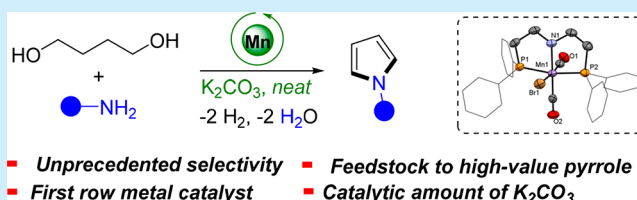


Sustainable Manganese-Catalyzed Solvent-Free Synthesis of Pyrroles from 1,4-Diols and Primary Amines

Jannik C. Borghs,[†] Yury Lebedev,[‡] Magnus Rueping,^{*,†,‡} and Osama El-Sepelgy^{*,†}[†]Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany[‡]KAUST Catalysis Center (KCC), King Abdullah University of Science and Technology (KAUST), Thuwal 23955-6900, Saudi Arabia

Supporting Information

ABSTRACT: A general and selective metal-catalyzed conversion of biomass-derived primary diols and amines to the highly valuable 2,5-unsubstituted pyrroles has been developed. The reaction is catalyzed by a stable nonprecious manganese complex (1 mol %) in the absence of organic solvents whereby water and molecular hydrogen are the only side products. The manganese catalyst shows unprecedented selectivity, avoiding the formation of pyrrolidines, cyclic imides, and lactones.

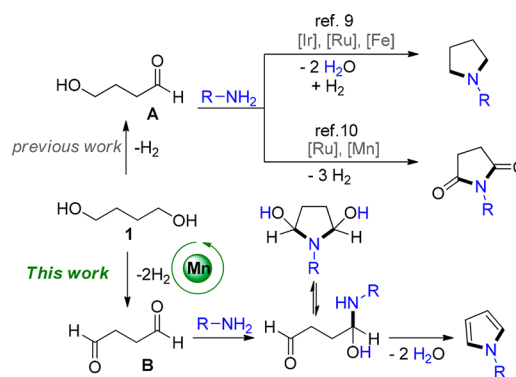


The discovery of new sustainable catalytic systems for upgrading renewable feedstocks to value-added fine and bulk chemicals represents a central challenge for chemists.¹ In this context, lignocellulosic biomass-derived alcohols offer a green alternative to mutagenic alkyl halides. Thus, substantial work was dedicated to the metal-catalyzed activation of alcohols by hydrogen shuttling with transfer of hydrogen from the alcohol to the final product. Besides, the catalytic dehydrogenation of alcohols leads to *in situ* formation of carbonyl intermediates which can undergo coupling reactions via condensation cascades to give more complex target molecules.²

Pyrroles represent an important class of synthetic intermediates which have found numerous applications in medicinal and advanced materials chemistry.³ While 2,5-substituted pyrroles are conventionally prepared through the Paal–Knorr synthesis,⁴ approaches for the synthesis of N-substituted pyrroles, and in particular 2,5-unsubstituted pyrroles, include the Clauson–Kaas reaction⁵ as well as N-alkylation of pyrrole. However, these methods may suffer from the formation of stoichiometric amounts of waste and limited substrate scope. More modern methods rely on the ruthenium- or iron-catalyzed condensation of the more expensive 2-butyne-1,4-diol with primary amines to give N-substituted pyrroles.⁶ Recently, a chemoenzymatic synthesis of N-substituted pyrrole was achieved via an olefin metathesis–aromatization cascade.⁷

A selective catalytic synthesis of N-substituted pyrroles from the readily available 1,4-butanediol (**1**) would be an ideal alternative, producing water and hydrogen gas as the only side products. However, the reaction of diol **1** with primary amines often leads to a mixture of pyrrolidine, cyclic imide, pyrrole, and lactone (Scheme 1).⁸ Saturated pyrrolidine can be accessed from the primary diol **1** and amines using iridium,

Scheme 1. Metal-Catalyzed Coupling of Primary Diols and Primary Amines



ruthenium and iron catalysts.^{6a,9} Furthermore, Hong et al. reported the selective synthesis of cyclic imides using PNNH–Ru catalyst, whereas a base-metal-catalyzed version was recently reported by Milstein using the PNNH–Mn complex.¹⁰ Moreover, the cyclization of 1,4-dialdehyde to γ -butyrolactone was outlined using ruthenium bisphosphine diamine catalyst.¹¹ In contrast, a general catalytic system to access pyrroles from diol **1** and primary amines has not been reported so far, although it could provide a desirable green and sustainable synthesis.¹²

Manganese is the third most abundant transition metal in the Earth's crust and has recently been recognized by several groups including ours as a sustainable alternative for Ru and Ir (de)hydrogenation catalysis.^{13–17} Indeed, several catalytic systems have been developed for the hydrogenation of polar

Received: November 2, 2018

and nonpolar bonds,¹⁵ dehydrogenation reactions,¹⁶ and hydrogen autotransfer.¹⁷ Encouraged by these advances and our experience in metal–ligand cooperative catalysis,^{18,19} we envisioned the possibility of developing a new catalytic system for the efficient *in situ* generation of the dialdehyde **B** from the diol **1**. This reactive intermediate **B** would likely undergo condensation with a primary amine to afford the corresponding pyrrole upon dehydration of the cyclic hemiaminal intermediate, whereas the pyrrolidine and imide synthesis typically involves the reaction between the primary amine and the hydroxyaldehyde intermediate **A**.^{9,10}

Here, we report our results on the sustainable transformation of the readily available diols and primary amines to pyrroles in a highly chemoselective fashion using an earth-abundant metal complex based on the inexpensive base metal manganese.

We started our study by the preparation of different manganese complexes bearing air- and moisture-stable ligands (**Mn-1**–**Mn-3**). For example, the manganese complex **Mn-3** could be readily prepared from the commercially available “MACHO” PNP pincer ligand and the inexpensive manganese precursor, $\text{Mn}(\text{CO})_5\text{Br}$. Suitable crystals of **Mn-3** were obtained and characterized by X-ray diffraction (Figure 1).

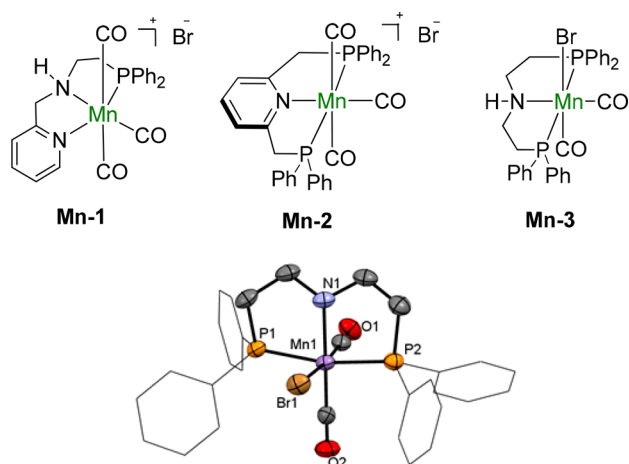


Figure 1. Manganese complexes used in this study and the single-crystal X-ray structure of **Mn-3** with ellipsoid set at 50% probability level.

Subsequently, the reaction between 1,4-butanediol (**1**) and *n*-hexylamine (**2a**) was thoroughly investigated in order to find the appropriate reaction conditions for the synthesis of the desired pyrrole **3a** while suppressing the formation of the undesired side products **3a'** and **3a''** (Table 1). To evaluate the most efficient catalyst, the manganese complexes **Mn-1**–**Mn-3** were tested in combination with Cs_2CO_3 in 1,4-dioxane as a solvent. Indeed, the application of **Mn-1** bearing a PNN ligand led to full conversion with 24% of the desired pyrrole **3a** along with 29% of the imide **3a'** (Table 1, entry 1). The high yield of the imide may be explained by the presence of the hemilabile pyridine ligand. In contrast, the pyridyl-based PNP pincer complex **Mn-2** showed low reactivity and excellent chemoselectivity toward the formation of the desired pyrrole **3a**. To our delight, **Mn-3** bearing a backbone N–H group resulted in 47% yield of pyrrole **3a** and 10% of cyclic imide **3a''** (Table 1, entry 3). We then turned our attention toward fine-tuning of the catalytic system by investigating different solvents

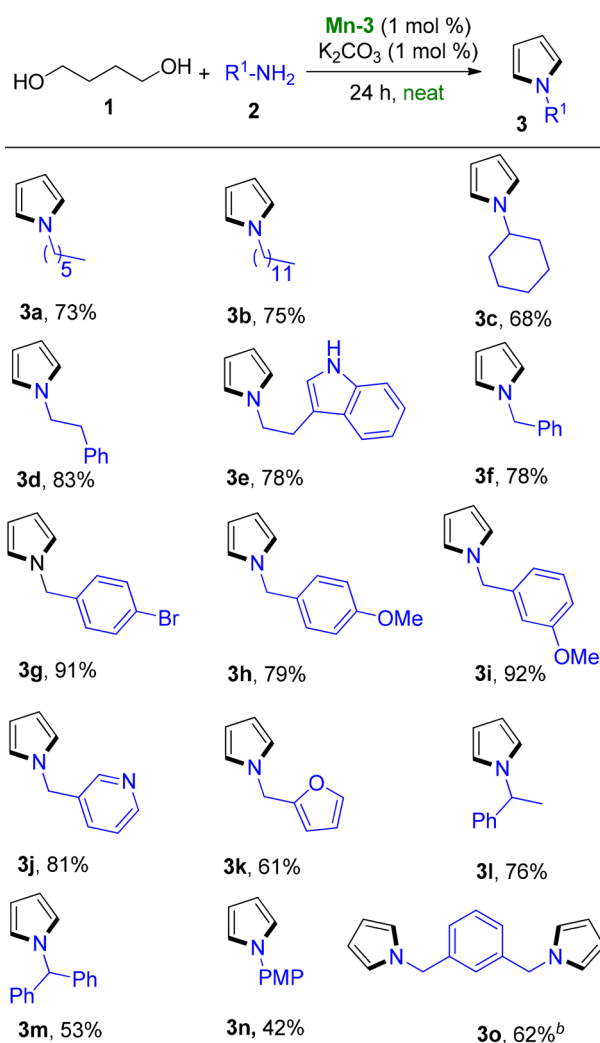
Table 1. Optimization of the Reaction Conditions^a

entry	[Mn] (mol %)	base (mol %)	conv. [%]	yield of 3a:3a':3a'' [%]
1	Mn-1 (2)	Cs_2CO_3 (3)	99	24:29:00
2	Mn-2 (2)	Cs_2CO_3 (3)	99	11:00:00
3	Mn-3 (2)	Cs_2CO_3 (3)	99	47:10:01
4 ^b	Mn-3 (2)	Cs_2CO_3 (3)	99	41:13:01
5 ^c	Mn-3 (2)	Cs_2CO_3 (3)	99	40:10:02
6 ^d	Mn-3 (2)	Cs_2CO_3 (3)	99	57:02:06
7 ^d	Mn-3 (2)	<i>t</i> -BuOK (3)	99	54:03:03
8 ^d	Mn-3 (2)	KOH (3)	99	60:02:10
9 ^d	Mn-3 (2)	K_2CO_3 (3)	99	62:02:05
10 ^{d,e}	Mn-3 (2)	K_2CO_3 (3)	99	41:00:06
11 ^d	Mn-3 (1)	K_2CO_3 (1)	99	77:00:09
12 ^d	$\text{Mn}(\text{CO})_5\text{Br}$ (3)	Cs_2CO_3 (5)	95	<5
13 ^d	-	Cs_2CO_3 (5)	95	<5

^aReaction conditions: **1** (0.5 mmol) and **2a** (1.0 mmol) in 1,4-dioxane (1.0 M) at 150 °C for 24 h under argon atmosphere. Conversions and yields were determined by GC using mesitylene (0.2 mmol) as an internal standard. ^bReaction in toluene. ^cReaction in CPME. ^dNeat conditions. ^e4 Å mol sieves added. It is worth noting that the difference between yields and conversion is attributed to the formation of oligomeric side products that cannot be detected by GC analysis.

and bases. When 1,4-dioxane was replaced by toluene or CPME, both yield and selectivity slightly decreased (Table 1, entries 4–5). Surprisingly, running the reaction under neat conditions led to improved reactivity and selectivity (Table 1, entry 6). The influence of different bases, such as *t*-BuOK, KOH, and K_2CO_3 , was also examined (Table 1, entries 7–9). We found that the inexpensive K_2CO_3 could be used as a catalyst activator providing 62% of pyrrole **3a** and only trace amounts of **3a'** and **3a''**. Unfortunately, the addition of 4 Å molecular sieves did not improve the yield (Table 1, entry 10). Gratifyingly, decreasing the manganese catalyst and base loading to 1 mol % afforded the desired product **3a** in 77% yield (Table 1, entry 11). Use of manganese pentacarbonyl bromide or only the base did not afford any product, indicating the crucial role of the metal–ligand catalyst (Table 1, entries 12 and 13).

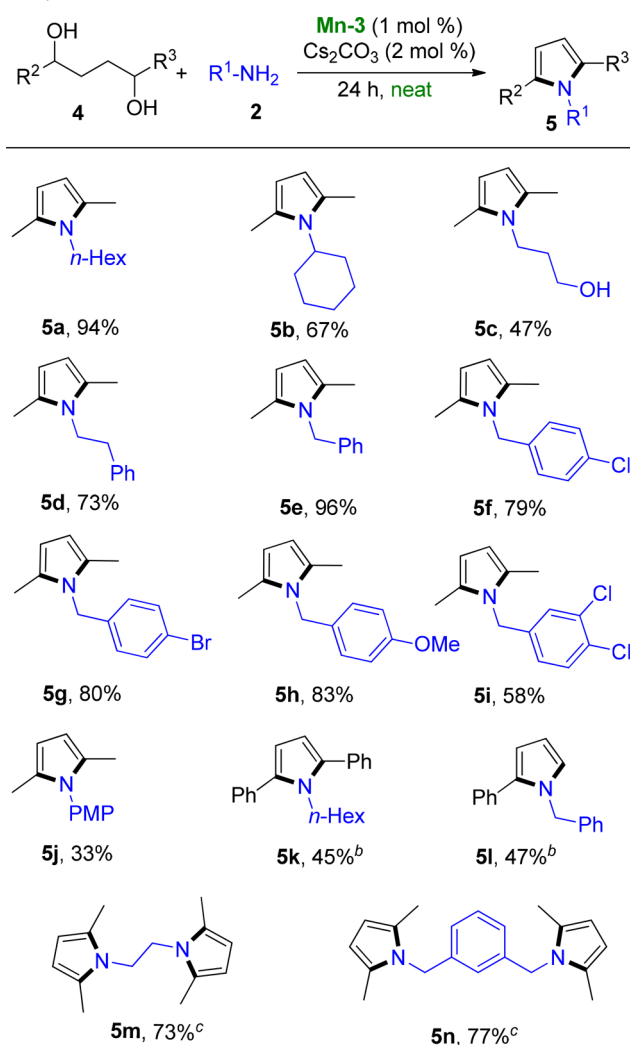
In order to demonstrate the general applicability of the reaction, a variety of primary amines were reacted with 1,4-butanediol (**1**) as a coupling partner (Scheme 2). Long-chain primary amines reacted smoothly with **1**, leading to the pyrroles **3a** and **3b** in good yields. When cyclohexyl amine was used as a substrate, the desired product **3c** was obtained in 68% yield. Slightly better yield was obtained when phenylethylamine was used, and the corresponding pyrrole **3d** was obtained in very good yield. Likewise, the reaction could also be applied successfully to medically relevant tryptamine, affording the pyrrole **3e** in 78% yield. Furthermore, benzylamines bearing electron-withdrawing and electron-donating groups were successfully reacted and provided the corresponding pyrroles **3f**–**3i** in moderate to good yields. Interestingly, amines bearing heterocycles such as pyridine and furane could also be used as coupling partners providing the desired pyrroles **3j** and **3k** in moderate to good yields. In addition, α -

Scheme 2. Manganese-Catalyzed Coupling of Primary Amines with 1,4-Butanediol^a

^aReaction conditions: 1 (0.5 mmol), 2 (1.0 mmol), Mn-3 (0.005 mmol), and K₂CO₃ (0.005 mmol) at 150 °C for 24 h. ^bDiamine (0.5 mmol) and 1 (1.5 mmol).

substituted amines such as α -methylbenzylamine and benzhydrylamine were successfully applied and afforded the pyrroles 3l and 3m in moderate to good yields. Utilizing aromatic amines such as *para*-methoxy aniline appeared to be more challenging due to the lower nucleophilicity, and only 42% of the desired product 3n could be isolated. Next, we successfully extended the scope by accessing symmetrical bispyrrole 3o from the corresponding diamine.

Encouraged by these results, we decided to further expand the scope and to use secondary diols, such as 2,5-hexanediol (4a) as a coupling partner (Scheme 3).⁸ In analogy to Scheme 2, different α -branched and unbranched primary amines and aniline derivatives are tolerated, and the desired substituted pyrroles 5a–5i were obtained in good to excellent yields. However, the PMP-derived pyrrole 5j was obtained in only 33% yield. In order to further prove the generality of the presented catalytic system, mono- and diphenylbutanediol were investigated and readily converted to the corresponding pyrroles 5k and 5l in moderate yields. Finally, further extension led to the synthesis of the symmetrical bispyrroles 5m and 5n in good yields.

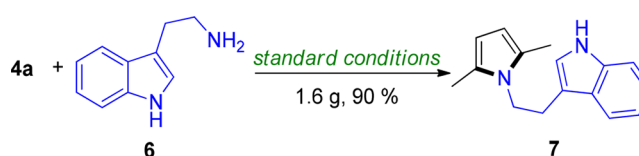
Scheme 3. Scope of Different Symmetrical and Unsymmetrical Diols^a

^aReaction conditions: 4 (0.5 mmol), 2 (1.0 mmol), Mn-3 (0.005 mmol), and Cs₂CO₃ (0.01 mmol) at 150 °C for 24 h. ^bMn-3 (0.01 mmol) and Cs₂CO₃ (0.025 mmol). ^cDiamine (0.5 mmol) and diol (1.5 mmol).

To demonstrate the practicability of this newly developed methodology, we conducted a gram-scale synthesis of the tryptamine-substituted pyrrole 7, and the desired product was isolated in excellent yield without the need of purification by chromatography (Scheme 4).

In summary, we report a general and selective synthesis of N-substituted pyrroles from low-cost renewable diols and primary amines. The reaction is catalyzed by a well-defined, bench-stable, homogeneous base metal catalyst which circumvents the use of stoichiometric amounts of mutagenic reagents

Scheme 4. Gram-Scale Synthesis of Tryptamine-Substituted Pyrrole 7



and produces water and hydrogen gas as the sole byproducts. The high potential of this catalytic system was demonstrated by the synthesis of a wide variety of pyrroles in good to excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03506.

Experimental data (PDF)

■ Accession Codes

CCDC 1863450 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: magnus.rueping@rwth-aachen.de.

*E-mail: osama.elsepelgy@rwth-aachen.de.

ORCID

Yury Lebedev: 0000-0003-2985-6876

Magnus Rueping: 0000-0003-4580-5227

Osama El-Sepelgy: 0000-0003-3131-4988

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.C.B. is thankful for financial support of the German Federal Environmental Foundation (DBU).

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