	6	12	50	44	6
5	50	6	0	99	84	16
6[d]	50	2	4	29	11	18
7[d]	100	0.5	0.5	99	33	66 (63)
8[e]	100	2	4	<5	<5	<5

Reaction conditions: in a glovebox, an Ace® pressure tube was charged with propiophenone **a1** (0.5 mmol, 66 µL), MeOH, toluene, Mn complex **5** (3 mol%, 8.4 mg), and base, in that order. The closed pressure tube was then heated at 120 °C for 20 h. [a] 5 mol% of Mn complex **5** (14 mg); [b] Propiophenone **a1** (1.5 mmol, 198 µL), Mn complex **5** (1.5 mol%, 16 mg); [c] NMR yield determined by ^{1}H NMR spectroscopy and compared with GC/MS, on the crude mixture. Isolated yield in parentheses; [d]: 100 °C; [e]: no Mn catalyst

In the presence of catalyst **5** (5 mol%) and NaO*t*Bu (20 mol%), the ketone was converted in 93% yield, the major product being the desired isobutyrophenone **b1**, isolated in 55% yield (entry 1). It is worth nothing that 1,5-diphenyl-2,4-dimethylpenta-1,5-dione **c1** resulting from the Michael addition of the enolate on to the transient enone **e1** is the sole by-product observed at the end of the reaction, indicating that the hydrogenation step is relatively slow compared to the Michael addition.[25] None of the possible side products *ie* alcohol **d1**, resulting from transfer hydrogenation,[26] enone **e1**, or methyl ether **f1** were detected by ^{1}H NMR or GC-MS in the crude mixture. Diluting the reaction mixture and increasing the amount of base to 0.5 equivalent finally allowed full conversion and good selectivity toward the desired methylated ketone **b1** (90% NMR yield, entry 2).

The catalyst loading could be decreased to 3 mol % keeping high conversion and good selectivity (entry 3) but further lowering to 1.5 mol% had a detrimental effect on conversion (entry 4). This model reaction could be carried out in pure MeOH with comparable results (Entry 5) but during the reaction scope development, it appeared that toluene greatly improved the solubility of most substrates (*vide infra*, Table 2). Lowering the temperature to 100 °C resulted in a drastic decrease of the conversion rate to 29 % (entry 6). Different alternative bases such as *t*BuOK, KHMDS, or K_3PO_4, have been evaluated leading to similar conversions and selectivities (Table S1, ESI).

Finally, reasoning that 1,5 diketones are valuable products as starting materials for the synthesis of pyridines[27] or cyclic alkenes,[28] the formation of **c1** was tentatively optimized. Carrying out the reaction at higher concentration in the presence of catalyst **5** (3 mol%) and a stoichiometric amount of base at 100 °C afforded the 1,5-diphenyl-2,4-dimethyl-penta-1,5-dione **c1** in 66% yield (Table1, entry 7).[29] A blank test omitting the manganese catalyst (Table1, entry 8) led to no conversion.

With the optimized conditions in hand, a series of ketones were methylated with methanol (Table 2). Propiophenone **a1** and acetophenone **a2** led to the same product, namely, isobutyrophenone **b1,** in 87% and 67% NMR yield, respectively.

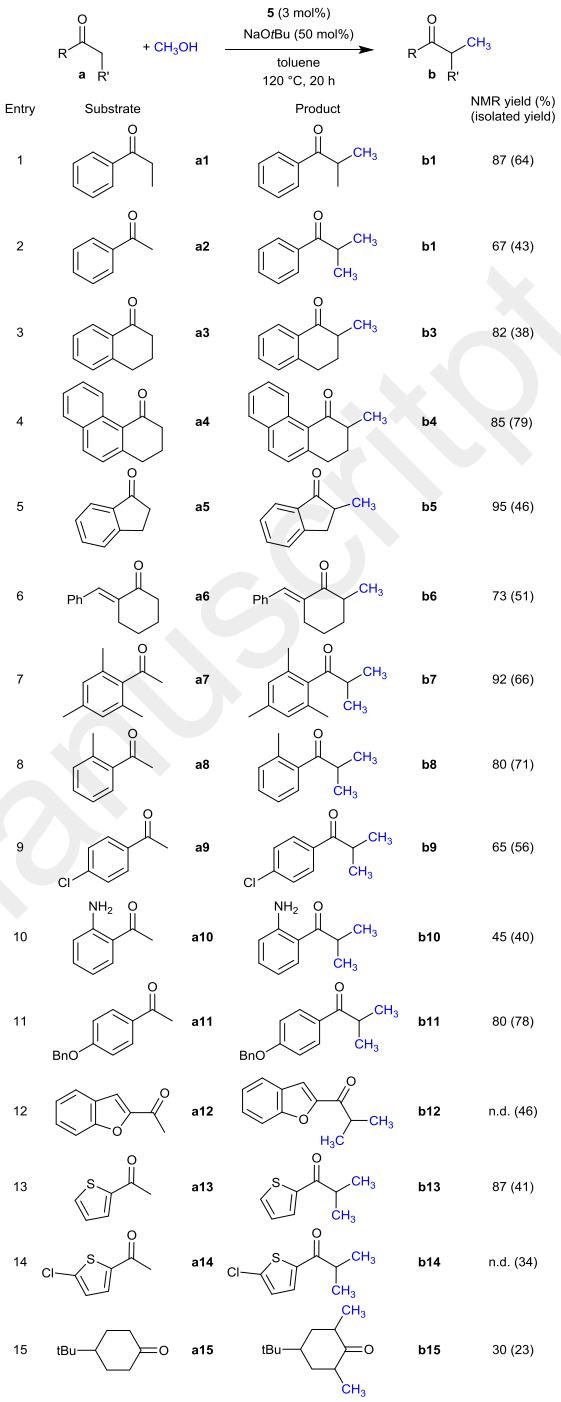

Table 2: Scope of the α-methylation of ketones with methanol in the presence of **5** as a precatalyst.

It is worth noting that in the case of acetophenone **a2**, which is less sterically hindered than **a1**, more 1,5-diketone was formed, Cyclic ketones including α-tetralone **a3**, 2,3-dihydrophenanthren-4(1*H*)-one **a4**, 1-indanone **a5**, and 2-benzylidenecyclohexanone **a6** were methylated with moderate to good yields (82%, 85%, 95%, and 73%, respectively). Steric hindrance actually disfavored the formation of the undesired 1,5-diketones, allowing the double methylation of 2',4',6'-trimethylacetophenone **a7**, and 2'-methylacetophenone **a8** in

high yields (92%, and 80%, respectively). This protocol is also tolerant toward chlorinated substrate **a9** to afford the corresponding 4-chloroisobutyrophenone **b9** (65%), this being in line with the functional group tolerance observed for the hydrogenation of ketones.[30] In the case of 2'-aminoacetophenone **a10**, the methylation occurred at the α-position of the carbonyl function, the isobutyrophenone derivative being obtained as the major product. This result contrasts with the *N*-methylation of 4'-aminoacetophenone using the same catalyst under similar reaction conditions where the methylation occurred at the nitrogen.[23b] It is likely that intramolecular hydrogen bonds N-H…O favor the formation of the enolate and direct the selectivity. Besides, we have previously noticed that ortho-substituted anilines were more difficult to methylate.[18] 2-Acetylbenzofuran **a12** and thiophenes derivatives **a13** and **a14** were α-methylated under these conditions (entries 12-14). 4-Tert-butylcyclohexanone **a15** was dimethylated in moderate yield (30%) due to the formation of the corresponding undesired 1,5-diketone. The methylation of propiophenone **a1** also proceeded well in the presence of competing substrates such as fluoro- and trifluoromethyl-benzene, 1-octene or 4-nitrotoluene (Table S2, E.S.I).

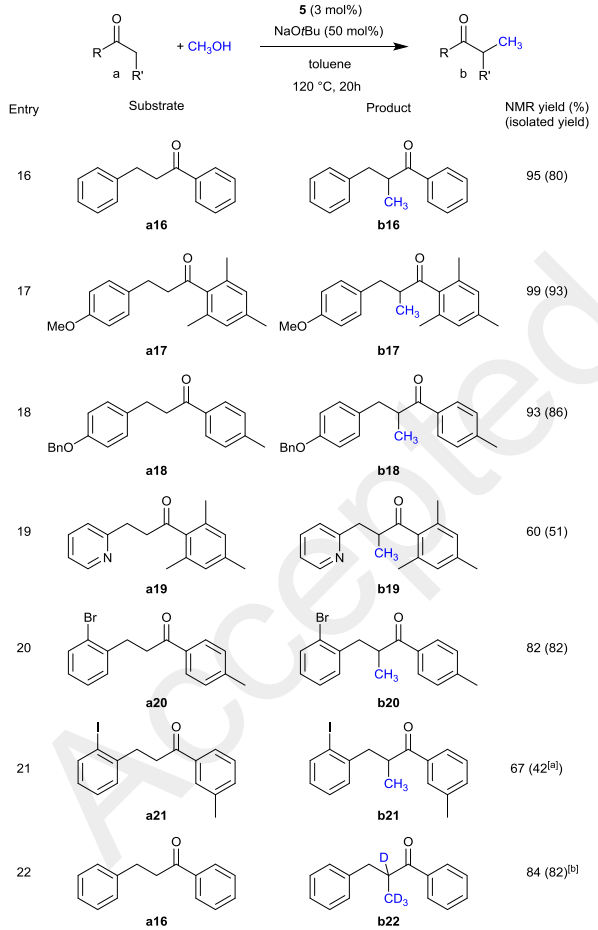

Table 2. (Continued) Typical reaction conditions: in a glovebox, an Ace® pressure tube was charged with ketone (0.5 mmol), MeOH (2 mL), Toluene (4 mL), **5** (3 mol%, 8.4 mg) and NaOtBu (50 mol%, 24.0mg), in that order. The closed pressure tube was then heated at 120 °C for 20 h. Yield were determined by analysis of ^{1}H NMR of the crude mixture and confirmed with GC-Mass analysis. [a] 10% of deiodination product was identified. [b] CD_3OD instead of MeOH

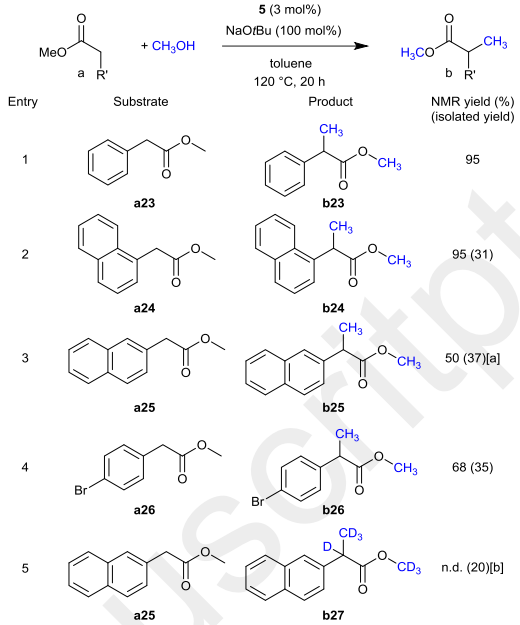

Table 3. Scope of the α-methylation of esters with methanol in the presence of **5** as a precatalyst. . (Conditions: In a glovebox, an Ace® pressure tube was charged with ester (0.5 mmol), MeOH (2 mL), Toluene (4 mL), **5** (3 mol%, 8.4 mg) and NaOtBu (100 mol%, 48.1 mg), in that order. The closed pressure tube was then heated at 120 °C for 20 h. Yield were determined by analysis of ^{1}H NMR of the crude mixture and confirmed with GC/MS analysis. [a] 50 mol % of *t*BuOK (24 mg) was used [b] CD_3OD instead of MeOH, 48 h.

Dihydrochalcone **a16**, in which the transient enolate and enone are stabilized by the phenyl ring, was methylated in very high yield (95%). A series of dihydrochalcones derivatives **a17**-**a21** were subsequently methylated. The presence of a pyridinyl moiety in **a19** had a detrimental impact on the yield of the reaction (60%). Interestingly, the catalytic system tolerated brominated substrate (**a20**), but dehalogenation (about 10%) was observed with the iodo derivative **a21**. Finally, deuterated methanol CD_3OD was successfully employed as an alkylating agent allowing the introduction of the deuterated CD_3 fragment in **b22** (82% isolated yield).

The scope of the reaction was finally extended to the catalytic α-methylation of esters (Table 3),[31] which has barely been achieved, even using noble metals precatalysts.[11d] Under the same reaction conditions as above yet in the presence of one equivalent of base, several aryl acetic esters **a23**-**a26** were methylated with methanol in moderate to good yields (Table 4), including brominated substrates (**a26**) or deuterated product (**b27**). It is worth nothing that isolation of the methylated esters as pure products was difficult, thus leading to low yields.

In conclusion, the first manganese-catalyzed α-alkylation of ketones using methanol as green alkylating reagent was achieved in the presence of a manganese catalyst based on a 2,6-diaminopyridine scaffold. The defined protocol could be successfully extended to the even more challenging esters derivatives, demonstrating further the great potential of

manganese catalysis in the field of (de)-hydrogenation reactions.
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Conflicts of interest

There are no conflicts to declare.

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