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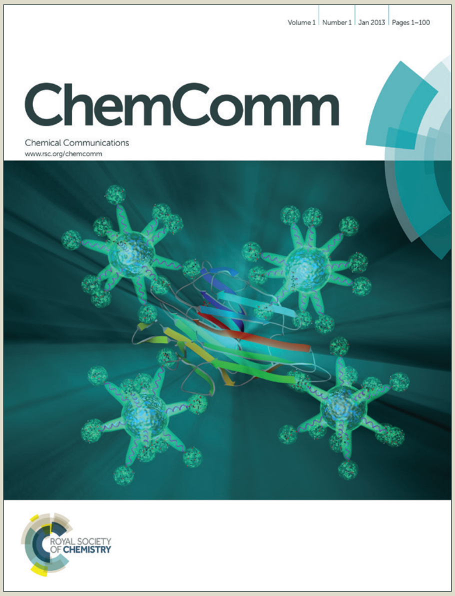

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One-Pot Atom-efficient Synthesis of Bio-renewable Polyesters and Cyclic Carbonates through Tandem Catalysis

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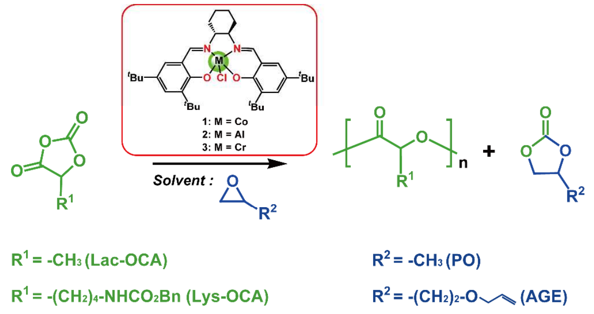
One-pot synthesis of well-defined bio-renewable polyesters and cyclic carbonates in high yields was successfully realized for the first time by way of a tandem reaction using metal salen complexes as catalyst. This tandem process offered unprecedented opportunities for the atom-efficient production of two relevant compounds.

Bio-renewable polyesters have received increasing attention over the last few years due to their application in biomedical field such as drug delivery vesicles, bone screws and scaffolding or suture wire.[1-2] Most bio-renewable polyesters are synthesized by the step-growth copolymerization of diesters and diols.[3-4] This process offers functional diversity due to the wide availability of diesters and diols, but high vacuum removal of small molecule byproducts are required to achieve high molecular weight polymer.[5] Other polyesters are prepared by the ring-opening polymerization (ROP) of cyclic esters, such as β-lactones, lactide, and ε-caprolactone.[6-9] ROP allowed a much higher degree of control in terms of molecular weight, end-group fidelity and even polymer tacticity. However, polyester synthesis by ROP of cyclic esters is largely limited to monomers that do not contain high levels of functional groups.

Ring-opening copolymerization of *O*-carboxyanhydride (OCA) monomer is an alternative way to synthesize polyesters. ROP of OCA, by releasing a molecule of CO_2, is able to generate side-chain-functionalized polyesters effectively.[10] Taking advantage of the OCA ROP strategy, Bourissou *et al.* have reported the synthesis and ROP of L-gluOCA, the *O*-carboxyanhydride derived from glutamic acid.[11] Well-controlled polymers with pendant carboxylic acid groups are shown to be accessible under mild conditions via DMAP-catalyzed ROP. Cheng *et al.* have reported the design and synthesis of polyesters bearing pendant hydroxyl groups by integrating the ROP of *O*-benzyl-L-serine carboxyanhydrides.[12] We recently develop a strategy to synthesize a new OCA monomer (lysine-OCA) and amino-functionalized renewable polyester from an abundant low-cost natural resource: lysine, and the resultant lysine-based polyester showed excellent cell compatibility.[10] Although significant successes were accomplished for the polymerization of OCAs, use of easily accessible catalysts that exhibit high activities and high atom efficiency, have not been reported. To suppress unwanted CO_2 release, the attempt to develop a single tandem catalyst to connect two independent catalytic cycles for the production of polyesters and the formation of cyclic carbonates from CO_2 and epoxide has attracted our interest (**Scheme 1**). Tandem catalysis involves the sequential or concurrent action of two or more catalytic cycles in a single reactor to generate a product with minimum workup, or change in conditions.[13] These new catalytic strategies that take advantage of *in situ* produced intermediates have several advantages over multistep syntheses, including atom economy, time- and cost-savings, waste reduction and energy consumption. However, there are only few examples in the literature in which a single metal complex is able to link independent catalytic cycles for the synthesis of polymers.[14-15]

As we all know, salen catalysts (H_2 salen = *N,N'*-bis(3,5-di-tert -butylsalicylidene)-1,2-cyclohexanediimine) can be considered as useful platforms for the development of new reactions.[16-18] We hypothesized that metal complexes based on the specific tetradentate salen ligand would have the potential to act as tandem catalysts due to their unique robustness and versatility,[19] as well as the documented performance for the synthesis of polyesters or cyclic carbonates.[20] In this communication, as shown in **Scheme 1**, we report the use of simple salen catalysts for the one-pot atom-efficient production of polyesters and cyclic carbonates by way of a tandem reaction. Compared with common ROP of lysine-OCA, the tandem process can accelerate the polymerization of lysine-OCA due to the coupling reaction of epoxide with CO_2 released from polymerization, thus leading to polymers with improved yield.



Scheme 1. Tandem synthesis of polyesters and cyclic carbonates catalyzed by metal salen complexes.

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Table 1. Ring-opening Polymerization of OCA catalyzed by **1-3** [a]

Entry	Monomer	Initiator [I]	[PPNCl]/[I]	[OCA]/[I]	Time (h)	Yield [b]	M_n (M_n*) (kDa) [c]	M_w/M_n [c]
1	Lac-OCA	**1**	-	50	1	100/0	3.8 (3.7)	1.4
2	Lac-OCA	**1**	2	50	1	100/20	4.1 (3.7)	1.4
3	Lac-OCA	-	2	50	1	95/0	20.4 (3.5)	1.2
4	Lac-OCA	**1**	2	50	5	100/82	2.2 (3.7)	1.1
5	Lac-OCA	**1**	5	50	1	100/100	2.9 (3.7)	1.4
6	Lac-OCA	**1**	5	100	1	100/32	5.7 (7.3)	1.1
7	Lac-OCA	**1**	5	25	1	100/100	1.5 (1.9)	1.2
8	Lac-OCA	**2**	5	50	1	100/25	3.4 (3.7)	1.1
9	Lac-OCA	**2**	10	50	1	100/46	5.3 (3.7)	1.3
10	Lac-OCA	**3**	5	50	1	100/80	2.9 (3.7)	1.3
11[d]	Lac-OCA	**1**	5	50	1	100/97	2.0 (3.7)	1.1
12	Lys-OCA	**1**	5	50	8	67/100	11.1 (8.9)	1.1
13[e]	Lys-OCA	**1**	5	50	8	53/--	13.1 (7.1)	1.1
14	Lys-OCA	**1**	10	50	1	92/76	14.5 (12.2)	1.1
15[e]	Lys-OCA	**1**	10	50	1	61/--	9.4 (8.2)	1.1

[a] Reactions performed with [OCA] = 0.25 M at 20 °C in neat propylene oxide. [b] Y^1 = conversion in polymer, Y^2 = conversion in cyclic carbonate with respect to OCA conversion. [c] M_n and M_w/M_n of polymer determined by GPC, the expected M_n* was calculated from the equation: (M_w of OCA − M_w of CO_2) × [OCA]/[I] × Yield % + the molar mass of the initiators. [d] Polymerization performed with [OCA] = 0.25 M at 20 °C in neat allyl glycidyl ether. [e] Polymerization performed with [OCA] = 0.25 M at 20 °C in CH_2Cl_2.

The catalytic performances of the different salen complexes were evaluated using OCA of lactic acid (Lac-OCA) in the presence of an excess of propylene oxide (PO), which was used as a solvent. Representative results were summarized in **Table 1**. We first investigated the cobalt (III) system **1**. Much to our dismay, the reaction of Lac-OCA at monomer-to-initiator ratios of 50 in the presence of **1** for 1 h only afforded poly(lactic acid) (PLA) without the formation of cyclic propylene carbonate (PC) (**Table 1 entry 1**), indicating the resulting catalytic system was not an effective catalyst for the overall tandem process. Gratifyingly, We observed that the addition of cocatalyst [PPN]Cl ($[PPN]^+$= bis(triphenylphosphoranylidene)iminium) produced PC in low yield under the same reaction conditions (**entry 2**). These results indicated that the cobalt complexes derived from (salen)CoCl and onium salt should be the active species.[21-22] It has already been demonstrated that this type of binary catalyst system of salen complex in conjunction with [PPN]Cl generally contained only one specific active-site(**Figure S1)**, and the lewis basic cocatalyst could reversibly coordinate with the active metal center, increased the electron density on the metal and labilizes the trans ligand to it.[23-24] As a control experiment, the reaction was performed using [PPN]Cl without (salen)CoCl, and PLA could be isolated. However, no cyclic carbonate formation was observed (**entry 3**). Furthermore, the polymerization was not controlled as a too high experimental M_n was obtained (experimental 20.4 kDa *versus* calculated M_n of 3.6kDa). This observation further indicated that both (salen)CoCl **1** and [PPN]Cl was necessary for the tandem synthesis of polyesters and cyclic carbonates.

The optimization of the molar ratio between (salen)CoCl and [PPN]Cl was then explored and it was observed that the yield of PC was improved with an increased amount of [PPN]Cl for a constant reaction time of 1 h (entries 2, 5). The highest activity was obtained with 5 equivalents of [PPN]Cl leading to 100 % yield for PC (**entry 5** and **Figure S2**). This was in accordance with former studies that illustrated that the generation of the six coordinate anion trans-(salen)MX_2^- occurred more easily with at least 2 equivalents of [PPN]Cl.[25] We also showed that the formation of propylene carbonates was time-dependent and increased with the reaction time. In the presence of 2 equivalents of [PPN]Cl, the PC yield was 20 and 82 % after 1h and 5h, respectively (**entries 2** and **4**).

As shown in **Figure 1**, the M_n values of the resulting polyesters at monomer-to-initiator ratios of 50 and 100 were 2.9 kDa and 5.7 kDa, respectively, both of which were in excellent agreement with the calculated M_n values (3.7 kDa and 7.3kDa, respectively), suggesting that (salen)CoCl/[PPN]Cl showed significant control for the ROP of Lac-OCA and gave the polymer with the expected molecular weights and narrow molecular weight distributions.

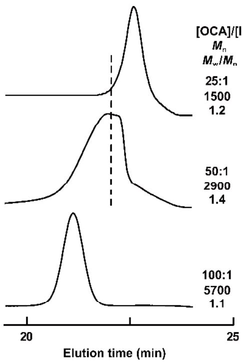

Figure 1. GPC curves of the polymers obtained by the ROP of Lac-OCA with (salen)CoCl/[PPN]Cl as the catalyst at different monomer-to-initiator ratios.

We also investigated the catalytic behavior of Al(III) complex **2** and the Cr(III) complex **3**. Both metal complexes can catalyze the tandem reaction of Lac-OCA and PO, although the PC yield for complex **2** and **3** were lower than that for the cobalt analogue **1** (**entries 8-10**). For example, in the presence of 5 equivalents of [PPN]Cl, only 25% of PC was obtained in 1h for aluminum complex **2** (**entry 8**) *vs.* 100% with the cobalt complex **1** (**entry** 5). At the end of the tandem process, the remaining PO can be recovered by vacuum distillation and may be used for the next batch. Then the residue was filtrated to separate propylene carbonate from the polyester (**Figure S3** and **S4**).

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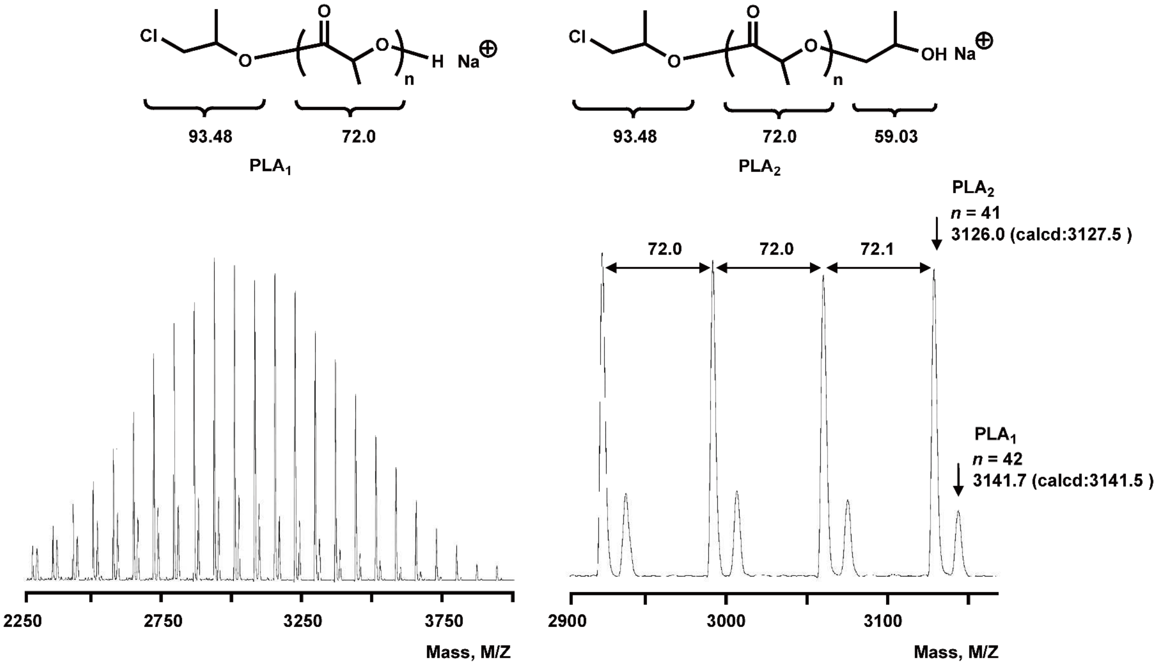

Figure 2. MALDI-TOF-MS spectra of polymers prepared by the ROP of Lac-OCA (**Table 1, entry 8**).

When allyl glycidyl ether (AGE) was used as a solvent instead of PO, quantitative and controlled polymerization of 50 equivalents of Lac-OCA using (salen)CoCl/[PPN]Cl was also observed after 1h ($M_{n,\,exp}$ = 2.0 kDa; M_w/M_n = 1.1), along with cyclic carbonate in 97% yield (**entry 11** and **Figure S5**).

Other monomer, lysine(Cbz)-OCA (Lys-OCA) was screened to explore the tandem process (entries 12-15). (salen)CoCl/[PPN]Cl was used as the catalyst because it exhibited higher activity in the tandem reaction of Lac-OCA and PO. We were delighted to find that the tandem reaction of Lys-OCA with PO in the presence of (salen)CoCl **1** in conjunction with 10 equivalents of [PPN]Cl within 1 h to afford the corresponding polyesters in 92% yield with molecular weight of 14.5kDa ($M_{n,\,theo}$ = 12.2kDa) (**entry 14**), along with cyclic carbonate in 76% yield (**Figure S6**).

In addition to offering unprecedented opportunities for the atom-efficient production of two relevant compounds, the tandem process can accelerate the polymerization of Lys-OCA. Polymerization of Lys-OCA using (salen)CoCl and 5 equivalents of [PPN]Cl in CH_2Cl_2 produced polymer with only 53% yield. When PO was used as a solvent, polymer with higher yield (67%) was obtained (entries 12-13). Especially, at 10 equivalents of [PPN]Cl, only 61% yield of polymer was obtained in CH_2Cl_2 with (salen)CoCl/[PPN]Cl (**entry 15**) *vs.*92% in PO with the same catalyst (**entry 14**), further indicating that the tandem reaction of OCA with PO was beneficial for the polymerization.

The resulted PLA obtained with metal salen and [PPN]Cl was analyzed by MALDI-TOF-MS to determine the chemical composition. The MALDI-TOF-MS measurement provided direct evidence that the ROP of Lac-OCA catalyzed by metal salen complex was initiated by an alkoxide ($ClCH_2CH(CH_3)O$) complex resulting from the insertion of PO into the metal-Cl bond.[26] The MALDI-TOF spectrum consists of a series of peaks separated by a 72 Da interval, which corresponds to the molecular weight of the monomer unit (**Figure 2**). Two kinds of PLA structures were observed from MALDI-TOF-MS measurement, PLA$_1$: 3141.5 = 93.48 (M_w of alkoxide) + 42 × 72.0 (M_w of OCA − M_w of CO_2) + 1.0 (M_w of H end) + 23.0 (M_w of Na^+), PLA$_2$: 3127.5 = 93.48 (M_w of alkoxide) + 41 × 72.0 (M_w of OCA − M_w of CO_2) + 58.03 (M_w of PO) + 1.0 (M_w of H end) + 23.0 (M_w of Na^+), indicating that a substantial fraction of the polymer chains were terminated by PO. In addition, the molecular weight of each individual peak was close to the calculated value; *i.e.,* a polymer possessing one initiator moiety at the α-end and the sodium ion from the salt for MALDI-TOF MS analysis. These results again suggested that salen-catalyzed ROP of OCA monomer was initiated by an alkoxide.

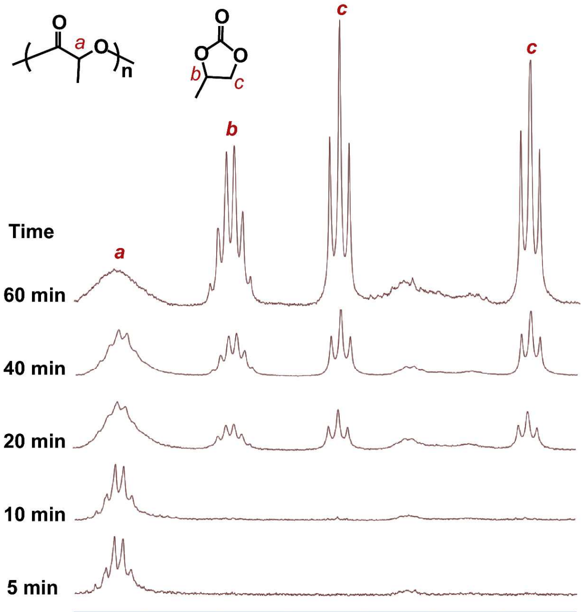

Figure 3. ^1H NMR spectra recorded at regular intervals in $CDCl_3$ during the reaction of Lac-OCA and PO in the presence of (salen)CoCl/[PPN]Cl. [PPNCl]/[I]=5; [OCA]/[I]=50.

To investigate the mechanism occurring during the tandem catalysis, a series of the crude mixture of the reaction was analyzed by ^{1}H NMR spectroscopy in $CDCl_3$ at 20 °C (**Figure 3**). Five ^{1}H NMR spectra were recorded at regular intervals over a period of 1 h during the reaction of Lac-OCA and PO in the presence of (salen)CoCl/[PPN]Cl (**Figure 3**). These ^{1}H NMR spectra and conversion *vs* time curves of the tandem reaction from ^{1}H NMR (**Figure S8**) clearly indicated a two-steps sequential reaction. The formation of the polyesters was followed by the cycloaddition of CO_2 to epoxide. Possibly, the cyclization reaction started when an epoxide co-monomer replaced a metal-bound polymeric chain. By nucleophilic attack of Cl^- group on epoxide, which was activated by the Lewis acidic metal center, an alkoxide active species was generated *in situ*, and the reaction of epoxide and CO_2 proceeded simultaneously to form a carbonate. Then, cyclic carbonate was produced by the backbiting of a metal-carbonate into an adjacent alkoxide linkage.[27]

In conclusion, we demonstrated the first tandem catalytic system that allowed one-pot synthesis of bio-renewable polyesters and cyclic carbonates in high yields, through the incorporation of CO_2 released from the initial step. This process provided access to a range of well-defined polyesters with narrow molecular weight distributions. To our knowledge, these binary catalyst systems offered unprecedented opportunities for the atom-efficient production of two relevant compounds.

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Notes and references

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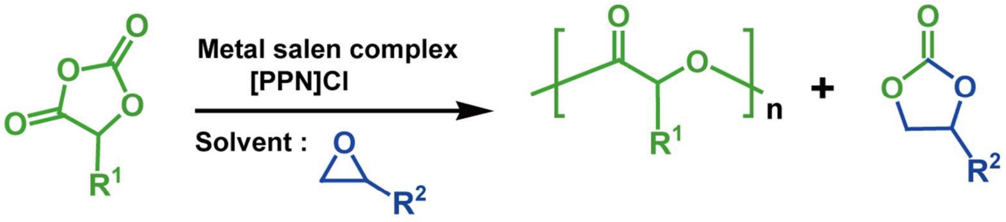

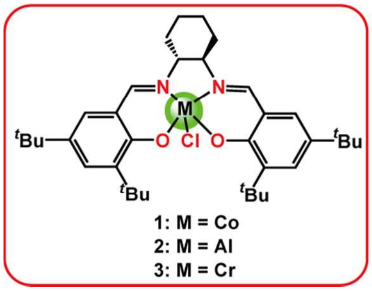

- ◆ *One-pot and full-atom economy*
- ◆ *Improved polymer yield*
- ◆ *Higher yield of cyclic carbonates*
- ◆ *Well-defined bio-renewable polyesters*
- ◆ *Narrow MWDs*

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