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Synthesis of α-substituted cyclic boronates *via* titanium-catalyzed cyclization of vinyl boronates with dihaloalkanes†

Ximei Tian[ab] and Lipeng Wu *[ac]

Cyclic boronates are versatile synthons for organic synthesis and for introducing ring systems into bioactive molecules. Existing synthetic methods have narrow substrate scope and the synthesis of α-substituted cyclic boronates is still elusive. Furthermore, no general method for synthesizing cyclic boronates with different ring sizes and hetero atom containing rings is available. Herein, we present a new and general synthetic method for synthesizing α-substituted cyclic boronates. Our approach has the advantage of using earth-abundant Ti as the catalyst and readily available dihaloalkanes, such as dichloromethane, as the reactant. Cyclic boronates that are otherwise difficult to access, such as α-substituted cyclic boronates with three-, four-, five-, and six-membered rings, heteroatom-containing rings, and cyclic boronates with spiro rings, are readily obtained.

Alkyl boronates are synthetically valuable compounds in organic chemistry,[1–7] and they also find applications in medicinal chemistry, an example is bortezomib, which is an approved drug for treating relapsed multiple myeloma and mantle cell lymphoma.[8,9] Therefore, significant efforts have been devoted to developing new synthetic methodologies for their preparation. Among them, the synthesis of cyclic boronates has attracted particular attention in recent years. Cyclic boronates are versatile synthons for functionalizing ring systems and introducing them into molecular architectures. The latter is a pivotal strategy in drug design and biological studies,[10–12] which can improve the lipophilicity[13] and metabolic stability of compounds,[14] and provide entropically favorable binding *via* conformational constraint of drug molecules (Fig. 1A).[15,16] In this respect, methodologies such as C–H boration of cycloalkanes,[17–21] hydroboration of cyclopropenes,[22–24] reaction of allylic carbonates, phosphonates, or homoallylic sulfonates with diboron,[25–27] cyclopropanation of alkenyl boronates with ethyl diazoacetate,[28] decarboxylative borylation of *N*-hydroxyphthalimide esters of cyclic carboxylic acids,[29,30] borylation of benzyltrimethylammonium with cyclic rings,[31] reaction of lithiated 1,1-diborylalkanes with α-halo small rings,[32,33] and several other recent advances[34–40] have been developed that

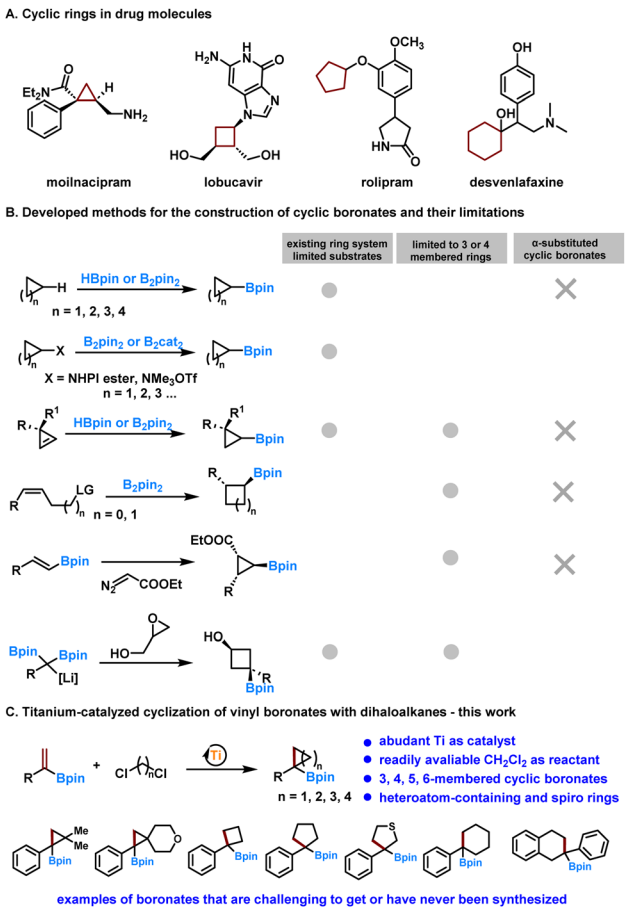

Fig. 1 (A) Representative drug molecules containing ring systems; (B) recently developed methods for the construction of cyclic boronates and their limitations; (C) titanium-catalyzed cyclization of vinyl boronates with dihaloalkanes for the synthesis of structurally diverse cyclic boronates.

[a]*State Key Laboratory of Low Carbon Catalysis and Carbon Dioxide Utilization, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou, 730000, P. R. China. E-mail: lipengwu@licp.cas.cn*

[b]*University of Chinese Academy of Sciences, Beijing, 100049, P. R. China*

[c]*College of Material Chemistry and Chemical Engineering, Key Laboratory of Organosilicon Chemistry and Material Technology, Ministry of Education, Hangzhou Normal University, Hangzhou, 311121, P. R. China*

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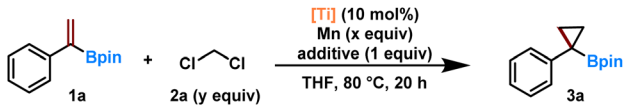
essentially extended the availability of cyclic boronates (Fig. 1B). However, despite these achievements, several limitations remain: (1) many methods depend on existing ring systems, which limit the availability of the starting material; (2) methods that do not rely on existing ring systems are generally limited to the synthesis of three-membered ring boronates, and the synthesis of boronates with other four-, five-, or six-membered rings or spiro rings remains elusive; and (3) no general method for the synthesis of α-substituted cyclic boronates, which contain a quaternary carbon center, is available.[12,32,33,37–39,41–43] Noticed that, it is very challenging to obtain α-substituted cyclic boronates using most of the developed methods such as C–H boration of cyclopropanes and hydroboration of cyclopropenes (Fig. 1B). Therefore, the development of novel and versatile synthetic methodologies is essential.

Recently, transition-metal-catalyzed reductive cyclopropanation of alkenes with *gem*-dihaloalkanes or its analogs (Simmons–Smith type reaction) was developed as an efficient method for constructing the cyclopropane motif.[44–54] Their application for the synthesis of α-substituted cyclopropyl boronates were also studied.[55,56] We also noticed that an excess amount of early-transition metal titanium(II) complexes or sub-stoichiometric titanium(III) complexes could be used to promote the cyclopropanation of *gem*-dihalides or thioacetals with alkenes or allylic alcohols.[57–61] Taken together, and in line with our interest in exploring titanium as a potential catalyst for various synthetic valuable transformations,[62–64] herein, we report the success of our investigation of titanium as a catalyst for the reductive cyclization of α-substituted vinyl boronates for the synthesis of structurally diverse cyclic boronates. Our system features the advantages of using readily available and inexpensive titanium as the catalyst and dichloromethane or other dihaloalkanes as the reactant. As a result, α-substituted cyclic boronates with three-, four-, five-, and six-membered rings, including heteroatom-containing rings, which are otherwise difficult to obtain, were readily produced. In addition, cyclic boronates with spiro rings were successfully accessed using this method (Fig. 1C).

To start the investigation, 1-phenyl vinyl boronate (**1a**, 0.2 mmol) was reacted with dichloromethane (**2a**, 1.0 mmol) using Mn (2 equiv.) as the reductant in THF (1 mL) at 80 °C (Table 1). Among the titanium complexes investigated, Cp_2TiCl_2 was the most efficient catalyst, giving the target product **3a** in 35% yield (Table 1, entries 1–5). The addition of LiCl improved the yield of **3a** to 48% (entries 6–8). The low yield of **3a** was mainly due to the low conversion; thus, the yield of **3a** was further improved by enhancing the amount of Mn and dichloromethane (entries 9–12). Under these conditions, an 80% yield of **3a** was obtained at 80 °C; enhancing the temperature to 120 °C only slightly improved the yield of **3a** to 87% (entry 13). Despite the minimally improved yield, to ensure good reproducibility and generality, we conducted the subsequent substrate scope studies at 120 °C.

Various 1-substituted vinyl boronates **1** were then reacted with dichloromethane **2a** to produce the corresponding α-substituted cyclopropyl boronates **3** (Scheme 1). Vinyl boronates

Table 1 Titanium-catalyzed cyclization of vinyl boronate **1a** with DCM – condition optimization[a]

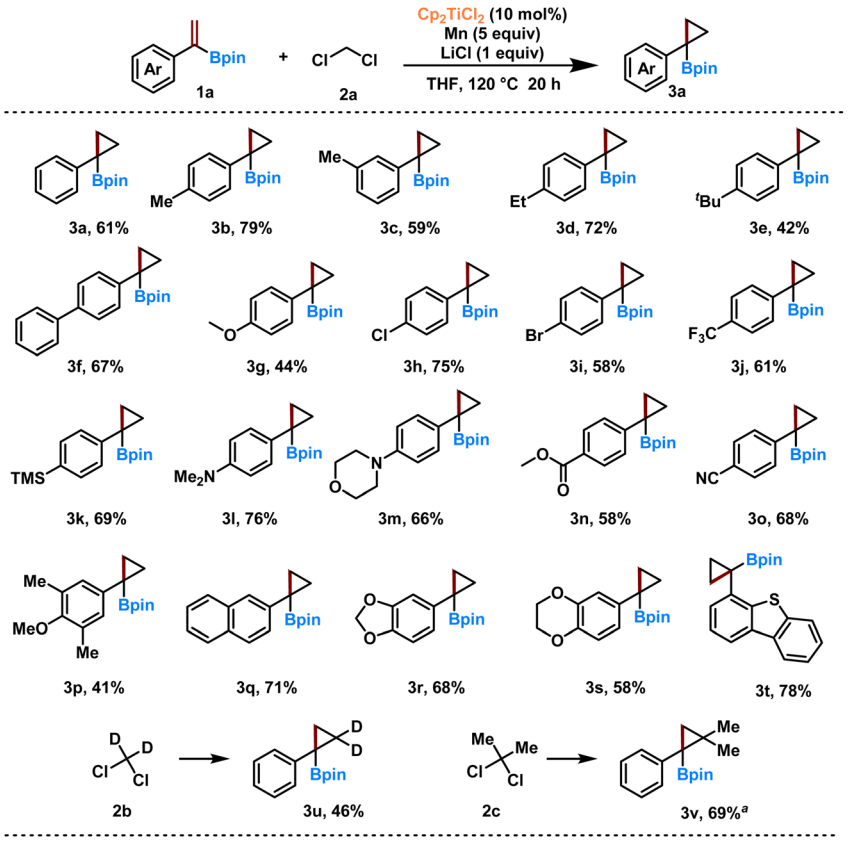


Entry	[Ti]	Additives	*x*	*y*	Yield of **3a**[b] (%)
1	$Cp^*_2TiCl_2$	—	2	5	8
2	$InTiCl_3$	—	2	5	14
3	$CpTiCl_3$	—	2	5	16
4	Cp^*TiCl_3	—	2	5	17
5	Cp_2TiCl_2	—	2	5	35
6	Cp_2TiCl_2	TMS-Cl	2	5	23
7	Cp_2TiCl_2	$MgCl_2$	2	5	40
8	Cp_2TiCl_2	LiCl	2	5	48
9	Cp_2TiCl_2	LiCl	4	5	53
10	Cp_2TiCl_2	LiCl	5	5	62
11	Cp_2TiCl_2	LiCl	5	8	72
12	Cp_2TiCl_2	LiCl	5	10	80
13[c]	Cp_2TiCl_2	LiCl	5	10	87

[a] Reaction conditions: **1a** (0.2 mmol), Mn (*x* equiv.), **2a** (*y* equiv.), cat. (10 mol%), additive (1 equiv.), THF (1 mL) in 15 mL pressure tube, stirring, 80 °C, 20 h. [b] Yields were determined by GC with dodecane as internal standard. [c] Reaction was performed at 120 °C.

substituted with electron-donating groups such as –Me, –Et, –^{t}Bu, –Ph, –MeO reacted well to give the products **3a–g** in 42–79% isolated yields. Interestingly, halide groups on the phenyl ring, such as –Cl, –Br, and –CF_3, remained intact under the reaction conditions to give **3h–j** (58–75% yields). In addition, heteroatom-containing groups such as –TMS, –Me_2N, and morpholine had no deleterious effects on the results (**3k–m**, 66–76% yields). Functional groups such as ester and nitrile were also suitable, giving the corresponding products **3n** and **3o** in moderate yields of 58% and 68%, respectively. Vinyl boronates with multi-substituted and fused benzene rings, including 1,3-benzodioxole, 2,3-dihydrobenzo[*b*][1,4]dioxine, and dibenzothiophene, reacted well to give the corresponding cyclic boronates **3q–t** in 58–78% yields. Interestingly, when deuterated dichloromethane (**2b**) was used, the corresponding d_2-labeled cyclic boronate **3u** was obtained. The presence of the *gem*-dimethyl group is believed to improve the potency or eliminate metabolic liabilities of biologically active compounds.[47,65] We then successfully applied 2,2-dichloropropane (**2c**) for the dimethylcyclopropanation with vinyl boronates, and product **3v** was obtained in good yield. Unfortunately, the current system does not work for aliphatic vinyl boronates (Scheme S1†).

The developed method was then applied to the synthesis of cyclic boronates, which are not easily accessible by other methods (Scheme 2). We were pleased that when using 1,3-dichloropropane (**2d**) as the reactant, α-substituted cyclopentyl boronates **4a–d** could be obtained. More interestingly, using bis(chloromethyl)sulfane (**2e**) as the dichloroalkane partner, products **5a–f** with S-containing 5-membered rings were produced. To our knowledge, cyclic boronates like **5** have never been successfully synthesized. Then, 1,4-dichlorobutane (**2f**)



Scheme 1 Substrate scope for the Ti-catalyzed synthesis of α-substituted cyclopropyl boronates-reaction conditions: **1** (0.2 mmol), **2** (10 equiv.), Cp_2TiCl_2 (10 mol%), Mn (5 equiv.), LiCl (1 equiv.), THF (1 mL), 15 mL pressure tube, 120 °C, 20 h; isolated yields; [a]2 equivalent of **2c**.

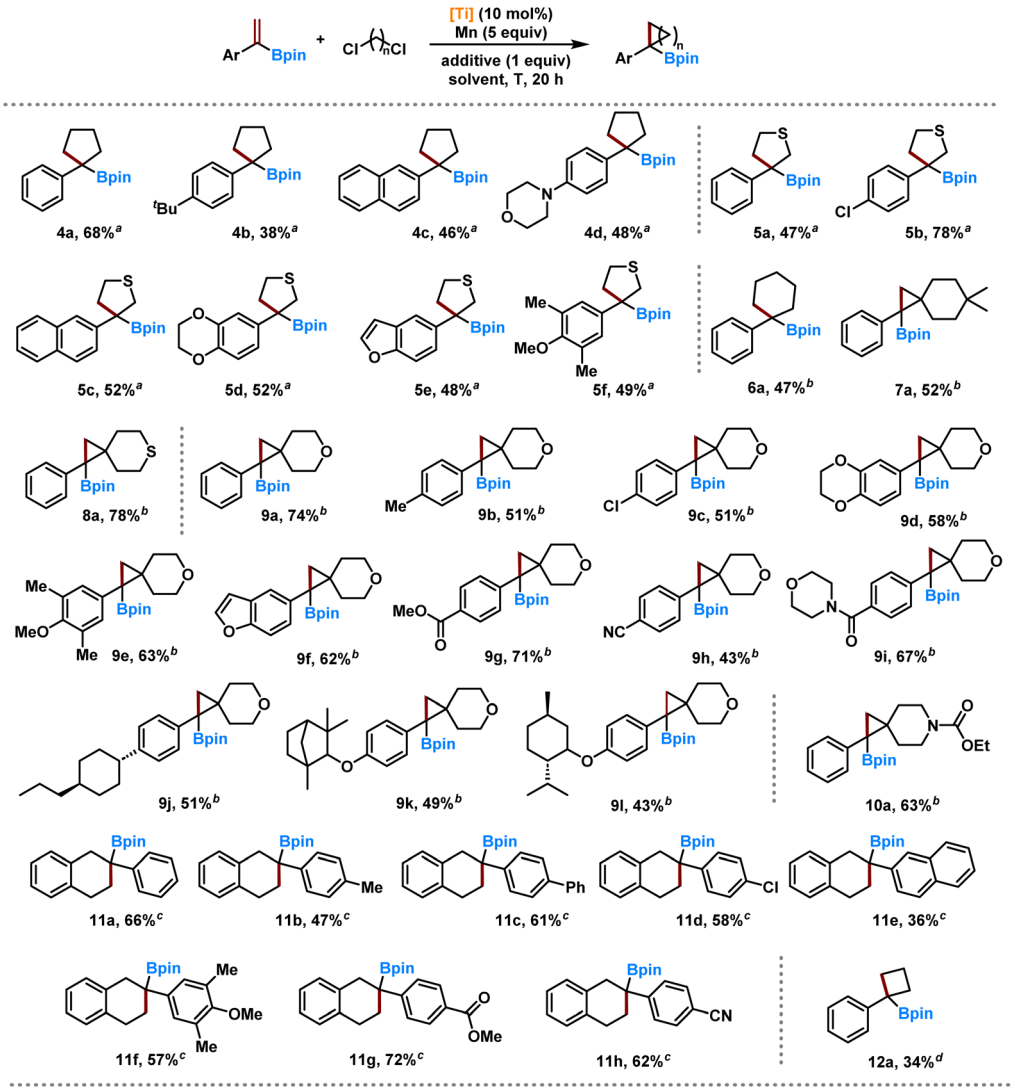
was also successfully applied for the cyclization reaction, and α-substituted cyclohexyl boronate **6a** was obtained.

To synthesize spirocyclic boronates, 1,1-dichloro-4,4-dimethylcyclohexane (**2g**) was reacted with vinyl boronate **1a**, and we found that the target spirocyclic boronate **7a** was produced in moderate yield. Inspired by this result, 4,4-dichlorotetrahydro-2*H*-thiopyran (**2h**) and 4,4-dichlorotetrahydro-2*H*-pyran (**2i**) were subjected to the reaction with vinyl boronates substituted with various functional groups, and the corresponding spirocyclic boronates **8a** and **9a–h** were obtained.

To our knowledge, no other methods have been reported for the synthesis of boronates such as **7–9**. We further extended our methodology to synthesize more complex compounds and biomolecule-derived spirocyclic boronates **9i–l**, including fenchol and menthol-derived molecules. Finally, spirocyclic boronate **10a**, with a nitrogen-containing ring, was obtained in 63% yield by reacting ethyl 4,4-dichloropiperidine-1-carboxylate with **1a**.

We also examined the use of 1,2-bis(bromomethyl)benzene (**2j**) as the dihaloalkane partner, the reaction of which with vinyl boronates would produce the corresponding benzene-fused cyclic boronates **11**. Surprisingly, **2j** reacted readily with vinyl boronates in the presence of Mn, even without a Ti catalyst, giving **11a** in 35% GC yield. This might be due to the high reactivity of the benzylic bromide moiety, which generates a benzylic radical just in the presence of Mn. Adding 1 equiv. of a Lewis acid $AlCl_3$, which is believed to facilitate the radical addition, increased the yield of **11a** to 75% GC yields. Nevertheless, various substituted vinyl boronates reacted well, including –Cl, –COOMe, and –CN substituted derivatives (**11a–h**). Finally, efforts toward the synthesis of cyclobutyl boronate were conducted using 1,2-dichloroethane, and cyclobutyl boronate **12a** was obtained in 34% yield under the optimized conditions using $TiCl_4$.

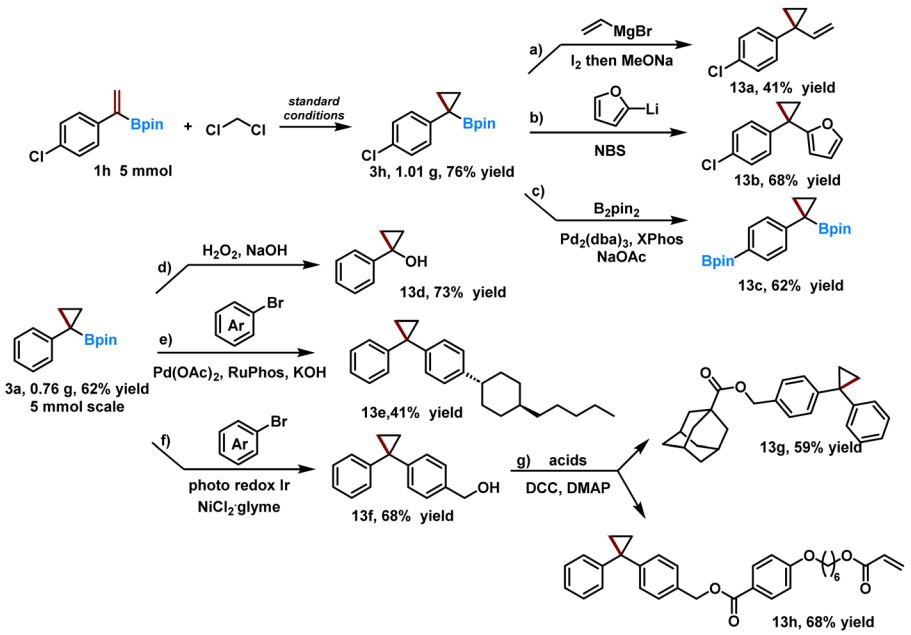
Having generated a range of α-substituted cyclic boronates, the robustness of our method for gram-scale synthesis was assessed and it was found that boronates **3a** and **3h** were produced in 62% and 76% isolated yields on a 5 mmol scale (Scheme 3). The synthetic utility of these compounds was demonstrated in a series of downstream transformations. First, olefination of **3h** with vinyl magnesium bromide produced terminal alkene **13a** in 41% yield. Treating **3h** with furan-2-yllithium followed by NBS afforded the arylated product **13b** in 68% yield. The aryl chloride moiety could also be further borylated to produce bis-boronates **13c** with one alkyl and aryl boronate functionality. The oxidation and Suzuki–Miyaura coupling of **3a** were also performed, giving 1-phenylcyclopropanol **13d** and the corresponding arylation product **13e**. The arylation of **3a** with a tethered free hydroxyl group was also achieved using a photo/Ni dual catalysis, the product of which could be further derivatized with 1-adamantanecarboxylic acid and 4-((6-(acryloyloxy)hexyl)oxy)benzoic acid to produce the corresponding products **13g** and **13h**.



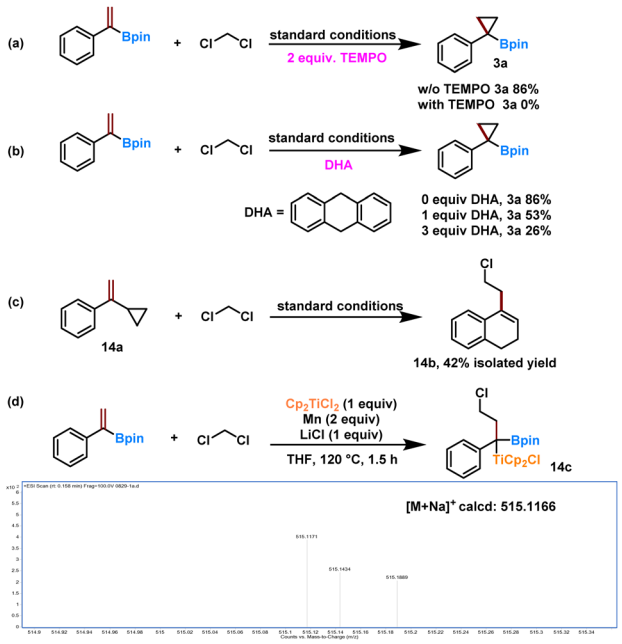
Scheme 2 Substrate scope for the Ti-catalyzed synthesis of α-substituted cyclic boronates-reaction conditions: [a]vinyl boronate (0.2 mmol), dichloroalkane (2 equiv.), Cp*$TiCl_3$ (10 mol%), Mn (5 equiv.), LiCl (1 equiv.), THF (1 mL), 15 mL pressure tube, 80 °C, 20 h, isolated yields; [b]$InTiCl_3$ (10 mol%), 120 °C; [c]vinyl boronate (0.2 mmol), bis(bromomethyl)benzene (2 equiv.), 1 equiv. $AlCl_3$ in 1 mL DMA, 40 °C for 20 h, isolated yields; [d]40 mol% $TiCl_4$, 60 °C, isolated yields after oxidation.

Several control experiments were then conducted to shed light on the potential reaction mechanism. Initially, we carried out radical inhibitor experiments by adding the radical scavengers 2,2,6,6-tetramethylpiperidinyl-1-oxide (TEMPO) or 9,10-dihydroanthracene (DHA) to the standard reaction (Scheme 4). We found that the inclusion of TEMPO (2 equiv.) shut down the reaction completely (Scheme 4a) and that adding increasing amounts of DHA led to a gradual reduction in the yield of **3a** (Scheme 4b). These results indicate that a radical species might be involved in the reaction. Further support for this was obtained from radical clock experiments in which the ring-opening product **14b** was obtained in 42% yield when (1-cyclopropylvinyl)benzene (**14a**) was allowed to react with dichloromethane (Fig. S1 and 2†). The production of **14b** provided additional support for a radical reaction pathway and indicated the stepwise activation of the two –Cl moieties from dichloromethane. Moreover, the mass fragment corresponding to a possible α-boryl alkyl titanium intermediate **14c** was observed by HRMS in the stoichiometric reaction after reaction for 1.5 h.

We proposed the following reaction mechanism based on the above experimental results and literature reports (Fig. 2). First, $Cp_2Ti^{III}Cl$ is generated from the reduction of $Cp_2Ti^{IV}Cl_2$ by Mn. The former is well known as a single-electron transfer (SET) agent[66–71] that can activate the dihaloalkane species to form the monochloroalkyl radical species **A**. Radical addition to the vinyl boronates produces radical species **B** in which the boryl group can stabilize the neighboring carbon radical. Radical capture by $Cp_2Ti^{III}Cl$ then generates the key α-boryl alkyl titanium intermediate **C** (*m*/*z* fragment observed by HRMS), which undergoes reductive ring closure to the cyclic boronates with the regeneration of $Cp_2Ti^{IV}Cl_2$.[60]



Scheme 3 Gram-scale synthesis and synthetic utilization. (a) 0.5 mmol **3h**, 2 mmol vinyl magnesium bromide (1.0 M in THF), 2 mmol I_2, 4 mmol NaOMe; (b) 0.5 mmol **3h**, 0.66 mmol furan, 0.66 mmol ^{n}BuLi (1.6 M in THF), 0.6 mmol NBS; (c) 0.5 mmol **3h**, 0.51 mmol B_2pin_2, 1 mol% $Pd_2(dba)_3$, XPhos 2 mol%, 0.6 mmol NaOAc; (d) 0.5 mmol **3a**, NaOH (2 M aq., 1 mL), H_2O_2 (30% aq., 0.5 mL); (e) 0.5 mmol **3a**, 10 mol% $Pd(OAc)_2$, 20 mol% RuPhos, 2 mmol KOH, 1 mmol aryl bromide; (f) 1.0 mmol **3a**, 0.5 mmol aryl bromide, 1 mol% $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$, 0.75 mmol morpholine, 5 mol% $NiCl_2$ glyme and 5 mol% dtbbpy; (g) 0.5 mmol corresponding acids, 0.75 mmol **13f**, 10 mol% DMAP, 0.55 mmol DCC. For detailed conditions, please refer to the ESI.†



Scheme 4 Mechanistic studies: (a and b) radical inhibitor experiments by adding TEMPO or DHA to the standard catalytic reaction; (c) radical clock experiment using **14a** as the substrate; (d) HRMS spectrum shows the formation of a key intermediate.

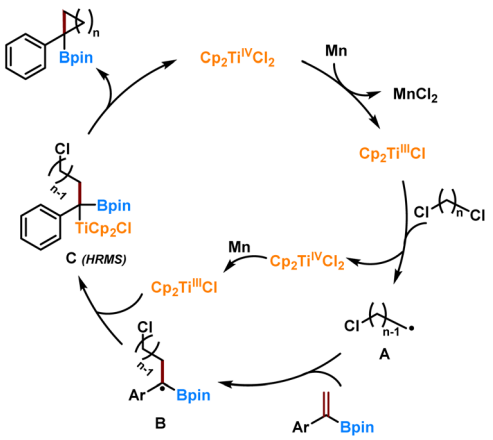


Fig. 2 Proposed catalytic cycle.

A new synthetic method for the general synthesis of α-substituted cyclic boronates has been developed and is presented herein. This method has the advantages of using earth-abundant Ti as the catalyst and readily available dihaloalkanes, such as dichloromethane, as the reactant. As a result, α-substituted cyclic boronates with three-, four-, five-, and six-membered rings and heteroatom-containing rings, which are difficult to access using other methods, were readily obtained. Moreover, cyclic boronates with spiro rings were also gained. Studies on the mechanism indicate a Ti-catalyzed stepwise reductive cyclization pathway.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

L. Wu, X. Tian conceived the project and designed the experiments. X. Tian performed the experiments and analyzed the data. L. Wu, X. Tian wrote the manuscript. All the authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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