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Mn(II)-catalysed alkylation of methylene ketones with alcohols: direct access to functionalised branched products†

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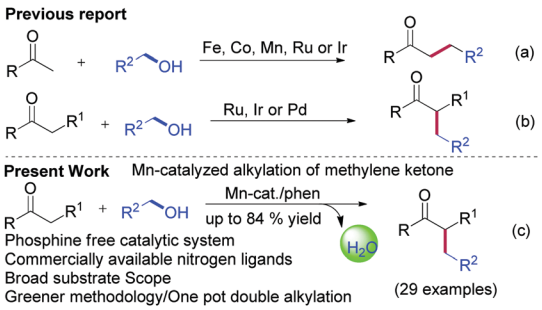
Herein an operationally simple alkylation of methylene ketones with primary alcohols is reported. Use of an inexpensive and earth abundant Mn/1,10-phenanthroline system enables direct access to a series of functionalised branched ketones including one-pot sequential double alkylation and Alzheimer's drug donepezil. Preliminary mechanistic investigation, determination of the rate and order of reactions and deuterium labeling experiments support the participation of the hydrogen-borrowing strategy for the ketone alkylation.

Branched α,α-di-substituted ketones are ubiquitous in natural products and pharmaceuticals and broadly used as valuable intermediates in multi-step organic synthesis.[1] In general, pre-functionalised alkyl halides with toxic bases are used for their synthesis, relieving stoichiometric waste.[2] Therefore, development of green and sustainable technology for α,α-di-substituted ketones is in demand. In this direction, transition-metal catalysed alkylation of ketone enolates using primary alcohols is an attractive approach for the synthesis of di-substituted branched products. Such processes follow the redox neutral or borrowing hydrogen (BH) approach for the construction of new C–C bonds and generate water as the sole byproduct (Scheme 1).[2]

Unfortunately, to date, synthesis of branched di-substituted ketones has scarcely been known and is relatively underdeveloped (Scheme 1, eqn (a) and (b)).[3] For instance, only Ir-[4a–e] and Ru-catalysts[4f] (homogeneous) and Pd-,[4g–i] Ni-,[3a,b] or Ag/Mo-catalysts[4j,k] (heterogeneous) were reported for alkylation of methylene ketones with primary alcohols, providing such branched ketones.

Notably, recently there has been potential drive in catalysis research to replace noble metal-catalysts with more highly abundant base metals due to the potential toxicity, low natural abundance and expensive nature of noble metals.[5a,c] Therefore, key catalytic transformations involving earth abundant metal catalysts such as Fe, Mn, Ni and Co would be more attractive and sustainable alternatives.[5a–c] However, to date, applications of homogeneous Fe, Mn, and Co-based catalysts have been only limited to the monoalkylation of acetophenones with alcohols pertaining to the linear ketones and have never been demonstrated for the branched products.[3e,f]



Scheme 1 (a) Metal-catalysed alkylation of methyl ketones. (b) Precious metal catalysed alkylation of methylene ketones. (c) Mn-catalysed sustainable synthesis of di-substituted branched ketones.

Notably, in this direction, utilisation of manganese for such (de)hydrogenative coupling would be a potential sustainable alternative, as manganese is the third most earth-abundant metal. Indeed, recently manganese complexes were utilised for various key catalytic transformations such as the synthesis of amines with alcohols following the borrowing hydrogen approach;[6] N-formylations of amines with methanol;[7] synthesis of pyrroles[8a] and quinolines;[8b,c] four-component synthesis of pyrimidines using three different alcohols with amidines,[8d] imines,[9] cyclic amides and imides,[9] and unsaturated nitriles;[10] C-alkylation of ketones,[3f] methanol to CO_2 and H_2,[9] and hydrogenation of alcohols to esters,[9] double bonds and nitriles were also realized.[11]

It is worth mentioning that most of these manganese-complexes employ pyridinyl-core PNP ligands, diethylamine-core PNP ligands, PN^3P ligands and triazinyl-core PN^5P ligands to achieve higher catalytic efficiency.[9] Nevertheless, often major concerns associated with these phosphine based pincer ligands are their highly expensive nature in comparison to base-metal

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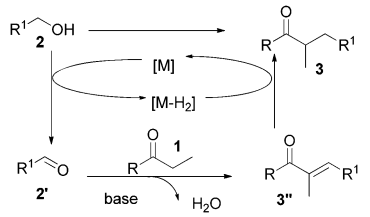


Scheme 2 Manganese catalysed alkylation of methylene ketones.

catalysts, multi-step synthesis and storage and handling under standard laboratory environments.[9]

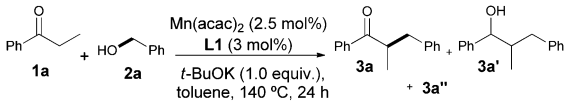
In our continuous efforts recently we started a research program to establish sustainable catalytic transformations using renewable resources in combination with inexpensive metal catalysts using commercially available bench stable ligands.[12] To our delight, very recently we demonstrated the nickel-catalysed α-alkylation of methylene ketones with primary alcohols to yield a series of α,α-di-substituted branched products. Unfortunately, in the case of sterically hindered 1,2-diphenyl ethanone we observed only a moderate product yield when a combination of 5 mol% $NiBr_2$ and 6 mol% 1,10-phenanthroline was used.[12d] Considering this challenge, we wondered whether a suitable manganese catalyst with a nitrogen ligand could be beneficial for such *gem*-di-substituted ketones.[12d]

Nevertheless, to the best of our knowledge, to date, no manganese-catalysed BH protocol (dehydrogenation, condensation and hydrogenation) for coupling of primary alcohols with methylene ketone has been known (Scheme 2).[9] Herein, we report the first example using a manganese catalysed route with inexpensive nitrogen ligands for the synthesis of α,α-di-substituted branched products. Notably, in this process only water is released as the byproduct, rendering them sustainable or environmentally benign.

To further optimise the efficient catalytic protocol, a combination of 2.5 mol% $Mn(acac)_2$, 3 mol% **L1** and *t*-BuOK in toluene was used in the model reaction of propiophenone **1a** with benzyl alcohol **2a**, which resulted in branched ketone **3a** in 72% isolated yield (Table 1, entries 1 and 2). Next, application of different Mn-catalysts, ligands **L2–L6** and different bases and solvents did not display any improvement in the catalytic activity (Table 1, entries 3–12, ESI,† Tables S1–S5). However, control experiments revealed the independent role of each component to achieve higher product yields (Table 1, entries 13 and 14). Notably, in some cases we observed the formation of reduced alcohol **3a′** and 5–10% of the corresponding enone **3a″** during the GC-MS analysis of the crude reaction mixture (Table 1 and Scheme 2). After having the optimal conditions, we utilised 1,2-diphenyl ethanone with a variety of functionalised alcohols, which resulted in the branched products in good to excellent yields (Table 2). Benzyl alcohols substituted with electron rich methyl, ethyl or iso-propyl groups yielded the desired *gem*-di-substituted ketones **3b–3e** in 69–84% yield, respectively (Table 2).

Pleasingly, methoxy (**2e**), fluoro (**2f**), chloro (**2g**) and trifluoromethyl (**2h**) substituted benzyl alcohols efficiently transformed into the branched ketones **3f–3i** in up to 80% yield (Table 2).

Table 1 Discovery of the reaction conditions[a]



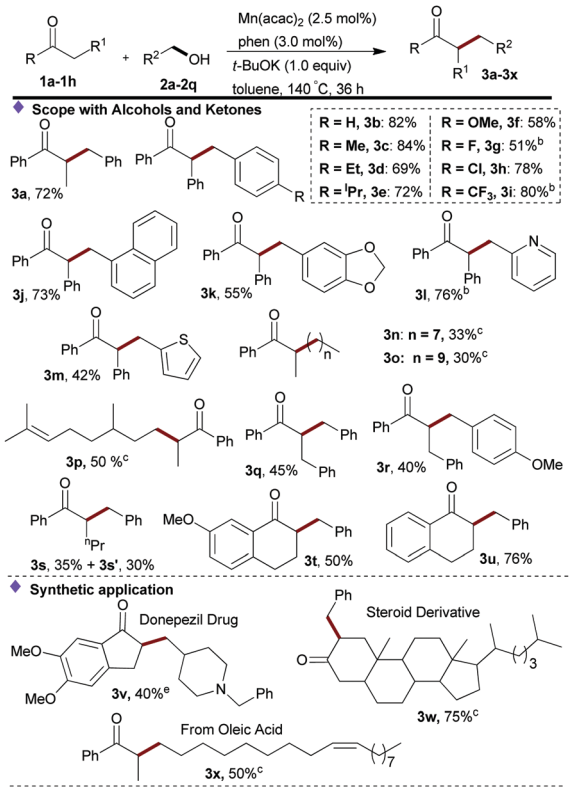
Entry	Deviation from the standard conditions	Conv. (%) 3a	3a′
1	—	72 (67)[b]	18
2	**36 h**	**80 (72)[b]**	**20**
3	$Mn(CO)_5Br$	45	50
4	**L2**	42	58
5	**L3**	27	68
6	**L4**	22	30
7	**L5**	15	42
8	**L6**	57	24
9	*t*-BuONa	37	47
10	K_2CO_3	14	33
11	K_3PO_4	4	0
12	Cs_2CO_3	0	0
13	No base	0	0
14	No catalyst, no ligand	<15	<25

Reaction conditions: [a] Unless otherwise specified, propiophenone **1a** (0.25 mmol), benzyl alcohol **2a** (0.3125 mmol), $Mn(acac)_2$ (2.5 mol%), phen (3 mol%), *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under a nitrogen atmosphere, 140 °C oil bath, 24 h reaction time. [b] Isolated yield (average of two runs). **L1** = 1,10-phenanthroline. **L2** = 2,9-dimethyl-1,10-phenanthroline. **L3** = 4,4′-dimethylbipyridine. **L4** = 2,2′-biquinoline. **L5** = bipyridine. **L6** = 1,2-bis(dimethylamino)ethane (TMEDA).

Gratifyingly, when 1-naphthylmethanol (**2i**), heteroaryl substituted benzyl alcohol (**2j**) and 2-pyridinemethanol (**2k**) were employed, they furnished the di-substituted ketones **3j–3l** in 55–76% yields respectively. Importantly, 2-thiophenemethanol (**2l**) efficiently participated under the manganese-catalysed conditions to give **3m** in 42% yield (Table 2). Notably, the catalytic performances of alkyl alcohols **2m** and **2n** were sluggish and resulted in **3n** and **3o** (30–33%) after 24 h. However, renewable terpenoid intermediate citronellol (**2o**) furnished the di-substituted ketone **3p** in 50% yield. This chemo-selective transformation represents the synthetic potential of the optimised protocol (Table 2). Moreover, benzyl substituted phenyl ketone (**1c**) resulted in **3q–3r** in up to 45% yield. Again, application of *n*-propyl substituted phenyl ketone (**1d**) gave a moderate yield of **3s** along with 30% reduced alcohol **3s′** (Table 2). Pleasingly, tetralone derivatives **1e** and **1f** gave the desired α-substituted ketones **3u** and **3t** in up to 76% isolated yield. After having witnessed the excellent catalytic efficiency, we explored the optimised protocol for the synthesis of donepezil, known as the best-selling drug for the treatment of Alzheimer's disease.[13] Pleasingly, using the present manganese catalyzed protocol, donepezil **3v** was obtained in moderate yield (Table 2). Remarkable application of 4-cholesten-3-one (**1h**) with benzyl alcohol **2a** resulted in an excellent yield of α-benzylated product **3w** (Table 2). Interestingly, fatty acid derived oleyl alcohol **2q** upon reaction with **1a** efficiently transformed into the corresponding di-substituted ketone **3x** without much affecting the double bond (Table 2).

Notably, the catalytic protocol is tolerant to halides (F and Cl), alkyl, methoxy, trifluoromethyl and 1,3-dioxolone moieties including the thiophene and pyridine groups. Application of

Table 2 Mn-catalysed alkylation of methylene ketones[a]



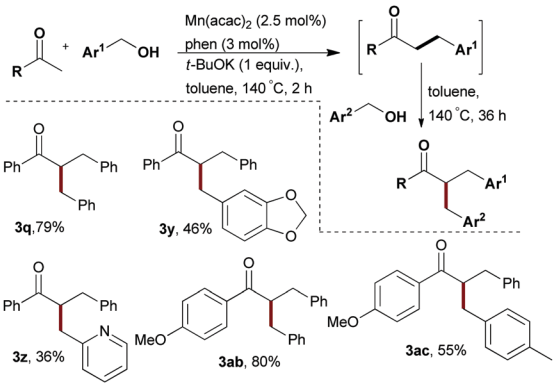
Reaction conditions: [a] Unless otherwise specified, propiophenone **1a** (0.25 mmol), benzyl alcohol **2a** (0.3125 mmol), $Mn(acac)_2$ (2.5 mol%), phen (3 mol%), *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under a nitrogen atmosphere, 140 °C oil bath, 36 h reaction time. [b] *t*-BuOK (0.375 mmol) was used. [c] 24 h reaction time.

reducible functionalities such as citronellol and fatty acid alcohols significantly broadens the scope of the established protocol.

Next, we demonstrated the manganese-catalysed one-pot sequential bis-alkylation of ketones with two different benzyl alcohols using a single catalyst (Table 3). We chose acetophenone and 4-methoxy acetophenone with electronically different benzyl alcohols. Remarkably, the first step resulted in the selective mono-benzylation of acetophenone to the linear ketones, then a sequential addition of second alcohols resulted in hetero-α,α-di substituted ketones in up to 80% yield (Table 3).

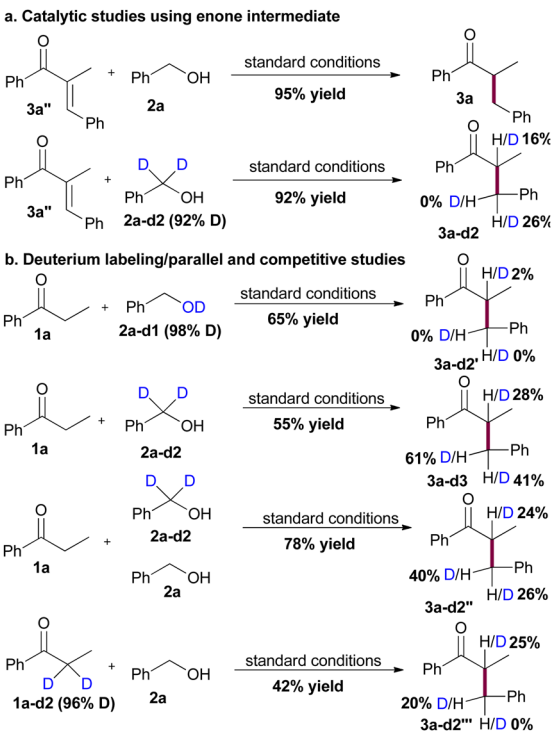
Mechanistically, we envisioned that manganese catalysed α-alkylation might involve *in situ* multi-step processes such as dehydrogenation of an alcohol to the carbonyl compound followed by base catalysed condensation to intermediate enone **3a″**. In the next step *in situ* hydrogenation of the enone resulted in the branched ketone **3a** (Scheme 2).[9] To evidence this, enone **3a″** was independently prepared and was employed with **2a** and **2a-d2** (92% D) under standard conditions. The desired branched ketones **3a** and **3a-d2** were obtained in quantitative yields and exhibited 16% and 26% deuterium incorporation at the α-and β-positions of **3a-d2** (Scheme 3a and ESI,† Scheme S3). However, when α-alkylation using methylene ketone **1a** with **2a-d1** (98% D) was performed, we detected only <2% deuterium incorporation in the branched ketone using ^{1}H-NMR and GC-MS analysis

Table 3 Sequential one pot double alkylation using a single catalyst



Reaction conditions: acetophenone **1** (0.25 mmol), benzyl alcohol **2a** (0.25 mmol), $Mn(acac)_2$ (2.5 mol%), phen (3 mol%), *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under a nitrogen atmosphere, 140 °C oil bath. After 2 h alcohol **2** (0.3125 mmol) in toluene (0.5 mL) was added under a nitrogen atmosphere, 140 °C oil bath, 36 h.

(Scheme 3b and ESI,† Scheme S4). Further, we independently performed parallel and crossover experiments using a 1 : 1 mixture of **2a** and **2a-d2** under the standard catalytic conditions of Table 2. Interestingly, the resulting ketones were obtained in 55–77% yield and displayed variable ratios of the H/D-scrambled product or deuterium incorporation at the α- and β-positions (Scheme 3b and ESI,† Schemes S1 and S2).[14] However, catalytic experiments using methylene ketones



Scheme 3 Preliminary mechanistic studies. Reaction conditions: [a] unless otherwise specified, propiophenone **1a** (0.1 mmol), benzyl alcohol **2a** (0.125 mmol), $Mn(acac)_2$ (2.5 mol%), phen (3 mol%), *t*-BuOK (0.1 mmol), toluene (1.0 mL), Schlenk tube under a nitrogen atmosphere, 140 °C oil bath, 36 h reaction time.

1a-d2 (96% D) with benzyl alcohol **2a** displayed the H/D-scrambled product in 42% yield (Scheme 3b and ESI,† Scheme S5).

It is worth mentioning that all these deuterium labeling experiments as well as the formation of H/D-scrambled products provide evidence for the involvement of the borrowing hydrogen strategy under manganese catalysis.[12,14] Further, incorporation of deuterium at variable amounts in the α- and β-positions in the branched ketones also strongly supports the micro-reversible transformation for the alkylation process. Next, we demonstrated the rate and order of the alkylation process using kinetic studies. The experimental outcomes displayed first order kinetics with respect to methylene ketone **1a** while considering a steady state approximation for benzyl alcohol (ESI,† Scheme S6).

In conclusion, we have developed an inexpensive and phosphine free manganese-catalysed practical route for the synthesis of branched di-substituted ketones. Utilisation of renewable alcohols with a variety of aryl and alkyl methylene ketones yielded the functionalised branched products in up to 84% yield. As a highlight, we have demonstrated the sequential one-pot double alkylation to functionalise hetero bis-alkylated ketones using 2.5 mol% Mn-catalyst. To establish the synthetic utility of the catalytic protocol; Alzheimer's drugs, functionalization of steroid hormones and fatty acid derivatives has been demonstrated. Preliminary mechanistic investigation, kinetic studies to determine the rate and order of reaction and a series of deuterium labeling studies were performed to establish the borrowing hydrogen approach for ketone alkylation.

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Conflicts of interest

There are no conflicts to declare.

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