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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 $[R_2Ga(\mu\text{-}\beta\text{-blocker})]_2$ catalysts and $[R_2Ga(\mu\text{-OR})]_2$/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 Zn[3] and Mg[4] 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 $[R_2Ga(\mu\text{-OR})]_2$, 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 $[R_2Ga(\mu\text{-OR})]_2$ complexes resulted in the formation of heteroselective $[R_2Ga(\mu\text{-OR})]_2$/LB catalytic systems offering tuneable heteroselectivity in the range of $0.5 < P_r \leq 0.85$ (P_r = probability of *racemo* linkages in PLA).[10,11] On the other hand, the addition of N-heterocyclic carbenes or organosuperbases to $[R_2GaOR]_2$ led to isoselective species, resulting in a facile stereoselectivity switch,[12,13] which allowed for the synthesis of stereodiblock PLA copolymers.[13] Therefore $[R_2Ga(\mu\text{-OR})]_2$, 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 $[R_2Ga(\beta\text{-blocker})]_2$ (Scheme 1a) or stereoselective $[R_2Ga(\beta\text{-blocker})]_2$/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 $[R_2Ga(\mu\text{-OR})]_2$/H-(β-blocker) (Scheme 1b) and $[R_2Ga(\mu\text{-OR})]_2$/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 $[R_2Ga(\beta\text{-blocker})]_2$ active species in the ROP of lactide, we investigated the synthesis, structure and activity of $[Me_2Ga(\mu\text{-OCHRCH}_2\text{NHR}')]_2$ (R = H, R′ = Me (**1**); R = H, R′ = ^{i}Pr (**2**); R = CH_2OPh, R′ = ^{i}Pr (**3**)) in the ROP of *rac*-LA, where HOCHRCH$_2$NHR' mimics the main skeleton of β-blockers[16] (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 $[Me_2Ga(O,X)]_2$ 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). Noteworthily, 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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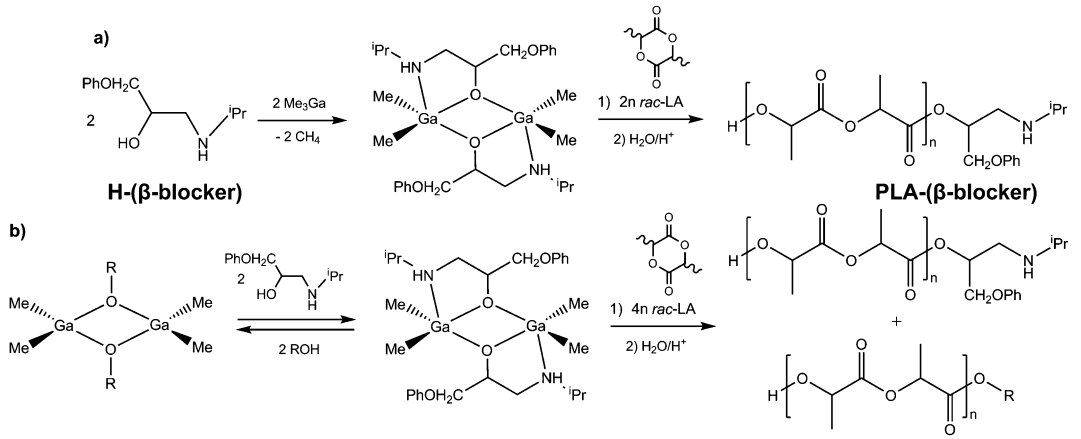
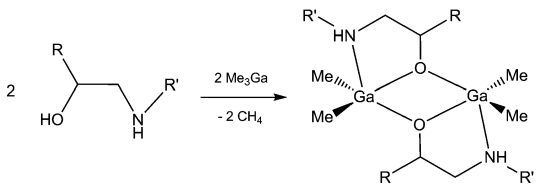
† Electronic supplementary information (ESI) available: Crystallographic data of **1–3**; ^{1}H and ^{13}C NMR for **1–3**; details of *rac*-LA polymerisation, including ^{1}H and ^{13}C NMR and MALDI-TOF spectra of PLA. CCDC 1569393–1569395. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7nj03089d



Scheme 1 Synthesis of PLA-(β-blocker) conjugates with $[Me_2Ga(\beta\text{-blocker})]_2$ 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.



H-**A** R = H; R' = Me
H-**B** R = H; R' = ^{i}Pr
H-**C** R = CH_2OPh; R' = ^{i}Pr

1 R = H; R' = Me
2 R = H; R' = ^{i}Pr
3 R = CH_2OPh; R' = ^{i}Pr

Scheme 2 Synthesis of $[Me_2Ga(\mu\text{-}OCHRCH_2NHR')]_2$ (**1–3**).

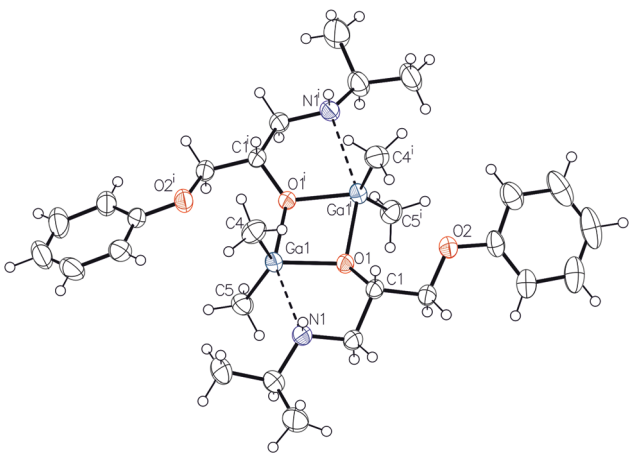


Fig. 1 Molecular structure of **3** with ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond length (Å) and angles (deg): Ga(1)–O(1) 1.9452(11), Ga(1)–O(1)^i 2.0717(11), Ga(1)–C(4) 1.9648(18), Ga(1)–C(5) 1.9578(18), Ga(1)–N(1) 2.5478(14), N(1)–Ga(1)–O(1)^i 152.51(5), O(1)–Ga(1)–O(1)^i 77.12(5), Ga(1)–O1–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 $[Me_2Ga(\mu\text{-}OCH(Me)CO_2Me)]_2$ 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 $[Me_2Ga(\beta\text{-blocker})]_2$, 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 $[R_2Ga(\beta\text{-blocker})]_2$, 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 $[Me_2Ga(\mu\text{-}OCH(Me)CO_2Me)]_2$,[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 $OCH_2CH_2NH^iPr$, 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 HO–PLA–$OCH_2CH_2NH^iPr$, 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_r of 0.85 (Table 1, entries 3 and 4), as well as isoselective polymerisation using **2**/DBU (P_r = 0.22, Table 1, entry 5), indicated the facile modification of the tacticity of PLA, in the range of P_r between 0.22 and 0.85, for HO–PLA–$OCH_2CH_2NH^iPr$ and potentially HO–PLA–(β-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 $[R_2Ga(\beta\text{-blocker})]_2$ catalytic centres using the immortal ring-opening polymerisation (iROP) of lactide with $[Me_2Ga(\mu\text{-OR})]_2$/H-(β-blocker) catalytic systems (Scheme 1b).

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

No.	Cat.	T [°C]	Time [h]	Conv. [%]	10^{-3} M_n[b]	10^{-3} M_n[c]	$Đ$	P_r[d]	P_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**/piridine(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 CH_2Cl_2. [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 CH_2Cl_2, using conventional calibration. [d] Probability of *racemo* linkages in PLA calculated on the basis of homonuclear decoupled ^{1}H NMR spectra according to Chamberlain *et al.*[18] [e] Probability of *racemo* linkages in PLA calculated on the basis of ^{13}C 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] $[Me_2Ga(\mu\text{-OR})]_2$/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 $[Me_2Ga(\mu\text{-OR})]_2$/H-(β-blocker), we focused on $[Me_2Ga(\mu\text{-OCH(Me)CO}_2\text{Me})]_2$/(H-**A**) or (H-**B**) as well as $[Me_2Ga(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2$/(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 $[Me_2Ga(\mu\text{-OCH(Me)CO}_2\text{Me})]_2$/(H-**A**) or (H-**B**) as well as $[Me_2Ga(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2$/(H-**B**), (H-**C**) or H-atenolol to the presence of both $[Me_2Ga(\mu\text{-OCH(Me)CO}_2\text{Me})]_2$ and $[Me_2Ga(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2$ complexes, as well as $[Me_2Ga(\mu\text{-}\mathbf{A})]_2$ (**1**), $[Me_2Ga(\mu\text{-}\mathbf{B})]_2$ (**2**), $[Me_2Ga(\mu\text{-}\mathbf{C})]_2$ (**3**) or $[Me_2Ga(\mu\text{-atenolol})]_2$ 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).

$[Me_2Ga(\mu\text{-OCH(Me)CO}_2\text{Me})]_2$/(H-**B**) polymerised *rac*-LA at 40 °C and 70 °C, which led to the formation of both HO–PLA-(μ-OCH(Me)CO_2Me) 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)CO_2Me 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)CO_2Me) (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)CO_2Me) and HO–PLA-(**A**–**B**) using $[Me_2Ga(\mu\text{-OCH(Me)CO}_2\text{Me})]_2$/(H-**A**) (see Fig. S69 and S70, ESI†). On the other hand, the polymerisation of *rac*-LA with $[Me_2Ga(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2$/(H-**B**) led to the formation of essentially only HO–PLA-**B** chains indicating essentially no insertion of *rac*-LA into the Ga–$O_{aryloxide}$ bond of $[Me_2Ga(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2$ under the investigated conditions. The activity of $[Me_2Ga(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2$/(H-**B**) was almost the same as in the case of $[Me_2Ga(\mu\text{-OCH(Me)CO}_2\text{Me})]_2$/(H-**B**) which was in line with the formation of $[Me_2Ga(\mu\text{-}\mathbf{B})]_2$ species. The formation of dimeric catalytic species allowed for the heteroselective polymerisation of *rac*-LA using both $[Me_2Ga(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2$/(H-**B**)/pyridines and $[Me_2Ga(\mu\text{-OCH(Me)CO}_2\text{Me})]_2$/(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 $[Me_2Ga(\mu\text{-OCH(Me)CO}_2\text{Me})]_2$/2ROH (*rac*-LA/Ga = 50) (I), $[Me_2Ga(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2$/2ROH (*rac*-LA/Ga = 25) (II), and $[Me_2Ga(\mu\text{-OC}_6\text{H}_4\text{OMe})]_2$/2ROH (*rac*-LA/Ga = 100) (III) in toluene

No.	ROH/LB	T [°C]	Time [h]	Conv. [%]	10^{-3} M_n[b]	10^{-3} M_n[c]	$Đ$	P_r[d]	P_r[e]
1	H-**B**(I)	70	24	90	3.2	4.4	1.20	0.50	—
2	H-**B**(I)	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 CH_2Cl_2, using conventional calibration. [d] Probability of *racemo* linkages in PLA calculated on the basis of homonuclear decoupled ^{1}H NMR spectra according to Chamberlain *et al.*[18] [e] Probability of *racemo* linkages in PLA calculated on the basis of ^{13}C 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.

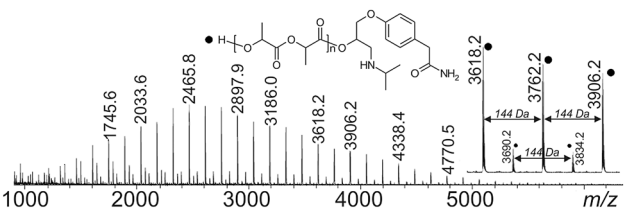


Fig. 2 MALDI-TOF spectrum of PLA obtained with $[Me_2Ga(\mu\text{-}OC_6H_4OMe)]_2$/H-atenolol (1 : 2) at 70 °C (Table 2, entry 11). The distribution refers to PLA with OH and atenolol end groups, with K^+.

$[Me_2Ga(\mu\text{-}OC_6H_4OMe)]_2$/(H-**B**), without the addition of an external Lewis base, which could be associated with the interaction of dialkylgallium alkoxides with HOC_6H_4OMe, released upon formation of $[Me_2Ga(\mu\text{-}\mathbf{B})]_2$. 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 $[Me_2Ga(\mu\text{-}OR)]_2$/R'OH/LB catalytic systems. Although $[Me_2Ga(\mu\text{-}OCH(Me)CO_2Me)]_2$/(H-**B**)/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 $[Me_2Ga(\mu\text{-}OC_6H_4OMe)]_2$/(H-**C**) (Table 2, entries 9 and 10) as well as $[Me_2Ga(\mu\text{-}OC_6H_4OMe)]_2$/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 $[R_2Ga(\mu\text{-}\beta\text{-blocker})]_2$ 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 $[R_2Ga(\mu\text{-}OR)]_2$/H-(β-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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