Transesterification of α-Amino Esters Catalyzed by a Tetranuclear Zinc Cluster: $Zn_4(OCOCF_3)_6O$

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Abstract: Transesterification of amino acid ester derivatives was developed using a tetranuclear zinc cluster, $Zn_4(OCOCF_3)_6O$, as the catalyst. Because the reaction conditions were very mild, a variety of N-protective groups and functional groups on side chains were tolerated.

Key words: transesterification, esters, zinc, amino acids, clusters

Amino acids are the most important organic components, and their N-protected esters are utilized as building blocks for synthesizing natural and non-natural peptides[1] as well as medicinal compounds such as antiviral,[2] anticancer,[3] anti-inflammatory,[4] and anti-ischemic[5] agents. Tremendous efforts in both academic and industrial laboratories have been directed toward developing highly efficient synthetic methodologies to prepare N-protected amino acid esters from the corresponding amino acids without any racemization. Coupling reactions of N-protected amino acids and alcohols assisted by condensation reagents[6] such as DCC[7] are used to prepare the corresponding esters, but these reactions produce more than a stoichiometric amount of waste, and in some cases racemization is induced despite the controlled conditions. With respect to environmental concerns, catalytic transesterification,[8] in which treatment of a methyl ester with alcohol directly affords the corresponding ester, is an attractive alternative for preparing a variety of N-protected amino acid esters. Although many catalysts, such as aluminum alkoxide,[9] titanium alkoxide,[10] and distannoxane,[11] have been extensively applied to the transesterification of various esters, catalytic transesterification of N-protected amino acid esters has been rarely investigated due to severe side reactions, such as the decomposition of functional groups at side chains, cleavage of N-terminal protective groups, and epimerization at the α-position of the amino acid.[12] We recently developed a μ_4-oxo-tetranuclear zinc cluster $[Zn_4(OCOCF_3)_6O]$ (**1**) (Figure 1) as a versatile catalyst that efficiently catalyzed the transesterification of various methyl esters under mild conditions preserving various functional groups sensitive to acidic and basic conditions.[13] In our previous report, transesterification was successfully applied to a few glycine esters and dipeptides.[13b] These preliminary results encouraged us to investigate the transesterification of α-amino acid esters with a broader scope of N-protective groups, alcohols, and side chains.

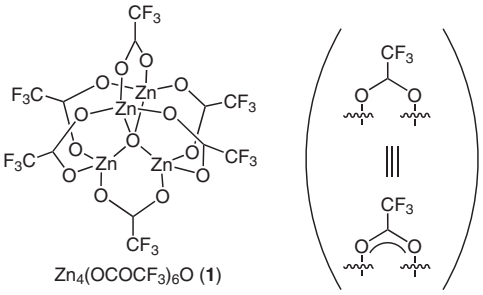

Figure 1 Structure of the μ-oxo tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$ (**1**)

We examined the Zn cluster catalyzed transesterification of various N-protected glycine methyl esters (such as **2aa**) with 1-butanol (**3b**) in refluxed diisopropyl ether for 18 hours, and the results are summarized in Table 1. All reactions proceeded smoothly without any deprotection to afford the corresponding butyl esters in high yield. Moreover, a shorter reaction time (18 h) than those in preliminary studies (up to 42 h) was sufficient in most cases.[13b] Noteworthy was that carbamate groups such as Cbz (**2aa**) and Boc (**2ba**) remained intact (Table 1, entries 1 and 2), in sharp contrast to report that transesterification reactions of substrates with these carbamate protection groups results in an exchange of the alkoxy moiety of the carbamate group by externally added alcohol in the presence of titanium alkoxide.[14] Other carbamates, such as Fmoc (**2ca**), Alloc (**2da**), and Troc (**2ea**), also did not decompose during the reaction course (Table 1, entries 3–5). Because the transesterification conditions were completely neutral, Ns (**2fa**) and Fmoc (**2ca**) groups, which are sensitive to basic conditions and nucleophiles, did not decompose at all (Table 1, entries 3 and 6). No ring opening of the Pht group was observed in the reaction of Pht-glycine methyl ester (**2ga**), and butyl ester **2gb** was obtained in 95% after refluxing for 24 hours (Table 1, entry 7).

Scope and limitations for alcohols were explored by the transesterification of Cbz-glycine methyl ester (**2aa**), and the results are summarized in Table 2. Reactions of **2aa**

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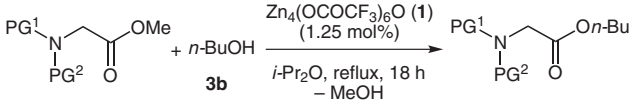
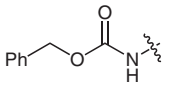
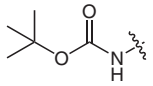
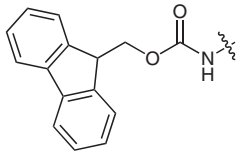
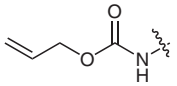
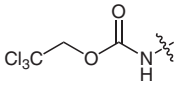
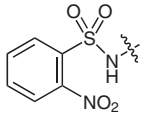
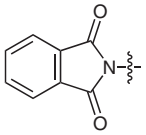
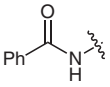
Table 1 Transesterification of Glycine Methyl Esters with Various N-Protective Groups[a]

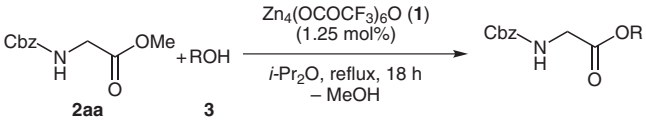


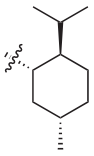
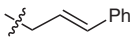
Entry	$(PG^1)(PG^2)N$	Methyl ester	Yield of butyl ester **2** (%)[b]
1		**2aa**	**2ab** 97
2		**2ba**	**2bb** 99
3		**2ca**	**2cb** 95
4		**2da**	**2db** 93
5		**2ea**	**2eb** 98
6[c]		**2fa**	**2fb** 84
7[d]		**2ga**	**2gb** 95
8		**2ha**	**2hb** 93

[a] Reaction conditions: A mixture of methyl ester (1.0 mmol), **3b** (1.2 mmol), and **1** (0.0125 mmol, 1.25 mol%) in *i*-Pr_2O (1.7 mL) was refluxed for 18 h under an argon atmosphere.
[b] Isolated yield.
[c] 12% of the starting material was recovered (95% based on the recovered starting material).
[d] Reaction time was 24 h.

with primary alcohols, 1-octadecanol (**3c**) and neopentyl alcohol (**3d**), gave the corresponding esters **2ac** in 90% and **2ad** in 99% yield (Table 2, entries 1 and 2). Secondary alcohols, 4-heptanol (**3e**) and cyclohexanol (**3f**), also worked well to give the corresponding esters **2ae** in 79% and **2af** in >99% yield (Table 2, entries 3 and 4), while reaction with D-menthol (**3g**) was rather slow, presumably due to steric hindrance, and was completed by a prolonged reaction time (48 h) to afford Cbz-glycine D-menthyl ester (**2ag**) in 92% yield without any epimerization at the 1-position of the menthyl group (Table 2, entry 5).[13b] The reactions with *tert*-butanol (**3h**) and phenol (**3l**) were limited and did not proceed due to their low nucleophilicity (Table 2, entries 6 and 10), in accordance with the previous observation for **1**-catalyzed transesterification.[13b] Reactions with allylic alcohols **3i** and **3j** (Table 2, entries 7 and 8) and benzyl alcohol **3k** (Table 2, entry 9)[13b] proceeded with good yields without any side reactions, such as ether formation of allylic alcohols or benzyl alcohol.

Table 2 Transesterification of Cbz-Glycine Methyl Ester with Various Alcohols[a]



Entry	R	3	Yield of product **2** (%)[b]
1	n-$C_{18}H_{37}$	**3c**	**2ac** 90
2	CH_2t-Bu	**3d**	**2ad** 99
3	$CH(n\text{-Pr})_2$	**3e**	**2ae** 79
4	*c*-Hex	**3f**	**2af** >99
5[c]		**3g**	**2ag** 92
6	*t*-Bu	**3h**	**2ah** n.d.[d]
7	allyl	**3i**	**2ai** 98
8		**3j**	**2aj** 99
9	Bn	**3k**	**2ak** 96
10	Ph	**3l**	**2al** n.d.[d]

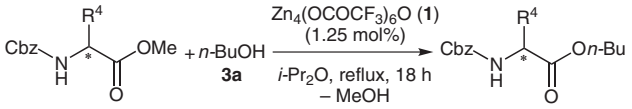
[a] Reaction conditions: A mixture of Cbz-glycine methyl ester (**2aa**, 1.0 mmol), alcohol **3c–l** (1.2 mmol), and **1** (0.0125 mmol, 1.25 mol%) in *i*-Pr_2O (1.7 mL) was refluxed for 18 h under argon atmosphere.
[b] Isolated yield.
[c] Reaction time was 48 h.
[d] Product was not detected.

The present transesterification was applied to the conversion of various methyl esters of *N*-Cbz-protected amino acids to the corresponding butyl esters, in which steric congestion at the α-position and applicability of the functional group were systematically assessed, and the results are summarized in Table 3. Transesterification of the methyl esters of alanine (**4aa**), leucine (**7aa**), proline (**8aa**), and phenylalanine (**9aa**) with 1-butanol (**3b**) proceeded smoothly to give the corresponding butyl esters **4ab**, **7ab**, **8ab**, and **9ab** in high yield (Table 3, entries 1 and 6–8).

Reaction rates of methyl esters of valine (**5aa**) and isoleucine (**6aa**), both of which have congested secondary aliphatic side chains, were retarded, and the transformations were suppressed, resulting in rather low yields of 41% for **5ab** and 44% for **6ab** (Table 3, entries 2 and 4); however, the addition of DMAP (20 mol%)[15,16] accelerated these transesterifications, increasing the yields to 95% and 90%

yields, respectively (Table 3, entries 3 and 5). Phenylglycine derivatives are, in general, racemized much more easily than any natural amino acid esters in peptide coupling reactions operated under basic conditions because of the higher acidity of the proton at the benzylic chiral center.[17] The catalyst **1** was advantageous in that no racemization was observed for the smooth transesterification of *N*-Cbz-protected phenylglycine methyl ester **10aa** with **3b** to give **10ab** (Table 3, entry 9). Because the phenolic hydroxy group did not participate in the present catalysis, *N*-Cbz-protected tyrosine methyl ester **11aa** reacted without the protection of the hydroxy group (Table 3, entry 10). This catalyst system could be applied to the transesterification of other *N*-Cbz-protected amino acid methyl esters bearing an additional protective group, such as MOM ether (**13aa**), thioether (**14aa** and **15aa**), a trityl group on imidazole (**20aa**), and different kinds of functionalities such as cyano (**18aa**) and indole (**19aa**) groups (Table 3, entries 12–14 and 17–19). Double transesterification of Cbz-aspartic acid α,β-dimethyl ester (**16aa**) with four equivalents of 1-butanol (**3b**) afforded the corresponding α,β-dibutyl ester **16ab** in 91% (Table 3, entry 15). The reaction of Cbz-asparagine methyl ester (**17aa**) bearing a primary amide group on the side chain afforded Cbz-asparagine butyl ester (**17ab**) in only 25% yield because intramolecular cyclization occurred, affording a cyclic imide **22** (Figure 2) in 45% yield (Table 3, entry 16). Unfortunately, the reaction of N^{α}-Cbz-N^{ω}-Ts-arginine methyl ester (**21aa**) with 1-butanol resulted in a low yield (33%), presumably due to the coordinating nature of the guanidine group (Table 3, entry 20).

Table 3 Transesterification of Methyl Esters Derived from Various Amino Acids[a]



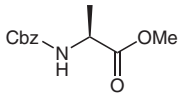
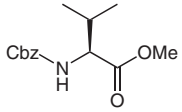
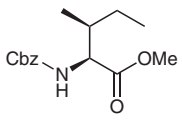
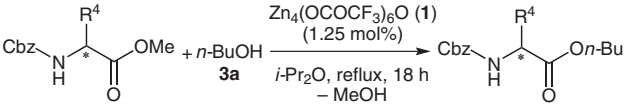
Entry	Methyl ester	Yield of butyl ester (%)[b]
1	 **4aa**	**4ab** 95
2	 **5aa**	**5ab** 41
3[c]	**5aa**	**5ab** 95
4[d]	 **6aa**	**6ab** 44
5[c,d]	**6aa**	**6ab** 90

Table 3 Transesterification of Methyl Esters Derived from Various Amino Acids[a] (continued)



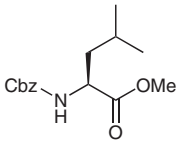
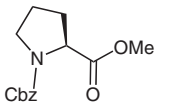
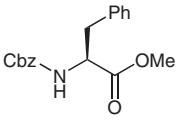
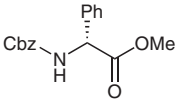
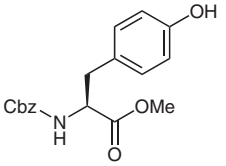
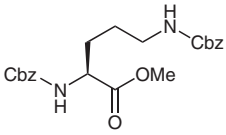
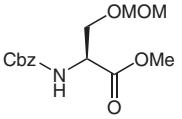
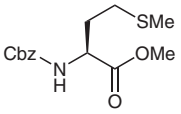
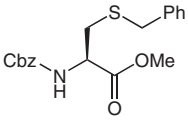
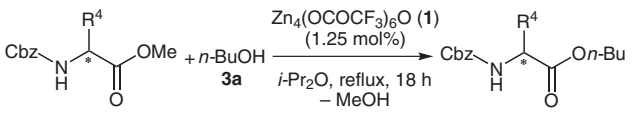
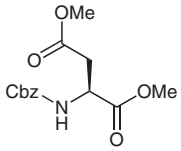
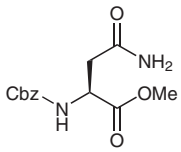
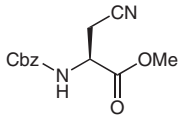
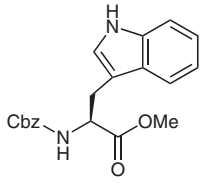
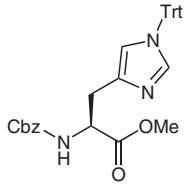
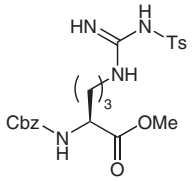
Entry	Methyl ester	Yield of butyl ester (%)[b]
6	 **7aa**	**7ab** 97
7	 **8aa**	**8ab** 97
8	 **9aa**	**9ab** 96
9	 **10aa**	**10ab** 90
10	 **11aa**	**11ab** 87
11	 **12aa**	**12ab** 90
12	 **13aa**	**13ab** 87
13[e]	 **14aa**	**14ab** 84
14	 **15aa**	**15ab** 84

Table 3 Transesterification of Methyl Esters Derived from Various Amino Acids[a] (continued)



Entry	Methyl ester	Yield of butyl ester (%)[b]
15[f,g]	 **16aa**	**16ab** 91 (dibutyl ester)
16[h]	 **17aa**	**17ab** 25
17	 **18aa**	**18ab** 79
18	 **19aa**	**19ab** 99
19[f]	 **20aa**	**20ab** 76
20	 **21aa**	**21ab** 33[i]

[a] Reaction conditions: A mixture of methyl ester (1.0 mmol), 1-BuOH (**3b**, 1.2 mmol), and **1** (0.0125 mmol, 1.25 mol%) in *i*-Pr_2O (1.7 mL) was refluxed for 18 h under an argon atmosphere.
[b] Isolated yield.
[c] DMAP (0.20 mmol, 20 mol%) was added to the reaction mixture.
[d] Reaction time was 20 h.
[e] Reaction time was 16 h.
[f] Reaction time was 24 h.
[g] 1-BuOH (4.0 mmol) was used.
[h] Cyclic imide **22** was obtained in 45% yield.
[i] Estimated by ^{1}H NMR analysis.

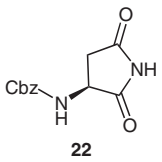


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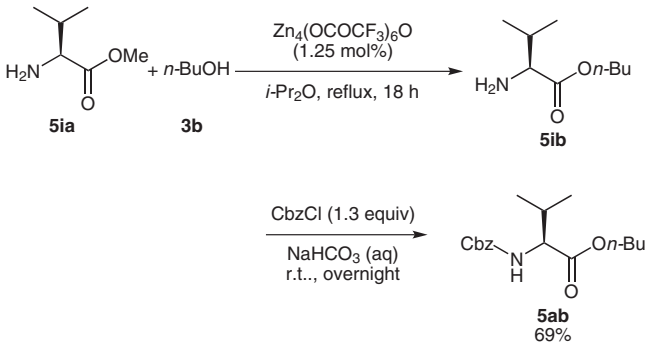
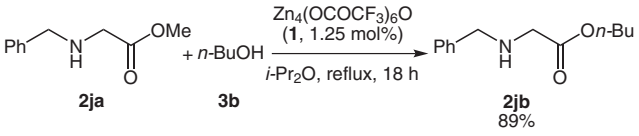
Figure 2

We previously reported that the zinc cluster **1** served as a catalyst for the hydroxy group selective acylation of amino alcohols, in which the hydroxy group was acylated in a highly chemoselective manner in the presence of a nucleophilic aliphatic amino group.[13a] We anticipated that this selectivity allowed for the transesterification of amino acid esters bearing a primary or secondary aliphatic amino group. In fact, transesterification of N-protection-free valine methyl ester **5ia** with 1-butanol (**3b**) afforded the butyl ester **5ab** in 69% yield upon treatment with CbzCl (Scheme 1).[18] As a substrate with a secondary aliphatic amino group, the reaction of *N*-benzyl glycine methyl ester **2ja** gave the corresponding butyl ester **2jb** in 89% yield (Scheme 2). Acylation of the amino group was not observed in either reaction.



Scheme 1



Scheme 2

In this report, we demonstrated the zinc cluster **1** catalyzed transesterification of various α-amino acid methyl esters with alcohols other than tertiary alcohol and phenol. The greatest advantage of this reaction protocol is its tolerance to many functional groups on the amino acid side chains, including heterocycles, MOM ether, and aliphatic amino groups, and a wide scope of N-protective groups such as Cbz, Boc, Fmoc, Alloc, Troc, Ns, and Fmoc. The addition of a catalytic amount of DMAP improved the yields for the transesterification of sterically hindered less reactive esters. In addition, we demonstrated that N-protection-free amino acid esters could be transesterified without amide formation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) No peak corresponding to amide was found in the ^{1}H NMR spectrum of the crude product before Cbz protection.