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Authors: Magnus Rueping

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Manganese Catalyzed Multicomponent Synthesis of Pyrroles *via* Acceptorless Dehydrogenation Hydrogen Autotransfer Catalysis - Experiment and Computation

Jannik C. Borghs,[a] Luis Miguel Azofra,[b] Tobias Biberger,[a] Oliver Linnenberg,[c] Luigi Cavallo,*[b] Magnus Rueping*[a][b] and Osama El-Sepelgy*[a]

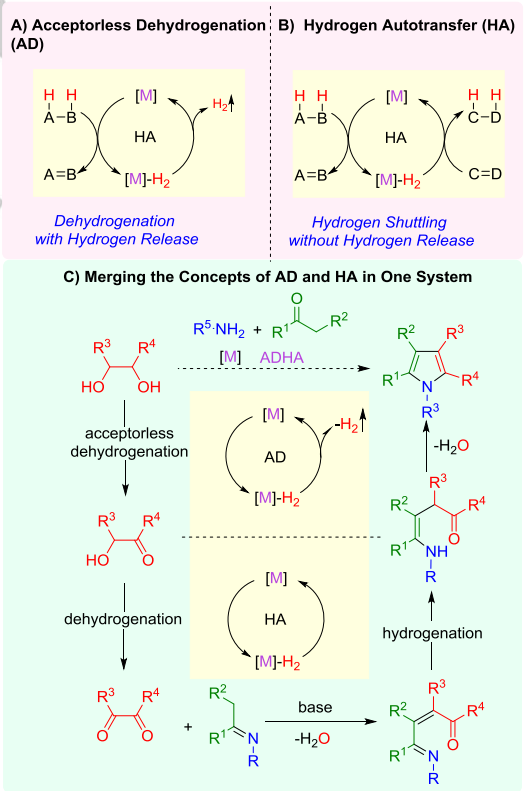
Abstract: A new base metal catalyzed sustainable multicomponent synthesis of pyrroles from readily available substrates is reported. The developed protocol utilizes an air and moisture stable catalyst system and has been utilized to replace mutagenic α-haloketones by readily abundant 1,2-diols. Moreover, the presented method is catalytic in base and the sole by-products of this transformation are water and hydrogen gas. Experimental and computational mechanistic studies indicate that the reaction takes place *via* a combined acceptorless dehydrogenation hydrogen autotansfer methodology.

Multicomponent reactions are valuable sustainable processes for the construction of complex molecules in one pot from three or more substrates. This strategy merges several elementary reaction steps, which lead to minimize the amount of waste, and simplifies the workup and purification steps.[1]

Pyrroles represent prominent and important chemical motifs in medicinal-, agro- and advanced material chemistry. Classical synthetic routes suffer from drawbacks mainly due to the generation of substantial amounts of waste produced during the multi-step pre-functionalization of substrates or by-product formation.[2] Accordingly, there is a continuous need to develop new catalytic systems which allow the direct and atom-economic conversion of renewable and readily available substrates to pyrroles.

Alcohols can be obtained from renewable biomass resources and present promising sustainable feedstock chemicals. The utilization of alcohols as substrates in the synthesis of fine chemicals will hence contribute not only to the reduction of toxic chemical waste but also to decrease CO_2 emissions by avoiding the use of carbon fossil sources.[3] One of the key concepts for alcohol functionalization is hydrogen autotransfer (HA), which has become a powerful tool for utilizing abundant alcohols as building blocks for environmentally benign C-C and C-N bond formations, releasing water as the only by-product (Scheme 1A).[4] A related concept is the acceptorless dehydrogenation (AD) which permits the conversion of alcohols to carbonyl compounds by liberating hydrogen gas without the need for a stoichiometric oxidant (Scheme 1B).[5]

Following the concept of HA, pyrroles can be synthetized from unsaturated 1,4-diols and primary amines.[6] Furthermore, catalytic systems have been developed for the synthesis of pyrroles using the AD concept from 1,4-diols and primary amines or secondary alcohols and amino alcohols.[7] Moreover, Beller and co-workers have reported three-component synthesis of pyrroles using $[Ru_3(CO)_{12}]$/Xantphos catalytic system. The authors proposed that the reaction might proceed *via* the AD concept.[8]



Scheme 1. Acceptorless Dehydrogenation (AD) and Hydrogen Autotransfer (HA) Catalysis.

The replacement of noble metal catalyst by first row transition metal catalysts is highly desirable due to ecological and economic benefits and may also lead to the discovery of new chemical reactivity.[9] Manganese is the third most abundant

[a] J. C. Borghs, T. Biberger, Prof. Dr. M. Rueping and Dr. O. El-Sepelgy
Institute of Organic Chemistry
RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: magnus.rueping@rwth-aachen.de
E-mail: Osama.Elsepelgy@rwth-aachen.de
[b] Dr. L. M. Azofra, Prof. Dr. M. Rueping, Prof. Dr. L. Cavallo
KAUST Catalysis Center (KCC)
King Abdullah University of Science and Technology (KAUST)
Thuwal 23955-6900 (Saudi Arabia)
E-mail: Luigi.Cavallo@kaust.edu.sa
[c] O. Linnenberg
Institute of Inorganic Chemistry
RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)

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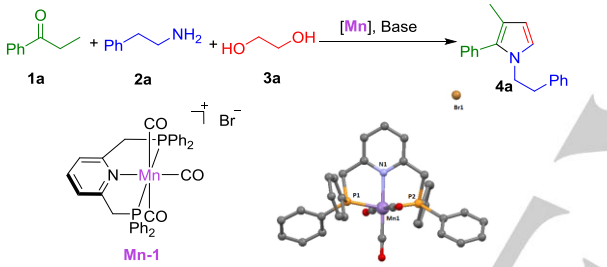
transition metal in the earth crust and is recognized as a sustainable alternative for toxic noble metal catalysts.[10-12] In our continuous effort to develop new sustainable transformations enabled by metal-ligand catalysts[13,14], we now report an unprecedented manganese catalyzed construction of pyrroles starting from readily available substrates: 1,2-diols, ketones and primary amines (Scheme 1C). Notably, our experimental and computational mechanistic studies on this multicomponent reaction suggest that the reaction proceeds *via* a unified acceptorless dehydrogenation hydrogen autotransfer strategy. To the best of our knowledge, this is the first study that prove the involvement of both processes of AD and HA in heterocyclic synthesis.[15] In fact, we found that this strategy is crucial for the successful activation of the vicinal 1,2-diols, providing a greener alternative for the mutagenic α-haloketones.[16]

We commenced our experimental study by synthesizing various manganese pincer complexes and identified **Mn-1** to be most effective for the desired transformation. The new PNP^{Ph}-based complex is bench stable and thus enables an operationally simple, glovebox-free reaction set up. Suitable crystals of **Mn-1** could be grown and were characterized by X-ray diffraction (Table 1 top).

Table 1. Optimization of the Reaction Conditions.[a]



entry	catalyst	solvent	base	yield [%]
1	**Mn-1**	*t*-amyl alcohol	KO*t*Bu	65
2	$Mn(CO)_5Br$	*t*-amyl alcohol	KO*t*Bu	<5
3	-	*t*-amyl alcohol	KO*t*Bu	<5
4	**Mn-1**	toluene	KO*t*Bu	20
5	**Mn-1**	1,4-dioxane	KO*t*Bu	28
6	**Mn-1**	Me-THF	KO*t*Bu	16
7	**Mn-1**	CPME	KO*t*Bu	16
8	**Mn-1**	*t*-amyl alcohol	KOH	43
9	**Mn-1**	*t*-amyl alcohol	K_2CO_3	23
10	**Mn-1**	*t*-amyl alcohol	Cs_2CO_3	41
11[b]	**Mn-1**	*t*-amyl alcohol	KO*t*Bu	86
12	**Mn-1**	neat	KO*t*Bu	70

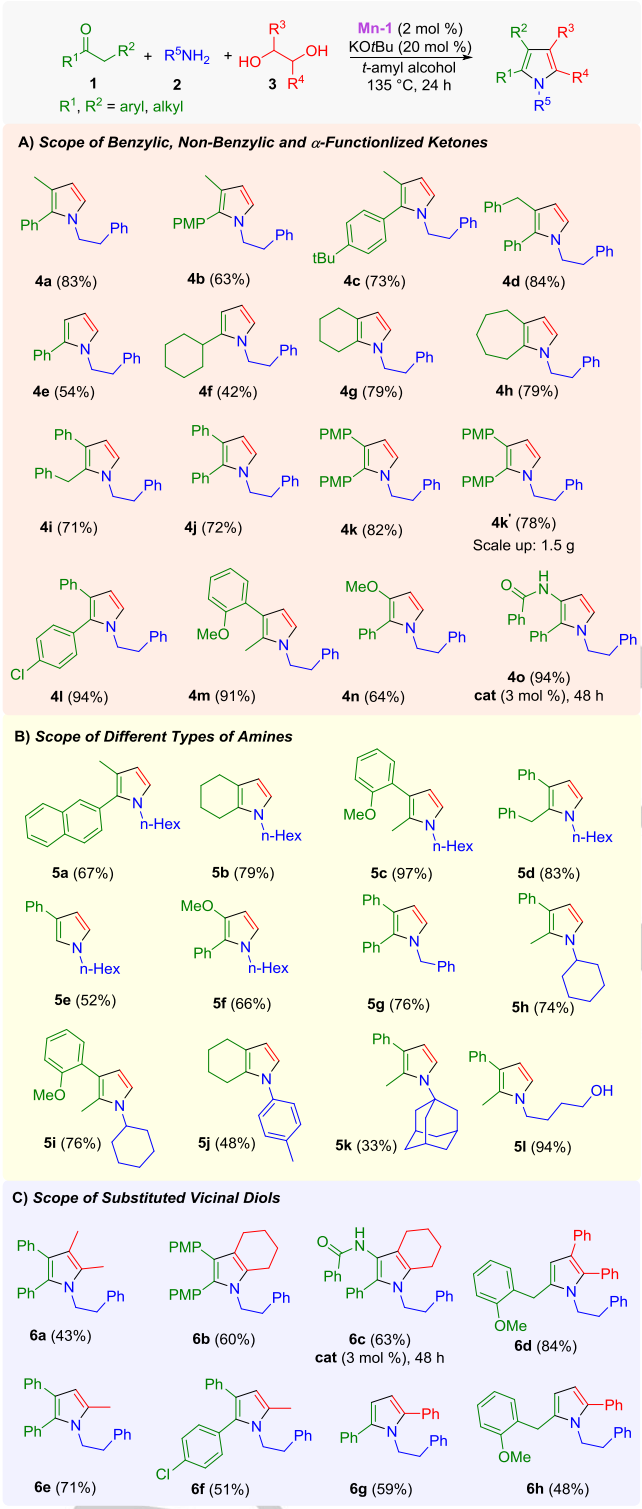
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), **3a** (1.5 mmol), [**Mn**] catalyst (2 mol %) in *t*-amyl alcohol (0.5 M), 135 °C, 24 h under argon atmosphere. Yield determined by GC using mesitylene as an internal standard. [b] 1.0 M reaction mixture. CPME = cyclopentyl methyl ether.

For our model reaction system, we investigated the formation of the substituted pyrrole **4a** by using propiophenone (**1a**), 2-phenylethylamine (**2a**) and ethylene glycol (**3a**). Thus, a solution containing substrates in dried solvent, Mn-complex and 20 mol% of a base was heated to 135 °C for 24 h. To our delight, by applying **Mn-1**, promising catalytic activity was observed and the desired pyrrole was obtained in 65% yield (Table 1, entry 1). Control experiments demonstrated the crucial role of both, the metal and the pincer ligand. (Table 1, entries 2, 3). Next, we further optimized other reaction parameters. Our investigation identified polar protic solvents to be most effective for the desired transformation (Table 1, entries 1, 8-10), whereas unpolar solvents were detrimental to the reaction (entries 4-7) Screening of various bases confirmed that inexpensive KO*t*Bu is best for this transformation (entries 8-10). Further experiments revealed that increasing the concentration to 1.0 M offers an increased yield of 86% (entry 11).

Having established optimal conditions for the heterocyclization, we moved on to demonstrate the applicability of our catalytic system. An array of aryl and alkyl ketones in combination with 2-phenylethylamine (**2a**) and ethylene glycol (**3a**) as model substrates (Scheme 2A) could be transformed into the corresponding pyrroles. Initially we were interested in using various less active and challenging non-benzylic ketones. Pleasingly, all the shown examples bearing different substituents were isolated in high yields **4a**–**4h**. Noteworthy, abundant alkyl ketones were also successfully converted to the corresponding bicyclic products **4g** and **4h** in very good yields. When we turned our attention to the use of benzylic ketones we obtained the respective pyrroles **4i**-**4m**. To prove the scalability, we conducted a gram scale synthesis of the pyrrole **4k**' and the desired product was isolated in 78% yield. Regarding its importance in medicinal chemistry[17] we also targeted heteroatom substituted pyrroles by applying the respective α-functionalized ketones. In fact, an α-alkoxy ketone showed high reactivity and could be transformed into the product **4n** in good yield. Importantly, the benzamide containing pyrrole **4o** was obtained in excellent yield (94%). Next, various amines were tested in combination with different ketones while keeping ethylene glycol as a coupling partner (Scheme 2B). All corresponding pyrroles were obtained in moderate to excellent yields. Specifically, different ketones in combination with *n*-hexylamine afforded products in good yields **5a**-**5f**. It was further demonstrated that different amines such as benzylamine or cyclohexylamine were also suitable for this cascade transformation **5g**-**5i**. Despite its weak nucleophilicity, toluidine showed significant reactivity and could be transformed into *N*-aryl substituted pyrrole **5j** in moderate yield. Gratifyingly, even the sterically demanding 1-adamantylamine could be converted to the respective pyrrole **5k**. To our delight, an amino alcohol was selectively converted to the pyrrole **5l**.

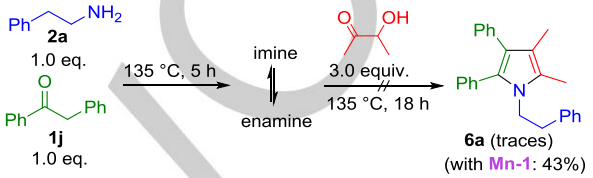
In order to provide highly substituted pyrroles, we employed an array of different vicinal diols giving the corresponding pyrroles in high yields (Scheme 2C). Interestingly, symmetrical disubstituted aromatic, aliphatic as well as cyclic diols could be used for this transformation giving good yields of the corresponding fully-substituted pyrroles **6a**-**6c** and tetra-substituted pyrrole **6d**. If mono-substituted unsymmetrical diols were employed, two regioisomers can be formed. However, in all cases either a single regioisomer or a very high regioselectivity (95:5) was obtained with substitution occurring in R^4 in pyrroles **6e-6h**. It is important to note that when the 1-(2-methoxyphenyl)propan-2-one was used as a ketone in combination with ethylene glycol, the C-H alkylation usually takes place at the benzylic carbon (Scheme 2A, example **4m**). To our surprise, using the same ketone in combination with phenyl or diphenyl substituted diols, the alkylation reaction

occurs on the free methyl group affording a different regioisomer (Scheme 2C, examples **6d** and **6h**). This observation led to the synthesis of new highly substituted pyrroles which are difficult to prepare by means of other methods.



Scheme 2. Scope of the Manganese Catalyzed Acceptorless Dehydrogenation Hydrogen Autotransfer.

Afterwards we decided to conduct experiments to prove the role of the metal-ligand catalyst. When we performed the reaction shown in Scheme 3 without catalyst and replacing the 1,2-diol by an α-hydroxy ketone, only trace amounts of the pyrrole **6a** were observed. However, when 2,3-butandiol and **Mn-1** were used, **6a** was obtained in 43% yield (Scheme 3). Furthermore, we have analyzed the reaction atmosphere of the model reaction using gas chromatography (Table 1, entry 11) and detected the presence of hydrogen gas. These experimental results indicate that the metal-ligand complex not only catalyzes the AD process but also the HA process.



Scheme 3. Experimental Mechanistic Investigations

We subsequently carried out a detailed DFT study and selected the multicomponent reaction between glyceraldehyde, propiophenone and *n*-hexylamine catalyzed by **Mn-1** as the model reaction.[18,19] Initially, the uncatalyzed reaction between the primary amine and the ketone leads to the formation of an imine which is in equilibrium with the corresponding enamine. The latter may undergo a C-H or N-H addition reaction with the *in situ* generated glycolaldehyde or glyoxal. This establishes the existence of four plausible reaction pathways (see Fig. S3). The DFT calculations, the experimental investigations and the observed selectivity (Scheme 2, examples **6e** - **6h**) suggest that the reaction most likely occurs through the C-H alkylation of enamine with *in situ* generated glyoxal (See SI for details).

Figure 1 illustrates that the Mn complex acts as a catalyst for acceptorless dehydrogenation hydrogen autotransfer processes. The first catalytic cycle involves AD of ethylene glycol to glycolaldehyde and hydrogen gas (Figure 1A). The second catalytic cycle involves a crucial HA process consisting of metal catalyzed activation of glycoladehyde by shuttling a hydrogen molecule required for the hydrogenation of the azadiene intermediate (Figure 1B). Specifically, the ethylene glycol dehydrogenation (AD cycle) starts with one of the -OH groups of ethylene glycol interacting with the [Mn] species **A** to give complex **B**, with a slightly endergonic binding Gibbs free energy of 4.0 kcal mol^{-1} at 135 °C and using 1-butanol as solvent. This complex is characterized by the presence of two interactions, in which Mn acts as electrophilic center *via* a Mn···O interaction, while the sp^2 carbon in one of the arms of the non-innocent PNP ligand acts as nucleophilic center through a C···H interaction with the H atom of the ethylene glycol OH group. Proton transfer from the alcohol occurs *via* transition state **B-C** with a free energy barrier of 10.3 kcal mol^{-1} from **A**, and leads to intermediate **C** laying -2.2 kcal mol^{-1} below **A**. This aromatization-dearomatization process has been thoroughly studied in metal-PNP and PNN complexes as an important process providing the lowest energy pathways.[20]

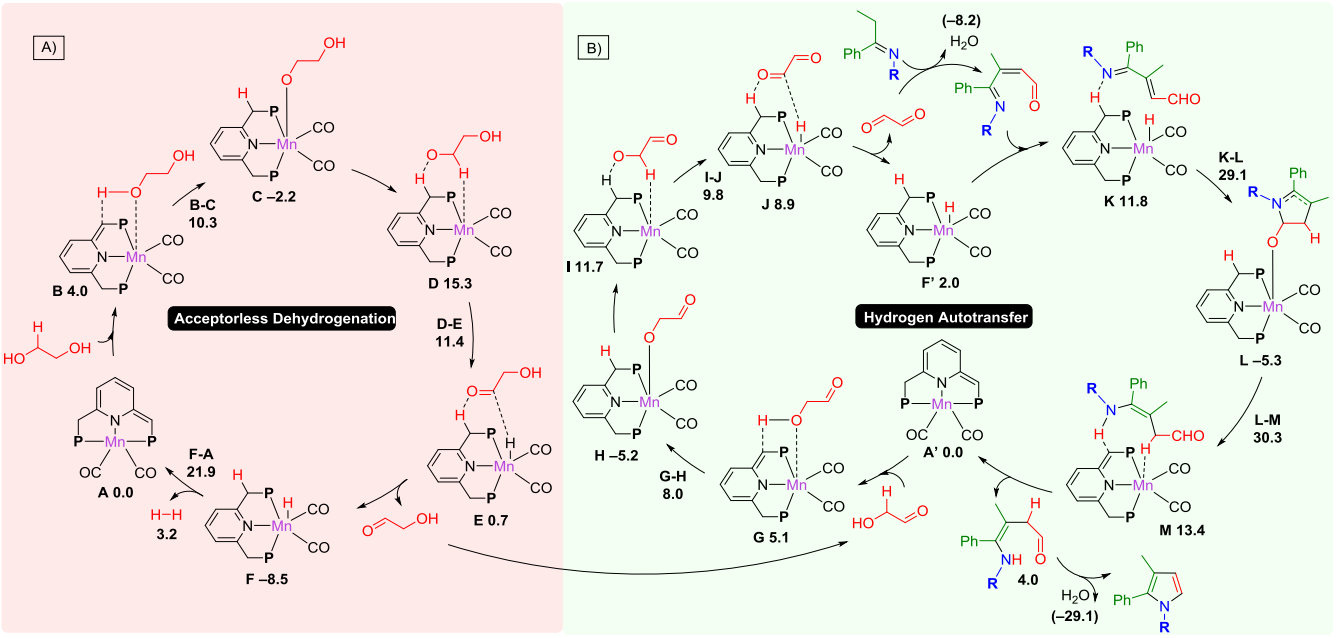


Figure 1. Proposed reaction mechanism of the heterocyclization *via* a unified acceptorless dehydrogenation hydrogen autotransfer concept catalyzed by **Mn-1**. Calculated Gibbs free reaction and activation energies at 135 °C, are shown in kcal mol^{-1} at the M06/TZVP//PBE/SVP(H,C,N,O,P)-TZVP(Mn) computational level using 1-butanol as solvent. Note: **P** and **R** groups refer to PPh_2 and *n*-hexyl, respectively.

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The following hydride transfer occurs *via* the formation of complex **D**, which represents the highest energy intermediate of the dehydrogenation cycle, 15.3 kcal mol^{-1} relative to **A**. The hydride transfer occurs through transition state **D-E**. This is assumed to be an almost barrier-free process, as transition state **D-E** is only 1.1 kcal mol^{-1} above intermediate **D** when electronic energies in solution at the PBE/SVP(H,C,N,O,P)-TZVP(Mn) level of theory are considered (*i.e.*, the computational protocol used to locate geometries). The resulting [Mn]-H_2···glycolaldehyde complex **E** is located 0.7 kcal mol^{-1} above **A**. The following release of glycolaldehyde is exergonic by 8.5 kcal mol^{-1} and leads to **F**. The acceptorless dehydrogenation cycle closes with the regeneration of the catalyst by H_2 release, in a process presenting a kinetics penalty of 30.5 kcal mol^{-1} relative to **F**.

We have also carried out calculations for the case in which proton and hydride transfers from glyceraldehyde to the Mn(I)-PNP catalytic species occurs *via* a concerted pathway. The corresponding activation Gibbs free energy is 3.4 and 2.3 kcal mol^{-1} less stable than those computed for transition states **B-C** and **D-E**, respectively. In this line, the proposal of a step-wise mechanism in which hydride transfer might occur before the proton transfer during AD cycle indicates disfavored kinetics, with an activation barrier of 59.8 kcal mol^{-1} relative to **A**.

Subsequently the HA cycle has been investigated by DFT analysis (Figure 1B). The first part of the HA process involves the dehydrogenation of glycoaldehyde to glyoxal by the hydrogen transfer to the Mn- and N-centers that also result in the hydrogenated catalytic species, **F´**. In this process, proton transfer exhibits a Gibbs free activation energy of 8.0 kcal mol^{-1}, **G-H**, while hydride transfer is carried out *via* the formation of complex **I**, 11.7 kcal mol^{-1}, also through a barrier-less process.

The second part of the HA process involves the endergonic interaction between the manganese species **F´** bearing shuttled hydrogen molecule with the azadiene intermediate that has resulted from a C-H alkylation reaction. This intermediate is formed by the addition of glyoxal with the enamine compound, a coupling that is exergonic by 8.2 kcal mol^{-1}. In more detail, hydride transfer from the Mn atom to the sp^2 carbon atom positioned β to the CHO group occurs *via* transition state **K-L** and Gibbs free activation energy of 27.1 kcal mol^{-1} relative to **F´**. The proton transfer occurs through transition state **L-M** and a free energy barrier of 35.6 kcal mol^{-1} relative to **L**. This penalty represents the highest kinetics impediment of the whole reaction in which the Mn(I)-PNP catalytic species participates since partial cyclization of the substrate is seen in **L** by N→C(sp^2)HO bond formation. Finally, the released hydrogenated azadiene can undergo cyclization to the observed pyrrole derivative with a free energy gain of 29.1 kcal mol^{-1}.

In conclusion, we have reported a new base metal catalyzed heterocondensation cascade *via* acceptorless dehydrogenation hydrogen autotransfer methodology. The reaction is catalyzed by a new homogeneous base metal catalyst based on an inexpensive and air stable manganese complex bearing a PNP ligand. The great potential of our catalytic system was demonstrated by the synthesis of more than 35 different substituted pyrroles in good yields using renewable substrates and only catalytic amounts of base. Importantly, water and hydrogen gas are the sole by-products. Computational studies support an acceptorless dehydrogenation hydrogen autotransfer reaction mechanism in which the metal-ligand complex plays a dual role for the acceptorless dehydrogenation of ethylene glycol followed by non-typical hydrogen autotransfer process.

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Keywords: Acceptorless Dehydrogenation, Hydrogen Autotransfer, Base Metals, Alcohols, Heterocycles

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[19] Optimized geometries were located using the PBE functional together with the SVP basis set for main group atoms and the TZVP basis set for Mn. Single-point energy refinement calculations were done at M06/TZVP level. Solvent effects (1-butanol) were included *via* the PCM model at both steps. All calculations have been performed through the facilities provided by the Gaussian09 package. See the Supporting Information for full computational details.

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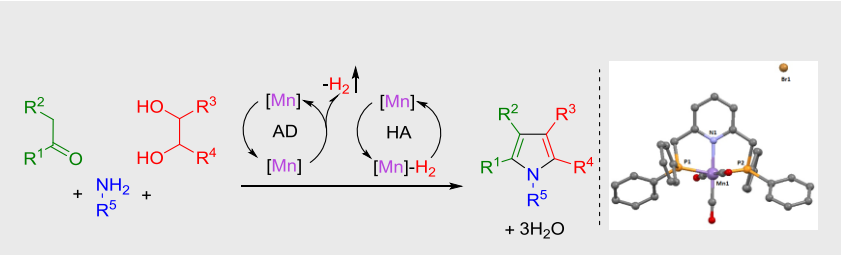

Jannik C. Borghs,Luis Miguel Azofra,Tobias Biberger, Oliver Linnenberg, Luigi Cavallo, Magnus Rueping,* Osama El-Sepelgy**

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Title Multicomponent Synthesis of Pyrroles via Acceptorless Dehydrogenation Hydrogen Autotransfer Manganese Catalysis - Experiment and Computation