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Enzyme-Like Catalysis via Ternary Complex Mechanism: Alkoxy-Bridged Dinuclear Cobalt Complex Mediates Chemoselective O-Esterification over N-Amidation

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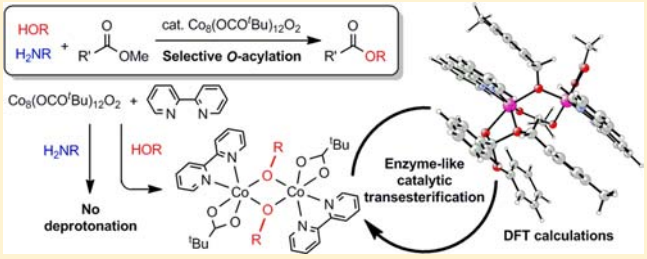
Supporting Information

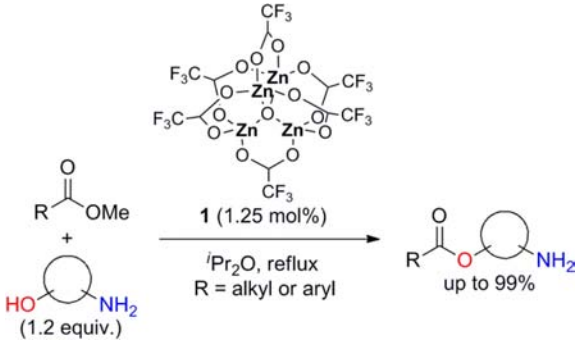
ABSTRACT: Hydroxy group-selective acylation in the presence of more nucleophilic amines was achieved using acetates of first-row late transition metals, such as Mn, Fe, Co, Cu, and Zn. Among them, cobalt(II) acetate was the best catalyst in terms of reactivity and selectivity. The combination of an octanuclear cobalt carboxylate cluster $[Co_4(OCOR)_6O]_2$ (**2a**: R = CF_3, **2b**: R = CH_3, **2c**: R = ^{t}Bu) with nitrogen-containing ligands, such as 2,2′-bipyridine, provided an efficient catalytic system for transesterification, in which an alkoxide-bridged dinuclear complex, $Co_2(OCO^tBu)_2$-$(bpy)_2(\mu_2$-OCH_2-C_6H_4-4-$CH_3)_2$ (**10**), was successfully isolated as a key intermediate. Kinetic studies and density functional theory calculations revealed Michaelis−Menten behavior of the complex **10** through an ordered ternary complex mechanism similar to dinuclear metallo-enzymes, suggesting the formation of alkoxides followed by coordination of the ester.



INTRODUCTION

Ester and amide bonds are ubiquitous chemical bonds abundant in natural and synthetic organic compounds.[1] A common synthetic protocol is the acylation of alcohols and amines with carboxylic acid, acid chloride, or acid anhydride. These processes usually require stoichiometric amounts of a condensation reagent or base, resulting in the formation of more than stoichiometric amounts of chemical waste. Catalytic transesterification[2,3] and ester−amide exchange reactions[4] are desirable for the synthesis of diverse esters from the perspective of atom economy and environmental concerns. Because amino groups have higher nucleophilicity than hydroxy groups, the use of these reagents for competitive reactions with hydroxy and amino functional groups selectively produces the amide. Inverse chemoselectivity was first reported for lipase-catalyzed O-acylation of hydroxy groups in serine by trifluoroethyl acetate in the presence of primary alkyl amino groups.[5] Recently, we found that a trifluoroacetate-bridged μ_4-oxo-tetranuclear zinc cluster, $Zn_4(OCOCF_3)_6O$ (**1**), served as an efficient catalyst for chemoselective transesterification of methyl esters with alcohols,[6−8] even in the presence of primary or secondary amino groups, to afford the corresponding esters as the first artificial catalyst system for O-selective transesterification over N-amidation (Scheme 1),[7] although O-selective acetylation by activated enol esters as acylating reagents was reportedly catalyzed by $Y_5(O^iPr)_{13}O$.[9] Soon after our report, Ishihara and co-workers reported that a catalyst mixture of $La(O^iPr)_3$ and 2-(2-methoxyethoxy)ethanol, which might generate dinuclear La^{3+} species, facilitated the transesterification of methyl esters with an equimolar amount of alcohol, resulting in selective acylation of the hydroxy group, even in the presence of amino groups.[10]

Scheme 1



Here, we report that a wide variety of first-row transition-metal carboxylates serve as O-selective catalysts, and a new catalyst system based on Co(II)-carboxylate clusters that

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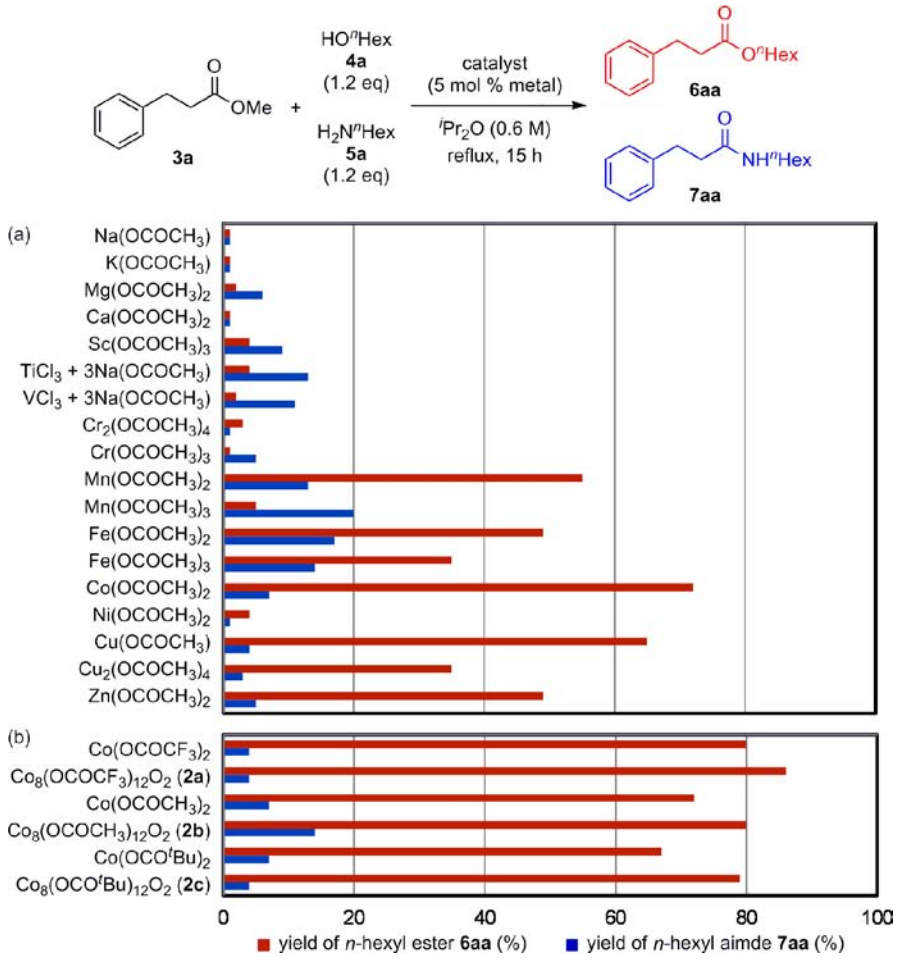

Figure 1. Catalytic activity and chemoselectivity of (a) various acetates and (b) cobalt carboxylate compounds for acylation of *n*-hexanol (**4a**) and *n*-hexylamine (**5a**) with methyl 3-phenylpropionate (**3a**). Yields were determined by GC analysis of the crude reaction mixture and based on the mean of duplicate runs.

functioned as O-selective acylation catalysts. Further, we reveal the ternary complex mechanism of the alkoxy-bridged dinuclear cobalt complex obeying Michaelis–Menten kinetics and report density functional theory (DFT) calculations of the reaction mechanism.

RESULTS AND DISCUSSION

Catalyst screening of various carboxylates for chemoselective acylation of alcohols over amines was initiated by a test reaction of methyl 3-phenylpropanoate (**3a**) with a 1:1 mixture of *n*-hexanol (**4a**, 1.2 equiv) and *n*-hexylamine (**5a**, 1.2 equiv) in the presence of various metal acetates, $M_n(OCOCH_3)_m$ (5 mol % metal), in refluxed diisopropyl ether for 15 h, and the results are shown in Figure 1. The acetate salts of group 1 elements (Na, K) and group 2 elements (Mg, Ca) had almost no catalytic activity. For early and middle transition metals in an oxidation state of three, such as Sc(III), Ti(III), V(III), Cr(III), and Mn(III), amidation prevailed over esterification, despite the low catalytic activities of these acetates. To our surprise, however, most acetate complexes of middle and late first-row transition metals in an oxidation state of two showed moderate catalytic activity and sufficient chemoselectivity, producing O-acylated product **6aa** over N-acylated product **7aa**. Among them, $Mn(OCOCH_3)_2$, $Fe(OCOCH_3)_2$, $Co(OCOCH_3)_2$, $[Cu(OCOCH_3)_2]_2$, and $Zn(OCOCH_3)_2$ had relatively high catalytic activity. The Cu(I) compound $Cu(OCOCH_3)$ also served as an O-selective catalyst, while $Ni(OCOCH_3)_2$ had very low catalytic activity. Notably, in the absence of *n*-hexylamine, transesterification was comparably very slow or compressed to almost no reaction, clearly indicating that *n*-hexylamine improved the catalytic activity of carboxylate compounds of first-row transition metals, such as Mn(II), Fe(II), Co(II), Cu(II), Cu(I), and Zn(II), by maintaining their unique nature of O-selective acylation, although we previously reported that the additive effects of amines and N-heteroaromatics significantly enhance the catalytic activity of zinc cluster **1** for transesterification.[8]

We selected Co(II) as the best metal to study the mechanistic details of O-selective acylation due not only to its high catalytic activity and chemoselectivity but also to its potential advantages based on UV–vis spectroscopic characterization, although Cu(I) and Mn(II) also showed interesting reactivity.[11] In addition, a pivalate-bridged octanuclear cluster, $Co_8(OCO^tBu)_{12}O_2$,[12] has the dimeric structure of a μ-oxo tetranuclear unit analogous to zinc clusters, $Zn_4(OCOR)_6O$, which are superior catalysts compared with the corresponding simple salts $Zn(OCOR)_2{\cdot}xH_2O$.[6] Since the introduction of a more electron-deficient ligand, such as trifluoroacetate, to the tetranuclear zinc cluster entity further improved catalytic activity, we next examined the catalytic performance of some carboxylate salts of cobalt, formulated as $Co(OCOR)_2$ (R = CF_3, CH_3, and ^{t}Bu) as well as the corresponding carboxylate-

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bridged clusters, $Co_8(OCOR)_{12}O_2$ (**2a**: R = CF_3; **2b**: R = CH_3; **2c**: R = ^{t}Bu). We prepared carboxylate-bridged μ-oxo cobalt clusters **2a—c** according to previously reported procedures[12−15] and confirmed that the cluster **2c** existed in equilibrium with its half segment, $Co_4(OCO^tBu)_6O$, in a solution state (see Supporting Information). The effects of nuclearity and carboxylate ligands on cobalt atoms were investigated, and the results are summarized at the bottom of Figure 1. Tuning the electronic character of the carboxylate ligand, i.e., acetate, pivalate, and trifluoroacetate, led to an increase in the electron-withdrawing ability, thereby improving the catalytic activity based on the increased yields (80% of **6aa** along with only 4% of **7aa**) upon the use of $Co(OCOCF_3)_2$, compared with those of $Co(OCOCH_3)_2$ (**6aa**: 72%, **7aa**: 7%) and $Co(OCO^tBu)_2$ (**6aa**: 67%, **7aa**: 7%); as expected, the pivalate complex had almost the same catalytic performance as the acetate complex. The most notable finding was that clusters **2a—c** had better catalytic activities than the corresponding carboxylate salts. Among the cobalt clusters **2a—c** tested for O-selective acylation, trifluoroacetate cluster **2a** was selected as the best catalyst because it had the highest catalytic activity (86% of **6aa**). As a result of ligand screening, we selected 2,2′-bipyridine (**8a**) as the best chelating nitrogen ligand for the purpose of isolating and detecting any cobalt species (see Table S1). The catalytic activity of zinc cluster **1** was also improved by the addition of **8a**.

To gain mechanistic insight into the cobalt cluster-catalyzed transesterification, we performed control experiments with **2c**, the most soluble cobalt cluster compared with **2a** and **2b**, which are hardly soluble in toluene, to elucidate the solution behavior of cobalt clusters by UV−vis spectroscopy and to isolate any key intermediate species. The addition of **8a** to **2c** in toluene dramatically altered its absorption spectrum, as shown in Figure 2. The addition of **8a** (up to 20 equiv.) increased absorbance at

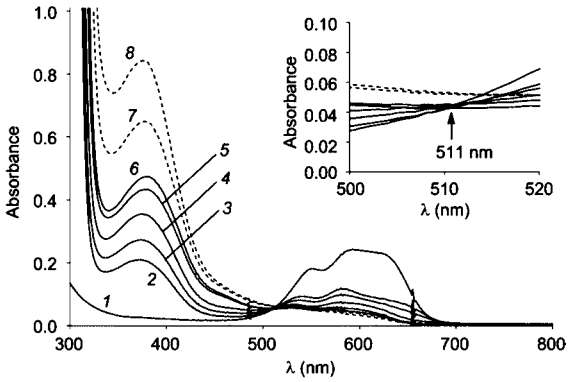
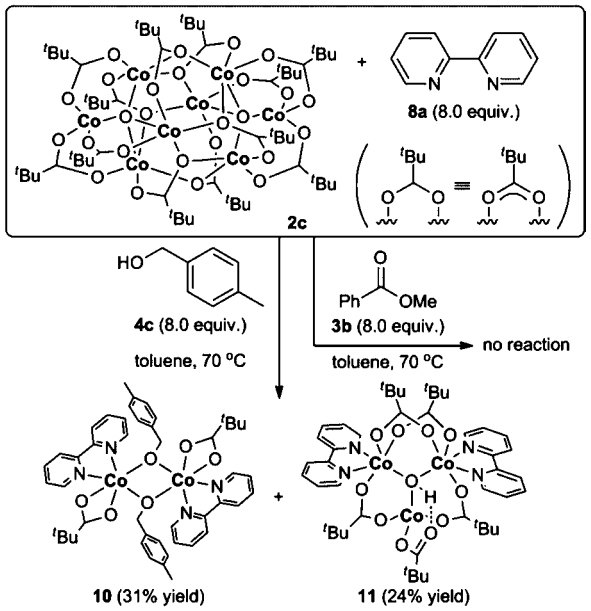


Figure 2. Electronic absorption spectra of $[Co_4(OCO^tBu)_6O]_2$ (**2c**) in toluene solutions of **8a** at 25 °C. $[Co^{2+}] = 1.46 \times 10^{-3}$ M. The loadings of **8a** referring to curves 1—8 are 0, 1, 2, 4, 8, 16, 50, and 100 mol ratio to Co^{2+} ion, respectively.

around 375 nm and decreased absorbance in the 500−700 nm wavelengths with an isosbestic point appearing at 511 nm with up to 16 equiv of **8a**. Such a decrease in the band intensities was attributed to the change in the coordination number at the cobalt center from 4 to a higher number, probably 6. The addition of excess amounts of **8a** to the solution of **2c** induced a deviation from the isosbestic point, suggesting the irreversible formation of a mononuclear species, *cis*-$Co(OCO^tBu)_2(bpy)_2$ (**9**),[16] which was isolated and characterized by X-ray analysis.

We then turned our attention to verifying the reactivity of the in situ-generated Co(II) species supported by **8a** (Co/**8a** = 1/1) toward esters and alcohols. The addition of 8.0 equiv (Co/**3b** = 1/1) of methyl benzoate (**3b**) to the mixture of **2c** and **8a** in toluene did not change the spectrum, indicating that **3b** could not interact with any cobalt centers (Scheme 2). In

Scheme 2



sharp contrast, the addition of 4-methylbenzyl alcohol (**4c**) (Co/**4c** = 1/1) led to a clear change in the UV−vis spectrum: a new dinuclear complex **10** in 31% yield and a known trinuclear complex **11**[17] in 24% yield were isolated from the reaction mixture (yields based on Co), where **11** was a product of the protonation of the μ-oxo moiety of **2c** by the alcohol **4c** and **10** was a product comprising the alkoxide fate of **4c**. Alternatively, complex **10** was prepared in 76% yield by treating a 1:2 mixture of $Co(OCO^tBu)_2$ and **8a** with 1 equiv of the potassium salt of **4c**. Complex **10** was crystallographically characterized (Figure 3). Both cobalt atoms adopt a pseudo octahedral geometry supported by two oxygen atoms of a chelating carboxylate, two nitrogen atoms of 2,2'-bipyridine, and two oxygen atoms of the

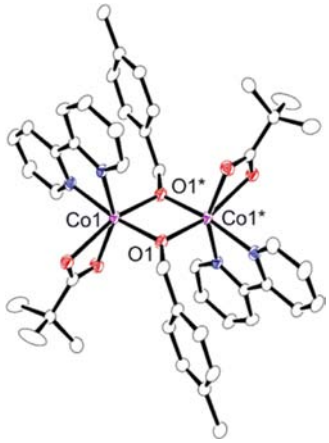


Figure 3. Crystal structure of complex **10**. All H-atoms and the solvent molecule (toluene) were omitted for clarity.

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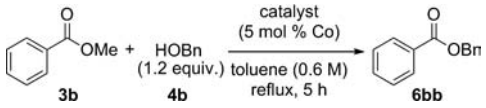
two bridging alkoxides. The C_2 axis passes through the center of the '$Co_2(\mu\text{-}O)_2$' core, whose planarity is indicated by the sum (359.80°) of its internal angles.

The catalytic activity of the alkoxide-bridged cobalt dinuclear complex **10** and the trinuclear complex **11** along with the mononuclear complex **9** are exemplified by the transesterification of **3b** with **4b** (Table 1). Complexes **10** and **11** had

Table 1. Transesterification Catalyzed by Isolated Cobalt Pivalate Complexes[a]



entry	catalyst		yield of **6bb** (%)[b]
1	*cis*-$Co(OCO^tBu)_2(bpy)_2$	**9**	59
2	$Co_2(\mu_2\text{-}OCO^tBu)_2(bpy)_2(\mu_2\text{-}OCH_2\text{-}(4\text{-}Me\text{-}C_6H_4))_2$	**10**	95 (4)[c]
3[d]			56
4	$Co_3(\mu_2\text{-}OCO^tBu)_5(\mu_3\text{-}OH)(bpy)_2$	**11**	97

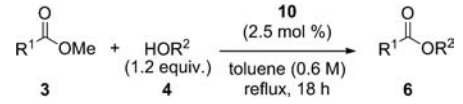
[a]2.0 mmol scale. [b]Determined by GC analysis. Average of two runs. [c]Yield of 4-methylbenzyl benzoate (**6bc**). [d]Catalyst loading: 0.05 mol % (TON = 1120, TOF = 224 h^{-1}).

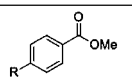
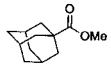
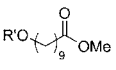
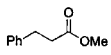
almost the same catalytic activities (99% for **10**; 97% for **11**), but **10** was the most efficient catalyst for this reaction, as **10** had high catalytic activity of TON = 1120 and TOF = 224 h^{-1} upon reducing the catalyst loading of **10** to 0.05 mol %. A notable aspect of complex **10** was its catalytic performance for O-selective acylation of the competitive reaction of **3a** with **4a** and **5a**, in which only 4% of amide **7aa** was detected for an excellent total yield (94%) of two esters, **6aa** (90%) and **6ac** (4%). When the mononuclear complex **9** was used as the catalyst, the product **6bb** was obtained in a moderate yield (59% yield). The lower catalytic activity of mononuclear complexes for transesterification has been noted for $Zn(OCOCF_3)_2(DMAP)_2$.[8]

We next investigated the substrate scope of esters **3** and alcohols **4** for the **10**-catalyzed transesterification, and the results are summarized in Table 2. Acylations of aminoalcohols with primary and secondary amino groups were smoothly promoted with excellent chemoselectivity (entries 1 and 2). The present method was successfully applied to aromatic esters bearing electron-withdrawing and -donating groups at the *para*-position (entries 3 and 4). The transesterification of highly congested methyl 1-adamantanecarboxylate successfully proceeded with the catalyst **10** (entry 5). Aliphatic ester with acid-sensitive THP ether group was converted to the corresponding ester in good yield without the loss of protecting group (entries 6). The secondary alcohol **4g** was also applicable to this reaction (entry 7).

To elucidate the origin and mechanism of chemoselective transesterification, we investigated the stoichiometric reaction and performed kinetic studies of the reaction of phenyl benzoate (**12**) with **4c** using **10** as the catalyst. We used **12** as a substrate because the once-liberated phenol could not react with the resulting 4-methylbenzyl benzoate (**6bc**), thus preventing the reverse reaction. We first conducted the stoichiometric reaction of **10** with the phenyl ester **12** and the alcohol **4c** in toluene, where transesterification of **12** with **4c** proceeded irreversibly to give $PhCOOCH_2\text{-}C_6H_4\text{-}4\text{-}CH_3$ (**6bc**) and PhOH. In the controlled reaction of **10** with 2 equiv of **12** in toluene, we detected a new peak due to

Table 2. Substrate Scope for the Complex 10-Catalyzed Transesterification[a]

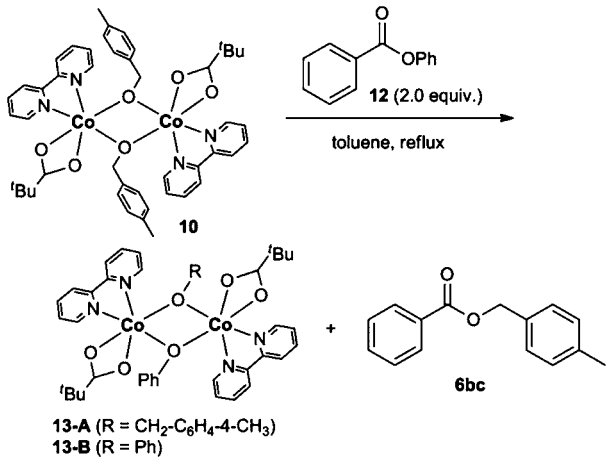


entry	ester		alcohol	yield of **6** (%)[b]
1[c]		R = H (**3b**)	 (**4d**)	90 (nd[d]),(3)[e]
2[c]		**3b**	 (**4e**)	85 (nd[d]),(5)[e]
3		R = Br (**3c**)	HO^nBu (**4f**)	94
4		R = OMe (**3d**)	**4f**	91
5[g]		(**3e**)	**4f**	80
6		R' = THP (**3f**)	**4f**	93
7[h]		(**3g**)	HOCy (**4g**)	83

[a]2.0 mmol scale. [b]Isolated yield. Amino esters were isolated after Boc protection. [c]Diisopropyl ether was used as a solvent. [d]Not detected. [e]Yield of hydroxy amide. [f]Yield of the diacylated product at both of O- and N-positions. [g]Reaction time: 72 h. [h]Reaction time: 40 h.

$[Co_2(OCO^tBu)_2(bpy)_2(OPh)]^+$ by ESI-MS measurement (see Figure S2). Thus, during the catalytic transformation, the alkoxide ligands bridging the two cobalt atoms in **10** were replaced by phenoxides of the phenyl ester **12** to form phenoxide-bridged species **13-A** or **13-B** in Scheme 3.

Scheme 3



Under pseudo first-order conditions of excess amounts of **12** (9.87×10^{-2} M) and **4c** (1.31×10^{-1} M), the initial velocities of the transesterification catalyzed by various amounts of **10** ($1.12\text{–}6.69 \times 10^{-4}$ M) were estimated based on ^1H NMR measurements by minimizing the paramagnetic anisotropy due to Co(II) in complex **10**. Consistent with the Michaelis–Menten models of enzymatic reaction mechanisms, we

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collected the initial velocity data at 60 °C to produce the $1/[S]$ vs $1/v$ plots shown in Figure 4a,b. Both plots of $1/[\mathbf{12}]$ against

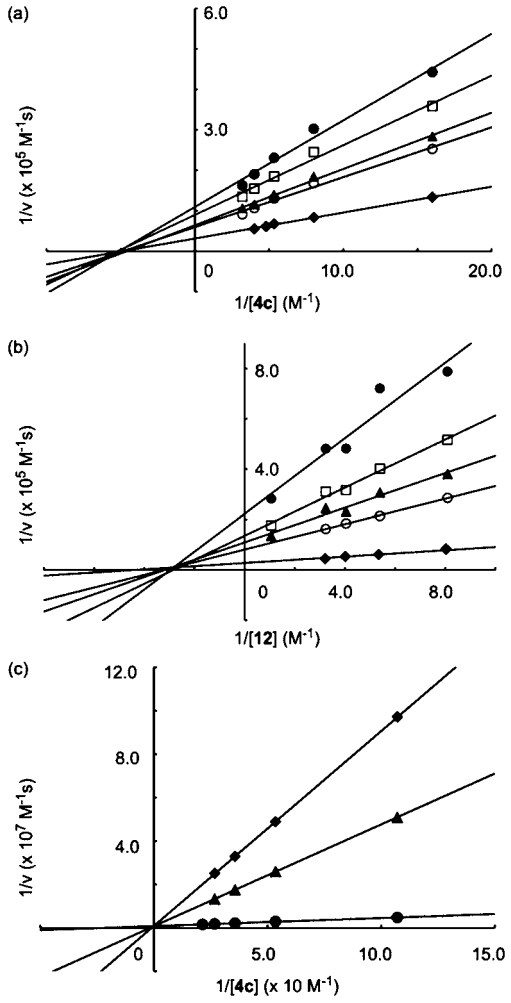

Figure 4. $1/[S]$ vs $1/v$ plots of initial velocity data of the complex **10**-catalyzed transesterification of **12** with **4c** in toluene at 60 °C. Conditions: (a) $[\mathbf{10}] = 6.03 \times 10^{-4}$ (M), $[\mathbf{12}] = 1.24$ (●), 1.85 (□), 2.47 (▲), 3.09 (○), 9.40 (◆) ($\times 10^{-1}$ M); (b) $[\mathbf{10}] = 6.03 \times 10^{-4}$ (M), $[\mathbf{4c}] = 0.63$ (●), 1.25 (□), 1.87 (▲), 3.12 (○), 7.57 (◆) ($\times 10^{-1}$ M); (c) $[\mathbf{10}] = 4.65 \times 10^{-4}$ (M), $[\mathbf{12}] = 8.63 \times 10^{-1}$ (M), [PhOH] = 0.0 (●), 1.83 (▲), 3.66 (◆) ($\times 10^{-2}$ M).

$1/v$ and that of $1/[\mathbf{4c}]$ against $1/v$ produced a series of straight lines intersecting at a single point to the left of the ordinate, consistent with a ternary complex mechanism. Because complex **10** already contains deprotonated **4c** as a bridging alkoxide ligand, a so-called catalyst−substrate complex just like an enzyme−substrate complex, the sequence of substrate binding and product release was definitely determined in the order of the first alcohol **4c**, followed by the coordination of **12** to form a ternary complex as a key intermediate. Michaelis−Menten constants were estimated by a Lineweaver−Burk plot[18] as $K_{m,\mathbf{4c}} = 4.51 \times 10^{-2}$ (M) and $K_{m,12} = 1.09 \times 10^{-1}$ (M).

Ultimately, we conducted an inhibition experiment with phenol in the transesterification of a fixed concentration of the phenyl ester **12** and variable concentrations of alcohol **4c**, and the obtained initial velocity data are plotted in Figure 4c. The observed alteration of the $K_{m,\mathbf{4c}}$ with no change in V_{max} is characteristic of the competitive inhibition between **4c** and phenol, and a Dixon plot[19] afforded the inhibition constant (K_i) of phenol as 1.59×10^{-3} (M), a smaller value than that of $K_{m,\mathbf{4c}}$. The small value of K_i indicates that the phenol strongly bound to the Co atom of the catalyst **10**, consistent with very small exchange of the phenoxide ligand in **13** with alcohol **4c** and the phenolic substrates remaining intact in any catalytic reaction.

Based on the above-described experimental results as well as DFT calculations (see below), a schematic of the possible catalytic cycle for the transesterification of **12** and **4c** using **10** is shown in Figure 5. The first step is the coordination of ester **12** to one of the cobalt atoms of complex **10**, resulting in the formation of a ternary complex **14-A** with η^1-coordination of the pivalate moiety. Intramolecular nucleophilic attack of the benzyloxy moiety to the coordinated ester **12** proceeds through transient species **15-A** and **15-B**, leading to another ternary complex **14-B** coordinated by a transesterificated product **6bc**. Liberation of **6bc** from **14-B** proceeds smoothly to generate the half-phenoxide-bridged dinuclear complex **13-A**. Under excess amounts of **4c**, intramolecular exchange of the phenoxy ligand in **13-A** by **4c** regenerates **10** along with phenol. For standard transesterification of esters and primary alcohols other than phenol, these steps are all assumed to be reversible. Reversible alkoxy ligand exchange is possible for the labile Co(II) ion, consistent with the findings that Co(III) compounds in argon atmosphere conditions and Co(II) compounds under air conditions had very low catalytic activity due to the inertness of a closed-shell d^6 Co(III) species for any ligand exchange reaction.

To gain more insight into the mechanism of the reaction, we performed DFT calculations using the B3LYP-D functional[20] (see Supporting Information for details). We began our computational investigation by studying the binding of phenyl benzoate **12** to complex **10**. The adopted computational scheme allowed us to locate a ternary complex (**14-A**). Ternary complex **14-A** was slightly higher in energy (+3.2 kcal/mol) than the separated **10** and **12**, mainly due to a loss of entropy in the binding. As discussed above, the kinetic measurements indicated that this ternary complex should exist, but the results of the calculations were not consistent with the kinetic measurements. From **14-A**, the transition state (TS1, Figure 6) for the nucleophilic attack of the benzyloxy group on the ester was 17.6 kcal/mol higher than the ternary complex (20.8 kcal/mol higher than the isolated **10** and **12**). This TS led to the formation of tetrahedral intermediate **15-A**, which, after reorganization, gave tetrahedral intermediate **15-B** in which the phenoxy group coordinates to one of the cobalt atoms. Note that at TS1 one of the acetate ligands became a bidentate bridging ligand between the two metal ions. Also, there is of course a transition state for the reorganization step, but it is expected to be considerably lower in energy compared to the preceding and following TSs and will thus not influence the mechanism. From **15-B**, dissociation of the phenoxy group can occur through TS2 (20.5 kcal/mol higher than that of **10** + **12**, see Figure 6), leading to the formation of intermediate **14-B** in which the final product is weakly bound to the complex. To restart the cycle, it is necessary to exchange the phenoxy group with a benzyloxy group and release product **6bc**. This process is exergonic by 5.3 kcal/mol and leads to the formation of complex **10**.

Before initiating the catalytic cycle, the formation of an alkoxide species such as **10** is a key step, because cobalt precursors have no alkoxide ligands. In this context, the superiority of the cobalt cluster **2c** over the mononuclear compound **9** as well as the simple salt of cobalt pivalate,

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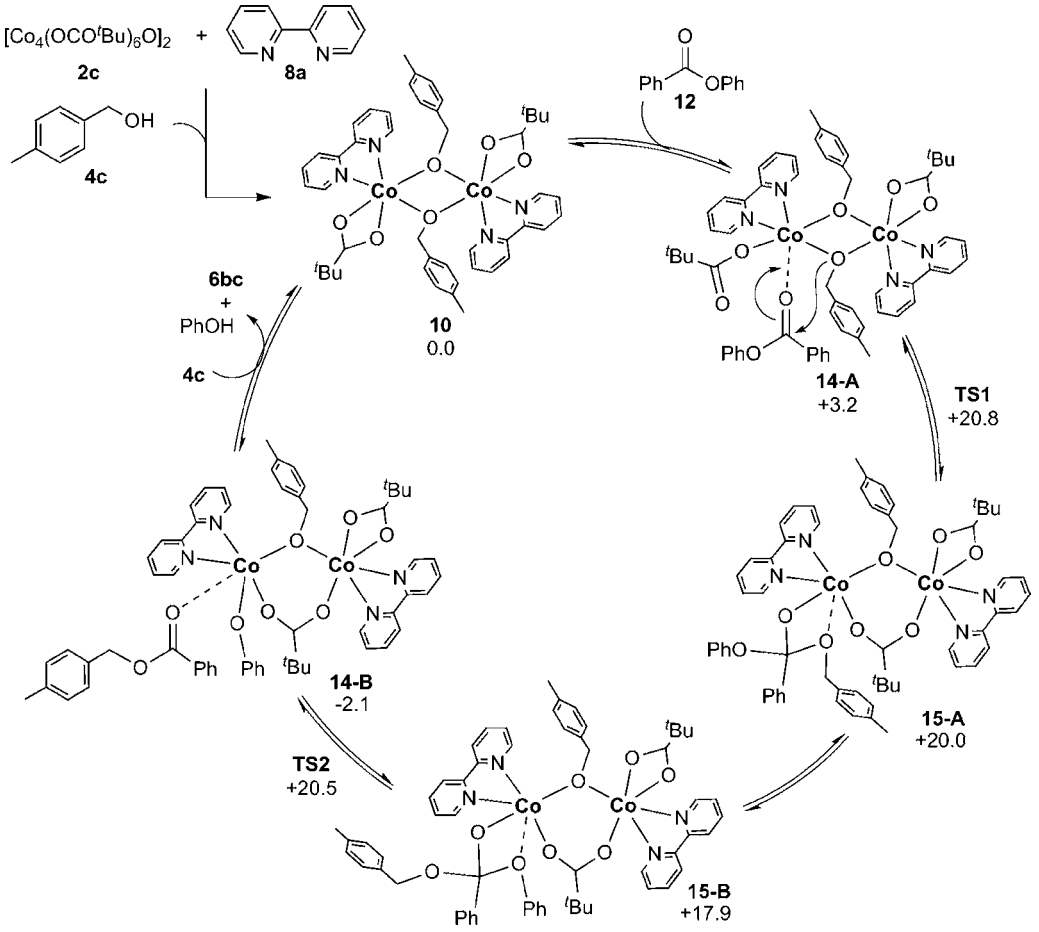

Figure 5. Possible reaction mechanism for transesterification of phenyl ester **12** with alcohol **4c** catalyzed by cobalt cluster **2c**, calculated using the B3LYP-D method. Energies are in kcal/mol.

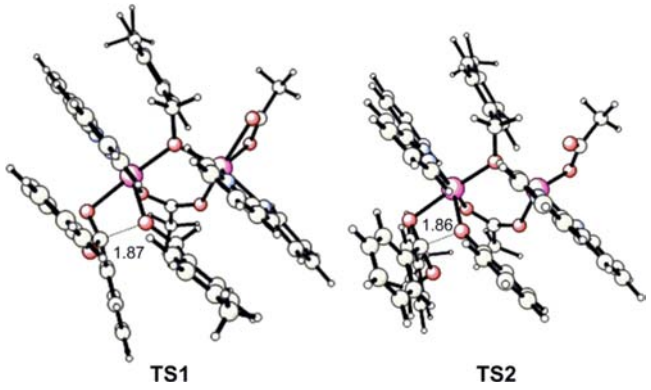

Figure 6. Optimized transition states TS1 and TS2 based on DFT calculations. Distances are in Å.

$Co(OCO^tBu)_2$, combined with **8a**, is due to the basic μ-oxo moiety that deprotonated **4c** to form the catalytically active alkoxide species **10**. In fact, the function of basic oxo species has been noted in tin catalyst systems: Otera et al. reported an efficient catalyst system of distannoxane,[21] which has a μ-oxo moiety and therefore might facilitate the exchange of its original ligands to alkoxide, and Houghton and Mulvaney proposed such a process in the stannoxane-catalyzed urethane synthesis.[22]

Kinetic studies revealed that complex **10** mediated transesterification through the ternary complex mechanism, where alcohol was first incorporated into the metal center through the formation of μ-alkoxy ligation that was stabilized by two cobalt centers similar to the active site of metallo-enzymes, such as aminopeptidase and phosphoesterase.[23] On the other hand, no amide complex was detected when amines were added to the cobalt clusters, whereas amines coordinated to metals to generate the corresponding cobalt mononuclear complexes. In other words, the cobalt cluster system is able to deprotonate alcohols; however, amines are not deprotonated and instead coordinate to the metal center because the pK_a value of amine is naturally higher than that of the corresponding alcohol. The chemoselectivity of the catalyst **10** remained high even when **10** was treated with amine before the addition of ester and alcohol; thus, the possible formation of cobalt-amide species could be excluded (see Supporting Information). Such a clear difference between alcohols and amines in the deprotonation step for generating the corresponding alkoxides and amides plays an important role in determining the hydroxy group selectivity in transesterification in the presence of amines. Based on the fact that early transition-metal carboxylates favorably assisted the acylation of the amino group, it is likely that the chemoselectivity depends on the Lewis acidity of the metal centers. Thus, cobalt ions of the cobalt cluster behave as a Lewis acid and its μ-oxo moiety acts as a Brønsted base to deprotonate alcohols.

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CONCLUSION

The findings of the present study indicate that some carboxylate compounds of first-row late transition metals, such as Mn(II), Fe(II), Co(II), and Cu(I), exhibit unique O-selectivity with appropriately high catalytic activity in the transesterification of alcohols in the presence of primary or secondary amines. In such catalytic systems, the addition of amines was essential to produce high catalytic activity, and among them, cobalt was the best metal in terms of not only catalytic activity and chemoselectivity but also its applicability for mechanistic studies, leading us to select the system of octanuclear cobalt clusters **2c** and **8a**. Transesterification catalyzed by the combined system of **2c** and **8a** proceeded through the formation of the key intermediate alkoxide-bridged cobalt dinuclear complex **10**, which performed enzyme-like catalysis following the Michaelis–Menten mechanism via a ternary complex formation. We also confirmed that the advantages of cluster complexes as catalyst precursors are the deprotonation ability of the basic μ-oxo moieties in the cobalt cluster and stabilization of the alkoxy ligand by bridged dinuclear complexation. Deprotonation of nucleophiles was thus the most important step not only for achieving high catalytic activity but also for determining the chemoselectivity, resulting in the chemical differentiation of alcohols and amines.

ASSOCIATED CONTENT

Supporting Information

Characterization data for all new compounds, synthetic procedures, detailed experimental data, crystallographic data (CIF) for **9**–**11**, and Computational details and Cartesian coordinates of all stationary points. These materials are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Larock, R. In *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999. (b) Mulzer, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1992; Vol *6*. (c) Otera, J. In *Esterification*; Wiley-VCH: Weinheim, 2003.

(2) For reviews, see: (a) Otera, J. *Chem. Rev.* **1993**, *93*, 1449. (b) Hoydonckx, H. E.; De Vos, D. E.; Chavan, S. A.; Jacobs, P. A. *Top. Catal* **2004**, *27*, 83. (c) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971. (d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

(3) For selected recent examples, see: (a) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Tetrahedron Lett.* **2002**, *43*, 879. (b) Chen, C.-T.; Kuo, J.-H.; Ku, C.-H.; Weng, S.-S.; Liu, C.-Y. *J. Org. Chem.* **2005**, *70*, 1328. (c) Ishihara, K.; Niwa, M.; Kosugi, Y. *Org. Lett.* **2008**, *10*, 2187. (d) Kondaiah, G. C. M.; Reddy, L. A.; Babu, K. S.; Gurav, V. M.; Huge, K. G.; Bandichhor, R.; Reddy, P. P.; Bhattacharya, A.; Anand, R. V. *Tetrahedron Lett.* **2008**, *49*, 106. (e) Magens, S.; Ertelt, M.; Jatsch, A.; Plietker, B. *Org. Lett.* **2008**, *10*, 53. (f) Magens, S.; Plietker, B. *J. Org. Chem.* **2010**, *75*, 3715. (g) Weng, S.-S.; Ke, C.-S.; Chen, F.-K.; Lyu, Y.-F.; Lin, G.-Y. *Tetrahedron* **2011**, *67*, 1640.

(4) For selected examples, see: (a) Kuroki, Y.; Ishihara, K.; Hanaki, N.; Ohara, S.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1221. (b) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 10039. (c) Sabot, C.; Kumar, K. A.; Meunier, S.; Mioskowski, C. *Tetrahedron Lett.* **2007**, *48*, 3863. (d) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453. (e) Price, K. E.; Larrivée-Aboussafy, C.; Lillie, B. M.; McLaughlin, R. W.; Mustakis, J.; Hettenbach, K. W.; Hawkins, J. M.; Vaidyanathan, R. *Org. Lett.* **2009**, *11*, 2003. (f) Yang, X.; Birman, V. B. *Org. Lett.* **2009**, *11*, 1499. (g) Ohshima, T.; Hayashi, Y.; Agura, K.; Fujii, Y.; Yoshiyama, A.; Mashima, K. *Chem. Commun.* **2012**, *48*, 5434.

(5) Gardossi, L.; Bianchi, D.; Klibanov, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 6328.

(6) (a) Iwasaki, T.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *J. Org. Chem.* **2008**, *73*, 5147. (b) Iwasaki, T.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Synlett* **2009**, *10*, 1659. (c) Iwasaki, T.; Agura, K.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Chem.—Eur. J.* **2010**, *16*, 11567. (d) Hayashi, Y.; Ohshima, T.; Fujii, Y.; Matsushima, Y.; Mashima, K. *Catal. Sci. Technol.* **2011**, *1*, 230. (e) Maegawa, Y.; Agura, K.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Synlett* **2012**, *23*, 137.

(7) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944.

(8) Maegawa, Y.; Ohshima, T.; Hayashi, Y.; Agura, K.; Iwasaki, T.; Mashima, K. *ACS Catal.* **2011**, *1*, 1178.

(9) Lin, M. -H.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 997.

(10) Hatano, M.; Furuya, Y.; Shimmura, T.; Moriyama, K.; Kamiya, S.; Maki, T.; Ishihara, K. *Org. Lett.* **2011**, *13*, 426.

(11) Further studies of Cu(I) and Mn(II) systems are in progress.

(12) Sidorov, A. A.; Fomina, I. G.; Ponina, M. O.; Aleksandrov, G. G.; Nefedov, S. E.; Eremenko, I. L.; Moiseev, I. I. *Russ. Chem. Bull., Int. Ed.* **2000**, *49*, 958.

(13) Blake, A. B. *Chem. Commun. (London)* **1966**, 569.

(14) Fomina, I. G.; Aleksandrov, G. G.; Dobrokhotova, Zh. V.; Proshenkina, O. Yu.; Kiskin, M. A.; Velikodnyi, Yu. A.; Ikorskii, V. N.; Novotortsev, V. M.; Eremenko, I. L. *Russ. Chem. Bull., Int. Ed* **2006**, *55*, 1909.

(15) Dobrokhotova, Zh. V.; Fomina, I. G.; Kiskin, M. A.; Sidorov, A. A.; Novotortsev, V. M.; Eremenko, I. L. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 256.

(16) Mikhailova, T. B.; Malkov, A. E.; Sidorov, A. A.; Fomina, I. G.; Aleksandrov, G. G.; Golovaneva, I. F.; Demyanovich, V. M.; Novotortsev, V. M.; Ikorskii, Eremenko, I. L. *Russ. J. Inorg. Chem.* **2002**, *47*, 1829.

(17) Aleksandrov, G. G.; Fomina, I. G.; Sidorov, A. A.; Mikhailova, T. B.; Zhilov, V. I.; Ikorskii, V. N.; Novotortsev, V. M.; Eremenko, I. L.; Moiseev, I. I. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 1200.

(18) Lineweaver, H.; Burk, D. *J. Am. Chem. Soc.* **1934**, *56*, 658.

(19) Dixon, M. *Biochem. J.* **1953**, *55*, 170.

(20) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Grimme, S. *J. Comput. Chem.* **2006**, *27*, 1787.

(21) (a) Orita, A.; Mitsutome, A.; Otera, J. *J. Org. Chem.* **1998**, *63*, 2420. (b) Otera, J.; Danoh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307. (c) Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383. (d) Otera, J. *Acc. Chem. Res.* **2004**, *37*, 288. (e) Xiang, J.; Orita, A.; Otera, J. *Adv. Synth. Catal.* **2002**, *344*, 84. (f) Xiang, J.; Toyoshima, S.; Orita, A.; Otera, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3670.

(22) Houghton, R. P.; Mulvaney, A. W. *J. Organomet. Chem.* **1996**, *517*, 107.

(23) For reviews, see: (a) Cleland, W. W.; Hengge, A. C. *Chem. Rev.* **2006**, *106*, 3252. (b) Sreedhara, A.; Cowan, J. A. *J. Biol. Inorg. Chem.* **2001**, *6*, 337. (c) Hegg, E. L.; Burstyn, J. N. *Coord. Chem. Rev.* **1998**, *173*, 133. (d) Krämer, R. *Coord. Chem. Rev.* **1999**, *182*, 243. (e) Weston, J. *Chem. Rev.* **2005**, *105*, 2151. (f) Jedrzejas, M. J.; Setlow, P. *Chem. Rev.* **2001**, *101*, 607. (g) Kimura, E. *Curr. Opin. Chem. Biol.* **2000**, *4*, 207. (h) Kobayashi, M.; Shimizu, S. *Eur. J. Biochem.* **1999**, *261*, 1. (i) Vitale, L. *Food Technol. Biotechnol.* **1999**, *37*, 29. (j) Liu, C.; Wang, L. *Dalton Trans.* **2009**, 227. (k) Gahan, L. R.; Smith, S. J.; Neves, A.; Schenk, G. *Eur. J. Inorg. Chem.* **2009**, 2745. (l) Liu, C.; Wang, M.; Zhang, T.; Sun, H. *Coord. Chem. Rev.* **2004**, *248*, 147.