Heterocycles

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Manganese-Catalyzed Multicomponent Synthesis of Pyrimidines from Alcohols and Amidines

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Abstract: The development of catalytic reactions for synthesizing different compounds from alcohols to save fossil carbon feedstock and reduce CO_2 emissions is of high importance. Replacing rare noble metals with abundantly available 3d metals is equally important. We report a manganese-complexcatalyzed multicomponent synthesis of pyrimidines from amidines and up to three alcohols. Our reaction proceeds through condensation and dehydrogenation steps, permitting selective C–C and C–N bond formations. β -Alkylation reactions are used to multiply alkylate secondary alcohols with two different primary alcohols to synthesize fully substituted pyrimidines in a one-pot process. Our PN5P-Mn-pincer complexes efficiently catalyze this multicomponent process. A comparison of our manganese catalysts with related cobalt catalysts indicates that manganese shows a reactivity similar to that of iridium but not cobalt. This analogy could be used to develop further (de)hydrogenation reactions with manganese complexes.

he selective linkage of alcohols to important classes of chemical compounds is an opportunity to develop more sustainable chemistry.^[1] Alcohols can be obtained from indigestible and abundantly available lignocellulose biomass,^[2,3] and thus the development of alcohol re-functionalization reactions can contribute to the conservation of our fossil carbon resources and the reduction of CO₂ emissions. A variety of reactions have been developed recently to catalytically synthesize aromatic N-heterocyclic compounds, such as pyrroles,^[4,5] pyridines,^[6] pyrimidines,^[7] and others,^[8] from alcohols.^[9] These reactions have been catalyzed by rare noble metals, mostly based on Ir and Ru. A more sustainable approach would be the use of catalysts based on abundantly available 3d metals, such as Co, Fe, and Mn (nonprecious or base metals), to additionally conserve our rare noble metal resources. Milstein and co-workers recently introduced a cobalt-catalyzed synthesis of pyrroles from diols and amines^[10] (Scheme 1, top). This reaction was discovered by Crabtree and co-workers using a Ru catalyst.^[5a] The nonprecious metal manganese, the third most abundant metal in the earth's crust, has been overlooked in recent years with regard to catalysis involving a (de)hydrogenation step.^[11] We recently introduced a variety of nonprecious metal catalysts for reactions involving (de)hydrogenation steps^[11d, 12-15] and



Pyrimidine synthesis based on a manganese catalyst instead of iridium
 First Mn-catalyzed synthesis of aromatic N-heterocycles from alcohols
 First Mn-catalyzed β-alkylation of alcohols (borrowing hydrogen/ hydrogen autotransfer concept)

Scheme 1. Synthesis of aromatic N-heterocycles from alcohols catalyzed by base-metal catalysts and corresponding methodology development using noble metals.

report here on a manganese-catalyzed version of the multicomponent reaction of alcohols and amidines to form pyrimidines^[7] (Scheme 1, bottom). The reaction can be carried out to give fully substituted pyrimidines in a 3component or a consecutive 4-component reaction. Multicomponent reactions are especially attractive in organic chemistry since they allow the synthesis of large libraries of diversely functionalized products from simple starting materials. Our synthetic method is especially useful for forming selectively alkylated and/or arylated pyrimidines. Mn catalysts stabilized by PN₅P ligands^[16] catalyze our reaction efficiently. Related Co catalysts are nearly inactive.

The reaction between 1-phenylethanol (1a), benzyl alcohol (2a), and benzamidine (3a) to pyrimidine 4a was investigated to develop a base-metal-catalyzed version of the 3-component pyrimidine synthesis (Table 1, top). After optimization of common reaction parameters (solvent, base, base amount, substrate ratio; see the Supporting Information for details), a library of Mn complexes stabilized by PN_3P or PN_3P ligands was tested to find the most active precatalyst (Table 1, complexes A–G). The complexes stabilized with

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Communications

Table 1: Precatalyst screening of the model reaction.[a]

ОН ОН	Ph	recatalyst (2 mol %) <i>t</i> -BuOK (1.1 eq)	. N	Ph
Ph + Ph 1a 2a	⁺ H ₂ N ∕∽NH ⊂ 3a	1,4-dioxane 120 °C, 20 h – 3 H ₂ , – 2 H ₂ O	Ph	Ph 4a
	Precatalys	st R	Х	Yield ^[b] of 4a
R	Α	Me	Ν	83%
, , , , , , , , , , , , , , , , , , ,	В	Ph	Ν	96%
X' ~X	с	4-CF ₃ (C ₆ H ₄)-	Ν	85%
нӎ́́ӎ∕҄ӎ	D	Н	Ν	92%
(<i>i</i> -Pr) ₂ P-Mn-P(<i>i</i> -P	r) ₂ E	C₃H₅NH-	Ν	89 %
Br	F	Н	СН	48%
	G	Me	СН	54%

[a] Reaction conditions: 1-phenylethanol (1.0 mmol), benzyl alcohol (1.0 mmol), benzamidine (0.50 mmol), *t*-BuOK (0.55 mmol), precatalyst (0.01 mmol, 2 mol%) 1,4-dioxane (1 mL), 120°C (oil bath temperature), 20 h. [b] Yield was determined by GC with dodecane as the internal standard.

triazine-based ligands bearing a phenyl (B) or H (D) substituent in the 4-position gave the highest yield of 4a. We also tested three cobalt complexes that were recently reported by our group^[12a,13a,14] as active catalysts for borrowing hydrogen/hydrogen autotransfer (BH/HA) applications, and only unreacted starting materials were obtained (see the Supporting Information). In summary, the best yield was obtained when precatalyst **B** $(2 \mod \%)$ was applied, the reaction was run in 1,4-dioxane with 1.1 equiv t-BuOK as the base, and an excess of alcohols (1.5-2 equiv) with respect to the amidine was used. The complexes used can be obtained on a gram scale in high yields in two steps from commercially available diamines and the corresponding Mn carbonyl precursor. With these conditions in hand, we explored the substrate scope of this 3-component reaction (Table 2). To start with, different secondary alcohols were employed, and aromatic (4b-d), heteroaromatic (4e,f), and aliphatic (4g,h) moieties were tolerated to give the corresponding pyrimidines in acceptable to good yields of isolated product (66-79%). When ethanol ($\mathbf{R}^1 = \mathbf{H}$) was used to contribute the C2 fragment, the 2,4-substituted pyrimidine 4i was isolated in 50% yield. Through variation of the primary alcohol, aliphatic substituents were introduced to give the corresponding products 4j,k. A secondary alcohol in combination with methanol as a C1 building block^[17] (instead of ethanol and another primary alcohol) gave the 2,4-substituted pyrimidine 4i. A more electron-rich *para*-methoxyphenyl group (4l) as well as a methyl (4m) and an amino group (4n) could be installed in the 2-position when the corresponding amidine (or guanidine) was used.

We next focused on the use of secondary alcohols with a substituent in the β -position, which can give rise to fully substituted pyrimidines. The alkylation of a secondary carbon atom by BH/HA methods is known to be more difficult,^[17,18] but the corresponding pyrimidines **5** (Table 3) could be isolated in moderate to good yields with a slight increase in the base amount (1.5 equiv) and an adapted substrate ratio (1.1 equiv primary alcohol). The use of cyclic alcohols, for

Table 2: Scope of the 3-component pyrimidine synthesis.[a]

R ¹ ·	$\begin{array}{c} OH \\ + \\ R^2 \\ 2 \\ 3 \end{array}$	³ B (2 mol %) [★] -BuOK (1.1 eq) 1,4-dioxane 120 °C, 20 h - 3 H ₂ , - 2 H ₂ O	→ R ¹	$ \begin{array}{c} $
Entry	Product	R	4	Yield ^[b]
1 2 3 4 5 6 7 8		$R^{1} = Ph$ $R^{1} = PMP$ $R^{1} = 3 \cdot Cl \cdot (C_{6}H_{4}) \cdot R^{1} = 2 \cdot thienyl$ $R^{1} = 2 \cdot thienyl$ $R^{1} = 3 \cdot pyridyl$ $R^{1} = iso \cdot propyl$ $R^{1} = cyclopropyl$ $R^{1} = H$	4b 4c 4d 4e 4f 4g 4h 4i	79% 73% 71% 73% 73% 66% 70% 50%
9 10 11		$R^2 = cyclohexyl$ $R^2 = n$ -pentyl $R^2 = H$	4j 4k 4i	53 % 62 % 44 %
12 13 14	Ph PMP	$R^3 = PMP$ $R^3 = Me$ $R^3 = NH_2$	4 l ^[c] 4 m ^[c] 4 n ^[c]	68 % 57 % 62 %

[a] Reaction conditions: Secondary alcohol (1.5 mmol), primary alcohol (1.5 mmol), amidine/guanidine (1 mmol), *t*-BuOK (1.1 mmol), **B** (0.02 mmol, 2 mol%) 1,4-dioxane (2 mL), 120°C (oil bath temperature), 20 h. [b] Yields of isolated products. [c] Corresponding amidine or guanidine hydrochloride with 1 additional equiv of *t*-BuOK was used.
PMP=para-methoxyphenyl.

Table 3: Synthesis of pyrimidines with alkylation of methylene carbon atoms. $^{[a]}$



[a] Reaction conditions: Secondary alcohol (1.5 mmol), primary alcohol (1.1 mmol), amidine (1.0 mmol), *t*-BuOK (1.5 mmol), **B** (0.02 mmol, 2 mol%) 1,4-dioxane (2 mL), 120 °C oil bath, 20 h. [b] Yields of isolated products. PMP=*para*-methoxyphenyl.

example, gave the corresponding products **5a–c**, which feature annulated aliphatic rings (ring size: 7, 8, or 12 carbon atoms). Two primary alcohols, of which one contributes the C2 building block, can give rise to 2,4,5-substituted pyrimidines (e.g., **5d** in good 75 % yield). Fully and differently substituted pyrimidines can also be obtained as demonstrated for **5f**.

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Finally, we became interested in whether the manganese catalyst is also able to catalyze a preceding β -alkylation reaction between a secondary and a primary alcohol. A manganese-catalyzed version of this reaction has not been reported, but would lead to the corresponding β -alkylated alcohol (or ketone). Subsequent addition of another primary alcohol and an amidine would give the pyrimidine in a one-pot process. Indeed, when we investigated the reaction between 1-phenylethanol (1.0 equiv) and 1-propanol (1.1 equiv) under the typical reaction conditions, the conversion of 1-phenylethanol was quantitative after 5 h (see the Supporting Information for details). Impressed by the good activity of the catalyst, we decided to use it to develop a consecutive 4-component reaction. The overall reaction to give tetrasubstituted pyrimidines **5** (Table 4, top) gave the

Table 4: Synthesis of tetrasubstituted pyrimidines by a consecutive 4-component reaction.^[a]



[a] Reaction conditions: Secondary alcohol (2.0 mmol), primary alcohol (2.2 mmol), *t*-BuOK (2.0 mmol), precatalyst **B** (0.05 mmol, 5 mol%) and 1,4-dioxane (1 mL) were heated for 5 h at 120 °C (oil bath temp.). Afterwards, amidine (1.0 mmol) and primary alcohol (1.1 mmol) were added as a solution in 1,4-dioxane (2 mL) and the reaction was heated under reflux for 20 h. [b] Yields of isolated products. [c] The β -alkylation reaction was run in a closed system. PMP=*para*-methoxyphenyl.

best yields when an excess of alcohols, 2.0 equiv of *t*-BuOK (employed at the beginning), and 5 mol% precatalyst **B** (2.5 mol% with respect to the first β -alkylation reaction, since 2 equiv of alcohols are employed) were used. The primary alcohol of the β -alkylation reaction (Table 4) was varied, which allowed the installation of a quasi-benzylic methyl group (**5e**, from methanol) and longer aliphatic moieties in the pyrimidine 5-position (**5g–j**). For example, 1-cyclopropyl ethanol was used to install a cyclopropane moiety to the pyrimidine ring and the corresponding product **5k** was obtained in good 70% yield.

In summary, we report the first example of a Mn-catalyzed synthesis of aromatic N-heterocycles from alcohols. This is a multicomponent reaction in which selective dehydrogenation and condensation steps lead to selective C-C and C-N bond formations. Through a 3-component reaction, fully substituted, 2,4- substituted, and 2,4,5-substituted pyrimidines can be obtained. In combination with the β -alkylation of secondary alcohols by primary alcohols, a reaction that has not yet been described for Mn catalysts, a consecutive 4component process was developed to give fully substituted pyrimidines in a one-pot procedure. Both multicomponent methods are strong regarding the synthesis of selectively alkylated and arylated products. Precatalysts stabilized by PN₅P ligands (triazine backbone) are about twice as efficient as those stabilized by PN₃P ligands (pyridine backbone). Notably, both Ir^[7] and Mn complexes catalyze the two distinct reactions (BH/HA and ADC) efficiently under similar reaction conditions. Co complexes stabilized by such ligands are nearly inactive in the ADC step. The (double) diagonal relationship Mn-Ru-Ir could be an explanation for the analogous catalytic reactivity between Mn and Ir observed here. Considering the many applications of Ir catalysts in (de)hydrogenation reactions, we feel that manganese has a great potential to partially replace Ir in such reactions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: borrowing-hydrogen reactions · dehydrogenative coupling · maganese · pincer complexes · pyrimidines

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Manganese-Catalyzed Multicomponent Synthesis of Pyrimidines from Alcohols and Amidines



Something borrowed: A manganese complex stabilized by a PN₅P-pincer ligand catalyzes the multicomponent synthesis of pyrimidines from amidines and up to three (different) alcohols. The



consecutive 4-component reaction combines the concept of borrowing hydrogen or hydrogen autotransfer with dehydrogenation condensation to permit selective C-N and C-C bond formation.