Sustainable Synthesis of Quinolines and Pyrimidines Catalyzed by Manganese PNP Pincer Complexes

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S *Supporting Information*

ABSTRACT: This study represents the first example an environmentally benign, sustainable, and practical synthesis of substituted quinolines and pyrimidines using combinations of 2-aminobenzyl alcohols and alcohols as well as benzamidine and two different alcohols, respectively. These reactions proceed with high atom efficiency via a sequence of dehydrogenation and condensation steps that give rise to selective C−C and C−N bond formations, thereby releasing 2 equiv of hydrogen and water. A hydride Mn(I) PNP pincer complex recently developed in our laboratory catalyzes this process in a very efficient way. A total of 15 different quinolines and 14 different pyrimidines were synthesized in isolated yields of up to 91 and 90%, respectively.

Nitrogen-containing heterocycles such as pyridines, pyrroles, pyrimidines, and quinolines are ubiquitous core structures of many naturally occurring and biologically active molecules.[1,2] They have found broad applications as pharmaceuticals, flavors, agrochemicals, and dyes[3,4] and are prominently represented in medicinal chemistry.[5] Accordingly, there is a continuous need for new synthetic processes that allow the preparation of highly functionalized N-heterocycles, preferably in an atom-economical and sustainable fashion.

During the past decade, acceptorless dehydrogenation (AD) of alcohols[6] has become a powerful tool for the benign construction of complex organic molecules using sustainable and abundant alcohols as coupling reagents, as they are readily available by a variety of industrial processes and can be obtained renewably via fermentation or catalytic conversion of lignocellulosic biomass.[7] Catalytic AD of alcohols is an oxidant-free, atom-economical approach for the oxidation of alcohols to form carbonyl compounds, which subsequently can be converted into other useful organic materials such as amines, imines, amides, and esters. In these transformations, only dihydrogen and water are generated as nontoxic byproducts in the initial steps. Despite the significance of such C−C and C−N bond-forming reactions, homogeneous catalysts mostly employ precious metals such as Ru,[8] Rh,[9] and Ir.[10] In comparison, the same reactions with catalysts that utilize nonprecious, earth-abundant metals like Mn,[11,12] Fe,[13−15] Co,[16−18] and Ni[19] are much less developed. Moreover, the preparation of biologically interesting N-heterocycles by employing N−H or C−H alkylation has scarcely been explored.

In 2011, Crabtree and co-workers described the Ru-catalyzed formation of pyrroles from 1,4-diols and amines.[20] In 2013, the groups of Beller,[21] Kempe,[22] Milstein,[23] and Saito[24] reported efficient Ir- and Ru-catalyzed two- and three-component pyrrole syntheses in which secondary alcohols, diols, and primary alcohols were coupled. In the same year, Ir- and Ru-catalyzed formations of functionalized pyridines were described by the groups of Kempe,[25] Milstein,[26] and Liu and Sun.[27] Later on, Kempe and co-workers also reported the first multi-component synthesis of pyrimidines from amidines and different alcohols (Scheme 1).[28] The catalytic formation of quinolines was reported by the groups of Shim,[29] Yus,[30] Verpoort,[31] Milstein,[26] and Liu and Sun[27] via a Ru-catalyzed indirect Friedländer synthesis involving oxidative cyclization of 2-aminobenzyl alcohol with either ketones or alcohols (Scheme 1). To date, however, precious metals have been used as catalysts, and in terms of sustainability, they ought to be replaced by inexpensive and widely abundant first-row base metals.[32] It is noteworthy that the first Fe- and Co-catalyzed pyrrole syntheses were reported by Yan and Barta[33a] and Milstein and co-workers[33b] in 2016.

Intrigued by these recent discoveries in the area of nitrogen-containing heterocycles, we began to explore the potential of well-defined Mn(I) PNP pincer complexes with pyridine and triazine backbones as catalysts for the preparation of N-heterocycles. We describe here an efficient synthesis of substituted quinolines from amino alcohols and alcohols as well as the synthesis of pyrimidine derivatives via a three-component reaction utilizing benzamidine and two different alcohols as key feedstocks. Despite the fact that Mn is the third most abundant transition metal in the Earth's crust, after Fe and Ti, catalytic application of Mn(I) complexes in dehydrogenation catalysis is still rare. Seminal progress in this area includes the dehydrogenative coupling of alcohols and amines to form imines selectively and the conjugative addition of nonactivated nitriles by the group of Milstein[11] and our group[12] as well as the hydrogenation of ketones, aldehydes, nitriles, and esters.[34,35]

Initially, the catalysts A−E[12,35,36] (Scheme 2) at a catalyst loading of 5 mol % were screened for the synthesis of 2,4-diphenylquinoline from 2-aminobenzyl alcohol (1.0 equiv) and 1-phenylethanol (1.5 equiv) in toluene (4 mL) at 140 °C in a closed vial for 24 h in the presence of base (Table 1). The products were analyzed by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy

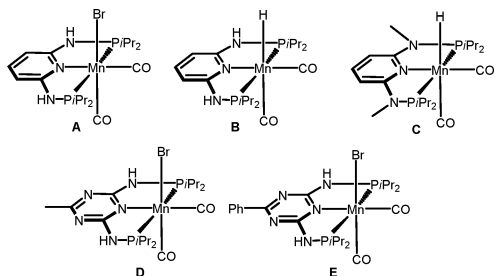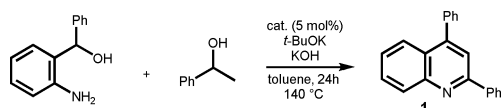**Scheme 1. Examples of the Catalytic Syntheses of Quinolines and Pyrimidines with Alcohols as Key Feedstocks**
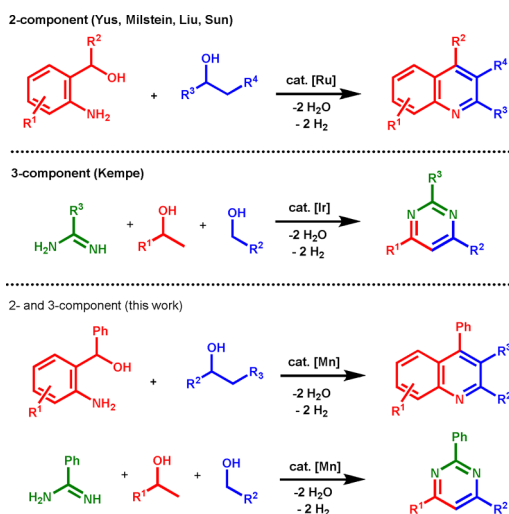

Scheme 2. Mn(I) PNP Pincer Complexes Tested as Catalysts

Table 1. Catalyst Screening for the Synthesis of Quinolines from 2-Aminobenzyl Alcohol and 1-Phenylethanol[a]

entry	cat.	yield [%][b]	entry	cat.	yield [%][b]
1	A	84	4	C	0
2	B	86	5	D	53
3[c]	B	28	6	E	72

[a]Reaction conditions: 1.0 mmol of 2-aminobenzyl alcohol, 1.5 mmol of 1-phenylethanol, 2.1 mmol of tBuOK, 0.5 mmol of KOH, 4 mL of toluene. [b]Isolated yields. [c]Without KOH.
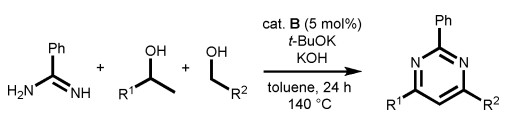
and identified by comparison with authentic samples. Lower temperatures, shorter reaction times, and lower catalyst loadings resulted in a significant drop in yields (see the Supporting Information). The best results were achieved with **A** and **B** in the presence of tBuOK and KOH in a 4.2:1 ratio (entries 1 and 2). In the absence of KOH, the yield dropped significantly from 86 to 28% (entry 3). The role of stoichiometric amounts of base is not fully understood at this stage. One role is to deprotonate the PNP ligand, but another role may be to facilitate the condensation reaction, i.e., the liberation of water. Catalyst **C** bearing NMe linkers was catalytically inactive (entry 4), emphasizing the importance of the acidic NH moieties for the catalytic reaction. Catalysts **D** and **E** featuring a triazine backbone turned out to be less active (entries 5 and 6).
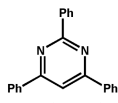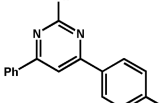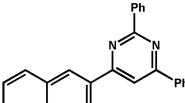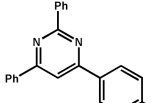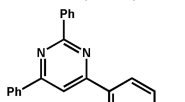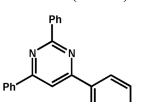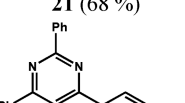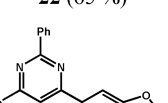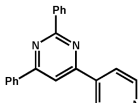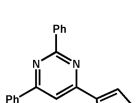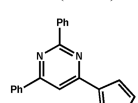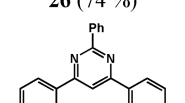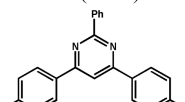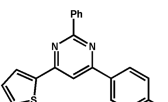
Table 2. Synthesis of Quinolines Using 2-Aminobenzyl Alcohols and Secondary Alcohols[a,b]
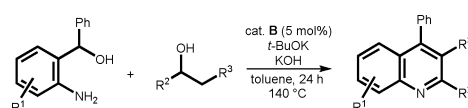
entry	product	entry	product
1	**1** (86 %)	2	**2** (91 %)
3	**3** (84 %)	4	**4** (67 %)
5	**5** (64 %)	6	**6** (82 %)
7	**7** (71 %)	8	**8** (79 %)
9	**9** (78 %)	10	**10** (84 %)
11	**11** (83 %)	12	**12** (61 %)
13	**13** (68 %)	14	**14** (73 %)
15	**15** (86 %)	16	**16** (88 %)

[a]Reaction conditions: 1.0 mmol of 2-aminobenzyl alcohol, 1.5 mmol of alcohol, 2.1 mmol of tBuOK, 1 mmol of KOH, 4 mL of toluene. [b]Isolated yields are shown.

Having established complex **B** as the most efficient catalyst in the series, this methodology was applied to other substrates utilizing a series of substituted benzyl alcohols, cyclic aliphatic alcohols, 1-indanol, and heterocyclic systems starting from 1-(thiophen-2-yl)ethanol and 1-(pyridin-4-yl)ethanol. The reaction is regioselective with regard to the carbonyl component formed in situ, taking place at its less substituted position (Table 2). All of the quinoline derivatives were isolated in good to excellent yields (61−91%). The reaction gave good yields

Table 3. Three-Component Pyrimidine Synthesis Using Benzamidine and Primary and Secondary Alcohols[a,b]

entry	product	entry	product
1	**17** (86 %)	2	**18** (90 %)
3	**19** (84 %)	4	**20** (81 %)
5	**21** (68 %)	6	**22** (65 %)
7	**23** (80 %)	8	**24** (58 %)
9	**25** (75 %)	10	**26** (74 %)
11	**27** (77 %)	12	**28** (88 %)
13	**29** (79 %)	14	**30** (72 %)

[a]Reaction conditions: 1.0 mmol of benzamidine, 1.5 mmol of primary alcohol, 1.2 mmol of secondary alcohol, 1.5 mmol of *t*BuOK, 1.5 mmol of KOH, 4 mL of toluene. [b]Isolated yields are shown.

not only with 1-phenylethanol (entry 1) but also with other related 4-substituted phenyl alcohols (entries 1−3) independent of the electronic nature of the substituent (electron-donating group in the methyl and methoxy derivatives (entries 2, 6, and 7) or an electron-withdrawing group in the halide derivatives (entries 3−5). The yields were also good for heterocyclic derivatives (pyridyl and thienyl; entries 8 and 9). In the case of aliphatic alcohols and 1-indanol (entries 12−14), the yields are generally slightly lower than for the benzylic and heterocyclic alcohols (entries 1−11, 15, and 16).

In order to further demonstrate the potential of Mn(I) catalyst **B** in AD processes combined with condensation reactions, the synthesis of substituted pyrimidines via a three-component process was also studied. Under similar conditions

as described above for the preparation of quinolines, a total of 14 different pyrimidines were synthesized. Variation of the primary and secondary alcohols led to the formation compounds **17−30** in 58−90% yield (Table 3). Aryl chlorides, fluorides, amines, and heterocycles such as pyridines and thiophenes as well as benzo[*d*][1,3]dioxole were tolerated. The whole process is an efficient, selective, and high-yielding single-step procedure.

In conclusion, this study represents the first example of an environmentally benign, sustainable, and practical synthesis of both substituted quinolines and pyrimidines catalyzed by a well-defined hydride Mn(I) PNP complex. Quinolines can be regioselectively assembled from 2-aminobenzyl alcohols and secondary alcohols, while pyrimidines are obtained via a three-component process utilizing benzamidine and two different alcohols. The selective C−C and C−N bond formations proceed with the liberation of 2 equiv of dihydrogen (acceptorless dehydrogenation) and the elimination of water (condensation). The optimized reaction conditions allow the presence of a wide range of typical organic functional groups. This preliminary study clearly demonstrates that base-metal catalysts begin to challenge precious-metal catalysts despite the fact that Ir catalysts, in this particular case, are still slightly more efficient and functional-group-tolerant. Nevertheless, this work may contribute to the development of waste-free sustainable base-metal catalysis.

■ ASSOCIATED CONTENT

⑤ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10433.

Synthetic procedures and ^{1}H and ^{13}C{^{1}H} NMR spectra of all organic products (PDF)

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Notes

The authors declare no competing financial interest.

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