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Dialkylgallium alkoxides – a tool for facile and stereoselective synthesis of PLA–drug conjugates†

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Herein, a method for the synthesis of PLA-(β-blocker) conjugates with a tunable stereostructure of the PLA fragment is demonstrated using stereoselective [R₂Ga(μ-β-blocker)]₂ catalysts and [R₂Ga(μ-OR)]₂/H-(β-blocker) catalytic systems for the ring-opening polymerisation (ROP) and immortal ring-opening polymerisation (iROP) of racemic lactide (*rac*-LA), respectively.

The growing interest in polylactide (PLA) – a biodegradable and biocompatible polymer – is due to its numerous applications,¹ ranging from packaging to medical materials including PLA–drug conjugates and PLA-based drug delivery systems.² While PLA–drug conjugates could be synthesized, among others, by the polymerisation of lactide using non-toxic Zn³ and Mg⁴ complexes, a catalyst was crucial for the modification of the PLA structure and properties of the PLA–drug conjugates.^{4a} However, although the tacticity of PLA can affect its physico-chemical properties,⁵ including the degradation rate of PLA–drug conjugates,⁶ both the synthesis of PLAs of different stereostructures, including PLA copolymers built of blocks of different tacticity,⁷ and their use in order to tailor the drug release properties of PLA–drug conjugates or drug delivery systems based on PLA,^{6,8} are in their infancy. We have shown that dialkylgallium catalysts [R₂Ga(μ-OR)]₂, which constitute a rare example of gallium catalysts for the polymerisation of lactide or other cyclic esters,⁹ can catalyse the polymerisation of *rac*-LA to PLA in a controlled and stereoselective manner,¹⁰ leading to a non-cytotoxic PLA.⁶ Dialkylgallium alkoxides exhibit unique features with regard to the stereoselective polymerisation of *rac*-lactide (*rac*-LA). In this case the addition of a Lewis base (LB),

such as pyridines or THF, to non-selective [R₂Ga(μ-OR)]₂ complexes resulted in the formation of heteroselective [R₂Ga(μ-OR)]₂/LB catalytic systems offering tuneable heteroselectivity in the range of 0.5 < P_r ≤ 0.85 (P_r = probability of *racemo* linkages in PLA).^{10,11} On the other hand, the addition of N-heterocyclic carbenes or organosuperbases to [R₂GaOR]₂ led to isoselective species, resulting in a facile stereoselectivity switch,^{12,13} which allowed for the synthesis of stereodiblock PLA copolymers.¹³ Therefore [R₂Ga(μ-OR)]₂, which exhibits low reactivity towards different functional groups,¹⁴ should be considered as an interesting catalyst for the synthesis of PLA–drug conjugates, additionally offering easy modification of the tacticity/stereostructure of PLA. We hereby demonstrate that PLA-(β-blocker) conjugates with a tunable stereostructure of the PLA can be synthesized by the polymerisation of *rac*-LA with [R₂Ga(β-blocker)]₂ (Scheme 1a) or stereoselective [R₂Ga(β-blocker)]₂/LB catalysts. Importantly, we also show that dialkylgallium alkoxides can be applied for the stereoselective immortal ring-opening polymerisation (iROP) of *rac*-LA. In this case [R₂Ga(μ-OR)]₂/H-(β-blocker) (Scheme 1b) and [R₂Ga(μ-OR)]₂/H-(β-blocker)/LB catalytic systems offer a facile and stereoselective synthesis of PLA-(β-blocker) conjugates.¹⁵

In order to confirm the structure of [R₂Ga(β-blocker)]₂ active species in the ROP of lactide, we investigated the synthesis, structure and activity of [Me₂Ga(μ-OCHRCH₂NHR')]₂ (R = H, R' = Me (1); R = H, R' = ⁱPr (2); R = CH₂Oph, R' = ⁱPr (3)) in the ROP of *rac*-LA, where HOCHRCH₂NHR' mimics the main skeleton of β-blockers¹⁶ (Scheme 2). For 1–3, which were isolated as colourless crystals, the X-ray analysis revealed the presence of dimers in the solid state (Fig. 1, see the ESI† for the structure of 1 and 2). Although, the dimeric structure of 1–3 is typical for [Me₂Ga(O,X)]₂ where (O,X) represents a monoanionic alkoxide bidentate ligand with Lewis base functionality,¹⁴ the lack of reactivity of the secondary amine group of A–C towards Ga–Me is noteworthy prior to further synthesis of PLA(A–C) as well as PLA–atenolol conjugates (see below). Noteworthy, a weak Ga–N bond to the fifth coordinate site of gallium was observed for 1–3, while the Ga–N bond distances increased in the order 1 (2.333(4) Å) < 2 (2.359(1) Å) < 3 (2.548(1) Å) with growing steric hindrances on the R and R' substituents.

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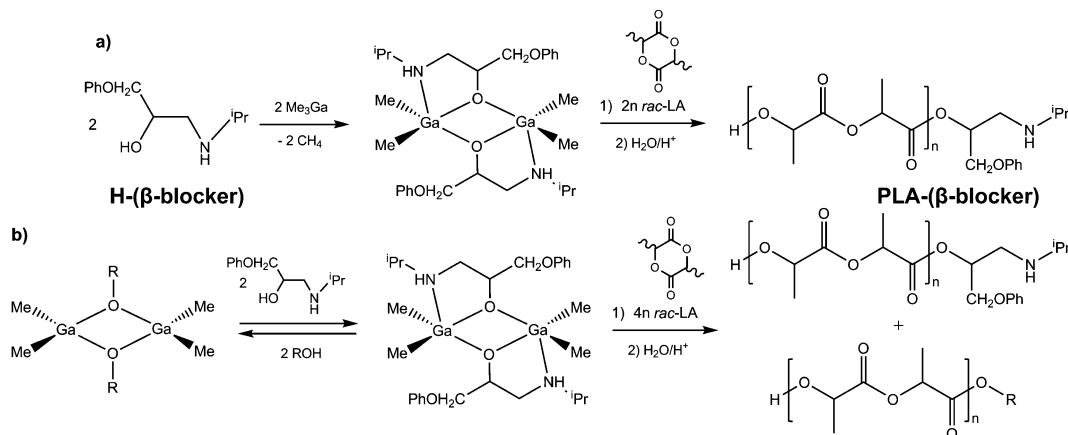
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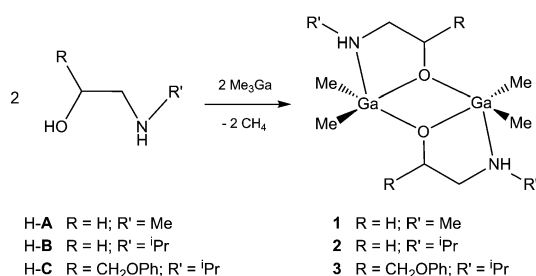
† Electronic supplementary information (ESI) available: Crystallographic data of 1–3;

¹H and ¹³C NMR for 1–3; details of *rac*-LA polymerisation, including ¹H and ¹³C NMR and MALDI-TOF spectra of PLA. CCDC 1569393–1569395. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7nj03089d





Scheme 1 Synthesis of PLA-(β -blocker) conjugates with $[\text{Me}_2\text{Ga}(\beta\text{-blocker})]_2$ catalytic centres using ROP (a) and iROP (b) of *rac*-LA. H- β -blocker represents a skeleton characteristic for β -blockers,¹⁶ and β -blocker represents a respective alkoxide anion with a deprotonated OH group. OR represents an alkoxide group.



Scheme 2 Synthesis of $[\text{Me}_2\text{Ga}(\mu\text{-OCHRCH}_2\text{NHR}')_2]$ (**1–3**).

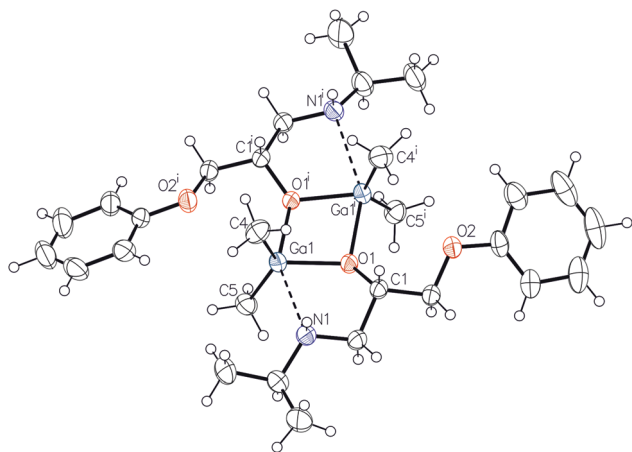


Fig. 1 Molecular structure of **3** with ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond length (Å) and angles (deg): Ga(1)–O(1) 1.9452(11), Ga(1)–O(1)ⁱ 2.0717(11), Ga(1)–C(4) 1.9648(18), Ga(1)–C(5) 1.9578(18), Ga(1)–N(1) 2.5478(14), N(1)–Ga(1)–O(1)ⁱ 152.51(5), O(1)–Ga(1)–O(1)ⁱ 77.12(5), Ga(1)–O(1)–Ga(1)ⁱ 101.21(5); *i* = 1 – *x*, +*y*, 3/2 – *z*.

As the structures of **1–3** were similar, both in the solid state and solution (see the ESI[†]), to $[\text{Me}_2\text{Ga}(\mu\text{-OCH}(\text{Me})\text{CO}_2\text{Me})_2]$ which mimics active centres in the ROP of lactide,^{10,11} we expected that PLA–drug conjugates could be synthesized due to insertion of lactide into the Ga–O_{alkoxide} group of **1–3**, moreover, in a stereoselective fashion. In this case, the weak Ga–N chelate bond, as well as Ga–O=C resulting from the interaction

of the growing PLA chain with gallium,¹⁰ should not affect the insertion of lactide into the Ga–O_{alkoxide} bond of **1–3** or any other $[\text{Me}_2\text{Ga}(\beta\text{-blocker})]_2$, which is advantageous in comparison with *e.g.* analogous aluminium complexes, which form considerably stronger chelate bonds with both Lewis base functionalities of alkoxide ligands or growing PLA chains.¹⁷ Furthermore, the weakest Ga–N bond for **3**, in which the structure of **C** mimics a whole main skeleton of β -blockers, indicates that the insertion of lactide into the Ga–O_{alkoxide} bond of any $[\text{R}_2\text{Ga}(\beta\text{-blocker})]_2$, should be facilitated in comparison with model **1** or **2** complexes. Finally, the propagating species in the *rac*-LA polymerisation with **1–3** should be similar to propagating species in the case of $[\text{Me}_2\text{Ga}(\mu\text{-OCH}(\text{Me})\text{CO}_2\text{Me})_2]$,^{11,13a} and therefore allow for the stereoselective polymerisation. Our reasoning was confirmed by the activity and stereoselectivity of compound **2** in the ROP of *rac*-LA (Table 1).

Compound **2** catalysed polymerisation of *rac*-LA at 40 °C and 70 °C showing similar activities and stereoselectivities to dialkylgallium alkoxides already reported by us.^{10,11,13a} Importantly, the interaction of a secondary amine group of $\text{OCH}_2\text{CH}_2\text{NH}^i\text{Pr}$, typical for β -blockers, with gallium neither had an adverse effect on the activity of the investigated catalysts nor affected the insertion of *rac*-LA into the Ga–O_{alkoxide} bond. The latter led to the essentially exclusive formation of $\text{HO-PLA-OCH}_2\text{CH}_2\text{NH}^i\text{Pr}$, which was clearly evidenced by MALDI-TOF spectroscopy (see the ESI[†]). Importantly, the heteroselective polymerisation of *rac*-LA with **2**/pyridine and **2**/DMAP catalytic systems leading to the heterotactically enriched PLA up to P_T of 0.85 (Table 1, entries 3 and 4), as well as isoselective polymerisation using **2**/DBU (P_T = 0.22, Table 1, entry 5), indicated the facile modification of the tacticity of PLA, in the range of P_T between 0.22 and 0.85, for $\text{HO-PLA-OCH}_2\text{CH}_2\text{NH}^i\text{Pr}$ and potentially $\text{HO-PLA-(}\beta\text{-blocker)}$ conjugates. Although the approach presented on Scheme 1a and discussed above indicates the possibility of the synthesis of PLA-(β -blocker) conjugates, it would not be the most convenient one, *e.g.* due to possible reactivity of drugs towards Me_3Ga . Therefore we focused on the possibility of the synthesis of $[\text{R}_2\text{Ga}(\beta\text{-blocker})]_2$ catalytic centres using the immortal ring-opening polymerisation (iROP) of lactide with $[\text{Me}_2\text{Ga}(\mu\text{-OR})]_2/\text{H-(}\beta\text{-blocker)}$ catalytic systems (Scheme 1b).



Table 1 Polymerisation of *rac*-LA with **2** in toluene

No.	Cat.	<i>T</i> [°C]	Time [h]	Conv. [%]	10 ^{−3} <i>M</i> _n ^b	10 ^{−3} <i>M</i> _n ^c	<i>D</i>	<i>P</i> _r ^d	<i>P</i> _r ^e
1	2	70	24	85	6.1	8.1	1.13	0.50	—
2	2	40	144	75	5.4	6.7	1.12	0.50	—
3 ^h	2/pyridine(1 : 6)	40	144	67	4.8	7.4	1.12	0.60	0.59
4 ^{g,h}	2/DMAP (1 : 6)	40	120	92	6.6	11.0	1.15	0.84	0.86
5 ^a	2/DBU ^f (1 : 6)	−20	18	94	6.8	7.3	1.38	0.22	0.22

^a In CH₂Cl₂. ^b Expected *M*_n [g mol^{−1}] value calculated according to LA/Ga ratio and conversion. ^c *M*_n [g mol^{−1}] determined by gel permeation chromatography (GPC) in CH₂Cl₂, using conventional calibration. ^d Probability of *racemo* linkages in PLA calculated on the basis of homonuclear decoupled ¹H NMR spectra according to Chamberlain *et al.*¹⁸ ^e Probability of *racemo* linkages in PLA calculated on the basis of ¹³C NMR.¹⁹ ^f DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. ^g Possibility of transesterification reactions revealed by MALDI-TOF (see the ESI). ^h Reference polymerisations of 50 equiv. of *rac*-LA with 3 equiv. of pyridine or DMAP revealed essentially no PLA formation.

Although metal complexes have been shown to polymerise *rac*-LA in an immortal and stereoselective fashion in the presence of alcohols,²⁰ [Me₂Ga(μ-OR)]₂/R'OH have not been demonstrated so far to catalyse the iROP of heterocyclic monomers. In order to demonstrate the possibility of the synthesis of PLA-(β-blocker) conjugates using immortal ring-opening polymerisation (iROP) of *rac*-LA with [Me₂Ga(μ-OR)]₂/H-(β-blocker), we focused on [Me₂Ga(μ-OCH(Me)CO₂Me)]₂/(H-A) or (H-B) as well as [Me₂Ga(μ-OC₆H₄OMe)]₂/(H-B), (H-C) or H-atenolol (β-blocker) catalytic systems. Notably, dialkylgallium alkoxides and aryloxides are not prone to the reaction with alcohols leading to the evolution of alkane and formation of dialkoxide or trialkoxide gallium species.¹⁴ On the other hand, the exchange of alkoxide groups between dialkylgallium alkoxides and alcohol added should lead in the case of [Me₂Ga(μ-OCH(Me)CO₂Me)]₂/(H-A) or (H-B) as well as [Me₂Ga(μ-OC₆H₄OMe)]₂/(H-B), (H-C) or H-atenolol to the presence of both [Me₂Ga(μ-OCH(Me)CO₂Me)]₂ and [Me₂Ga(μ-OC₆H₄OMe)]₂ complexes, as well as [Me₂Ga(μ-A)]₂ (1), [Me₂Ga(μ-B)]₂ (2), [Me₂Ga(μ-C)]₂ (3) or [Me₂Ga(μ-atenolol)]₂ species (Scheme 1b).¹¹ The formation of the latter catalytic centres resulted in the formation of PLA-A, PLA-B, PLA-C, as well as PLA-atenolol conjugates (Table 2).

[Me₂Ga(μ-OCH(Me)CO₂Me)]₂/(H-B) polymerised *rac*-LA at 40 °C and 70 °C, which led to the formation of both HO-PLA-(μ-OCH(Me)CO₂Me) and HO-PLA-B chains, as evidenced by

MALDI-TOF spectroscopy (see the ESI[†]). Moreover, the presence of PLA chains of similar *M*_n, as shown by GPC, indicated the presence of equilibrium and quick exchange of alkoxide groups OCH(Me)CO₂Me and H-B at the gallium centre under polymerisation conditions. However, as the molecular weight of the end groups of the resulting HO-PLA-(μ-OCH(Me)CO₂Me) (104.1 Da) and HO-PLA-B (103.2 Da) chains were almost the same, we confirmed the formation of both HO-PLA-(μ-OCH(Me)CO₂Me) and HO-PLA-(A-B) using [Me₂Ga(μ-OCH(Me)CO₂Me)]₂/(H-A) (see Fig. S69 and S70, ESI[†]). On the other hand, the polymerisation of *rac*-LA with [Me₂Ga(μ-OC₆H₄OMe)]₂/(H-B) led to the formation of essentially only HO-PLA-B chains indicating essentially no insertion of *rac*-LA into the Ga-O_{aryloxy} bond of [Me₂Ga(μ-OC₆H₄OMe)]₂ under the investigated conditions. The activity of [Me₂Ga(μ-OC₆H₄OMe)]₂/(H-B) was almost the same as in the case of [Me₂Ga(μ-OCH(Me)CO₂Me)]₂/(H-B) which was in line with the formation of [Me₂Ga(μ-B)]₂ species. The formation of dimeric catalytic species allowed for the heteroselective polymerisation of *rac*-LA using both [Me₂Ga(μ-OC₆H₄OMe)]₂/(H-B)/pyridines and [Me₂Ga(μ-OCH(Me)CO₂Me)]₂/(H-B)/pyridines (Table 2, entries 3, 4, 6–8), which is in agreement with the mechanism of heteroselective polymerisation of *rac*-LA with dialkylgallium alkoxides recently suggested by us.¹¹ The latter suggests an increase in heteroselectivity observed in the case of

Table 2 Polymerisation of *rac*-LA with [Me₂Ga(μ-OCH(Me)CO₂Me)]₂/2ROH (*rac*-LA/Ga = 50) (I), [Me₂Ga(μ-OC₆H₄OMe)]₂/2ROH (*rac*-LA/Ga = 25) (II), and [Me₂Ga(μ-OC₆H₄OMe)]₂/2ROH (*rac*-LA/Ga = 100) (III) in toluene

No.	ROH/LB	<i>T</i> [°C]	Time [h]	Conv. [%]	10 ^{−3} <i>M</i> _n ^b	10 ^{−3} <i>M</i> _n ^c	<i>D</i>	<i>P</i> _r ^d	<i>P</i> _r ^e
1	H-B(I)	70	24	90	3.2	4.4	1.20	0.50	—
2	H-B(II)	40	144	62	2.2	3.3	1.20	0.50	—
3 ^{a,g}	H-B(I)/pyr (1 : 6)	40	144	72	2.6	3.9	1.20	0.58	0.58
4 ^g	H-B(I)/DMAP (1 : 6)	40	120	91	3.3	5.0	1.24	0.83	0.85
5	H-B(II)	70	24	81	2.9	5.2	1.18	0.53	—
6 ^a	H-B(II)/pyr (1 : 60)	40	144	96	3.5	3.9	1.43	0.79	0.85
7 ^a	H-B(II)/γ-pic (1 : 6)	40	144	85	3.1	3.2	1.53	0.70	0.75
8 ^a	H-B(II)/γ-pic (1 : 60)	40	144	92	3.3	3.6	1.46	0.83	0.87
9	H-C(II)	40	240	94	3.4	4.4	1.40	0.61	0.66
10 ^a	H-C(II)/pyr (1 : 6)	40	240	93	3.3	4.1	1.46	0.61	0.68
11	H-atenolol(II)	70	24	99	—	—	—	—	—
12	H-atenolol(III)	40	720	93	13.4	19.9	1.71	0.56	0.57
13	H-atenolol(III) ^f	70/40	24/288	87	12.5	19.2	1.67	0.67	0.69

^a Pyr = pyridine, γ-pic = γ-picoline. ^b Expected *M*_n [g mol^{−1}] value calculated according to LA/Ga ratio and conversion. ^c *M*_n [g mol^{−1}] determined by gel permeation chromatography (GPC) in CH₂Cl₂, using conventional calibration. ^d Probability of *racemo* linkages in PLA calculated on the basis of homonuclear decoupled ¹H NMR spectra according to Chamberlain *et al.*¹⁸ ^e Probability of *racemo* linkages in PLA calculated on the basis of ¹³C NMR.¹⁹ ^f *rac*-LA : Ga = 20 (no LB)/80 (DMAP : Ga = 3 : 1). ^g Reference polymerisations of 50 equiv. of *rac*-LA with H-B/pyr (1 : 3) and H-B/DMAP (1 : 3) revealed essentially no PLA formation and the conversion of 6% (atactic PLA), respectively.



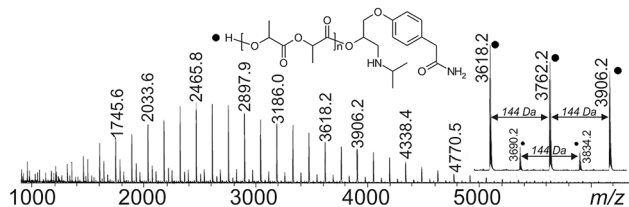


Fig. 2 MALDI-TOF spectrum of PLA obtained with $[\text{Me}_2\text{Ga}(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2/\text{H-atenolol}$ (1 : 2) at 70 °C (Table 2, entry 11). The distribution refers to PLA with OH and atenolol end groups, with K^+ .

$[\text{Me}_2\text{Ga}(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2/(\text{H-B})$, without the addition of an external Lewis base, which could be associated with the interaction of dialkylgallium alkoxides with $\text{HOC}_6\text{H}_4\text{OMe}$, released upon formation of $[\text{Me}_2\text{Ga}(\mu\text{-B})]_2$. Importantly, the results discussed above clearly show that heteroselective polymerisation of *rac*-LA with dialkylgallium alkoxides in the presence of a Lewis base works also under iROP conditions with $[\text{Me}_2\text{Ga}(\mu\text{-OR})]_2/\text{R'OH/LB}$ catalytic systems. Although $[\text{Me}_2\text{Ga}(\mu\text{-OCH}(\text{Me})\text{CO}_2\text{Me})]_2/(\text{H-B})/\text{DBU}$ (1 : 2 : 2) led to predominantly isotactic PLA ($P_r = 0.22$), both GPC and MALDI-TOF were in this case inconclusive for the controlled and immortal nature of *rac*-LA polymerisation (see the ESI†).

We confirmed also the possibility of the synthesis of PLA-(β -blocker) conjugates using $[\text{Me}_2\text{Ga}(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2/(\text{H-C})$ (Table 2, entries 9 and 10) as well as $[\text{Me}_2\text{Ga}(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2/\text{H-atenolol}$ (Table 2, entries 11–13). In both cases the formation of essentially only HO-PLA-C or HO-PLA-atenolol (Fig. 2) under applied polymerisation conditions was evidenced by MALDI-TOF (see the ESI†). Finally, both controlled and heteroselective iROP of *rac*-LA, as well as facile modification of the stereostructure of PLA, was demonstrated by the synthesis of the HO-(atactic-PLA)-*b*-(heterotactically enriched-PLA)-atenolol conjugate (Table 2, entry 13).

We showed that dialkylgallium alkoxides can be applied for the facile synthesis of PLA-drug conjugates, using as an example the synthesis of HO-PLA-(β -blocker) conjugates in the presence of $[\text{R}_2\text{Ga}(\mu\text{-}\beta\text{-blocker})]_2$ catalytic centres. Moreover, the stereostructure of the PLA fragment of HO-PLA-(β -blocker) can be easily tuned by the simple modification of the catalytic system. Importantly, the use of $[\text{R}_2\text{Ga}(\mu\text{-OR})]_2/\text{H}(\beta\text{-blocker})$ for the synthesis of HO-PLA-(β -blocker) demonstrated for the first time that dialkylgallium alkoxides/aryloxides can be used in the immortal ROP of lactide. The latter opens new synthetic pathways of both PLA-drug conjugates and PLA copolymers of novel architectures. Both are currently being investigated in our research group.

Conflicts of interest

The authors declare no competing financial interest.

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