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Efficient and chemoselective imine synthesis catalyzed by a well-defined PN³-manganese(II) pincer system†

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The highly efficient reductive amination of aldehydes with ammonia (NH₃) and hydrogen (H₂) to form secondary imines is described, as well as the dehydrogenative homocoupling of benzyl amines. Using an air-stable, well-defined PN³-manganese(II) pincer complex as a catalyst precursor, various aldehydes are easily converted directly into secondary imines using NH₃ as a nitrogen source under H₂ in a one-pot reaction. Importantly, the same catalyst facilitates the dehydrogenative homocoupling of various benzylamines, exclusively forming imine products. These reactions are conducted under very mild conditions, without the addition of any additives, yielding excellent selectivities and high yields of secondary imines in a green manner by minimizing wastes.

Imines and amines serve as valuable intermediates found in numerous biologically active compounds.¹ In particular, imines find extensive applications as fine chemicals and intermediates within the pharmaceutical and agrochemical industries.^{1c} Traditionally, the synthesis of amine products has involved the reduction of nitrile compounds by employing stoichiometric amounts of metal hydrides, hydrosilanes and boron reagents.² However, these methods generate substantial amounts of waste and thus are not environmentally benign. Recently, there has been a growing interest in utilizing earth-abundant metal complexes for the synthesis of imines from nitriles when compared to their higher congeners.³

Among the 3d transition metals, manganese-catalyzed reactions are in high demand due to their ready availability and

lower toxicity when compared to other transition metals of higher atomic number.⁴ Pincer manganese complexes, in particular, have gained widespread recognition as active and selective catalysts in modern chemistry, particularly for imine synthesis *via* Acceptorless Dehydrogenative Couplings (ADC) of amines and alcohols, as illustrated in (Fig. 1a).⁵ In most of these catalytic reactions, the benign by-products produced are H₂ and H₂O. For instance, the pioneering work by Milstein introduced the use of a lutidine-based PNP pincer manganese(I) complex as a highly efficient catalyst for the ADC of amines and alcohols.^{6,7}

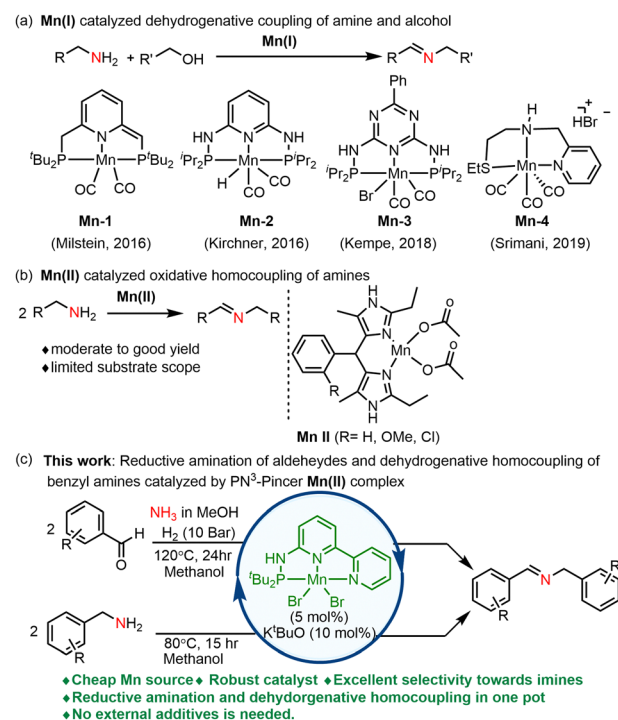


Fig. 1 (a) Previously reported Mn(I) catalyst for the imine synthesis. (b) Previous report on Mn(II) catalyst for the imine synthesis. (c) This work.

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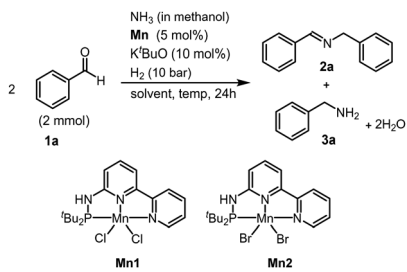


Subsequent advancements in this field include Kirchner's disclosure of PNP manganese complexes ligated with 2,6-diaminopyridine⁸ and Kempe's development of PNP-Mn complexes derived from triazines, allowing for the synthesis of imines with switchable bases.⁹ In 2019, Srimani introduced a phosphine-free Mn(I) complex for ADC of amines and alcohols.¹⁰ However, it is worth noting that the preparation of these catalysts typically involves expensive Mn(I) precursors, such as Mn(CO)₅Br, and often necessitates harsh reaction conditions, including the use of strong bases as additives and high temperatures. More recently, our research group conducted a cost analysis, revealing that Mn(II)-based pincer complexes utilizing MnX₂ (where X = Cl, Br) are more cost-effective than Mn(I) pincer complexes derived from Mn(CO)₅Br precursors for hydrogenation of aldehydes.¹¹ There has been only one report of a Mn(II) complex employed in the oxidative homocoupling of amines to imines, albeit with limited substrate scope and moderate to good yields of imine products (Fig. 1b).¹² Therefore, the use of cheap Mn(II) catalyst precursor and study of ligand environment is crucial to enhance the reactivity of such catalysts is of great interest. Herein, we report an air-stable, well-defined PN³-manganese(II) pincer catalyzed synthesis of imines using various aldehydes and NH₃ in one pot under mild reaction conditions. Notably, under similar reaction conditions, a range of benzylamines undergo dehydrogenative homocoupling, yielding the desired imine products in excellent yields (Fig. 1c).

PN³-pincer complexes are known for their distinctive reactivity attributed to metal–ligand cooperation, particularly with the central pyridine ring bearing an NH arm.¹³ In contrast, PN³(P) pincer complexes exhibit thermodynamic and kinetic properties that set them apart from analogues with CH₂ arms.^{14,15} To the best of our knowledge, the reductive amination of carbonyl compounds with NH₃ is associated with selectivity issues in primary and secondary amines formation and hydrogenation of carbonyl compounds to corresponding alcohols.^{16,17} As previously reported by Jagadeesh and Beller, PNP pincer nickel catalyzed reductive amination of aldehydes with NH₃ afforded primary amines exclusively with minor secondary imine product.¹⁸ Only a few examples involving expensive catalysts based on Rh, Ru, and Ir have been reported for the synthesis of amines from carbonyl compounds and NH₃.¹⁹ Despite these noteworthy achievements, there are currently no reports on the transformation of carbonyl compounds, such as aldehydes, into secondary imines using Mn(II) complexes.

We started our investigation with use of aldehyde as a substrate and ammonia as a nitrogen source. Initially, we considered employing our prepared PN³-manganese(II) pincer complexes, **Mn1** and **Mn2**, as developed by our group.¹¹ The initial reaction was carried out using benzaldehyde as a model substrate, NH₃ in methanol (3.0 equiv.) under H₂ (5 bar) using **Mn1** catalyst (3 mol%) in methanol as the solvent. This led to the formation of the imine product, **2a**, in a 71% yield, accompanied by the production of benzylamine, **3a**, at a 10% yield (Table 1, entry 1). NMR and GC analysis confirmed that benzylamine could serve as an intermediate during the reaction, subsequently undergoing dehydrogenative homocoupling to exclusively form the imine product. Gratifyingly, increasing the catalyst loading from 3 mol% to

Table 1 Optimization of the reaction conditions for the reductive amination of aldehydes^a



| Entry | Mn (mol%) | Solvent | T (°C) | Conv. (%) | Yield ^b (2a , 3a) |
|----------------|------------|---------|--------|-----------|--|
| 1 | Mn1 | MeOH | 120 | 75 | 71, 10 |
| 2 ^c | Mn1 | MeOH | 120 | 89 | 83, 5 |
| 3 | Mn1 | Toluene | 120 | 70 | 71, 2 |
| 4 | Mn2 | MeOH | 120 | 100 | 93, 5 |
| 5 | Mn2 | Toluene | 120 | 75 | 71, 2 |
| 6 | Mn2 | THF | 100 | 60 | 55, 4 |

^a For the reaction, benzaldehyde (2.0 mmol), **Mn cat** (3–5 mol%), K^tBuO (10 mol%), NH₃ in methanol (6.0 mmol) and H₂ (5 bar) were heated in an autoclave. ^b Determined by GC-MS using mesitylene as an internal standard and NMR yields using mesitylene as an internal standard. ^c The 5.0 mol% catalyst is used.

5 mol% significantly improved both the conversion and yield of **2a** (83%, Table 1, entry 2). Exploring alternative solvents, such as toluene, resulted in a decrease in imine product yield (71%, Table 1, entry 3, see ESI,† Table S1). When the reaction was performed using **Mn2** catalyst under the same reaction conditions shown in entry 1, to our delight, the imine product was obtained with an excellent yield, indicating the superior activity of **Mn2** catalyst over **Mn1** (Table 1, entry 4). The screening of other solvents such as toluene and THF, dropped in conversion and yield respectively (Table 1, entries 5 and 6). Using MeOH, good conversion was observed (Table S1, entry 5, ESI†). The lower conversion was observed when the reaction temperature was reduced to 80 °C (Table S1, entries 6 and 7, ESI†). Without a catalyst, only a trace amount of benzylamine was detected in GC-MS (see ESI,† Table S1). Performing the reaction using other alcohols provided good conversion of the products (Table 1, entries 10 and 11). Under high hydrogen pressure (35 bar) and prolonged reaction times, hydrogenated imine products were formed (Table 1, entry 12).

Using the standard reaction conditions, we systematically explored the substrate scope of aldehydes. A range of aromatic aldehydes, including those bearing electron-withdrawing substituents such as halogens (F, Cl, Br) at the *para* position, readily yielded imine products in exceptional yields (Table 2, entries 1–5). In the case of the hydrogenation of 4-(dimethylamino)benzaldehyde, an imine product was obtained with a 76% yield, alongside some unreacted substrate (Table 2, entry 6). Employing 1-naphthaldehyde as the substrate resulted in the formation of the corresponding imine with an excellent yield (Table 2, entry 7).

We then expanded our investigation to include aldehyde substrates containing heteroatoms. Notably, when the reaction utilized picolinaldehyde under analogous conditions, the imine product was formed without altering the pyridine ring's involvement during the reaction course (Table 2, entry 8). The sulfur-containing



Table 2 Optimization of the reaction conditions for the reductive amination of aldehydes^a

| Entry | Substrate | Product | Yield ^b (%) |
|-------|-----------|---------|------------------------|
| 1 | | | 90 |
| 2 | | | 92 |
| 3 | | | 91 |
| 5 | | | 88 |
| 6 | | | 76 |
| 7 | | | 91 |
| 8 | | | 68 |
| 9 | | | 65 |
| 10 | | | 88 |

^a For the reaction, aldehyde (2.0 mmol), NH₃ in methanol (3.0 equiv.), **Mn2** (3 mol%), K^tBuO (10 mol%), H₂ (10 bar) in benzene (1.0 mL).

^b Isolated yields.

aldehyde, thiophene-2-carbaldehyde, proved to be a suitable substrate for conversion into an imine product with a moderate yield (Table 2, entry 9). Additionally, other aldehydes derived from feedstock, such as furfural, efficiently underwent this transformation, resulting in good yields of imine products (Table 2, entry 10).

As we performed the sequential reductive amination of aldehydes with NH₃ and dehydrogenative homocoupling of amines formed *in situ* to corresponding secondary imine product in one pot. During these chemical transformations, the amine species acted as an intermediate reactant, prompting us to investigate the potential utility of amines as primary substrates in our protocol. A dehydrogenative homocoupling of amines was previously reported by us using PN³P-Ru pincer catalysts *via* the aromatization–dearomatization of the NH arm of the PN³P ligand.^{13b} Therefore, we also commenced our study with benzylamine as a substrate.

Following a thorough screening of reaction conditions (Table S2, see ESI[†] for details), we determined that 3.0 mol% of **Mn2** catalyst at 80 °C in methanol solvent provided optimal conditions for synthesizing imines with excellent yields. Subsequently, we explored various benzylamine substrates. In the cases involving electron-withdrawing groups, such as *para*-trifluorocarbon-substituted benzylamine, the imine product

was obtained in a very good yield (Table S4, entry 1, ESI[†]). Likewise, methyl-substituted (*m,p*-CH₃) benzylamines underwent reductive homocoupling to yield the imine product with higher yields (Table S4, entries 2 and 3, ESI[†]). The bulkier *tert*-butyl group (^tBu) at the *para*-position of benzyl amine found to be a suitable substrate for this conversion gives an excellent yield of imine product (Table S4, entry 4, ESI[†]). We further examined whether electron-donating groups attached to benzylamine would impact this transformation. In the case of methoxy (*m,p*-OCH₃) functionalized benzylamines, imine products were obtained in good yield while preserving the integrity of the methoxy group (Table S4, entries 5 and 6, ESI[†]).

To gain insights into the underlying mechanism, we conducted a series of control experiments. Firstly, we initiated a reaction employing benzyl alcohol, a substrate we had previously reported to undergo hydrogenation to an aldehyde using the **Mn2** catalyst.¹¹ Upon completion of this reaction, no benzylamine product was detected, indicating that alcohol formation did not occur during the process (Scheme S3-3a, ESI[†]). In a separate experiment, we arranged a reaction employing both benzyl alcohol and benzylamine to investigate the possibility of a dehydrogenative coupling between alcohol and amine. However, no imine product was formed, effectively ruling out the occurrence of cross-coupling products (Scheme S3-3b, ESI[†]). Lastly, we conducted a reaction using equimolar amounts of two distinct aldehydes, namely benzaldehyde and *p*-tolualdehyde, under the standard reaction conditions. This resulted in the detection of a mixture of three products through GC-MS and ¹H-NMR analysis, yielding **2a** (28%), **2i** (20%), and **5a** (40%), respectively. This experiment underscored the versatility of our protocol for synthesizing secondary imines from two different benzaldehydes (Scheme S3-3c, ESI[†]).

Based on our experimental findings and insights derived from previous literature, **Mn2** may initially undergo dearomatization upon exposure to ^tBuOK, leading to the formation of a dearomatized Mn species which is likely to be converted to a manganese hydride species, **Mn2-H** (see S4 in ESI[†] for the scheme of a plausible mechanism).^{20,21} In the subsequent step, the reaction between benzaldehyde and NH₃ results in an arylmethanimine intermediate that can then proceed to undergo hydrogenation, yielding benzylamine, which can be dehydrogenated, concomitantly releasing H₂ molecules, in an equilibrium. In the final step, the dehydrogenative coupling of benzylamine and benzaldehyde or arylmethanimine leads to the formation of the homocoupled imine product, accompanied by the elimination of water or ammonia, respectively.^{13b}

In conclusion, we have successfully developed a highly efficient PN³-Mn pincer catalyst for the reductive amination of aldehydes using ammonia under mild reaction conditions and a hydrogen atmosphere (10 bar). This method allows for the facile conversion of various aldehydes into secondary imines, utilizing ammonia as a nitrogen source, with the concomitant generation of water as a byproduct. Furthermore, this protocol has been extended to diverse benzylamines, facilitating their oxidative homocoupling to yield imines with outstanding yields. Notably, these reactions are conducted under exceptionally mild conditions, obviating the need for additional additives. Importantly,



this methodology exhibits broad applicability, ensuring the synthesis of imine products without the formation of mixtures comprising primary, secondary, and tertiary amine products or aldehyde reduction products. Further mechanistic investigations on the elucidation of the role and oxidation state of Mn complexes are ongoing and will be reported in due course.

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Conflicts of interest

The authors declare no competing financial interest.

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