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Phosphine Free Mn-complex catalysed dehydrogenative C-C and C-Heteroatom bond formation: a sustainable approach to synthesize quinoxaline, pyrazine, benzothiazole and quinoline derivatives†

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Herein first sustainable synthesis of quinoxalines, pyrazines and benzothiazoles catalysed by phosphine free Mn(I) complex via acceptorless dehydrogenative coupling (ADC) is reported. This method is also applied successfully to synthesize quinolines via dehydrogenation (removal of H_2) and condensation (removal of H_2O) reaction between 2-aminobenzyl alcohols and secondary alcohols.

In the context of rapid depletion of fossil fuel and growing awareness towards environmental safety as well as economic benefits, the development of atom economical, environmentally benign catalytic reactions using alternative raw material is presently an area of intense research. In this perspective, acceptorless dehydrogenative coupling (ADC) reaction is an extremely powerful approach to synthesize a diverse range of useful building blocks. Abstraction of hydrogen atoms from the adjacent atomic position of an organic substrate is a thermodynamically uphill process. This is usually attained by stoichiometric amount of oxidant or H_2 acceptor and hence result in generation of copious waste. Thus, ADC and hydrogen autotransfer (HA) reactions are well-recognized sustainable process[1-2] as it does not need any external oxidant or prefunctionalization of substrates.

Nitrogen-containing heterocycles have attracted significant attention, as they are present in a large number of bioactive molecules,[3] natural products,[4] drugs,[5] vitamins,[6] agrochemicals,[7] dyes[8] and flavors.[9] Thus, there is a growing interest to develop new sustainable, one-pot synthetic strategies for the preparation of diversely functionalized heterocyclic compounds. Very recently, ADC approach has been largely applied to synthesize a wide range of heterocyclic compounds.[10] A ruthenium catalysed sustainable synthesis of pyrrole directly from 1,4-diol and amines was developed by Crabtree and co-workers.[11] In 2013, methods to synthesize diversely substituted pyrrole or pyridine derivatives catalysed by iridium or ruthenium complex were developed by the group of Kempe,[12] Milstein[13] and Saito.[14] In the same year, Beller and co-workers also developed an efficient and selective synthesis of pyrroles via three-component coupling catalysed by ruthenium.[15] Subsequently, noble metal catalysed synthesis of a wide variety of heterocycles are reported.[16] Despite the high significance of these classical methods employing noble metal, the development of environmentally benign, earth-abundant 3d transition metal catalyst is extremely desirable in terms of sustainability and cost-effectiveness. Of late, cobalt pincer complexes have been effectively applied to synthesize different N-heterocycles.[17]

Although manganese is found to be the third most abundant transition metal[18] in the earth's crust, the catalytic de(hydrogenative) reactions with manganese is still in its nascent stage.[19] The seminal work on manganese catalysed ADC reactions reported by the group of Milstein,[20] Beller[18,21] Kirchner[22] and Kempe[23] triggered an upswing in the advancement of manganese catalysed sustainable synthesis of complex organic molecules.[24] However, the application of Mn-complex towards the synthesis of heterocycles from biomass-derived starting materials is rare. Very recently, manganese catalysed synthesis of N-heterocycles such as pyrrole,[25] pyrimidine and quinoline was described by the group of Kirchner [22a] and Kempe.[23] Most of these de(hydrogenative) reactions catalysed by manganese complexes use phosphine based ligands. Due to the well-known air and moisture sensitivities and the expensive nature of phosphine ligands, the development of phosphine free Mn complex to catalyse ADC reaction would be a significant advance.

Herein, we have prepared the new NNS-Mn(I) complex by refluxing the corresponding ligands with $MnBr(CO)_5$ in THF[26] (See ESI† for the characterization data of the complexes). The complexes have been applied for the synthesis of the diverse range of heterocycles such as quinoxaline, pyrazine, quinoline and benzothiazole via catalytic dehydrogenation and condensation reaction. To the best of our knowledge, Mn-

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† Electronic Supplementary Information (ESI) available: Experimental details; characterization data, copies of ^{1}H NMR and ^{13}C NMR spectra of all the compounds; CCDC 1855184. For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/x0xx00000x

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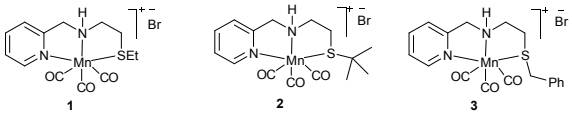


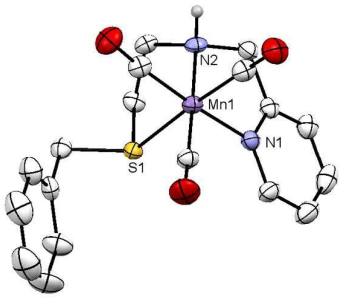
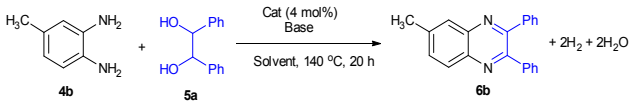


Fig 1. Tridentate ligand derived NNS-Mn(I) complexes and the molecular structure of **3** with thermal ellipsoid 30% probability level (all the hydrogens except N2 and the counter ion are not shown for the clarity).

complex mediated sustainable synthesis of quinoxalines, pyrazine and benzothiazole using dehydrogenative approach is not yet reported.

At the outset, we have selected catalyst **1**-**3** to synthesize quinoxaline and pyrazine from 1,2-diamine and 1,2-diol since these are an important class of heterocyclic compounds and have various applications. First, the reaction between 3,4-diaminotoluene and 1,2-diphenylethane-1,2-diol was taken as a model system to find out the optimum reaction condition for the synthesis of quinoxaline. Thus, refluxing a toluene solution containing 3,4-diaminotoluene (1.0 mmol), 1,2-diphenylethane-1,2-diol (1.3 mmol), cat **1** (0.04 mmol) and KOH (0.27 mmol) for 20 h gave 53% isolated yield of the desired quinoxaline. Keeping the other conditions unaltered, when xylene was used as a solvent, the yield was improved to 57% (Table 1, entry 2). Under the similar condition, using xylene solvent, cat **2** gave 66% yield whereas cat **3** gave 50% of the desired product (Table 1, entries 4 and 5). Thus, cat **2** was found to be the best choice for this reaction. Next, the reaction was studied under the neat condition in the presence of cat **2**, gratifyingly 79% desired quinoxaline was isolated. The yield of the desired product was decreased with low catalyst loading or with a lower amount of base (Table 1, entries 12 and 13). Under the optimized reaction condition, $MnBr(CO)_5$ gave a significantly lower amount of **6b**. We also investigated the catalytic activity of the equimolar mixture of $MnBr(CO)_5$ (4 mol%) and 2-(tert-butylthio)-N-(pyridin-2-ylmethyl)ethan-1-amine ligand (4 mol%) under the same condition. Only 17% **6b** was obtained after 20 h via in situ protocol. After optimization, the present protocol has been applied to synthesize diverse range of quinoxaline and pyrazine from 1,2-diamine and 1,2-diols. Initially, 1,2-disubstituted vicinal diols were reacted with different 1,2-diaminobenzene and it has been observed that 1,2-diaminobenzene having electron donating group gave slightly better yield compared to the electron withdrawing group.

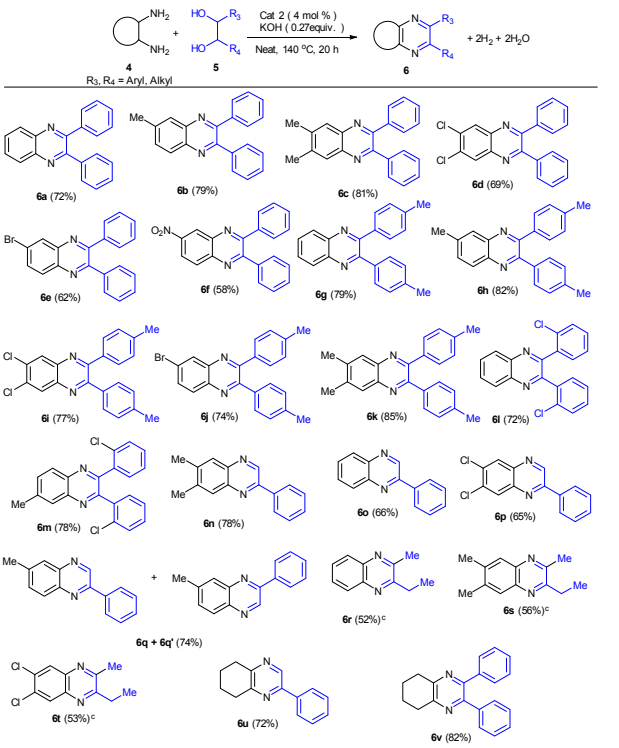
Table 1 Optimization of the reaction conditions for the synthesis of quinoxaline[a]



Entry	Cat.	Solvent (ml)	Base (mmol)	Yield (%)[b]
1	Cat-**1**	Toluene (3)	KOH (0.27)	53
2	Cat-**1**	Xylene (3)	KOH (0.27)	57
3	Cat-**2**	Toluene (3)	KOH (0.27)	62
4	Cat-**2**	Xylene (3)	KOH (0.27)	66
5	Cat-**3**	Xylene (3)	KOH (0.27)	50
6	Cat-**2**	Neat	KOH (0.27)	79
7[c]	Cat-**2**	Neat	KOH (0.27)	60
8	Cat-**2**	Neat	NaOH (0.27)	52
9	Cat-**2**	Neat	$NaHCO_3$ (0.27)	19
10	Cat-**2**	Neat	Na_2CO_3 (0.27)	23
11	Cat-**2**	Neat	K_2CO_3 (0.27)	34
12[d]	Cat-**2**	Neat	KOH (0.27)	46
13	Cat-**2**	Neat	KOH (0.13)	52
14[e]	Cat-**2**	Neat	KOH (0.27)	51
15	$Mn(CO)_5Br$	Neat	KOH (0.27)	14

[a] Conditions: 3,4-diaminotoluene (1 mmol), 1,2-diphenylethane-1,2-diol (1.3 mmol), base (0.27 mmol), cat (0.04 mmol), 20 h, under argon. [b] Isolated yield. [c] 1:1 ratio of 4b and 5a. [d] 2 mol% cat 2. [e] 10 h.

Table 2 Synthesis of quinoxaline and pyrazine from 1,2-diamine and 1,2-diol[a,b]



[a] Conditions: 1,2-Diamine (1 mmol), 1,2-diol (1.3 mmol), KOH (0.27 mmol), Cat **2** (0.04 mmol), 20 h under argon. [b] Isolated yield. [c] 36 h.

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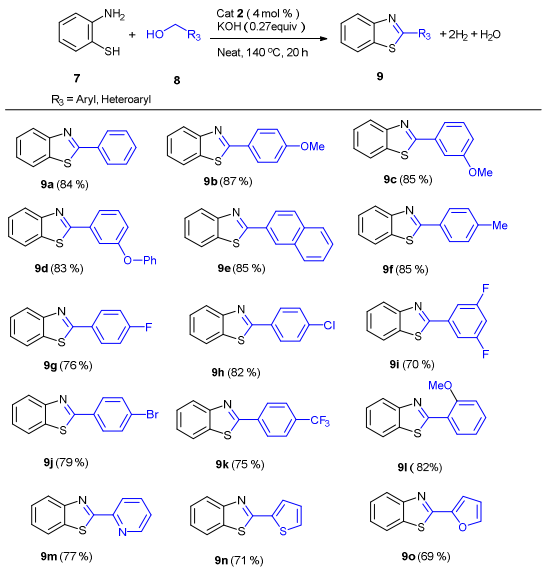
Table 3 Synthesis of benzothiazole through acceptorless dehydrogenative coupling of 2-aminothiophenol with primary alcohol[a,b]

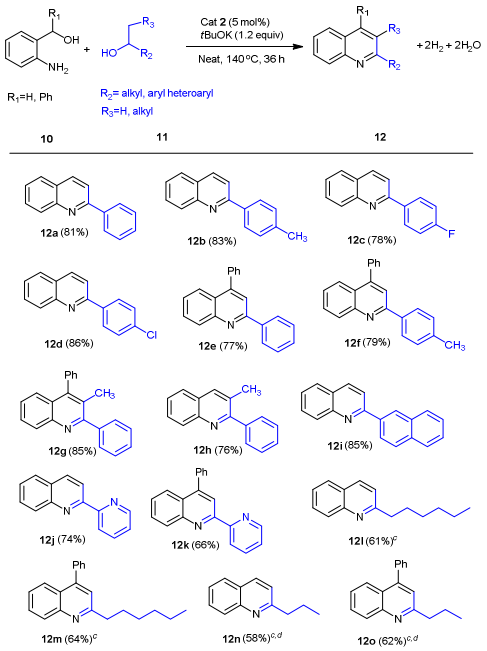


[a] Conditions: 2-aminothiophenol (1 mmol), alcohol (1.3 mmol), KOH (0.27 mmol), Cat **2** (0.04 mmol), 20 h under argon. [b] Isolated yield.

Under the optimized reaction condition, monosubstituted vicinal diols reacted smoothly with o- phenylenediamine, 4,5-Dimethyl-1,2-phenylenediamine, 4,5-dichloro-*o*-phenylenediamine, and 3,4-diaminotoluene and led to the desired product **6n-6p** in good yield. Notably, 3,4-diaminotoluene gave a mixture of two isomeric quinoxaline derivatives **6q** and **6q'**. The aliphatic 1,2-diol gave a moderate yield of **6r-6t**. Furthermore, employing 1,2-dicyclohexyl amine as substrate led to the formation of pyrazine derivatives in excellent yield (72%-82%).

Encouraged by this result we wanted to apply our methodology to synthesize 2-substituted benzothiazole via dehydrogenative coupling of alcohol and 2-aminothiophenol. The reaction proceeds well with the benzyl alcohols possessing both electron-donating and electron-withdrawing group in the aromatic nucleus gave an excellent yield of the desired benzothiazole. Not only m- and p- substituted benzyl alcohols, but also o-substituted benzyl alcohol gave an excellent yield of **9l**. It is interesting to note that halo substituted benzyl alcohol were well tolerated and the desired halo-substituted benzothiazoles **9g-9j** were obtained in an excellent yield, which could be further used for functionalization. Heteroaryl alcohols such as 2-thiophenemethanol, furfuryl alcohol and 2-pyridinemethanol worked successfully under the optimized reaction condition and afforded good yield of expected products. Next, we were interested in exploring the synthesis of quinoline derivatives via simultaneous C-C and C-N bond formation through dehydrogenative condensation reaction of secondary alcohol with 2-aminobenzyl alcohol. Thus, when 2-aminobenzyl alcohol (1.0 mmol) and 1-phenylethanol (1.3 mmol) was heated at 140 °C in the presence 5 mol% cat **2** and *t*BuOK (1.2 equiv.) for 36 h, 81% desired quinoline was

Table 4 Synthesis of quinoline from 2-aminobenzyl alcohol and secondary alcohol[a,b]



[a] Conditions: 2-aminobenzyl alcohol (1 mmol), secondary alcohol (1.3 mmol), *t*BuOK (1.2 mmol), Cat **2** (0.05 mmol), under argon. [b] Isolated yield. [c] 48 h. [d] 1.5 mmol secondary alcohol.

isolated. Here the excess base is required probably to assist the condensation reaction. It is worth mentioning that the amount of the base used in our protocol is substantially lower than the previously reported PNP-Mn(I)complex.[22a] When the reaction was performed in the toluene solvent or with the lower amount of *t*BuOK (0.56 equiv), the yield dropped to 72% and 56% respectively. To study the scope of the reaction, different 1-aryl ethanol having both electron-withdrawing as well as electron-donating group has been tested. In all the cases good to excellent yield was observed. Next, to synthesize 2,3,4- trisubstituted quinoline derivative, 1-Phenyl-1-propanol was treated with 2-Aminobenzhydrol, gratifyingly 85% 3-methyl-2,4-diphenylquinoline was obtained. The performance of cat **2** was further investigated towards more challenging aliphatic alcohols. Thus, 2-aminobenzyl alcohol reacted with 2-octanol to give 61% of the desired quinoline after 48 h. The reactions with aliphatic alcohols were found to be slower compared to the benzyl alcohols and a moderate to good yield of the corresponding quinoline derivatives were obtained. In all the cases, the C-C condensation occurred at the less hindered side of the in situ formed carbonyl compound.

In summary, we report the first example of an environment-friendly sustainable protocol to synthesize quinoxalines, pyrazine and benzothiazole catalysed by molecularly defined air stable Mn(I) complex. A wide range of functional groups survives well under these optimized reaction conditions. This expedient protocol has been successfully extended to synthesize a variety of quinoline derivatives via concurrent formation of C-C and C-N bond. The usage of earth-abundant

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biocompatible manganese metal and non-phosphine ligand system makes this protocol attractive.

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Conflicts of interest

There are no conflicts to declare.

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TOC

Sustainable synthesis of quinoxalines, pyrazines, benzothiazoles and quinolines catalysed by phosphine free Mn(I) complex.