Synthesis of Functional and Boronic Acid-Containing Aliphatic Polyesters via Suzuki Coupling

Journal:	*ChemComm*
Manuscript ID	CC-COM-03-2019-001975.R1
Article Type:	Communication

COMMUNICATION

Synthesis of Functional and Boronic Acid-Containing Aliphatic Polyesters *via* Suzuki Coupling

Tomohiro Kubo, Georg M. Scheutz, Tristin S. Latty, Brent S. Sumerlin*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Imparting additional functionalities along the side chains of polyesters remains a challenge due to the laborious nature of monomer synthesis and limited polymer functionalization methods for polyesters. To address this challenge, a carbon-carbon bond forming reaction was studied to introduce pendent functional groups in polylactides. This functionalization approach was applied for preparing boronic acid-containing polylactides, an unexplored class of polymers.

Polyester-based commercial products have been widely utilized in various industries such as packaging and textiles. Additionally, some polyesters have been used in the biomedical arena due to their biocompatibility and degradability.[1,2] For example, the first synthetic absorbable suture was developed using polyglycolide.[3] Recent collective efforts in the field of polymeric nanomedicine have expanded the role of polyesters.[4] Polylactides (PLAs) are a particularly attractive class of polyesters due to their well-defined properties such as hydrophobicity, biocompatibility, and their ease of preparation. For example, drugs and other therapeutics have been covalently conjugated with PLAs.[5–8] This conjugation strategy, known as the Ringsdorf model, can provide high drug loading and circumvent solubility and stability issues.[9–12] However, one of the major hurdles of such an approach is synthesizing precursor polymers with synthetic handles for such conjugations.

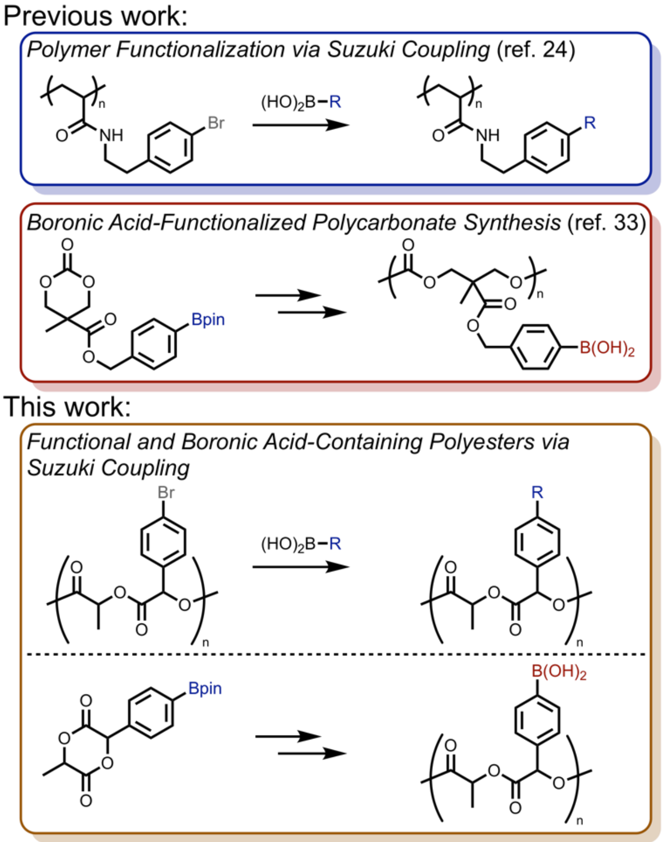
One approach to prepare side-chain functional PLAs is through incorporating reactive functional groups in the monomer structure.[13,14] Various syntheses of lactone monomers with a handle for functionalization (*e.g.*, hydroxyl, carboxyl alkene, alkyne, epoxy) have been reported.[15–21] Limitations for preparing functional PLAs include the laborious monomer synthesis and the necessity to protect certain functional groups during polymerization. Furthermore, reaction conditions that are too harsh for the ester linkages of the polymer backbone cannot be used for post-polymerization modification, thus limiting the scope of available chemical transformations.

In the pursuit for efficient reactions amenable for synthesizing functional PLAs, Suzuki coupling, a metal-catalyzed carbon-carbon bond formation reaction, was deemed to be a promising candidate. Suzuki coupling is generally highly efficient, demonstrates functional group tolerance, and proceeds under mild reaction conditions.[22] Importantly, the two coupling partners, aryl halides and boronic esters, do not interfere during ring-opening transesterification polymerization (ROTEP), a common polymerization technique to synthesize PLAs.[23] In 2017, Magenau and coworkers demonstrated the post-polymerization modification of aryl bromide-containing polyacrylamides *via* Suzuki coupling (Scheme 1).[24] The reaction featured high efficiency for a variety of boronic acid substrates under mild conditions. We envisioned that this coupling modification strategy offers a useful route to modify PLAs in a highly efficient and modular manner.

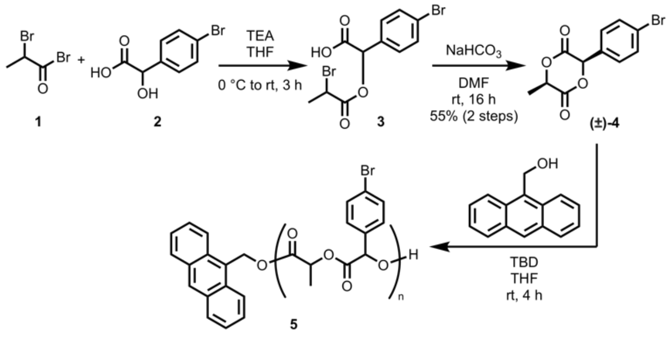
In this study, we demonstrated the synthesis of functional PLA derivatives employing a Suzuki coupling strategy. A polyester with pendent aryl bromide moieties was prepared by a two-step monomer synthesis followed by ROTEP. The efficiency and functional group tolerance of the Suzuki coupling between the aryl bromide polyester with various boronic acid substrates were examined. Furthermore, this synthetic

---

George & Josephine Butler Polymer Research Laboratory, Center for Macromolecular Science & Engineering, Department of Chemistry, University of Florida, PO Box 117200, Gainesville, Florida 32611, United States
Email: sumerlin@chem.ufl.edu
Electronic Supplementary Information (ESI) available: Experimental details, additional figures, and characterization data. See DOI: 10.1039/x0xx00000x



Scheme 1 Approaches to functionalize polymers *via* Suzuki coupling and to synthesize boronic acid-functionalized degradable polymers



Scheme 2 Synthesis and polymerization of lactone monomer with aryl bromide functionality (**4**)

approach was applied to prepare pendent boronic acid-containing PLAs.

The target lactone monomer **4** containing an aryl bromide functionality was synthesized according to Scheme 2. 2-Bromopropionyl bromide (**1**) and 4-bromomandelic acid (**2**) were combined in the presence of triethylamine (TEA) to give carboxylic acid **3**. After a standard aqueous work-up, the purity of product **3** was determined to be ~70% as measured by ^{1}H NMR spectroscopy, with unreacted **2** and the hydrolyzed product of **1** (*i.e.*, 2-bromopropionic acid) as byproducts. Since no detrimental cross-reactivity of these byproducts under the reaction conditions of the next step was observed, the product mixture of **3** was used without further purification. To synthesize lactone **4**, a solution of **3** in DMF was slowly added into a solution of $NaHCO_3$ in DMF. The slow addition method favored the formation of the cyclic product **4** by an intramolecular cyclization reaction. The cyclized monomer **4** could be obtained in good purity and satisfactory yield (55% in two steps) without chromatographic purification after a simple work-up. Furthermore, this reaction sequence was easily scaled up to a multi-gram scale, demonstrating the practicality of this method to access functional lactones.

The polymerization of monomer **4** was performed to prepare polyesters with pendent aryl bromide groups (**5**) (Scheme 2). 9-Anthracenemethanol, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), and acetic acid were used as initiator, catalyst, and quenching agent, respectively. The comparison of the ^{1}H NMR integration areas of the PLA backbone methine protons (H_c and H_d) with the signals from chain-end anthracene groups (H_a) revealed a ratio of approximately 100:1 of repeat unit to initiator, indicating efficient initiation by 9-anthracenemethanol (Figure 1). Changing the ratio of monomer to initiator allowed for controlling the molecular weight of polyester **5** (Figure S1). Size-exclusion chromatography (SEC) analysis indicated a monomodal and symmetric peak for the synthesized polymers with narrow dispersity (M_n = 7,300 g/mol, M_w/M_n = 1.11, Figure S2), suggesting that successful polymerization of functional lactone monomer **4** was achieved to afford well-defined PLAs that can undergo downstream functionalization.

Post-polymerization modification of the aryl bromide-containing PLA was performed *via* Suzuki coupling (Scheme 3). Polyester **5**, a boronic acid containing the moiety to be appended to the polymer, catalyst, and base were charged in a vial and purged with argon. After the addition of solvent, the solution was warmed to 50 ˚C to promote the coupling reaction. The product was obtained by filtering the reaction mixture and precipitating the resultant solution into methanol. When 4-vinylphenylboronic acid was used to form polymer **6**, ^{1}H NMR analysis revealed >95% conversion to the coupled product (Figure 2, Figure S3). Specifically, the integration values of the vinyl protons of the functionalized product **6** ($H_{b'}$, $H_{c'}$, and $H_{e'}$) were compared with the integration values of the backbone

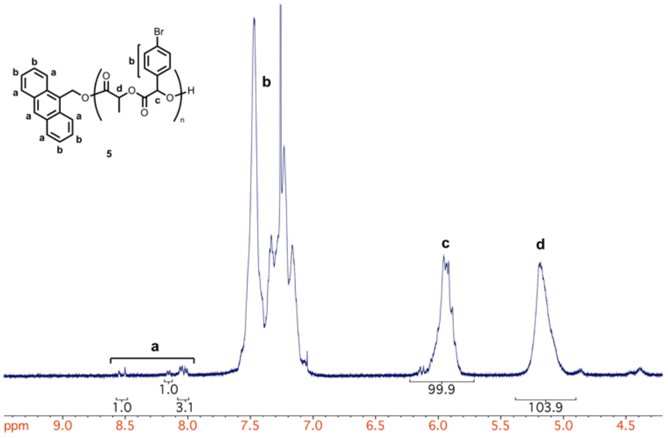
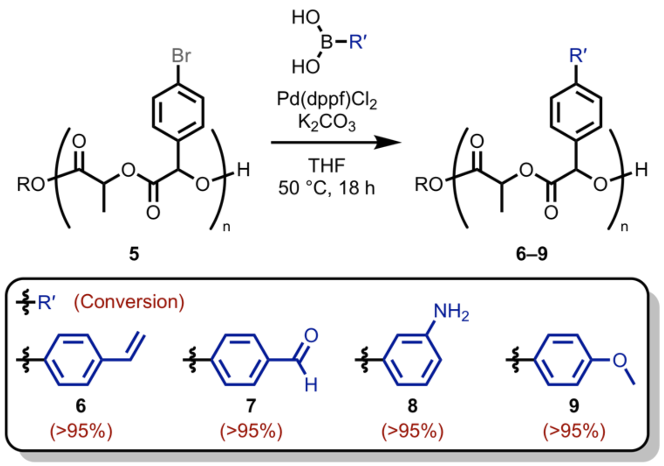


Fig. 1 ^{1}H NMR spectrum of **5**, indicating the initiation of each polymer chain by 9-anthracenemethanol.



Scheme 3 Post-polymerization modification of polyester **5** *via* Suzuki coupling

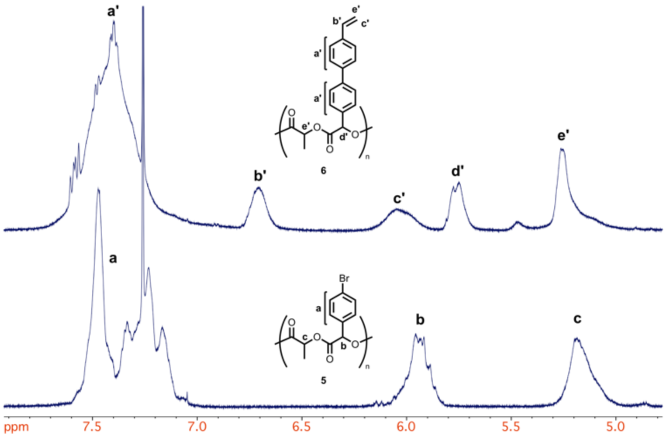
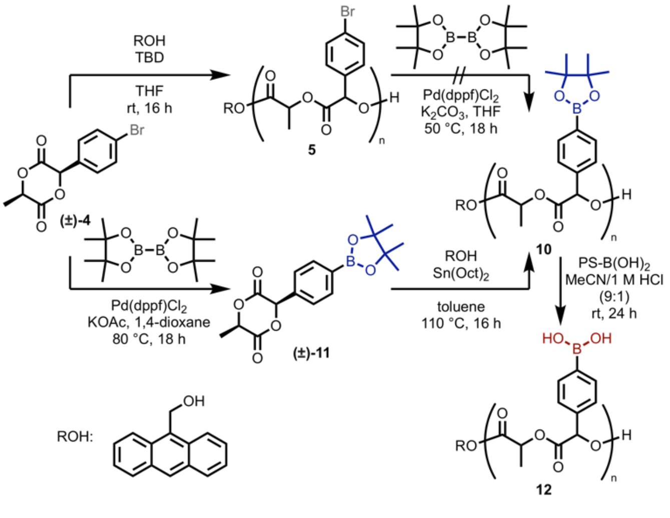


Fig. 2 ^{1}H NMR spectra of **5** (bottom) and **6** (top), confirming successful polymer modification.

methine protons (H$_{d'}$). SEC analysis of product **6** showed a monomodal and symmetric peak, suggesting the absence of chain-chain coupling events (Figure S4). Major advantages of this modification approach *via* Suzuki coupling include the functional group tolerance and the applicability of a wide variety of commercially available boronic acid substrates. High conversions of functionalization were accomplished with aldehyde, amine, and methoxy-containing phenylboronic acids to afford polymers **7**, **8**, and **9**, respectively. The success of each functionalization was indicated by ^{1}H NMR spectroscopy and SEC analysis (Figure S5–S9). Therefore, the incorporation of functionalities that are not compatible with ROTEP was achieved through efficient post-polymerization modification without necessitating any protecting groups. These pendent functional groups can be used to install various scaffolds *via* downstream functionalization. This functional group tolerance and modularity, coupled with the high efficiency, demonstrates the power of this Suzuki coupling-based post-polymerization modification strategy.

To further expand the scope of this approach, we employed Suzuki coupling for the generation of PLAs with pendent boronic acid groups. Boronic acid-containing polymers are an important class of polymers for biomedical applications.[25–27] Due to their ability to participate in dynamic-covalent bonding with diols such as sugars, numerous investigations on this class of macromolecular materials have been performed.[28–32] Although several promising ways to synthesize boronic acid-containing degradable polymers such as polycarbonates have been established and used,[33–36] access to well-defined polyesters with boronic acid functionalities remains unaccomplished. Herein, we present the use of Suzuki coupling as a facile and effective approach to address this need.

To achieve the straightforward synthesis of a boronic acid-containing PLA, bis(pinacolato)diboron was used for the modification of **5** *via* Suzuki coupling to furnish the pinacol-protected boronic acid-containing polyester **10** (Scheme 4). However, the conversion of this functionalization was low, possibly due to the steric crowding along the polymer backbone caused by the bulky pinacol protecting group. An alternative approach to synthesize **10** was developed through the direct polymerization of pinacol-protected lactone monomer **11**, which was synthesized *via* Suzuki coupling of **4** with bis(pinacolato)diboron. Polymerization of **11** with Sn(Oct)$_2$ was performed in toluene at 110 °C.[37] SEC analysis indicated successful polymerization, as judged by a monomodal and symmetric polymer signal (M_n = 6,700 g/mol, M_w/M_n = 1.22, Figure S10). The removal of pinacol groups was performed using polymer-bound boronic acids to furnish the polyester with boronic acid side chains **12**. The conversion of the removal of pinacol group was ~90% as determined by ^{1}H NMR analysis that showed the reduction of the methyl protons of pinacol groups (Figure S11). To examine whether polymer degradation occurred during the deprotection reaction, polymer **5** was subjected to the same reaction conditions established for the deprotection of **10**.[38] No significant hydrolysis was observed by SEC analysis after 96 h of reaction time (Figure S12). Therefore, the straightforward synthesis of boronic acid-containing PLAs was accomplished by the combination of Suzuki coupling and post-polymerization modification.



Scheme 4 Synthesis of boronic acid-containing polyesters

In conclusion, we demonstrated that Suzuki coupling is an efficient and modular reaction for preparing functional PLA derivatives. The functional group tolerance of Suzuki coupling enabled the incorporation of alkene, amine, aldehyde, and methoxy functionalities in the side chains of PLAs through post-polymerization modification without protecting groups. Furthermore, Suzuki coupling was employed to introduce a boronic ester functionality in a lactone monomer that enabled the synthesis of polyesters with pendent boronic acids.

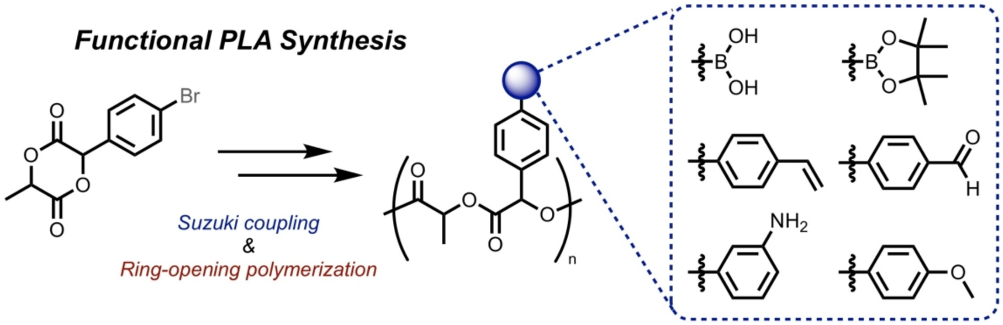
This material was supported, in part, by the Citrus Research Board of California (5300-171) and is based upon work supported by the National Science Foundation (DMR-1606410).

Conflicts of interest

There are no conflicts to declare.

Notes and references

1. A.-C. Albertsson and I. K. Varma, *Biomacromolecules*, 2003, **4**, 1466–1486.
2. R. P. Brannigan and A. P. Dove, *Biomater. Sci.*, 2017, **5**, 9–21.
3. E. J. Frazza and E. E. Schmitt, *J. Biomed. Mater. Res.*, 1971, **5**, 43–58.
4. R. Tong, N. P. Gabrielson, T. M. Fan and J. Cheng, *Curr. Opin. Solid State Mater. Sci.*, 2012, **16**, 323–332.
5. N. Kolishetti, S. Dhar, P. M. Valencia, L. Q. Lin, R. Karnik, S. J. Lippard, R. Langer and O. C. Farokhzad, *Proc. Natl. Acad. Sci.*, 2010, **107**, 17939–17944.
6. Y. Yu, J. Zou, L. Yu, W. Ji, Y. Li, W.-C. Law and C. Cheng, *Macromolecules*, 2011, **44**, 4793–4800.
7. D. E. Borchmann, N. ten Brummelhuis and M. Weck, *Macromolecules*, 2013, **46**, 4426–4431.
8. D. E. Borchmann, R. Tarallo, S. Avendano, A. Falanga, T. P. Carberry, S. Galdiero and M. Weck, *Macromolecules*, 2015, **48**, 942–949.
9. H. Ringsdorf, *J. Polym. Sci.: Polym. Symp.*, 1975, **51**, 135–153.
10. N. Larson and H. Ghandehari, *Chem. Mater.*, 2012, **24**, 840–853.
11. B. S. Tucker, S. G. Getchell, M. R. Hill and B. S. Sumerlin, *Polym. Chem.*, 2015, **6**, 4258–4263.
12. J. A. Alfurhood, H. Sun, C. P. Kabb, B. S. Tucker, J. H. Matthews, H. Luesch and B. S. Sumerlin, *Polym. Chem.*, 2017, **8**, 4983–4987.
13. R. Tong, *Ind. Eng. Chem. Res.*, 2017, **56**, 4207–4219.
14. G. Becker and F. R. Wurm, *Chem. Soc. Rev.*, 2018, **47**, 7739–7782.
15. W. W. Gerhardt, D. E. Noga, K. I. Hardcastle, A. J. García, D. M. Collard and M. Weck, *Biomacromolecules*, 2006, **7**, 1735–1742.
16. M. Leemhuis, C. F. van Nostrum, J. A. W. Kruijtzer, Z. Y. Zhong, M. R. ten Breteler, P. J. Dijkstra, J. Feijen and W. E. Hennink, *Macromolecules*, 2006, **39**, 3500–3508.
17. F. Jing and M. A. Hillmyer, *J. Am. Chem. Soc.*, 2008, **130**, 13826–13827.
18. M. Rubinshtein, C. R. James, J. L. Young, Y. J. Ma, Y. Kobayashi, N. C. Gianneschi and J. Yang, *Org. Lett.*, 2010, **12**, 3560–3563.
19. I. A. Barker, D. J. Hall, C. F. Hansell, F. E. Du Prez, R. K. O'Reilly and A. P. Dove, *Macromol. Rapid Commun.*, 2011, **32**, 1362–1366.
20. J. A. Castillo, D. E. Borchmann, A. Y. Cheng, Y. Wang, C. Hu, A. J. García and M. Weck, *Macromolecules*, 2012, **45**, 62–69.
21. K. R. Delle Chiaie, L. M. Yablon, A. B. Biernesser, G. R. Michalowski, A. W. Sudyn and J. A. Byers, *Polym. Chem.*, 2016, **7**, 4675–4681.
22. N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483.
23. M. A. Hillmyer and W. B. Tolman, *Acc. Chem. Res.*, 2014, **47**, 2390–2396.
24. D. H. Howe, R. M. McDaniel and A. J. D. Magenau, *Macromolecules*, 2017, **50**, 8010–8018.
25. J. N. Cambre and B. S. Sumerlin, *Polymer*, 2011, **52**, 4631–4643.
26. W. L. A. Brooks and B. S. Sumerlin, *Chem. Rev.*, 2016, **116**, 1375–1397.
27. G. Vancoillie and R. Hoogenboom, *Polym. Chem.*, 2016, **7**, 5484–5495.
28. J. N. Cambre, D. Roy, S. R. Gondi and B. S. Sumerlin, *J. Am. Chem. Soc.*, 2007, **129**, 10348–10349.
29. A. P. Bapat, D. Roy, J. G. Ray, D. A. Savin and B. S. Sumerlin, *J. Am. Chem. Soc.*, 2011, **133**, 19832–19838.
30. J. J. Cash, T. Kubo, A. P. Bapat and B. S. Sumerlin, *Macromolecules*, 2015, **48**, 2098–2106.
31. J. J. Cash, T. Kubo, D. J. Dobbins and B. S. Sumerlin, *Polym. Chem.*, 2018, **9**, 2011–2020.
32. W. L. A. Brooks, C. C. Deng and B. S. Sumerlin, *ACS Omega*, 2018, **3**, 17863–17870.
33. Y. E. Aguirre-Chagala, J. L. Santos, B. A. Aguilar-Castillo and M. Herrera-Alonso, *ACS Macro Lett.*, 2014, **3**, 353–358.
34. Y. E. Aguirre-Chagala, J. L. Santos, Y. Huang and M. Herrera-Alonso, *ACS Macro Lett.*, 2014, **3**, 1249–1253.
35. N. H. Park, Z. X. Voo, Y. Y. Yang and J. L. Hedrick, *ACS Macro Lett.*, 2017, **6**, 252–256.
36. Y. Wang, X. Ke, Z. X. Voo, S. S. L. Yap, C. Yang, S. Gao, S. Liu, S. Venkataraman, S. A. O. Obuobi, J. S. Khara, Y. Y. Yang and P. L. R. Ee, *Acta Biomater.*, 2016, **46**, 211–220.
37. Organocatalytic ROTEP was unsuccessful under the reaction conditions we explored.
38. Due to the incompatibility of **12** with the SEC system, polymer **5** was chosen as a model compound.



739x238mm (72 x 72 DPI)