

## Conference paper

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# Transition-metal clusters as catalysts for chemoselective transesterification of alcohols in the presence of amines<sup>1</sup>

**Abstract:** Acylation is one of the most abundant organic transformations of alcohols (esterification) and amines (amidation). Because of the greater nucleophilicity of the amino group compared to the hydroxyl group and the stability of amides compared to esters, *N*-acylation occurs predominantly in organic synthetic reactions. We reported that the  $\mu$ -oxo-tetranuclear zinc cluster  $Zn_4(OCOCF_3)_6O$  efficiently catalyzes highly chemoselective acylation of hydroxyl groups in the presence of primary and secondary alkyl amino groups to afford the corresponding esters in high yields. Not only zinc carboxylate complexes but also various carboxylate complexes of first-row late transition metals, such as Mn, Fe, Co, and Cu, become catalysts for such the hydroxy group-selective acylation in the presence of amines. Among these carboxylate compounds, we found that the combination of an octanuclear cobalt carboxylate cluster  $[Co_4(OCOR)_6O]_2$  ( $R = CF_3, CH_3$ , and  $^tBu$ ) with nitrogen-containing ligands such as 2,2'-bipyridine show sufficient catalytic activity toward *O*-selective transesterification. Notably, an alkoxide-bridged dinuclear complex,  $Co_2(OCO^tBu)_2(bpy)_2(\mu_2-OCH_2-C_6H_4-4-CH_3)_2$ , was successfully isolated as a key intermediate that proceeds with Michaelis–Menten behavior through an ordered ternary complex mechanism similar to dinuclear metallo-enzymes, suggesting that the formation of alkoxides, followed by coordination of the ester, is responsible for the unique *O*-selective acylation.

**Keywords:** acylation; catalysts; chemoselectivity; clusters; cobalt; OMCOS-17; zinc.

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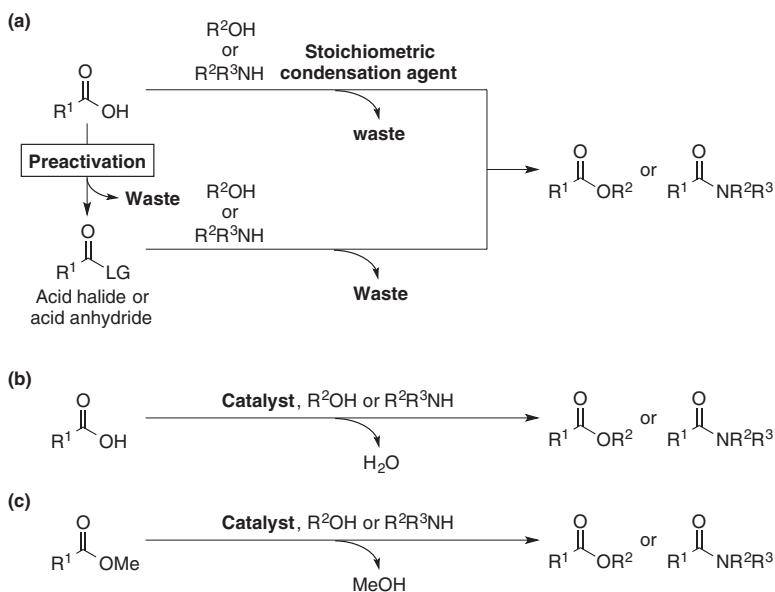
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## Introduction

Esters and amides are ubiquitous functional groups in natural and synthetic organic compounds [1]. These functional groups are typically synthesized by acylation of the corresponding alcohol and amine with a stoichiometric amount of acylating reagents such as acid halides and acid anhydrides, although stoichiometric amounts of base are required to capture acidic co-products such as hydrochloric acid and carboxylic acids (Fig. 1a). Another standard method of synthesizing esters and amides is a condensation reaction of any carboxylic acid with an appropriate alcohol and amine under suitable condensation reagents, but the carboxylic acids have some disadvantages, such as low solubility in common organic solvents, and acidity, which leads to the decomposition of acid-sensitive functionalities (Fig. 1b). Transesterification and amidation starting from lower esters such as methyl esters are easy to handle due to their high solubility and stability, thereby providing a rational synthetic protocol with respect to atom-economy and environmental concerns (Fig. 1c).

When alcohol and amine coexist, a common reaction occurs in which the nucleophilic amine selectively attacks the carbonyl group of ester to give the corresponding amide.

Accordingly, under standard acylating conditions, acylation of alcohol in the presence of a free amino group requires the selective protection of a free amine, followed by esterification of a hydroxyl group, and

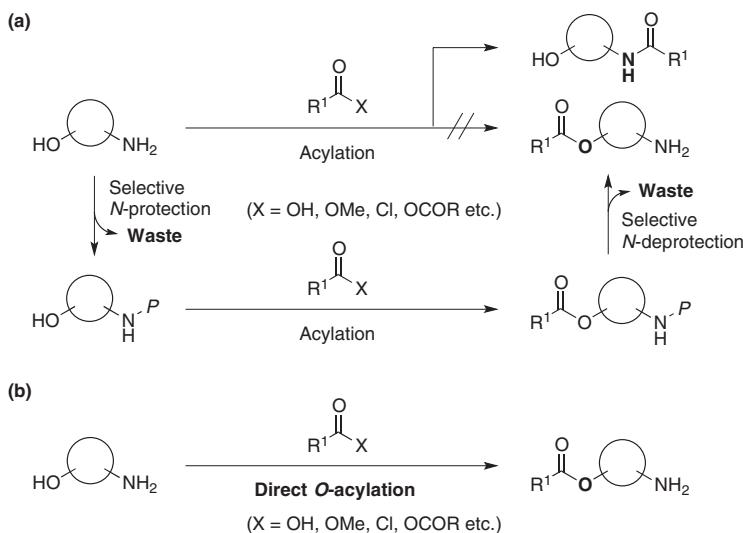


**Fig. 1** Esterifications and amidations: (a) general method for synthesis of esters and amides from carboxylic acids; (b) catalytic condensation of carboxylic acids with alcohols or amines; (c) catalytic transesterification or ester-amide exchange reaction.

then deprotection of the amine moiety (Fig. 2a). Thus, although selective direct *O*-esterification over *N*-amidation of aminoalcohols is a challenging task in synthetic organic chemistry, it is worth developing to minimize the reaction process and reduce chemical waste (Fig. 2b) [2]. Herein, we concisely review chemoselective acylation of the hydroxy group in the presence of amino groups, and report our recent achievements on *O*-selective esterification of aminoalcohols catalyzed by zinc and cobalt clusters.

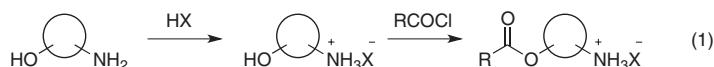
### Chemoselective acylation of alcohols in the presence of amines

Pre-protonation of alkyl amino groups by highly acidic reagents such as hydrochloric acid and trifluoroacetic acid is a straightforward route for the esterification of aliphatic amino alcohols (eq. 1). A unique example was reported by Takata and Kihara et al. who used rotaxane compounds for a *O*-selective acylation followed



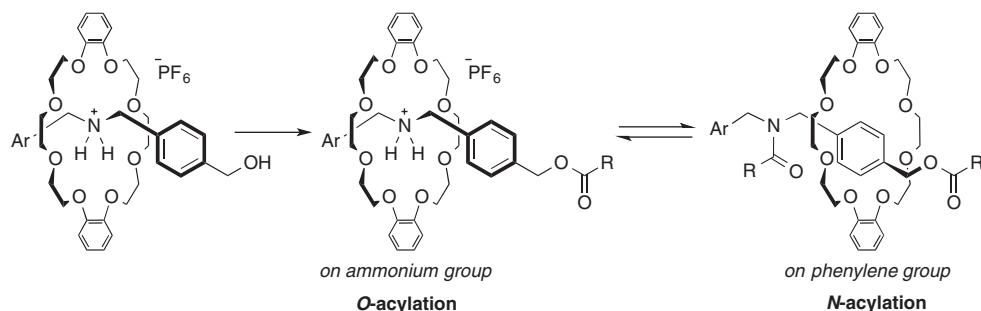
**Fig. 2** (a) Common strategy for esterification of aminoalcohols; (b) direct esterification of amino alcohols.

by *N*-acylation to lock the rotaxane structure (Scheme 1) [3]. Copper ions were coordinated in a chelating fashion to amino acid functionalities so that the hydroxyl group was esterified, and then removed by hydrogen sulfide [4] or 8-hydroxyquinoline (Scheme 2) [5].

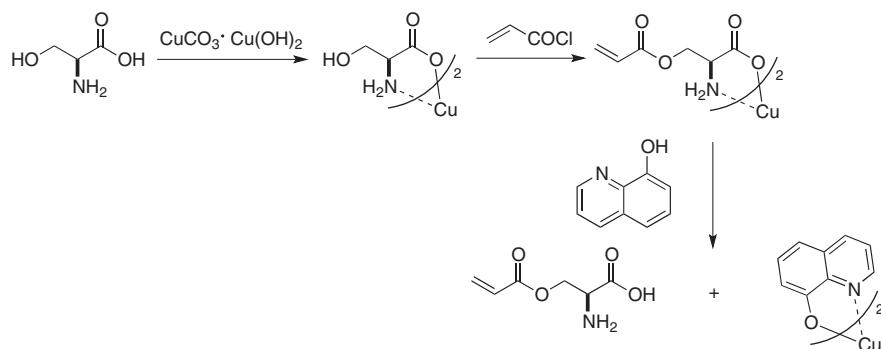


Enhancement of the nucleophilicity of the hydroxyl group is another strategy used for the chemoselective acylation of aromatic substrates. Selective *O*-acylation of phenols in the presence of aromatic amino groups is accomplished by acylating reagents bearing a specific leaving group, such as *N*-methyl-*N*-nitroso [6] and 2-bipyridinyl groups [7] in which a proton of the hydroxyl group is accepted via a concerted proton transfer, as schematically depicted in Fig. 3.

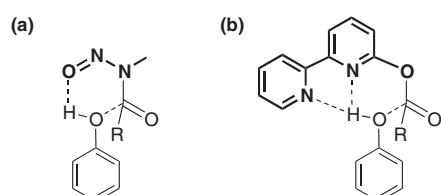
Studer et al. developed *N*-heterocyclic carbene (NHC), which mediates the chemoselective acylation of alcohols in the presence of amines (eq. 2) [8]. The DFT calculations on NHC- $\text{H}_2\text{NMe}$  and NHC-HOMe indicate that the stronger hydrogen bonding energy for NHC-HOMe than that for NHC- $\text{H}_2\text{NMe}$  elongates the O-H bond.



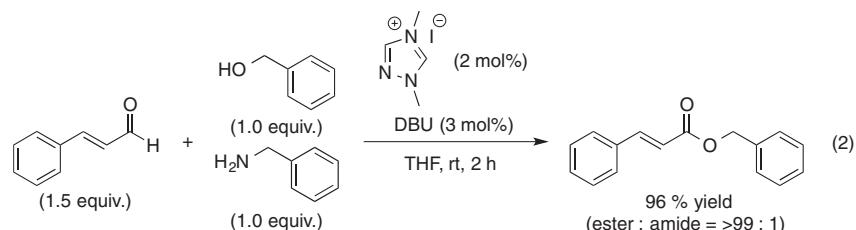
**Scheme 1** *O*-selective acylation of rotaxane compounds.



**Scheme 2** *O*-selective acylation of Cu-chelated amino acid derivatives.



**Fig. 3** Possible transition state in acylation of phenol with specific acyl donor. (a) *N*-methyl-*N*-nitroso group; (b) 2-bipyridinyl group.



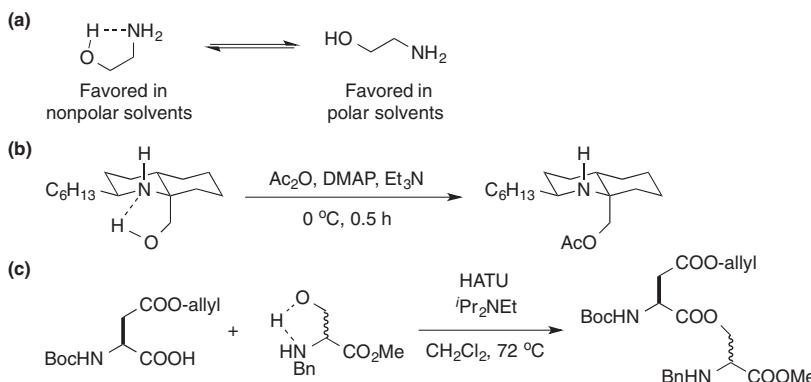
The 1,2- and 1,3-amino alcohols are unique in that they act in intramolecular hydrogen bonding of the hydroxy group with the amino group in nonpolar solvent, and as non-hydrogen-bonded molecules in polar solvent (Fig. 4a). Such hydrogen bonding enhances the nucleophilicity of the oxygen atom, while attenuating the nucleophilicity of the nitrogen, which results in an inversion of reactivity toward the acylation. Maeng and Funk demonstrated chemoselective *O*-esterification for the synthesis of cytotoxin fasicularin (Fig. 4b) [9]. Using the same synthetic strategy, Piarulli and Gennari et al. conducted *O*-selective acylation of (*R*)-*N*-benzyl-serine methyl ester using HATU to afford the corresponding ester compound (Fig. 4c) [10].

Some enzymes act to fix the transition state conformation in favor of *O*-acylation. Lipase catalyzes the selective *O*-acylation of the serine moiety of a dipeptide, (*S*)-Phe-(*S*)-Ser(OH)-NH- $\beta$ -Naph, even in the presence of highly nucleophilic  $\alpha$ -NH<sub>2</sub> group of Phe, to give the *O*-acetylated product, (*S*)-Phe-(*S*)-Ser(OAc)-NH- $\beta$ -Naph, in 98 % yield[11]. Molecular modeling studies suggest that such *O*-selectivity is caused by interference with the hydrogen transfer in the transition state [12].

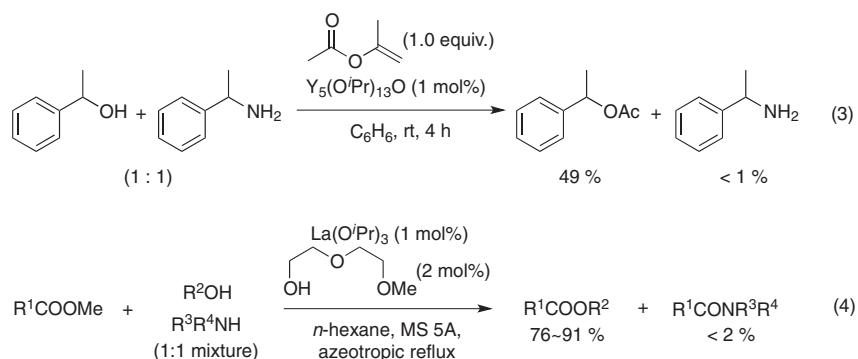
## Metal-catalyzed *O*-selective acylation

### Yttrium catalysts

Lin and RajanBabu reported yttrium-catalyzed selective *O*-acylation over *N*-amidation using Y<sub>5</sub>(O*i*Pr)<sub>13</sub>O as a catalyst to promote the selective *O*-acetylation of amino alcohols without the formation of the amide by activated acylation reagents such as vinyl or isopropenyl acetate [13]. When a stoichiometric mixture of 1-phenylethanol and 1-phenylethanamine is treated with the yttrium catalyst and isopropenyl acetate, the alcohol quantitatively converts to *O*-acetate and only a trace amount of the *N*-acetyl derivative is detected (eq. 3). Recently, Ishihara et al. also reported that a La(O*i*Pr)<sub>3</sub>-2-(2-methoxyethoxy)ethanol catalyst system catalyzes the chemoselective transesterification of methyl esters in the presence of amines (eq. 4) [14].

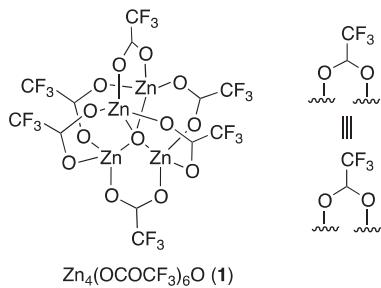
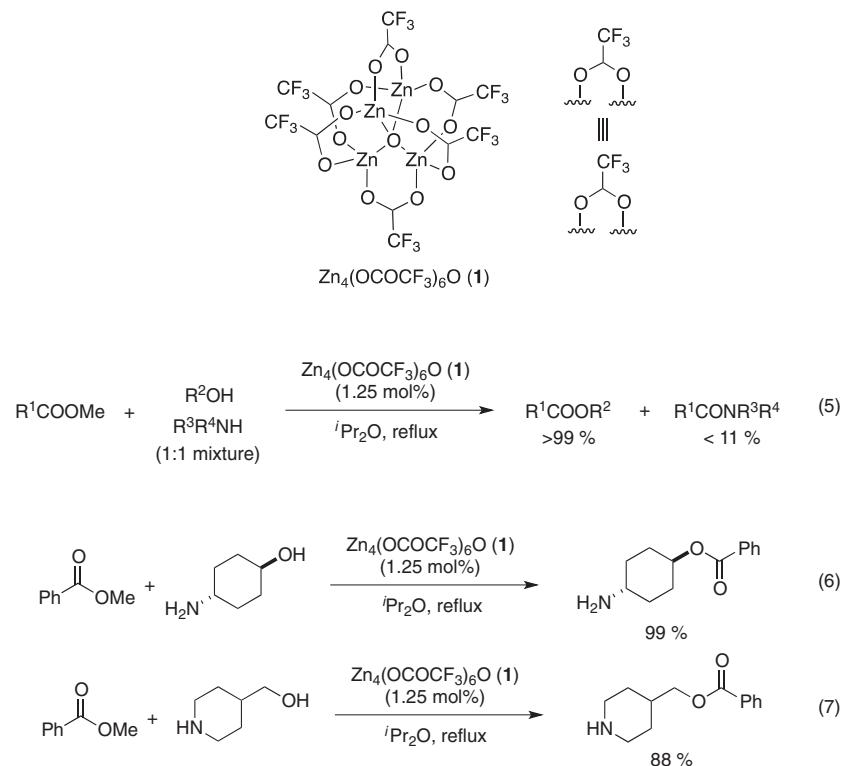


**Fig. 4** Intramolecular hydrogen bonding of the hydroxy group with the amino group in 1,2-amino alcohols. (a) The lone pair of electrons on the nitrogen atom is used to form the intramolecular hydrogen bond with the hydrogen atom on the hydroxy group; (b) and (c) examples of chemoselective *O*-acylations of 1,2-amino alcohols under basic conditions.



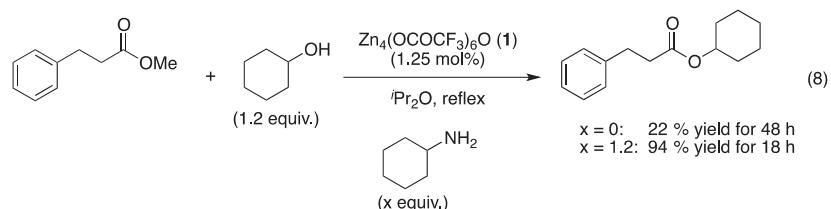
## Zinc catalysts

We reported that the zinc cluster  $\text{Zn}_4(\text{OCOCF}_3)_6\text{O}$  (**1**) [15] effectively catalyzes the hydroxy group-selective acylation with unactivated methyl esters in the presence of primary and secondary aliphatic amino groups (eq. 5) [15b]. The present method provides a new protocol to directly convert amino alcohols to the corresponding amino esters without the use of protecting groups, outlined in Fig. 2a. Representative examples are the transesterification of methyl benzoate with amino alcohols such as *trans*-4-aminohexane-1-ol and 4-piperidinemethanol to give the corresponding amino esters without any amides (eqs. 6 and 7), while ethanolamine and *cis*-4-aminohexane-1-ol predominantly produce the corresponding amides via intramolecular *O,N*-rearrangement of the initially generated amino esters. In addition, under refluxing conditions in excess amounts of EtOAc, the alcohols are acetylated in high yield while hydroxyl group selectivity is maintained [15d].



### Amine additive effects

The addition of catalytic amounts of amines and *N*-heteroaromatics to zinc catalyst **1** has drastic additive effects on the transesterification of alcohols to increase the catalytic activity compared with the original reactivity of **1**. A typical example is shown in eq. 8: in the presence of cyclohexylamine, transesterification proceeds smoothly to reach 94 % yield while maintaining the *O*-selectivity [15h]. DMAP works better than primary amines, facilitating the transesterification of sterically demanding esters and alcohols (Scheme 3). In fact, in the presence of a catalytic amount (20 mol%) of DMAP, transesterification of methyl adamantine-1-carboxylate and 1-butanol under toluene refluxing conditions for 90 h affords 94 % yield, which is greatly improved compared with only a trace amount obtained with no additive and 29 % yield by the addition of cyclohexylamine. We propose that the addition of DMAP stabilizes the clusters with lower nuclearities and enhances catalytic activity for transesterification.

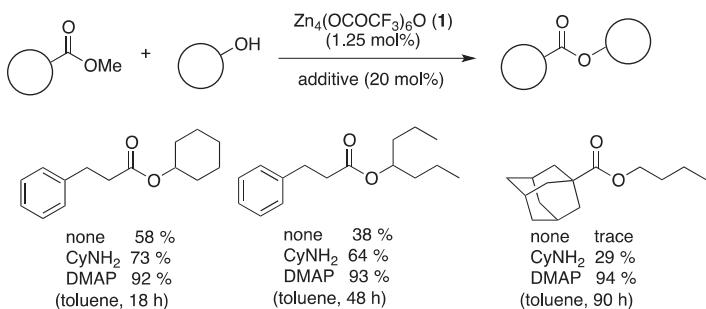


### Cobalt catalysts

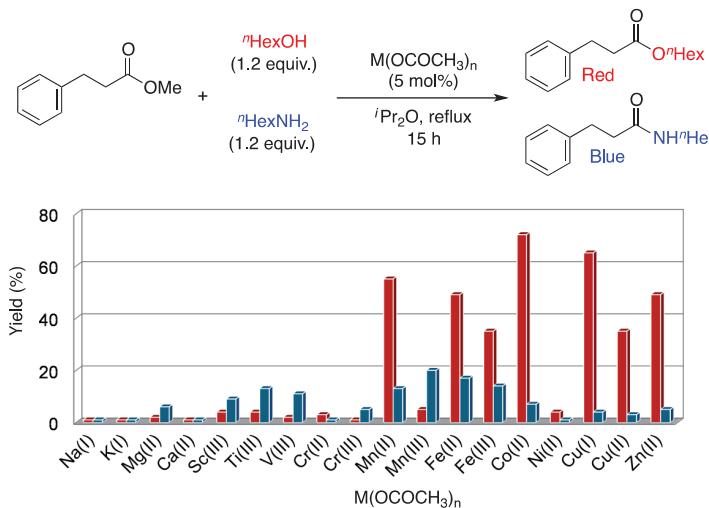
Because zinc and yttrium cluster complexes show high hydroxyl group selectivity and the additive of amines and *N*-heteroaromatic compounds to zinc cluster catalyst **1** improved catalytic activity, we tested the catalytic performance of various metal carboxylates for chemoselective acylation of alcohols over amines [15i]. Scheme 4 shows the results of the test reaction of methyl 3-phenylpropanoate with a 1:1 mixture of *n*-hexanol (1.2 equiv) and *n*-hexylamine (1.2 equiv) in the presence of various metal acetates,  $M_n(OCOCH_3)_m$  (5 mol% metal). Acetate complexes of middle and late first-row transition metals in an oxidation state of two show moderate catalytic activity and maintain sufficient chemoselectivity, producing *O*-acylated product (blue bar) over *N*-acylated product (red bar). Without the addition of *n*-hexylamine, the catalytic activity of transesterification is suppressed to almost no reaction or low yield, and the addition of *n*-hexylamine interacts with carboxylate compounds of Mn(II), Fe(II), Co(II), Cu(II), Cu(I), and Zn(II) to give catalytically active species that catalyze *O*-selective acylation.

### Dinuclear cobalt complex

We selected a pivalate-bridged octanuclear cluster,  $\text{Co}_8(\text{OCO}'\text{Bu})_{12}\text{O}_2$  (**2**) [16], to elucidate *O*-selective transesterification [15i]. Ligand screening revealed that not only monodentate amines and *N*-heteroaromatics, but

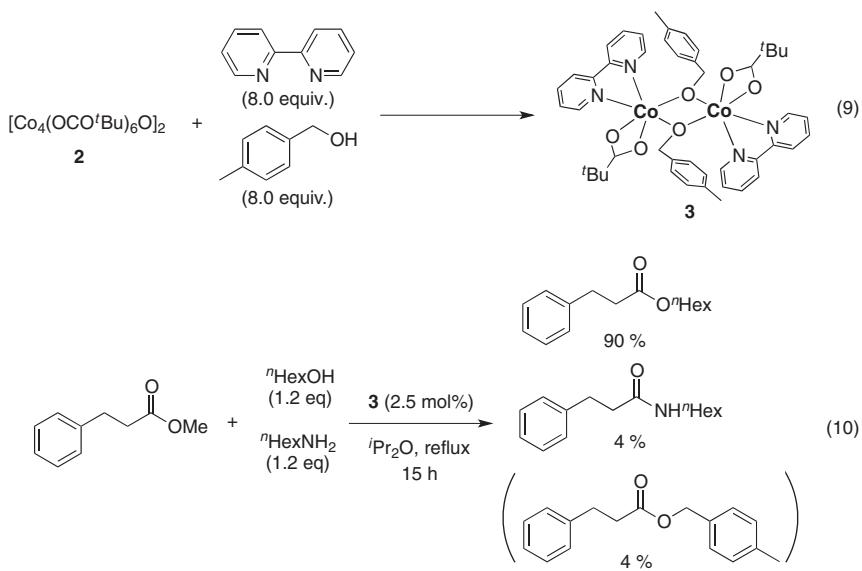


**Scheme 3** Additive effects of the zinc cluster-catalyzed transesterification.



**Scheme 4** Catalytic activity and chemoselectivity of various metal acetates for acylation of *n*-hexanol and *n*-hexylamine with methyl 3-phenylpropionate.

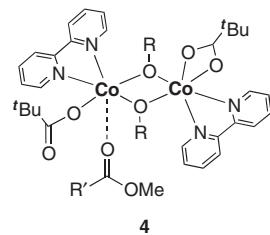
also chelating ligands, including acyclic and cyclic ligands, have suitable additive effects, and finally we selected 2,2'-bipyridine. The reaction of **2** with 2,2'-bipyridine (8 equiv) in the presence of 4-methylbenzyl alcohol (8 equiv) afforded an alkoxide-bridged dinuclear complex  $\text{Co}_2(\text{OCO}^t\text{Bu})_2(\text{bpy})_2(\mu_2\text{-OCH}_2\text{-C}_6\text{H}_4\text{-4-CH}_3)_2$  (**3**) as a key intermediate (eq. 9), which we characterized by X-ray analysis. Notably, the isolated complex **3** showed hydroxyl group selectivity: competitive reaction of methyl 3-phenylpropanoate with a 1:1 mixture of *n*-hexanol (1.2 equiv) and *n*-hexylamine (1.2 equiv) in the presence of **3** (2.5 mol%) produces esters (totally 94 %) and an amide (4 %) (eq. 10).



## Mechanism

Kinetic studies and DFT calculations revealed Michaelis–Menten behavior of the complex **3** through the ordered ternary complex mechanism similar to dinuclear metallo-enzymes, suggesting the formation of alkoxides followed by coordination of the ester to give the ternary intermediate **4** with  $\eta^1$ -coordination of the pivalate moiety and intramolecular nucleophilic attack of the bridged alkoxy moiety to the coordinated ester. In contrast to the Co(II) ion of the active species, Co(III) compounds have very low catalytic activity due to

the inertness of a closed-shell  $d^6$  Co(III) species for any ligand exchange reaction. We therefore assumed that basic  $\mu$ -oxo moieties of the cobalt cluster play an important role in the initial deprotonation step of alcohols for producing alkoxo-bridged species.



## Conclusion

As summarized in this review, several efficient *O*-selective acylations in the presence of much more nucleophilic primary and secondary alkyl amino groups have been developed. In general, to reverse the innate reactivity of amino and hydroxyl groups, the protection of more reactive amino groups is necessary, resulting in the formation of more than stoichiometric amounts of chemical waste, which reduces the reaction efficiency. The catalytic *O*-selective acylation reactions described here clearly indicate that such innate chemoselectivity is reversible in a catalytic manner. A variety of carboxylate complexes of first-row late transition metals, such as Mn, Fe, Co, Cu, and Zn, catalyze the hydroxy group-selective acylation in the presence of amines. Mechanistic studies using Co complexes revealed that the reactions proceed with Michaelis–Menten behavior through an ordered ternary complex mechanism similar to dinuclear metallo-enzymes, suggesting that the formation of alkoxides followed by coordination of the ester is responsible for the unique *O*-selective acylation. Because of the high efficiency in terms of atom economy and step economy, these direct catalyses will be a powerful tool for organic synthesis, and further development of new catalyst-controlled chemoselective reactions is needed.

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