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Letter

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Dehydrogenative Cross-Coupling of Primary Alcohols to Form Cross-Esters Catalyzed by a Manganese Pincer Complex

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ABSTRACT: Base-metal-catalyzed dehydrogenative cross-coupling of primary alcohols to form cross-esters as major products, liberating hydrogen gas, is reported. The reaction is catalyzed by a pincer complex of earth-abundant manganese in presence of catalytic base, without any hydrogen acceptor or oxidant. Mechanistic insight indicates that a dearomatized complex is the actual catalyst, and indeed this independently prepared dearomatized complex catalyzes the reaction under neutral conditions.

KEYWORDS: manganese, pincer complex, dehydrogenation, primary alcohol, cross-ester, hydrogen

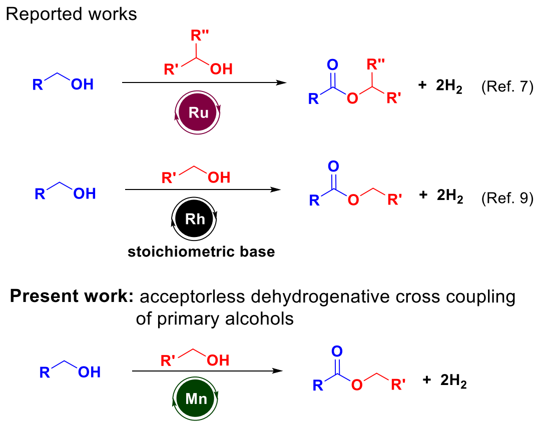
Esters constitute one of the most important classes of compounds in organic chemistry, and are used as bulk chemicals in commercial products and polymer industries. The esterification process has numerous applications in the production of synthetic intermediates, biologically active natural products, esters of oils and fats, polymers and pharmaceuticals.[1]

Esters are commonly prepared by the reaction of carboxylic acids or activated acid derivatives, e.g. acid chlorides or anhydrides, with alcohols.[2] In recent years, noble-metal based homogeneous catalysts have been developed for the dehydrogenative transformation of alcohols to esters using oxidants or hydrogen aceptors.[3] Heterogeneous catalytic systems based on supported noble-metal nanoparticles have also been developed for the transformation of alcohols to esters.[4] Although several catalytic procedures for esterification of alcohols to esters have been reported so far, less attention has been paid to the dehydrogenative cross coupling of different alcohols to form esters.

The acceptorless dehydrogenative homo-coupling of alcohols to esters catalyzed by ruthenium was reported by Shvo.[5] We reported metal–ligand cooperative ruthenium catalysts for dehydrogenative coupling of primary alcohols,[6] dehydrogenative cross coupling of primary alcohols with secondary alcohols[7] and transesterification of symmetrical ester with secondary alcohols to form esters.[8] The dehydrogenative cross coupling of two different primary alcohols to form esters with evolution of H_2 is rare. Xiao reported dehydrogenative cross coupling of primary alcohols to esters catalyzed by a dimeric rhodium catalyst in the presence of stoichiometric base [9] (Scheme 1).

Despite all of these well-established methodologies, the development of environmentally benign and cost-effective procedures for the synthesis of cross-esters continues to attract considerable interest. In this respect, acceptorless dehydrogenative coupling (ADC) reaction between primary alcohols appears as an environmentally friendly, oxidant-free, and atom-efficient catalytic cross coupling process that simultaneously produces cross esters and hydrogen.

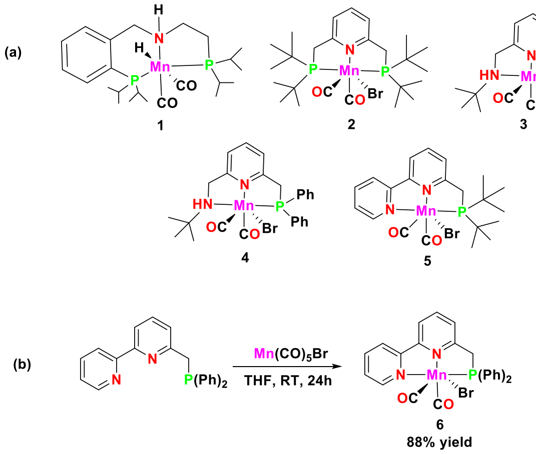
The application of complexes of earth abundant metals (Fe, Co, Ni, Mn) in homogeneous catalysis has attracted much recent attention.[10] Since our first report of a manganese pincer catalyst in 2016,[11] manganese has offered an attractive alternative to noble metal-based catalysts in the area of alcohol dehydrogenation chemistry.[12] Recently Gauvin and co-workers reported Mn-catalyzed dehydrogenative coupling of alcohols to form homo-esters.[13] We are not aware of reported base-metal catalyzed dehydrogenative cross-coupling of two different primary alcohols to form mainly cross-esters with evolution of H_2.



Scheme 1. Dehydrogenative cross coupling of two different alcohols to cross esters.

Herein we report such a reaction to produce cross-esters from two different primary alcohols under mild conditions. Moreover this acceptorless dehydrogenative cross-coupling reaction is catalyzed by a new manganese pincer complex.

In this study we have explored our previously reported manganese pincer complexes **1** to **5** (Scheme 2, a), which are very good catalyst for (de)hydrogenation of alcohols.[12a, 14] For this purpose, we have now prepared the new manganese pincer complex $Mn(^{Ph}PNN)(CO)_2Br$ (**6**). Treatment of our previously reported ^{Ph}PNN ligand[15] with one equivalent of $Mn(CO)_5Br$ at room temperature in THF led to formation of complex (**6**) in 88% yield (Scheme 2, b). The two carbonyl ligands of complex **6** give rise to two bands at 1838 and 1917 cm^{-1} in the IR spectrum in a 1:1 ratio, indicating a nearly 90° C-Mn-C angle. Single crystals of complex **6** suitable for X-ray diffraction were obtained by slow diffusion of pentane into a saturated solution of dichloromethane at -30 °C. The molecular structure of **6** exhibits an octahedral geometry with a meridional arrangement of the ^{Ph}PNN ligand. The CO ligands are orthogonal to each other (86.75°), in line with the IR spectrum (Figure 1, and SI).



Scheme 2. (a) Manganese pincer complexes (**1-5**) explored in this study. (b) Synthesis of Mn(^{Ph}PNN)(CO)$_2$Br (**6**). See Supporting Information (SI) for experimental details.

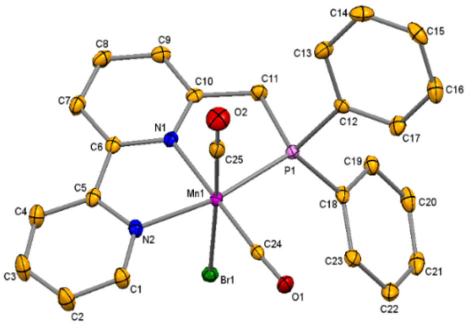
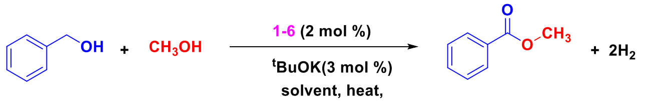


Figure 1. Molecular structure of Mn(^{Ph}PNN)(CO)$_2$Br (**6**) complex. Thermal ellipsoids are drawn at 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Mn1-Br1 = 2.5429(3), Mn1-N1 = 2.0301(12), Mn1-N2 = 2.0276(13), C24-O1 = 1.1611(18), C25-O2 = 1.188(4), Mn1-P1 = 2.2353(4). Selected bond angles (°): N1-Mn1-N2 = 79.09(5), Br1-Mn1-C25 = 176.22(11), N1-Mn1-P1 = 84.62(4), N2-Mn1-P1 = 163.12(4), N1-Mn1-C24 = 178.13(6), N1-Mn1-C25 = 94.94(11), Mn1-C24-O1 = 176.51(13), Mn1-C25-O2 =175.9(3), C24-Mn1-C25 =86.75(12). See Supporting Information (SI) for crystallography details.

In optimization studies, the coupling of benzyl alcohol with methanol was chosen as a model reaction. Reaction of benzyl alcohol (1 mmol), methanol (10 mmol), complex **1** or complex **2** (2 mol %) in presence of 3 mol % of potassium *tert*-butoxide (^{t}BuOK) in 2 mL of toluene at 110 °C in a closed Schlenk tube resulted after 24 h in formation of methyl benzoate in poor yield with a very small amount of benzyl benzoate (Table 1, entries 1 and 2). Under the same reaction conditions using complex **3** as catalyst 30% methyl benzoate and 45% conversion of benzyl alcohol were observed (Table 1, entry 3). Using complex **4** as catalyst, the alcohol conversion increased to 63%, giving 41% yield of the methyl ester product (Table 1, entry 4). Complex **5** was not an effective catalyst, leading to only 17% of methyl benzoate (Table 1, entry 5). Interestingly, using complex **6**, in which the ^{t}Bu$_2$P groups of **5** are replaced by Ph$_2$P groups resulted under the same conditions in high catalytic activity, perhaps due to decreased steric hindrance and higher Lewis acidity of the metal center, favoring a coordinated aldehyde intermediate. Thus, methyl benzoate was formed in 87% yield at 110 °C (Table 1, entry 6) and 93% at 120 °C, with 97 % benzyl alcohol conversion after 24h (Table 1, entry 7), as revealed by GC-MS and NMR. Analysis of the gas phase by GC indicated formation of H$_2$. Noteworthy the reaction does not require addition of an oxidant or hydrogen acceptor. Thus, Mn(^{Ph}PNN)(CO)$_2$Br (**6**) in the presence of catalytic ^{t}BuOK is an efficient catalyst for alcohol dehydrogenative coupling with methanol to form methyl esters. Good yields were obtained also after 12h (Table 1, entry 8). Using 1:5 molar ratio of benzyl alcohol and methanol produced 56% of methyl ester in addition to benzyl benzoate as self-coupled product (Table 1, entry 9). Unexpectedly, using methanol (2 mL) as solvent and one equivalent of benzyl alcohol at 110 °C in a closed Schlenk tube under the same conditions did not produce any ester product, perhaps due to lower actual reaction temperature (Table 1, entry 10). Employing methanol: THF (1:1) was not effective and resulted in only 43% of methyl benzoate with 50 % alcohol conversion after 24h (Table 1, entry 11).

Table 1. Manganese catalyzed dehydrogenative coupling of benzyl alcohol and methanol.

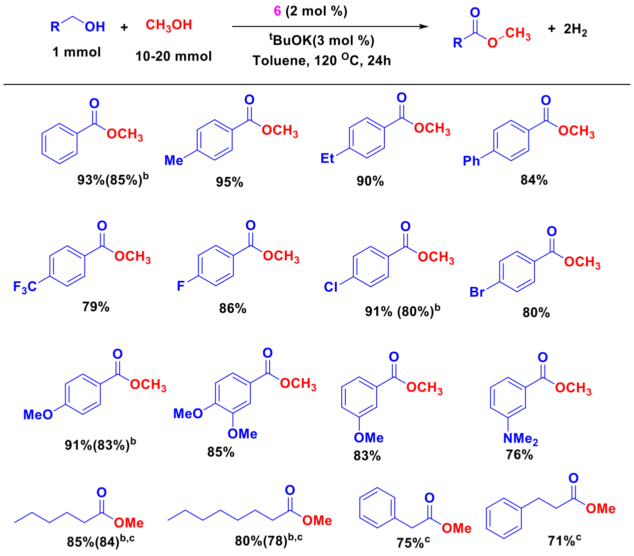


entry	[Mn]	solvent	temp.	conv.(%)	yield(%)
1^a	**1**	Toluene	110	25	16
2^a	**2**	Toluene	110	15	9
3^a	**3**	Toluene	110	45	30
4^a	**4**	Toluene	110	63	41
5^a	**5**	Toluene	110	25	17
6^a	**6**	Toluene	110	82	78
7^a	**6**	**Toluene**	**120**	**97**	**93**
8^b	**6**	Toluene	120	74	70
9^c	**6**	Toluene	120	99	56^d
10^e	**6**	Methanol	110	10	-
11^f	**6**	THF:CH$_3$OH	110	50	43

Reaction conditions: [a] benzyl alcohol (1 mmol), Mn-cat (0.02 mmol), ^{t}BuOK (0.03 mmol), methanol (10 mmol), 2 mL toluene, 24h. [b] Reaction time 12h. [c] 5 mmol CH$_3$OH used. [d] Rest of product was benzyl benzoate. [e] Benzyl alcohol (1 mmol), methanol (2 mL), **6** (0.02 mmol), ^{t}BuOK (0.03 mmol), [f] Benzyl alcohol (1 mmol), **6** (0.02 mmol), ^{t}BuOK (0.03 mmol), 2 mL 1:1 THF and methanol as solvent. All yields and conversions are calculated using GC-MS and ^{1}H NMR with mesitylene as internal standard.

The scope of this base-metal-catalyzed cross-coupling of primary alcohols with methanol using complex **6** was probed with different aromatic and aliphatic alcohols. As shown in Table 2, benzylic alcohols with electron donating or electron withdrawing groups were converted to the methyl esters in good to excellent yields. The para substituted benzyl alcohols (p-Me, p-Et, p-Ph, p-halo, p-CF$_3$, p-OMe) dehydrogenatively coupled with methanol to give methyl esters in excellent yields. Dehydrogenative coupling of m-substituted benzyl alcohols (m-OMe, m-N(CH$_3$)$_2$) with methanol also proceeded well. The methyl ester formation was tested also with primary aliphatic alcohols. Methyl esters of 1-hexanol and 1-ocatanol were formed in 85% and 80% yields, respectively, using a 1:20 molar ratio of alcohol and methanol. In a similar way, 2-phenyl ethanol and 3-phenyl propanol were also converted to the corresponding methyl esters in 75% and 71% yields, respectively (Table 2).

Table 2. Manganese catalyzed dehydrogenative coupling of primary alcohols with methanol.[a]

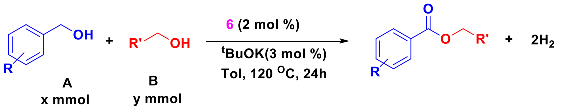


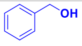
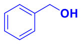
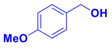
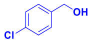
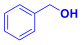
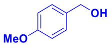
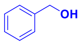
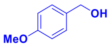
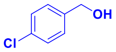
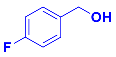
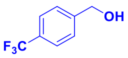
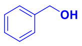
[a] Reaction conditions: alcohol (1 mmol), CH_3OH (10 mmol), **6** (0.02 mmol), ^{t}BuOK (0.03 mmol), toluene (2 mL), 120°C, 24 hrs. All yields are calculated using GC-MS and ^{1}H NMR with mesitylene as internal standard. [b] Isolated yields. [c] 20 mmol CH_3OH were used.

To evaluate the scope of the reaction, different aliphatic alcohols other than methanol were tested using this methodology. Reaction between benzyl alcohol and ethanol in 1:10 molar ratio, respectively, resulted in 82% yield of ethyl benzoate (Table 3, entry 1). As expected, lowering the amount of primary alcohol relative to benzyl alcohol resulted in a mixture of esters. Reaction between benzyl alcohol and ethanol in 1:5 molar ratio resulted in 67% of ethyl benzoate and 10% benzyl benzoate (Table 3, entry 2). p-OMe and p-Cl benzyl alcohols produced 85% and 80% of the corresponding ethyl benzoates when a 1:10 molar excess of ethanol was used (Table 3, entry 3 and 4). In a similar way propionic esters of different benzylic alcohols were synthesized in good yields using 1:5 molar ratio of benzylic alcohols and 1-propanol, respectively (Table 3, entry 4 and 5).

Next, the longer chain alcohols 1-butanol and 1-hexanol were explored. Interestingly, using a 1:1 molar ratio of 1-butanol and benzyl alcohol resulted in formation of n-butyl benzoate in 67% yield as cross-ester product. Only small amounts of the homo-coupled esters benzyl benzoate and butyl butyrate were formed as side products (5-10% each, see SI).The relatively selective formation of n-butyl benzoate may be due to faster dehydrogenation of benzyl alcohol to the aldehyde as compared with formation of the aliphatic aldehyde. As expected, increasing the amount of 1-butanol, resulted in higher yield of the cross-ester. Thus, reaction of 1.75 mmol of 1-butanol with one mmol of benzyl alcohol produced butyl benzoate in 80% yield (Table 3, entry 7 and 8). As shown in Table 3, benzyl alcohols bearing various electron-donating or electron-withdrawing substituents at the para position (p-OMe, p-Cl, p-F, p-CF3) dehydrogenatively coupled with 1-butanol to give selectivity the corresponding butyl benzoates (Table 3, entries 9–13). Formation of butyl butyrate was observed as the only homo coupled ester when excess 1-butanol was used. Coupling of one mmol of 1-hexanol with one mmol benzyl alcohol gave mixtures of esters in both closed and open systems (See SI); at 1:1.75 molar ratio of benzyl alcohol:1-hexanol, 63% of hexyl benzoate and 22% of hexyl hexanoate were obtained (Table 3, entry 14).

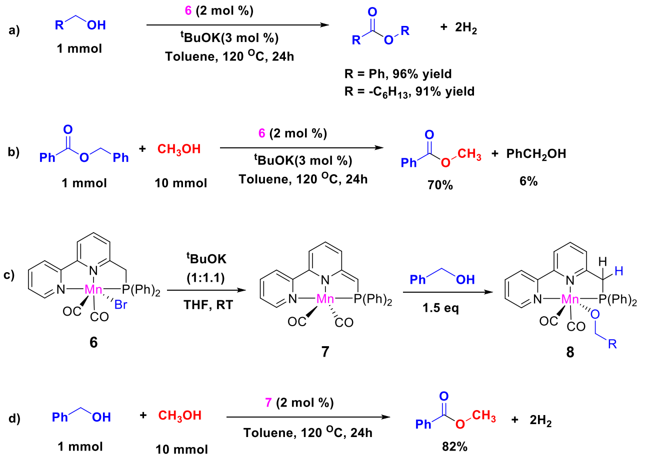
Table 3. Manganese catalyzed dehydrogenative cross-coupling of benzylic alcohols with different aliphatic alcohols.[a]



entry	A	B	x:y	Yield (%)[b]
1		Ethanol	1:10	82(78%)[c]
2		Ethanol	1:5	67
3		Ethanol	1:10	85
4		Ethanol	1:10	80
5		1-Propanol	1:5	78(75)[c]
6		1-Propanol	1:5	81
7		1-Butanol	1:1	67
8			1:1.75	80[d]
9		1-Butanol	1:1	73
10		1-Butanol	1:1	75
11		1-Butanol	1:1	73
12			1:1.75	84[d]
13		1-Butanol	1:1	65
14		1-Hexanol	1:1.75	63[e]

[a] Reaction conditions: benzyl alcohol (1 mmol), aliphatic alcohol (y mmol), **6** (0.02 mmol), ^{t}BuOK (0.03 mmol), toluene (2 mL), 120°C, 24 hrs. [b] All yields are calculated using GC and ^{1}H NMR with mesitylene as internal standard. [c] Isolated yield. [d] Butyl butyrate formed as side product. [e] Hexyl hexanoate formed as side product.

In experiments using just benzyl alcohols or long chain primary aliphatic alcohols under the above-mentioned reaction conditions self-coupled esters were formed (Scheme 3, a). However, we did not observe methyl formate or ethyl acetate formation using methanol or ethanol, likely due to volatility. Reaction of benzyl benzoate (1 mmol), methanol (10 mmol), complex **6** (2 mol %) in presence of 3 mol % of potassium *tert*-butoxide (^{t}BuOK) in 2 mL of toluene at 120 °C in a closed Schlenk tube resulted 70% methyl benzoate and 6% of benzyl alcohol after 24 h (Scheme 3, b).



Scheme 3. (a) Manganese catalyzed dehydrogenative self-coupling of alcohols and (b) coupling of benzyl benzoate with methanol. (c) alkoxy

complex **8** formation from complex **6** and (d) coupling of benzyl alcohol with methanol catalyzed by complex **7**.

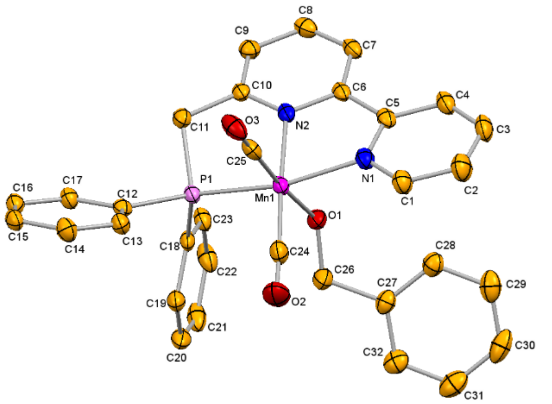
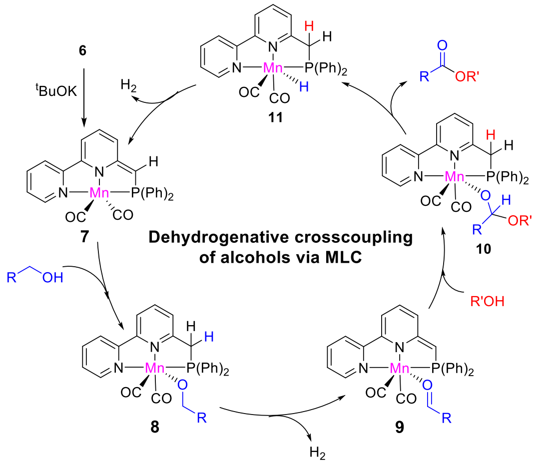


Figure 2. Molecular structure of Mn(^{Ph}PNN)(OCH$_2$Ph)(CO)$_2$ (**8**) complex. Thermal ellipsoids are drawn at 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Mn1-O1 = 2.0021(14), Mn1-N1 = 2.0349(17), Mn1-N2 = 2.0345(17), Mn1-P1 = 2.2359(6), O2-C24 = 1.168(3), O3-C25 = 1.173(2), Mn1-C24 = 1.780(2), Mn1-C25 = 1.761(2). Selected bond angles (°): N1-Mn1-N2 = 78.66(7), O1-Mn1-C25 = 174.82(8), N1-Mn1-P1 = 160.90(5), N2-Mn1-P1 = 82.86(5), N1-Mn1-C24 = 100.22(6), N1-Mn1-C25 = 93.86(11), Mn1-C24-O2 = 176.7(2), Mn1-C25-O3 =176.67(19), C24-Mn1-C25 =87.37(9), Mn1-O1-C26 = 126.67(13). See Supporting Information (SI) for crystallography details.

To gain the insight into the mechanism of the manganese catalyzed dehydrogenative cross coupling of alcohols, complex **6** was reacted with 1.1 equivalent of ^{t}BuOK in THF at room temperature to form the dearomatized complex Mn(^{Ph}PNN*)(CO)$_2$ (**7**) (Scheme 3, c). Complex **7** was characterized by IR and NMR spectroscopy (see SI). Employing the freshly prepared **7** (3 mol %) as a catalyst in the dehydrogenative coupling of benzyl alcohol and methanol at 120° C resulted in methyl benzoate in 82% yield after 24 hours *in the absence of any added base* (Scheme 3, d). Reaction of complex **7** and 1.5 equivalent of benzyl alcohol in THF (or toluene) at room temperature resulted in formation of the alkoxy complex Mn(^{Ph}PNN)(OCH$_2$Ph)(CO)$_2$ (**8**) by O-H activation through metal-ligand cooperation (MLC), as we observed previously in case of a similar Mn-PNN complex (Scheme 3, c).[14d] The alkoxy complex **8** was also characterized by IR, NMR and single crystallography (see SI). Crystal stucture of complex **8** showed a neutral octahedral manganese complex bearing a PNN pincer ligand, two mutually cis CO ligands (C24-Mn1-C25 =87.37°) and an alkoxy group (Figure 2, see SI). Heating complex **8** (^{31}P = 91 ppm) at 120 °C in toluene-*d$_8$* resulted in observation of benzyl benzoate by GC-MS (indicating some benzyl alcohol dissociation from **8** at that temperature) and two new peaks appeared in the ^{31}P{^{1}H} NMR at 98 ppm and 115 ppm, suggesting Mn-H complex formation. The formation of Mn-H complex (complex **11**) was confirmed by ^{1}H NMR spectroscopy (^{1}H NMR = -2.6 ppm, see SI) and by comparison with a separate reaction of complex **6** with an equimolar amount of NaBHEt$_3$ (See SI). We believe that complexes **7** and 8 are actual intermediates in the catalytic cycle.



Scheme 4. Plausible mechanism of manganese catalyzed dehydrogenative cross coupling of alcohols.

Based on the above observations, a plausible catalytic cycle for the Mn-catalyzed cross ester formation from two different primary alcohols is presented in Scheme 4. Reaction of the pre-catalyst **6** with the base generates the dearomatized complex **7**, which adds the alcohol via MLC to form the alkoxy complex **8**. Then β-H elimination (perhaps involving a non-classical alkoxide dissociation, assisted by the hydrogen bonded alcohol molecule, followed by hydride elimination from the dissociated alkoxide, as invoked for similar coordinatively saturated Mn-alkoxy complexes)[14d] generates the intermediate **9**, bearing a coordinated aldehyde. [16] Nucleophilic attack by the another alcohol on the aldehyde gives hemiacetal coordinated intermediate **10**, which upon β-H elimination forms the dihydride intermediate **11**, with liberation of ester molecule. Finally, dihydrogen loss from intermediate **11** regenerates the active catalyst **7** and completes the catalytic cycle. Formation of intermediate **9** with coordinated benzaldehyde, and perhaps also the nucleophilic attack on it by the aliphatic alcohols are likely preferred due to the electron-withdrawing nature of the phenyl ring, resulting in the observed selectivity.

In conclusion, we have demonstrated experimental conditions for the formation of cross-esters as major products using different primary alcohols. Moreover, this acceptorless dehydrogenative coupling reaction is catalyzed by a base metal catalyst. The reaction proceeds under homogeneous reaction conditions and is catalyzed by the new pincer catalyst Mn(^{Ph}PNN)(CO)$_2$Br (**6**) in presence of catalytic base, or in absence of base using the dearomatized complex **7**. A plausible mechanism is provided, supported by control experiments and the observation of intermediates **7** and **8** formed by metal-ligand cooperation.

ASSOCIATED CONTENT

Supporting Information

Experimental details, crystallographic data, NMR and IR spectra of complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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