Manganese Catalyzed Regioselective Dehydrogenative C- vs. N-Alkylation Enabled by a Solvent Switch: Experiment and Computation

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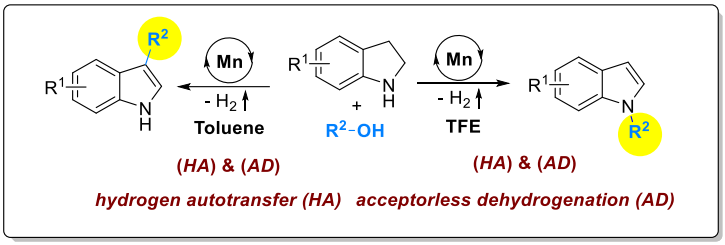
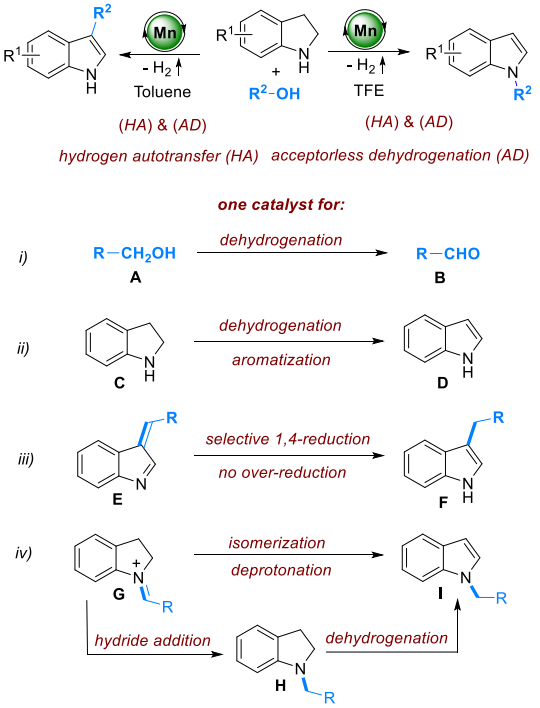
KEYWORDS: acceptorless dehydrogenation • alcohols • base metals • hydrogen autotransfer • amine dehydrogenation



ABSTRACT: The first base metal-catalyzed regioselective dehydrogenative alkylation of indolines using readily available alcohols as alkylating reagent is reported. A single air- and moisture-stable manganese catalyst provides access to either C_3- or N-alkylated indoles depending on the solvent used. Mechanistic studies indicate that the reaction takes place through a combined acceptorless dehydrogenation and hydrogen autotransfer strategy.

Indoles represent a prominent and important chemical motif in medicinal- and agrochemistry.[1] Several drugs like oxypertine, bufotenine or indomethacin are bearing this heterocyclic scaffold.[2] In the last years, the selective functionalization of indoles has attracted considerable attention.[3] One of the most common methods for alkylating indoles at C_3 position is the Lewis acid catalyzed Friedel-Crafts reaction using alkyl halides.[4] However, due to the generation of substantial amounts of inorganic salts and use of mutagenic (pseudo)haloalkanes it remains a wasteful and unsustainable approach. In this regard, abundant alcohols emerged as cheap and environmentally benign building blocks for C-C and C-N bond formations, following acceptorless dehydrogenation (AD) and hydrogen autotransfer (HA) reaction strategies.[5] Albeit, a lack of regioselectivity is observed for most of the recent methods that apply the dehydrogenative coupling protocol for indoles and these approaches typically functionalize either at indole C_3[6]- or N[7]-position. However, accessing both regioisomers with a single catalyst by omitting noble metals[8,9] and additional oxidants remains challenging[10] and to date no procedure applying a base metal-catalyzed regio- and chemoselective alkylation of indoles or indolines has been reported. The regioselective alkylation with a single catalyst is rather challenging as several reactions involving a hydrogen autotransfer (HA) or acceptorless dehydrogenation (AD), need to be catalyzed by the same catalyst in a chemoselective manner: i) the dehydrogenation of an alcohol **A** to provide an aldehyde **B**, which can

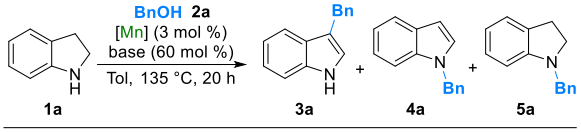
Scheme 1. Dehydrogenative Alkylation of Indolines.

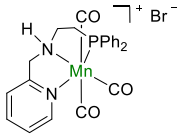


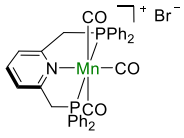
either react with indole **D** to give the corresponding imine **E** or alternately react with indoline **C** to give the iminium ion **G** resulting in either C- or N-alkylated product; ii) the dehydrogenative aromatization of indoline **C** to provide indole **D**; iii) the selective 1,4-reduction of **E** to give the C_3-alkylated indole **F** and iv) the formation of N-alkylated product **I** through an isomerization/deprotonation of **G** or alterative through a hydride addition/ dehydrogenation sequence via the N-alkylated product **H** (Scheme 1). Based on our interest in the area of base metal catalysis[9,11] we decided to investigate a manganese-catalyzed dehydrogenative alkylation of indolines using readily available alcohols as alkylating reagents. To the best of our knowledge, a single base metal complex catalyzing both, the AD of amines and the HA of alcohols in one protocol is not known. Beyond that, no manganese-catalyzed amine dehydrogenation has been reported so far. We here describe the development of a regioselective dehydrogenative alkylation using a single manganese catalyst and report an interesting solvent switch which allows a targeted N- vs C-functionalization (Scheme 1).

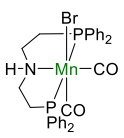
We commenced our investigations with the evaluation of different Mn-complexes as catalysts for the dehydrogenative coupling of indoline (**1a**) using benzyl alcohol (**2a**) in the presence of base to give either C_3- or N-alkylated indoles **3a** and **4a** or N-alkylated indoline **5a** as products (Table 1). Inspired by our latest results in dehydrogenative coupling protocols, we initially tested different bifunctional Mn(I) complexes. **Mn-1**, which is bearing a PNN-pyridyl based scaffold, remained unreactive in the presence of 60 mol % KO^{t}Bu (Table 1, entry 1). Also, the pyridyl based PNP complex **Mn-2** provided only trace amounts of **3a** (Table 1, entry 2). Interestingly, the NH-bridged PNP (Macho) complex **Mn-3** showed reactivity and the product **3a** was selectively obtained in moderate yield (Table 1, entry 3). Surprisingly the PNP analogue **Mn-4** provided only low conversion (Table 1, entry 4). Furthermore, N-methylated **Mn-5** yielded trace amounts of product, illustrating the necessity of the NH-moiety (Table 1, entry 5).[12] In order to further optimize the reaction conditions with **Mn-3**, different bases and solvents were evaluated (Table 1, entries 6-18). With cesium bases, such as Cs_2CO_3 or CsOH·H_2O, in toluene as solvent and with 1 mol % of catalyst the yields considerably increased to 63 and 98% (Table 1, entries 6 and 9). Decreasing the temperature by 10 °C reduced the yield significantly (Table 1, entry 10). The best results were obtained when 1 mol % of **Mn-3** was employed with 10 mol % of CsOH·H_2O in toluene (Table 1, entry 9). Conversely, by altering the solvent from apolar aprotic, such as toluene or ethers, to polar protic, such as 2,2,2-trifluoroethanol (TFE), a complete selectivity switch was observed (Table 1, entries 11-15). In fact, only *N*-alkylated indole **4a** and indoline **5a** were obtained without any presence of **3a**, when TFE was applied (Table 1, entry 15). Surprisingly, no other polar protic solvents such as *tert*-amyl alcohol or hexafluoroisopropanol (HFIP) afforded equally good results (Table 1, entries 13-14). Interestingly, switching the metal source from Mn to Ru resulted in a mixture of all three products (Table 1, entry 16). Using a mixture of TFE and toluene reduced the amount of undesired alkylated indoline **5a** (Table 1, entry 17). Finally, increasing the dilution and decreasing the amount of base to 10 mol % and alcohol to 1.5 equiv., the alkylated indole **4a** was obtained in excellent yield and remarkable selectivity (Table 1, entry 18). In the absence of base, PNP-ligand or **Mn-3**, no conversion was observed (Table 1, entries 19-21). With our optimized conditions in hand we subsequently explored the substrate scope for the regioselective coupling of different indolines and alcohols (Scheme 2).

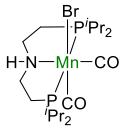
Table 1. Optimization of the Reaction Conditions.[a]

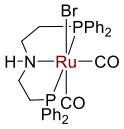


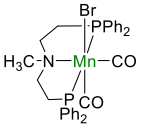

Mn-1


Mn-2


Mn-3


Mn-4


Ru-1


Mn-5

entry	cat.	base	solvent	yield (%) 3a:4a:5a
1	Mn-1	KO^{t}Bu	Tol	2:0:0
2	Mn-2	KO^{t}Bu	Tol	7:0:0
3	Mn-3	KO^{t}Bu	Tol	56:0:0
4	Mn-4	KO^{t}Bu	Tol	10:0:0
5	Mn-5	KO^{t}Bu	Tol	8:0:0
6[b]	Mn-3	Cs_2CO_3	Tol	63:0:0
7[b]	Mn-3	K_2CO_3	Tol	5:0:0
8[b]	Mn-3	NaH	Tol	47:0:0
9[b]	Mn-3	CsOH·H_2O	Tol	98:0:0
10[b,c]	Mn-3	CsOH·H_2O	Tol	80:0:0
11	Mn-3	CsOH·H_2O	1,4-dioxane	7:0:0
12	Mn-3	CsOH·H_2O	CPME	49:1:2
13	Mn-3	CsOH·H_2O	*t*-AmOH	29:2:1
14	Mn-3	CsOH·H_2O	HFIP	0:1:2
15	Mn-3	CsOH·H_2O	TFE	0:41:9
16	Ru-1	CsOH·H_2O	TFE	19:26:20
17	Mn-3	CsOH·H_2O	TFE/Tol 2:1	0:68:6
18[d,e,f]	Mn-3	CsOH·H_2O	TFE/Tol 2:1	0:98:0
19[e]	Mn-3	-	TFE or Tol	-
20[e,g]	$Mn(CO)_5Br$	CsOH·H_2O	TFE or Tol	-
21[e]	-	CsOH·H_2O	TFE or Tol	-

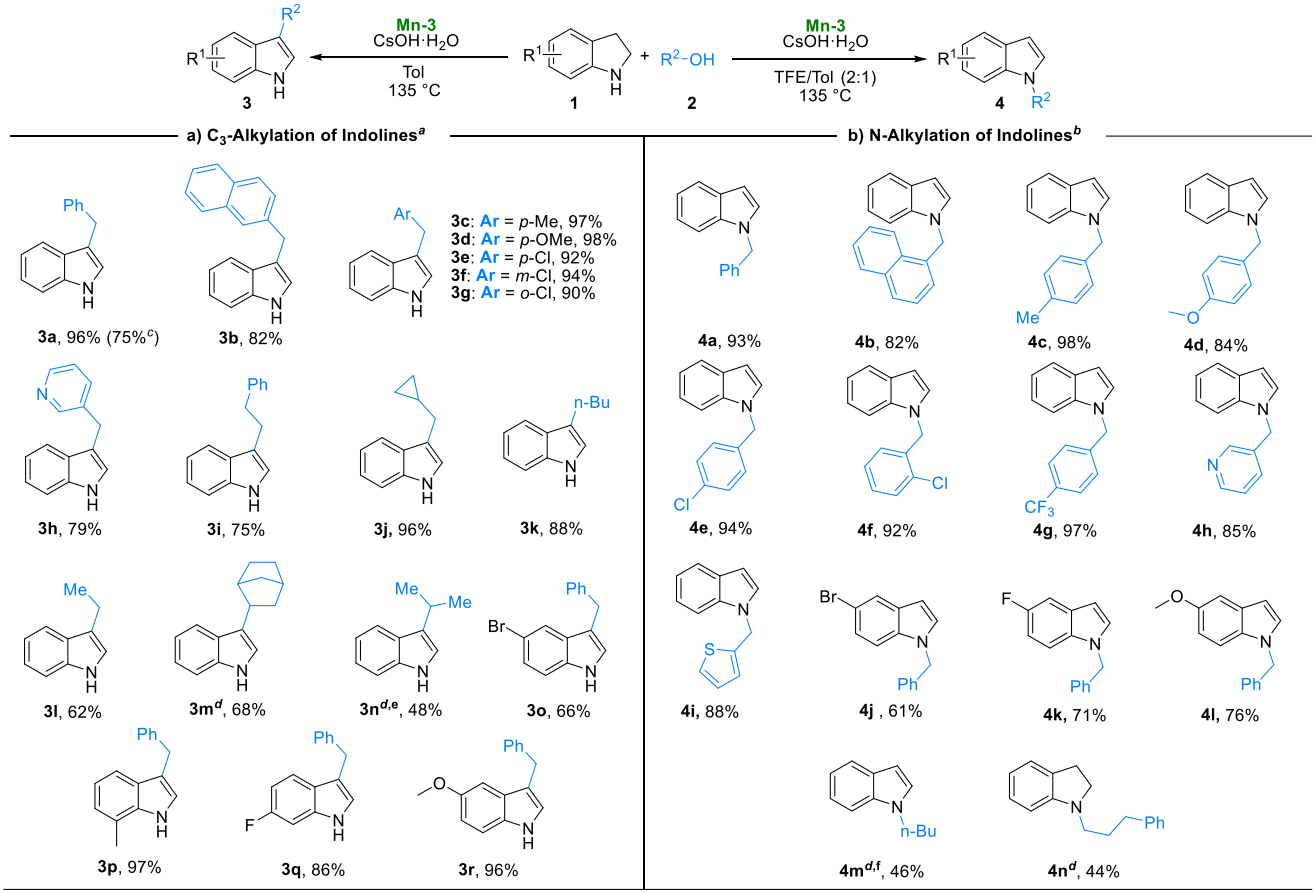
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol) in toluene (1.0 M) at 135 °C for 20 h under argon atmosphere. Yields were determined by GC analysis using ethylbenzene (0.2 mmol) as an internal standard. [b][Mn] (1 mol %). [c]125 °C. [d]0.17 M reaction mixture. [e]10 mol % base, 1.5 equiv. of benzyl alcohol. [f]36 h reaction time. [g][Mn] (5 mol %). Tol: toluene. CPME: cyclopentyl methyl ether. *t*-AmOH: tert-amyl alcohol. HFIP: 1,1,1,3,3,3-hexafluor-2-propanol. TFE: 2,2,2-trifluoroethanol.

Notably, all indoline starting materials were synthesized by a novel **Mn-3** catalyzed hydrogenation protocol starting from the corresponding indoles (see Supporting

Information for details). Initially, the dehydrogenative C_3-alkylation was investigated (Scheme 2a). Subjecting unsubstituted indoline **1** to the standard conditions using simple benzylic alcohols furnished alkylated indoles **3a-c** in good yields. Electron-donating and electron-withdrawing groups on the aromatic ring, regardless of their position, were tolerated and the desired products **3d-g** were obtained in good yields, demonstrating that steric hindrance of the substituents have no significant effect on the yield. Likewise, an alcohol bearing a heterocycle such as pyridine could also be used as the coupling partner (**3h**). Primary aliphatic alcohols were also successfully applied as alkylating reagents, affording the corresponding indoles **3i-l** in good yields. Gratifyingly, secondary alcohols such as norbonyl- or isopropyl alcohol, that are less prone to undergo condensation and hydrogenations,[6i,13] were also used as suitable coupling partners and the corresponding indoles **3m** and **3n** were obtained in moderate to good yields. In order to demonstrate the general applicability of the reaction, benzyl alcohol (**2a**) was coupled with a variety of substituted indolines providing the desired products **3o-r** in good to excellent yields.

Next, we investigated the substrate scope for the dehydrogenative N-alkylation of indolines (Scheme 2b). Under the optimized reaction conditions several benzylic alcohols were converted into the corresponding products **4a-c** in good yields. Electron-rich or electron-deficient alcohols were tolerated as well and were used efficiently as coupling partners to yield **4d-g** in high yields. Notably, heterocyclic alcohols bearing pyridine or thiophene moieties were successfully employed as alkylating reagents (**4h-i**). In addition, this transformation could be further extended to halide and methoxide substituted indolines and the corresponding *N*-benzyl substituted indoles **4j-l** were obtained in good yields. Moreover, also aliphatic alcohols appeared to be suitable coupling partners. As such, *N*-butyl indole was converted, although in lower yield (**4m**). However, N-alkylated indoline **4n** could be also obtained as main product, indicating an impeded dehydrogenation of the alkylated indoline or isomerization of the corresponding enamine intermediate. In order to better understand the reactions, several experiments were performed to investigate the formation of related intermediates and the mechanism in general (Scheme 3). The catalytic indoline dehydrogenation occurs in toluene providing indole in quantitative yield (Scheme 3a).

Scheme 2. Manganese-Catalyzed Dehydrogenative C_3- & N-Alkylation of Indolines.

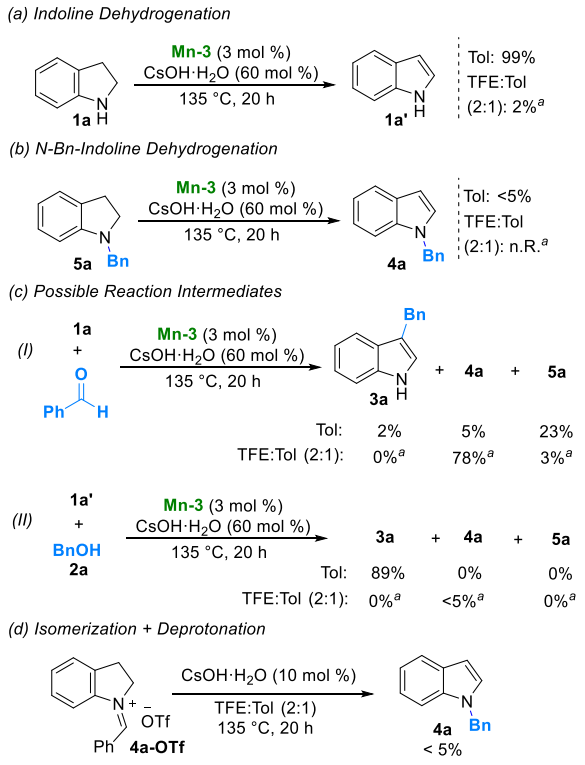


[a]All yields refer to the isolated products. Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), $CsOH·H_2O$ (0.3 mmol), **Mn-3** (1 mol %) in toluene (0.5 mL) at 135 °C for 20 h. [b]All yields refer to the isolated products. Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), $CsOH·H_2O$ (0.03 mmol), **Mn-3** (3 mol %) in toluene (0.6 mL) and TFE (1.2 mL) at 135 °C for 36 h. [c]Reaction on 1 mmol scale. [d]48 h reaction time and 4 mol % of **Mn-3**. [e]0.3 mL *i*-PrOH used. [f]*N*-Bu indoline observed as byproduct.

However, minor conversion was observed when TFE was added as co-solvent. Interestingly, *N*-benzyl indoline could not be dehydrogenated under the optimized conditions, indicating an alternative mechanism for the N-alkylation (Scheme 3b). Moreover, we anticipated aldehydes and ketones to be crucial intermediates.

Evidently, the coupling of indoline and benzaldehyde afforded a mixture of C_3- and N-alkylated products in toluene, suggesting that the initial dehydrogenation of indoline is critical for the regioselectivity (Scheme 3c). However, upon addition of TFE both high conversion and regioselectivity were observed and the N-alkylated indole **4a** was obtained along with traces of indoline **5a**. To further prove the necessity of indole as an intermediate for the C_3-alkylation, we carried out the alkylation reaction with benzylalcohol (**2a**). Indeed, when the reaction was performed in toluene, C_3-alkylated indole **3a** was provided as sole product, highlighting flexibility of the developed procedure. Importantly, upon addition of TFE, only traces of product were observed (Scheme 3c). To further understand the mechanism of the N-alkylation we performed a control reaction to exclude a base catalyzed isomerization/deprotonation of the iminium intermediate. Thus, indolium-triflate salt **4a-OTf** was reacted with CsOH·H_2O (Scheme 3d). However, only traces of product **4a** were formed. This result implies that the Mn-catalyst is involved in the process which would occur *via* an imine hydrogenation, indoline dehydrogenation sequence. Based on these results, we propose the following reaction mechanism for the regioselective dehydrogenative alkylation of indolines (Figure 1).

Scheme 3. Mechanistic Studies for the Divergent Alkylation of Indoline.



[a]10 mol % CsOH·H_2O used.

Initially, **Mn-3** reacts with CsOH to generate the active Mn-catalyst, which subsequently dehydrogenates the alcohol to the corresponding aldehyde. In toluene, the catalyst additionally converts indoline **1a** to indole **1a'** and releases hydrogen gas in an acceptorless dehydrogenation (AD) manner. Next, **1a`** and the aldehyde react to form intermediate **6**, which is then transformed to the final product **3** by the Mn-H_2 species (Hydrogen Autotransfer, HA). In contrast, no dehydrogenation of indoline **1a** occurs in the presence of TFE. Thus, the N-alkylation pathway occurs via the formation of indolinium species **7**.

The corresponding and more stable enamine **5** can be observed as a side product. Upon releasing hydrogen gas, the Mn* catalyst is regenerated again. The final product **4** is then provided by isomerization/deprotonation of **7**. In order to understand this process, we conducted computational studies to shed light on the mechanism for the N-alkylation. Under basic conditions, an indolium cation is formed. For the specific case of 1-butyl-3H-indol-1-ium (see Figure 2), the 18-electron Mn-H_2 species (**A**) acts as the hydride-borrowing catalyst. The free activation barrier for the hydride transfer from Mn to C_1 has been calculated as 17.7 kcal mol^{-1} [TS(**AB**)] under 1 atm and 135 °C reaction temperature in TFE. Thus, 1-butylindoline is formed (**B**, –8.3 kcal mol^{-1}) with the Mn(I) species being oxidized into a Mn(II) species. State C (–8.8 kcal mol^{-1}) represents a conformational minimum with the hydride on C_2 (five-membered ring) ready to be transferred back to Mn-catalyst. This process, characterized by TS(**CA**), shows a free activation barrier of 13.7 kcal mol^{-1} (22.5 kcal mol^{-1} relative to C) and represents the rate-limiting step of this cycle. Thus, the 1-butyl-3H-indol-1-ium cation is produced and the 18-electron Mn-H_2 species is regenerated.

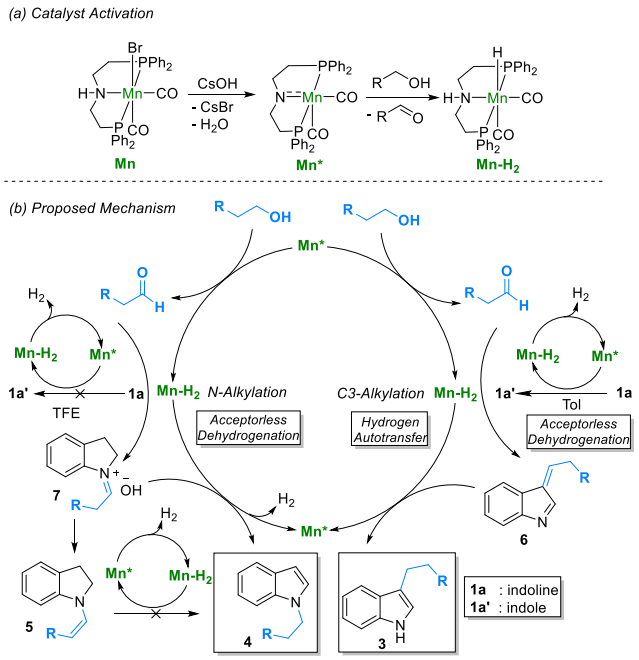


Figure 1. Proposed mechanism for the divergent dehydrogenative alkylation of indolines involving acceptorless dehydrogenation (AD) and hydrogen autotransfer (HA).

The proton abstraction by OH^- leading to the aromatized 1-butyl-1H-indole (**4m**) has been computed as a barrier-less process.

In order to rationalize the influence of TFE on the remarkable selectivity switch, we conducted further solvent screenings (see Supporting Information). It was found, that no other solvents with lower or higher pKa compared to TFE (12.37) could provide similar conversion and selectivity. TFE has been shown to accelerate condensation reactions through hydrogen-bonding activation[14] indicating that the fast condensation of indoline and the aldehyde is key for selective *N*-alkylation reaction. Furthermore, recent computational studies by Poater showed that polar protic solvents help to facilitate the β-hydride elimination during an acceptorless alcohol dehydrogenation process (AAD).[15]

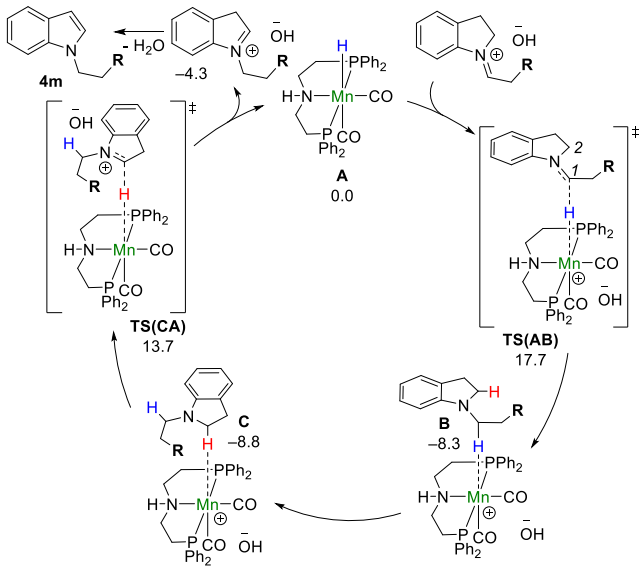


Figure 2. Reaction mechanism for the isomerisation of 1-butyl-ideneindolin-1-ium into 1-butyl-3*H*-indol-1-ium *via* Mn-catalyzed hydride borrowing. Free energy results (1 atm, 135 °C, kcal mol^{-1}) are shown at the PBE0/SVP level of theory in TFE (ε = 26.726) as solvent. Note: **R** refers to C_2H_5.

In summary, we have developed a new base metal-catalyzed regioselective dehydrogenative alkylation of indolines with readily available alcohols by applying a single manganese catalyst. This catalyst is able to catalyze the dehydrogenation of both, alcohols and indolines as well as the selective 1,2- and 1,4-reduction of imines using either acceptorless dehydrogenation (AD) and hydrogen autotransfer (HA) pathways or both processes. Additionally, we demonstrate that the selective N- or C-alkylation can be achieved by an interesting solvent polarity and acidity switch.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website

Experimental data include characterization data for all new compounds, NMR Spectra and computational details (PDF)

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Notes

The authors declare no competing financial interest

Funding Sources

Notes

Any additional relevant notes should be placed here.

ACKNOWLEDGEMENTS

This work was financially supported by the King Abdullah University of Science and Technology (KAUST), Saudi Arabia, Office of Sponsored Research (FCC/1/1974).

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