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Room temperature synthesis of α,β-unsaturated nitriles by manganese-catalysed base-free coupling of α-saturated nitriles with aldehydes

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α,β-Unsaturated nitriles have broad applications, from polymers to pharmaceuticals, but their synthesis still poses significant challenges, as it often involves multistep procedures, or the use of precious metal catalysts, or the generation of significant amounts of waste. Herein, we report a new approach to the synthesis of such nitriles through single-step coupling of α-saturated nitriles with aldehydes, catalysed by a pincer complex of earth-abundant manganese. This reaction proceeds at room temperature in the absence of base or other additives, does not require substrate pre-activation and generates water as the only byproduct. The catalytic system was shown to tolerate various functional groups, including base-sensitive ones, and afforded a wide range of unsaturated nitriles in generally high yields. α-Deuterated vinyl nitriles were also obtained by coupling CD_3CN with different aldehydes in one-step room temperature syntheses. Experimental and computational data demonstrate that the catalytic reaction involves reversible binding of the nitrile substrate across the metal–ligand framework of the pincer complex, leading to ketimido and enamido complexes as intermediates. The enamido species functions as a carbon nucleophile that forms a C–C bond with an aldehyde to generate a β-hydroxynitrile intermediate, which is subsequently dehydrated into the vinyl nitrile product.

Introduction

α,β-Unsaturated (vinyl) nitriles are a family of industrially important compounds, the simplest member of which, acrylonitrile, is produced globally on a multimillion tonne scale as a polymer precursor.[1a] More complex vinyl nitriles can be found among biologically active natural products and man-made pharmaceuticals (Fig. 1),[1–6] and are used in various fields of application, *e.g.*, agrochemicals, dyes and functional materials.[7] Such nitriles are also valuable building blocks in chemical synthesis, as they are key starting materials in conjugate addition reactions and can be readily transformed into other functional groups.[8]

A direct and atom-economical route to the synthesis of α,β-unsaturated nitriles is the condensation of α-saturated nitriles with aldehydes or ketones. Traditionally, this transformation is achieved through the Knoevenagel condensation, which requires a stoichiometric excess of strong bases, such as KOH or NaOH, at elevated temperatures (Scheme 1a).[9] However, these conventional base-mediated reactions suffer from significant drawbacks, including side-reactions, such as self-aldol condensation and the Cannizzaro reaction, leading to multiple side-products and reducing the overall atom economy.

Several alternative approaches have been developed to address these challenges. In 1998, Verkade and coworkers introduced nonionic superbases as catalysts for the synthesis of α,β-unsaturated nitriles directly from aldehydes and acetonitrile (CH_3CN) or benzyl nitrile.[10] In 2010, Tomioka and

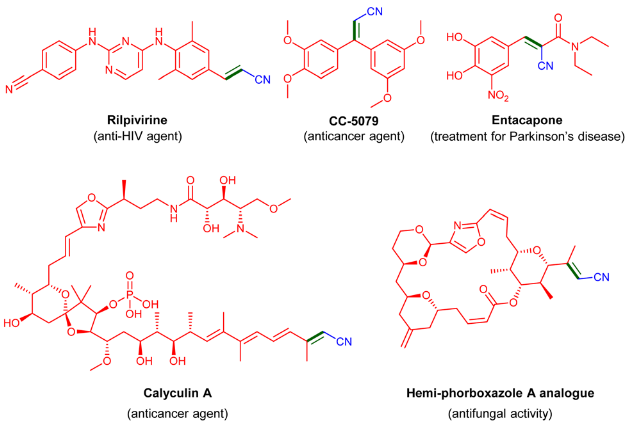

Fig. 1 Select examples of biologically active vinyl nitrile compounds.

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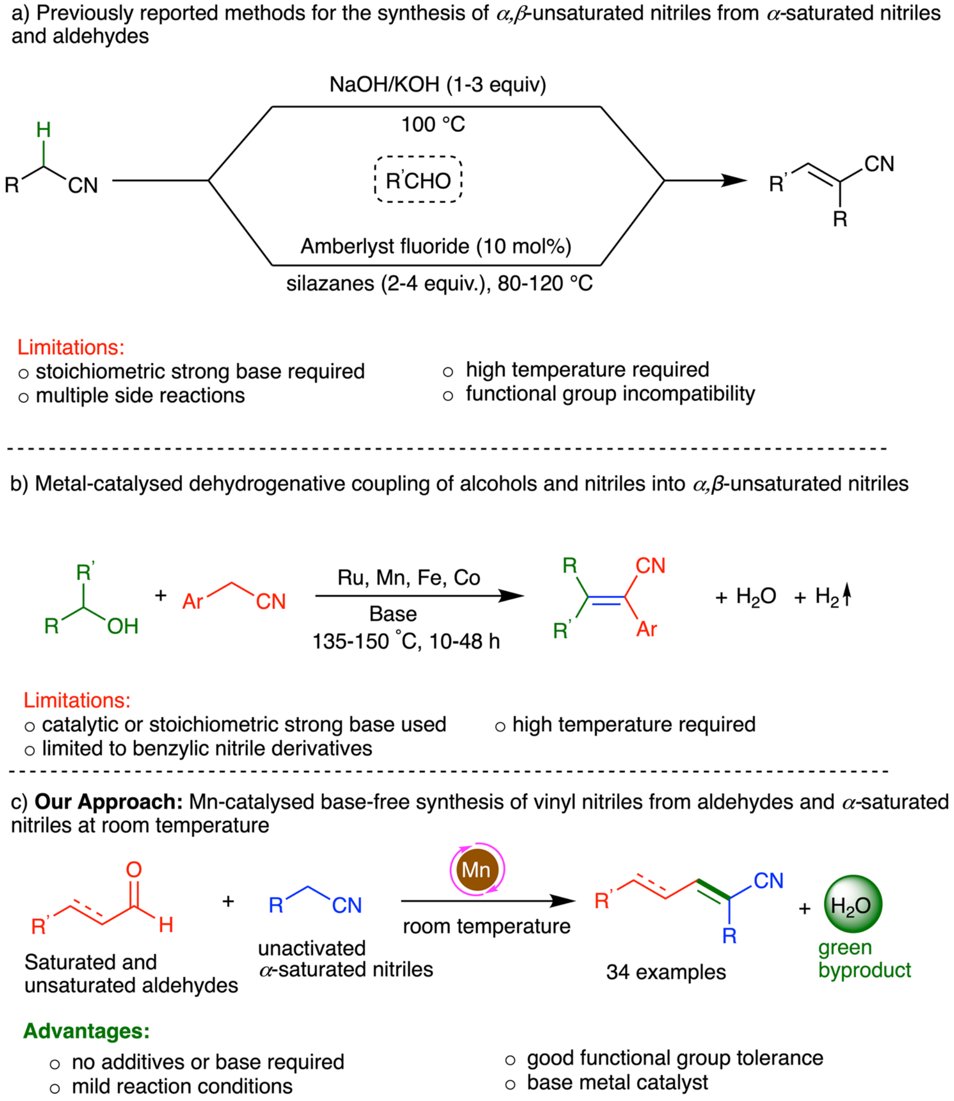


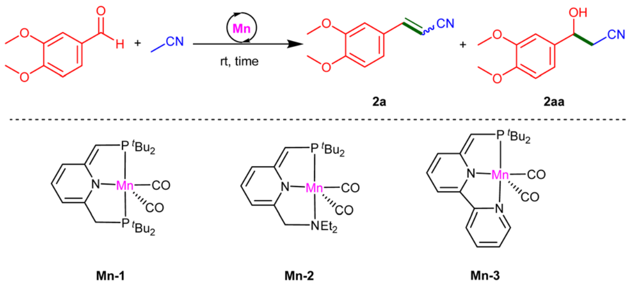
Scheme 1 Strategies for the synthesis of α,β-unsaturated nitriles from α-saturated nitriles. (a) Previously reported methods involving the coupling of α-saturated nitriles with aldehydes, promoted by stoichiometric base or heterogeneous catalysis.[9] (b) Metal-catalysed synthesis *via* dehydrogenative coupling of alcohols and α-saturated nitriles.[17] (c) Mn-catalysed synthesis from aldehydes and α-saturated nitriles under mild, neutral conditions (this work).

coworkers reported a three-step, single-pot (Z)-selective synthesis of acrylonitriles from CH_3CN and aldehydes, using stoichiometric amounts of *n*-BuLi and a boron reagent.[11] More recently, Lanari, Vaccaro and coworkers reported a heterogeneous fluoride-catalysed synthesis of vinyl nitriles by coupling α-saturated nitriles with aldehydes and ketones, in the presence of excess silazanes.[12] Several groups have also developed protocols for vinyl nitrile synthesis through direct α-olefination of α-saturated nitriles, using alcohols as olefination reagents *via* dehydrogenative coupling, but such procedures typically require high temperatures, and are mainly limited to benzylic nitriles (Scheme 1b).[17] Other notable approaches are Peterson olefination,[13] Wittig reactions,[14] carbocyanation of alkynes[15] and cross-metathesis.[16] While the above methods offer advantages, they also have significant drawbacks, including the use of expensive metals, high temperatures, long reaction times, and toxic reagents that are environmentally unfriendly and non-atom-economical, and may also be incompatible with common functional groups.[18] Therefore, it is essential to develop new methodologies for the synthesis of α,β-unsaturated nitriles that are both efficient and green.[19]

A highly useful strategy for C–C and C═C bond formation is transition metal-mediated *in situ* generation of carbon nucleophiles and their coupling with carbonyl compounds.[20,21] In 2013, we showed that benzylic nitriles can be activated by a rhenium pincer complex *via* metal–ligand cooperation (MLC), wherein the C≡N moiety adds reversibly across the metal–ligand framework through C–C bonding with the pincer backbone and Re–N coordination.[22,23] The nitriles activated in this manner were found to behave like Michael donors that can react with α,β-unsaturated esters and ketones to afford the corresponding C–C coupling products. We subsequently extended this approach to aliphatic nitriles through similar activation by a structurally analogous manganese pincer complex.[24] Both complexes exhibited catalytic Michael addition activity, which we termed "template catalysis", since each complex essentially serves as an anchor for the substrate, while C–C bond formation occurs outside the first coordination sphere. This catalytic strategy facilitates both electrophilic and nucleophilic attack on the metal-bound nitriles, enabling a wide range of organic transformations, including conjugate addition,[24] oxa- and aza-Michael addition,[25] hydration and α-deuteration,[26] and nitrile heterocoupling.[27] These processes are atom-economical, waste-free, and proceed under mild, neutral conditions. It should be noted that a similar base-free nitrile activation strategy has also been developed by Otten, de Vries and coworkers, using ruthenium pincer complexes.[28]

As mentioned above, there are various ways to synthesize vinyl nitriles from α-saturated nitriles and aldehydes, including catalytic ones, but they typically involve large amounts of additives or forcing conditions. Coupling of nitriles and aldehydes under mild conditions has been previously achieved using transition metal-based catalysts, but these systems afford β-hydroxynitriles, rather than α,β-unsaturated ones.[29] Herein, we present a Mn-catalysed direct condensation of unactivated α-saturated nitriles with aldehydes at room temperature, yielding α,β-unsaturated nitriles in a single synthetic step (Scheme 1c). This mild, base-free approach is highly functional-group tolerant, utilizes the nitrile substrates themselves as solvents, generates water as the sole byproduct, and offers a green, atom-economical pathway for the synthesis of unsaturated nitriles.

Table 1 Optimization of the catalytic conditions[a]



Entry	Catalyst	Time (h)	Aldehyde conversion (%)^b	Product yields (%)^c 2a	2aa
1	**Mn-1** (2 mol%)	24	94	80	12
2	**Mn-1** (3 mol%)	24	>99	99	—
3^d	**Mn-1** (3 mol%)	24	95	95	—
4^e	**Mn-1** (3 mol%)	24	10	9	—
5	**Mn-2** (3 mol%)	24	65	53	10
6	**Mn-3** (3 mol%)	24	60	34	20
7	—	48	—		

[a] General reaction conditions: 3,4-dimethoxybenzaldehyde (0.3 mmol), CH_3CN (1 mL) and catalyst (loading as indicated, relative to aldehyde) were stirred at room temperature for the indicated time under an N_2 atmosphere. [b] Conversion of 3,4-dimethoxybenzaldehyde was determined by GC analysis, using mesitylene as an internal standard. [c] Yields of products **2a** and **2aa** are for the isolated materials. [d] Mixture of CH_3CN (0.5 mL) and THF (0.5 mL) was used instead of neat CH_3CN. [e] Reaction was performed using 3,4-dimethoxybenzaldehyde (0.3 mmol) and CH_3CN (0.3 mmol) in THF (1 mL).

Results and discussion

At the outset of our study, we examined the catalytic activity of several Mn(I)-pincer complexes, **Mn-1**, **Mn-2** and **Mn-3** (Table 1), which we have previously employed as catalysts for the base-free coupling of nitriles with a variety of substrates.[24–27] Using 3,4-dimethoxybenzaldehyde and CH_3CN as our model substrates, we found that **Mn-1**, at a loading of 2 mol% *vs.* aldehyde, efficiently promotes their conversion into the corresponding α,β-unsaturated nitrile at room temperature, with CH_3CN itself being used as solvent (Table 1, entry 1). Thus, after 24 h, gas chromatographic (GC) analysis of the reaction mixture indicated 94% aldehyde conversion, with the vinyl nitrile product **2a** having been produced in 80% yield, accompanied by the β-hydroxynitrile **2aa** in 12% yield. The presence of this β-hydroxynitrile suggests that it is an intermediate that can undergo catalytic dehydration by **Mn-1** to afford the unsaturated product **2a**. Nevertheless, after extending the reaction time to 48 h, no significant change was observed in the product composition. Thus, we repeated this reaction with an increased catalyst loading of 3 mol%, and this allowed us to achieve essentially quantitative yield of **2a** within 24 h at room temperature (entry 2). Notably, no significant byproducts were observed, including the β-hydroxynitrile. When the neat nitrile was replaced with an equal volume of a 1 : 1 mixture of CH_3CN and THF, aldehyde conversion and the yield of **2a** slightly decreased (95% for both; entry 3). Reducing the amount of nitrile even further, to 1 equiv. per aldehyde, afforded poor results (entry 4), thereby indicating that CH_3CN must be used in excess for this transformation to be efficient. Complexes **Mn-2** and **Mn-3** were also found to be catalytically active, but exhibited lower performance than **Mn-1** under otherwise identical conditions, with reduced aldehyde conversions (≤65%) and the generation of product mixtures in lower yields (≤53% for **2a**, ≤20% for **2aa**; entries 5 and 6). Finally, in the absence of these manganese complexes, no product formation was observed at room temperature, even after 48 h (entry 7), clearly demonstrating the role of these complexes as catalysts in this unsaturated nitrile synthesis.

After establishing the optimal catalytic conditions (Table 1, entry 2), we applied them in a substrate scope investigation, employing a wide range of aldehydes and unactivated α-saturated nitriles (Fig. 2; data for product **2a** from Table 1 are duplicated here for comparative purposes). A gram-scale reaction of 3,4-dimethoxybenzaldehyde in CH_3CN gave **2a** in 89% yield, demonstrating the synthetic utility of our catalytic system. Benzaldehyde derivatives bearing electroneutral and electron-donating substituents, as well as polycyclic aromatic aldehydes, underwent smooth coupling with CH_3CN, affording the respective α,β-unsaturated nitriles, **2b–h**, in excellent yields (88–99%). Benzaldehydes featuring *para*-positioned electron-withdrawing groups, namely, chloride, trifluoromethyl and

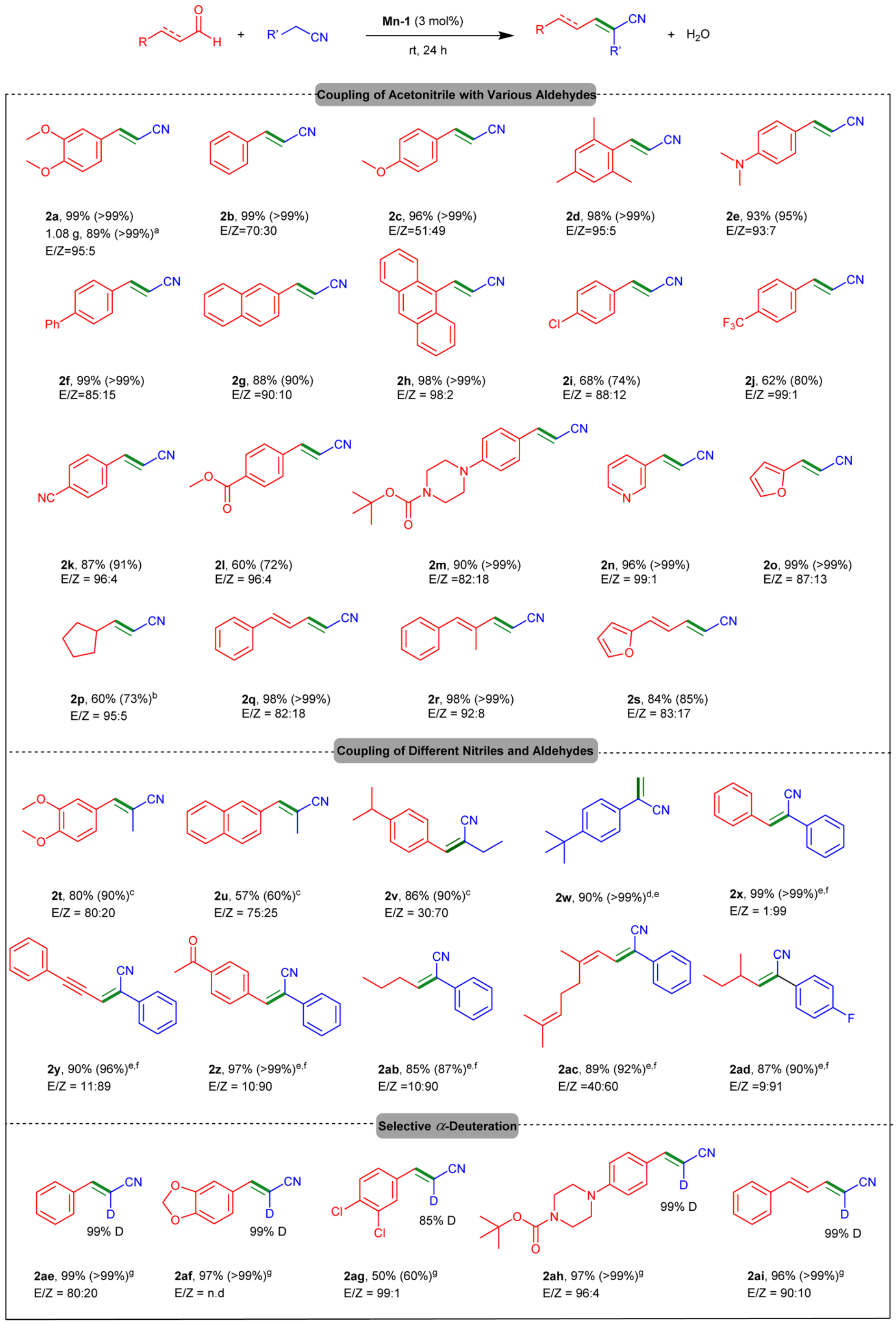


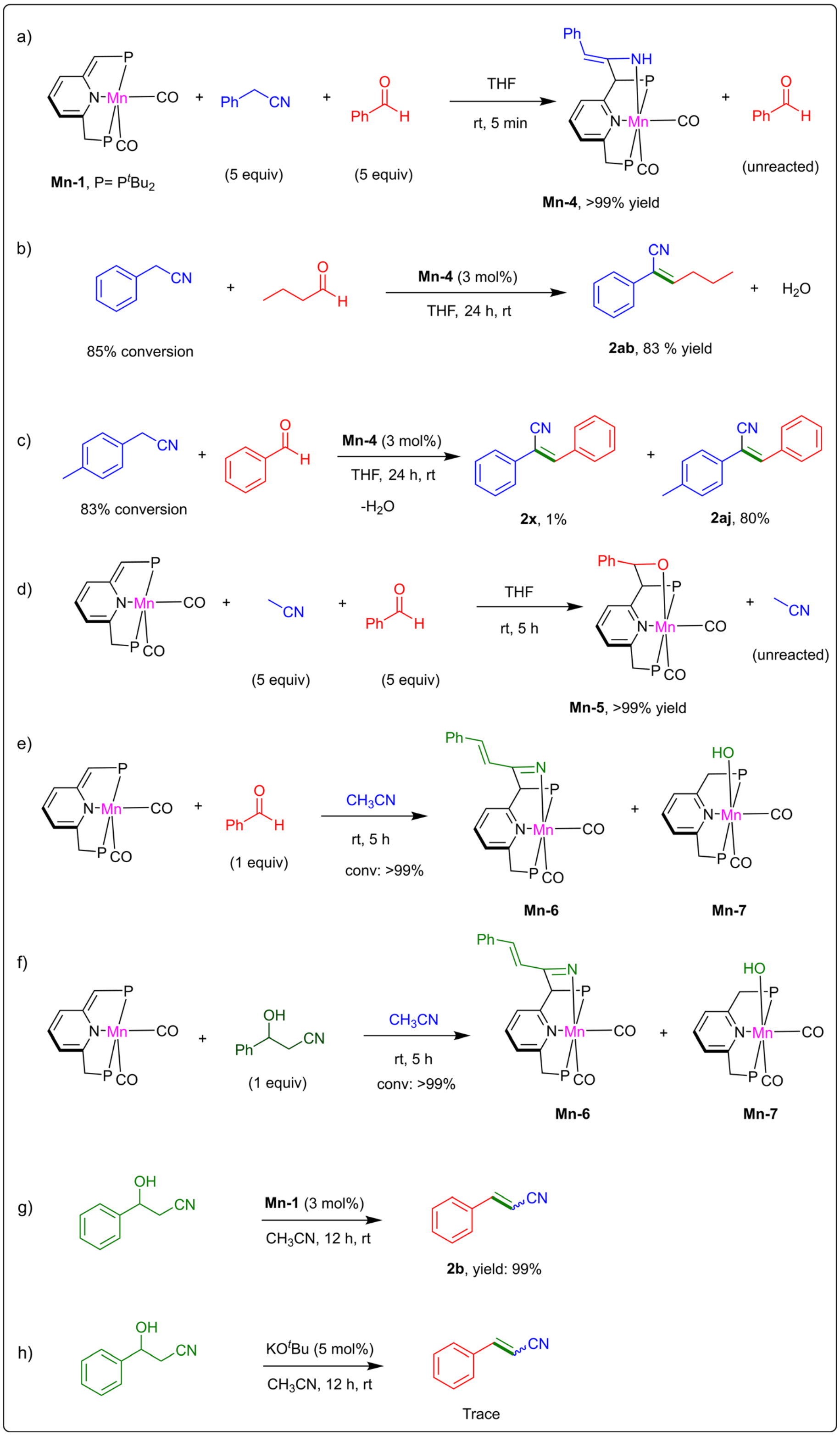
Fig. 2 Substrate scope for the coupling of nitriles with aldehydes catalysed by **Mn-1**. General reaction conditions: aldehyde (0.3 mmol), nitrile (1 mL) and **Mn-1** (3 mol% *vs.* aldehyde) were stirred at room temperature for 24 h [yields correspond to pure isolated products; values in parentheses are aldehyde conversions as determined by GC analysis (mesitylene was used as internal standard); *E*/*Z* ratios were determined by GC or ^{1}H NMR spectroscopic analysis of the crude reaction mixtures]. ^{a} Gram-scale experiment with increased amounts of reagents: aldehyde (6 mmol), CH_3CN (6 mL), **Mn-1** (3 mol% *vs.* aldehyde). ^{b} Reaction was conducted at 50 °C. ^{c} Increased amount of **Mn-1** (5 mol% *vs.* aldehyde). ^{d} The reagents were 2-(4-(*tert*-butyl)phenyl)acetonitrile (0.3 mmol), 37% aqueous formaldehyde (0.45 mmol, 1.5 equiv.) and **Mn-1** (3 mol% *vs.* nitrile). ^{e} Values in parentheses are nitrile conversions as determined by GC analysis (mesitylene was used as internal standard). ^{f} The amount of nitrile was 0.3 mmol and the solvent was THF (1 mL). ^{g} The reaction was carried out in CD_3CN (1 mL).

cyanide, were also effectively coupled with CH_3CN, leading to the vinyl nitriles **2i–k** in fair to high yields (62–87%). Importantly, base-sensitive functional groups, *i.e.*, ester and carbamate, were tolerated by our catalytic system, and the corresponding benzaldehydes reacted with CH_3CN to afford products **2l** and **2m** in 60 and 90% yield, respectively. Aldehydes with heteroaryl substituents, *i.e.*, 3-pyridyl and 2-furfuryl, were also compatible with our current catalytic protocol and afforded the desired unsaturated nitriles, **2n** and **2o**, in practically quantitative yields. When we attempted to use an alicyclic aldehyde, cyclopentanecarboxaldehyde, under the optimal reaction conditions, the respective vinyl nitrile product, **2p**, was obtained in poor yield. Nevertheless, raising the reaction temperature to 50 °C resulted in formation of this nitrile in 60% yield. A series of other aliphatic and α,β-unsaturated aldehydes were also examined as substrates, to be coupled with acetonitrile or propionitrile under the optimal catalytic conditions, but only marginal vinyl nitrile formation was observed (Fig. S6; see SI). Finally, the regioselectivity of our catalytic system was demonstrated when CH_3CN was directly coupled with three conjugated aldehydes, resulting in dienyl nitriles **2q–s** in high conversions and yields (84–98%). Conventional base-mediated Michael-type reactions of such carbonyl substrates usually give a mixture of 1,2- and 1,4-addition products, whereas our method exhibits very high 1,2-selectivity.[19c,30]

Having shown that the present catalytic system can couple CH_3CN with a host of aldehydes to generate the corresponding α,β-unsaturated nitriles in high efficiency and functional group tolerance, we turned our attention to other unactivated α-saturated nitriles as substrates (Fig. 2). Under the optimal catalytic conditions, albeit with a catalyst loading of 5 mol%, the reactions of propionitrile with 3,4-dimethoxybenzaldehyde and 2-naphthaldehyde proceeded smoothly, giving the vinyl nitriles **2t** and **2u** in fair to good yield (57–80%). Applying the same procedure to a solution of 4-isopropylbenzaldehyde in neat butyronitrile afforded the desired product, **2v**, in 86% yield. We were also able to synthesize a terminal disubstituted olefin by using aqueous formaldehyde as substrate. Thus, coupling it with (4-*tert*-butyl)phenylacetonitrile, in a THF solution, furnished the unsaturated nitrile **2w** in 90% yield.[31] 2,3-Diphenylacrylonitrile (**2x**) was obtained quantitatively from benzaldehyde and benzyl nitrile, and the same nitrile was also coupled with 3-phenylpropiolaldehyde to give the product **2y** in 90% yield. The chemoselectivity of our catalytic system was demonstrated through the reaction of benzyl nitrile with 4-acetylbenzaldehyde, which features two carbonyl functionalities – aldehyde and ketone – that may undergo condensation. In practice, however, only the aldehyde moiety reacted, furnishing the vinyl nitrile **2z** in 97% yield, whereas the ketone group remained intact. The linear aldehydes butyraldehyde and 3,7-dimethylocta-2,6-dienal reacted with benzyl nitrile to afford the products **2ab–ac** in very good yields (85–89%), and 2-methylbutyraldehyde was coupled with 4-fluorobenzyl nitrile to give **2ad** in a similarly high yield (87%). Notably, no double-bond migration was observed in product **2ac**, and both C═C bonds of the parent aldehyde remained in their respective positions. The *trans* isomers of the vinyl nitriles – denoted *E* for acetonitrile and propionitrile and *Z* for the heavier nitriles – are preferred across all substrates. Acetonitrile shows high *trans* selectivity, whereas the moderate stereoselectivity observed for other nitriles may arise from steric or electronic factors. Lastly, the ability to directly couple CH_3CN with a range of aldehydes has enabled us to synthesize α-deuterated vinyl nitriles, by using the commercially available isotopolog CD_3CN. Thus, various benzaldehyde derivatives, as well as cinnamaldehyde, were allowed to react with CD_3CN, selectively affording the corresponding α-deuterated α,β-unsaturated nitriles, **2ae–ai**, in generally high yields. Importantly, no deuterium incorporation was observed at other C–H positions in these products.[28a]

In order to gain insight into the underlying mechanism of our catalytic nitrile–aldehyde coupling system, stoichiometric experiments were performed (Scheme 2). When a THF solution of **Mn-1** was treated with 5 equiv. of benzyl nitrile and 5 equiv. of benzaldehyde at room temperature, the only observed product was the nitrile adduct of **Mn-1**, *i.e.*, the previously-reported rearomatized enamido complex **Mn-4** (enamine-containing species; Scheme 2a).[24] Notably, no other complexes were observed in solution, including the aldehyde adduct.[24,27] This simple competition experiment clearly indicates that **Mn-1** reacts preferentially with benzyl nitrile, rather than benzaldehyde. This points to the higher thermodynamic stability of the enamido complex, likely enhanced by conjugation between the C═N bond and phenyl group. In an attempt to probe the possible role of **Mn-4** as a catalytic intermediate, this complex was independently synthesized and used as catalyst for the coupling of benzyl nitrile with butyraldehyde. Thus, 0.3 mmol of each substrate and 3 mol% of **Mn-4** (loading relative to either substrate) were dissolved in THF, and the solution was stirred at room temperature for 24 h, after which the vinyl nitrile product **2ab** was isolated in 83% yield (Scheme 2b). This result is nearly identical to the one originally obtained with **Mn-1** (Fig. 2). Furthermore, when 4-methylbenzyl nitrile was allowed to react with benzaldehyde under the same catalytic conditions involving **Mn-4**, the expected product **2aj** was obtained in 80% yield (Scheme 2c), but was accompanied by a small amount of compound **2x**, which is derived from the enamido ligand of complex **Mn-4**. Taken together, the above stoichiometric experiments indicate that **Mn-4** is indeed an intermediate in the catalytic cycle.

As shown above, the present catalytic system can also efficiently couple aldehydes with unactivated aliphatic nitriles, namely, acetonitrile, propionitrile and butyronitrile (Fig. 2). Thus, as was done with the benzylic nitriles, we carried out a stoichiometric competition experiment wherein **Mn-1** was mixed with 5 equiv. of CH_3CN and 5 equiv. of benzaldehyde in THF, at room temperature (Scheme 2d). Interestingly, only the benzaldehyde adduct of **Mn-1**, *i.e.*, the previously-reported complex **Mn-5** was observed in solution,[32] in contrast to the abovementioned competition experiment involving benzyl nitrile, which resulted exclusively in the nitrile adduct. We have previously demonstrated that reaction of **Mn-1** with another aliphatic nitrile, propionitrile, is highly reversible at room temperature.[24] It generates two nitrile adducts, namely, a ketimido complex (imine-containing species), which is the predominant product, and an enamido complex, which is a minor product, but both complexes were found to be less stable than **Mn-1** and the free nitrile. In fact, they could be characterized only in the presence of excess nitrile at subambient temperatures. Hence, in our catalytic system, aliphatic nitriles must be used in large excess relative to the aldehyde, in order to outcompete this substrate for bonding to **Mn-1**, and to drive the formation of the unstable enamido



Scheme 2 Mechanistic studies. (a) Competition experiment involving the reaction of **Mn-1** with excess benzyl nitrile and benzaldehyde in THF. (b) Reaction of benzyl nitrile with butyraldehyde in THF, catalysed by the independently synthesized complex **Mn-4**. (c) Reaction of 4-methylbenzyl nitrile with benzaldehyde in THF, catalysed by **Mn-4**. (d) Competition experiment involving the reaction of **Mn-1** with excess CH_3CN and benzaldehyde in THF. (e) Stoichiometric reaction of **Mn-1** with benzaldehyde in CH_3CN. (f) Stoichiometric reaction of 3-hydroxy-3-phenylpropanenitrile with **Mn-1** in CH_3CN. (g) Reaction of 3-hydroxy-3-phenylpropanenitrile catalysed by **Mn-1** in CH_3CN. (h) Reaction of 3-hydroxy-3-phenylpropanenitrile with KO^{t}Bu (5 mol%) in CH_3CN.

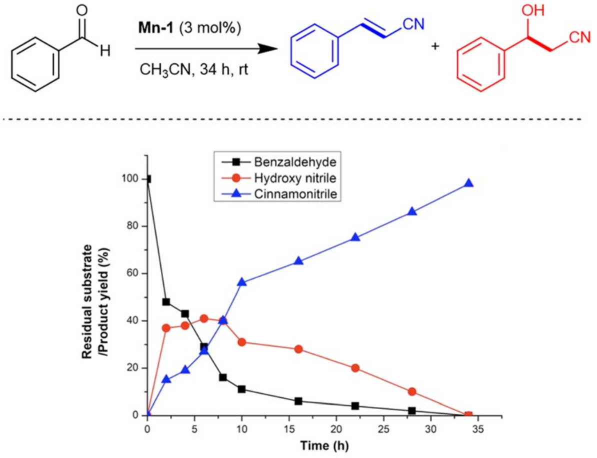
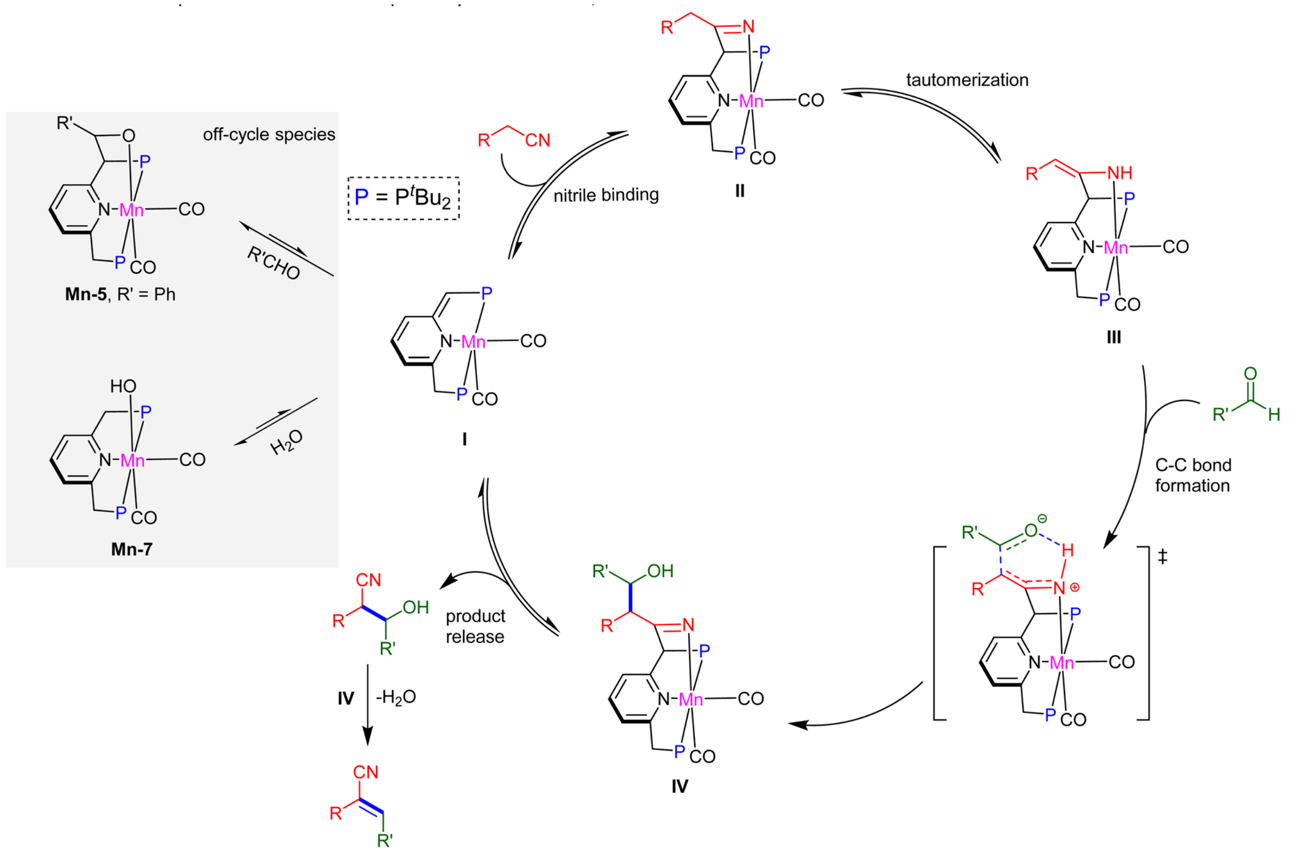


Fig. 3 Kinetic profile of the reaction between CH_3CN and benzaldehyde catalysed by **Mn-1**.

intermediate. Indeed, when **Mn-1** was treated with 1 equiv. of benzaldehyde in CH_3CN as solvent, the aforementioned benzaldehyde adduct was not detected. Instead, we observed complexes **Mn-6** and **Mn-7** (Scheme 2e), which are the cinnamonitrile and water adducts of **Mn-1**, respectively. The existence of these complexes, which were previously characterized by us,[26,27] is consistent with the occurrence of C–C coupling between benzaldehyde and CH_3CN, followed by dehydration to generate cinnamonitrile.

During the optimization of the catalytic conditions, we observed β-hydroxynitrile **2aa** as a minor product (Table 1, entry 1). In an attempt to examine our assertion that it is an intermediate en route to the α,β-unsaturated nitrile, an acetonitrile solution of **Mn-1** was treated, at room temperature, with 1 equiv. of 3-hydroxy-3-phenylpropanenitrile, an analog of **2aa** (Scheme 2f). This gave a mixture of the complexes **Mn-6** and **Mn-7**, as was observed for the reaction of **Mn-1** with benzaldehyde under the same conditions, thereby indicating that the β-hydroxynitrile is indeed a catalytic intermediate, and that it undergoes facile dehydration by **Mn-1** at room temperature. These conclusions were further corroborated when 3-hydroxy-3-phenylpropanenitrile was subjected to the optimal catalytic conditions, using CH_3CN as solvent and **Mn-1** at 3 mol% loading, resulting in the quantitative formation of cinnamonitrile (Scheme 2g). It should be noted that when this catalytic experiment was repeated, but with **Mn-1** having been replaced with the strong base KO^{t}Bu (5 mol%), only traces of cinnamonitrile were observed (Scheme 2h). This rules out a general-base dehydration mechanism and highlights the efficiency with which **Mn-1** catalyses this reaction at room temperature.

Time-resolved monitoring of the Mn-catalysed reaction of benzaldehyde in CH_3CN, using ^1H nuclear magnetic resonance (NMR) spectroscopy, enabled us to gain some kinetic insights.



Scheme 3 Proposed reaction mechanism for the direct synthesis of α,β-unsaturated nitriles from α-saturated nitriles and aldehydes catalysed by complex **Mn-1**.

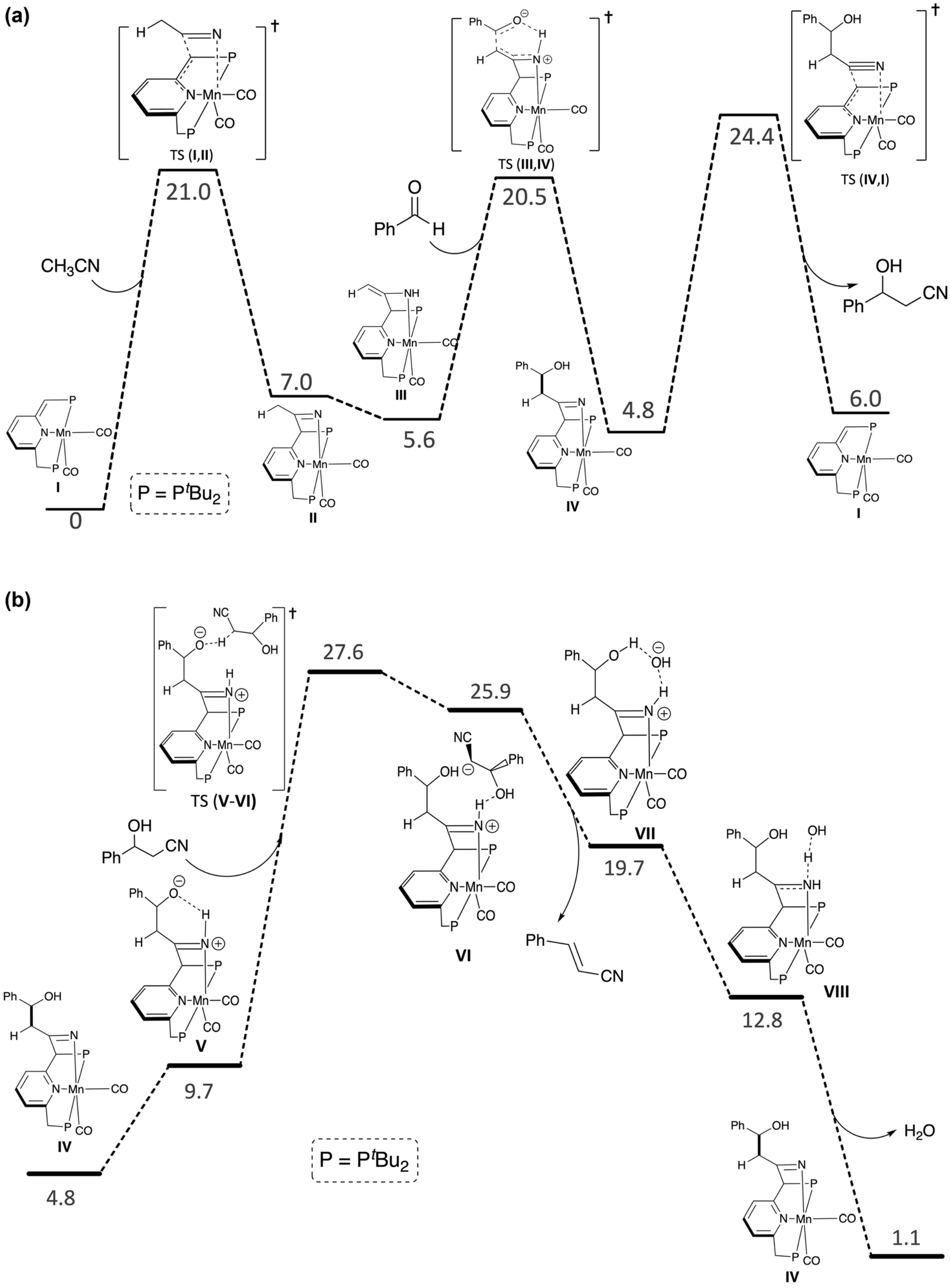


Fig. 4 Computed reaction profiles for the synthesis of cinnamonitrile from CH_3CN and benzaldehyde catalysed by **Mn-1** in CH_3CN as solvent. (a) C–C coupling between CH_3CN and benzaldehyde promoted by complex **I** (**Mn-1**). (b) Dehydration of the β-hydroxynitrile intermediate promoted by the *in situ*-generated complex **IV**. All energies are in kcal mol^{-1} and are referenced to complex **Mn-1** and the free reactants.

The time variation of the reaction mixture composition, under the optimal catalytic conditions, is presented in Fig. 3. As can be deduced from this data, the conversion of benzaldehyde exceeds 50% within the first 2 h at room temperature. During the same time, the β-hydroxynitrile intermediate reaches a yield of nearly 40%, whereas the product, cinnamonitrile, lags behind at 15%. Hydroxynitrile dehydration proceeds slowly, and the amount of cinnamonitrile exceeds that of the hydroxynitrile only after ∼8 h. These data indicate that hydroxynitrile dehydration is the rate-determining step for the overall reaction between the α-saturated nitrile and aldehyde to afford the α,β-unsaturated nitrile.

Based on the above experimental results, as well as our previous work,[24–27] we propose a catalytic cycle for the coupling of α-saturated nitriles with aldehydes, promoted by **Mn-1**, as depicted in Scheme 3. Using CH_3CN and benzaldehyde as representative substrates, this cycle was studied by density functional theory (DFT) calculations, with the temperature fixed at 298.15 K and CH_3CN set as the solvent. The computed reaction profiles are presented in Fig. 4.

The catalytic reaction begins with addition of a nitrile molecule to species **I** (complex **Mn-1**), and follows a template-type mechanism similar to the one reported in our previous work involving conjugate addition of nitriles to α,β-unsaturated carbonyl compounds.[24] Initially, the nitrile reacts with complex **I** to generate the ketimido intermediate **II** *via* MLC, a process that is endergonic for CH_3CN, with $\Delta G = 7.0$ kcal mol^{-1}. It is also endergonic for both propionitrile and benzyl nitrile, with $\Delta G = 6.0$ and 1.9 kcal mol^{-1}, respectively (see SI). Subsequently, **II** undergoes facile tautomerization into the enamido intermediate **III**, a reaction that is slightly exergonic for CH_3CN, with $\Delta G = -1.5$ kcal mol^{-1}. It is also exergonic for benzyl nitrile, but endergonic for propionitrile, with $\Delta G = -2.7$ and 0.8 kcal mol^{-1}, respectively (see SI). For both aliphatic nitriles, the ketimido and enamido intermediates are less stable than the parent complex **I** and free nitrile, whereas in the case of benzyl nitrile, the enamido intermediate is more stable. The latter species is apparently stabilized by conjugation between the C═N bond and aromatic ring, an effect which is absent for the aliphatic nitriles.[24] These computational results are consistent with our experimental observations, which showed that, in contrast to benzyl nitrile, an excess of the aliphatic nitrile is required for shifting the reaction equilibrium toward the enamido complex **III**. Moreover, they are in line with the results of our competition experiments involving benzaldehyde *vs.* benzyl nitrile or CH_3CN. Nevertheless, regardless of the exact identity of the nitrile and stability of its adduct, once intermediate **III** is generated, it functions as a carbon nucleophile that reacts with benzaldehyde through C–C bond formation, accompanied by proton transfer, to produce intermediate **IV**, which is a β-hydroxynitrile adduct. For CH_3CN, this is a slightly exergonic step ($\Delta G = -0.8$ kcal mol^{-1}) that passes through a concerted transition state, with an activation energy of 14.9 kcal mol^{-1}. The hydroxynitrile product can then dissociate from **IV**, with a kinetic barrier of 19.6 kcal mol^{-1}, thereby regenerating complex **I** and closing the catalytic cycle. Overall, the formation of hydroxynitrile is thermodynamically uphill by 6.0 kcal mol^{-1}, and is driven by the large excess of substrates in the reaction mixture. Moreover, it has an apparent activation barrier of 24.4 kcal mol^{-1}, which is consistent with a facile room temperature process.

As mentioned above, we have shown experimentally that the β-hydroxynitrile compound 3-hydroxy-3-phenylpropanenitrile undergoes facile dehydration into cinnamonitrile in the presence of **Mn-1**, but is not dehydrated by a strong Brønsted base. However, our computational results indicate that direct dehydration of the hydroxynitrile by **Mn-1** is kinetically unattainable at room temperature (see SI). Interestingly, our calculations suggest that dehydration is instead catalysed by the *in situ*-generated intermediate **IV**. As can be seen in Fig. 4b, this reaction is exergonic to the tune of 3.7 kcal mol^{-1}, and exhibits an internal kinetic barrier of 22.8 kcal mol^{-1}, giving an overall apparent activation energy of 27.6 kcal mol^{-1} for cinnamonitrile formation. The latter is 3.2 kcal mol^{-1} higher than the corresponding barrier for hydroxynitrile generation, in agreement with our experimental data, which indicates that dehydration of the hydroxynitrile is the rate-determining step.

It should be noted that, according to our proposed mechanism, complexes **Mn-5** and **Mn-7**, both of which were observed experimentally, are generated through side equilibria involving the addition of aldehyde or water to **Mn-1**, and are not directly involved in the catalytic cycle. Our calculations show that in the polar solvent acetonitrile, **Mn-5** is less stable than complexes **II** and **III** ($\Delta G = 8.9$, 7.0, and 5.6 kcal mol^{-1}, respectively), whereas in the gas phase **Mn-5** is the most stable of the three species ($\Delta G = -0.4$, 3.7, and 0.4 kcal mol^{-1}, respectively). Thus, the nitrile adduct **III** is thermodynamically preferred in the polar nitrile solvent, whereas **Mn-5** is preferred in the low-polarity solvent THF, in line with our experimental observations. The formation of **Mn-7** can be rationalized by its comparatively high stability ($\Delta G = -3.9$ kcal mol^{-1} in CH_3CN), which enables the effective trapping of water, as it is generated upon hydroxynitrile dehydration.

Our computational study also allows us to rationalize the lower catalytic activity observed for complexes **Mn-2** and **Mn-3**, as compared with **Mn-1**, through examination of their electronic structures (see SI). Natural bond orbital (NBO) analysis shows that the N-donor arms of the PNN ligands in **Mn-2** and **Mn-3** are less electron-donating than the corresponding P-donor arm of the PNP ligand in **Mn-1**. This reduces the overall electron density across the structures of complexes **Mn-2** and **Mn-3**, including that of the bridging C atom of the unsaturated pincer arm, which is crucial for metal–ligand cooperation. These electronic effects render **Mn-2** and **Mn-3** less efficient in activating the coordinated nitrile substrate and β-hydroxynitrile intermediate.

Conclusions

In this report, we have introduced a catalytic method for the synthesis of α,β-unsaturated nitriles *via* the coupling of unactivated α-saturated nitriles with aldehydes, promoted by a manganese-based catalyst. This reaction is carried out at room temperature, under base-free conditions and with no other additives, and, in most cases, utilizes the nitrile substrate as solvent. The catalytic protocol was shown to accommodate a broad range of substrates that includes various aliphatic and aromatic nitriles and aldehydes, and exhibit excellent functional group tolerance. Moreover, this method enables the selective synthesis of α-deuterated α,β-unsaturated nitriles, thereby demonstrating further synthetic utility. Based on experimental investigations and DFT calculations, we propose a template-type mechanism for this catalytic system, wherein the manganese pincer complex activates an incoming nitrile *via* metal–ligand cooperation, thereby forming an enamine-containing intermediate that behaves as a carbon nucleophile. The latter couples with an aldehyde to give a β-hydroxynitrile intermediate that is then dehydrated into the vinyl nitrile product. We believe that this new catalytic method represents a green, efficient alternative to existing techniques for the synthesis of vinyl nitriles.

Author contributions

D. M. and S. T. conceived and directed the project and designed the experiments. S. T. performed all of the experiments and analyzed their results. J. L., Y. L. and I. E. carried out the computational studies. M. M. provided insightful discussions. D. M., S. T. and M. M. prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The authors declare that all supporting data are available in the supplementary information (SI) and from the corresponding author upon reasonable request. Supplementary information: detailed experimental procedures, characterization data (^{1}H and ^{13}C NMR spectra), and a detailed description of the computational methods. See DOI: https://doi.org/10.1039/d5sc07492d.

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