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# PAPER



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## Runge–Kutta analysis for optimizing the Zncatalyzed transesterification conditions of MA and MMA with diols to maximize monoesterified products<sup>†</sup>

Terminal hydroxylated acrylates and methacrylates were prepared by catalytic transesterification of

acrylates and methacrylates with diols catalyzed by a system of a tetranuclear zinc alkoxide, [Zn(tmhd)

 $(OMe)(MeOH)]_4$  (1a), with 4 equiv. of 2,2'-bipyridine (L1). The reaction time to reach the equilibrium state was analyzed by kinetic studies and *a* curve-fitting analysis based on the Runge-Kutta method for

optimizing the best reaction conditions for mono-esterification. In addition to these kinetic analyses, DFT

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calculations estimated a proposed mechanism of the catalytic transesterification.

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### Introduction

Acrylates and methacrylates are highly attractive monomers,<sup>1</sup> and their polymers are often used as polymeric resins,<sup>2</sup> photoresists,<sup>3</sup> and coating materials.<sup>4</sup> These polymers exhibit high transparency and flexibility as well as biocompatibility and weatherability. The physical properties of poly(meth) acrylates are introduced by replacing the ester moiety of the monomers with any other preferred functional group.<sup>5</sup> Among functionalized (meth)acrylates, terminal hydroxylated (meth) acrylates have attracted special attention because of their hydrophilicity for emulsion paintings,<sup>6</sup> UV reactive diluents,<sup>7</sup> and adhesive compounds.8 Terminal hydroxylated olefinic esters have been prepared by acylation of diol compounds with (meth)acryloyl chlorides9 or transesterification of commercially available methyl (meth)acrylate with diols,10 but difficulties with the catalytic transesterification remain to be overcome, including (1) a long reaction time to transesterification, (2) a statistical mixture of terminal hydroxylated monomers and diol bis(meth)acrylates, and (3) contamination by undesired side reactions such as Michael addition<sup>11</sup> and polymerization<sup>12</sup> of olefinic moiety. Thus, methods for selective monoesterification of (meth)acrylates with diols using efficient catalytic systems under mild conditions are in high demand. Herein, we report that a unique alkoxy-bridged tetranuclear

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zinc complex functioned as an appropriate catalyst for the transesterification of methyl (meth)acrylate with a variety of diols, such as 1,4-butanediol, leading to an equilibrium state of a statistical mixture of terminal hydroxylated monomers and diol bis(meth)acrylates. We also report that the yield of the terminal hydroxylated monomers was maximized on the basis of in-depth kinetic analysis and DFT calculations of the reaction mechanism in which a mononuclear zinc catalyst worked as an active species.

### **Results and discussion**

The transesterification of carboxylic esters with alcohols remains an essential synthetic method in organic chemistry, and has been investigated using metal salt catalysts such as Al,<sup>13</sup> Ti,<sup>14</sup> Sn,<sup>15</sup> Zr,<sup>16</sup> La,<sup>17</sup> Zn,<sup>18</sup> and Fe<sup>19</sup> species. We previously reported that a trifluoroacetate-bridged  $\mu_4$ -oxotetranuclear zinc cluster, ZnTAC24®, served as an efficient catalyst for the transesterification of methyl esters with alcohols.<sup>20</sup> In the first trial, we evaluated the catalytic activity of ZnTAC24® with other commercially available Zn mononuclear complexes as well as an alkoxy-bridged tetranuclear complex (1a). Table 1 shows the results of the catalytic transesterification of MA or MMA with diol 2a mediated by 0.2 mol% of Zn precursors and 0.2 mol% of 2,2'bipyridyl in toluene at 85 °C for 3 h. The chemoselectivity of the transesterification reaction was defined as the selectivity of transesterification vs. Michael addition, and calculated by dividing the provided amounts of the monoesters 3a and diesters 4a by the converted amounts of MA or MMA. In the case of the transesterification of MA, ZnTAC24® and  $Zn(OAc)_2$  displayed low catalytic activity to afford monoesters



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Table 1 Comparison of the catalytic activity on several zinc precursors

	MA (5 mmol)	O <sub>++</sub> O <sub>4</sub> OH [M] (0.2 n Bpy (0 toluene, 2a -M (1.5 eq)	nol% on Zn) .2 mol%) 85 °C, 3 h leOH mon	$ \begin{array}{c} \begin{array}{c} & & \\ & & \\ & & \\ & & \\ \end{array} \end{array} \overset{O}{} \begin{array}{c} & & \\ & & \\ \end{array} \overset{O}{} \begin{array}{c} & & \\ \end{array} \overset{O}{} \end{array} \overset{O}{} \begin{array}{c} & & \\ \end{array} \overset{O}{} \end{array} \overset{O}{} \begin{array}{c} & & \\ \end{array} \overset{O}{} \end{array} \overset{O}{$		
		Conv. <sup>a</sup> [9	%]		Yield <sup>a</sup> [%]	
Entry	[M]	MA	2a	Chemoselectivity <sup>b</sup> [%]	Mono 3a	Di 4a
1	ZnTAC24®	65	30	72	37	10
2	$Zn(OAc)_2$	27	12	70	16	3
3	$Zn(acac)_2$	75	36	75	46	10
4	$Zn(tmhd)_2$	75	37	72	44	10
5	$Zn(hfac)_2 \cdot H_2O$	46	13	40	16	2
6	$[Zn(tmhd)(OMe)(MeOH)]_4$ (1a)	78	43	84	52	13

<sup>*a*</sup> Determined by GC analysis with triphenylmethane as an internal standard. <sup>*b*</sup> The chemoselectivity of transesterification reaction was calculated as dividing the provided amounts of the monoesters **3a** and diesters **4a** by the converted amounts of **MA**.



 $3a_{MA}$  in 37% and 16%, and diesters  $4a_{MA}$  in 10% and 3% yields, respectively (entry 1–2). Other Zn mononuclear complexes, such as Zn(acac)<sub>2</sub> and Zn(tmhd)<sub>2</sub>, which have two chelating acetylacetonate derivatives, exhibited more catalytic activity than ZnTAC24® (entries 3–4), whereas Zn(hfac)<sub>2</sub>·2H<sub>2</sub>O (HFAC = hexafluoroacetylacetonate) didn't display the same catalytic performance probably affected by existing water. Among several Zn precursors, the alkoxy-bridged tetranuclear complex (1a) exhibited the highest catalytic activity and highest chemoselectivity (entry 6) and was thus selected as the best catalyst precursor.

We then started to compare the catalytic performance of alkoxy-bridged tetranuclear complexes, [M(tmhd)(OMe)  $(MeOH)_x]_4$  (1a: M = Zn, 1b: M = Cu, 1c: M = Ni, 1d: M = Co, 1e: M = Fe, and 1f: M = Mn; *x* = 1 or 0; tmhd = 2,2,6,6-tetramethyl-3,5-heptanedione), for the transesterification of methyl acrylate (MA) and methyl methacrylate (MMA) with 1,4-butanediol (2a) to give the corresponding 4-hydroxybutyl (meth)acrylate (3a<sub>MA</sub> and  $3a_{MMA}$  and butane-1,4-diyl di[(meth)acrylate] ( $4a_{MA}$  and  $4a_{MMA}$ ) as a byproduct under the initial conditions (5.0 mmol of MA or MMA, 7.5 mmol of 2a, 0.05 mol% of complexes 1a-f, and 0.2 mol% of 2,2'-bipyridyl in toluene at 85 °C for 3 h), and the results are presented in Table 2. In the reaction of MA with 2a, a zinc tetranuclear complex, [Zn(tmhd)(OMe)(MeOH)]<sub>4</sub> (1a), exhibited the highest catalytic activity and monoester/diester ratio,  $3a_{MA}/(3a_{MA} + 4a_{MA})$ , to produce  $3a_{MA}$  in 52% yield with a high chemoselectivity (entry 1), while tetranuclear complexes of copper, nickel, and cobalt (1b-d) afforded 3a<sub>MA</sub> in low yield with low chemoselectivity as these catalysts preferentially mediated the Michael addition reaction of 2a with MA (entries 2-4). Manganese and iron tetranuclear complexes (1e and 1f) exhibited moderate catalytic activities with moderate

chemoselectivities, yielding 3aMA in 39% and 36% yield, respectively (entries 5 and 6). For the transesterification of MMA, complex 1a also exhibited the highest catalytic reactivity and chemoselectivity to give 3a<sub>MMA</sub> in 51% yield (entry 7). Unfortunately, the use of copper complex 1b produced notable side reactions of MMA. Complex 1b led to the polymerization of MMA, probably because copper(II) ions activate the double bond of MMA.<sup>21</sup> When complexes 1c, 1d, and 1e were used, the yields of 3a<sub>MMA</sub> decreased to 46%, 38%, and 19%, respectively, and the chemoselectivity of the transesterification reaction was lower than that when using zinc complex 1a (entries 9-11). The use of manganese complex 1f also caused the polymerization of MMA (entry 12), probably due to the softer ion character of Mn(II), which prefers to interact with a softer C=C double bond than the carbonyl group of MMA. We also compared the catalytic activity of complex 1a with a tin catalyst,  $SnO(n-oct)_2$ , which was used in several patents.<sup>22</sup> The tin catalyst showed much lower catalytic activity toward the transesterification of MA or MMA with 2a than complex 1a throughout the transesterification process over 10 h to an equilibrium of raw materials and transesterified products. Among the six alkoxybridged tetranuclear complexes and tin complex we tested, zinc complex 1a exhibited the highest catalytic activity and chemoselectivity as  $zinc(\pi)$  is the hardest metal ion on the basis of the HSAB theory, and zinc(II) ions interact preferentially with the carbonyl group, which is a harder functional group than the double bond of MA. Considering all entries, we selected zinc complex 1a as the best catalyst precursor among the tetranuclear complexes,  $[M(tmhd)(OMe)(MeOH)_x]_4$ .

Next, we surveyed the best pyridine-based bi- and tridentate ligands for the catalytic transesterification reaction of **MA** and **MMA** with **2a**. Table 3 provides the

Table 2 Screening of alkoxy-bridged tetranuclear complexes

R cat. (0.2 mol% on metal) R R R R Bpy (0.2 mol%) - O(200									
			R = H (MA) or Me (MMA) 2a (5 mmol) (1.5 eq)	, 85 °C, time. MeOH R = H ( <b>3a<sub>MA</sub></b> ) or Me ( <b>3</b>	a <sub>MMA</sub> ) R = H (4a	di a <sub>MA</sub> ) or Me (4a <sub>MMA</sub> )			
				Conv. <sup><i>a</i></sup> [%]					
Entry	R	Time. [h]	Cat.	(Meth)acrylate	2a	Chemoselectivity <sup>b</sup> [%]	Mono 3a	Di 4a	
1	Н	3	[Zn(tmhd)(OMe)(MeOH)] <sub>4</sub> (1a)	78	43	84	52	13	
2	Η	3	$[Cu(tmhd)(OMe)]_4$ (1b)	92	46	10	8	1	
3	Н	3	$[Ni(tmhd)(OMe)(MeOH)]_4$ (1c)	51	33	18	8	2	
4	Н	3	$[Co(tmhd)(OMe)(MeOH)]_4$ (1d)	57	29	46	17	9	
5	Η	3	$[Fe(tmhd)(OMe)(MeOH)]_4$ (1e)	67	32	65	36	7	
6	Η	3	$[Mn(tmhd)(OMe)(MeOH)]_4$ (1f)	78	30	60	39	7	
7	Me	3	$[Zn(tmhd)(OMe)(MeOH)]_4$ (1a)	65	35	>99	51	16	
8	Me	3	$[Cu(tmhd)(OMe)]_4$ (1b)	Gel.	Gel.	Gel.	Gel.	Gel.	
9	Me	3	$[Ni(tmhd)(OMe)(MeOH)]_4$ (1c)	57	26	93	46	7	
10	Me	3	$[Co(tmhd)(OMe)(MeOH)]_4$ (1d)	52	21	90	38	8	
11	Me	3	$[Fe(tmhd)(OMe)(MeOH)]_4$ (1e)	27	9	80	19	2	
12	Me	3	$[Mn(tmhd)(OMe)(MeOH)]_4$ (1f)	Gel.	Gel.	Gel.	Gel.	Gel.	
13	Н	10	Di- <i>n</i> -octyltin oxide	61	24	90	46	9	
14	Ме	10	Di- <i>n</i> -octyltin oxide	64	29	>99	53	13	

<sup>*a*</sup> Determined by GC analysis with triphenylmethane as an internal standard. <sup>*b*</sup> The chemoselectivity of transesterification reaction was calculated as dividing the provided amounts of the monoesters **3a** and diesters **4a** by the converted amounts of **MA** or **MMA**.



results of the experiments when using the best precursor 1a with an equimolar amount of a pyridine-based ligand per zinc atom at 85 °C for 3 h. Several ligands such as L1-L4 instead of pyridine-based derivatives were initially tested with 1a, however, they were proved inadequate for the transesterification with the zinc alkoxy-bridged tetranuclear complex compared to 2,2'-bipyridine L6 (entries 2-5 vs. entry 7). The use of pyridine ligand L5 and twice the amount of 2,2'-bipyridine ligand had no effect to improve activity or chemoselectivity (entries 6 and 8 vs. entry 7). The electronic effects were surveyed using 4,4'-disubstituted 2,2'bipyridyl ligands, L7-L9 as well as 4,4'-dibromo-2,2'bipyridyl (L10), and we found that electron-donating groups and halogen slightly decreased the yield and chemoselectivity of the transesterification reaction (entries 9-12). When an electron-withdrawing CF<sub>3</sub> group was introduced at the 5,5'-position of the 2,2'-bipyridyl ligand, almost same yield and chemoselectivity as for L6 were observed (entry 13). Entries 14-15 show the results of 6,6'substituted 2,2'-bipyridine, in which steric hindrance at the 6,6'-position reduced the catalytic activity compared with the standard condition, and 6,6'-hydroxy bipyridine completely blocked the transesterification (entry 15). We also evaluated the influence of rotation of the principal axis of 2,2'-bipyridine, by testing two phenanthroline ligands to avoid the rotation, but it reduced the total yields of the transesterification reaction (entries 16-17). In addition, we used 2,2'-biquinoline and 2,2':6',2"-terpyridine as ligands,

but lower catalytic activity and chemoselectivity were observed (entries 18-19).

To improve the yield of the monoesters 3a, we further modified the reaction conditions with the best catalyst 1a and the best ligand L1, and the results are provided in Table 4. When ether solvents, such as cyclopentyl methyl ether (CPME), tetrahydrofuran (THF), and diethyleneglycol dimethyl ether (diglyme), were used, the yield of monoester  $3a_{MA}$  was decreased (entries 2-4 vs. 1). In comparison with entry 1 and entries 5-6, increasing the equivalent of 2a versus MA improved the yield of  $3a_{MA}$  and the monoester/diester ratio. We also varied the amount of the catalyst: the more catalyst loaded, the more the Michael addition reaction proceeded, which means chemoselectivity was decreased (entries 7 and 8). When the reaction was conducted without complex 1a, no production of 3a<sub>MA</sub> was observed (entry 9). Entries 10-11 show how the reaction temperature affected the transesterification reaction. There was little change in the yield of  $3a_{MA}$  when the reaction temperature was increased from 65 °C to 75 °C and 85 °C. We adopted the same approach for MMA, and solvent changes resulted in a decreased yield of the monoester 3a<sub>MMA</sub> with CPME and gelation of the substrate mixtures with THF or diglyme (entries 13-15 vs. 12). Increasing the equivalent of 2a versus MMA in each 0.5 eq. from 1 to 2 eq. improved both the monoester/diester ratio and total yield (entries 16 and 17 vs. 12), and increasing the amount of loading catalyst 1a in each 0.1 mol% from 0.2 to 0.4 mol% finally led to gelation (entries 18 and 19 vs. 12). Entry 20 shows the result of the blank condition

#### Table 3 Screening of ligands

		OMe	a + HO → HO → HO → HO → HO → → → → → → → → → → → → → → → → → → →	.2 mol% on Zn) nd (L: X mol%) ene, 85 °C, 3 h -MeOH	$ \begin{array}{c} \begin{array}{c} & \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ $		
		(5 mmol)	(1.5 eq)		UNIC SAMA UN MAMA	Yield <sup>a</sup> [%]	
Entry	Ligand	<i>X</i> [mol%]	MA	2a	Chemoselectivity <sup>b</sup> [%]	Mono 3a	Di 4a
1	_	_	62	33	91	46	10
2	L1	0.2	62	26	58	26	10
3	L2	0.2	85	37	44	32	6
4	L3	0.2	33	10	0	_	_
5	L4	0.2	67	40	67	38	7
6	L5	0.4	64	37	80	43	8
7	L6	0.2	78	43	84	52	13
8	L6	0.4	78	32	66	43	9
9	L7	0.2	81	30	62	42	8
10	L8	0.2	80	37	66	44	9
11	L9	0.2	77	36	73	46	10
12	L10	0.2	72	34	79	47	10
13	L11	0.2	74	31	84	51	11
14	L12	0.2	60	30	96	46	11
15	L13	0.2	n.r. <sup><i>c</i></sup>	n.r. <sup>c</sup>	n.r. <sup>c</sup>	n.r. <sup>c</sup>	n.r. <sup><i>c</i></sup>
16	L14	0.2	80	42	60	40	8
17	L15	0.2	77	29	79	50	11
18	L16	0.2	44	19	70	24	6
19	L17	0.2	89	51	34	25	4

<sup>*a*</sup> Determined by GC analysis with triphenylmethane as an internal standard. <sup>*b*</sup> The chemoselectivity of transesterification reaction was calculated as dividing the provided amounts of the monoesters **3a** and diesters **4a** by the converted amounts of **MA**. <sup>*c*</sup> No reaction.



in which the transesterification reaction did not proceed without the zinc precursor 1a. The total yield of  $3a_{MMA}$  and  $4a_{MMA}$  steadily increased simply by increasing the reaction temperature, and side reactions such as the Michael addition reaction were never observed around the these studied reaction conditions.

With the optimized conditions in hand, we investigated the substrate scope of several diols, some of which contain secondary and tertiary hydroxyl groups as non-equivalent reaction sites (Table 5). We chose **MMA** as the other substrate because **MMA** did not afford Michael addition products. Ethylene glycol (**2b**) which has hydroxy groups at the 1,2-positions reacted with MMA, but the yields of  $3b_{MMA}$ and  $4b_{MMA}$  were very low (entry 2). In this case, we observed white precipitates after the reaction, indicating that the catalyst was deactivated by chelation of the 1,2-dihydroxy moiety onto the zinc metal to give a stable 5-membered metallacycle complex. The conversion of transesterification increased readily with extension of the linker, and the highest conversion was observed when we used **2a**, whereas extending one more methylene linker using 1,5-pentanediol (2d) decreased the conversion to 58% (entry 4). Diol 2e, which has primary and secondary hydroxy groups, mainly afforded monoester  $3e_{MMA}$  (entry 5), indicating that the sterically less hindered primary hydroxy groups were approximately four times more reactive than the secondary hydroxy groups. 1-Methyl-1,3-butandiol produced only 3-hydroxy-3-methylbutyl acrylate ( $3f_{MMA}$ ) in 18% yield over 3 h and 59% yield over 24 h, while diesterified byproduct  $4f_{MMA}$  was not observed. This result suggested that steric hindrance of the tertiary hydroxy group protected against conversion of the hydroxy group into the diester even over a 24 h reaction period (entries 6 and 7).

# Kinetics study of the transesterification of (methyl)acrylate and 1,4-butanediol

To clarify the reaction mechanism of the transesterification of **MA** and **MMA** with 1,4-butanediol catalyzed by **1a** with **L1**, we conducted kinetic studies<sup>23</sup> and tried to construct a reliable kinetic model of this reaction. Scheme 1a-c shows

#### Table 4 Screening reaction conditions

$ \begin{array}{c} R \\ + HO \\ + HO \\ R = H (MA) \text{ or } Me (MMA) \end{array} \begin{array}{c} 1a (Z mOl% \text{ on } Zn) \\ By (LE : Z mOl%) \\ solvent, temp. 3 h \\ - MeOH \\ mono \end{array} \begin{array}{c} R \\ + \int_{-\infty}^{R} O(+_{A}OH + - \int_{-\infty}^{R} O(+_{A}$										
				(1 eq)	(Yeq)	R = H ( $3a_{MA}$ ) or Me ( $3a_{MMA}$ ) R CONV. <sup><i>a</i></sup> [%]	= H ( <b>4a<sub>MA</sub>)</b> or Me	(4a <sub>MMA</sub> )	Yield <sup>a</sup> [%]	
Entry	R	Solvent	Y [equiv.]	<i>Z</i> [mol%]	Temp [°C]	(Meth)acrylate	2a	Chemoselectivity <sup>b</sup> [%]	Mono 3a	Di 4a
1	Н	Toluene	1.5	0.2	85	78	43	84	52	13
2	Н	CPME	1.5	0.2	85	83	34	56	40	7
3	Н	THF	1.5	0.2	85	78	34	76	48	11
4	Н	Diglyme	1.5	0.2	85	62	26	58	26	10
5	Н	Toluene	1	0.2	85	72	44	87	46	17
6	Н	Toluene	2	0.2	85	81	33	85	57	11
7	Н	Toluene	2	0.3	85	82	36	77	53	10
8	Н	Toluene	2	0.4	85	84	36	73	52	10
9	Н	Toluene	2	_	85	10	6	24	2	0
10	Н	Toluene	2	0.2	65	64	24	93	51	9
11	Н	Toluene	2	0.2	75	80	32	77	52	9
12	Me	Toluene	1.5	0.2	85	65	35	>99	51	16
13	Me	CPME	1.5	0.2	85	58	28	96	44	12
14	Me	THF	1.5	0.2	85	Gel.	Gel.	Gel.	—	—
15	Me	Diglyme	1.5	0.2	85	Gel.	Gel.	Gel.	_	_
16	Me	Toluene	1	0.2	85	52	41	>99	37	16
17	Me	Toluene	2	0.2	85	71	30	92	53	12
18	Me	Toluene	1.5	0.3	85	76	35	94	54	17
19	Ме	Toluene	1.5	0.4	85	Gel.	Gel.	Gel.	_	_
20	Ме	Toluene	1.5	_	85	n.r. <sup>c</sup>	n.r. <sup>c</sup>	n.r. <sup>c</sup>	_	_
21	Ме	Toluene	1.5	0.2	65	23	13	99	20	3
22	Me	Toluene	1.5	0.2	75	47	21	>99	40	9

<sup>*a*</sup> Determined by GC analysis with triphenylmethane as an internal standard. <sup>*b*</sup> The chemoselectivity of transesterification reaction was calculated as dividing the provided amounts of the monoesters **3a** and diesters **4a** by the converted amounts of **MA** or **MMA**. <sup>*c*</sup> No reaction.

#### Table 5 Substrate scope of diols

		(5	OMe + Diol 2 O (1.5 eq) MMA mmol)	1a (0.2 mol% on Zn) Bpy (L6: 0.2 mol%) → Monoester 3 + toluene, 85 °C, time. -MeOH	Monoester 3 + Diester 4			
				Yield <sup><math>a,b</math></sup> [%]				
Entry	Diol 2	Time [h]	Conv. [%]	Monoester 3		Diester 4		
1 2	2a 2b	3 3	65 24	$\begin{array}{c} \mathbf{3a_{MMA}}\\ \mathbf{AO} \overset{OH}{\searrow} (\mathbf{3b}) \end{array}$	51 15	$\begin{array}{c} 4a_{\mathbf{MMA}} \\ \overset{OA}{\swarrow} (\mathbf{4b}) \end{array}$	16 1	
3	2 <b>c</b>	3	31	AOOH $(3c)$	25	AOOA $(4c)$	4	
4	2 <b>d</b>	3	58	аоон ( <b>3d</b> )	42	AO $AO$ $(4d)$	11	
5	2e	3	26	$\stackrel{\text{AO}}{\longrightarrow} \stackrel{\text{OH}}{\longrightarrow} (3e)$	16 3	$AO \longrightarrow OA (4e)$	1	
6 7	2f 2f	3 24	18 59	$AO \longrightarrow OH (3f)$	18 59			

<sup>a</sup> Determined by GC analysis with triphenylmethane as an internal standard. <sup>b</sup> Calculated via FID relative sensitivity of each compound.



the proposed elementary reactions of this esterification process. The methyl (meth)acrylate (ME) and 2a are converted into the monoester (Mono) and MeOH under the rate constant  $k_1$ , and in the reverse reaction, the rate constant

and equilibrium constant are expressed as  $k_{-1}$  and  $K_1$  (Scheme 1a). In the same manner, the second transesterification proceeds with **Mono** and **ME** into the diester (**Di**) and MeOH, and the rate constant of each forward





and inverse reaction as well as the equilibrium constant are denoted as  $k_2$ ,  $k_{-2}$ , and  $K_2$  (Scheme 1b). Moreover, in the presence of Di and 2a, these compounds are transformed into 2 equiv. of Mono with rate constant  $k_3$ , and we termed the rate constant of the inverse reaction and the equilibrium constant of each as  $k_{-3}$  and  $K_3$  (Scheme 1c). We confirmed that complex 1a catalyzed all six elementary reactions of methyl acrylate by comparing the initial reaction rate of six elementary reactions with and without a catalytic amount of complex 1a.15 Especially in the case of MA, we considered four other elemental reactions with the rate constants  $k_4$ ,  $k_5$ ,  $k_6$ , and  $k_7$  to give four byproducts in very low yields, because several byproducts derived via Michael addition reaction were observed in GC and MS analyses (see ESI<sup>+</sup>). On the basis of the above-described kinetic model, the five ordinary differential equations for ME, 2a, Mono, Di, and MeOH (eqn (1)-(5)) as well as four additional ordinary differential equations for byproducts only in the case of MA were solved numerically for all simulations in this study.

The rate law is expressed by a reaction time (t[h]) and the rate constants for each compound were as follows:<sup>24</sup>

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between  $K_1$ ,  $K_2$ , and  $K_3$  is described in below (eqn (6)).

$$\frac{K_1}{K_2} = \frac{[\text{Mono}][\text{MeOH}]}{[\text{ME}][\text{BD}]} \div \frac{[\text{Di}][\text{MEOH}]}{[\text{Mono}][\text{ME}]} = \frac{[\text{Mono}]^2}{[\text{BD}][\text{Di}]} = K_3 \quad (6)$$

In the case of MA, the initial reaction was conducted under the following standard conditions<sup>26</sup> (a):  $[MA]_0/[2a]_0/[1a]$ (calculated on metal ions) =  $3.10 \text{ [mol kg}^{-1}$ / $6.19 \text{ [mol kg}^{-1}$ ]/ 8.26 [mmol kg<sup>-1</sup>], where  $[X]_0$  is the initial concentration of X. Under condition (a), the following rate constants were determined:  $k_1 = 23.0$ ,  $k_{-1} = 15.1$ ,  $k_2 = 18.9$ ,  $k_{-2} = 63.3$ ,  $k_3 = 63.3$ 103,  $k_{-3} = 20.1$  [kg<sup>2</sup> mol<sup>-2</sup> h<sup>-1</sup>]. To ensure the accuracy of the rate constants calculated under standard conditions, equivalents of 2a and 1a against MA were changed to the following conditions:  $[MA]_0/[2a]_0/[1a]$ , (b) = 3.72 [mol kg<sup>-1</sup>]/ 5.58 [mol kg<sup>-1</sup>]/8.26 [mmol kg<sup>-1</sup>], (c) 2.64 [mol kg<sup>-1</sup>]/6.61 [mol  $kg^{-1}$ /8.26 [mmol  $kg^{-1}$ ], (d) 3.10 [mol  $kg^{-1}$ ]/6.19 [mol  $kg^{-1}$ ]/ 12.4  $[\text{mmol kg}^{-1}]$ , (e) 3.10  $[\text{mol kg}^{-1}]/6.19$   $[\text{mol kg}^{-1}]/16.5$  $[mmol kg^{-1}]$ . In addition, to estimate the activation energies, the standard enthalpy change ( $\Delta H$ ), and the standard entropy change ( $\Delta S$ ), two other conditions with different temperatures were used with the same initial concentrations as in condition (a), (f) 65 °C, (g) 75 °C. Fig. 1 shows the experimental data (plots) and simulated results (lines), which were well fitted to the experiments and in accordance with the proposed kinetic model described in Scheme 1. All plots of conditions (b)-(e) are expressed by the set of the reaction rates  $k_1$ ,  $k_{-1}$ ,  $k_2$ ,  $k_{-2}$ ,  $k_3$ , and  $k_{-3}$ , which were estimated from condition (a). Thus, it is possible to predict how much MA and 2a transformed into Mono and Di at a certain catalyst concentration and a certain temperature from the initial concentrations of raw materials.

Next, we estimated the activation energies  $(E_{a1}, E_{a-1}, E_{a2}, E_{a-2}, E_{a3}, and E_{a-3})$  for the formation of **Mono** and **Di** from datasets in the conditions of (a), (f), and (g). The activation energy  $(E_a)$  was estimated using Mathcad software on the

$$\frac{\mathrm{d}[\mathrm{ME}]}{\mathrm{d}t} = [\mathrm{cat}](-k_1[\mathrm{ME}][2\mathbf{a}] + k_{-1}[\mathrm{Mono}][\mathrm{MeOH}] - k_2[\mathrm{ME}][\mathrm{Mono}] + k_{-2}[\mathrm{Di}][\mathrm{MeOH}] + \mathrm{BP}_{\mathrm{ME}})$$
(1)

$$\frac{d[2a]}{dt} = [cat] (-k_1 [ME] [2a] + k_{-1} [Mono] [MeOH] - k_3 [2a] [Di] + k_{-3} [Mono]^2 + BP_{BD})$$
(2)

$$\frac{d[Mono]}{dt} = [cat] (k_1 [ME] [2a] - k_{-1} [Mono] [MeOH] - k_2 [ME] [Mono] + k_{-2} [Di] [MeOH] + 2 (k_3 [2a] [Di] - k_{-3} [Mono]^2) + BP_{Mono})$$
(3)

$$\frac{\mathbf{d}[\mathbf{D}\mathbf{i}]}{\mathbf{d}t} = [\mathbf{cat}] \left( k_2 [\mathbf{M}\mathbf{E}] [\mathbf{M}\mathbf{o}\mathbf{n}\mathbf{o}] - k_{-2} [\mathbf{D}\mathbf{i}] [\mathbf{M}\mathbf{e}\mathbf{O}\mathbf{H}] - k_3 [2\mathbf{a}] [\mathbf{D}\mathbf{i}] + k_{-3} [\mathbf{M}\mathbf{o}\mathbf{n}\mathbf{o}]^2 + \mathbf{B}\mathbf{P}_{\mathrm{D}\mathbf{i}} \right)$$
(4)

$$\frac{\mathrm{d}[\mathrm{MeOH}]}{\mathrm{d}t} = [\mathrm{cat}](k_1[\mathrm{ME}][2a] - k_{-1}[\mathrm{Mono}][\mathrm{MeOH}] + k_2[\mathrm{ME}][\mathrm{Mono}] - k_{-2}[\mathrm{Di}][\mathrm{MeOH}] + \mathrm{BP}_{\mathrm{MeOH}})$$
(5)

For further investigation, Runge–Kutta curve-fitting analysis using Mathcad software<sup>25</sup> was conducted based on the experimental data of GC analysis on **ME**, **2a**, **Mono**, and **Di**, and the other details are presented in ESI.† The basic five plus additional four (only in the case of **MA**) ordinary differential equations generated were solved numerically for all the simulations in this study, where the relationship basis of the Arrhenius equation, in which  $k_{\rm T}$  (rate constant at T °C) is expressed as  $k_{\rm T'} = k_{\rm T} \exp[(E_{\rm a}/R)\{1/T\} - (1/T')]$ . The activation energies were determined to be  $E_{\rm a1} = 55.1$ ,  $E_{\rm a-1} = 39.7$ ,  $E_{\rm a2} = 49.7$ ,  $E_{\rm a-2} = 33.0$ ,  $E_{\rm a3} = 39.9$ ,  $E_{\rm a-3} = 41.2$  [kJ mol<sup>-1</sup>]. Finally,  $\Delta H$  values and  $\Delta S$  values were calculated from the estimated values of  $K_{65}$ ,  $K_{75}$ , and  $K_{85}$  by van't Hoff plot based on the van't Hoff equation,  $\ln(K_{\rm T}) = -\Delta H/RT + \Delta S/RT$ . As the





Fig. 1 Curve-fitting calculations for the transesterification of MA and 1,4-butanediol and estimated kinetic parameters using [Zn(tmhd)(OMe) (MeOH)]<sub>4</sub> as the catalyst in toluene.

determined the  $\Delta H$  and  $\Delta S$ of the result. we transesterification using **MA** as follows:  $\Delta H_1 = 15.4/\Delta H_2 =$  $16.7/\Delta H_3 = -1.36 \text{ [kJ mol}^{-1}\text{]}$  and  $\Delta S_1 = 46.8/\Delta S_2 = 36.3/\Delta S_3 =$ 10.5 [kJ K<sup>-1</sup> mol<sup>-1</sup>].<sup>15</sup>  $\Delta G$  was also determined based on the calculated values of  $\Delta H$  and  $\Delta S$  at 85 °C as follows:  $\Delta G_1$  =  $-1.41/\Delta G_2 = 3.70/\Delta G_3 = -5.11$  [kJ mol<sup>-1</sup>], which revealed a small energy gap between the substrates and products converting reversibly under this equilibrium transesterification reaction.

In the same way, the rate constants and kinetic- and thermodynamic parameters for the transesterification of **MMA** were estimated under the 7 conditions shown below:  $[\mathbf{MMA}]_0/[\mathbf{2a}]_0/[\mathbf{1a}]$ , (a') = 3.91 [mol kg<sup>-1</sup>]/5.86 [mol kg<sup>-1</sup>]/7.82 [mmol kg<sup>-1</sup>], (b') = 4.30 [mol kg<sup>-1</sup>]/4.30 [mol kg<sup>-1</sup>]/7.82 [mmol kg<sup>-1</sup>], (c') = 3.28 [mol kg<sup>-1</sup>]/6.57 [mol kg<sup>-1</sup>]/7.82 [mmol kg<sup>-1</sup>], (c') = 3.91 [mol kg<sup>-1</sup>]/5.86 [mol kg<sup>-1</sup>]/7.82 [mmol kg<sup>-1</sup>], (e') = 3.91 [mol kg<sup>-1</sup>]/5.86 [mol kg<sup>-1</sup>]/7.82 [mmol kg<sup>-1</sup>], (e') = 3.91 [mol kg<sup>-1</sup>]/5.86 [mol kg<sup>-1</sup>]/7.82 [mmol kg<sup>-1</sup>], as well as two conditions using the same initial concentrations as in condition (a') but at different temperatures, (f') 65 °C, (g') 75 °C. As a result, we determined the rate constants as,  $k_1' = 9.58/k_{-1}' = 5.61/k_2' = 15.4/k_{-2}' = 38.6/k_3' = 78.9/k_{-3}' = 18.4 [kg<sup>2</sup> mol<sup>-2</sup> h<sup>-1</sup>], and kinetic- and thermodynamic parameters as, <math>E_{a1}' = 84.6/E_{a-1}' = 69.2/E_{a2}' = 63.2/E_{a-2}' = 47.4/E_{a3}' = 53.3/E_{a-3}' = 53.8 [kJ mol<sup>-1</sup>]; <math>\Delta H_1' = 15.4/\Delta H_2' = 15.9/\Delta H_3' = -0.50 [kJ$ 

mol<sup>-1</sup>];  $\Delta S_1' = 50.6 / \Delta S_2' = 39.8 / \Delta S_3' = 10.8 \text{ [kJ mol<sup>-1</sup>]}; \Delta G_1' = -2.77 / \Delta G_2' = -1.59 / \Delta G_3' = -4.36 \text{ [kJ mol<sup>-1</sup>] (Fig. 2)}.$ 

To clarify the mechanism of this esterification reaction, DFT calculations<sup>27</sup> were performed with the dispersioncorrected B3LYP functional using MA and 2a as representative substrates. Although in the previous transesterification using  $[Zn_4(OCOR)_6O]$ ,<sup>20c</sup> we proposed mechanisms mediated by multinuclear complexes; in the case of an alkoxide-bridged cluster, a dinuclear pathway produced much higher energy than a mononuclear pathway (see ESI<sup>†</sup>). Thus, we excluded the dinuclear pathway and proposed the catalytic cycle by the zinc mononuclear complex (Fig. 3a). The alkoxide-bridged tetranuclear zinc cluster 1a is dissociated to four mononuclear complexes by the coordination of L1. Methoxide is then exchanged with 2a to give MeOH and complex A as catalytically active species. The first step of the transesterification is the coordination of MA to the zinc atom of complex A to form B, which has 23.5 kJ  $mol^{-1}$ higher energy than A. Then, intramolecular nucleophilic attack of the terminal alkoxide occurs to a carbonyl carbon of the coordinating MA via transition state TS1, leading to intermediates D via C. The free energy of TS1 is 54.4 kJ mol<sup>-1</sup> relative to the starting point at A, and the free energies of intermediates C and D are 53.6 kJ mol<sup>-1</sup> and



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Fig. 2 Curve-fitting calculations for the transesterification of MMA and 1,4-butanediol and estimated kinetic parameters using 1a as the catalyst in toluene.

44.6 kJ mol<sup>-1</sup>, respectively. The C–O bond cleavage proceeds *via* transition state **TS2**, resulting in the formation of **E**, and the calculated barrier for this concerted C–O bond cleavage step is 54.2 kJ mol<sup>-1</sup> relative to complex **A**. The monoester  $3a_{MA}$  and MeOH are released in the next step together with an intermolecular ligand exchange with additional 2a, and finally complex **A** is regenerated.

To continuously produce monoester preferentially, it is necessary to search for the best condition affording the maximum amount of monoester per unit of time. Thus, we demonstrated the reaction yield estimation based on kinetic parameters obtained by Runge-Kutta curve-fitting analysis (vide supra). The productivity, chemoselectivity, and yields of 3a<sub>MA</sub> and 3a<sub>MMA</sub> were plotted versus temperature (Fig. 4a, b, d and e) and equivalents of 2a (Fig. 4c and f). As shown in Fig. 4a, the kinetic model suggests that raising the reaction temperature is a straightforward approach to obtaining monoesterified product  $3a_{MA}$  in high yield in the case of MA. A higher reaction temperature over 80 °C, however, increases the risk of polymerization of MA and decreases the ratio of  $3a_{MA}/4a_{MA}$ . Accordingly, we fixed the reaction temperature to 85 °C for MA. We then started to search for the best equivalent of 2a versus MA according to the simulated kinetic model, in which an equilibration time

was defined when the yield of monoester 3a<sub>MA</sub> reached the highest value under a certain condition. The simulated kinetic model enabled us to determine the equilibration time depending on the initial condition, so the reaction condition was set as follows: [1a] (on metal ions) = 8.26  $[mmol kg^{-1}]$  (in the case of MA), the molar mass of toluene was 100 times larger than [1a]. The details of the simulated data are provided in the ESI.<sup>†</sup> In the case of MA, 1.2 equiv. of 2a provided the maximum yield of monoester  $3a_{MA}$  (2.29 mol  $kg^{-1}$ ) (Fig. 4c). The kinetic model of **MMA** suggests that increasing the reaction temperature is also a straightforward approach to obtaining monoesterified product  $3a_{MMA}$  in high yield (Fig. 4d) but this approach would decrease the ratio of 3a<sub>MMA</sub>/4a<sub>MMA</sub> and reach a minimum value at 110 °C (Fig. 4e). Thus, we fixed the reaction temperature to 85 °C and 105 °C for MMA, and set the reaction conditions as follows: [1a] (on metal ions) = 7.82 [mmol kg<sup>-1</sup>] (in case of MMA), the molar mass of toluene was 100 times larger than [1a], and then searched for the best equivalent of 2a versus MMA according to the simulated kinetic model under a certain condition. In the case of MMA, 1.3 equiv. of 2a would afford the maximum yield of the monoester 3a<sub>MMA</sub> as 2.20 [mol kg<sup>-1</sup>] at 85 °C and 2.37 [mol kg<sup>-1</sup>] at 105 °C (Fig. 4f).



Fig. 3 a) Proposed reaction mechanism and b) calculated free energy profile  $(kJ mol^{-1})$  for the transesterification of MA and 2a mediated by the zinc mononuclear complex in toluene.

Using the simulated best conditions, at 85 °C with 1.2 equiv. of 2a for MA or at 85 °C and 105 °C with 1.3 equiv. of 2a for MMA, we confirmed the accuracy of these kinetic models and reaction yield estimation by collecting experimental data for MA and MMA. When MMA was used as substrate, 50 ppm of 4-hydroxy-TEMPO free radical against MMA was added to prevent the polymerization because MMA required a longer reaction time to reach the equilibrium state. Fig. 5 shows an excellent correlative relationship between the estimated value derived from the kinetic model and the experimental result at 85 °C: the actual yields of  $3a_{MA}$  and  $4a_{MA}$  were 48.0% and 15.1% yield, respectively, and the estimated yields of  $3a_{MA}$  and  $4a_{MA}$  were 48.4 and 14.9%



**Fig. 4** Optimizing reaction conditions estimated by kinetic models. (a) Temperature effect on  $3a_{MA}$  productivity [mol kg<sup>-1</sup> h<sup>-1</sup>)]. (b) Temperature effect on  $3a_{MA}/4a_{MA}$  ratio. (c) **2a** equivalent effect to  $3a_{MA}$  yield [mol kg<sup>-1</sup>]. (d) Temperature effect on  $3a_{MMA}$  productivity [mol kg<sup>-1</sup> h<sup>-1</sup>)]. (e) Temperature effect on  $3a_{MMA}/4a_{MMA}$  ratio. (f) **2a** equivalent effect on  $3a_{MMA}$  yield [mol kg<sup>-1</sup>].

yield, respectively. The estimated value derived from the kinetic model and the experimental result for **MMA** also matched well. These results demonstrated that the reaction yield estimation based on kinetic studies could be reliably applied to predict the equilibrium state. This modeling





<sup>b</sup> 50 ppm of 4H-TEMPO against **MMA** was added before the reaction started

Fig. 5 A demonstration experiment of optimal reaction conditions based on kinetic models.

would be useful for predicting the compositional ratio of a crude mixture among MA, MMA, 2a, 3a, and 4a in each condition at any given point in time.

## Conclusions

In summary, we developed a new, efficient transesterification of methyl(meth)acrylates and diol compounds catalyzed by unique cubic cluster complexes and a 2,2'-bipyridine ligand system containing first-row late-transition metal centers. [Zn(tmhd)(OMe)(MeOH)]<sub>4</sub> was selected as the best precursor in terms of not only its catalytic activity but also its chemoselectivity for minimizing the influence of side reactions, such as the Michael addition reaction. We also describe our attempts to unravel the reaction mechanism of this equilibrium transesterification reaction and suggest a model that the Zn(II) mono-nuclear complex is generated to become a real active species by the cubane precursor and the bipyridine ligand. Moreover, kinetic studies and precise calculations based on the Runge-Kutta method for curvefitting analysis were conducted, and the derived kinetic parameters totally support the model presented above. Thus, we demonstrated the usefulness and potential to combine kinetic studies via curve-fitting analysis and computational DFT calculations to enhance the reliability of the suggested reaction mechanisms. Further studies to apply these findings to industrial synthesis are ongoing in our laboratory.

### Author contributions

T. K. wrote the manuscript with support from H. N. and K. M., and T. K. carried out experiments, kinetic study, and curve-fitting analysis. H. N. conducted the DFT calculations. S. A. contributed to the initial studies in an early stage of the project. K. Y., T. O. and K. M. supervised the project.

## Conflicts of interest

There are no conflicts to declare.

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