Organic LETTERS
Letter
Cite This: Org. Lett. 2018, 20, 4478−4481
pubs.acs.org/OrgLett

Cobalt-Catalyzed Acceptorless Dehydrogenative Coupling of Primary Alcohols to Esters

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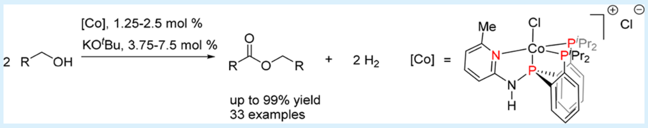
Supporting Information

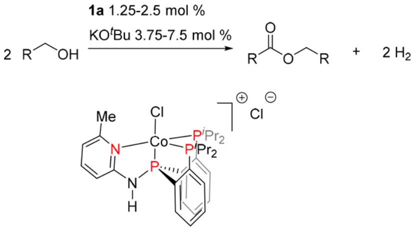
ABSTRACT: A novel catalytic system with a tripodal cobalt complex is developed for efficiently converting primary alcohols to esters. KO^{t}Bu is found essential to the transformation. A preliminary mechanistic study suggests a plausible reaction route that involves an initial Co-catalyzed dehydrogenation of alcohol to aldehyde, followed by a Tishchenko-type pathway to ester mediated by KO^{t}Bu.



Esters are a family of compounds that are common in organic chemistry and have found ubiquitous applications in the chemical, fragrance, and flavor industries.[1,2] Conventional ester production methods include esterification of carboxylic acids with alcohols, alcoholysis of acyl chlorides and acid anhydrides, carbonylation of alkenes with alcohols, transesterification, etc.[1,2] Despite these established methods, acceptorless oxidant-free dehydrogenative coupling of alcohols is an atom-economical and environmentally benign method for the synthesis of carbonyl compounds and their derivatives with hydrogen gas as the only byproduct.[3] This method takes advantage of inexpensive and readily available alcohols that can be obtained from biomass resources and fermentation. Homogeneous dehydrogenative coupling of primary alcohols to esters have been extensively studied with rare and expensive precious metal catalysts such as Ru,[4] Os,[5] and Ir.[6] With increasing concerns regarding the environment and costs, replacing precious metal catalysts with ones based on inexpensive, less toxic, and earth-abundant first row transition metals is very desirable and attractive, and it represents one of the most important directions of modern organometallic chemistry. However, such a transformation mediated by base metal catalysts is still a challenge, and examples are limited. Jones, Schneider and co-workers reported highly efficient PNP pincer ligand supported iron catalysts for dehydrogenation of primary alcohols to esters.[7] Jones and co-workers developed a TP′Ni(QR) (Tp′ = tris(3,5-dimethylpyrazolyl)borate, Q = quinolinate, R = CF$_3$) catalyst for dehydrogenative coupling of benzyl alcohol to benzyl benzoate.[8] Bernskoetter, Hazari, Holthausen, and co-workers presented methanol dehydrogenation to methyl formate by a PNP pincer stabilized iron complex.[9] Recently, Gauvin demonstrated the MnPNP complex-catalyzed dehydrogenation of primary alcohols to esters.[10]

We have recently developed a novel ^{iPr}PPPN^{H}Py^{Me} tetradentate tripodal ligand that featured metal−ligand cooperativity (MLC) by introducing a N−H linker connecting the pyridine ring and the phosphine moieties.[11] It has been demonstrated that the air-stable cobalt complex **1a** supported by this new ligand can mediate dehydrogenation of secondary alcohols to ketones.[11] Herein, we describe a catalytic system involving **1a** and KO^{t}Bu that can efficiently mediate acceptorless dehydrogenative homocoupling of primary alcohols to esters (Scheme 1). Although examples of cobalt-catalyzed dehydrogenation and dehydrogenative coupling reactions are available,[12] a systematic study on homogeneous cobalt catalysts for acceptorless dehydrogenative coupling of primary alcohols into esters has not been reported. In addition, this work represents the first example of base transition metal complexes supported by a tetradentate tripodal ligand that can efficiently catalyze such a transformation.

Scheme 1. 1a/KO^{t}Bu-Catalyzed Dehydrogenative Coupling of Primary Alcohols



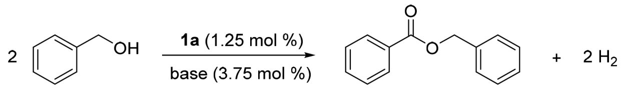
1a

Dehydrogenative homocoupling of benzyl alcohol to afford benzyl benzoate (**2**) is set as the model reaction for optimization. At 105 °C, when the reaction was carried out in a closed system under N$_2$, a yield of 37% resulted (Table 1, entry 1). An improved yield of 46% was observed in an open system under argon flow (Table 1, entry 1). When the temperature was raised to 125 °C with an open system, an

Received: June 6, 2018
Published: July 16, 2018

DOI: 10.1021/acs.orglett.8b01775
Org. Lett. 2018, 20, 4478−4481

Table 1. Screening of Reaction Conditions on Dehydrogenative Coupling of Benzyl Alcohol[a]



2

entry	cat.	base	solvent	temp (°C)	yield (%)[b]
1	**1a**	KO^{t}Bu	benzene	105	37,[c] 46[d]
2	**1a**	KO^{t}Bu	benzene	125	93,[d] >99, 91[e]
3	—	KO^{t}Bu	benzene	125	0
4	**1a**	—	benzene	125	0
5	**1a**	KO^{t}Bu	toluene	125	61
6	**1a**	KO^{t}Bu	THF	125	58
7	**1a**	KO^{t}Bu	1,4-dioxane	125	42
8	**1a**	NaO^{t}Bu	benzene	125	92
9	**1a**	KOH	benzene	125	44
10	**1a**	K$_2$CO$_3$	benzene	125	0

[a] Reaction conditions: alcohol (0.5 mmol), **1a** (1.25 mol %), KO^{t}Bu (3.75 mol %), and solvent (0.7 mL) were heated in a 15 mL reaction tube with an argon balloon on top for 24 h. [b] Yield was determined by ^{1}H NMR. [c] Reaction was run in a 100 mL pressure vessel. [d] Reaction was run in a 15 mL reaction tube under continuous argon flow. [e] Isolated yield (1 mmol scale).

excellent yield of 93% was achieved, but tremendous solvent loss was observed (Table 1, entry 2). Pleasingly, carrying out the reaction in a reaction tube with an argon balloon on top resulted in a full conversion of benzyl alcohol to benzyl benzoate (Table 1, entry 2). Control experiments showed that, in the absence of **1a**, no benzyl benzoate was produced (Table 1, entry 3). A base is also essential for the reaction, as no ester was generated without a base (Table 1, entry 4). With toluene, THF, or 1,4-dioxane as solvents, diminished yields were observed (Table 1, entries 5 to 7). KO^{t}Bu and NaO^{t}Bu are more efficient than KOH and K$_2$CO$_3$ (Table 1, entries 8 to 10). It is worth mentioning that only a trace amount of benzoic acid *tert*-butyl ester was formed, probably from dehydrogenative coupling of benzyl alcohol and KO^{t}Bu.

With the optimized conditions in hand (Table 1, entry 2), we explored the substrate scope of the ester formation reaction. Aromatic primary alcohols with electron-donating groups such as −OMe, −Me, and −iPr at the *para* position reacted smoothly to afford the corresponding esters in 79−90% isolated yields (Table 2, entries 1−3). Notably, substrates with electron-withdrawing groups at the *para* positions presented outstanding activities, with nearly full conversions to the desired esters (Table 2, entries 4−6). In addition, most *meta*-substituted substrates were transformed to corresponding esters well (Table 2, entries 7−11). Sterically hindered substrates such as 2-methyl benzyl alcohol and 1-naphthalenemethanol exhibited diminished yields (Table 2, entries 12 and 13). By comparison, 2-naphthalenemethanol afforded the desired ester in 91% yield (Table 2, entry 14). A reaction with 2-fluorobenzyl alcohol or 2-furfuryl alcohol showed no product at all (Table 2, entries 15 and 16). It is postulated that an electron donor (F or O) at the *ortho* position might coordinate with the cobalt complex in the reaction, thus deactivating the catalyst. Our previous study on nickel-catalyzed aldehyde decarbonylation showed a comparable result that *ortho* substituents significantly suppressed the Tishchenko reaction of coupling aromatic aldehydes to esters.[13] We were delighted to find that a number of disubstituted aromatic primary alcohols give 73−89% yields (Table 2, entries 18−22). Significantly, alkyl primary alcohols also furnished the reactions with good to excellent yields (Table 2, entries 23−30), albeit an increased catalyst loading or a higher reaction temperature (140 °C) was required. Lastly, diols such as benzene-1,2-dimethanol and 1,4-butanediol successfully afforded the desired lactones (Table 2, entries 31 and 32).

We then performed a preliminary mechanistic study to understand the catalyst activation process and reaction mechanism. Complex (^{iPr}PPPNPy^{Me})CoCl **1b** (Figure 1), synthesized by reacting **1a** with KO^{t}Bu,[11] showed comparable activity as **1a** in the presence of 2 equiv of KO^{t}Bu (Table S1, Supporting Information (SI)), indicating that **1b** is likely involved in the generation of the actual catalyst via dehydrohalogenation of **1a** by the base. To explore the possible roles of metal−ligand cooperativity (MLC) originated from the N−H linker in **1a**, a N−Me substituted complex [(^{iPr}PPPN^{Me}Py^{Me})CoCl]OTf **1c** (Figure 1) was synthesized.[11] Interestingly, a 92% benzyl benzoate yield was observed using **1c** as catalyst, which is close to those of **1a** and **1b**. These results suggest that the N−H linker may not play a significant role in this transformation.

To investigate the roles of KO^{t}Bu, reaction conditions with various ratios of **1b** and base were examined (Table S1, SI). No ester was formed without KO^{t}Bu. Interestingly, when 1 equiv of KO^{t}Bu was used (1.25 mol %), only a 4% ester yield was obtained. Since the amount of KO^{t}Bu is only sufficient in activating the cobalt precatalyst,[11] the generated Co active species may not be responsible for some essential step(s) toward ester formation. However, with further increasing KO^{t}Bu loadings to 2.5 mol %, the ester yield was significantly enhanced (88%), demonstrating another essential role of KO^{t}Bu besides precatalyst activation. Small quantities of aldehydes were detected as typical byproducts. We observed that KO^{t}Bu alone can efficiently mediate the Tishchenko reaction coupling aldehydes to esters at room temperature (see SI) as also reported by Berke and co-workers.[14] Interestingly, in the presence of 1 equiv of alcohol with respect to aldehyde, only a trace amount of ester was formed, indicating alcohol can be detrimental to the Tishchenko reaction (see SI). This is in contrast to the Ru alkoxide system for dehydrogenative alcohol coupling reported by Gauvin et al., where the alcohol does not show such adverse effects and a Tishchenko pathway is therefore proposed.[4j] However, when the temperature was raised to 125 °C, an improved 67% ester yield was obtained, suggesting the feasibility of the Tishchenko route (see SI). On the other hand, Beller et al. demonstrated that aldehyde (1 equiv with respect to alcohol) completely "poisons" the Ru catalyst in the dehydrogenative coupling of ethanol to ethyl acetate and a mechanism involving dehydrogenation of free or deprotonated hemiacetal by the Ru complex is proposed.[4e] However, for our Co/KO^{t}Bu system, a 61% yield of **2** resulted in the presence of equal amounts of benzyl alcohol and benzaldehyde,[15] indicating less deleterious effects of aldehydes on the Co catalyst. This is further supported by the observations that equal amounts of 4-fluoro benzyl alcohol and benzyldehyde led to a set of four esters from homo- and cross-couplings, and benzyl alcohol was formed as a result of hydrogen transfer (see SI). In light of the preceding experimental evidence, we envision a plausible route that involves an initial Co-catalyzed dehydrogenation of alcohol to aldehyde, followed by a Tishchenko-type pathway mediated by

DOI: 10.1021/acs.orglett.8b01775
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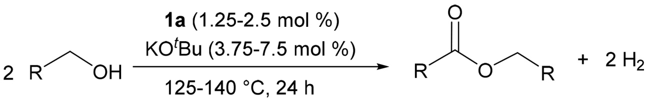
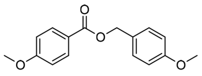
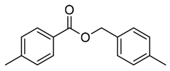
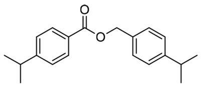
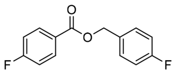
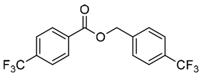
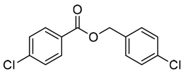
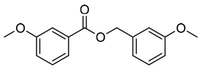
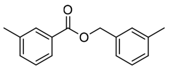
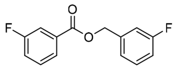
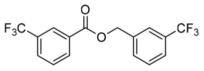
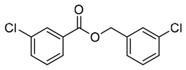
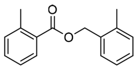
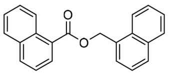
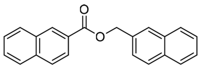
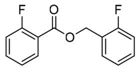
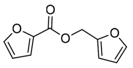
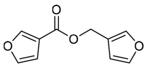
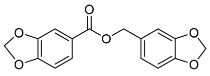
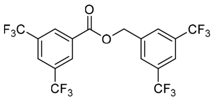
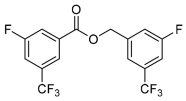
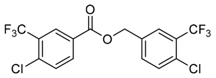
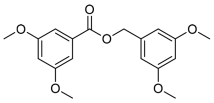
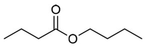
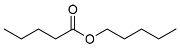
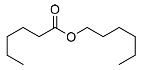
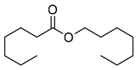
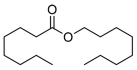
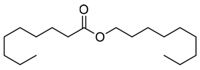
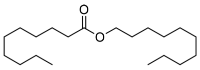
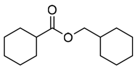
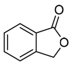
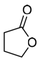
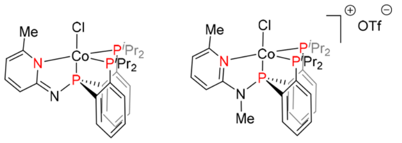
Table 2. Dehydrogenative Coupling of Primary Alcohols Catalyzed by Cobalt and KO^{t}Bu[a,b]



entry	product
1	 **3**, 81% (72%)
2	 **4**, 79% (74%)
3	 **5**, 92% (78%)
4	 **6**, >99% (95%)
5	 **7**, 95% (84%)
6	 **8**, >99% (92%)
7	 **9**, 92% (82%)
8	 **10**, 68% (62%)
9	 **11**, 92% (84%)
10	 **12**, 83% (74%)
11	 **13**, 98% (89%)
12	 **14**[d], 52%, 45%[c]
13	 **15**[d], 19%, 21%[c]
14	 **16**[d], 91% (89%)
15	 **17**[d], 0%
16	 **18**[d], 0%
17	 **19**[d], 30% (28%)
18	 **20**[e], 79% (71%)
19	 **21**[e], 84% (79%)
20	 **22**[e], 89% (81%)
21	 **23**[e], 87% (85%)
22	 **24**[e], 73% (69%)
23	 **25**[f], 62%, 61%[c]
24	 **26**[e], 72%, 69%[c]
25	 **27**[e], 81%, 82%[c]
26	 **28**[e], 72%, 67%[c]
27	 **29**[e], 86% (79%)
28	 **30**[e], 83%, 85%[c]
29	 **31**[e], 80% (72%)
30	 **32**[e], 67% (58%)
31	 **33**, >99% (93%)
32	 **34**[f], 96% (82%)

[a] Reaction conditions: alcohol (0.5 mmol), **1a** (1.25 mol %), KO^{t}Bu (3.75 mol %), benzene (0.7 mL) were heated in 15 mL reaction tube with argon balloon on top at 125 °C for 24 h. [b] Yield was determined by ^{1}H NMR with nitromethane as internal standard. Isolated yield is in bracket. [c] Yield was determined by GC. [d] Reaction was run with **1a** (2.5 mol %) and KO^{t}Bu (7.5 mol %) at 125 °C for 24 h. [e] Reaction was run in toluene (0.7 mL) with **1a** (2.5 mol %) and KO^{t}Bu (7.5 mol %) at 140 °C for 24 h. [f] Reaction was run in THF (0.7 mL) with **1a** (2.5 mol %) and KO^{t}Bu (7.5 mol %) at 125 °C for 24 h.



1b **1c**

Figure 1. **1a** derivatives (**1b** and **1c**) examined for dehydrogenative coupling of primary alcohols.

the base. However, we cannot completely exclude a concurrent pathway in which a base might also facilitate the generation of hemiacetal species,[4e] which are then dehydrogenated by the Co catalyst to give the final ester products. A comprehensive mechanistic investigation is currently underway in our laboratory.

Generation of a H_2 byproduct was confirmed by GC analysis of the headspace gas after the reaction (see Figure S1, SI). To examine whether the catalysis is homogeneous or heterogeneous, we carried out a mercury test (100 equiv with respect to **1b**) and noticed no detrimental effect on the reactivity (93% yield, see SI), suggesting a homogeneous catalytic system.

In conclusion, a novel catalytic system involving a cobalt complex supported by a tetradentate tripodal ligand and a base was reported to efficiently transform primary alcohols to esters via a plausible dehydrogenation and Tishchenko-type pathway. We expect that this study will contribute to green catalysis and advanced catalyst design with earth-abundant transition metals.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01775.

Experimental details, additional figures, and other results (PDF)

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Author Contributions

[§]K.P., B.P., and S.X. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by National Science Foundation (NSF-RUI, CHE-1465051). We thank support from FRCAC, URECA, and Clean Energy Fee Funds of MTSU.

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DOI: 10.1021/acs.orglett.8b01775