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Manganese Catalyzed *α*-Olefination of Nitriles with Secondary Alcohols

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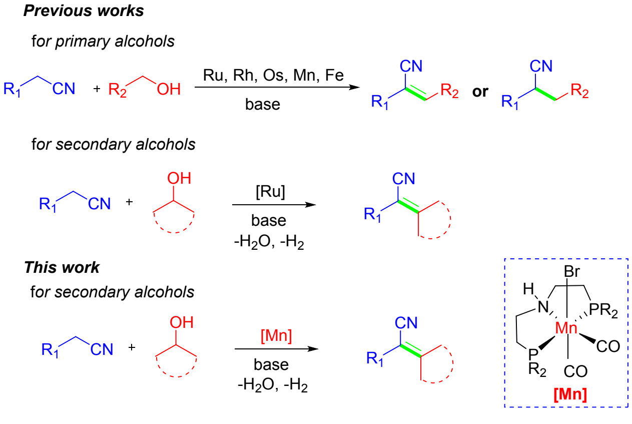
ABSTRACT: An expedient catalytic approach for *α*-olefination of nitriles using secondary alcohols with the liberation of molecular hydrogen and water as the only by-products is reported. This reaction is catalyzed by a molecularly defined manganese(I) pincer complex and operates in the absence of any hydrogen acceptors. A broad range of substrates including cyclic, acyclic, and benzylic alcohols as well as various nitrile derivatives such as arylmethyl and heteroarylmethyl nitriles are employed in the reaction to provide diverse range of *α*-vinyl nitriles in good to excellent yields. Mechanistic studies showed that the reaction proceeds *via* dehydrogenative pathway and the activation of *α*(C-H) bond of the alcohol is the rate determining step.

KEYWORDS: *manganese, α-olefination, alcohol, hydrogen, acceptorless dehydrogenation*

In recent years, the transition-metal catalysis has emerged as one of the most promising tools for C-C and C-N bond forming reactions in synthetic chemistry as a result of its efficiency, selectivity and versatility. Considering the major concern towards the depletion of fossil fuels, the use of abundantly available renewable resources is highly demanding.[1] In this regard, catalytic acceptorless dehydrogenative coupling (ADC)[2] is highly enlightened as an atom-economical and environmental benign process. ADC approach is very attractive due to its operational simplicity, the use of renewable resources based starting materials, and the generation of water as the only stoichiometric byproduct.

The tri-, and tetra-substituted olefins are of great significance in organic synthesis as well as in natural products and pharmaceutical industries. The *α,β*-substituted acrylonitriles are the key building blocks and intermediates in numerous synthetic transformations.[3] Remarkably, they have found manifold applications in the synthesis of high electron affinity polymers for light emitting diodes (LED) and in optoelectronic materials.[4] Various natural products and pharmaceuticals can be synthesized based on the unsaturated nitrile functionality.[5] For example, entacapone (for Parkinson's disease), CC-5079 (a potent antitumor agent), lanoconazole, and luliconazole (antifungal drugs) etc.[5b] The conventional synthesis of vinyl nitriles involving condensation of aldehydes and arylacetonitriles using stoichiometric or catalytic bases and is challenged by the side reactions such as self-condensation of the nitriles, the aldol reaction or the Cannizzaro reaction, and poor functional group tolerance towards base.[6, 7] With the progression of time, several other methods for the condensation of carbonyl compounds and nitriles have been devised. However, still the issues like the use of toxic reagent, tedious synthetic procedure, poor yields and generation of waste; limited the applicability of the classical methods.[8, 9] Hence, an alternative approach for the selective and efficient synthesis of *α,β*-unsaturated nitriles under mild reaction conditions using simple, easily available substrates are highly demanding.

The acceptorless dehydrogenation of renewable resource based alcohols[10] followed by condensation of the resultant carbonyl compounds with nitriles can offer a sustainable and atom-economical approach for the synthesis of vinyl nitriles with the formation of dihydrogen and water.[11] Employing this hydrogen auto transfer (HA)[2] concept, the *α*-olefination and *α*(C)-alkylation of nitriles using primary alcohols were reported under noble catalysis (Scheme 1).[8e, f, 12-15]

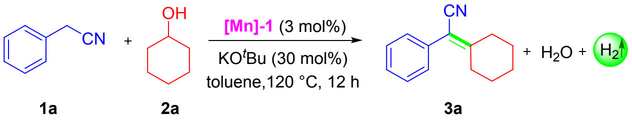


Scheme 1. Catalytic dehydrogenative coupling of nitriles with alcohols.

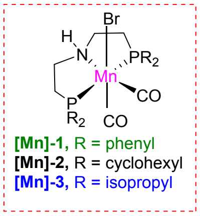
Although noble metals has made tremendous advances in the field of homogeneous catalysis, the earth-abundant first-row transition metals are economical, globally available to obtain, essential to life and thus often have less health and environmental impact as compared to the precious metals.[16, 17] Therefore, it is highly desired to surpass the reactivity and selectivity of the noble metal based catalyst systems by finding the base metal based alternatives.[17] Being the third most abundant metal in the earth crust, manganese can be a suitable substitute to the noble metal catalysts.[18] In 2017, research group of Milstein[19] and Maji[20] independently reported the manganese catalyzed α-olefination and α-alkylation of nitriles using primary alcohols, respectively. Of late, the research group of Xiao and Wang reported an iron(II)-catalyzed α-alkylation of nitriles using primary alcohols as alkylating agent.[21a] In 2019, El-Sepelgy and Rueping reported the first manganese catalyzed α-alkylation of nitriles with primary alcohols.[21b] Recently, base promoted α-alkylation was also described by Kundu and co-workers.[22] Further in 2019, the research group of Poater and Wang independently performed the computational studies on the α-olefination reaction of nitriles and alcohols and gave the mechanistic insights into this important reaction.[23] Despite of the several available methods for the α-olefination and α-alkylation of nitriles with primary alcohols, methods based on secondary alcohols remain scarce. Recently, Gunanathan *et al.* reported the pioneer work on ruthenium catalyzed α-olefination of nitriles using secondary alcohols.[24] Since, there are many potential benefits for studying catalysts based on the earth abundant metals (Fe, Co, Mn, Ni) over the noble metals (Ru, Rh, Ir, Os) in homogeneous catalysis and chemical synthesis, the use of earth-abundant metals is highly appreciated in catalytic transformations. To the best of our knowledge, the base-metal catalyzed α-olefination of nitriles using secondary alcohols is yet to be explored. Herein we report an elegant method for the acceptorless dehydrogenative coupling of nitriles and secondary alcohols to form vinyl nitriles with the liberation of molecular hydrogen and water as the by-products.

Initially, we have started to optimize the reaction conditions using phenylacetonitrile (**1a**) and cyclohexanol (**2a**) as the benchmark substrates. Reaction of phenylacetonitrile (0.5 mmol) with cyclohexanol (1.25 mmol, 2.5 eq.) using **[Mn]-1** (5 mol %) catalyst and KO^{t}Bu (30 mol %) in toluene solvent in a closed system at 120 °C for 16 h resulted in the almost complete conversion of nitrile with olefinic product in 65% isolated yield (Table 1, entry 1). Inspite of the complete conversion, the desired product yield was low. The ^{1}H NMR analyses indicated the formation of decent amount of α-alkylated product (not quantified) along with the aldol condensation product of the *in situ* generated cyclohexanone. The gas phase GC analysis of the reaction mixture indicated the liberation of H_2 gas during the reaction. Gratifyingly, with 2 eq. of alcohol and decrease in the reaction time to 10 h resulted in complete conversion of nitrile with 85% of the isolated olefinic product (Table 1, entry 2) and only a trace amount of alkylated product was observed. A similar outcome was obtained when 3 mol% of the catalyst was used after 12 h (Table 1, entry 3). Further varying the catalyst systems **[Mn]-2** and **[Mn]-3** didn't improve the yield of **3a** (Table 1, entries 4-5). Thus, the complex **1** found to be the efficient catalyst for the catalytic olefination of nitriles with secondary alcohols. In the absence of either of the catalyst system or the base, only trace amount of the product was observed (Table 1, entries 6-7). Also, the attempts to decrease the mol % of base ended up with the low yield of the desired product (Table 1, entry 8). Changing the base from KO^{t}Bu to either of NaO^{t}Bu, Cs_2CO_3, Na_2CO_3, KOH resulted in lower yield of the desired product (Table 1, entry 9). Also the solvent variation to *m*-xylene, n-octane or acetonitrile either ended with low to moderate yield or with no desired product (Table 1, entry 10). With increase in temperature, there was no effect in the product yield while decreasing the temperature (80 ^{o}C) further resulted in low yield of the product **3a**.

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



Entry	deviation from above	Yield of **3a** (%)[b]
1	alcohol (2.5 eq.), **[Mn]-1** (5 mol%), 16 h	65 (99)[c]
2	alcohol (2.0 eq.), **[Mn]-1** (3 mol%), 10 h	85 (>99)[c]
3	none	85 (>99)[c]
4	**[Mn]-2**	65 (90)[c]
5	**[Mn]-3**	50 (75)[c]
6	no catalyst	trace
7	no KO^{t}Bu	trace
8	15 mol% KO^{t}Bu	58
9	NaO^{t}Bu, Cs_2CO_3, KOH as base	<50
10	*m*-xylene, n-octane, 1,4-dioxane, CH_3CN as solvent	<60

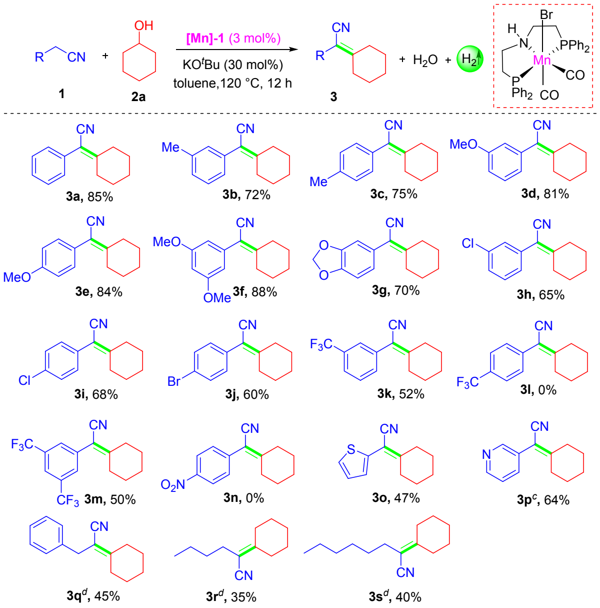


[Mn]-1, R = phenyl
[Mn]-2, R = cyclohexyl
[Mn]-3, R = isopropyl

[a]Reaction Conditions: phenyl acetonitrile **1a** (0.5 mmol), cyclohexanol **2a** (1.0 mmol), catalyst **[Mn]-1** (3 mol %), KO^{t}Bu (30 mol %) and toluene solvent (1.5 mL) were heated at 120 °C (oil-bath temperature) for 12 h under Ar atm. [b]Yield of the isolated product. [c]GC conversion of nitriles using mesitylene as an internal standard.

With the optimized reaction conditions, next we have examined the structural diversity of nitriles using cyclohexanol as the model substrate. As shown in table 2, the position as well as the nature of the substituents on aromatic ring has remarkable effect on the α–olefination reaction. The electron-donating substituents like methyl, methoxy (Table 2, **1b** to **1e**) as well as the mild electron withdrawing groups like halogens (Table 2, **1h** to **1j**) on either of the *meta* or *para* position of phenylacetonitrile afforded good yield of the α–olefinated product. Notably, the strong electron withdrawing groups like trifluoromethyl, nitro (Table 2, **1l** and **1n**) on *para* position failed to give the desired product. This may be the consequence of strong electron withdrawing resonance/reverse hyperconjugation effect operating on para position. Additionally, reaction with 3,5-di-methoxy (**1f**), 3,4-methylene (**1g**) and 3,5-bis-trifluoromethyl (**1m**) substituted aryl methyl nitriles provided the desired olefins in good to excellent yields. The compatibility of the catalytic olefination reaction was also examined with respect to the heteroaromatic nitriles. To our delight, moderate yield of the corresponding α–olefinated product was obtained with 2-thiophene nitrile and 3-pyridine nitrile (Table 2, products **3o** in 47% and **3p** in 64% yields). Indeed, 3-phenylpropionitrile marks a sufficient decrease in the yield of the corresponding 2-cyclohexylidene-3-phenylpropanenitrile product (**3q**). The gas chromatographic analysis indicated 60% conversion of starting material; however, 45% of the desired product was observed. Aliphatic nitriles such as hexanenitrile and octanenitrile require 6 mol% of **[Mn]-1** catalyst and 0.5 equivalent of a base to provide the α–olefinated product in lower yields (Table 2, products **3r** in 35%, and **3s** in 40% yields, respectively).

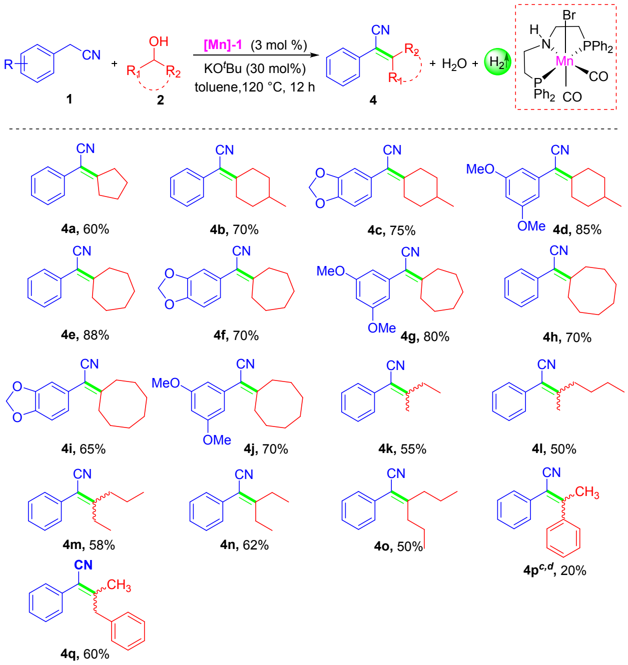
Table 2. Scope of manganese catalyzed α-olefination of nitriles with cyclohexanol.[a,b]



[a] Reaction Conditions: nitrile **1** (0.5 mmol), cyclohexanol **2a** (1.0 mmol), **[Mn]-1** (3 mol %), KO^{t}Bu (30 mol %) and toluene solvent (1.5 mL) were heated at 120 °C for 12 h under Ar atm. [b] Yield of the isolated products after purification. [c] The reaction was carried out for 8 h. [d] The reaction performed with **[Mn]-1** (6 mol %) and 50 mol% of KO^{t}Bu.

Lately, the scope with respect to a wide variety of secondary alcohols was investigated. Various cyclic as well as acyclic secondary alcohols showed good to excellent reactivity under the standard reaction conditions to deliver the desired α-olefinated products (Table 3). When cyclopentanol was reacted with phenylacetonitrile the corresponding α-olefinated product was obtained in 60% yield (**4a**). Similarly, 4-trans-methyl cyclohexanol also showed good reactivity with phenylacetonitrile, 3,4-(methylenedioxy)phenylacetonitrile and (3,5-dimethoxyphenyl)acetonitrile and afforded the corresponding α-olefinated products in 70% (**4b**), 75% (**4c**) and 85% (**4d**) yields, respectively. Interestingly, other cyclic secondary alcohols such as cycloheptanol and cyclooctanol also provided good yield of the desired products with differently substituted phenylacetonitriles under the standard reaction conditions (Table 3, products **4e** to **4j**). A number of asymmetric aliphatic alcohols such as 2-butanol, 2-hexanol, and 3-hexanol were investigated under the given set of conditions and it was observed that the corresponding olefinic products were obtained in moderate yield as *E*/*Z* mixture (Table 3, products **4k** to **4m**). Delightfully, symmetric acyclic alcohols such as 3-pentanol and 4-heptanol afforded the desired olefinic products in 62% (**4n**), and 50% (**4o**) yields, respectively. To check whether this protocol works for aromatic secondary alcohols, we have tried the reaction with 1-phenylethyl alcohol under the optimal reaction conditions for 16 h and the reaction mixture was analyzed using GC and GC-MS. It was found that only 10% of the desired product was formed. Later, under modified reaction conditions, 20% yield of product **4p** was obtained. The reaction worked well with 1-phenyl-2-propanol and the desired α-olefinated product was obtained as *E*/*Z* mixture in 60% yield (**4q**). Ultimately, a simple protocol for the synthesis of highly branched vinyl nitriles from readily available starting materials with the liberation of molecular hydrogen and water as the sole by products is reported.

Table 3. Scope of manganese catalyzed α-olefination of nitriles with secondary alcohols.[a,b]



[a] Reaction Conditions: nitrile **1** (0.5 mmol), alcohol (1.0 mmol), **[Mn]-1** (3 mol %), KO^{t}Bu (30 mol%) and toluene solvent (1.5 mL) were heated at 120 °C for 12 h under Ar atm. [b] Yield of the isolated products after purification. [c] The reaction performed with **[Mn]-1** (6 mol %) and 50 mol% of KO^{t}Bu. [d] 20% of C(α)-alkylated product was observed.

With the almost complete conversion in short period of time, the Mn-catalyst has been proven to be an excellent catalyst for the α–olefination reaction. In view of the activity of the catalyst, we have performed kinetic experiments to gain detailed information about the catalytic process. Monitoring the progress of the reaction indicated that around 1.2 equivalent of cyclohexanol was used for the reaction and the consumption of phenylacetonitrile follows an exponential decay. The rate of product formation is faster as 0.37 mmol of the α-olefinated product was observed just after the completion of 1 h. The intermediate cyclohexanone was also detected in GC which was consumed in due course of the reaction (Figure 1).

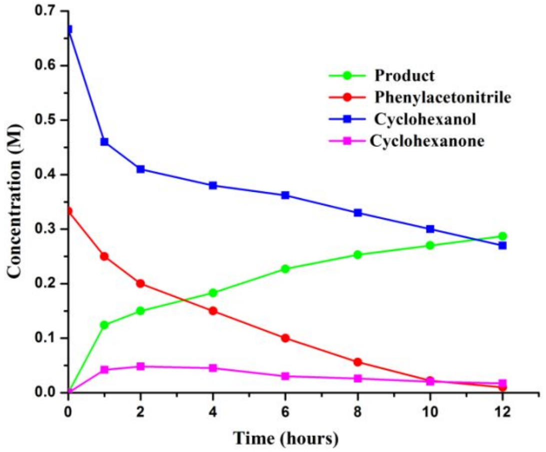


Figure 1. Kinetic profile of the Mn(I)-catalyzed α-olefination reaction of phenyl acetonitrile (**1a**) with cyclohexanol (**2a**).

Further to understand the effect of each of the reaction components on the *α*-olefination reaction, the rate order was determined using initial rate method. The order of reaction with respect to phenylacetonitrile comes out to be around 0.97 which indicated that the reaction is first order with respect to phenylacetonitrile and it plays a crucial role in the *α*-olefination reaction as the rate of product formation increases with increase in initial concentration of phenylacetonitrile (Figures 2 (A) and (B)).

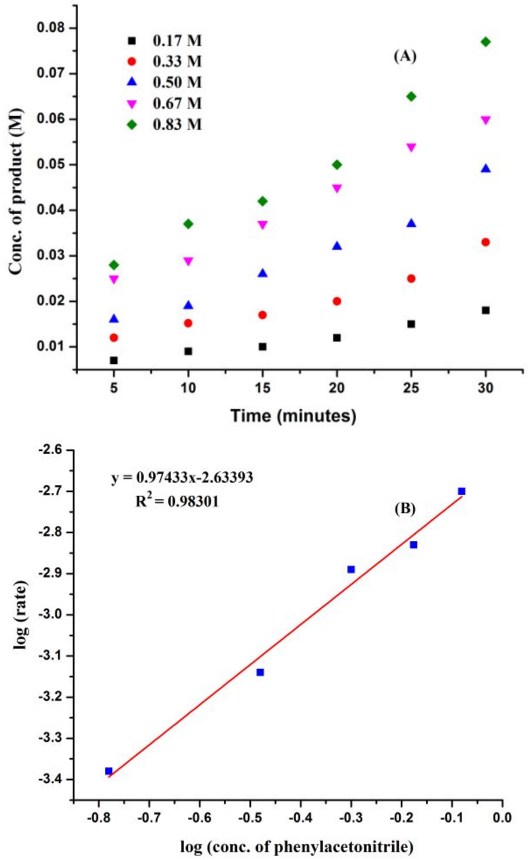


Figure 2. (A) Concentration versus time plot at various concentrations of (**1a**). (**B)** log(rate) versus log(conc.) graph of (**1a**).

The rate of the reaction also increases with the initial concentration of cyclohexanol (Figures 3 (A) and (B)). The catalyst showed fractional order dependence for the *α*-olefination reaction (Figure 4 (A) and (B)). Considering the role of catalyst in multiple steps during the reaction showed that the fractional order with respect to catalyst might be rational.

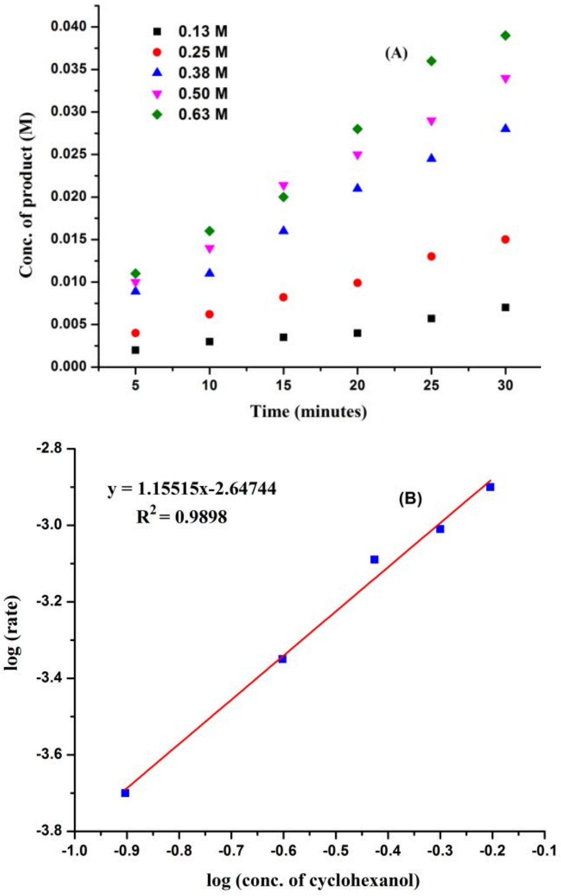


Figure 3. (A) Concentration versus time plot at various concentrations of (**2a**). **(B)** log(rate) versus log(conc.) graph of (**2a**).

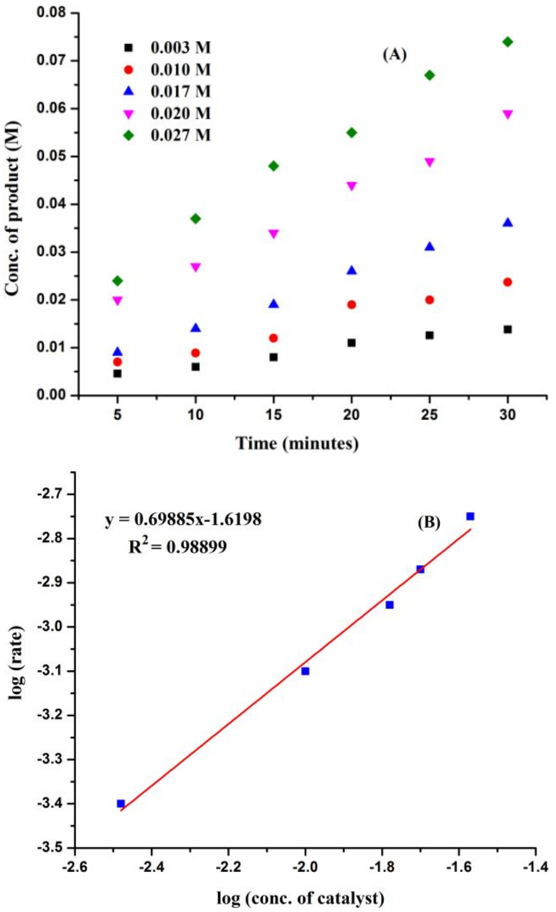
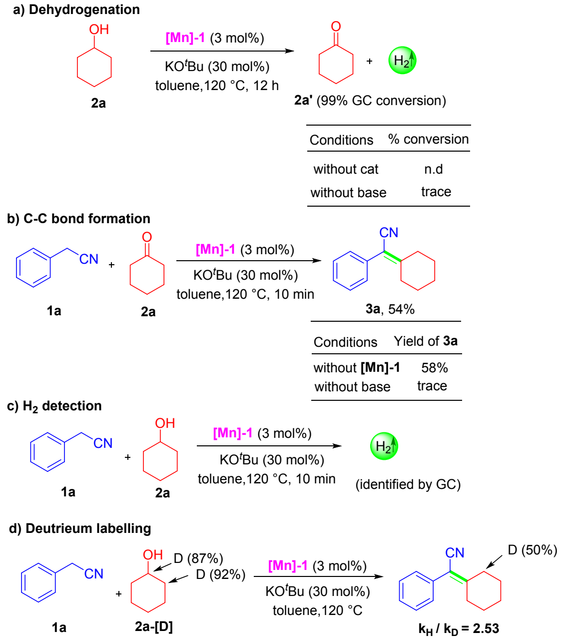


Figure 4. (A) Concentration versus time plot at various concentrations of catalyst. **(B)** log(rate) versus log(conc.) graph of catalyst.

To probe a plausible mechanism several control experiments were carried out under the standard reaction conditions. Firstly, the reaction of cyclohexanol under the standard conditions in the absence of nitrile was carried out. The GC-MS analysis of the crude mixture indicated the quantitative conversion of cyclohexanol to cyclohexanone (Scheme 2a). Recent computational studies by the research groups of Poater,[23a] and Wang[23b] showed that dehydrogenation of alcohols to give carbonyl compounds is energetically feasible. Indeed, the reaction failed with base alone. Further, the condensation of **1a** with **2a** under the standard reaction conditions was found to be fast and a similar rate was observed for the KO^{t}Bu catalyzed reaction (Scheme 2b). The observation is convincing in view of the free base available in the system, because activation of the precatalyst only consumes half the amount of base. Notably, the cubic tetramer (KO^{t}Bu)$_4$ based Knoevenagel condensation mechanism suggested by Lu *et al.* might be operative.[23b] Thus, in addition to the role as a catalyst activator, KO^{t}Bu can also play crucial role in the coupling step. These results strongly indicate that the manganese catalyst might not be involved in the C−C bond formation step while it is playing a major role in the activation of alcohols to give the corresponding ketones. Notably, the evolution of molecular hydrogen was quantitatively analyzed by gas chromatography (Scheme 2c). Further, the deuterium labeled cyclohexanol was prepared using the literature reported procedure[25] which was later used for the α-olefination reaction (Scheme 2d).



Scheme 2. Mechanistic studies.

The kinetic deuterium labeled experiment (Figure 5) indicated that the dissociation of C-H bond of cyclohexanol might be the moderately slow step in the reaction as the k_H/k_D ratio is 2.53.[20]

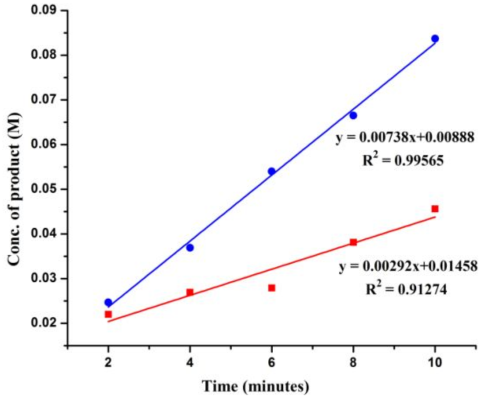
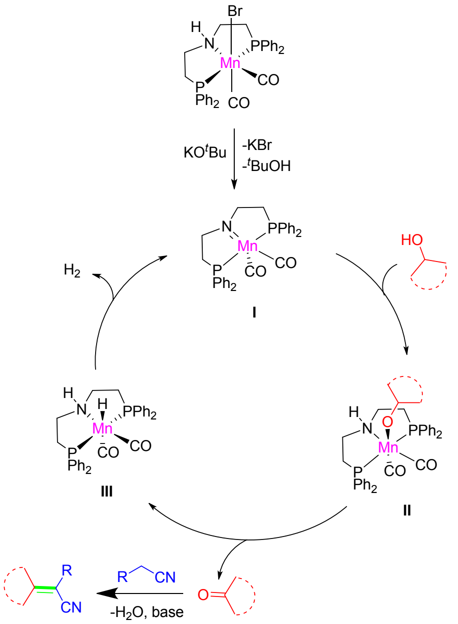


Figure 5. Time dependent formation of product **3a** using deuterium and normal cyclohexanol.

Next, we have performed competitive KIE to verify the k_H/k_D. Thus, two parallel reactions using nitrile (0.256 mmol), cyclohexanol (0.512 mmol) or cyclohexanol-D (0.512 mmol), **[Mn]-1** (3 mol%) and KOtBu (30 mol%) were performed under standard conditions (see ESI). It was found that with cyclohexanol and cyclohexanol-D the isolated yield of the product is 6.1 % and 14.3 %, respectively which indicates k_H/k_D = 2.34. Further, the competition reaction was carried out using both cyclohexanol (**2a**) and cyclohexanol-D (**2a-[D]**) together in a single screw cap pressure tube and kept the reaction under standard conditions for 2 h. After isolating the product using column chromatography, the KIE value was determined by NMR. It was found that 69% of the non-deuterated product and 31% of the deuterated product formed (see ESI). The KIE value is around 2.23. These results are in close agreement with the already mentioned k_H/k_D value, and provide a very strong support for the C–H cleavage being the RDS.[20]

Based on experimental results and the previous literature reports, a plausible catalytic cycle is depicted in Scheme 3. Initially, upon treatment with base, the precatalyst generates the coordinatively unsaturated reactive intermediate **I**. Further the O-H activation of the alcohol *via* proton transfer to the amido nitrogen of intermediate **I**, results in the formation of an alkoxy type intermediate **II**. At this point, the dehydrogenation takes place *via* the more likely base promoted *β*-hydrogen abstraction instead of the less probable *β*-hydride elimination (as shown by Beller and co-workers for *α*-alkylation of ketones with primary alcohols).[26] Thus, the intramolecular metal-ligand cooperation leads to ketone and the manganese hydride complex **III** that further liberates hydrogen gas to regenerate the catalytically active intermediate **I**. Eventually, the Knoevenagel condensation between *in situ* generated ketones and nitriles provides vinyl nitriles by elimination of water molecule.



Scheme 3. A plausible mechanism for the manganese-catalyzed *α*-olefination of nitriles.

CONCLUSION

In conclusion, we have reported an elegant example of base metal catalyzed *α*-olefination of nitriles using secondary alcohols to access diverse tri- or tetra-substituted vinyl nitriles. This straightforward protocol applies to a wide range of alcohols and nitriles. The use of earth-abundant manganese catalyst enlightened the process as an atom-economical and environment benign with the liberation of molecular hydrogen and water as the "green" side products. Based on several control, labeling, and kinetic experiments, it showed that the reaction proceeds *via* dehydrogenative pathway.

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Notes The authors declare no competing financial interest

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and spectral data for new compounds (PDF).

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