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Manganese-Catalyzed Direct C-C Coupling of α-C–H bonds of Amides and Ester with Alcohols via Hydrogen Autotransfer†

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Herein we report an efficient manganese-catalyzed C-alkylation of unactivated amides and *tert*-butyl acetate using alcohols as alkylating agents. This elegant approach exhibits broad substrate scope bearing aryl, heteroaryl, and aliphatic alcohols provided the C-C coupled products of amides *via* hydrogen auto-transfer strategy.

Transition-metal catalyzed C-alkylation of carbonyl compounds is one of the promising and elegant approaches for the construction of C-C bonds and has found diverse applications in organic synthesis; in particular, natural product synthesis, and peptide modifications.[1] Traditionally, the C-alkylation of carbonyl compounds has been achieved by a consecutive two-step process, consisting of the generation of carbonyl enolate by super bases, followed by nucleophilic substitution with an alkyl halide (Scheme 1a).[1-2] However, such transformations suffer from the formation of a stoichiometric amount of inorganic salt as by-product and utilization for mutagenic substrates as alkylating reagents. However, transition-metal catalyzed hydrogen auto-transfer (HA) strategy which uses the widespread alcohols as alkylating agents and thus, obviates the need for mutagenic substrates.[3] The direct C-C coupling of carbonyl compounds with alcohols mainly involves, the dehydrogenation of primary alcohol into an aldehyde, and a subsequent *in situ* condensation with an α-CH bond of carbonyl compounds to afford an α,β-unsaturated intermediate, and followed by catalytic hydrogenation with hydrogen generated from the initial dehydrogenation step. Thus, overall the net reaction is redox neutral and leads to water as the only side product. Among the carbonyl compounds,[3] α-C(sp^3)-alkylation of amides remains challenging and rarely reported. The reason is amide α-hydrogen possesses least acidic among the carbonyl compounds, thus reducing the susceptibility of amides towards the aldol condensation with aldehydes.[4] The transition-metal catalyzed C-alkylation of widely available inert amides would be a far more beneficial as this method can be used to allow for the facile modification of peptides.[2] In recent times, direct C-C alkylation of amides with primary alcohols *via* dehydrogenative pathway has been explored under the noble-metal catalysis.[5-9] In 2013, Huang group reported the first catalytic C-alkylation of acetamide with primary alcohols using Ir-based PNP-pincer complex.[8] Subsequently, the research group of Ryu has successfully developed Ru-catalyzed C-alkylation of acetamide with primary alcohols.[9] Huang and co-workers have developed PCP type Ir complex for C-alkylation of unactivated amides by primary alcohols (Scheme 1b).[10] It is noteworthy that all these methodologies are based on noble-metal catalysts. Amide like substrates such as oxindoles,[5-6] and 4-hydroxy-quinolones[7] was also explored with noble-metal catalyzed C-alkylation strategy; however, these protocols are limited to activated cyclic amide derivatives.

Of late, the replacement of noble metals with base metals for similar or better reactivity is one of the promising approaches in homogeneous catalysis and paid much attention.[11] In this regard, non-precious metals have been explored for the catalytic C-N and C-C bond forming reactions *via* HA strategy.[11-13] In particular, manganese, the third most earth-abundant 3d-transition element has paid much attention and effectively utilized for the acceptorless dehydrogenation reactions (AD).[13] A notable progress on Mn-catalyzed AD and HA reactions has been explored by the research groups of Milstein, Beller, Kirchner and Kempe.[11-13] Very recently, Kempe and co-workers have developed the first base-metal catalyzed C-alkylation of amides with alcohols using cobalt complexes stabilized by highly electron-rich phosphines PN_5P ligands.[14] The research group of Beller independently reported the C-alkylation of 2-oxindole with alcohols using PNP-pincer type

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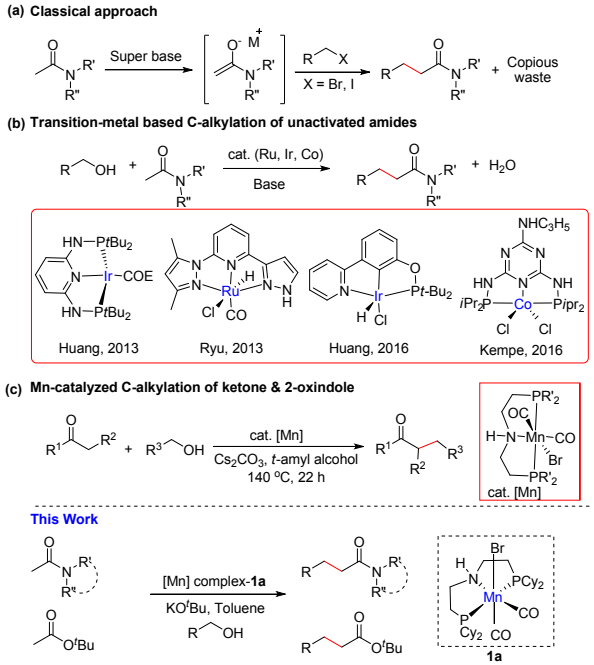
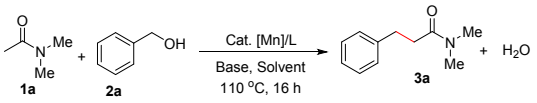
Mn-catalyst[13a] (Scheme 1c). Herein we report an efficient Mn-catalyzed direct C-C coupling of *tert*-amides (acyclic and cyclic) and ester with primary alcohols (aliphatic, aromatic and heterocyclic). The reaction catalyzed by the well-defined complex [Mn]-**1a** and operates *via* hydrogen auto-transfer strategy. The resulted α-alkylation of amides has been converted into the corresponding aldehyde and alcohol, and thus, this protocol can be used to extend the carbon backbone of primary alcohol derivatives by two units.



Scheme 1. Strategies for C-C coupling of α-C–H bonds of amides with alcohols.

The reaction between *N*,*N*-dimethylacetamide (**1a**, 1.0 mmol, 2 equiv,) and benzyl alcohol (**2a**, 0.5 mmol, 1 equiv) was chosen as the model substrate for optimization of Mn-catalyzed α-alkylation process (Table 1). The initial reaction was carried out by applying Mn-cat. **Ia** (0.5 mol%), and KO^{t}Bu (1.2 equiv) in toluene at 110 °C for 16 h and the desired C-alkylated amide **3a** was obtained in 82% yield with the 86% conversion of **2a** (Table 1, entry 1). Various Mn-complexes were also screened under optimal conditions (Table 2) and complex **Ia** was found to be efficient for this C-alkylation strategy. Interestingly, the reaction of catalytic amount of Mn-precursor ($Mn(CO)_5Br$) and ligand ($\mathbf{L_a}$) (i.e. 0.5 mol% of 1:1 mixture of Mn-salt and $\mathbf{L_a}$) in presence of KO^{t}Bu in toluene solvent at 110 °C for 16 h also yielded **3a** in 80% (Table 1, entry 2). The reactivity of other Mn-salts also was performed under optimized conditions. While Mn-complexes $Mn(OTf)_2$ and $Mn(OAc)_2$ failed to catalyze the reaction; however, the complex $MnCp^*(CO)_3$ showed poor reactivity and gave 50% yield of **3a** (Table 1, entry 3). Effect of various bases such as K_2CO_3, and NaO^{i}Pr was examined under standard conditions (Table 1, entries 1 and 6-7). When the reaction was carried out in the absence of a base or a catalyst, no product formation of **3a** was observed (Table 1, entries 10-11). These results confirmed that the combination of base and Mn-complex is necessary for the catalytic α-alkylation process. Interestingly, we didn't observe the amide bond activation under our catalytic conditions.[15]

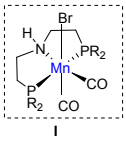
Table 1. Optimization of the reaction condition.[a]



Entry	Mn-complex	Ligand (L)	Base	Solvent	Conv. of **2a** (%)	Yield (%)[b]
1	**Ia**		KO^{t}Bu	toluene	86	82
2	$Mn(CO)_5Br$	$\mathbf{L_a}$	KO^{t}Bu	toluene	84	80
3	$MnCp^*(CO)_3$	$\mathbf{L_a}$	KO^{t}Bu	toluene	52	50
4	$Mn(OTf)_2$	$\mathbf{L_a}$	KO^{t}Bu	toluene	n.r.	n.r.
5	$Mn(OAc)_2$	$\mathbf{L_a}$	KO^{t}Bu	toluene	n.r.	n.r.
6	**Ia**		K_2CO_3	toluene	n.r.	n.r.
7	**Ia**		NaO^{i}Pr	toluene	60	54
8	**Ia**		KO^{t}Bu	CH_3CN	n.r.	n.r.
9	**Ia**		KO^{t}Bu	*m*-xylene	80	76
10	**Ia**		-	toluene	n.r.	n.r.
11	-		KO^{t}Bu	toluene	n.r.	n.r.

[a]The reaction was carried out with amide **1a** (1.0 mmol, 2 equiv), and alcohol **2a** (0.5 mmol, 1 equiv) using Mn-catalyst (0.5 mol%) in the presence of base (1.2 equiv), toluene (1 mL) heated at 110 °C for 16 h. Ligand ($\mathbf{L_a}$) = Bis(2-(dicyclohexylphosphino)ethyl)amine, n.r.- no reaction. [b]Isolated yields.

Table 2. Complex screened for the optimization.[a]



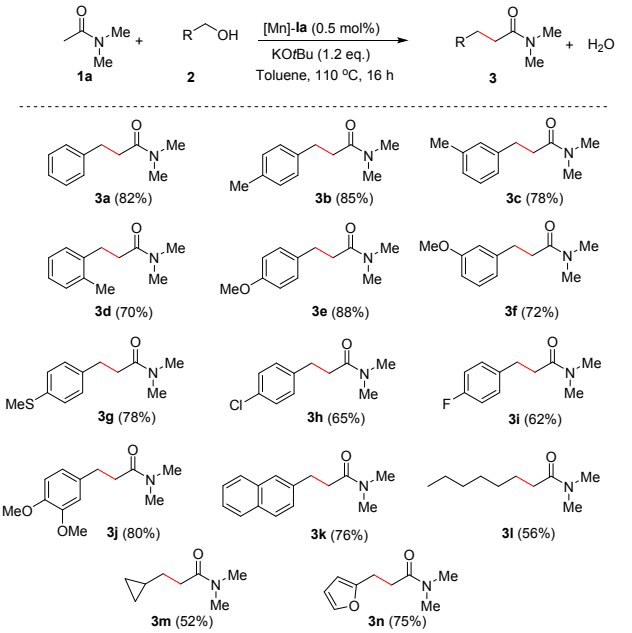
Complex	R	Yield (%)[b]
Ia	cyclohexyl	82
Ib	*t*-buty	76
Ic	phenyl	53

I

[a]The reaction was carried out with amide **1a** (1.0 mmol, 2 equiv), and alcohol **2a** (0.5 mmol, 1 equiv) using Mn-catalyst (**Ia-c**) (0.5 mol%) in the presence of base (1.2 equiv) heated at 110 °C for 16 h. [b]Isolated yield.

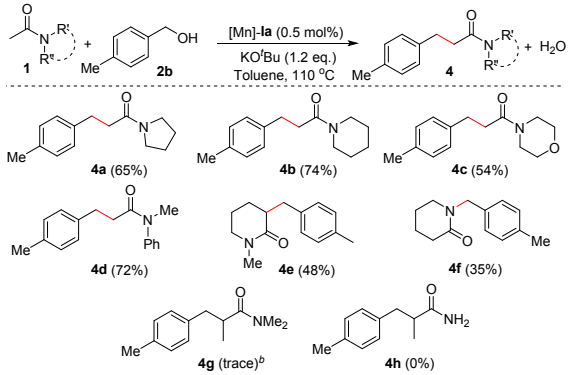
Having optimized condition in hand, next we explored the scope of the reaction by varying aromatic and aliphatic alcohols as the alkylating reagents (Scheme 2). Methyl substitution at the *ortho*, *meta,* and *para* position of benzyl alcohols furnished the corresponding α-alkylated amides **3b-d** in good to excellent yields (70-85%). Methoxy substitutions such as 4-OMe, 3-OMe, 3-SMe in the phenyl ring of benzyl alcohol showed the formation of corresponding amides **3e** in 88%, **3f** in 72%, **3g** in 78% isolated yields, respectively. When 4-chloro and 4-fluoro benzyl alcohol were subjected under our present Mn-catalysis, the reaction proceeded with the moderate yields of 65% of **3h** and **3i** in 62%. The 3,4-di-substitute benzyl alcohols also gave C-alkylated amide **3j** in 80% yield. A fused aromatic compound, 2-naphthyl methanol produced the corresponding amide **3k** in 76% yield. When the reaction was carried out with aliphatic alcohols as alkylating agents, a moderate yield of the corresponding amides (products **3l** 56%, **3m** in 52% yields) were obtained. Heteroaromatic alcohol such as furfuryl alcohol (**2n**) well tolerated and gave the expected **3n** in 75% isolated yield.

Overall, the reported Mn-catalytic system showed good reactivity of amide with alcohol substrate scope.



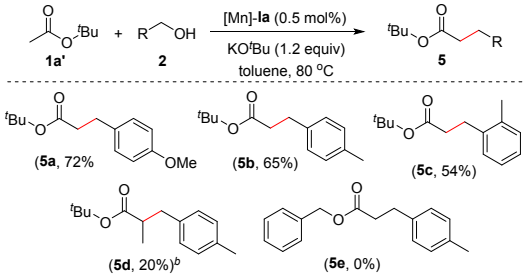
Scheme 2. Mn-catalyzed α-alkylation of amide: Scope of alcohols. Reaction conditions: **1a** (1.0 mmol, 2 equiv), **2** (0.5 mmol, 1 equiv), Mn-Cat. **Ia** (0.5 mol%), and KO^{t}Bu (1.2 equiv) in toluene were heated at 110 °C 16 h.

More importantly, the scope of the unactivated amides in the presence of Mn-catalyst was extended by applying cyclic amide derivatives (Scheme 3). *N*-Acetylated heterocyclic amines such as pyrrolidine, piperidine, and morpholine were successfully applied for the α(C)-alkylation reaction under optimized conditions which resulted in the corresponding amide derivatives (**4a-c**) in decent yields (65% of **4a**, 74% of **4b**, 54% of **4c**, respectively). Cyclic unactivated amide, *N*-methyl 2-piperidone gave 3-alkylated product **4e** in 48% isolated yield. In contrast, secondary cyclic amide, 2-piperidone preceded the catalytic alkylation process to form *N*-alkylated amide **4f** in 35% of yield over C-alkylation under standard conditions.[16] In case of propanamide (e.g *N,N*-dimethylpropanamide), a trace amount of α-alkylated product (**4g**) was observed. The poor reactivity of propanamide is presumably due to steric reasons.



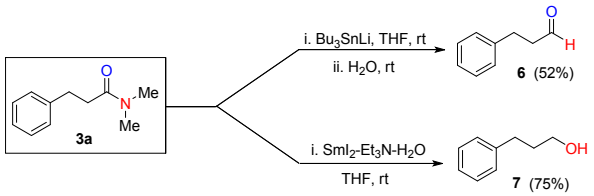
Scheme 3. Scope of amides. Reaction conditions: **1** (1.0 mmol, 2 equiv), **2b** (0.5 mmol, 1 equiv), Mn-Cat. **Ia** (0.5 mol%), KO^{t}Bu (1.2 equiv) in toluene were heated at 110 °C 16 h. [b] GC-MS analysis.

In light of the high activity of the PNP-Mn catalytic system, next we have explored the α(C)-alkylation of *tert*-butyl acetate under standard reaction conditions (Scheme 4). Thus, the reaction between *tert*-butyl acetate (**1a'**) and benzyl alcohol (**2**) in the presence of 0.5 mol% of catalyst **1a** at 80 °C to form a corresponding *C*-alkylated products **5** in moderate yields (54%-72%). In case of *t*-butyl propionate, ~20% yield of expected α-alkylated product (**5d**) was observed along with the transesterification product (benzyl propionate). However, in case of other activated esters (e.g.; benzyl acetate) mainly transesterification was observed.



Scheme 4. Scope of Mn-catalyzed α-alkylation *tert*-butyl acetate. Reaction conditions: **1a'** (1.0 mmol, 2 equiv), **2** (0.5 mmol, 1 equiv), Mn-Cat. **Ia** (0.5 mol%), KO^{t}Bu (1.2 equiv) in toluene were heated at 80 °C 12 h. [b] GC analysis.

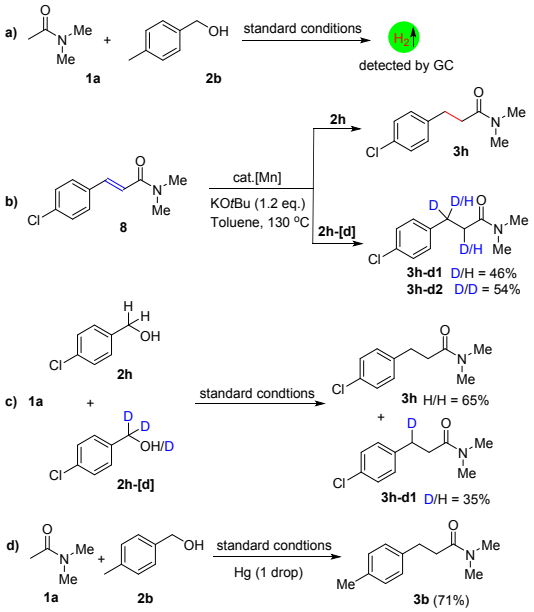
The scope of the present Mn-based α-alkylation strategy was further extended by synthetic transformations. The resulted α-alkylated amide was efficiently converted into the corresponding aldehyde and alcohol derivatives (Scheme 5). Thus, the α-alkylated amide **3a** was subjected to react with Bu_3SnLi in THF at room temperature to afford the corresponding aldehyde **6** in 52% yield. The amide **3a** was converted into the corresponding alcohol **7** in 75% yield catalyzed by samarium(II) iodide in alkaline medium.[17-18]



Scheme 5. Derivatization of α-alkylation of amide substrates.

Having established Mn-catalyzed α-alkylation process, we indented to carry out the mechanistic study.[19] Thus, the reaction of *N,N*-dimethylacetamide **1a** with benzyl alcohol **2b** under standard conditions, the evolution of H_2 gas was qualitatively observed on gas chromatography (GC). This result reveals that the initial step is the dehydrogenation step (Scheme 6a). To understand the mechanistic insight in the C-alkylation reaction, an α,β-unsaturated amide **8** was applied under standard catalytic conditions using benzyl alcohol **2b** as hydrogen donor. The GC-MS analysis of the crude mixture showed the formation of α-alkylated amide and the corresponding dehydrogenated product of **2b**, i.e., aldehyde. We believe that reduction pathway proceeds *via* the (transfer)hydrogenation by *in situ* generated hydrogen gas. To

evidence this, enone **8** was independently prepared and was employed with **2h** (4-chlorobenzyl alcohol) and **2h-[d]** (96% D) under standard Mn-catalyzed conditions. The desired product **3h** and **3h-[d]** were obtained, respectively (Scheme 6b). The product **3h-[d]** showed the formation of mono and di-deuterated amides with a ratio of 46% (**3h-d1**), and 54% (**3h-d2**), respectively. Similarly, the intermolecular competition reactions of **2h** and **2h-[d]** with **1a** were studied under the standard catalytic conditions (Scheme 6c). Based on the above experiments, it is clear that one of the two benzylic C-D/H bonds needs to be cleaved to initiate the α-alkylation reaction. Thus, the catalytic cycle involves the initial dehydrogenation of alcohol, followed by condensation of aldehyde with an amide to offer α,β-unsaturated amide followed by the (transfer)hydrogenation by the evolved hydrogen, and generating the final C-alkylated product. To determine if any heterogeneous Mn-particles were formed during the reaction, we performed the reaction in presence of Hg (Scheme 6d) indicates homogeneous character of Mn-catalyst.



Scheme 6. Mechanistic investigations.

Time-dependent experiment for direct alkylation of amide using alcohol was conducted using a manganese-catalyst to study the reaction kinetics (Fig. 1).

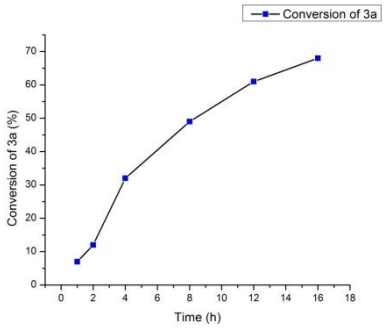


Figure 1. Reaction profile for the manganese-catalyzed formation of **3a**.

Based on this control experiments and literature precedents, a plausible mechanism for α-alkylation reaction catalyzed by PNP-Mn pincer complex is reported (Scheme 7).

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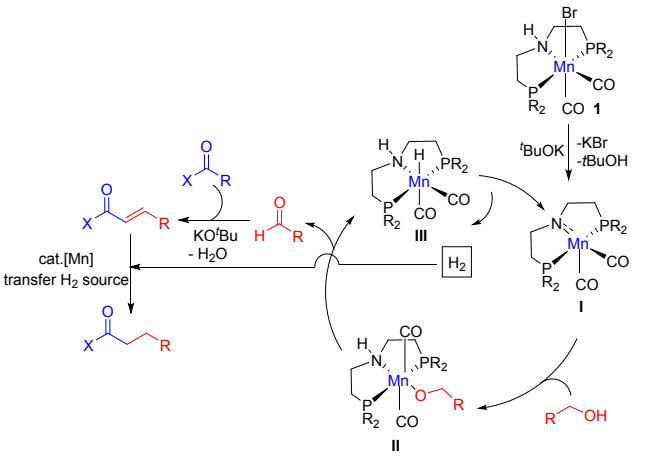

Scheme 7. A plausible mechanism.

Conclusions

In summary, we have reported an efficient manganese-catalyzed C-alkylation of unactivated amides and *tert*-butyl acetate using alcohols as alkylating agents. This elegant approach exhibits broad substrate scope bearing aryl, heteroaryl, and aliphatic alcohols provided the C-C coupled products of amides *via* hydrogen auto-transfer strategy. The scope of this methodology was applied for the synthesis of the corresponding alcohol and aldehyde, which showed the extension of carbon backbone of alkylating alcohol by two units.

Conflicts of interest

"There are no conflicts to declare".

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