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Manganese Catalyzed α-Alkylation of Nitriles with Primary Alcohols

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ABSTRACT. The manganese(I) complex bearing a bidentate hydrazone ligand efficiently catalyzes the α-alkylations of nitrile using primary alcohols as alkylating agents. α-Functionalized nitriles were selectively obtained in good to excellent yields. The reaction is environmentally benign producing water as the sole byproduct. Both benzylic and aliphatic alcohols could be used and functional groups were tolerated.

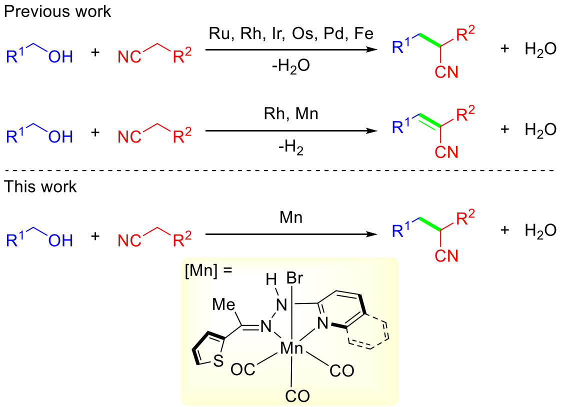
KEYWORDS. Homogeneous catalysis, bifunctional ligand, borrowing hydrogen, alcohols, manganese.

The construction of the carbon-carbon bond is one of the central goals in organic synthesis.[1] The search for alternative carbon resources is in demand considering depleting fossils fuels, climate change, and sustainability.[2] In this regard, the use of alcohols as an electrophile have gained much attention mostly due to their large availability and non-toxic nature.[3] α-Alkylated nitriles are valuable structural motifs for the construction of carboxylic acid derivatives, amines, ketones, oxazolines and several biologically active molecules.[4] Their traditional synthesis utilizes alkyl halides as alkylating agents in the presence of a stoichiometric amount of inorganic bases such as NaH or $NaNH_2$. The major drawbacks of such protocols are the toxicity of the alkylating agent, production of waste and less selective byproducts. The alternative α-alkylation reaction using alcohols as an alkylating agent via borrowing hydrogen strategy represents an atom-economical and environmentally benign protocol producing water as the sole byproduct.[3]

The pioneering work on ruthenium-mediated alkylations of acetonitrile was reported by Grigg et al.[5] Several state-of-the-art nitrile alkylations catalysts are developed based on the precious noble metals such as iridium,[6] rhodium,[7] ruthenium,[8] and osmium[9] (Scheme 1). However, considering the toxicity, cost and limited availability, the replacement of such metals with the abundant first-row-transition metals Fe, Mn, Co, Ni has become a highly desirable strategy to reduce the use of the noble metals in homogeneous catalysis.[10] In fact, much progresses in hydrogen auto-transfer catalysis for the alkylations of carbonyl derivatives and amines using complexes of base metals have been made.[11] During the preparation of this manuscript, Xiao and Wang et al. have elegantly disclosed PNP-Fe catalyzed alkylations of nitriles using primary alcohols.[12] Despite such advancement, however, to best of our knowledge, an earth-abundant metal manganese catalyzed α-alkylations of nitrile are not reported thus far.[13]

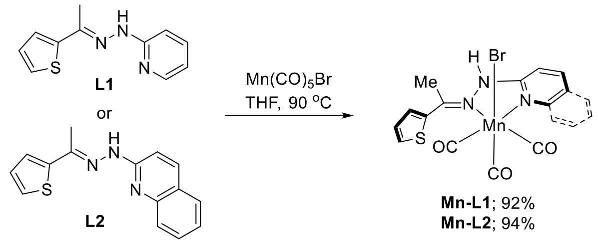
Being the third most abundant transition metal in the earth's crust, manganese has recently offered a valuable alternative to the noble metals.[14] From the pioneering work on manganese catalyzed dehydrogenative imine synthesis by Milstein et al.,[15] well-defined manganese complexes have been utilized in a variety of (de)hydrogenation and cascade reactions.[16] We have developed the olefination of methyl heteroarenes using alcohols catalyzed by an *in situ* generated manganese complex derived from bi-functional hydrazone pincer ligand.[17] The previous elegant work by Milstein et al. have shown that a PNP-Mn complex catalyzed the olefination reaction to deliver the α-olefinated nitrile with the liberation of H_2 (Scheme 1).[18]

Continuing our exploration on manganese catalysis with phosphine-free ligands,[13d, 17] we have recently envisioned that a manganese complex of bidentate hydrazone ligand might exhibit novel reactivity and selectivity for the alkylations of nitrile using alcohols as alkylating agents. Herein, we report on the synthesis of manganese(I)-complexes **Mn-L1**,**2** and their catalytic activity for the α-alkylations of arylacetonitriles using primary alcohols. The catalyst operates under low catalyst loading and tolerates several functional groups including iodine, bromine etc. (Scheme 1). To the best of our knowledge, the first-row-transition metal catalyzed nitrile alkylation reaction using alcohols as an alkylating agent under phosphine-free conditions is not reported thus far.



Scheme 1. State-of-the-art transition metal catalyzed coupling of alcohols with nitriles and this work.

To isolate the manganese complex, the precursor $Mn(CO)_5Br$ was reacted with the ligands **L1** and **L2** in THF at 90 °C (Scheme 2). Subsequent precipitation by addition of hexane resulted in the isolation of the complex **Mn-L1** and **Mn-L2** in 92% and 94% yield, respectively. The complexes were characterized by NMR, FT-IR and elemental analysis. Up to 1.28 ppm downfield in the ^{1}H NMR spectrum of Mn-**L1** in comparison to the free **L1** indicated the diminished electron density at the ligand because of the coordination to the manganese center. The $^{13}C\{^1H\}$ NMR signals at 224.1, 222.9, and 216.8 ppm and IR absorption at 2026, 1935, 1909 cm^{-1} are reminiscent of three carbonyls $Mn(CO)_3$ moiety. Single crystals of **Mn-L1** suitable for X-ray diffraction were obtained by recrystallization in THF (Figure 1).[19] The octahedral complex features bidentate meridional coordination of the potentially tridentate ligand **L1** with the following distances Mn(1)−N(1) (2.03 Å) and Mn(1)−N(3) (2.08 Å). The other two sites of the quasi-planner plane are occupied by the two-carbonyl ligands. The angles of N(1)−Mn(1)−C(12) (174°) and N(3)−Mn(1)−C(13) (172°) are in line with the linear arrangements of the coordinating nitrogen atoms with the carbonyls. The third carbonyl is linearly oriented *trans* to the bromide ligand in perpendicular to the manganese plane. The complex **Mn-L2** also shows similar spectroscopic signature (see the SI for details).



Scheme 2. Synthesis of manganese(I) complexes Mn-L1,2.

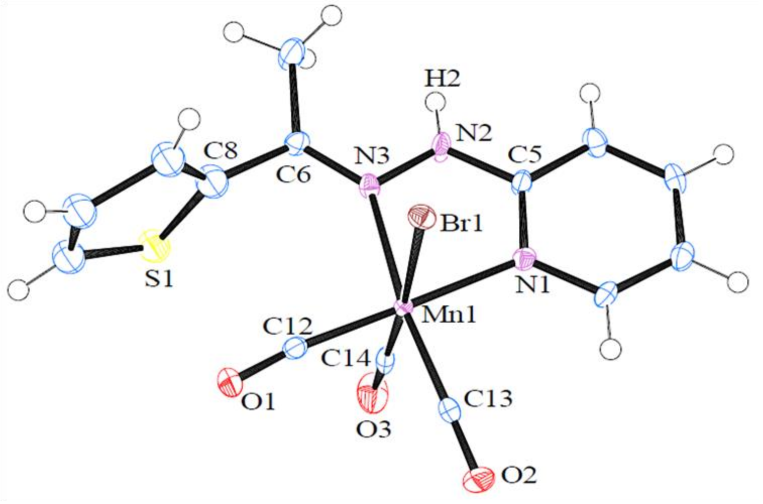
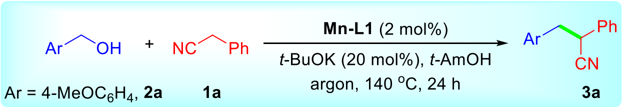


Figure 1. The molecular structure of Mn-L1 (50% probability ellipsoids).[19]

We then explored the catalytic activities of the manganese(I)-complexes **Mn-L1,2** for the alkylations of model substrate benzyl cyanide **1a** (Table 1). Thus, heating a solution of **1a** in the presence of 4-methoxybenzyl alcohol **2a** as the alkylating agent, 20 mol% *t*-BuOK and 2 mol% of **Mn-L1** in *t*-amyl alcohol at 140 °C resulted in the full conversion of **1a** and formation of 90% (GC yield) of the desired product **3a** (entry 1). The manganese complex **Mn-L2** displayed improved catalytic activity and the product was obtained in 93% GC yield and 88% isolated yield (entry 2). The reaction under this condition was found to be very selective; in contrast to the previous PNP-manganese catalyzed reaction,[17] the undesired 3-(4-methoxyphenyl)-2-phenylacrylonitrile **3a'** could not be detected. Control experiments showed traces of product formation in the absence of the ligand **L1** or *t*-BuOK (entries 3,4). While *t*-BuOK loading could be lowered to 5 mol% with a slight decrease in yield, the use of other bases e.g. *t*-BuONa, *t*-BuOLi, Cs_2CO_3, and KOH were found to be detrimental (entries 5,6). Other solvents like *t*-BuOH, toluene, 1,4-dioxane, and THF were also found to be less suitable (entry 7).

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



Entry	deviation from above	Yield (%)[b]
1	none	(90, >99)[c]
2	**Mn-L2**	88 (93, >99)[c]
3	no **L1**	trace
4	no *t*-BuOK	trace
5	5 mol% *t*-BuOK	71
6	*t*-BuONa, *t*-BuOLi, Cs_2CO_3, KOH as base	<53
7	*t*-BuOH, PhMe, 1,4-dioxane, THF as solvent	<60
8[d]	**Mn-L1**	86
9[d]	**Mn-L2**	88

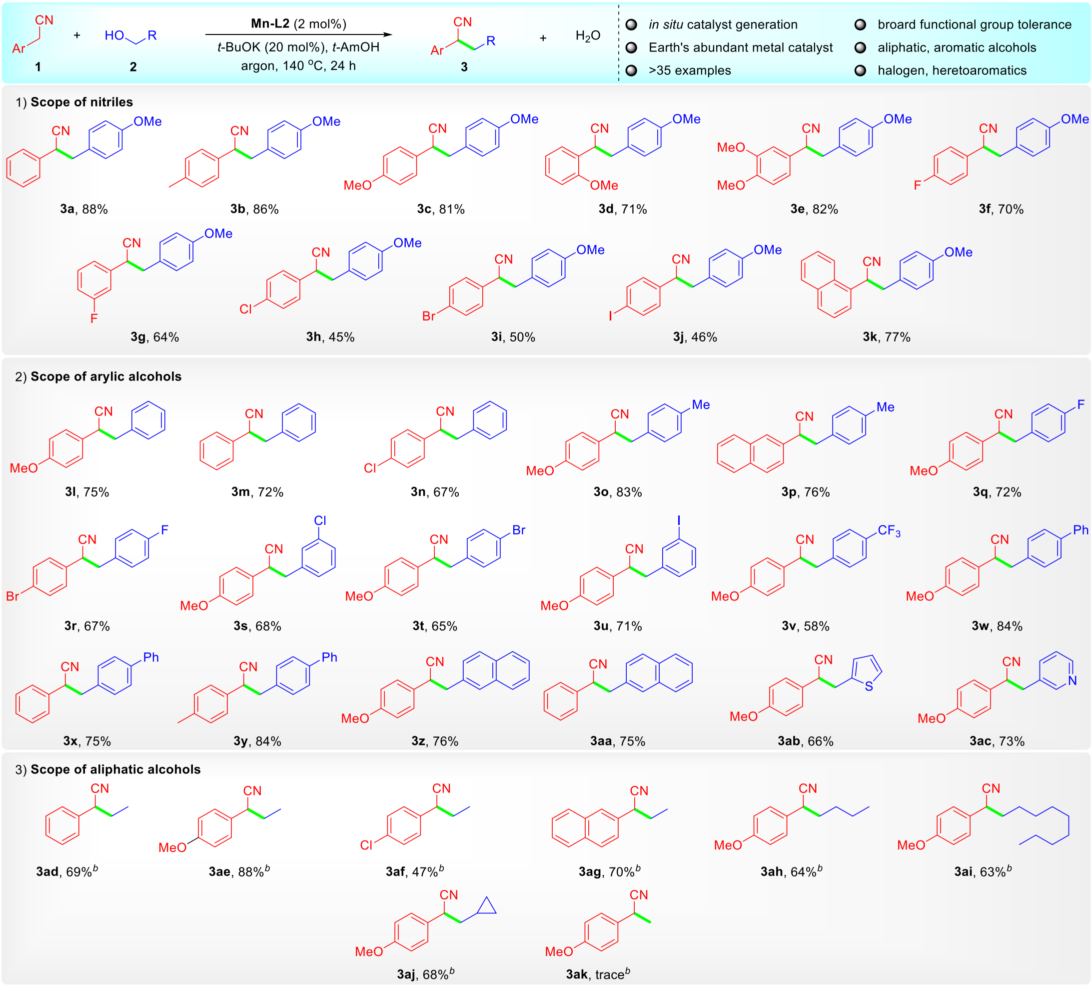
[a]Reaction conditions: **Mn-L1,2** (2 mol%), benzyl cyanide **1a** (0.2 mmol), alcohol **2a** (0.4 mmol), *t*-BuOK (0.04 mmol), and *t*-AmOH (0.4 mL) were heated at 140 °C (oil bath temperature) for 24 h under Ar. [b]Yield of the isolated product. [c](GC yield, conversion). Determined by GC using mesitylene as an internal standard. [d]The catalyst was generated *in situ* using an equimolar mixture of $Mn(CO)_5Br$ and **L1** or **L2**.

The *in situ* catalyst generation often enable rapid optimization and is considered to be largely applicable because of operational simplicity. Gratifyingly, when the *in situ* generated complexes **Mn-L1** and **Mn-L2** were used as catalysts, the alkylation reactions went in equal efficiency (Table 1, entries 8,9). Thus, the *in situ* generated protocol could be adopted for further study.

The generality of this protocol was then tested (Table 2). A variety of arylacetonitrile reacted with **2a** to deliver the α-alkylated nitriles **3** in good to excellent yields without the formation of vinyl nitrile or dialkylated product. Both electron-rich (**1b-e**) and electron-poor (**1f-j**) arylacetonitriles were alkylated in good yields. Halogens substituents including bromine (**1i**) and iodine (**1j**) were retained in the products. α-Alkylations of sterically hindered 2-(2-methoxyphenyl)acetonitrile (**1d**) and 1-naphthylacetonitrile (**1k**) were also proceeded successfully in 71% and 77% yields, respectively.

The scope was also examined with a wide range of primary alcohols. Benzylic alcohols with varying steric and electronic substituents on the phenyl ring are found to be a viable substrate for this alkylation reaction. Noticeably, the halide groups, in particular, chlorine (**2e**), bromine (**2f**), and iodine (**2g**) were retained under the reaction conditions, delivering the products **3s-3u** in 68-71% yields. Similarly, alcohols containing trifluoromethyl (**2h**), biphenyl (**2i**), naphthyl group (**2j**), coordinating hetero aromatic functional groups such as thiophenyl (**2k**), and pyridyl (**2l**) group could also be utilized for the alkylations reactions. Aliphatic alcohols also underwent smooth alkylation reactions. The ethylation of **1a,b,h,k** proceeded smoothly in 47-88% yields without the formation of any dialkylated product. Similar reactivities were also observed for higher alcohols e.g. *n*-butanol (**2n**) and *n*-octanol (**2o**) and the products **3ah**, **3ai** were obtained in 64% and 63% yields, respectively. Even strained cyclopropane methanol (**2p**) could be used to deliver the product **3aj** in 68% yield. However, methanol (**2q**) failed to deliver the product under this condition.

Table 2. The scope of the manganese-catalyzed α-alkylations of nitrile with primary alcohols.[a]

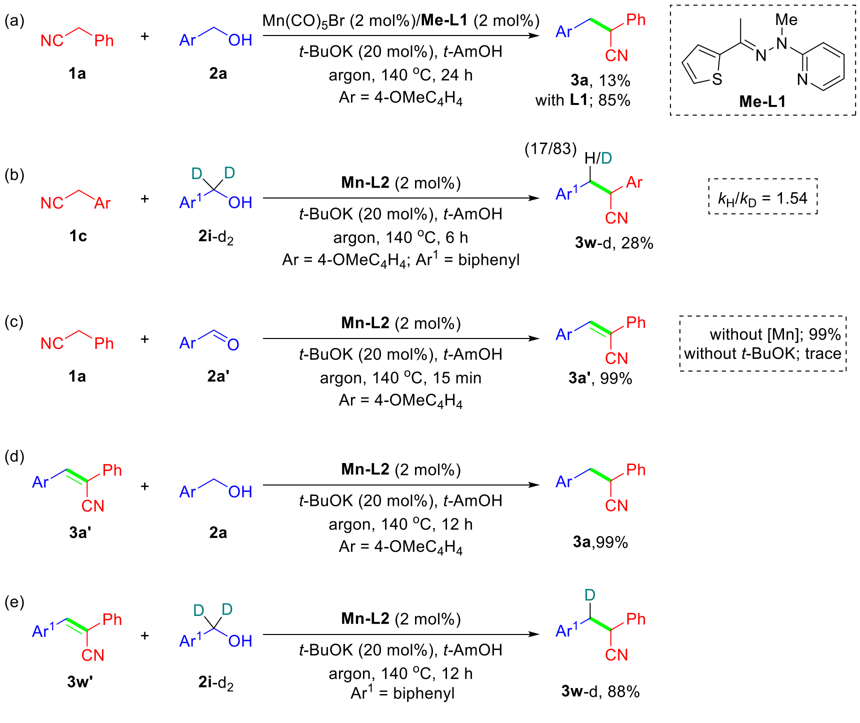


[a]Reaction conditions: **Mn-L2** (2 mol%, *in situ* generated), nitrile **1** (0.2 mmol), alcohol **2** (0.4 mmol), *t*-BuOK (0.04 mmol), and *t*-AmOH (0.4 mL) were heated at 140 °C (oil bath temperature) for 24 h under Ar. The yield of the isolated product. [b]1.0 mmol of alcohol was used.

Mechanistically, to probe the bi-functional behavior of the hydrazone ligand through the participation of the N-H, we have prepared the N-Me analog (**Me-L1**) of the ligand **L1**. The manganese complex derived from such ligand **Me-L1** was found to be inefficient (Scheme 3a; 13% in comparison to 86% with **L1**) for the alkylation reaction. This indicates an outer sphere mechanism involving the N-H group of the ligand for the (de)hydrogenation reaction. Kinetic monitoring of the reaction (see the SI for details) revealed exponential decay of **1a**. Whereas the intermediate aldehyde **2a'** and vinyl nitrile **3a'** remained in low concentration and the latter disappears after 18 h.

Deuterium labeling experiment using [α,α-D_2]biphenyl methanol (**2i**-d_2) shows 83% D-incorporation at the β-position of the nitrile group (Scheme 3b). Whereas, deuterium did not incorporate at the α-position. This indicates a deuteride transfer at the β-position of the intermediate vinyl nitrile **3w'**-d from a manganese deuteride intermediate. The protonation is then followed at the resulting α-carbanion. A competition experiment revealed a $k_H/k_D = 1.54$ which indicates that the dissociation of α-C-H bond in benzylic alcohol is a moderately slow step.

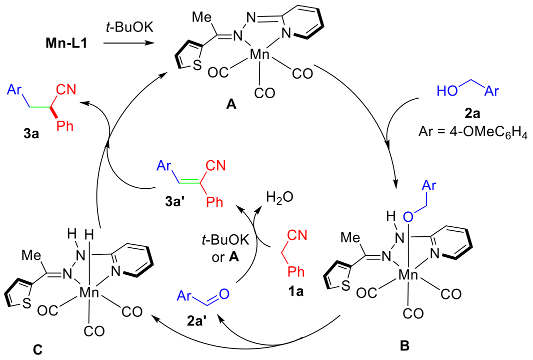
The aldol condensation under the reaction condition was found to be fast and a similar rate was observed for the *t*-BuOK mediated reaction (Scheme 3c). However, **3a'** did not form in the absence of *t*-BuOK. This revealed that the manganese catalyst might not be involved in the C−C bond formation step and a different mechanism is operative from previously observed by us[13d, 17] and others.[16q, 18, 20]



Scheme 3. Mechanistic experiments.

The hydrogenation of the intermediate **3a'** was found to be quantitative when **1a** was used as a hydrogen source under the reaction condition (Scheme 3d). The similar reaction with deuterium-labeled alcohol **2i**-d_2 resulted in the formation of the product **3w**-d in 88% yield (Scheme 3e). The ^{1}H NMR analysis of **3w**-d revealed exclusive deuterium incorporation at the β-position. This further indicates the conjugate reduction of **3w'**-d by a manganese deuteride intermediate generated via the dehydrogenation of **2i**-d_2.

A plausible mechanism is depicted in Scheme 4. The manganese complex **A** generated by the base-mediated salt elimination of the pre-catalyst **Mn-L1** dehydrogenates the primary alcohol **2a** in a moderately slow step. The intermediacy of a manganese-alkoxy complex **B**, as isolated by Milstein,[16p] Liu,[16o] us,[17] and Yu,[13e] is proposed. The fast *t*-BuOK or **A** mediated aldol condensation of the liberated aldehyde **2a'** with the nitrile **1a** generates the vinyl nitrile **3a'**. Facile outer-sphere hydrogenation of **3a'** then yields the desired product **3a** and closes the catalytic cycle. In such a process the manganese complex **C** transfers the hydride at the β-position of the vinyl nitrile **3a'**.



Scheme 4. Proposed mechanism.

In conclusion, we have presented the first example of a base-metal catalyzed α-alkylations of nitrile using primary alcohols as alkylating agents under phosphine-free condition. The protocol provides a useful method for the selective synthesis of α-branched nitriles in an environmentally benign manner. The novel bifunctional hydrazone ligand enables the switch in the reaction mode to hydrogen-borrowing versus previously reported acceptorless dehydrogenative coupling. The homogeneous catalysis with earth-abundant transition metals is a valuable option to save rare noble-metal resources. We believe the developed procedure will set forth further development in base-metal catalysis.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data and NMR spectra of compounds and complexes, X-ray crystallographic analysis for **Mn-L1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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BRIEFS. The first example of non-pincer manganese(I)-complex catalyzed α-alkylation of nitriles with primary alcohols is reported.

SYNOPSIS.