RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2024, **14**, 12978

Development of an imidazole-based *N,N*-bidentate ligand for the manganese catalyzed direct coupling of nitriles with alcohols†

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Received 1st February 2024
Accepted 15th April 2024

DOI: 10.1039/d4ra00817k

rsc.li/rsc-advances

3d-Metal catalyzed borrowing hydrogen (BH) reactions represent powerful and environmentally friendly approaches for the direct coupling of alcohols with nitriles to assemble various important branched nitriles. The development of simple and efficient ligands is a crucial issue in this field. In this study, we designed a series of readily available *N,N*-bidentate ligands that demonstrated good efficiency in the Mn-catalyzed BH reaction of alcohols and nitrile derivatives, yielding the targeted nitriles in moderate to good yields. Remarkably, the mildness and practicality of this protocol were further demonstrated by the successful synthesis of anipamil *via* a two-cascade borrowing hydrogen procedure.

Introduction

α-Alkylated nitriles are not only widely present in numerous biologically active molecules, pharmaceuticals, and light-emitting diodes but also serve as versatile building blocks for the synthesis of diols, lactones, lactams, amino alcohols, and cyclic amine derivatives.[1–4] Considering the significant importance of these scaffolds, tremendous efforts have been dedicated to developing efficient methodologies for α-alkylated nitriles. Traditionally, a general approach for accessing these compounds involved the condensation of nitriles with ketones, aldehydes, or alkyl halides under strong base-promoted conditions.[5,6] However, this traditional strategy faced a significant challenge in overcoming multiple side reactions, such as self-condensation of the nitriles, the aldol reaction, or the Cannizzaro reaction. It also needed to expand the functional group tolerance towards stoichiometric strong bases while avoiding the generation of copious wastes. Alternatively, the borrowing hydrogen (BH) strategy, using alcohol as an efficient alkylating agent, offers an atom-economical and environmentally benign tool for constructing new C–C bonds with water as the sole byproduct.[7] A breakthrough in this field was made by Grigg and co-workers in 1981, who reported a ruthenium-catalyzed alkylation of nitriles with alcohols to deliver α-alkylated nitriles.[8] Since then, several other noble metals such as Ir,[9] Rh,[10] Os[11] and Ru[12] have been successfully employed as efficient catalysts in the direct coupling of nitriles and alcohols. However, considering the toxicity, cost, and limited availability of noble metals, the development of abundant first-row-transition metal catalysts (Fe,[13] Co,[14] Ni,[15] Mn[16]) has become a highly attractive strategy to reduce the use of noble metals in homogeneous catalysis.

Manganese, the third most abundant transition metal in the earth's crust, has emerged as an efficient catalyst in borrowing hydrogen (BH) reactions, replacing precious metals (Scheme 1). In 2018, Maji and co-workers introduced a phosphine-free bidentate ligand derived from the condensation of thiophen-2-yl ketone and pyridine-containing hydrazine.[16a] They applied this ligand in the first Mn-catalyzed α-alkylation of aryl nitriles with alcohols. Soon after, the groups of Reuping and El-Sepelgy demonstrated the utility of the Mn-PNP complex for the same reaction, synthesizing a diverse range of substituted alkylated nitriles.[16b] Notably, the PNP ligand's instability due to the easy oxidation of P(III) to P(V) was recognized. Recently, Mukherjee's group identified a simple Mn catalyst, generated *in situ* from $Mn(CO)_5Br$ and 2,2′-bipyridine, for this reaction, albeit with high catalyst loading and a narrow substrate scope.[17] Despite the significant advances in Mn-based catalytic systems for α-alkylation of aryl nitriles, the discovery of a cheap and efficient Mn catalyst remains a great challenge.

In our previous work, we developed several powerful imidazole-based tridentate ligands for Mn-catalyzed asymmetrical hydrogenation of various ketones, leading to highly enantioenriched alcohols.[18] Recognizing the crucial role of the imidazole moiety in these ligands, we envisioned that combining the imidazole group with another nitrogen component could yield a readily available and efficient ligand for Mn-

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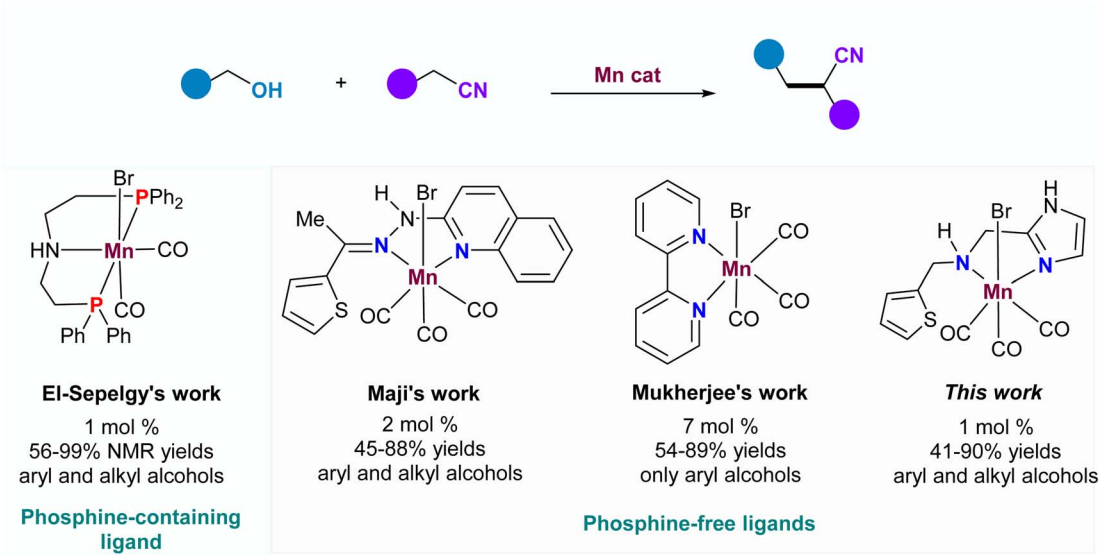
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of all the compounds. See DOI: https://doi.org/10.1039/d4ra00817k

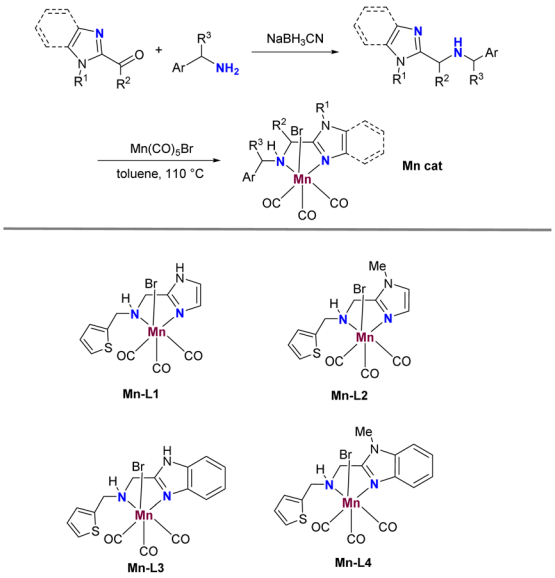


Scheme 1 Manganese catalyzed α-alkylation of nitriles with alcohols.

catalyzed α-alkylation of aryl nitriles with alcohols. Herein, in our continuous interest in this field,[19] we report a simple imidazole-based *N*,*N*-bidentate ligand-assisted Mn-catalyzed efficient synthesis of α-alkylated nitriles through a BH process. This protocol demonstrates a broad substrate scope with good functional tolerance at low catalyst loading (26 examples, 41–90% yields) and is applicable in the total synthesis of anipamil.

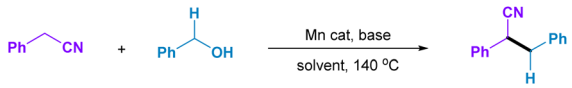
Results and discussion

The currently developed imidazole-based *N*,*N*-bidentate ligands **L1–L4** can be easily obtained in yields ranging from 47% to 65% by treating imidazole aldehydes or ketones with amines in MeOH under reductive conditions (Scheme 2). Subsequently, the Mn catalysts **Mn-1–Mn-4** are prepared by coordinating $Mn(CO)_5Br$ with **L1–L4** in toluene at reflux. With these catalysts in hand, our studies commenced by screening them for the α-alkylation of benzonitrile with benzyl alcohol (Table 1). Initially, the screening of Mn catalysts revealed that NH unprotected imidazole ligands provided better yields compared to those



Scheme 2 Synthetic route for the novel Mn catalyst.

Table 1 Optimization of reaction conditions[a]

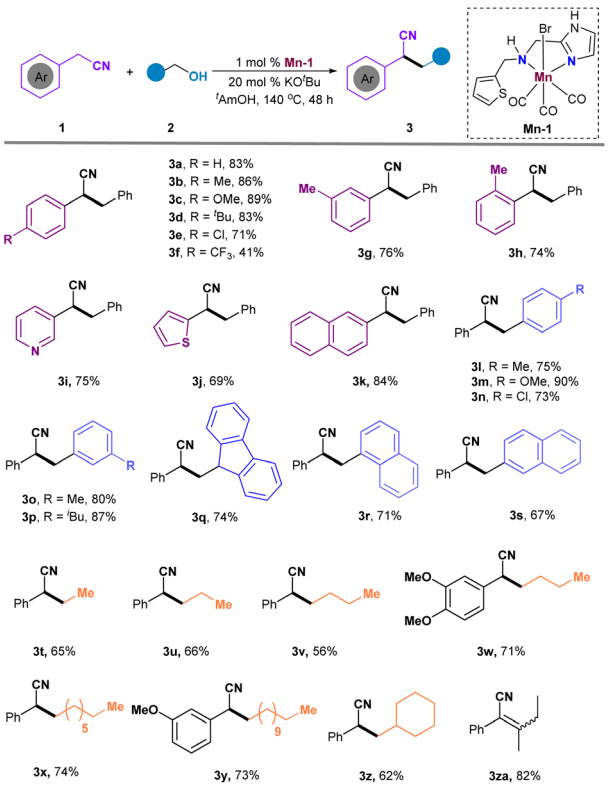


Entry	Cat.	Base	Solvent	Yield[b] (%)
1	**Mn-1**	KO^{t}Bu	^{t}AmOH	75
2	**Mn-2**	KO^{t}Bu	^{t}AmOH	35
3	**Mn-3**	KO^{t}Bu	^{t}AmOH	70
4	**Mn-4**	KO^{t}Bu	^{t}AmOH	41
5	**Mn-1**	KO^{t}Bu	Toluene	62
6	**Mn-1**	KO^{t}Bu	Xylenes	64
7	**Mn-1**	KO^{t}Bu	^{t}BuOH	63
8	**Mn-1**	KO^{t}Bu	THF	21
9	**Mn-1**	KO^{t}Bu	1,4-Dioxane	43
10	**Mn-1**	^{t}BuOLi	^{t}AmOH	15
11	**Mn-1**	^{t}BuONa	^{t}AmOH	46
12	**Mn-1**	AcONa	^{t}AmOH	30
13	**Mn-1**	KOH	^{t}AmOH	59
14[c]	**Mn-1**	KO^{t}Bu	^{t}AmOH	72
15[c,d]	***Mn-1***	***KO^{t}Bu***	***^{t}AmOH***	***83***
16	—	KO^{t}Bu	^{t}AmOH	Trace
17[c,d,e]	**Mn-1**	KO^{t}Bu	^{t}AmOH	78

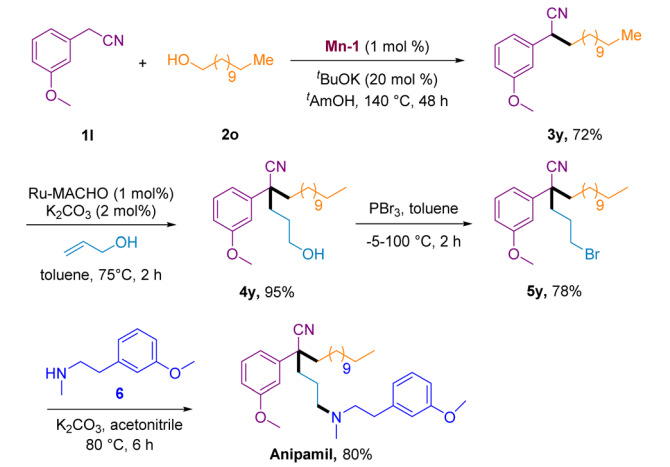
[a] General conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), **Mn cat.** (2 mol%), ^{t}BuOK (20 mol%) were dissolved in *t*-AmOH (1.5 mL) and heated to 140 °C for 36 h. [b] Isolated yield. [c] 1 mol% of **Mn-1** was used. [d] Stirred for 48 h. [e] 10 mmol scale.

protected by a methyl group, and **Mn-1** emerged as the optimal catalyst for this reaction (Table 1, entries 1–4). A subsequent examination of solvents showed that ^{t}AmOH yielded better results than others (Table 1, entries 5–9). Moreover, bases containing potassium resulted in higher yields than those with lithium and sodium, with KO^{t}Bu proving to be the best base, offering **3a** in a 75% yield (Table 1, entries 10–13). Additionally, a slight decrease in yield was observed when reducing the catalyst loading from 2 mol% to 1 mol% (Table 1, entry 14). Fortunately, extending the reaction time to 48 h with 1 mol% of **Mn-1** showed improved conversion, yielding the desired **3a** in 83% (Table 1, entry 15). As expected, the reaction failed to yield α-alkylated nitrile without the presence of **Mn-1** (Table 1, entry 16). Notably, the reaction could be successfully conducted on a 10 mmol scale, yielding **3a** in 78% (Table 1, entry 17).

With the optimized reaction conditions established, our focus shifted to exploring the substrate scope for accessing α-alkylated nitriles (Scheme 3). Initial examination of aryl rings adjacent to the nitrile group revealed that electron-donating substituents on benzene rings (Me-, CH_3O-, and ^{t}Bu-) provided higher yields (**3b**, 86%; **3c**, 89%; **3d**, 83%) compared to the electron-withdrawing group (**3f**, 41%). Importantly, halide groups like chlorine were retained under the reaction conditions, yielding product **3e** in an acceptable yield. The substituent position had minimal impact on the reaction outcomes; *ortho*-substituted aryl nitrile showed lower yield than those with *meta*- or *para*-substituents (**3a**, 83% *vs.* **3g**, 76% *vs.* **3h**, 74%). Additionally, heteroaryl-substituted nitriles were compatible, delivering products **3i**, **3j**, and **3k** in 69–84% yields. A variety of aromatic primary alcohols were screened, showing no significant electron and steric effects and producing the targeted products **3l**-**3p** in moderate to good yields. Fluorenyl and naphthyl groups were also tolerated, generating the desired **3q**–**3s** in 67–74% yields. The reaction proceeded smoothly with primary alkyl alcohols, yielding **3t**–**3z** in moderate to good yields. Unfortunately, when the primary alcohol is changed to a secondary alcohol, the hydrogenation product cannot be obtained, but the dehydrogenation product **3za** can be obtained in 82% yield.



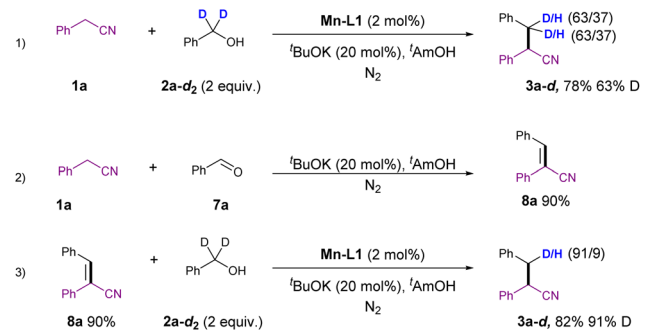
Scheme 3 Substrate scope.



Scheme 4 Total synthesis of anipamil.

To showcase the scalability and utility of this method, we applied it to the synthesis of the calcium channel blocker anipamil (Scheme 4). Initially, a 5 mmol scale of 3-methoxyphenylacetonitrile **1y** underwent a **Mn-1**-catalyzed BH reaction with 1-dodecanol to yield secondary nitrile **3y** in 72% yield after 48 h. Subsequently, the second BH coupling reaction of **3y** with propylene alcohol, enabled by a Ru-MACHO catalyst, proceeded smoothly to generate tertiary nitrile **4y** in 95% yield. The bromination of nitrile **4y** with PBr_3 led to the formation of **5y** in 78% yield. Finally, the nucleophilic attack of **6** on **5y** resulted in the generation of the calcium channel blocker anipamil in an 80% yield.

A series of control experiments were conducted to gain a preliminary understanding of the reaction mechanism, as depicted in Scheme 5. Firstly, the reaction of **1a** with deuterated benzyl alcohol **2a-*d*$_2$** resulted in the formation of deuterated



Scheme 5 Control experiments.

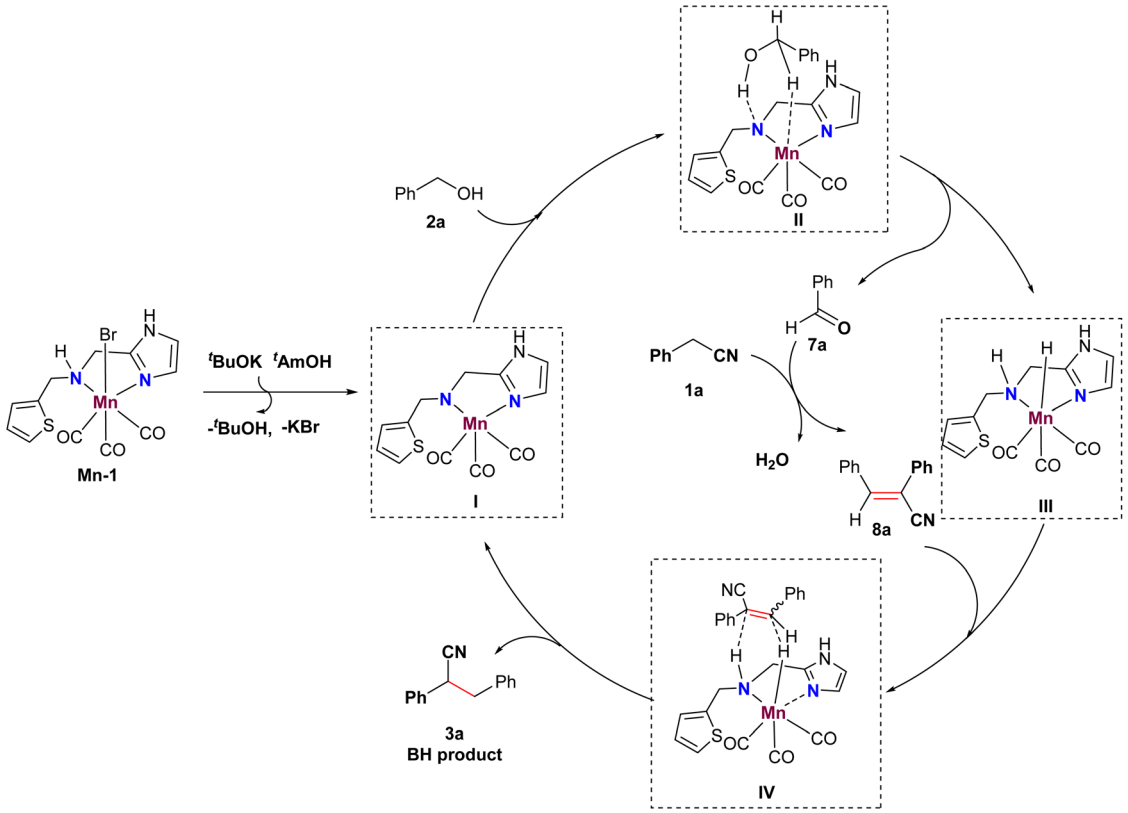


Fig. 1 Plausible reaction mechanism.

product **3a-*d*** in 78% yield, with a 63% deuteration at the β-position of the nitrile group. This implies that the hydride originated from the alcohol **2a-d_2** (Scheme 5(1)). Subsequently, the condensation of **1a** with benzaldehyde led to the formation of unsaturated aryl nitrile **8a** in 90% yield. This intermediate was successfully reduced to **3a-*d*** in 82% yield, with 91% deuteration under standard conditions using deuterated benzyl alcohol **2a-d_2** as a hydrogen transfer reagent (Scheme 5(2) and (3)). These experiments suggested that the aldehyde may be the key intermediate in this reaction, further confirming that the hydrogen source comes from the alcohol.

Based on these observations and previous literature,[20] we propose a plausible mechanism illustrated in Fig. 1. Initially, an active Mn catalyst **I** is formed with the assistance of a base, initiating the dehydrogenative process of alcohol **2a** to produce aldehyde **7a**, along with Mn-D species **III** through a six-membered Mn complex **II**. Subsequently, aldehyde **7a** and phenylacetonitrile **1a** undergo a Knoevenagel-type condensation to yield α,β-substituted acrylonitriles **8a**. Finally, the Mn-D species **III** facilitates the reduction of acrylonitriles **8a** *via* a transient state **IV**, leading to the formation of nitrile **3a** and the regeneration of active Mn catalyst **I**.

Conclusions

In conclusion, we have developed a series of novel *N*,*N*-bidentate ligands for the Mn catalyzed borrowing hydrogenation of alcohols with nitriles. This procedure featured a broad substrate scope with a good functional tolerance under simple conditions to provide the secondary nitriles in moderate to good yields (26 examples, 41–90% yields). Remarkably, the mildness and practicality of this protocol was further demonstrated by the synthesises of anipamil *via* two-cascade borrowing hydrogen procedure. Mechanistic studies were also conducted, which confirmed that the hydride came from the alcohol and aldehyde was the key intermediate. The present cheap metal-catalyzed mild, general strategies are expected to be of high interest to scientists in academia and industry.

Experimental

General procedure for the synthesis of α-alkylated nitrile

To a mixture of **Mn-1** catalyst (1 mol%), KO^{t}Bu (0.2 eq.), nitrile (1.0 mmol) and primary alcohol (0.5 mmol), 1.5 mL of ^{t}AmOH was added. Then, the reaction was stirred under Ar in a pressure tube (ACE pressure tube, 15 mL). The reaction was stirred at 140 °C for 48 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL) for three times. The combined organic layers were washed by brine and dried over magnesium sulfate and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20 : 1–10 : 1) to give the desired product.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 22078298, 22178315 and 22378363), Fundamental Research Funds for the Provincial Universities of Zhejiang (No. RF-B2023008), Natural Science Foundation of Zhejiang Province (No. LQ24B060008) and key research and development program of Zhejiang Province (No. 2023C03117) for financial support.

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