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A green and sustainable catalytic protocol for methoxymethylation of primary amides using methanol with dihydrogen release†

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A highly efficient and selective catalytic method for the methoxymethylation of primary amides with the liberation of dihydrogen under Mn(i) catalysis is reported. This marks the first report on the synthesis of *N*-(methoxymethyl)benzamide derivatives, including the synthesis of pharmaceutically important amides through the interrupted borrowing hydrogen (IBH) strategy. The current method showcases a broad substrate scope and utilizes methanol as a methoxy methylating agent and solvent medium. The present unprecedented strategy obviates the need for toxic reagents and multi-step synthesis protocols. Mechanistic, kinetic studies and isotopic labeling experiments were also performed to gain mechanistic insights.

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1. A highly efficient and selective catalytic method for the methoxymethylation of primary amides, with the concurrent liberation of dihydrogen under Mn(i) catalysis, is reported. This represents the first synthesis of *N*-(methoxymethyl)benzamide derivatives, including pharmaceutically significant amides, through the interrupted borrowing hydrogen (IBH) strategy.
2. The method demonstrates a broad substrate scope, utilizing methanol both as a methoxymethylating agent and solvent.
3. This novel approach eliminates the need for toxic reagents and multi-step synthesis protocols, offering a greener and more sustainable alternative. Additionally, the reusability of the homogeneous catalyst is successfully demonstrated.

Nitrogen-containing motifs are pivotal in medicinal chemistry and drug discovery, with over 80% of FDA-approved small molecule drugs incorporating at least one nitrogen atom. This underscores their critical role in pharmaceutical research and development.¹ The development of atom- and step-efficient catalytic methods for functionalizing nitrogen-containing compounds has significantly advanced organic synthesis. Recently, attention has been directed toward simple modifications of nitrogen-containing molecules, such as amines, amides, sulfonamides, and N-heterocycles, which can dramatically influ-

ence the biological and physiological properties of active pharmaceutical compounds.² In this context, the synthesis of *N*-(methoxymethyl) amides, using methanol as a greener C1 building block, is particularly noteworthy. Methanol is widely available, cost-effective, and recognized as a greener liquid organic hydrogen carrier, with an annual global production of around 70 million tons.³ However, significant challenges exist in synthesizing *N*-(methoxymethyl) amides due to the low nucleophilicity of amides and the high activation energy required for methanol dehydrogenation. *N*-(Methoxalkyl)benzamides, important for their presence in natural toxins like pederin and their use in synthetic herbicides, illustrate the broader significance of this motif.⁴ Despite its potential, and to the best of our knowledge, a green and step-economical synthesis method for *N*-(methoxymethyl) amides using methanol has not yet been realized.

In recent years, significant attention has been given to transition metal-catalyzed C-X (X = carbon or a heteroatom) bond-forming reactions through the borrowing hydrogen (BH) or hydrogen auto-transfer (HA) strategy, which is regarded as a highly promising and environmentally friendly method with

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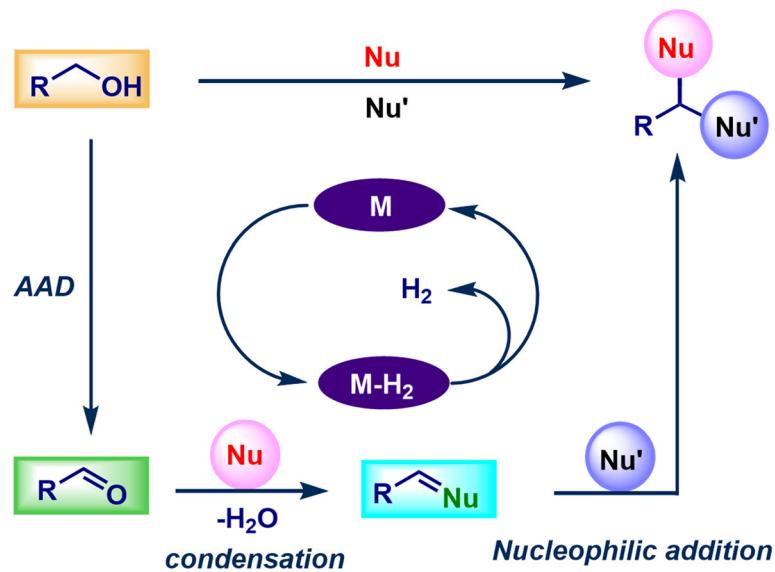


exceptional atom economy.⁵ Numerous studies have highlighted the use of 3d-transition metals in borrowing hydrogen catalysis, particularly in facilitating C–C and C–N bond formation.⁶ In contrast, the interrupted borrowing hydrogen (IBH) strategy remains relatively underexplored and is rarely reported in the field of transition metal catalysis.⁷ The HA/BH strategy begins by dehydrogenating easily accessible alcohols, which then combine with various nucleophilic partners (C or N) to form an unsaturated intermediate. Following this, the intermediate undergoes selective hydrogenation to yield the desired end product. This approach involves borrowing hydrogen from one of the starting materials, primarily alcohols, acting as the hydrogen donor. Conversely, in the IBH strategy, the reduction of unsaturated intermediates is interrupted, enabling the *in situ* conjugate addition of various nucleophiles, ultimately leading to the formation of diversified products.⁸ A limited number of eco-benign synthesis methods for

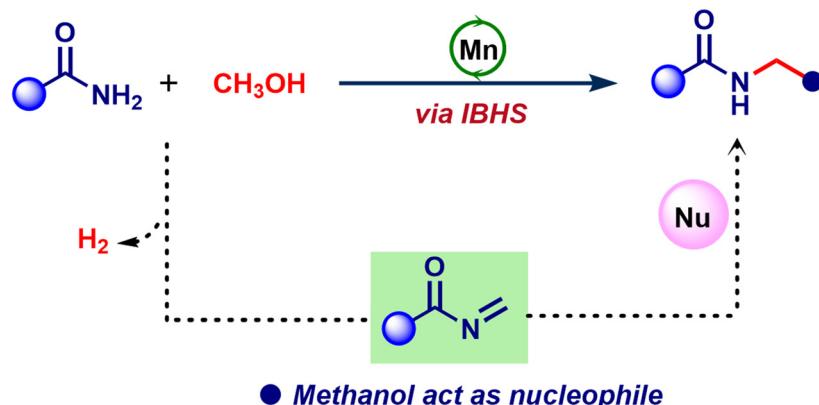
N-methylated amides under transition-metal catalysis *via* the HA/BH approach have been reported.⁹ Herein, we report a highly efficient and selective catalytic method for the methoxymethylation of primary amides using methanol with the liberation of dihydrogen. This marks the first report on the synthesis of *N*-(methoxymethyl)benzamide derivatives through the IBH strategy. The current method showcases a broad substrate scope and operates under molecular Mn-catalysis. Interestingly, we illustrated the extensive utility of this approach by broadening its application to the functionalization of biologically active compounds (Scheme 1).

Recently, molecularly defined PNP-Mn(i) complexes have emerged as significant catalysts in (de)hydrogenation and related transformations.¹⁰ Building on this, we have developed various synthetic organic transformations, including C–C and C–N bond-forming reactions, using a dehydrogenation strategy facilitated by a robust PNP-Mn(i) catalytic system under mild

(a) General scheme of Interrupted borrowing hydrogen (IBH) strategy



(b) Methoxymethylation of primary amides using methanol under Mn-catalysis: *This work*



Scheme 1 (a) General scheme of the IBH strategy, (b) Mn-catalyzed *N*-methoxymethylation of primary amides using methanol.



conditions.¹¹ Inspired by these advancements, we established a novel synthetic approach for the functionalization of nitrogen-containing motifs, such as amides. Specifically, we systematically explored several key parameters for the Mn-catalyzed synthesis of *N*-(methoxymethyl)amide derivatives using methanol (Table 1).

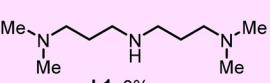
To investigate the [Mn]-catalyzed synthesis of *N*-(methoxymethyl)benzamide, benzamide **1** was chosen as the model substrate. We thoroughly screened various [Mn] catalysts, ligands, bases, solvents, and reaction temperatures (Table 1). After systematic studies, the optimal conditions for this transformation were found to be a catalytic amount of [Mn]/**L7** (5 mol% $\text{Mn}(\text{CO})_5\text{Br}$ and 5 mol% **L7**) along with K_2CO_3 (1 mmol) in methanol (3 mL) at 130 °C (oil-bath temperature). Under these conditions, the desired product **1a** was obtained in an 83% isolated yield (Table 1, entry 1). The product was completely analyzed using GC-MS, HRMS, and NMR spec-

troscopy techniques. The necessity of each compound was systematically studied under standard conditions. It was observed that, under the current Mn-catalyzed conditions, ligands **L5** and **L6** (a two methylene-bridged PNP ligand) produced the desired product **1a**, in decent yield, demonstrating similar reactivity compared to the current phosphine-free NNN ligand system (**L1-L4**). Notably, under the optimized reaction conditions, no product formation (**1a**) was observed in the absence of the [Mn] catalyst and base, and both unreacted starting materials were recovered from the reaction mixture (Table 1, entries 13 and 14). Performing the reaction at 150 °C resulted in a very slight increase in the yield of **1a** (Table 1, entry 12). Among the various [Mn] catalysts screened for the present interrupted borrowing hydrogen (IBH) reaction, freshly prepared $\text{Mn}(\text{CO})_5\text{Br}$ exhibited superior catalytic activity, providing the highest yield of **1a** (Table 1, entries 1-3). Subsequently, we investigated the influence of various bases, and K_2CO_3 was found to be an optimal base for facilitating this reaction (Table 1, entries 1 and 6-8). Thus, K_2CO_3 was identified as the optimal base for this transformation, yielding the maximum amount of **1a** under the optimal reaction conditions (Table 1, entry 1). Notably, a maximum yield of **1a** was achieved by using 1 equivalent of K_2CO_3 (Table 1, entry 15).

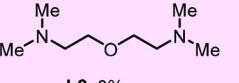
In order to show the generality of the present catalytic protocol, diverse benzamides were reacted with methanol under optimal reaction conditions (Scheme 2). The present catalytic system exhibited excellent tolerance towards a wide array of amides, including aromatic, aliphatic, cyclic, acyclic, conjugated, di- and tri-substituted amides, yielding up to 89% of the corresponding *N*-(methoxymethyl)benzamide derivatives. The present catalytic conditions show excellent reactivity towards amide derivatives containing electron-releasing groups at different positions (especially *para*-, *meta*-, and *ortho*-positions) on the aromatic ring. These substrates yielded the corresponding moderate to good yields (products **1a-3a**, **10a-12a**, and **14a-15a**), with up to 89% isolated yield. Observations revealed that benzyl alcohols substituted with halides, such as *p*-chloro (**4a**), *p*-bromo (**7a**), *p*-iodo (**9a**), *o*-bromo (**13a**) and *m*-iodo (**18a**) groups, yielded the products in moderate yields. Interestingly, *p*-fluoro, *p*-nitro, and *o*-fluoro substituted amides (**5** and **6**) yielded the unsubstituted *N*-(methoxymethyl)benzamide. Indeed, under our standard catalytic conditions, the fluoro and nitro groups underwent an SN_{Ar} -type reaction with methanol. Gratifyingly, benzamides containing amino groups underwent tandem *N*-methylation (*via* the BH strategy) and *N*-methoxymethylation reactions (*via* the IBH strategy) and yielded products **8a** (71%) and **25a** (76%) in very good yields. Furthermore, the cyclic amide, cyclohexyl carboxamide, smoothly underwent *N*-methoxymethylation and yielded the product **16a** in 51% yield. Notably, aliphatic amides, including hexanamide and pivalamide, yielded the corresponding products **19a** and **20a** in yields of 54% and 56%, respectively. Multi-substituted amides (di/tri-substituted; **22a-26a**) with electron-donating groups at various positions yielded the corresponding *N*-(methoxymethyl) substituted products in moderate to good yields. It is noteworthy that the present cata-

Table 1 Optimization of reaction condition^{a,b}

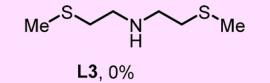
Entry	Reaction conditions	Yield of 1a (%)
1	Standard conditions	83 ^b
2	MnCl_2 instead of $\text{MnBr}(\text{CO})_5$	n.d
3	$\text{Cp}^*\text{Mn}(\text{CO})_3$ instead of $\text{MnBr}(\text{CO})_5$	n.d
4	NiCl_2 instead of $\text{MnBr}(\text{CO})_5$	n.d
5	CoCl_2 instead of $\text{MnBr}(\text{CO})_5$	n.d
6	Cs_2CO_3 instead of K_2CO_3	78
7	KOH instead of K_2CO_3	26
8	KO^*Bu instead of K_2CO_3	42
9	L4 instead of L7	n.d
10	L5 instead of L7	56 ^b
11	L6 instead of L7	32 ^b
12	At 150 °C	84
13	Absence of catalyst	n.d
14	No K_2CO_3	n.d
15	1 eq. of K_2CO_3	65 ^b



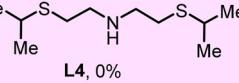
L1, 0%



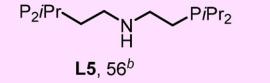
L2, 0%



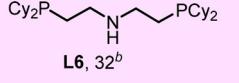
L3, 0%



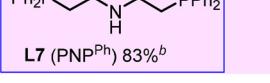
L4, 0%



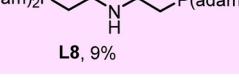
L5, 56^b



L6, 32^b



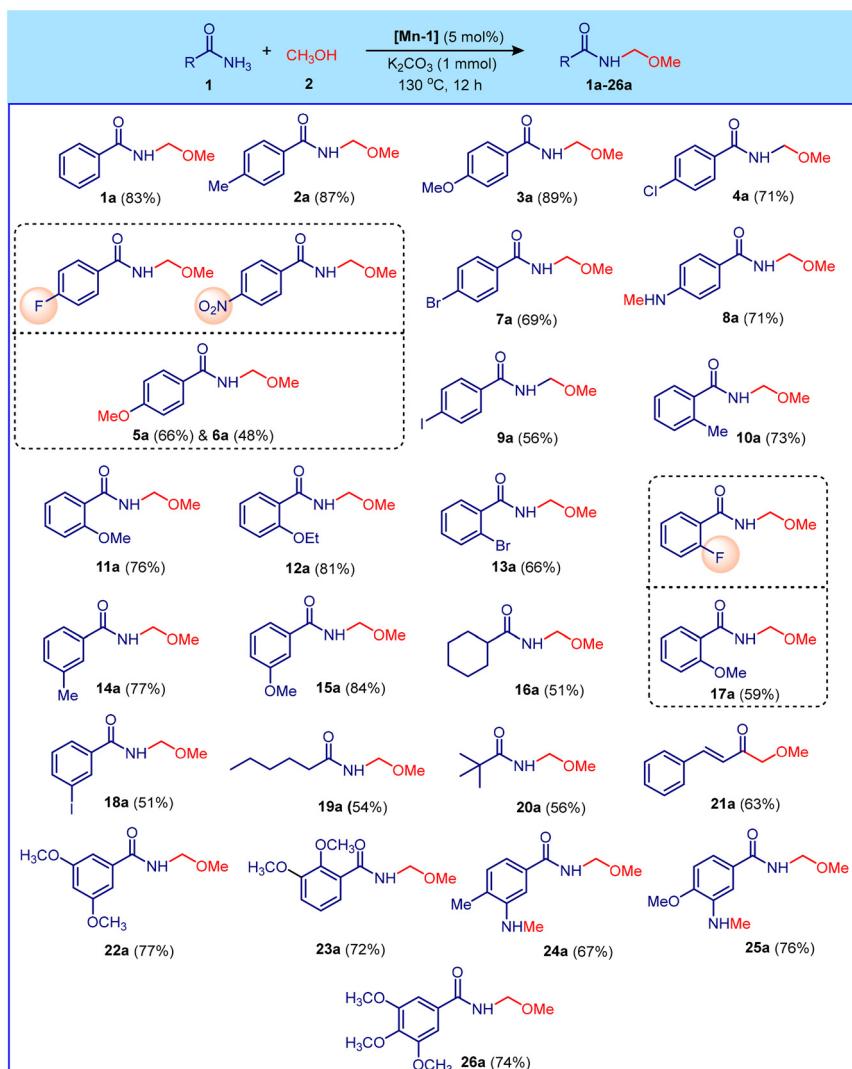
L7 (PNP^{Ph}) 83%^b



L8, 9%

^a Reaction conditions: substrate **1** (0.5 mmol), **2** (3 mL), cat. $\text{Mn}(\text{I})$ (5 mol%), ligand **L7** (5 mol%) and K_2CO_3 (1.5 eq.) were heated at 130 °C (silicone oil bath temperature) for 12 h under an argon atmosphere. Yields were determined with a GC instrument using *m*-xylene as an internal standard. ^b Isolated yield. n.d = not detected.

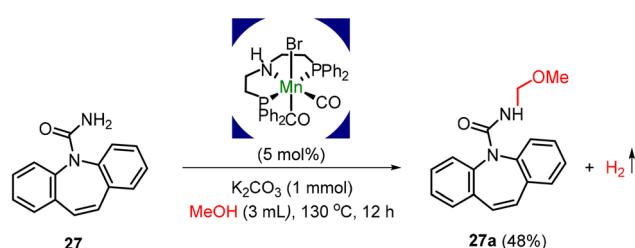




Scheme 2 Manganese catalyzed synthesis of *N*-(methoxymethyl)amide derivatives. Reaction conditions: substrate **1** (0.5 mmol), methanol (3 mL), **[Mn-1]** (5 mol%), and K_2CO_3 (1 mmol) were heated at 130°C (silicone oil-bath temperature) for 12 h under an argon atmosphere. Isolated yield.

lytic system exhibited good tolerance towards cinnamamide, leading to the desired product **21a** (in 63% yield) with a retained olefinic bond. Notably, under the present catalytic conditions, we did not observe any formation of *N*-methylated amide. In most cases, unreacted primary amide was recovered. Thus, the established catalytic protocol is general, efficient, and selective in producing *N*-methoxymethylated amides in moderate to very good yields under eco-friendly, step-economical conditions.

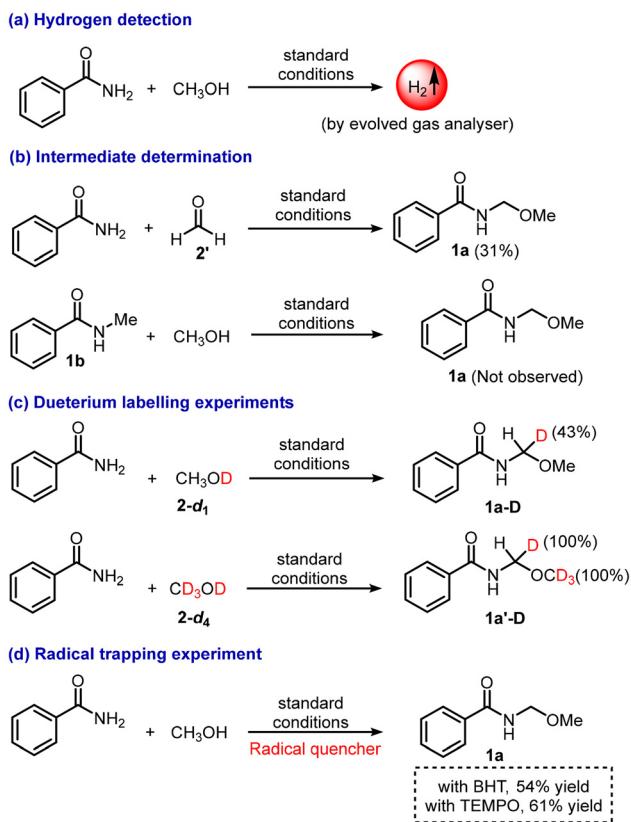
A simple alteration to the structure can significantly alter the physiological and biological properties of nitrogen-containing pharmaceutically active molecules. As a result, subjecting *5H*-dibenzo[*b,f*]azepine-5-carboxamide, **27**, to methanol under standard reaction conditions yielded the corresponding *N*-methoxymethylated product **27a**, isolated in a yield of 48%. The derivatives of *5H*-dibenzo[*b,f*]azepine-5-carboxamide exhibit anticonvulsant effects and possess properties for blocking brain sodium channels (Scheme 3).¹²



Scheme 3 Application of the present protocol: synthesis of pharmaceuticals.

To gain mechanistic insights into the present manganese-catalyzed *N*-methoxymethylation of primary amides using methanol, several control experiments were performed. Initially, the liberation of molecular H_2 from the standard reaction was qualitatively analyzed using an evolved gas analyzer (Scheme 4a). Indeed, when an amide (**1**) was reacted with for-





Scheme 4 Control experiments. Standard conditions: primary amide (0.5 mmol), methanol (3 mL), **[Mn-1]** (5 mol%) and K_2CO_3 (1.5 eq.) heated in an oil bath at 130 °C for 12 h.

maldehyde (**2'**) under the current catalytic conditions in the absence of methanol, the expected product (**1a**) was not obtained. However, in the presence of methanol as the solvent, the expected product was obtained in 31% yield. This result suggests that methanol is indispensable for the reaction and that a slow and steady release of formaldehyde is required for the reaction to proceed (Scheme 4b). Performing the reaction with *N*-methyl benzamide in the presence of methanol did not yield the corresponding *N*-(methoxymethyl) substituted product, suggesting that *N*-methyl benzamide does not act as a reaction intermediate (Scheme 4b). Following this, we conducted deuterium labelling experiments to demonstrate that the reaction proceeds *via* the IBHS mechanism. Subsequently, two separate deuterium labelling experiments were conducted using methanol-d₁ (CH_3OD) and methanol-d₄ (CD_3OD) with benzamide under the current manganese-catalyzed conditions, resulting in the formation of the corresponding deuterium-incorporated products **1a-D** and **1a'-D**. Confirmation of the formation of two distinct products from these experiments highlighted the role of methanol as both a C₁ source and a nucleophile in the reaction, indicating that it follows the IBHS pathway (Scheme 4c). Interestingly, the presence of radical scavengers like TEMPO and BHT resulted in the product being obtained in satisfactory yields. This outcome demonstrates

that the current reaction mechanism deviates from the single electron transfer mechanism (Scheme 4d).

Finally, a kinetic analysis was conducted for the Mn-catalysed synthesis of *N*-(methoxymethyl) benzamide using methanol, as depicted in Fig. 1. The progress of the reaction was monitored using ¹H NMR spectroscopy, and the reaction mixture was analyzed at regular intervals. The time-dependent analysis of product formation revealed complete consumption of benzamide within a span of 8 hours. Additionally, the formation of the methoxymethylated product increased gradually over the course of the reaction. The data presented reflect the average of two separate sets of experiments conducted independently.

Kinetic studies employing the initial rate approximation were conducted to ascertain the order of each substrate for the synthesis of *N*-(methoxymethyl)benzamide using methanol (Fig. 2(A–F)). According to graph [A], as the concentration of **1** increases, the reaction rate exhibits dependence, yielding a positive slope of 1.09 when plotting $\log(\text{rate})$ against $\log(\text{conc. of } \mathbf{1})$. Hence, it indicates that the reaction is first order with respect to the concentration of **1**. Likewise, as the concentration of the base increases, there is no observable alteration in the reaction rate over time. The plot of $\log(\text{rate})$ vs. $\log(\text{conc. of base})$ exhibits a negative slope of 6.4. This indicates that the reaction is not influenced by the concentration of the base. Moreover, the relationship between the reaction rate and various loadings of the manganese catalyst revealed a positive slope of 0.67 when plotting $\log(\text{rate})$ against $\log(\text{conc. of cat.} [\mathbf{Mn-1}])$. This implies a fractional order with respect to the concentration of the Mn catalyst. The rate order of the synthesis of *N*-(methoxymethyl)benzamide using methanol was determined using the initial rate method with various reaction components. The slope of the linear fitting represents the reaction rate. The order of the reaction was then determined by plotting $\log(\text{rate})$ vs. $\log(\text{conc.})$ for a particular component. Hence, the rate of the reaction depends on the concentration of **1** and the concentration of the manganese catalyst and is independent of the concentration of methanol and the base. From the above

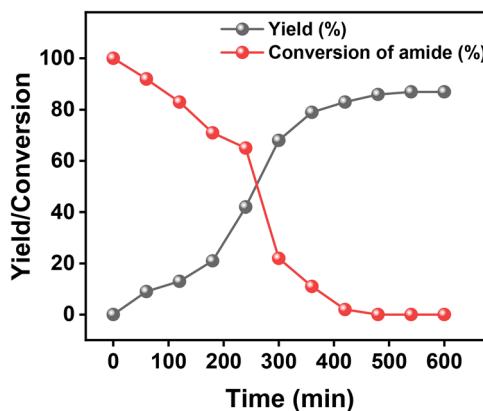


Fig. 1 Kinetic profile for the Mn-catalysed methoxymethylation of benzamide.



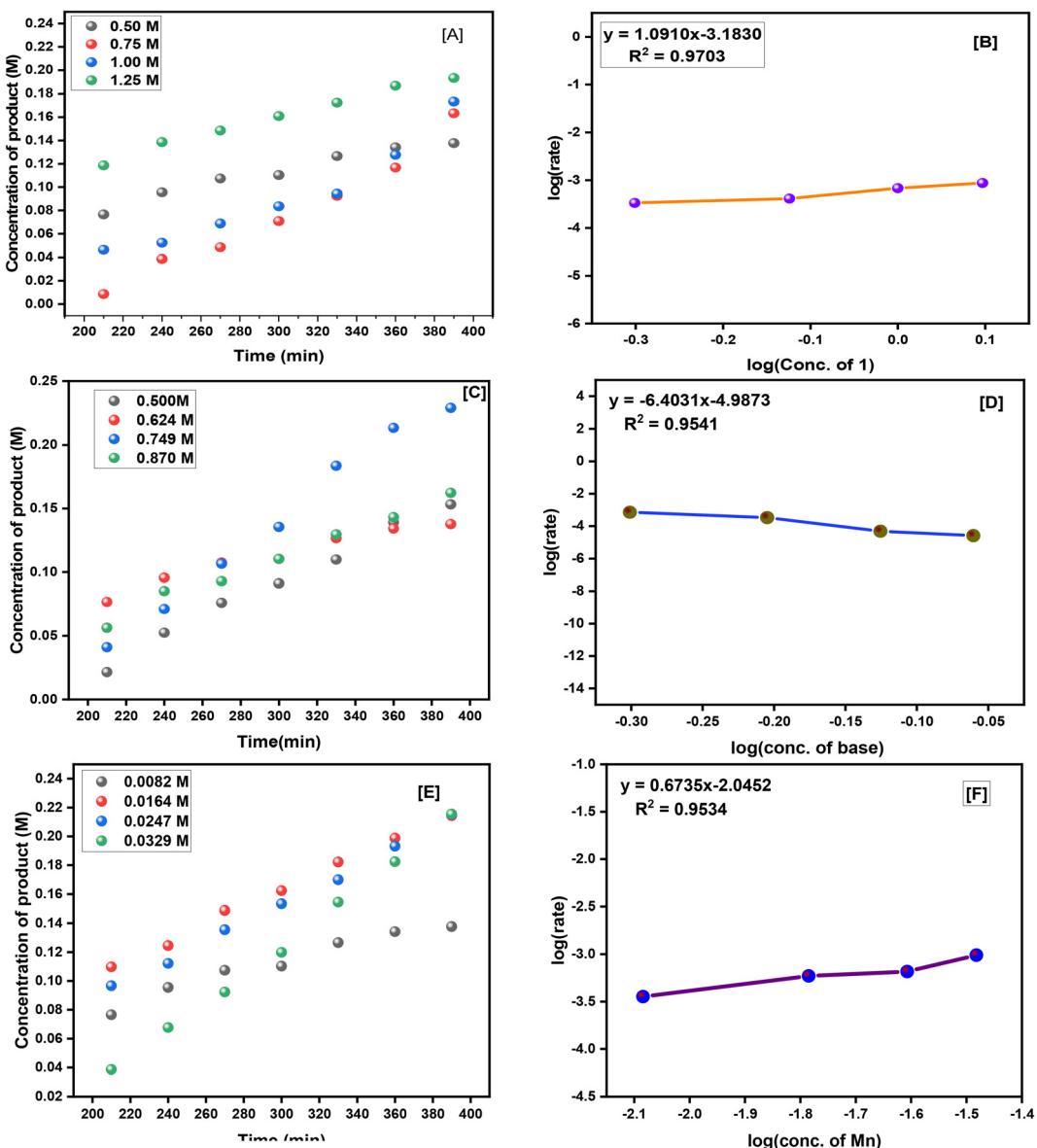


Fig. 2 Kinetic studies. The graph of [A] conc. of product vs. time with increasing conc. of 1. [B] Log (rate) vs. log (conc. of 1). [C] Conc. of product vs. time with increasing conc. of base. [D] Log (rate) vs. log (conc. of base). [E] Conc. of product vs. time with increasing conc. of Mn catalyst. [F] Log (rate) vs. log (conc. of [Mn-1]).

kinetic results, the rate equation for the synthesis of *N*-(methoxy-methyl)benzamide using methanol is as follows:

$$\text{Rate} = k [\text{conc. of 1}]^{1.09} * [\text{conc. of Mn}]^{0.67}$$

The reusability of the homogeneous Mn(1)PNP-catalyzed *N*-methoxymethylation of amides using methanol was effectively demonstrated, as illustrated in Fig. 3. To assess the catalyst's durability, a reaction between benzamide (**1**) and methanol was conducted under standard conditions. Fresh starting materials were periodically added to the reaction mixture every 12 hours, without introducing an additional Mn(1)PNP complex. Remarkably, the desired *N*-methoxymethylated

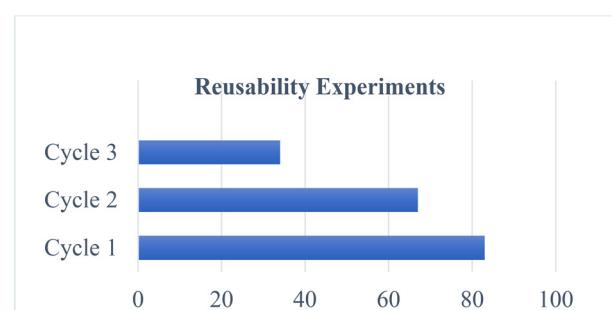


Fig. 3 Recyclability test of the Mn-catalysed *N*-methoxymethylation reaction (of benzamide with methanol).



product (**1a**) was successfully obtained in moderate yield after three reaction cycles. However, a noticeable decline in catalytic activity was observed beyond the third cycle. This reduction in efficiency is likely due to the gradual decomposition of the metal complex. It is worth noting that reports on the reusability of soluble homogeneous catalytic systems, particularly for dehydrogenation and related transformations, are exceedingly rare in the literature.¹³ This study thus highlights a significant step forward in demonstrating the potential for recycling homogeneous catalysts in these types of reactions.

Based on control experiments and the literature,¹⁰ a plausible mechanism is proposed in Scheme 5. Initially, in the presence of a base, precatalyst **I** *in situ* forms the coordinatively unsaturated reactive amido intermediate **II**. Subsequently, methanol activation *via* metal-ligand cooperation (MLC)¹⁴ leads to the formation of a methoxy intermediate **III**. Complex **III** undergoes β -hydride elimination, resulting in the formation of the corresponding carbonyl compound and intermediate **IV**. Alternatively, the initial dehydrogenation process may proceed *via* an outer-sphere mechanism. Upon treatment of the carbonyl compound with benzamide, an *N*-methylene amide intermediate is generated. This intermediate then follows the IBHS pathway, where methanol acts as a nucleophile. The nucleophilic action of methanol interrupts the reduction of the *N*-methylene amide intermediate, facilitating an *in situ* conjugate addition. This process ultimately leads to the formation of an *N*-methoxymethyl amide.

In conclusion, we report the Mn(*i*)-catalyzed unprecedented methoxymethylation of primary amides using methanol. This

reaction proceeds under benign conditions, with hydrogen gas as the only byproduct. Notably, we demonstrate the broad applicability of this innovative approach by extending its use to the functionalization of biologically active compounds. Mechanistic studies and isotopic labeling experiments suggest that the reaction proceeds *via* the IBH strategy.

Data availability

The data supporting this article have been included as part of the ESI.[†]

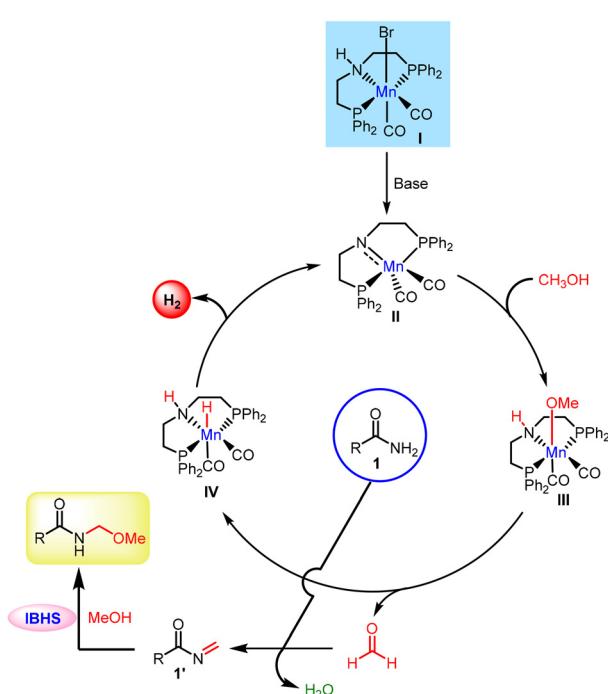
Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Scheme 5 A plausible mechanism for the manganese-catalyzed methoxymethylation of primary amides using methanol with the liberation of dihydrogen.

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