Transesterification

Chemoselective Transesterification of Acrylate Derivatives for Functionalized Monomer Synthesis Using a Hard Zinc Alkoxide Generation Strategy

Daiki Nakatake,[a] Ryo Yazaki,[a] and Takashi Ohshima*[a]

Abstract: A new practical method for the synthesis of functionalized acrylate derivatives with the view to prepare functional polymers was explored. Hard zinc alkoxide generation enabled the highly chemoselective transesterification of acrylate derivatives over the undesired conjugate addition, which caused polymerization. The combined use of the catalytic zinc cluster $Zn_4(OCOCF_3)_6O$ and 4-(dimethylamino)pyridine delivered various functionalized acrylate derivatives through the transesterification of commercially available methyl acrylate derivatives with functionalized alcohols under mild conditions.

Introduction

Functional polymers with unique properties, such as ion transfer, metal chelation, and water absorbability and repellency, are widely applicable to daily life and are produced on an industrial scale.[1] These polymers are generally prepared by polymerization of the corresponding functionalized monomers. Acrylate derivatives are broadly used as monomer units and are synthesized by acylation of alcohols by using acryloyl chlorides with more than a stoichiometric amount of base. Although this method is highly reliable for the industrial-scale production of acrylate derivatives, inevitable generation of more than a stoichiometric amount of coproduct is a drawback. Recently, atom-economical catalytic methods were developed, including (1) strong-acid-catalyzed condensation reactions of acrylic acids with alcohols, (2) strong-base-catalyzed ester interchange reactions, and (3) strong-acid- or strong-base-catalyzed transesterification. However, their narrow functional group compatibility is problematic.[2] Therefore, an alternative catalysis for the synthesis of functionalized monomers with broad functional group compatibility remains in high demand. Toward this aim, catalytic transesterification of inexpensive and commercially available methyl acrylate derivatives would offer industrial prospects, because only a lower alcohol is generated as a coproduct and the reaction could potentially be performed under almost-neutral conditions.[3,4] Difficulties controlling the chemoselectivity between transesterification and conjugate addition, however, have limited application to the synthesis of functionalized monomers, especially the synthesis of highly reactive and unstable unsubstituted acrylates.[5–7]

We previously developed the μ-oxotetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$ (**1**) as an efficient catalyst for the chemoselective transesterification of various methyl esters with various alcohols through the concerted action of two metal centers similar to dinuclear metalloenzymes (Figure 1).[8] Oxophilic zinc precatalyst **1** in situ generates a highly nucleophilic zinc alkoxide species, which allows chemoselective acylation of hydroxy groups over innately more nucleophilic amino groups. Thus, we hypothesized that hard Lewis acid/Brønsted base cooperative zinc catalyst **1** would generate highly nucleophilic hard zinc

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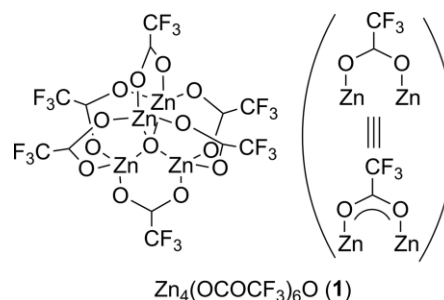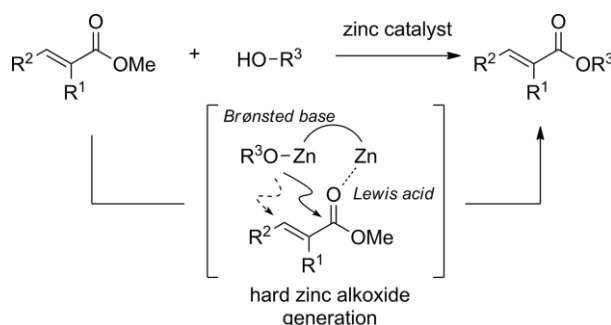
Figure 1. Structure of hard Lewis acid/Brønsted base zinc cluster catalyst **1**.

Scheme 1. Hard zinc alkoxide generation strategy for chemoselective hard transesterification over soft conjugate addition.

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alkoxides, and thereby, hard transesterification of acrylate derivatives would be preferred over soft conjugate addition through simultaneous activation of both coupling partners under mild conditions (Scheme 1).[9] Moreover, the features of zinc catalyst **1** (inexpensive, low toxicity, and colorless) are well suited for the synthesis of functionalized monomers. Herein, we report that zinc catalyst **1** catalyzes highly chemoselective transesterification for the synthesis of functionalized acrylate derivatives in high yields without undesired polymerization.

Results and Discussion

We began our investigation by using benzyl alcohol (**3a**) and 2 equivalents of methyl methacrylate (**2a**) as model substrates, and the reactions were performed in toluene at 80 °C to avoid vaporization of low-boiling **2a** (b.p. 100 °C) and thermal popcorn polymerization at an elevated temperature (Table 1).[10,11] Zinc cluster catalyst **1** provided transesterification product **4aa**, but only in 30 % yield (Table 1, entry 1).[12] We recently reported that the combined use of **1** and N-heteroaromatics generated more active lower-nuclear Zn species that significantly enhanced the reaction rate.[8c,8e,8f] In addition, the electron-donating nature of N-heteroaromatics enhanced the nucleophilicity of the active zinc alkoxide species. Thus, we evaluated N-heteroaromatics as ligands. A monodentate ligand, 4-(dimethylamino)pyridine (DMAP, **5**), drastically improved the yield. 1-Methylimidazole (NMI, **6**) and our originally developed bis(imidazole) ligand **7** afforded slightly inferior results (Table 1, entries 3 and 4).[8e] Next, we investigated the amount of methyl
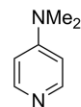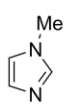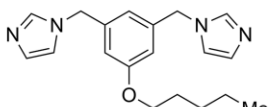
methacrylate (**2a**) with DMAP (**5**) as the ligand. Increasing the amount of **2a** improved the yield of **4aa** (Table 1, entries 5–8). We found that neat conditions with the use of 20 equivalents of **2a** were optimal, and desired product **4aa** was isolated in 94 % yield (Table 1, entry 9). Notably, all reactions proceeded in a highly chemoselective manner without undesired conjugate addition. Whereas no polymerized product was detected under the optimized conditions, polymerization predominantly occurred at higher temperatures, which indicated that a lower reaction temperature was important to obtain the desired unstable product in high yield (Table 1, entry 10). It is noteworthy that the use of a slight excess amount of methyl methacrylate (**2a**) was enough to obtain product **4aa** in high yield in the presence of 4 Å molecular sieves (Table 1, entries 11 and 12).[13] We also confirmed that unreacted methyl methacrylate (**2a**) almost completely remained (see Table 1 footnote) and no other side products were observed.[14,15]

We next examined the scope of the alcohol (Table 2). Methyl methacrylate (**2a**) and methyl acrylate (**2b**), which is more prone to undesirable conjugate addition, were selected as representative acrylate derivatives. Upon using methyl acrylate (**2b**) under the optimized conditions, transesterification proceeded exclusively, and product **4ba** was isolated in 99 % yield. The present catalysis could be run on gram scale by using 1.0 mol-% of the zinc catalyst, and product **4ba** was isolated in 1.3 g (85 % yield). Upon incorporated various functional groups,

Table 1. Optimization of the reaction conditions.[a]

| Entry	Ligand (mol-%)	**2a** (equiv.)	Conversion (%) [b]
1	—	2.0	30
2	DMAP (**5**) (20)	2.0	73
3	NMI (**6**) (20)	2.0	67
4	bis(imidazole) (**7**) (10)	2.0	70
5	**5** (20)	1.0	51
6	**5** (20)	3.0	77
7	**5** (20)	5.0	81
8	**5** (20)	10	89
9	**5** (20)	20 (neat)	94
10[c]	**5** (20)	20 (neat)	—
11[d,e]	**5** (20)	1.2	80
12[d,f]	**5** (20)	2.0	87

[a] Conditions: **3a** (1.0 mmol), toluene (2.0 mL). [b] Conversion was calculated by ^{1}H NMR spectroscopy. [c] Heated at reflux (110 °C, oil bath). [d] 4 Å molecular sieves (150 mg) were added. [e] Unreacted **2a** (0.39 mmol) remained. [f] Unreacted **2a** (1.08 mmol) remained.

Table 2. Scope of alcohols by using methyl methacrylate (**2a**) and methyl acrylate (**2b**).[a]

1	**4aa**: 95% yield **4ba**: 99% yield **4ba**: 85% yield[b]	2	**4ab**: 97% yield **4bb**: 99% yield
3	**4ac**: 88% yield **4bc**: 87% yield	4	**4ad**: 83% yield **4bd**: 94% yield
5	**4ae**: 91% yield **4be**: 95% yield	6	**4af**: 92% yield **4bf**: 96% yield
7	**4ag**: 89% yield **4bg**: 99% yield	8	**4ah**: 79% yield[c] **4bh**: 85% yield[c]
9	**4ai**: 80% yield[c] **4bi**: 83% yield[c]	10	**4aj**: 86% yield[c] **4bj**: 82% yield[c]

[a] Yields of isolated products are shown. Conditions: **2** (20.0 mmol), **3** (1.0 mmol). [b] Reaction was performed on gram scale (9.3 mmol) by using 1.0 mol-% of the catalyst. [c] Conditions: **2** (10.0 mmol), **3** (1.0 mmol), toluene (2.0 mL).

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such as aryl bromide, nitro, and an acid-sensitive methoxy-methyl (MOM) protecting group, the corresponding products were isolated in high yields (Table 2, entries 2–4). The reactions of both an aryl-conjugated olefin and a Z olefin also proceeded smoothly without any negative effects (Table 2, entries 5 and 6). We next focused on ether functional groups, because they are generally incorporated into hydrophilic polymers. Incorporation of ether functional groups by the catalytic transesterification of acrylate derivatives, however, remains difficult, because the stabilized α-carbon-centered radicals of these ether functionalities promote undesired polymerization under harsh conditions. Fortunately, an alcohol with a phenoxy ether moiety was applicable to the present zinc catalysis (Table 2, entry 7). Moreover, tetraethylene glycol monomethyl ether (3h), which has a polyether functionality, was incorporated, and the corresponding product was isolated in high yield (Table 2, entry 8). Further functional group compatibility was demonstrated by reaction with an alcohol possessing a highly coordinative chiral oxazoline functionality (Table 2, entry 9), and both 2a and 2b were transformed into the corresponding products in high yields. It is noteworthy that highly labile monomers 4aj and 4bj, having aldehyde functionalities, were obtained in high yields (Table 2, entry 10), which thus highlights the utility of the present zinc catalysis for the synthesis of various functionalized acrylate derivatives.

Our zinc catalysis was not confined to β-unsubstituted acrylate derivatives (Scheme 2). β-Substituted methyl crotonate (2c) was also a good substrate, and corresponding benzyl ester 4ca was obtained in high yield. The use of a slight excess amount of benzyl alcohol (3a) with 1 equivalent of methyl cinnamate (2d) provided transesterification product 4da cleanly in high yield. In both reactions, no isomerization of the E olefins was observed.
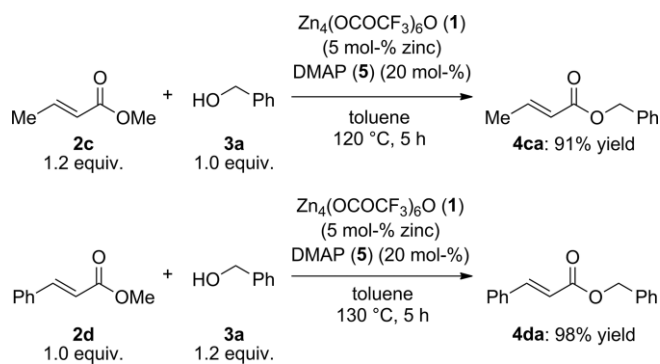
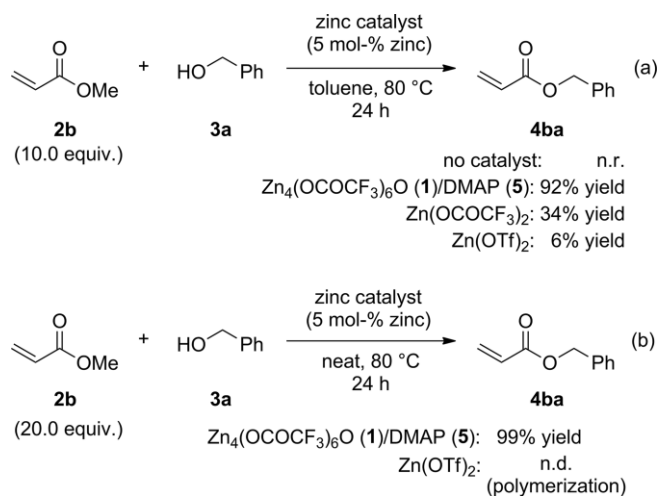Scheme 2. Scope of β-substituted methyl acrylates.

Further utility of the present chemoselective transesterification was demonstrated by the synthesis of widely utilized bis(acrylate) derivatives from diols (Table 3). Double acylation of an alkanediol having unsaturated linkers, benzene or an alkyne, proceeded smoothly to afford desired products 9ba–bc in high yields (Table 3, entries 1–3). Phenoxy ether was intact, and both the primary and less-reactive secondary hydroxy groups were acylated in high yields (Table 3, entry 4). Hydrophilic tetraethylene glycol was cleanly converted into bis(acrylate) derivative 9be (Table 3, entry 5). Upon using the triol, tris(acrylate) derivative 9bf was isolated in 63 % yield (Table 3, entry 6).[16]

Table 3. Scope of diols and triol.[a]
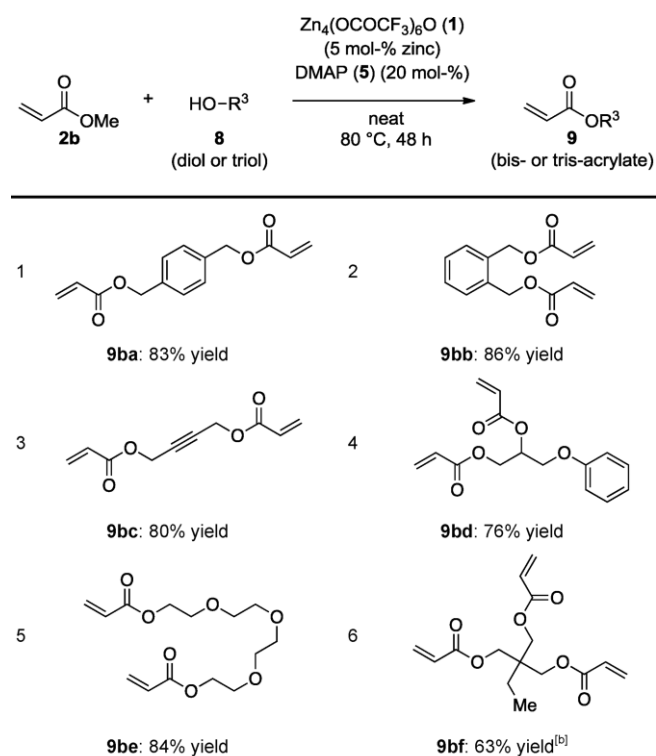
[a] Yields of isolated products are shown. Conditions: 2b (20.0 mmol), 8 (1.0 mmol). [b] Conditions: 2b (20.0 mmol), 8f (1.0 mmol), toluene (2.0 mL), 72 h.

To demonstrate our hard zinc alkoxide generation strategy for chemoselective hard transesterification over soft conjugate addition, various zinc catalysts were evaluated by using toluene as the solvent (Scheme 3, a). In the absence of a catalyst, no reaction was observed. The identified optimal catalyst system, Zn$_4$(OCOCF$_3$)$_6$O (1) with DMAP (5), exclusively delivered desired product 4ba in high yield. Although high chemoselectivity was observed by using Zn(OCOCF$_3$)$_2$, a low chemical yield was ob-

Scheme 3. Control experiments of zinc catalysts (n.r.: no reaction, n.d.: not detected).

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served.[17] The strong Lewis acid zinc trifluoromethanesulfonate [Zn(OTf)$_2$] exhibited poor catalytic performance. To facilitate Zn(OTf)$_2$ catalysis, the reaction was performed under neat conditions (Scheme 3, b). Whereas the combined use of Zn$_4$(OCOCF$_3$)$_6$O (1) and DMAP (5) provided the product in 99 % yield without undesired polymerization, Zn(OTf)$_2$ promoted only polymerization, presumably initiated by the conjugate addition of the alcohols,[18,19] which suggested that hard zinc alkoxide generation was crucial for highly chemoselective transesterification.

Conclusion

In summary, we developed a highly chemoselective transesterification of acrylate derivatives through hard zinc alkoxide generation. High functional group compatibility, including the hydrophilic ether functionality, clearly demonstrated the utility of the present zinc catalysis for the synthesis of functionalized monomers. Further application of the present catalysis for the preparation of functionalized monomers with novel features and functional evaluation of their polymers are underway.

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[13] 4 Å Molecular sieves were used to remove the methanol generated.

[14] Although product 4aa was observed in high yield by using a slight excess amount of 2a (Table 1, entries 11 and 12), we used neat conditions to evaluate the substrate scope because both methyl methacrylate (2a) and methyl acrylate (2b) are inexpensive. 2a: $18/500 mL, 2b: $20/500 mL from TCI America as of May 2016.

[15] We also performed the reaction without Zn(OCOCF$_3$)$_2$ (1). In these cases, no reaction was observed by using DMAP or trifluoroacetic acid as a catalyst.

[16] Along with tris(acrylate) product 9bf, bis(acrylate) product was obtained in 34 % yield.

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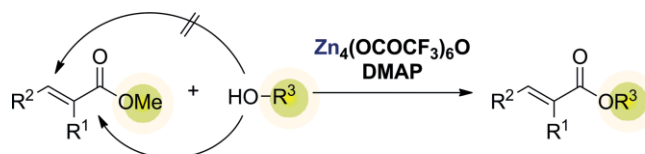European Journal
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Transesterification

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Chemoselective Transesterification of Acrylate Derivatives for Functionalized Monomer Synthesis Using a Hard Zinc Alkoxide Generation Strategy

- **Highly chemoselective**
- **Functionalized monomer**

We develop a highly chemoselective transesterification of acrylate derivatives by using a hard zinc alkoxide generation strategy. High functional group compatibility, including the hydrophilic ether functionality, clearly demonstrates the utility of the present zinc catalysis for the synthesis of functionalized monomers.