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# Iterative assembly-line synthesis of polypropionates with full stereocontrol

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## ABSTRACT:

The polypropionate motif is ubiquitous, being characteristic of the most important family of natural products for human health, the polyketides. Numerous strategies have been devised to construct these molecules with high stereocontrol, but certain stereoisomers remain challenging to prepare. We now describe the development of an iterative assembly-line strategy for the construction of polypropionates. An assembly line strategy for the synthesis of deoxypolypropionates has already been described. However, the introduction of carbinol units required the development of new building blocks and new reaction conditions. This has been achieved by the use of enantioenriched lithiated  $\alpha$ -chlorosilanes [1-((2'-lithiochloromethyldimethylsilyl)-methyl)-2-(methoxymethyl)-pyrrolidine], thus enabling the programmed synthesis of polypropionates in a fully stereocontrolled manner, including the stereochemically challenging *anti-anti* isomers. The versatility of the approach is exemplified in its extension to the synthesis of 1,3-related polyols. The methodology now allows access to a much wider family of polyketide natural products with stereochemistry being dialled in at will.

## INTRODUCTION

Polypropionates are common structural motifs in what is arguably the most important family of natural products, the polyketides.<sup>1-3</sup> They have been extensively mined, investigated and exploited as chemotherapeutic agents for the promotion of human health.<sup>4-6</sup> Polyketide-derived drugs include antibiotics, cancer chemotherapeutics, immunosuppressants, cholesterol-lowering agents, and antifungals.<sup>7-10</sup> Their structural and stereochemical complexity, coupled with their important biological activity, have made them attractive targets for over half a century. This intense interest has resulted in the development of important types of methodology for the stereocontrolled synthesis of polypropionates<sup>11-13</sup> including Evans' aldol,<sup>14</sup> and more recently, Krische's catalytic crotylation reactions.<sup>15-16</sup> Indeed, the synthesis of highly complex polyketide

natural products using Evans' methodology has been one of the major achievements in organic synthesis of the 20<sup>th</sup> century. However, this methodology often involved numerous redox processes, which can now be avoided using Krische's 21<sup>st</sup> century catalytic crotylations, providing a step change in efficiency. Powerful though these methods are, and despite extensive investigations into the asymmetric synthesis of acyclic molecules, certain structural motifs, for example, the *anti-anti* isomers, remain difficult to make with high diastereoselectivity.<sup>17-18</sup>

In recent years, we have developed iterative synthetic strategies that allow the synthesis of acyclic molecules containing multiple contiguous stereogenic centers through reagent-controlled homologation of boronic esters. This process enabled the conversion of a simple boronic ester into a molecule bearing 10 contiguous methyl substituents with full stereocontrol in an effectively "one-pot" process, without purification of intermediates.<sup>19</sup> Different stereoisomers could be obtained simply by modifying the sequence of chiral reagents added. Moreover, the power of this approach was demonstrated in two short syntheses of polydeoxypropionate natural products, (+)-kalkitoxin and (+)-hydroxyphthioceranic acid (Figure 1a).<sup>20</sup> The core of these complex molecules was constructed by iterative homologations of boronic esters by using chiral lithiated benzoate esters (*S/R*)-**1** and chloromethyl lithium **2**<sup>21</sup> as key building blocks. As with Krische's and also Negishi's ZACA methodology,<sup>22-23</sup> no redox processes or functional-group interconversions were required between iterations, enhancing the efficiency of the process. However, polydeoxypropionates represent only a small subset of the vast family of polyketide natural products, the majority containing polypropionates, that is, carbon chains with alternating methyl- and hydroxyl groups. Thus, in order to extend our iterative methodology to the much larger class of polyketide natural products,<sup>24-26</sup> new carbenoid building blocks bearing oxygen functionality were required. However, even if a carbenoid could be identified bearing a protected oxygen, boronic esters possessing  $\beta$ -ethers present problems with further homologation because the boronate complex is prone to undergo  $\beta$ -elimination rather than the desired 1,2-migration (Figure 2a).<sup>27-28</sup> To avoid this competing reaction, we considered masking the oxygen functionality as a silyl group. The stereoretentive oxidative cleavage of silicon-carbon bonds, by

using reactions conditions developed by Tamao and Fleming, and variants thereof, is well described.<sup>29</sup> Using this approach, we now describe our success in developing an iterative assembly-line synthesis strategy to encompass the synthesis of the much larger class of polyketide natural products, the polypropionates (Figure 1b). By alternating the addition of a novel class of chiral  $\alpha$ -silylchloromethylolithium reagents (*S/R*)-**3** with lithiated benzoate esters (*S/R*)-**1** multiple times, simple boronic esters have been transformed into carbon chains bearing alternating hydroxyl and methyl groups. Furthermore, because each iterative homologation shows very high levels of reagent control, and is blind to pre-existing stereogenic centers present in the boronic ester, this methodology enables stereochemistry to be dialled in at will with essentially full control.

## RESULTS AND DISCUSSION

We began our studies by identifying a suitable organosilyl reagent for the key stereocontrolled lithiation–borylation reactions. However, like a phenyl group, the silyl group renders an adjacent carbanion configurationally unstable even at low temperature thereby making control of stereochemistry especially challenging.<sup>30–32</sup> Indeed, using a silyl-substituted lithiated carbamate generated by the deprotonation of TMSCH<sub>2</sub>OCb (Cb = *N,N*-diisopropylcarbamoyl) with *s*-BuLi in the presence of (–)-sparteine in a lithiation–borylation reaction, the homologated boronic ester was obtained, but in racemic form.<sup>33</sup> Moreover, Blakemore and co-workers recently reported that  $\alpha$ -silylmethylolithium carbenoid **4**, generated in the presence chiral isopropyl-substituted bis(oxazoline) (BOX) ligand, reacted with phenethyl pinacol boronic ester **6a** to give  $\alpha$ -silylalkyl boronic ester **7** in 69% yield but with only moderate enantioselectivity (57% ee, Figure 2b).<sup>34</sup> In contrast, related reactions of benzylic organolithiums in the presence of the same chiral bis(oxazoline) ligand have been shown to give high enantioselectivity,<sup>35–36</sup> showing that phenyl- and silyl-stabilized carbanions behave quite differently. We therefore considered an alternative approach (Figure 2c) based on the work of Chan and co-workers. They reported that lithiated benzylsilane **10** bearing a tethered chiral (methoxymethyl)-pyrrolidinomethyl moiety could be trapped with alkyl halides in good yield and high diastereoselectivity (Figure 2d).<sup>37</sup> In detailed

mechanistic studies, Strohmann showed that the alkylation of lithiated benzyloxy silanes **10** occurs with inversion of configuration.<sup>38-39</sup> We therefore re-designed the  $\alpha$ -silyl benzoate ester, as used by Blakemore, to incorporate the chiral (methoxymethyl)pyrrolidinomethyl side-arm. Subjecting the new organosilyl reagent **5** to the lithiation–borylation reaction with a primary alkylboronic ester smoothly provided the desired product **8a** in high yield (80%) with high diastereoselectivity (Figure 2c). Although the reaction worked well with a simple primary boronic ester, we observed no conversion with the more hindered *i*-propylboronic ester **6b** under the same reaction conditions. We therefore explored the use of additives to promote the reaction<sup>40</sup> (see Supplementary Information p. 20 for full details) and found that using  $\text{Mg}(\text{ClO}_4)_2$  in  $\text{CF}_3\text{CH}_2\text{OH}$  gave the product **8b** in high yield and high d.r. The reaction was monitored by ReactIR, revealing that both the lithiation of the  $\alpha$ -silylmethyl benzoate ester and its trapping by the boronic ester occurred essentially instantaneously at  $-78\text{ }^\circ\text{C}$  ( $<2$  min). After addition of  $\text{Mg}(\text{ClO}_4)_2$  in  $\text{CF}_3\text{CH}_2\text{OH}$  at  $-78\text{ }^\circ\text{C}$ , rapid 1,2-migration ensued to form **8b** (see Supplementary Information p. 38–39 for details). The absolute configuration and diastereomeric purity of  $\alpha$ -silylalkyl boronic ester (*S,S*)-**8a** was determined by HPLC analysis of the corresponding chiral allylic alcohol, obtained by Zweifel olefination<sup>41</sup> followed by Tamao oxidation<sup>42</sup> of the resulting allyl silane (see Supplementary Information p. 34–37 for details). Assuming that lithiated  $\alpha$ -silylmethyl benzoate ester **5** was generated with the same sense of diastereoselectivity as that confirmed for Chan’s  $\alpha$ -benzyloxy silane **10**, its trapping with the boronic ester must have taken place with retention of configuration, thus contrasting with the invertive trapping of organolithium **10** with  $\text{MeI}$ .<sup>38</sup> We believe that the more pronounced tetrahedral nature of organolithium **5** together with its potential to complex with the oxygen atoms of the boronic ester, thereby directing the reagent to the same face as the lithium atom, accounts for the origin of the retention of configuration observed.<sup>43</sup>

In order to promote the 1,2-migration of the intermediate boronate complex **9** and avoid the use of  $\text{Mg}(\text{ClO}_4)_2$  we considered replacing the benzoate ester group (OTIB group) with a better leaving group ( $\text{Cl}^-$ ). Indeed, one of the benefits of using the tethered chiral auxiliary approach is that small

groups with high leaving-group ability (such as Cl<sup>-</sup>) can be incorporated, the directing and stabilising attributes of the benzoate ester group, which are required for sparteine-mediated generation of lithium carbenoids, now being excess to requirements. Thus, the ammonium salt of  $\alpha$ -chloromethyl silane **12**, was prepared and deprotonated using 2.0 equiv. of *s*-BuLi in Et<sub>2</sub>O at -78 °C, followed by treatment with phenylethyl boronic ester **6a** to give the homologated  $\alpha$ -silylalkyl boronic ester (**8a**, Table 1) in excellent yield (92%) and very high d.r. In the case of *i*-propylboronic ester **6b**, 1,2-metallate rearrangement occurred while warming to room temperature without the need for additional Lewis acids, thus providing the corresponding product (**8b**, Table 1) in high yield with complete stereocontrol. As  $\alpha$ -chloromethyl silane **12** was clearly the superior reagent, compared to the corresponding benzoate, we tested its scope with a range of boronic esters (Table 1). In general, the homologations of enantioenriched boronic esters with lithiated  $\alpha$ -chloromethyl silane **3** proceeded smoothly to provide the corresponding products **8** in high yields with excellent levels of diastereoselectivity. Despite, the limitations in functional-group tolerance that are normally associated with reactions involving organolithiums, for example, the incompatibility of electrophilic carbonyl groups, OH and NH groups, and carbon-based acids (terminal alkynes and carbonyl groups with  $\alpha$ -hydrogen atoms), a range of functional groups were tolerated, including alkenes **8c**, protected alcohols **8d**, *tert*-butyl esters **8j**, and azides **8k**. The tolerance of sterically hindered esters and azides, which can react with organolithiums, is attributed to the rapid trapping of the organolithium with the desired boronic ester functional group, as confirmed by the aforementioned ReactIR studies. Additionally, heterocycle-containing substrates, for example, thiophene-, pyridine- and Boc-protected pyrrolidine-containing boronic esters, could be homologated to give the corresponding products, **8f-h**, respectively, in good yield and high levels of diastereoselectivity. To explore possible matched and mis-matched effects, the two enantiomers of the  $\alpha$ -chloromethyl silane (*S,S/R,R*)-**3** were reacted with three different chiral boronic esters. In all cases the products were obtained in good yield (Table 1, **8i-k**) and in only one case was a slight mis-matched effect observed (Table 1, *syn*-**8h** vs. *anti*-**8h**). These results show that reagent control dominates over substrate control,

an essential feature to its broader synthetic utility. The products contain rich functionality as the C–B bond in the resulting geminal borosilanes **8** can be selectively functionalized over C–Si bonds through a wide array of stereospecific transformations<sup>44</sup>, including Zweifel olefination,<sup>41</sup> arylation,<sup>45</sup> and alkynylation<sup>46</sup> giving access to a valuable class of chiral organosilanes.

Having demonstrated the scope of the reaction with different boronic esters, we then turned our attention to developing a protocol for iterative homologation. The building blocks used as the key repeat units were 1) chiral lithiated  $\alpha$ -chloromethyl silanes (*S,S*)-**3** and (*R,R*)-**3**, in which the silyl moiety is a surrogate for an oxygen atom and 2) chiral lithiated benzoate esters (*S*)-**1** and (*R*)-**1**, which were readily available in high e.r.<sup>19</sup> from the corresponding stannanes, which were in turn synthesized using Hoppe–Beak sparteine-mediated lithiation.<sup>47–49</sup> We initially targeted the challenging all-*anti* stereotetrad in our studies.

We began by subjecting the  $\alpha$ -silylalkyl boronic ester *ent*-**8a** to initial homologation with (*R*)-**1**, a reaction that worked well, giving the homologation product **13** in good yield and high d.r. (Figure 3). However, a subsequent homologation with (*R,R*)-**3** failed. We believe that coordination of the pyrrolidine nitrogen atom to the boron atom of the boronic ester attenuates its reactivity, preventing boronate-complex formation. Indeed, many signals in the <sup>1</sup>H-, <sup>11</sup>B-, and <sup>13</sup>C-NMR spectra of boronic ester **13** were broad indicating nitrogen–boron coordination. We therefore needed to remove the amino group to allow subsequent homologation to take place and considered using photoredox catalysis. Amino silanes have been used as precursors for  $\alpha$ -amino radicals, generated through photoredox catalysis, but the focus has always been on the fate of the carbon-centred radical, not the silyl moiety.<sup>50–51</sup> We reasoned that upon oxidation of the amino group, attack of the silyl group by MeOH would give the  $\alpha$ -amino radical **22** and the desired methoxysilane (**14**, Figure 4). We therefore tested the reaction of amino silane *ent*-**8a** in the presence of Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub> [dF(CF<sub>3</sub>)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] (**15**), methylacrylate **16** (to trap the  $\alpha$ -amino radical **22**) in MeOH:MeCN by using blue LEDs as the light source and were pleased to isolate methoxysilane **14** in 79% yield. This experiment not only shows a new method

for replacing the amino side-arm of the silane **8** with a methoxy group but it also provides further evidence of the fate of the silyl moiety in photoredox reactions. After photoredox cleavage, subsequent homologation of the resulting boronic ester **14** with (*R*)-**1** was successful, affording the product **17a** in high yield (86%) and with high d.r. More importantly, the next homologation of boronic ester **17a** with (*R,R*)-**3** was also successful, providing the corresponding product in 80% yield with slight erosion of diastereoselectivity (94:6), presumably due to a small mismatched effect. Furthermore, the double homologation/photoredox cleavage sequence could be performed with only a single chromatographic purification. Thus, following lithiated chlorosilane homologation of **17a**, photoredox replacement of the aminomethyl group for a methoxy group and subsequent homologation with the lithiated TIB ester (*R*)-**1**, provides **19a** that could be taken on in a further set of homologations. At this stage, chromatographic purification of **19a** allowed the separation of the desired product from minor diastereomers to give diastereomerically pure material (>95:5) in good yield. Zweifel olefination followed by a modified Tamao oxidation of silane gave all-*anti*-stereotetrad **20** in 92% yield over 2 steps with >95:5 d.r. It should be noted that oxidation of the methoxysilane under standard Tamao conditions<sup>42</sup> using aqueous H<sub>2</sub>O<sub>2</sub> instead of urea-H<sub>2</sub>O<sub>2</sub> led to the formation of a much more stable cyclic siloxane, which was resistant to oxidation under the reaction conditions.

Having demonstrated a highly effective assembly-line synthesis protocol, we sought to target specific diastereoisomers. As illustrated in Table 2, different stereotetrads **25a–d** could be assembled through four iterative homologations of boronic esters with chiral building blocks (*S/R*)-**1** and (*S,S/R,R*)-**3** in the appropriate order to incorporate four alternating stereogenic centers bearing silyl and methyl groups followed by one further methylene insertion reaction with **2** (Table 2, entries 1–4). After oxidation, polypropionate stereotetrads **26a–d** were obtained in good yields with >95:5 diastereomeric ratios in all cases. Notably, our iterative, reagent-controlled homologation enabled the synthesis of the stereochemically challenging *anti-anti* isomer **26a** with complete stereocontrol, and with the same ease as any of the other stereoisomers. Additionally, the scale of the synthetic sequences could be increased from 0.5 to



2.5 mmol level without compromising on yield or diastereoselectivity. The versatility of the approach was showcased further through the synthesis of 1,3-related polyols.<sup>52</sup> In this case, phenethyl boronic ester **6a** was treated with (*R,R*)-**3** followed by photoredox cleavage and a one-carbon Matteson homologation with **2**, and then this sequence was repeated two further times to give the boronic ester **27c** with full stereocontrol (Table 2, entry 5). The final sequence, conducted on boronic ester **27c**, consisted of homologation with (*R,R*)-**3**, photoredox cleavage, and Zweifel olefination resulted in vinylsilane **28** in moderate yield (52%) with excellent diastereoselectivity. Finally, silane **28** was oxidized to the corresponding 1,3-related tetrols **29** in 56% yield with >95:5 d.r.

## CONCLUSIONS

In conclusion, we have demonstrated that the lithiated  $\alpha$ -silyl carbenoid **3**, which can be generated with high diastereocontrol by incorporating a chelating side-arm, can be successfully employed in the reagent-controlled homologation of boronic esters to provide  $\alpha$ -silylalkyl boronates with very high stereocontrol. Coupling this new building block with our established building blocks (lithiated benzoate esters) enables iterative homologation of boronic esters for the rapid and diastereoselective syntheses of polypropionates. This method is highly versatile as different diastereomers can be targeted simply by adjusting the sequence and the configuration of the reagents that are added. For example, the all-*anti* polypropionate stereotetrad, which remains challenging to synthesize with high selectivity by current aldol or crotylation strategies, could be easily prepared in good yield with excellent stereoselectivity by using our iterative assembly-line synthesis methodology. In addition, the scope of our approach was also extended to the synthesis of 1,3-related polyacetates by using chiral lithiated  $\alpha$ -chloromethyl silanes and  $\alpha$ -chloromethyl lithium as key building blocks. This iterative methodology opens the door for its application, not just to a much wider family of polyketide natural products, but also to polyketide-inspired unnatural products using a broader set of building blocks.

## References

1. Rohr, J. A new role for polyketides. *Angew. Chem. Int. Ed.* **39**, 2847–2849 (2000).

2. Koskinen, A. M. P. & Karisalmi, K. Polyketide stereotetrads in natural products. *Chem. Soc. Rev.* **34**, 677–690 (2005).
3. Hertweck, C. The biosynthetic logic of polyketide diversity. *Angew. Chem. Int. Ed.* **48**, 4688–4716 (2009).
4. Rimando, A. M. & Baerson, S. R. (Eds). *Polyketides: biosynthesis, biological activity, and genetic engineering* (American Chemical Society, 2006).
5. Weissman, K. J. & Leadlay, P. F. Combinatorial biosynthesis of reduced polyketides. *Nat. Rev. Microbiol.* **3**, 925–936 (2005).
6. Koehn, F. E. & Carter, G. T. The evolving role of natural products in drug discovery. *Nat. Rev. Drug Discovery* **4**, 206–220 (2005).
7. Newman, D. J. & Cragg, G. M. Natural products as sources of new drugs over the last 25 years. *J. Nat. Prod.* **70**, 461–477 (2007).
8. Butler, M. S., Robertson, A. A. B. & Cooper, M. A. Natural product and natural product derived drugs in clinical trials. *Nat. Prod. Rep.* **31**, 1612–1661 (2014).
9. Omura, S., Eds. *Macrolide antibiotics. Chemistry, biology, and practice* (Academic Press, 2002).
10. Paterson, I. & Findlay, A. D. Recent advances in the total synthesis of polyketide natural products as promising anticancer agents. *Aust. J. Chem.* **62**, 624–638 (2009).
11. Hoffmann, R. W. Stereoselective syntheses of building blocks with three consecutive stereogenic centers: important precursors of polyketide natural products. *Angew. Chem. Int. Ed.* **26**, 489–503 (1987).
12. Li, J. & Menche, D. Direct methods for stereoselective polypropionate synthesis: a survey. *Synthesis* 2293–2315 (2009).
13. Schetter, B. & Mahrwald, R. Modern aldol methods for the total synthesis of polyketides. *Angew. Chem. Int. Ed.* **45**, 7506–7525 (2006).
14. Evans, D. A. *et al.* Chiral enolate design. *Pure Appl. Chem.* **53**, 1109–1127 (1981).

15. Dechert-Schmitt, A.-M. R., Schmitt, D. C., Gao, X., Itoh, T. & Krische, M. J. Polyketide construction via hydroxyalkylation and related alcohol C–H functionalizations: reinventing the chemistry of carbonyl addition. *Nat. Prod. Rep.* **31**, 504–513 (2014).
16. Feng, J., Kasun, Z. A. & Krische, M. J. Enantioselective alcohol C–H functionalization for polyketide construction: unlocking redox-economy and site-selectivity for ideal chemical synthesis. *J. Am. Chem. Soc.* **138**, 5467–5478 (2016).
17. Chen, M. & Roush, W. R. Highly stereoselective synthesis of *anti,anti*-dipropionate stereotriads: a solution to the long-standing problem of challenging mismatched double asymmetric crotylboration reactions. *J. Am. Chem. Soc.* **134**, 3925–3931 (2012).
18. Cheng, B. & Trauner, D. A highly convergent and biomimetic total synthesis of portentol. *J. Am. Chem. Soc.* **137**, 13800–13803 (2015).
19. Burns, M. *et al.* Assembly-line synthesis of organic molecules with tailored shapes. *Nature* **513**, 183–188 (2014).
20. Balieu, S. *et al.* Toward ideality: the synthesis of (+)-kalkitoxin and (+)-hydroxyphthioceranic acid by assembly-line synthesis. *J. Am. Chem. Soc.* **137**, 4398–4403 (2015).
21. Sadhu, K. M. & Matteson, D. S. (Chloromethyl)lithium: efficient generation and capture by boronic esters and a simple preparation of diisopropyl (chloromethyl)boronate. *Organometallics* **4**, 1687–1689 (1985).
22. Xu, S., Li, H., Komiyama, M., Oda, A. & Negishi, E.-i. One-step homologation for the catalytic asymmetric synthesis of deoxypropionates. *Chem. Eur. J.* **23**, 149–156 (2017).
23. Xu, S. & Negishi, E.-i. Zirconium-catalyzed asymmetric carboalumination of unactivated terminal alkenes. *Acc. Chem. Res.* **49**, 2158–2168 (2016).
24. Gati, W. & Yamamoto, H. Second generation of aldol reaction. *Acc. Chem. Res.* **49**, 1757–1768 (2016).
25. Lin, L. *et al.* Catalytic asymmetric iterative/domino aldehyde cross-aldol reactions for the rapid and flexible synthesis of 1,3-polyols. *J. Am. Chem. Soc.* **137**, 15418–15421 (2015).

26. Zheng, K., Xie, C. & Hong, R. Bioinspired iterative synthesis of polyketides. *Front. Chem.* **3**, 1–17 (2015).
27. Matteson, D. S. Functional group compatibilities in boronic ester chemistry. *J. Organomet. Chem.* **581**, 51–65 (1999).
28. Vedrenne, E., Wallner, O. A., Vitale, M., Schmidt, F. & Aggarwal, V. K. Homologation of boronic esters with lithiated epoxides for the stereocontrolled synthesis of 1,2- and 1,3-diols and 1,2,4-triols. *Org. Lett.* **11**, 165–168 (2009).
29. Jones, G. R. & Landais, Y. The oxidation of the carbon-silicon bond. *Tetrahedron* **52**, 7599–7662 (1996).
30. Basu, A. & Thayumanavan, S. Configurational stability and transfer of stereochemical information in the reactions of enantioenriched organolithium reagents. *Angew. Chem. Int. Ed.* **41**, 716–738 (2002).
31. Hoffmann, R. W., Rühl, T. & Harbach, J. On the configurational stability of  $\alpha$ -hetero-substituted benzyllithium compounds. *Liebigs Ann. Chem.* **1992**, 725–730.
32. Schweifer, A. & Hammerschmidt, F. Formal and improved synthesis of enantiopure chiral methanol. *Tetrahedron* **64**, 7605–7610 (2008).
33. Aggarwal, V. K. *et al.* Asymmetric synthesis of tertiary and quaternary allyl- and crotylsilanes via the borylation of lithiated carbamates. *Org. Lett.* **13**, 1490–1493 (2011).
34. Barsamian, A. L., Wu, Z. & Blakemore, P. R. Enantioselective synthesis of  $\alpha$ -phenyl- and  $\alpha$ -(dimethylphenylsilyl)alkylboronic esters by ligand mediated stereoinductive reagent-controlled homologation using configurationally labile carbenoids. *Org. Biomol. Chem.* **13**, 3781–3786 (2015).
35. Nakamura, S., Nakagawa, R., Watanabe, Y. & Toru, T. Highly enantioselective reactions of configurationally labile  $\alpha$ -thioorganolithiums using chiral bis(oxazoline)s via two different enantiodetermining steps. *J. Am. Chem. Soc.* **122**, 11340–11347 (2000).

36. Lange, H., Huenerbein, R., Fröhlich, R., Grimme, S. & Hoppe, D. Configurationally labile lithiated *O*-benzyl carbamates: application in asymmetric synthesis and quantum chemical investigations on the equilibrium of diastereomers. *Chem. Asian J.* **3**, 78–87 (2008).
37. Chan, T. H. & Pellon, P. Chiral organosilicon compounds in synthesis. Highly enantioselective synthesis of arylcarbinols. *J. Am. Chem. Soc.* **111**, 8737–8738 (1989).
38. Strohmann, C., Lehmen, K., Wild, K. & Schildbach, D. A highly diastereomerically enriched benzyllithium compound: the molecular structure and the stereochemical course of its transformations. *Organometallics* **21**, 3079–3081 (2002).
39. Strohmann, C., Buchold, D. H. M., Seibel, T. Wild, K. & Schildbach, D. Syntheses and crystal structures of highly diastereomerically enriched lithiated benzylsilanes in the presence of external donor molecules: experiment and theory. *Eur. J. Inorg. Chem.* 3453–3463 (2003).
40. Bagutski, V., French, R. M. & Aggarwal, V. K. Full chirality transfer in the conversion of secondary alcohols into tertiary boronic esters and alcohols using lithiation-borylation reactions. *Angew. Chem. Int. Ed.* **49**, 5142–5145 (2010).
41. Evans, D. A., Crawford, T. C., Thomas, R. C. and Walker, J. A. Studies directed toward the synthesis of prostaglandins. Useful boron-mediated olefin syntheses. *J. Org. Chem.* **41**, 3947–3953 (1976).
42. Tamao, K., Ishida, N., Tanaka, T. & Kumada, M. Hydrogen peroxide oxidation of the silicon-carbon bond in organoalkoxysilanes. *Organometallics* **2**, 1694–1696 (1983).
43. Stymiest, J. L., Bagutski, V., French, R. M. & Aggarwal, V. K. Enantiodivergent conversion of chiral secondary alcohols into tertiary alcohols. *Nature* **456**, 778–782 (2008).
44. Leonori, D. & Aggarwal, V. K. Lithiation-borylation methodology and its application in synthesis. *Acc. Chem. Res.* **47**, 3174–3183 (2014).
45. Bonet, A., Odachowski, M., Leonori, D. Essafi, S. & Aggarwal, V. K. Enantiospecific  $sp^2$ – $sp^3$  coupling of secondary and tertiary boronic esters. *Nat. Chem.* **6**, 584–589 (2014).
46. Wang, Y., Noble, A., Myers, E. L. & Aggarwal, V. K. Enantiospecific alkynylation of alkylboronic esters. *Angew. Chem. Int. Ed.* **55**, 4270–4274 (2016).

47. Hoppe, D. & Hense, T. Enantioselective synthesis with lithium/(-)-sparteine carbanion pairs. *Angew. Chem. Int. Ed.* **36**, 2282–2316 (1997).
48. Beak, P., Baillargeon, M. & Carter, L. G. Lithiation of ethyl 2,4,6-triisopropylbenzoate adjacent to oxygen: the  $\alpha$ -lithioalkyl alcohol synthon. *J. Org. Chem.* **43**, 4255–4256 (1978).
49. Hoppe, D., Marr, F. & Brüggemann, M. *Organolithiums in enantioselective synthesis*; Hodgson, D. M., Ed. (Springer, 61–137, 2003).
50. Miyake, Y., Ashida, Y., Nakajima, K. & Nishibayashi, Y. Visible-light-mediated addition of  $\alpha$ -aminoalkyl radicals generated from  $\alpha$ -silylamines to  $\alpha,\beta$ -unsaturated carbonyl compounds. *Chem. Commun.* **48**, 6966–6968 (2012).
51. Espelt, L. R., McPherson, I. S., Wiensch, E. M. & Yoon, T. P. Enantioselective conjugate additions of  $\alpha$ -amino radicals via cooperative photoredox and Lewis acid catalysis. *J. Am. Chem. Soc.* **137**, 2452–2455 (2015).
52. Bode, S. E., Wolberg, M. & Müller, M. Stereoselective synthesis of 1,3-diols. *Synthesis* 557–588 (2006).
53. The original blue LED graphic was obtained from clipshrine website: ([www.clipshrine.com/LED-Light-Emitting-Diode-Red-16393-cv-b.html](http://www.clipshrine.com/LED-Light-Emitting-Diode-Red-16393-cv-b.html)). It is freely available and has no copyright associated with it.

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## **Additional information**

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at [www.nature.com/reprints](http://www.nature.com/reprints). Correspondence and requests for materials should be addressed to V.K.A.

## **Data Availability Statement**

All data is in the supplementary information file which contains full experimental procedures and chemical compound information. It is available in the online version of the paper. Reprints and permissions information is available online at [www.nature.com/reprints](http://www.nature.com/reprints). Correspondence and requests for materials should be addressed to V.K.A.

## **Author contributions**

V.K.A. and E.L.M. conceived and directed the project. T.B. and J. M. F. conducted and designed the experiments and analyzed the data. V.K.A., E.L.M. and T.B. co-wrote the paper.

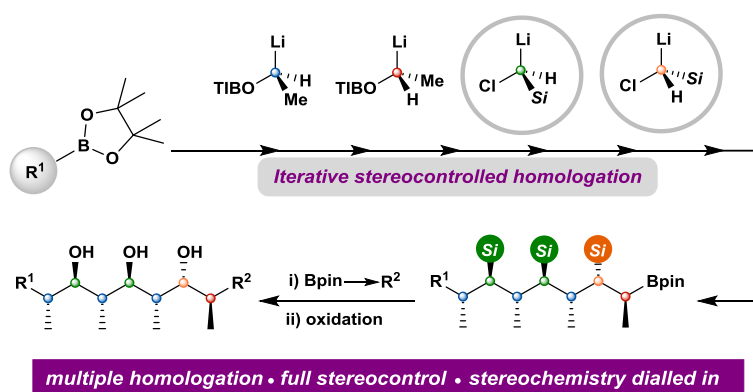
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## **Competing financial interests**

The authors declare no competing financial interest.

## **Table of contents**



Polypropionates can be grown, one-carbon atom at a time, using the iterative homology of boronic esters. This assembly-line strategy was enabled through the use of enantioenriched lithiated  $\alpha$ -chlorosilanes, as masked carbinol units. Polypropionates were obtained in a fully stereocontrolled manner, including the stereochemically challenging *anti-anti* isomers.

### List of figure captions

**Figure 1. Iterative assembly-line strategy for polyketide synthesis.** **a**, Iterative homology of boronic esters by using chiral lithiated benzoate esters and chloromethyl lithium as previously applied to the highly efficient syntheses of polydeoxypropionate natural products, (+)-kalkitoxin and (+)-hydroxyphthioceranic acid. **b**, This work, demonstrating an iterative assembly-line strategy for the construction of more complex, hydroxy-containing polypropionates by using a novel class of chiral lithiated  $\alpha$ -chlorosilanes and chiral lithiated benzoate esters. TIB, 2,4,6-triisopropylbenzoyl; FGI, functional-group interconversion; pin, pinacolato.

**Figure 2. Issues associated with homology of  $\beta$ -alkoxy boronic esters and possible solutions using a silyl group as a masked-oxygen functionality for iterative homologies.** **a**, Competing processes in the homology of boronic esters bearing  $\beta$ -alkoxy groups where elimination dominates over 1,2-migration. **b**, Bis(oxazoline)-mediated reagent-controlled homology of boronic esters is only moderate enantioselectivity. **c**, This work: enantioenriched lithiated  $\alpha$ -silyl carbenoid possessing a tethered chiral side-arm can be used to homology boronic esters with very high stereocontrol. **d**, Chan's highly diastereoselective reaction of lithiated  $\alpha$ -benzylsilane **9**. BOX, bis(oxazoline); PG, protecting group; sp, sparteine.

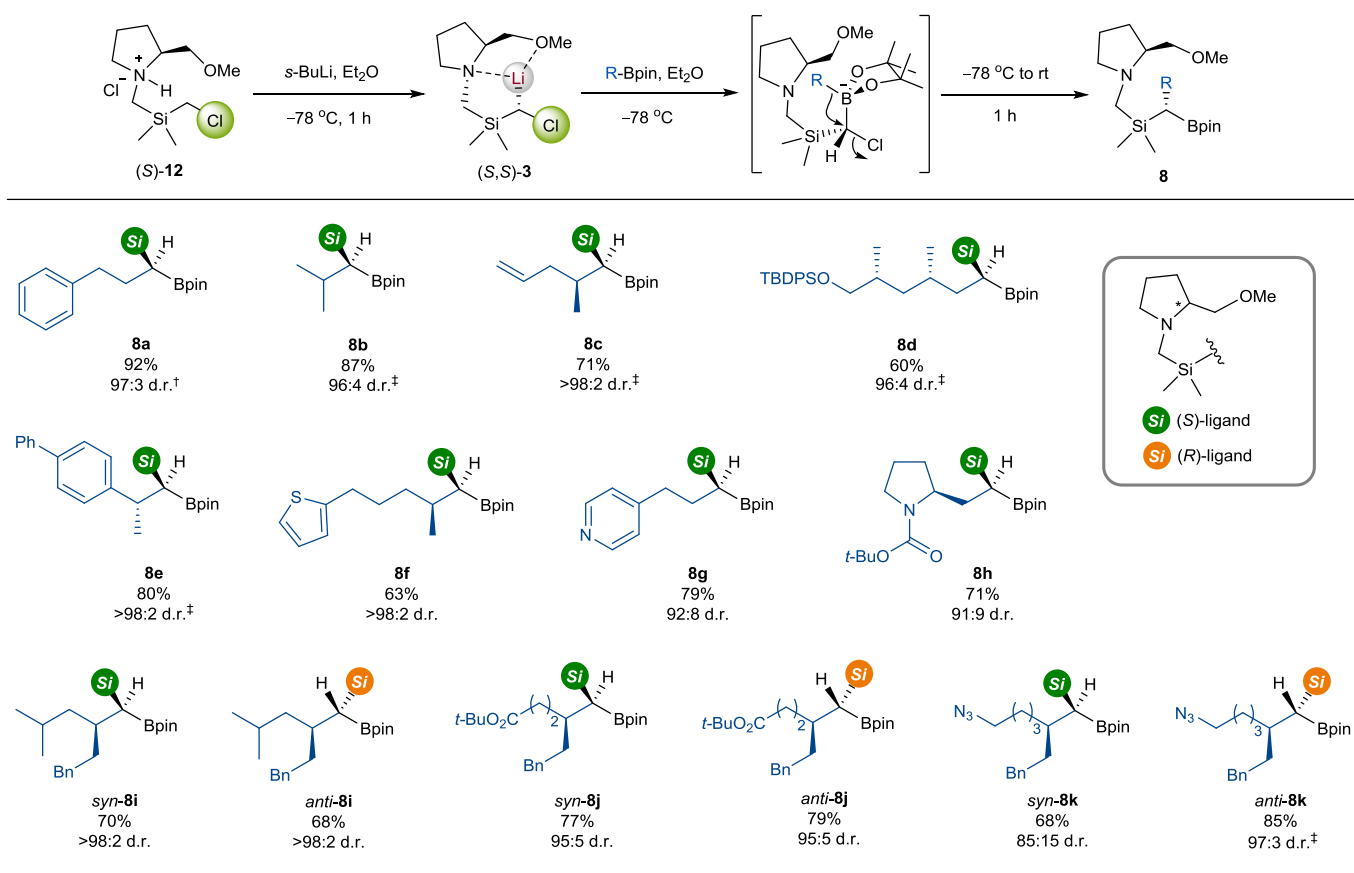
**Figure 3. Development of assembly-line synthesis protocol for the construction of polypropionates.** **a**, Photoredox cleavage was conducted on the boronic ester *ent*-**8a**, followed by consecutive homologies with lithiated benzoate ester (*R*)-**1** and lithiated  $\alpha$ -chlorosilane (*R,R*)-**3** to afford **18a** with high diastereoselectivity. **b**, **17a** was subsequently subjected to a double-homology/photoredox cleavage sequence to give the boronic ester **19a** with full



stereocontrol. Zweifel olefination followed by a modified Tamao oxidation gave all-*anti*-stereotetrad **20** in good yield with high diastereoselectivity. LEDs, light-emitting diodes.

**Figure 4. Proposed catalytic cycle for the photoredox cleavage of the aminosilane **8a**.** A single-electron oxidation of the tertiary amine of *ent*-**8a** by the excited Ir(III)\* species gives intermediate radical cation **21** followed by attack on the silyl group by MeOH to provide the desired methoxysilane **14** and the  $\alpha$ -amino radical **22**, which is subsequently trapped by the Michael acceptor to form the alkyl radical **23**. Finally, the reduction of radical **23** by the Ir(II) species gives, after protonation by MeOH, by-product **24**, with concomitant regeneration of the photocatalyst. Ir(III), Ir<sup>III</sup>[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub>.

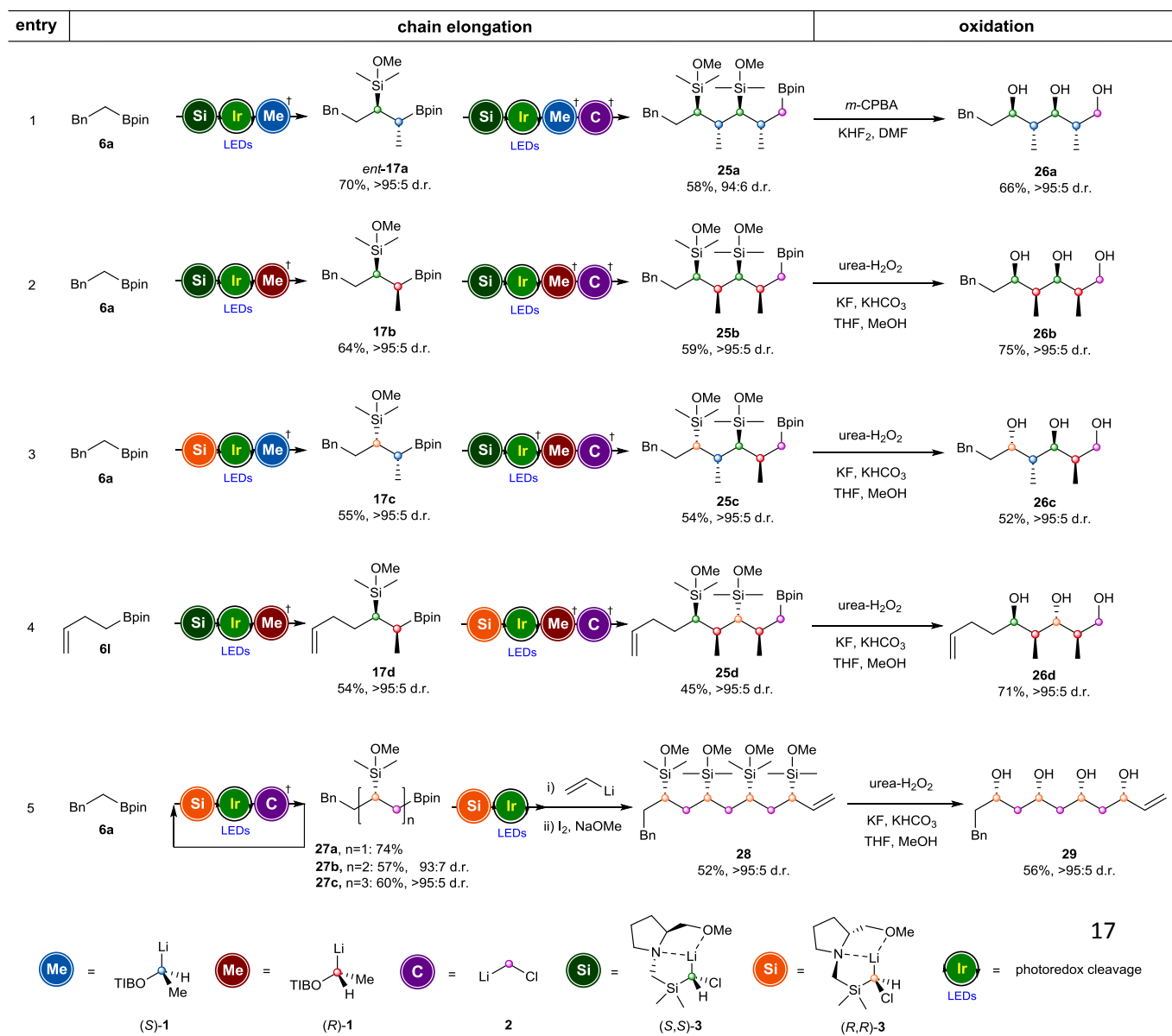
**Table 1. Stereocontrolled homologation of lithiated  $\alpha$ -chloromethyl silane **3** with various boronic esters**



Reaction conditions: Chlorosilane (1.3 equiv), *s*-BuLi (2.4 equiv) in Et<sub>2</sub>O (0.2 M) at -78 °C for 1 h, then boronic ester (1.0 equiv) in Et<sub>2</sub>O (0.2 M) at -78 °C for 1 h, then rt for 1 h (see the Supplementary Information for full details). The e.r.

values of chiral starting boronic esters are as follows: **6c** (99:1), **6d** (>95:5 d.r.), **6e** (99:1), **6f** (98:2), **6h** (98:2), **6i** (99:1), **6j** (95:5), **6k** (99:1). Isolated yields and diastereomeric ratios are shown below the structure of products. Unless otherwise noted, d.r. values were determined by <sup>1</sup>H-NMR spectroscopy of the purified material. In several cases (**8d** and **8k**) we confirmed that no diastereomeric enrichment occurred upon chromatography. >98:2 indicates that we cannot see the other diastereoisomer and we know where it comes. † The d.r. value was determined by chiral SFC. ‡ d.r. values were determined by <sup>1</sup>H-NMR spectroscopy of the crude material. TBDPS, *tert*-butyldiphenylsilyl.

**Table 2. Iterative assembly-line synthesis of polypropionates and a 1,3-related polyacetate.**



Isolated yields and diastereomeric ratios are shown below the structure of products (see the Supplementary Information for full details). † Chromatographic purification was conducted at this stage. Investigations also showed that the first product after homologation of *ent*-**17a**, **17b**, **17c**, and **17d** had d.r. values of 94:6, 93:7, 90:10, and >95:5, respectively, showing that chromatographic purification removes minor diastereomers and contributes to the high d.r. values quoted. *m*-CPBA, *meta*-Chloroperoxybenzoic acid.