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

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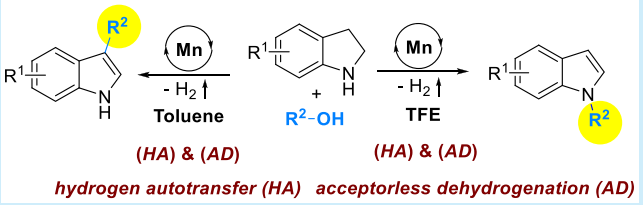
ABSTRACT: The first base metal-catalyzed regioselective dehydrogenative alkylation of indolines using readily available alcohols as the alkylating reagent is reported. A single air- and moisture-stable manganese catalyst provides access to either C_3- or N-alkylated indoles depending on the solvent used.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



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Indoles represent a prominent and important chemical motif in medicinal chemistry and agrochemistry.[1] Several drugs like oxypertine, bufotenine, or indomethacin include this heterocyclic scaffold.[2] In the past several years, the selective functionalization of indoles has attracted considerable attention.[3] One of the most common methods for alkylating indoles at the 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 the use of mutagenic (pseudo)haloalkanes, it remains a wasteful and unsustainable approach. In this regard, abundant alcohols have emerged as cheap and environmentally benign building blocks for C−C and C−N bond formation, following acceptorless dehydrogenation (AD) and hydrogen autotransfer (HA) reaction strategies.[5] However, 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 at the indole C_3-[6] or N-position.[7] 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 either react with indole **D** to give the corresponding imine **E** or react with indoline **C** to give the iminium ion **G** resulting in either a C- or an 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 alternatively through a hydride addition/dehydrogenation sequence via the N-alkylated product **H** (Scheme 1). On the basis of 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 that allows a targeted N- versus 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 a base to give either C_3- or N-alkylated indoles **3a** and **4a** or N-alkylated indoline **5a** as the product (Table 1). Inspired by our latest results in dehydrogenative coupling protocols, we initially tested different bifunctional Mn(I) complexes. **Mn-1**, which includes 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).

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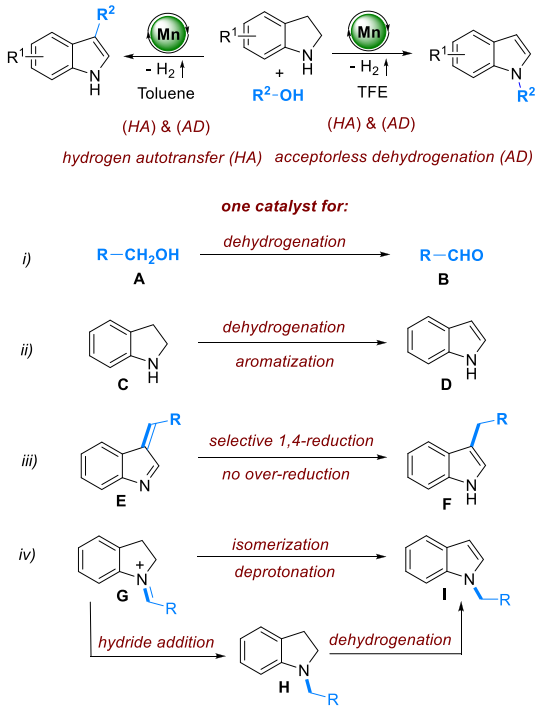
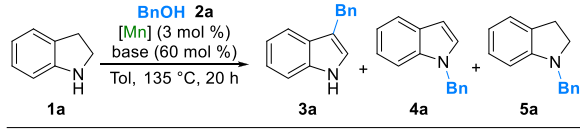
Scheme 1. Dehydrogenative Alkylation of Indolines

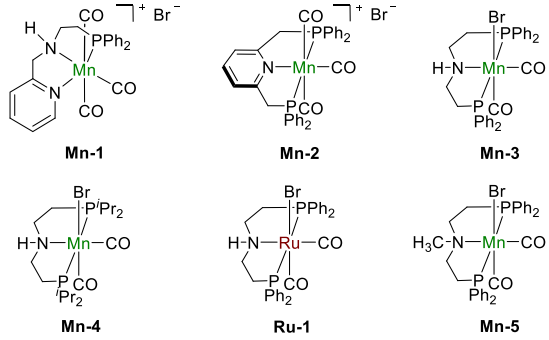


Surprisingly, the PNP analogue **Mn-4** provided only low conversion (Table 1, entry 4). Furthermore, N-methylated **Mn-5** yielded trace amounts of product, illustrating the necessity of the NH moiety (Table 1, entry 5).[12] To further optimize the reaction conditions with **Mn-3**, different bases and solvents were evaluated (Table 1, entries 6–18). With cesium bases, such as Cs_2CO_3 or $CsOH·H_2O$, with toluene as the solvent, and with 1 mol % catalyst, the yields considerably increased to 63% and 98% (Table 1, entries 6 and 9, respectively). Decreasing the temperature by 10 °C reduced the yield significantly (Table 1, entry 10). The best results were obtained when 1 mol % **Mn-3** was employed with 10 mol % $CsOH·H_2O$ in toluene (Table 1, entry 9). Conversely, with a chance in 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 in the absence of **3a**, when TFE was applied (Table 1, entry 15). Surprisingly, no other polar protic solvents such as *tert*-amyl alcohol and hexafluoroisopropanol (HFIP) afforded equally good results (Table 1, entries 13 and 14, respectively). 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, we obtained the alkylated indole **4a** 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).

Notably, all indoline starting materials were synthesized by a novel **Mn-3**-catalyzed hydrogenation protocol starting from the corresponding indoles (see the Supporting Information for details). Initially, the dehydrogenative C_3-alkylation was investigated (Scheme 2a). Subjecting unsubstituted indoline **1a** 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 the steric hindrance of the substituents has 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

Table 1. Optimization of the Reaction Conditions[a]





entry	catalyst	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**	$CsOH·H_2O$	2:1 TFE/Tol	0:68:6
18[d–f]	**Mn-3**	$CsOH·H_2O$	2:1 TFE/Tol	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) and **2a** (0.4 mmol) in toluene (1.0 M) at 135 °C for 20 h under an argon atmosphere. Yields were determined by GC analysis using ethylbenzene (0.2 mmol) as an internal standard. Abbreviations: Tol, toluene; CPME, cyclopentyl methyl ether; *t*-AmOH, *tert*-amyl alcohol; HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol; TFE, 2,2,2-trifluoroethanol. [b]With 1 mol % Mn. [c]At 125 °C. [d]For a 0.17 M reaction mixture. [e]With 10 mol % base, 1.5 equiv of benzyl alcohol. [f]With a 36 h reaction time. [g]With 5 mol % Mn.

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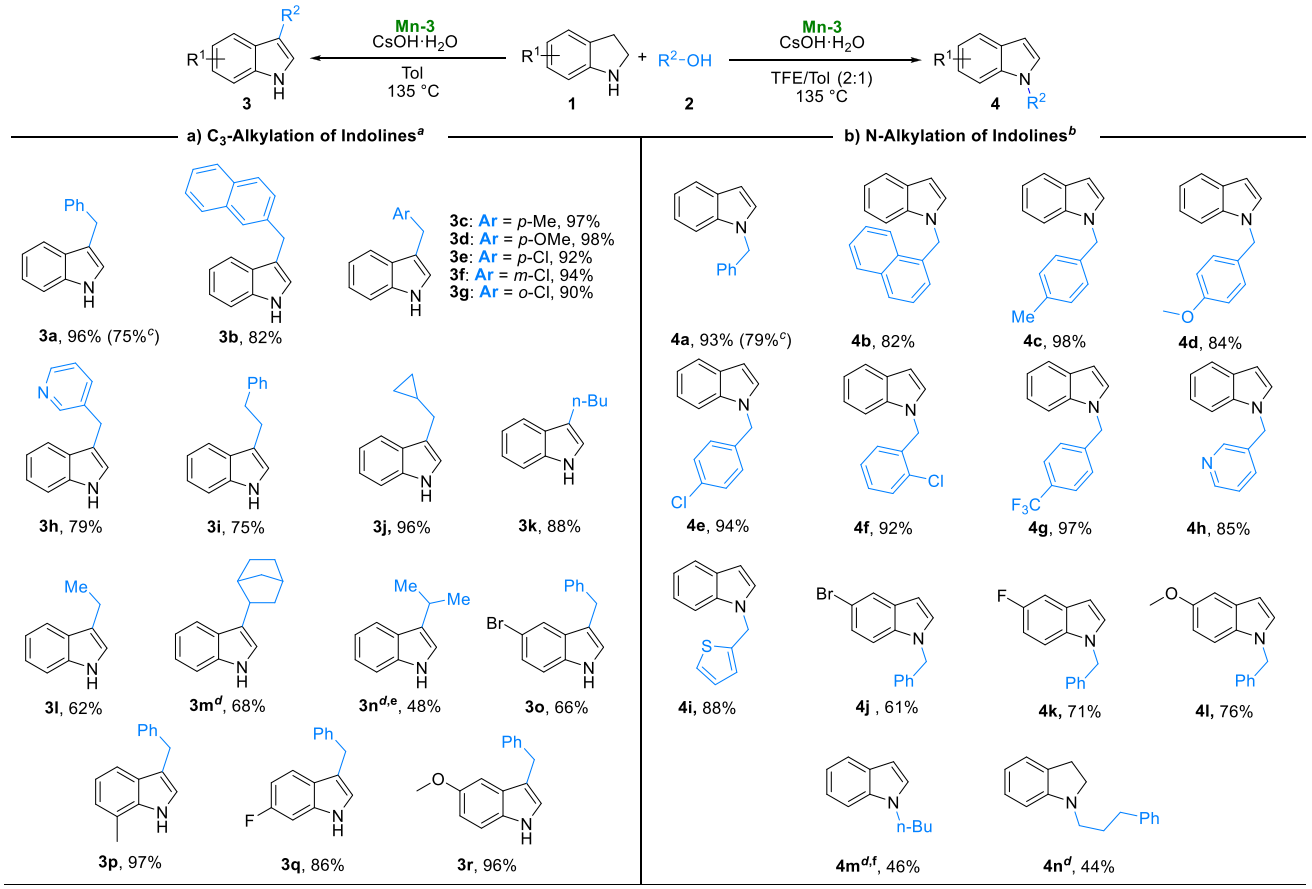
Scheme 2. Manganese-Catalyzed Dehydrogenative C_3- and N-Alkylation of Indolines



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

corresponding indoles **3i−l** in good yields. Gratifyingly, secondary alcohols such as norbonyl or isopropyl alcohol, which are less prone to undergoing 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. 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 used efficiently as coupling partners to give **4d−g** in high yields. Notably, heterocyclic alcohols bearing pyridine or thiophene moieties were successfully employed as alkylating reagents (**4h** and **4i**). 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 a lower yield (**4m**). However, N-alkylated indoline **4n** could be also obtained as the main product, indicating an impeded dehydrogenation of the alkylated indoline or isomerization of the corresponding enamine intermediate. 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).

However, minor conversion was observed when TFE was added as a 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 the sole product, highlighting flexibility of the developed procedure. Importantly, upon addition of TFE, only traces of the product were observed (Scheme 3c). To further understand the mechanism of the N-

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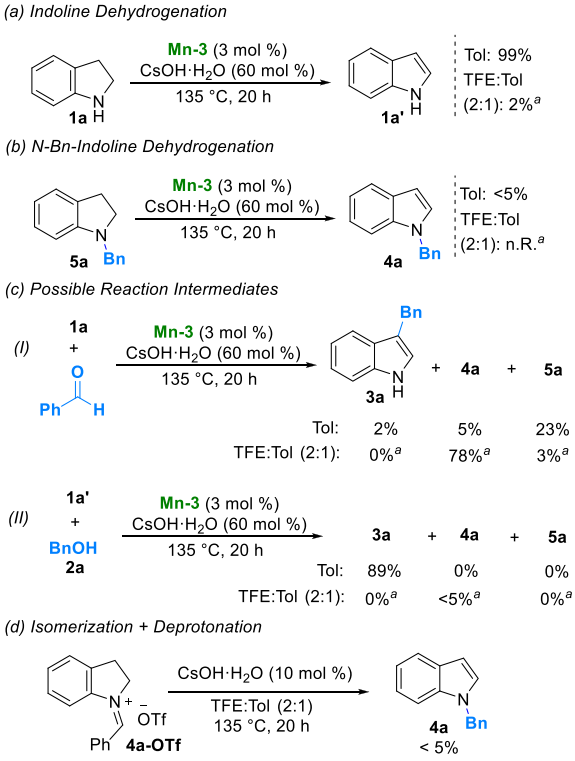
Scheme 3. Mechanistic Studies for the Divergent Alkylation of Indoline



[a]With 10 mol % $CsOH·H_2O$.

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 that would occur via an imine hydrogenation, indoline dehydrogenation sequence. On the basis of these results, we propose the following reaction mechanism for the regioselective dehydrogenative alkylation of indolines (Figure 1).

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 the release of hydrogen gas, the Mn* catalyst is regenerated again. The final product **4** is then provided by isomerization/deprotonation of **7**. To understand this process, we conducted computational studies to shed light on the mechanism for the N-alkylation. Under basic conditions, an indolinium cation is formed. For the specific case of 1-butyl-3*H*-indol-1-inium (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}

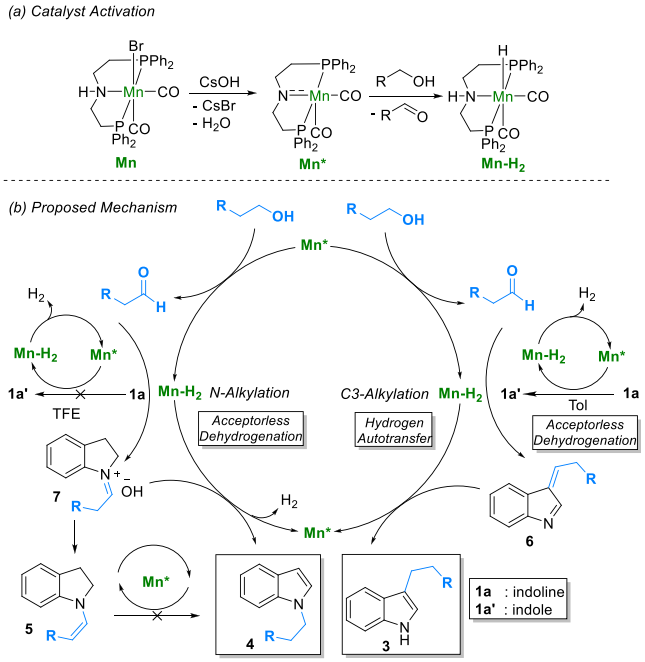


Figure 1. Proposed mechanism for the divergent dehydrogenative alkylation of indolines involving acceptorless dehydrogenation (AD) and hydrogen autotransfer (HA). The proton abstraction by OH^- leading to the aromatized 1-butyl-1H-indole (**4m**) has been computed as a barrierless process.

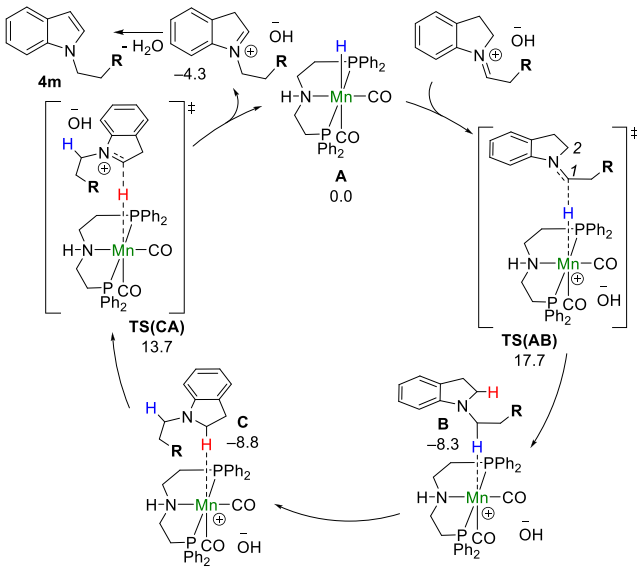


Figure 2. Reaction mechanism for the isomerization of 1-butylideneindolin-1-inium into 1-butyl-3*H*-indol-1-inium via Mn-catalyzed hydride borrowing. Free energy results (1 atm, 135 °C, kcal mol^{-1}) are shown at the PBE0/SVP level of theory with TFE (ε = 26.726) as the solvent. **R** refers to C_2H_5.

[TS(**AB**)] under 1 atm and 135 °C 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 the 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

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step of this cycle. Thus, the 1-butyl-3*H*-indol-1-inium cation is produced, and the 18-electron $Mn-H_2$ species is regenerated.

To rationalize the influence of TFE on the remarkable selectivity switch, we conducted further solvent screenings (see the Supporting Information). It was found that no other solvents with a lower or higher pK_a compared to that of 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 the 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]

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 can 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 at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01270.

Experimental data, including characterization data for all new compounds, NMR spectra, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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