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ARTICLE

A Highly Stable but Highly Reactive Zinc Catalyst for Transesterification Supported by Bis(imidazole) Ligand

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We designed highly active and practical bis(imidazole)/zinc complexes for transesterification reactions. X-ray crystallographic analysis was used to confirm the structures of the zinc complexes and an equivalent of bis(imidazole) ligand was crucial for high catalytic activity. The octahedral zinc complex **8c** was prepared in up to multigram scale by mixing $Zn(OCOCF_3)_2 \cdot xH_2O$ and meta-bis(imidazolylmethyl)benzene ligand **7j** (two equivalents to zinc ion) and storable under air at room temperature for at least 9 months. The stable nature of the catalyst was amenable to recovery/reuse at least five times without a significant loss of reactivity. The transesterification reaction proceeded without strict reaction conditions, and expanded substrate generalities, including sterically demanding secondary and tertiary alcohols, were applicable. Remarkably, the present zinc catalyst proved highly effective for valuable monomer synthesis from readily available methyl acrylate derivatives. Chemoselective transesterification reactions of unprotected-amino alcohols were also achieved, using not only simple methyl ester but also unprecedented dimethyl carbonate.

Introduction

The development of catalyst-promoted atom-economical and environmentally benign processes is a topic of great interest in modern organic chemistry. Among these types of processes, ubiquitous ester bond formation is a fundamental and well-studied methodology.[1] Ester synthesis is commonly performed in synthetic organic chemistry using carboxylic acid with alcohol under stoichiometric amounts of condensation reagent or treatment of a highly reactive acylating reagent, such as acyl chloride and acid anhydride, due to the reliability of these methods, but the inevitable formation of more than a stoichiometric amount of co-product is a drawback. Although catalyst-promoted ester formation between carboxylic acid and alcohol is an ideal method in terms of atom-economy,[2] there remains much room for improvement in terms of practicality due to the use of acidic conditions at high reaction temperature, resulting in narrow functional group compatibility. An attractive alternative method of ester synthesis is transesterification promoted by a catalytic amount of metal reagent.[3] The transesterification process generates only nontoxic lower alcohols and is performed under almost neutral conditions, allowing for high functional group compatibility. Furthermore, the handling ease as well as the high stability and high solubility of esters in most organic solvents compared with the corresponding carboxylic acids

makes them advantageous as a starting material. Several metal-catalyzed transesterification reactions were recently reported.[4,5] Most of these methods, however, require the use of toxic metal salt or tediously strict reaction conditions. In addition, the application of sterically demanding alcohols to catalytic transesterification remains difficult. Therefore, the development of highly active nontoxic metal catalyzed transesterification reactions without strict attention to air and moisture conditions is highly desirable for practical utility. Here we report a highly stable but highly active bis(imidazole)/zinc complex as a nontoxic metal catalyst for transesterification reactions. A newly designed zinc complex led to expanded substrate generality and reuse at least five times without loss of activity under air atmosphere.

Results and discussion

We previously reported μ-oxo-tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$ (**1**) and μ-oxo-octanuclear cobalt cluster $[Co_4(OCO\text{-}t\text{-}Bu)_6O]_2$ (**2**) as efficient pre-catalysts for the transesterification of various methyl esters and alcohols (Figure 1).[5]

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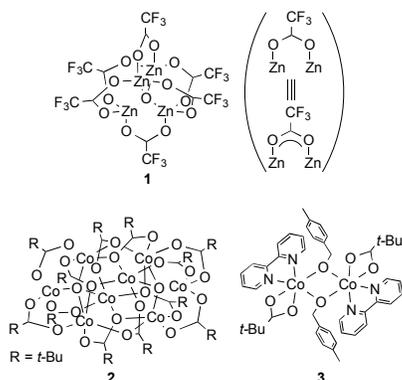
Fig 1. The Structures of $Zn_4(OCOCF_3)_6O$ (**1**), $[Co_4(OCO-t-Bu)_6O]_2$ (**2**) and Alkoxide-bridged Dinuclear Cobalt Complex (**3**)

A unique hydroxyl group-selective acylation in the presence of much more nucleophilic amino groups is also catalyzed by these clusters.[5c,5i] In addition, our studies on *N*-heteroaromatic additive effects and reaction mechanisms revealed the following: (1) Addition of *N*-heteroaromatics, such as DMAP, drastically accelerates the zinc and cobalt cluster-catalyzed transesterification; (2) Such additives coordinate to the metals and stabilize clusters with lower nuclearities; and (3) Alkoxide-bridged dinuclear metal complex **3** is the active species in this catalytic cycle.[5f,5i] In addition, kinetic studies and density functional theory calculations revealed Michaelis−Menten behavior of complex **3** through an ordered ternary complex mechanism, similar to dinuclear metallo-enzymes. Based on these results, we expected that proper multidentate *N*-heteroaromatic ligands could stabilize active dinuclear metal complexes, leading to enhanced catalytic activity. Thus, several *N*-heteroaromatic additives were investigated with zinc cluster **1**. To facilitate comparison of the additive effects, less reactive and sterically demanding cyclohexanol (**5a**) was selected as a model substrate in the presence of 2.5 mol% zinc. Without a ligand, zinc cluster catalyst **1** delivered the corresponding transesterification product **6aa** in only 10% yield (Table 1, entry 1). As expected, DMAP (**7a**), a previously identified optimal ligand, greatly enhanced the catalytic activity, providing the product in 74% yield (entry 2).[5i] *N*-Methylimidazole (**7b**) had almost the same catalytic activity as DMAP (79% yield; entry 3). On the other hand, *N*-methylbenzimidazole (**7c**) had almost no effect (15% yield; entry 4), presumably due to the lower coordination ability of the nitrogen atom. A bulkier alkyl substituent on the imidazole nitrogen was also less effective than a methyl substituent (entry 5). We then turned our attention to multidentate ligands. Because imidazole was easier to modify than DMAP, we synthesized various ligands bearing two or more imidazole units[6] and examined their effects on transesterification. First, we performed the reaction with *ortho*-, *meta*-, and *para*-bis(imidazolylmethyl)benzenes (**7e**-**g**). While detrimental effects were observed with the use of *para*- and *ortho*-substituted ligands (entries 6 and 8), *meta*-substituted ligand

7f afforded the desired product in higher yield (89% yield; entry 7). Encouraged by these results, we examined further modifications of *meta*-substituted ligand **7f**. Additional substituents on **7f** largely impacted the solubility of the zinc complexes. Zinc complexes with pentyloxy, benzyloxy, and *tert*-butyl substituted ligands (**7h**, **7i**, and **7j**) exhibited high solubility in chlorobenzene to furnish **6aa** in high yield (entries 9–11), whereas poorly soluble complexes derived from methyl and bromo substituted ligands (**7k** and **7l**) resulted in low yield (entries 12 and 13). Other ligands with different backbones were also examined. Bis(imidazolylmethyl)naphthalene **7n** and 1,1'-methylene bis(imidazole) (**7o**) afforded poor results (entries 15 and 16). Although *cis*-bis(imidazolylmethyl)cyclohexane **7p** gave results comparable to **7f** (entry 17), we selected **7f** and its derivatives based on their synthetic efficiency as optimal ligands for further investigation. Finally, the effects of tridentate ligand 1,3,5-tris(imidazolylmethyl)benzene (**7q**) were investigated, but only diminished reactivity was observed due to the low solubility of the corresponding zinc complex (entry 18).[7]

Table 1. Evaluation of Ligand for Transesterification

1. No Ligand 10%	2. 7a: 74%	3. 7b: 79%
4. 7c: 15%	5. 7d: 66%	6. 7e: 71%
7. 7f: 89%	8. 7g: 29%	9. 7h: 87%
10. 7i: 80%	11. 7j: 84%	12. 7k: 58%
13. 7l: 52%	14. 7m: 19%	15. 7n: 47%
16. 7o: 11%	17. 7p: 92%	18. 7q: 24%
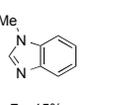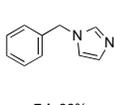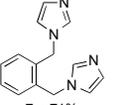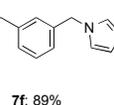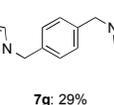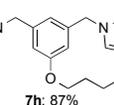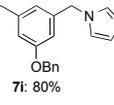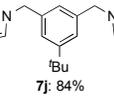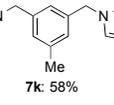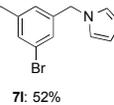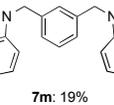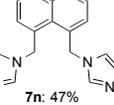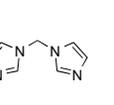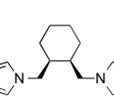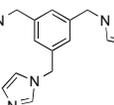
Conditions: **4a** (1.0 mmol), **5a** (1.2 mmol), PhCl (1.7 mL). Yields were determined by GC analysis using nonadecane as an internal standard. In entries 2 - 5, 10 mol% ligand was used. In entry 18, 3.3 mol% ligand was used.

To gain structural information about the active zinc complexes derived from *meta*-bis(imidazolylmethyl)benzene ligands, we obtained single crystal of these complexes by mixing $Zn_4(OCOCF_3)_6O$ (**1**) and ligand **7f** for X-ray crystallographic analysis (Scheme 1). Interestingly, changing the metal-ligand ratio greatly affected the structures of the complexes. When two equivalents of ligand **7f** to zinc ion was used, a trans octahedral structure occupying two trifluoroacetates in an apical position was observed, and the trans octahedral zinc complex **8a** formed a one-dimensional infinite chain structure. On the other hand, use of one equivalent of **7f** to zinc ion resulted in tetrahedral complex **8b**. The two distinct zinc complexes **8a** and **8b** were subjected to the transesterification reaction. Although octahedral complex **8a** served as an efficient catalyst similar to *in situ* prepared zinc catalyst from **1** and **7f** (2 equiv), the low-soluble tetrahedral complex **8b** did not catalyze the transesterification reaction, indicating that octahedral complex **8a** is an actual pre-catalyst.[8]
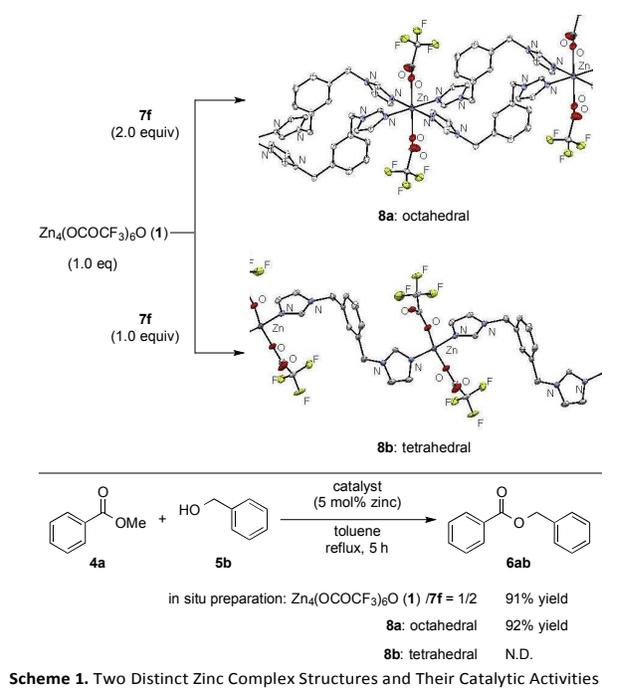
Scheme 1. Two Distinct Zinc Complex Structures and Their Catalytic Activities

In a similar way, octahedral complex **8c** was prepared in 91% yield as a white crystal simply by mixing $Zn(OCOCF_3)_2 \cdot xH_2O$ with *tert*-butyl substituted ligand **7j** in THF under reflux conditions, and **8c** had an infinite network structure (Scheme 2). Zinc complex **8c** was synthesized in 3.8-gram scale, and it was bench-stable and storable without strict concern regarding air and moisture, demonstrating identical catalyst activity for at least 9 months.[9]
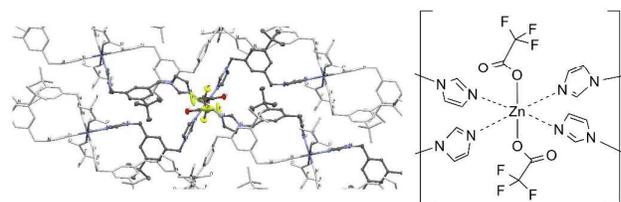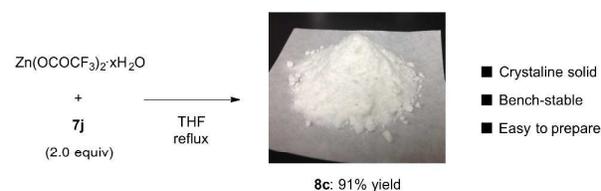
Scheme 2. Highly Stable Crystalline Zinc Complex **8c** and X-Ray Crystallographic Structure

The initially developed tetranuclear zinc cluster **1** is hygroscopic and must be handled under argon atmosphere. Although the commercially available zinc cluster

Zn$_4$(OCOCF$_3$)$_6$O•CF$_3$CO$_2$H,[5g,10] which has almost identical catalytic activity and functional group tolerance to **1**, and is more stable and less hygroscopic, it still absorbs moisture when subjected to high humidity. On the other hand, complex **8c** was highly stable compared with the zinc clusters and not hygroscopic, making it possible to handle without strict concern regarding air or moisture. The high stability of **8c** against moisture was demonstrated in the water-addition control experiment (Scheme 3). Even in the presence of five equivalents of water (100 equiv to zinc ion), zinc complex **8c** provided product **6ab** in quantitative yield after 21 h with a slightly decreased reaction rate, presumably because reaction temperature was decreased under azeotropic conditions. On the other hand, the reaction rate of Zn$_4$(OCOCF$_3$)$_6$O (**1**) catalysis was significantly retarded by the addition of water, and **6ab** was formed in only moderate yield even after 21 h.
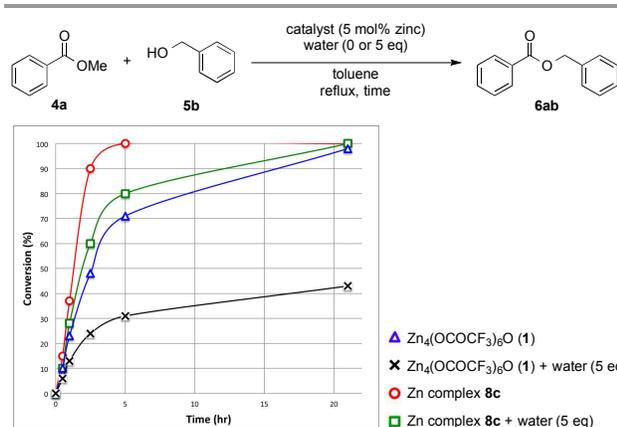
Scheme 3. Reaction Profiles of Zinc Cluster (**1**) and Zinc Complex **8c** Catalyzed Transesterifications in the Presence of Water

The highly stable nature of zinc complex **8c** against water prompted us to investigate the possibility of recovery and reuse of the catalyst while our efforts to recover zinc cluster **1** were unsuccessful. Using methyl benzoate (**4a**) and benzyl alcohol (**5b**) as model substrates, the transesterification reaction was performed in gram scale. After refluxing the reaction mixture for 5 h under air atmosphere, volatiles, including the desired product **6ab**, were removed under reduced pressure. The residue was washed with *n*-hexane, and the remaining zinc complex was subjected to the next reaction cycle. The recovered zinc complex was reused five times without a significant loss of catalytic activity (average over 95% yield; Scheme 4). After five runs, zinc complex **8c** was recovered in 91% yield. NMR analysis of the recovered zinc complex confirmed that no decomposition of **8c** occurred, clearly demonstrating the highly stable nature of the bis(imidazole)/zinc complex.[11] Alternatively, zinc complex **8c** can be recovered and reused using simple deposition and decantation techniques.[11] The exact structure of the active catalyst species is not clear, but based on our previous mechanistic studies, zinc complex **8c** is likely a pre-catalyst,

and at an elevated temperature an active zinc alkoxide species may be efficiently generated from octahedral zinc species supported by four *N*-imidazolyl ligands and two trifluoroacetates. In the early stage of the reaction, zinc complex **8c** and zinc alkoxide species are soluble because of the existence of alcohol. As the reaction progresses, alcohol **5b** would be converted into the corresponding ester **6ab** and the resulting volatile methanol removed from the reaction mixture. Toward the end of the reaction, the total amount of alcohols decreases, and thus, zinc complex **8c** would be reconstructed and precipitated from the reaction mixture.

Run	yield (%)
1	96
2	97
3	97
4	97
5	97
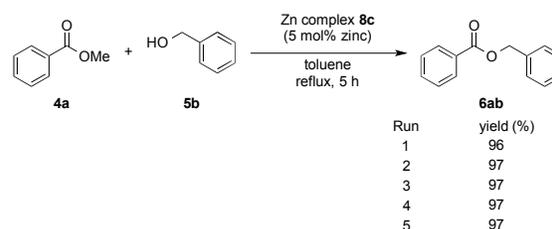
Scheme 4. Recovery and Reuse Experiment using Zinc Complex **8c**

The zinc complex, which achieves a good balance between high catalytic activity and high stability, led to investigation of the substrate scope with a variety of esters **4** and alcohols **5** in the presence of 5 mol% of the isolated zinc complex **8c** (Table 2).[12] All reactions catalyzed by zinc complex **8c** were performed under an air atmosphere without strict concern regarding moisture. Sterically demanding secondary alcohols, (+)-menthol (**5c**), cholesterol (**5d**) and borneol (**5e**), were applicable and the corresponding esters were obtained in high yield (entries 1–3). A sterically congested electrophile, methyl *o*-toluate (**4b**), proved to be good substrate (entry 4). Highly coordinative 2-pyridinemethanol (**5f**) was successfully acylated with ibuprofen methyl ester (**4c**), providing ibuprofen piconol **6cf**, which is the pro-drug of ibuprofen (entry 5). It is noteworthy that transesterification of a tertially alcohol, adamantanol (**5g**), also proceeded to afford **6dg** under xylene reflux conditions using zinc complex derived from zinc cluster **1** and pentyloxy-substituted ligand **7h** due to the high solubility of **7h** in xylene (entry 6).[4p,13] When Zn$_4$(OCOCF$_3$)$_6$O (**1**) itself was used as the catalyst, product **6dg** was not observed, even at elevated temperature. Benzyl formate (**6eb**) was obtained in high yield from ethyl formate (**4e**) (entry 9).[14] Silyl and tertiary amino groups were tolerated (entries 8 and 9). Moreover, α-amino ester **4f** was successfully transesterificated to **6fj** without a decrease in enantiopurity (entry 10). From a practical point of view, readily available methyl acrylate (**4g**) and methyl methacrylate (**4h**) are considered attractive starting materials for more valuable monomer synthesis. These acrylate derivatives undergo polymerization not only in harsh acidic/basic conditions but also at high temperature. In addition, competition between transesterification and conjugate addition often results in a low chemical yield.

Therefore, catalytic transesterification of methyl acrylate derivatives remains a formidable task. We found that the combination of $Zn_4(OCOCF_3)_6O$ (**1**) and pentyloxy-substituted ligand **7h** efficiently catalyzed the transesterification of methyl acrylate (**4g**) and methyl methacrylate (**4h**) (entries 11 and 12). These findings suggest the high utility of the present zinc catalysis for conversion of readily available **4g** and **4h** to more useful monomers.

Table. 2 Substrate Scope

Conditions: **4** (1.0 mmol), **5** (1.2 mmol), solvent (2.0 mL). Isolated yields after column chromatography. [b] In situ prepared zinc complex with **7h** was used under an argon atmosphere.

Although we previously developed the optimized catalyst conditions using $Zn_4(OCOCF_3)_6O$ (**1**) with DMAP, the highly nucleophilic nature of DMAP posed a potential risk of side reactions, such as nucleophilic addition of DMAP. Therefore, to demonstrate the utility of the present zinc catalyst, transesterification of the labile α-chloroester **4i** was examined (Scheme 5). While the catalyst generated *in situ* from **1** with DMAP resulted in low yield, the newly developed zinc complex **8c** delivered benzyl ester **6ib** in high yield, highlighting the enhanced functional group compatibility of the new zinc catalyst.[15]

Scheme 5. Comparison of Functional Group Compatibility Between Zinc Complex **8c** and *in situ* Prepared $Zn_4(OCOCF_3)_6O$ (**1**)/DMAP Catalyst

Zinc complex **8c** catalyzed the formation of not only ester but also carbonate and carbamate utilizing cheap and safe dimethyl carbonate (**9a**) (Table 3).[4p,16] Mono transesterification of **9a** with benzyl alcohol (**5b**) and cyclohexanol (**5a**) predominantly occurred to generate unsymmetrical carbonates **10aa** and **10ab** in high yield (entries 1 and 2). The reaction with adamantanol (**5g**) gave the corresponding product **10ag** in 93% yield with a prolonged reaction time (entry 3). The use of diols **11** with various functionalities afforded cyclic carbonates **12** through intramolecular second transesterification (entries 4–7). Chloro, allyloxy, phenoxy, and morpholinyl groups at the 3-position of 1,2-hydroxypropane survived during the catalysis without side reactions, such as epoxidation. We then examined the formation of carbamate from dimethyl carbonate (**9a**) and 1,2-amino alcohols **13**, but the reaction conditions for 1,2-diols using an excess amount of **9a** gave only undesired *N*-methoxycarbonyl and bis(methoxycarbonyl) compounds, probably through an initial *O*-methoxycarbonylation and subsequent intramolecular *O*□*N* methoxycarbonyl transfer reaction, and a second *O*-methoxycarbonylation. To prevent such side reactions, we optimized the reaction conditions, and chiral oxazolidinones **14a** and **14b** were successfully obtained in high yields from the corresponding chiral 1,2-amino alcohols **13a** and **13b** using 1.05 equivalent of diethyl carbonate (**9b**) under toluene reflux conditions (0.5 M; entries 8 and 9).

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Table 3. Transesterification using Dimethyl Carbonate
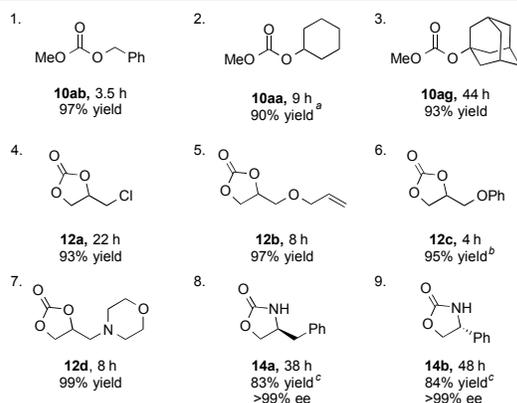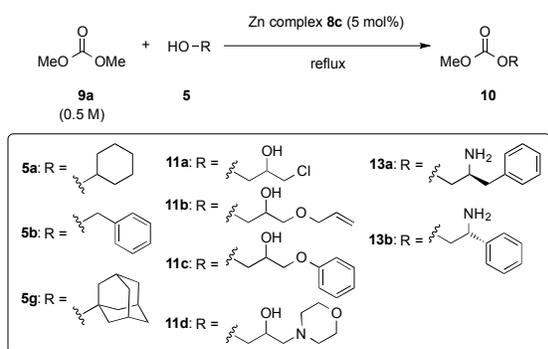
Conditions: **9a** (2.0 mL), **5** (1.0 mmol). Isolated yields after column chromatography. [a] Product **10aa** was isolated as a ethyl acetate solution due to the highly volatile nature of **10aa**. [b] Diethyl carbonate (**9b**) was used instead of **9a**. [c] Diethyl carbonate (**9b**) (1.05 equiv) was used and toluene was used as solvent (0.5 M).

Finally, chemoselective acylation and methoxy carbonylation of the hydroxyl group over the innately more nucleophilic amino group were performed using zinc complex **8c** (Scheme 6).[17] Similar to zinc cluster **1**, zinc complex **8c** catalyzed *O*-selective acylation of amino alcohol **13c** with methyl benzoate (**4a**), and following *N*-Boc protection to facilitate isolation, the desired ester **15** was isolated in 93% yield in two steps with excellent chemoselectivity (>20/1; Scheme 6).[4o,5c,5i,18,19] This unique chemoselective reaction was extended to transesterification of dimethyl carbonate (**9a**). Even in the presence of excess amount of **9a** (ca. 24 equiv, using as a solvent), the corresponding unsymmetrical carbonate **16** was isolated in 86% yield with high chemoselectivity, while zinc cluster **1** afforded much lower chemoselectivity (ca. 2/1). To the best of our knowledge, this is the first example of the chemoselective (hydroxyl group *vs* amino group) transesterification of carbonate.
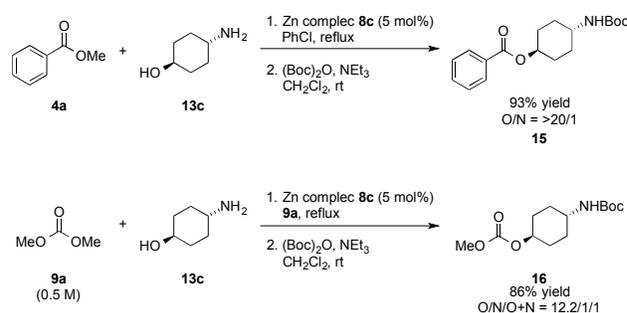
Scheme 6. *O*-Selective Transesterification of Amino Alcohol

Conclusions

We developed a highly stable but reactive bis(imidazole)/zinc catalyst for transesterification. The zinc complex **8c** could be prepared in multigram scale using a simple procedure. A water addition experiment revealed the high stability of zinc complex **8c** compared to $Zn_4(OCOCF_3)_6O$ (**1**). The stable nature of the zinc complex **8c** allowed for its recovery and reuse in transesterification reactions while maintaining the same catalytic activity. Even after five runs, zinc complex **8c** could be recovered in 91% yield without any decomposition based on ^{1}H-NMR analysis. The zinc complex catalyzed transesterification reaction with enhanced efficiency. Tertiary alcohol, previously not an applicable substrate, could also be used and the corresponding product was isolated in high yield. Labile acrylate derivatives could be transesterificated over 1,4-addition, indicating that the present zinc complex catalysis could be useful for the synthesis of various monomers using readily available methyl acrylate derivatives. Various cyclic carbonates and oxazolidinones were synthesized in high yield using dimethyl or diethyl carbonate. In addition, zinc complex **8c** catalyzed the chemoselective transesterification of unprotected-amino alcohols using dimethyl carbonate with better chemoselectivity than $Zn_4(OCOCF_3)_6O$ (**1**). To the best of our knowledge, this is the first example of chemoselective transesterification using dimethyl carbonate.

Acknowledgements

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7 Further ligand screening data is described in Supporting Information.

8 To remove the solubility factor of zinc complex (**8b** was low soluble), highly soluble zinc complex with ligand **7h** was prepared *in situ* and subjected to transesterification. As shown in the scheme below, 1.25 mol% of tetranuclear zinc cluster **1** with 10 mol% ligand **7h** was also afforded superior result, suggesting that the use of 2.0 equivalents of ligand to zinc ion is crucial for obtaining high catalytic activity.

Zn$_4$(OCOCF$_3$)$_6$O (**1**) (1.25 mol%), ligand **7h** (x mol%), toluene reflux, 1 h

x = 10 : 73% yield
5 : 32% yield
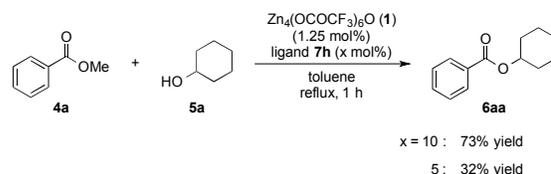
9 Bench-stable complex **8c** showed high catalytic activity after 9 month (reaction of **4a** with **5b**, 99% yield). Complex **8a** was also bench-stable and easy to prepare. However, it was difficult to use as a catalyst because of low solubility. Thus we generally employed isolated complex **8c** or in situ prepared zinc complex with ligand **7h** for transesterification reaction.

10 Commercially available as ZnTAC24^{TM} from TAKASAGO and STREM.

11 See the Supporting Information for details

12 Complex **8c** catalyzed transesterification efficiently upon prolonged reaction time when toluene instead of chlorobenzene was used as solvent. See the Supporting Information for details.

13 Catalytic transesterification of carboxylic esters with tertiary alcohols remains a formidable task.[4p] Non-catalytic transesterification with tertiary alcohols, see: (a) R. A. Rossi and R. H. Rossi, *J. Org. Chem*., 1974, **39**, 855. (b) M. G. Stanton and M. R. Gagne, *J. Org. Chem*., 1997, **62**, 8240. (c) V. A. Vasin and V. V. Razin, *Synlett,* 2001, 658.

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15 In situ prepared zinc complex with ligand **7h** gave decreased yield of **6ib**, presumably because uncoordinated ligand **4h** would promote the undesired side-reaction.

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19 While Zn$_4$(OCOCF$_3$)$_6$O (**1**) itself afforded excellent yield and chemoselectivity in the reaction of **4a** with **13c** in diisopropyl ether as solvent[5c], less satisfactory result was obtained in PhCl. In the reaction of **9a** with **13c**, Zn$_4$(OCOCF$_3$)$_6$O (**1**) gave inferior result (59% yield of **16**, O/N/O+N = 3.5/1/1.4).