



Cite this: *Chem. Commun.*, 2025, 61, 17420

Received 18th May 2025,  
Accepted 23rd September 2025

DOI: 10.1039/d5cc02804c

rsc.li/chemcomm

# Nitrile hydration and $\alpha$ -deuteration of amides catalyzed by a PC<sub>NHC</sub>P Mn(I) pincer complex

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Amides are prevalent structural motifs in nature and important functional groups in synthetic organic chemistry. Amide synthesis typically requires harsh reaction conditions necessitating alternative strategies that are atom economic, catalytic, and easy to perform. Here we present the efficient hydration of nitriles, catalyzed by a manganese(I) PC<sub>NHC</sub>P pincer complex, that furnishes a diverse set of amides with excellent functional group compatibility. The reaction occurs at moderate temperatures (90 °C) and produce the corresponding amides in excellent yields (up to 99%). Deuterated amides can also be accessed via subsequent H/D exchange with D<sub>2</sub>O using the same catalyst.

In recent years, earth-abundant metals have increasingly been investigated as suitable replacements for precious metal catalysts in organic syntheses.<sup>1</sup> Their low toxicity, high availability, and low environmental impact contribute to their sustainable footprint when combined with chemical reactions that exhibit a high atom economy.<sup>2</sup> One such reaction is the hydration of nitriles to form amides.

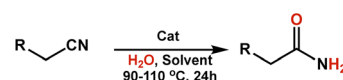
Amides are important constituents in a variety of organic compounds including agrochemicals, pharmaceuticals, and most importantly, biomolecules (*i.e.*, proteins).<sup>3</sup> Their synthesis generally relies on the condensation of an amine with a carboxylic acid, ester, or acyl chloride, typically requiring harsh conditions and additives.<sup>3,4</sup> As result, developing practical approaches for amide synthesis is particularly attractive. One such approach is the hydrolysis of nitriles that generally requires forcing reaction conditions or is catalyzed by precious metals such as gold,<sup>5</sup> ruthenium,<sup>6</sup> rhodium,<sup>7</sup> platinum,<sup>8</sup> and palladium.<sup>9</sup>

In recent years approaches have been developed that (i) use earth-abundant metal catalysts, (ii) are highly atom economic, and (iii) proceed under mild reaction conditions.<sup>10</sup> For example, Milstein and co-workers have shown that secondary amides can be directly synthesized from alcohols and amines through dehydrogenative coupling.<sup>11</sup> The same authors used a different

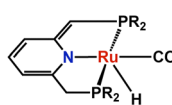
approach when demonstrating that primary amides could also easily be accessed through the hydration of nitriles *via* manganese mediated “template catalysis” (Fig. 1A).<sup>12</sup> Piers and co-workers on the other hand, developed the nickel catalyzed hydration of nitriles that is mechanistically distinct from template catalysis (Fig. 1A), and proceeds *via* a nickel hydroxide intermediate.<sup>13</sup> Yet, besides the contributions from Milstein and Piers, there are not many examples of well-defined catalysts that use earth-abundant metals for catalytic nitrile hydration (Fig. 1).<sup>14</sup>

Instead of relying on metal-ligand cooperativity, our group has focused on developing earth-abundant metal catalysts with strong-field PC<sub>NHC</sub>P pincer ligands.<sup>15</sup> Recently, our group demonstrated that Mn(I) PC<sub>NHC</sub>P pincer complexes are highly active catalysts for the  $\alpha$ -methylation of ketones,<sup>16</sup> and the

## (A) Nitrile Hydration

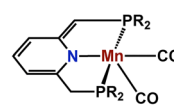


### Ruthenium



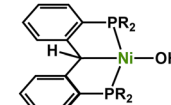
Otten  
*Chem. Sci.* 2019, 10, 10647

### Manganese



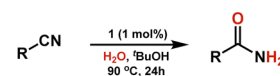
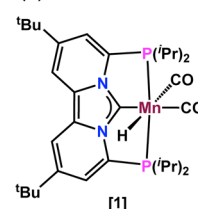
Milstein  
*ACS Catal.* 2021, 11, 10239

### Nickel



Piers  
*Dalton Trans.* 2015, 44, 12082

## (B) This Work



- ✓ Excellent Yields (upto 99%)
- ✓ No Additives
- ✓ Accessible Temperatures (90 °C)
- ✓ Large Scope (26 examples)
- ✓ H/D Exchange for  $\alpha$ -deuteration

Fig. 1 (A) Excerpt of the state-of-the-art. (B) Herein reported manganese catalyzed hydration of nitriles.

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hydrogenation<sup>17</sup> and cyano-alkylation of  $\alpha,\beta$ -unsaturated ketones.<sup>15c</sup> Here we present the efficient hydration of a variety of nitriles catalyzed by our previously reported catalyst  $[(PC_{NHC}P)Mn(CO)_2H]$  (Fig. 1B; **1**).<sup>16</sup>

The reaction occurs at moderate temperature (90 °C) and exhibits excellent functional group compatibility. The corresponding amides are isolated in excellent yields and could afterwards be deuterated *via* subsequent H/D exchange. Mechanistic studies indicate a formal Lewis acid catalyzed pathway in which water is reversibly deprotonated, which is further discussed in this report.

We became interested in the hydration of nitriles because of the facile H/D exchange between our previously reported complex **1** and D<sub>2</sub>O (Fig. 2). Addition of 20 equiv. of D<sub>2</sub>O to a solution of  $[(PC_{NHC}P)Mn(CO)_2H]$  (**1**) in THF resulted in the clean formation of  $[(PC_{NHC}P)Mn(CO)_2D]$  (**2**) as judged by <sup>1</sup>H, <sup>2</sup>H, and <sup>31</sup>P NMR spectroscopy (Fig. S1–S3). The H/D exchange suggest that complex **1** can, at least transiently generate hydroxide anions that are beneficial for nitrile hydration as shown by Piers and co-workers.<sup>13</sup> Indeed, our optimization protocol (Table S1) shows that heating a solution of benzyl cyanide in THF or *tert*-butanol in the presence of H<sub>2</sub>O (5 equiv.) and catalyst **1** (1 mol%), resulted in the quantitative formation of 2-phenylacetamide. Using other manganese Lewis acids such as  $Mn(OTf)_2(CH_3CN)_2$ , or other manganese complexes such as  $[(PC_{NHC}P)Mn(CO)_2Br]$  (**3**) or  $[(PC_{NHC}P)Mn(CO)_3][PF_6]$  (**4**), did not result in the formation of any detectable product (Table S1).

With the optimized conditions established, we proceeded to establish the scope of the herein reported hydration reaction with a variety of electronically and sterically differentiated nitriles (Table 1). As shown in Table 1, various electron deficient benzyl cyanides could be converted to their corresponding 2-phenylacetamides **5b–5d** in near quantitative yields (98–99%). Likewise, 2-phenoxyacetonitrile was quantitatively converted to 2-phenoxyacetamide **5e** (Table 1). Besides benzyl cyanides, (substituted) benzonitriles could also be selectively converted to their corresponding benzamides (**5f–5o**). With these substrates, both electron withdrawing groups (*e.g.*, –F, –Cl, –Br, –CF<sub>3</sub>) and electron donating groups (*e.g.*, –OMe) are well tolerated and their corresponding benzamides **5i–5n** were all isolated in excellent yields (Table 1). Functional groups such as ketones (**5o**), alcohols (**5p**) or heteroaromatics (**5p–5s**) were also compatible with our established protocol yielding the corresponding amides in excellent yields. Even simple aliphatic nitriles could be converted to their corresponding amides (**5t–5y**), although sterically encumbered nitriles (**5v** and **5z**) or

nitriles bearing long alkyl chains (**5x**) showed somewhat diminished yields (Table 1).

Compared to Milstein's Mn–PNP pincer catalyst, which hydrates nitriles through a metal–ligand cooperativity,<sup>12</sup> involving ketimido and enamido intermediates, our Mn(I)–PC<sub>NHC</sub>P pincer complex promotes nitrile hydration *via* a Lewis-acid pathway without the need for such cooperativity. As such our system still enables a broad substrate scope and high yields under mild and additive-free conditions. Notably, our approach uniquely enables isotope labeling at the amide stage, where the activated  $\alpha$ -methylene of the amide undergoes selective H/D exchange in the presence of D<sub>2</sub>O and catalyst **1**. For example, 2-phenylacetamide (**5a**) was quantitatively deuterated in THF under mild conditions (Fig. S73 and S74). Whereas Milstein's Mn–PNP system achieves  $\alpha$ -deuteration at the nitrile stage under specific solvent regimes, our Mn–PC<sub>NHC</sub>P catalyst provides a complementary late-stage route, granting practical access to deuterated amides directly from the amide products, providing a green methodology for facile H/D exchange.<sup>18</sup>

With the substrate scope established, we next sought to elucidate the underlying mechanism of the herein reported nitrile hydration reaction. While prior studies on the cyanoalkylation of  $\alpha,\beta$ -unsaturated ketones suggested that complex **1** can activate nitriles at elevated temperatures, such pathways are unlikely here due to the absence of an activatable  $\alpha$ -CH group in many substrates.<sup>15c</sup> Instead, we propose that, based on our H/D exchange experiments (Fig. 2), hydroxide ions are formed upon deprotonation of water by complex **1**. This hypothesis is further supported by the fact that H<sub>2</sub> inhibits the reaction (Scheme S11), suggesting that water activation is crucial in forming the reactive intermediate **I** (Scheme 1).<sup>19</sup> After the initial activation step, the bound nitrile undergoes nucleophilic attack at the nitrile-carbon by the hydroxide ion, forming an imide intermediate (**III**), which tautomerizes to the manganese amide **IV** (Scheme 1). Protonation of intermediate **IV**, releases the amide and regenerates the active catalyst (**I**).

The involvement of **IV** in the herein proposed mechanistic scenario is based on additional control experiments that demonstrated that **IV** could also be isolated after heating a solution of **1** (1.0 equiv.), benzyl cyanide (8.0 equiv.), and excess H<sub>2</sub>O (1.0 mL) in *tert*-butanol, at 90 °C for 48 h. The identity of **IV** was unequivocally established by X-ray crystallography (Fig. 3) and *via* independent synthesis (Fig. S6 and S7). Furthermore, **IV** catalyzes the hydration of benzyl cyanide to 2-phenylacetamide in 95% yield, supporting its role in the catalytic cycle (Scheme S8).

To gain mechanistic insight, we performed detailed kinetic studies on the model reaction of phenylacetonitrile in THF-d<sub>8</sub>. Monitoring substrate consumption at different catalyst loadings revealed exponential decay profiles, and linear fits upon plotting the natural logarithm of the substrate concentration *versus* time, confirming a first-order dependence. Subsequent kinetic studies also established first-order dependence with respect to catalyst, substrate, and H<sub>2</sub>O, affording an overall third-order rate law that does not indicate catalyst saturation behavior (Fig. S9–S11). Furthermore, performing Temperature dependent experiments between 70 and

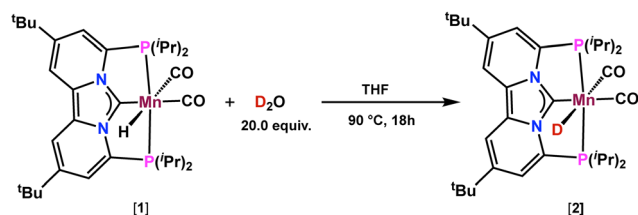


Fig. 2 H/D exchange on manganese complex **1** by D<sub>2</sub>O.



Reaction scheme showing the synthesis of primary amides (5a-5z) from nitriles (R-CN) using 1 (1 mol%), H<sub>2</sub>O, tBuOH, 90 °C, 24h.

Chemical structures of the products (5a-5z) are shown, along with their yields:

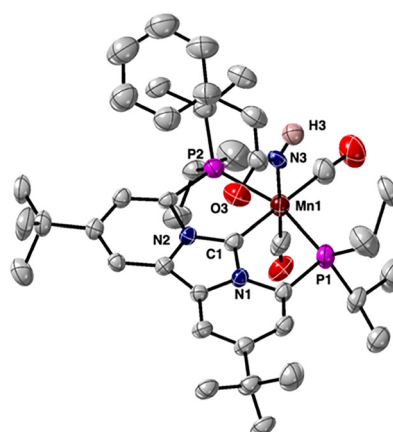
- 5a: 99%
- 5b: 99%
- 5c: 98%
- 5d: 98%
- 5e: 99%
- 5f: 98%
- 5g: 99%
- 5h: 99%
- 5i: 99%
- 5j: 99%
- 5k: 99%
- 5l: 99%
- 5m: 98%
- 5n: 97%
- 5o: 98%
- 5p: 85%
- 5q: 99%
- 5r: 99%
- 5s: 99%
- 5t: 64%
- 5u: 99%
- 5v: 71%
- 5w: 99%
- 5x: 78%
- 5y: 96%
- 5z: 25%

The diagram illustrates a proposed 'pausable mechanism' for the formation of a Mn(I) complex with a diazo ligand. The mechanism proceeds through several steps:

- Complex (I):** A Mn(I) complex with a diazo ligand ( $\text{N}_2\text{C}=\text{R}$ ) and a terminal hydroxyl group ( $\text{OH}^-$ ).
- Complex (II):** A Mn(I) complex with a diazo ligand ( $\text{N}_2\text{C}=\text{R}$ ) and a terminal hydroxyl group ( $\text{OH}^-$ ).
- Complex (III):** A Mn(I) complex with a diazo ligand ( $\text{N}_2\text{C}=\text{R}$ ) and a terminal hydroxyl group ( $\text{OH}^-$ ).
- Complex (IV):** A Mn(I) complex with a diazo ligand ( $\text{N}_2\text{C}=\text{R}$ ) and a terminal hydroxyl group ( $\text{OH}^-$ ).

The mechanism involves the coordination of the diazo ligand to the Mn(I) center, followed by the loss of a terminal hydroxyl group to form a diazo complex. This complex then undergoes further transformations, including the coordination of a terminal hydroxyl group and the loss of a terminal hydroxyl group, leading to the formation of a Mn(I) complex with a diazo ligand and a terminal hydroxyl group.

100 °C yielded activation parameters of  $\Delta G^\ddagger = 26.9 \text{ kcal mol}^{-1}$  and  $\Delta S^\ddagger = -36.1 \text{ cal mol}^{-1} \text{ K}^{-1}$ . The relatively low barrier and large



negative entropy suggest a highly ordered transition state in which substrate, catalyst, and hydroxide are preorganized, consistent with hydroxide attack as the rate-determining step.<sup>6g,20</sup> This hypothesis was further supported by the

observed secondary kinetic isotope effect of  $K_{\text{H}}/K_{\text{D}} = 1.538$  measured with  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$ . The observed secondary kinetic isotope effect also rules out protonolysis of the manganese-amide (**IV**) as the rate determining step, as the  $K_{\text{H}}/K_{\text{D}} = 1.538$  is relatively small.<sup>20</sup> Overall, these kinetic data support the plausible mechanism shown in Scheme 1, involving nucleophilic attack of transiently generated hydroxide ions on the bound nitrile.

In conclusion, we have demonstrated a practical method for accessing amides *via* a manganese catalyzed hydration reaction of the corresponding nitriles. Our methodology is compatible with a wide variety of functional groups and can be applied to a range of aromatic and aliphatic nitriles. By using  $\text{D}_2\text{O}$  the corresponding  $\alpha$ -deuterated amides could be accessed, either *via* hydration of the nitrile, or *via* H/D exchange at the amide. Mechanistic studies involving reaction kinetics, Deuterium-labeling, and intermediate characterization suggest that the manganese-catalyzed hydration reaction proceeds through water deprotonation, followed by nucleophilic attack of the resulting hydroxide ion on the metal-coordinated nitrile.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Associated Professor Graham de Ruiter (graham@technion.ac.il). The published article includes all datasets generated or analyzed during this study.

Supplementary information: Synthetic procedures and characterization data. See DOI: <https://doi.org/10.1039/d5cc02804c>.

CCDC 2451223 [**IV**] contains the supplementary crystallographic data for this paper.<sup>21</sup>

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