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Borylation

Enantioconvergent Borylation of α-Benzoyl Alkyl Bromides by Zinc Catalysis

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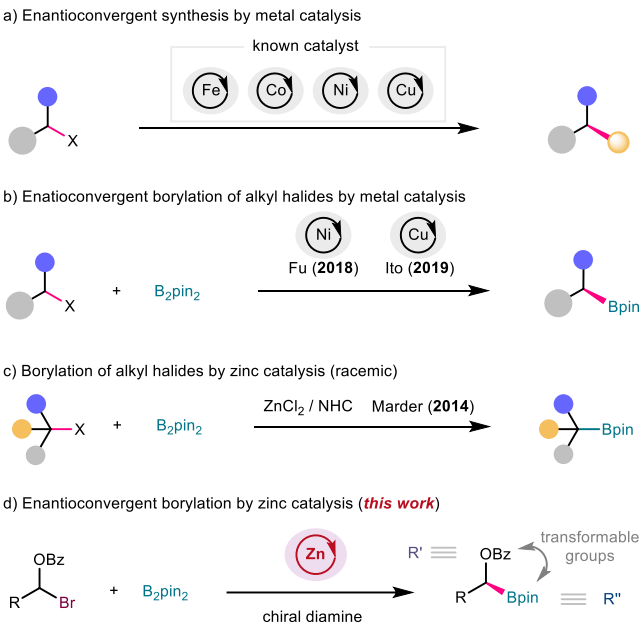
Abstract: The direct synthesis of chiral compounds from racemic alkyl halides is highly valued in organic synthesis. In this study, we present the first zinc-catalyzed enantioconvergent transformation of alkyl halides, which is enabled by substrate design and commercial diamine ligands. Chiral C─B bonds with dual transformable groups were successfully synthesized with high yield and enantioselectivity. This method also facilitates the construction of two convertible functional groups on the same carbon atom, thereby converting them into diverse chiral functional groups. Mechanistic study reveals that the Zn(II)-Bpin complex serves as the critical species for radical initiation, while the interaction between the ester group of the substrate and the catalyst is crucial in determining chirality. Notably, Zn(II) maintains its oxidation state throughout the catalytic cycle.

Introduction

Asymmetric catalysis has been developed as an essential tool for constructing chiral architectures in modern organic synthesis.[1,2] The recent development of catalytic enantioconvergent functionalization of alkyl halides has especially drawn much attention across the synthetic community because it breaks through the limitations of the traditional asymmetric catalysis to use prochiral functional groups.[3–6] Catalysts are essential for achieving enantioconvergent functionalization of alkyl halides.[7,8] While transition metals including Fe,[9–12] Co,[13–17] Ni,[18–41] and Cu[42–61] catalysts have dominated this field through sophisticated ligand engineering (Scheme 1a), the catalytic potential of earth-abundant zinc in enantioconvergent transformations remains unexplored.

Among various bond constructions, the C─B bond occupies a privileged position due to its unique transformative potential in constructing diverse chemical bonds.[62] To date, only two isolated examples employing Ni and Cu catalysts have achieved enantioconvergent construction of chiral C─B bonds from racemic benzyl chlorides, as described by Fu[31] and Ito,[56] respectively (Scheme 1b). Benefiting from the low inversion barrier of alkyl carbon radicals, the enantioconvergent coupling of alkyl halides generally proceeds via radical intermediates. Typically, Zn salts worked as Lewis acid catalysts.[63–68] Nevertheless, Marder's work on the zinc-catalyzed radical process enabling the borylation of alkyl halides (Scheme 1c)[69] has stimulated further exploration into achieving enantioconvergent coupling by zinc catalysis.

In this context, we herein disclose the first zinc-catalyzed enantioconvergent borylation of alkyl halides (Scheme 1d).



Scheme 1. Metal-catalyzed enantioconvergent cross-couplings.

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Additional supporting information can be found online in the Supporting Information section

Systematic screening identified chiral diamines as the optimal ligand, enabling the conversion of α-benzoyl alkyl halides into enantioenriched organoboronates with dual transformable groups (benzoyl and boryl). This modular strategy not only establishes zinc as a competitive player in enantioconvergent catalysis but also provides a versatile platform for molecule design.

Results and Discussion

Reaction Development

The enantioconvergent borylation was initiated using α-benzoyl alkyl bromide (**1a**), which contains an α-ester group, as the substrate and B_2Pin_2/^{i}PrMgCl as the borylation reagent (Scheme 2). Theoretically, the α-ester group in **1a** can decrease the pyramidalization of the C-centered radical and stabilize it via conjugation. Concurrently, the carbonyl moiety of **1a** can bind with Zn or the asymmetric ligand, thereby inducing the generation of stereospecific product. Systematic screening revealed that $ZnCl_2$ in combination with chiral diamine ligand **L9** provided optimal conditions for synthesizing enantioenriched alkylboronates bearing two transformable groups[70–73] (benzoyl and boryl moieties). Comparative studies with $FeCl_2$, $CoCl_2$, $NiCl_2$, and CuCl (entries 2–5) demonstrated the unique catalytic efficacy of zinc salts in this transformation. Under standard conditions (entry 1), the reaction delivered product **3a** in 83% yield with 94:6 enantiomeric ratio (e.r.). Reducing the loading of **L9** to 15% resulted in a higher yield yet relatively lower e.r. of **3a** (entry 15). Conducting the reaction at 0 °C resulted in a slight decrease in enantiomeric ratios (entry 6). Ligand architecture is proved critical for enantioselectivity control. Fully *N*-substituted ligands **L1** and **L4** (entries 7 and 10) completely suppressed reactivity. Racemic products with **L2** and **L8** (entries 8 and 14) indicated insufficient chiral induction without the phenyl group in ligand. The reactions using ligands **L3**, **L5,** and **L6** all gave **3a** in low enantiomeric ratios (entries 9, 11, 12). The use of ligand **L7** gave **3a** in a relatively high e.r. yet with a low yield (entry 13). Increasing the loading of ligand **L7** to 25 mol% led to a marginal improvement in the e.r., while the yield remained unsatisfactory (entry 18). Control experiments established the indispensability of both $ZnCl_2$ and **L9**: no reaction occurred without the $ZnCl_2$ (entry 16), while ligand omission (entry 17) provided racemic **3a** quantitatively, confirming the key role of chiral ligand in stereochemical control.

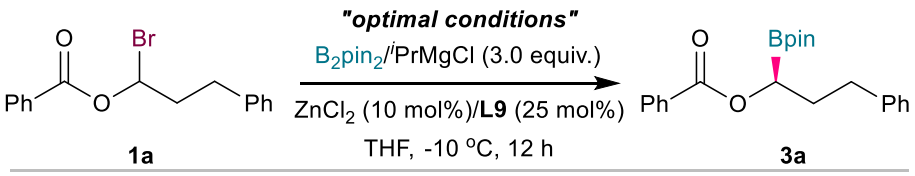
Mechanistic Study

Mechanistic studies were then performed to determine whether the reaction proceeded via a radical pathway. When using benzyl bromide **1u** under standard conditions, we observed the homocoupling product **3ua** of benzyl bromide instead of the expected borylation product **3ub** (Scheme 3a). Furthermore, the addition of a stoichiometric amount of the radical inhibitor TEMPO completely inhibited the borylation reaction (Scheme 3b). Under standard conditions, radical clock experiments were performed using substrates **1v** and **1w**, affording cyclized product **3va** and ring-opened product **3wa**, with no detectable formation of products **3vb** and **3wb**. The formation of cyclized product **3va** and ring-opened product **3wa** suggests a radical mechanism (Scheme 3c). An electron paramagnetic resonance (EPR) experiment was conducted using the spin trapping reagent DMPO, and EPR active signals were detected, and high-resolution mass spectrum confirmed the molecular weights of DMPO-adducted carbon radicals (see details in Supporting Information). These results strongly indicated the involvement of a radical mechanism in this enantioconvergent borylation reaction. The e.e. of the ligand has a linear relationship with the e.e. of the product (Scheme 3d), which reveals that the enantioselectivity determining step might involve a single ligand and a mono-zinc species. Under the optimized conditions, we employed 25 mol% of the ligand to suppress racemization of the product arising from the background reaction.[74]

DFT calculations suggest a possible dissociative electron transfer (DET) pathway for radical generation. The mechanism pathway of Scheme 3e was proposed by combining in situ NMR experiments with DFT (see Supporting Information for details). In the DET pathway (Scheme 3e), the formation of intermediate **Int3** is likely a relatively slow process. Subsequently, the formation of anionic Zn(II)-Bpin complex **Int8** through the transmetalation of Bpin group is exergonic by 9.0 kcal mol^{-1}, a thermodynamically favorable step that may drive **Int3** formation. Given that Zn–Bpin complexes have been reported to mediate the borylation of MeI to afford MeBpin,[75] we propose that **Int8** may interact with the substrate **1a** via a DET pathway by DFT calculations. The energy barrier of DET process, which is calculated using the modified Marcus theory (see Supporting Information for details), is 19.6 kcal mol^{-1}. Meanwhile, the overall energy uphill for the formation of radical **R1** is only 3.9 kcal mol^{-1}, which indicates the radical mechanism through transmetalation and DET is reliable for this reaction.

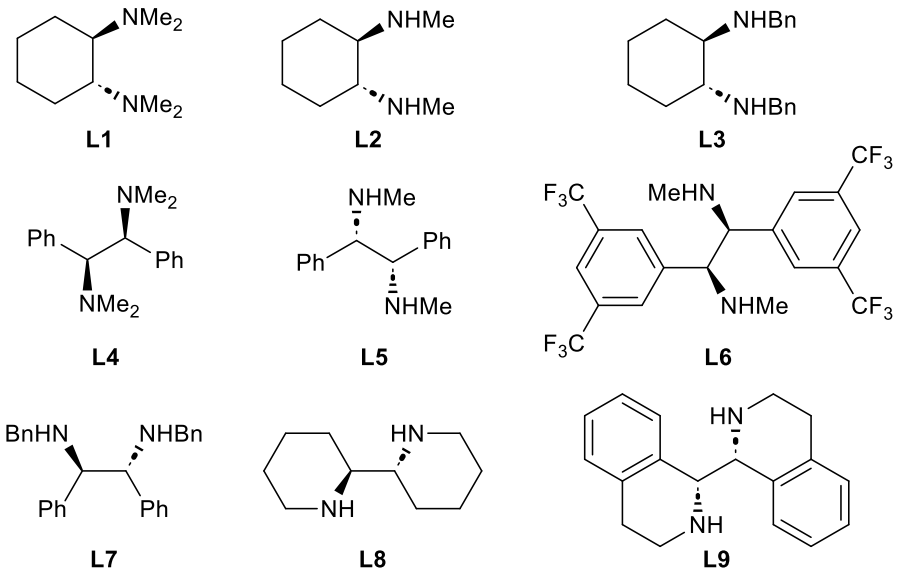
The Origin of Enantioselectivity

Under standard conditions, we evaluated the effect of R′ substituent in tuning the enantioselectivity of the resulting products (Scheme 4). The α-methyl (**1aa**) and α-silyl (**1ab**) substrates both produced racemic products, indicating the lack of ester groups may result in less interaction with the catalyst, which lead to carbon radicals with changeable configurations. The α-benzoylmethyl (**1ac**) and α-carboxylmethyl (**1ad**) substrates contained carbonyl groups that are presumed to have improved interaction with the catalyst, however, failed to achieve enantioselective synthesis due to the limited capacity of —CO—CH_2— fragment in delocalizing carbon radical. The absence of conjugation showed insufficiency in restricting the conformation of radical intermediate. In summary, the α-ester group interacts with the Zn catalyst and conjugates with the radical, thereby constraining the conformation of the radical intermediate. Thus, the α-ester group plays a critical role in enabling enantioselective catalysis.

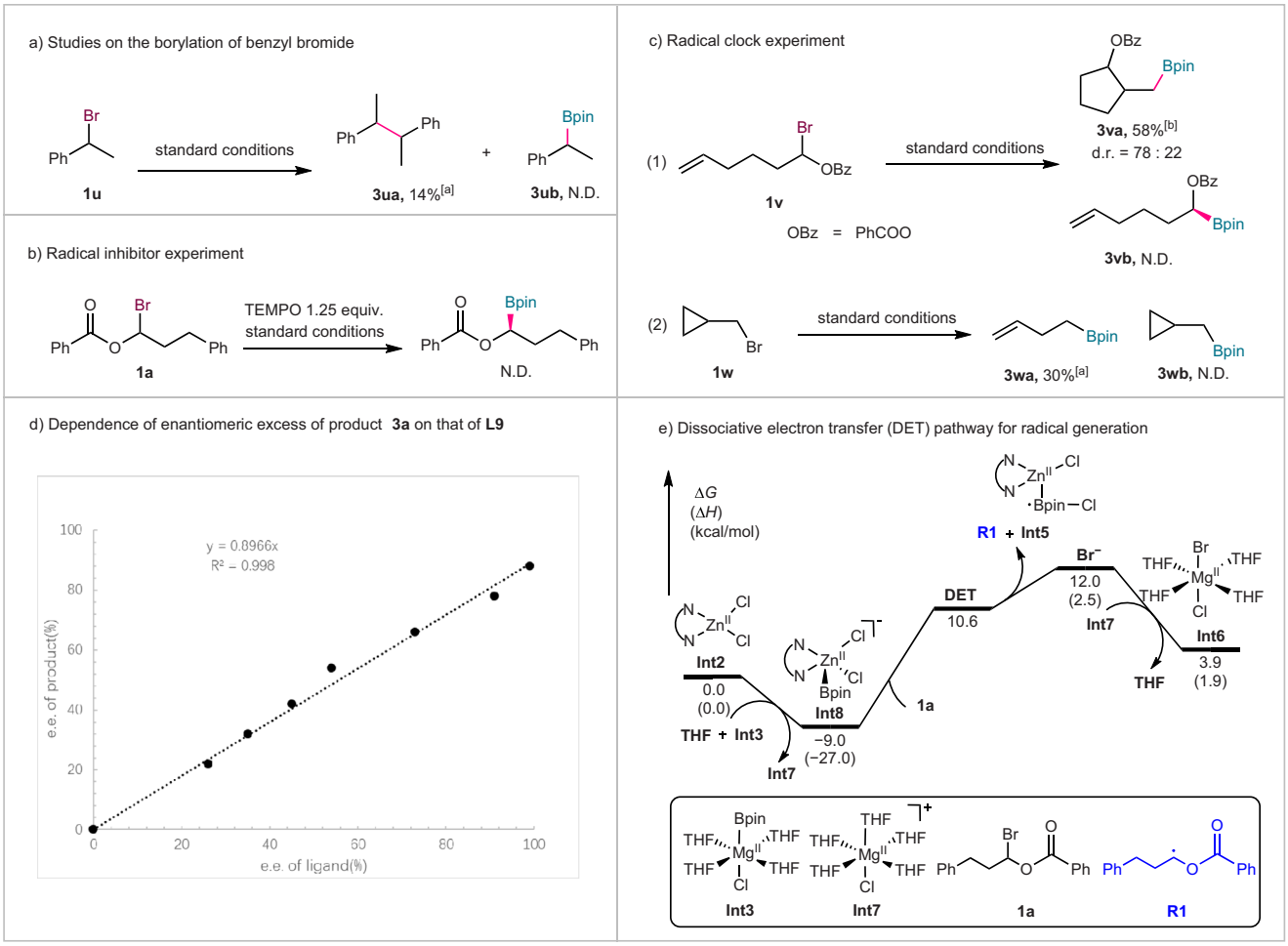


1a 3a

Entry	Condition variations	Yield of **3a**	e.r.
1	none	83%	94:6
2	$FeCl_2$	32%	50:50
3	$CoCl_2$	0%	-
4	$NiCl_2$	0%	-
5	CuCl	36%	51:49
6	0 °C	87%	92:8
7	**L1**	0%	-
8	**L2**	40%	50:50
9	**L3**	37%	76:24
10	**L4**	0%	-
11	**L5**	36%	74:26
12	**L6**	34%	73:27
13	**L7**	4%	87:13
14	**L8**	41%	50:50
15[a]	**L9**	90%	91:9
16	no $ZnCl_2$	0%	-
17	no **L9**	99%	50:50
18	**L7** (25 mol%)	17%	89:11



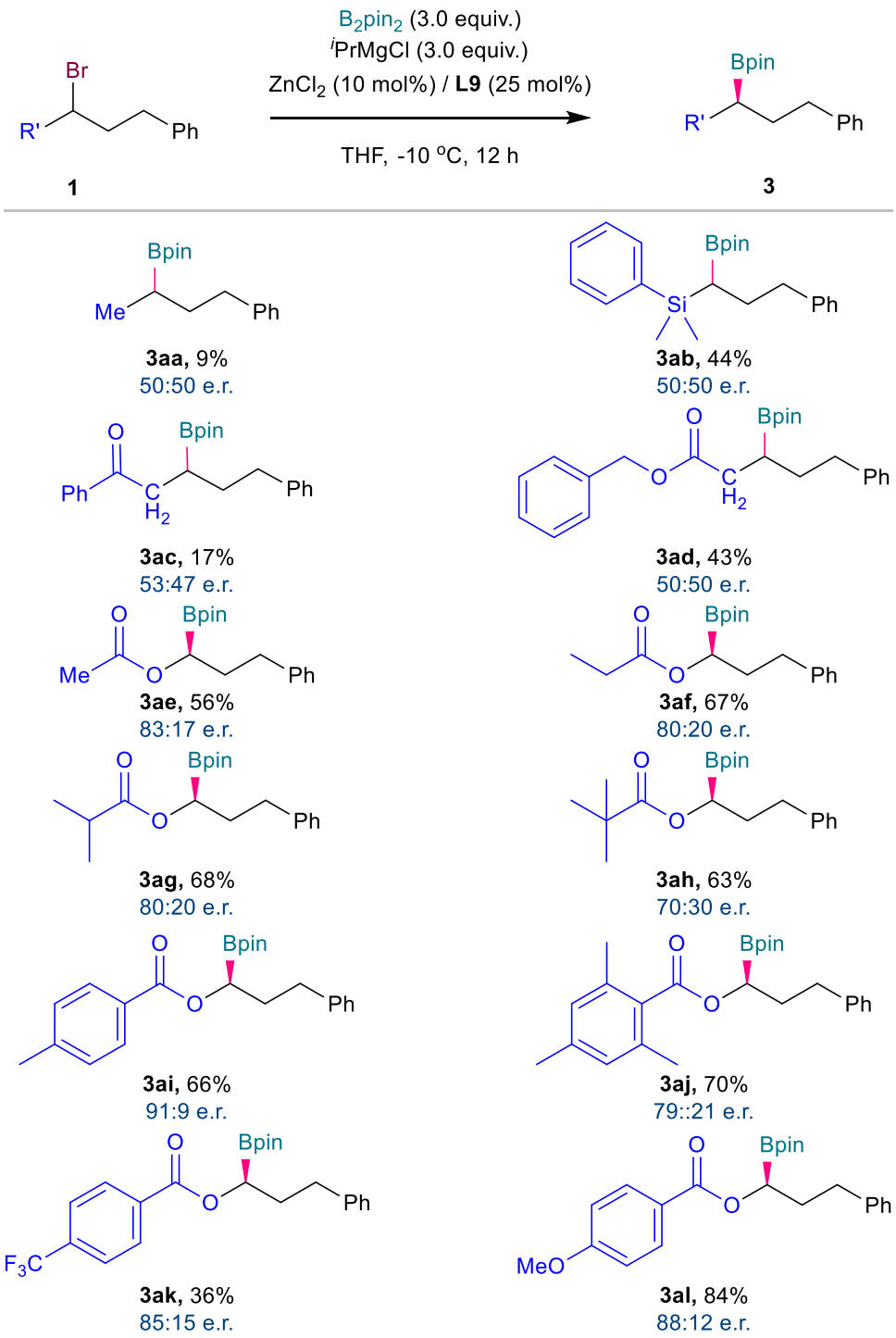
Scheme 2. Optimization of the enantioconvergent borylation reaction conditions. Unless otherwise specified, all reactions were carried out using **1a** (0.25 mmol), B_2pin_2 (3.0 equiv.), ^{i}PrMgCl (3.0 equiv.), catalysts (10 mol%), ligands (25 mol%) at -10 °C for 12 h. Entries 1–6 and 16–18: the yields were determined by NMR using CH_2Br_2 as the internal standard. Entries 7–14: B_2pin_2 (1.5 equiv.), ^{i}PrMgCl (1.5 equiv.), ligands (15 mol%), 0 °C, and the yields were determined by GC analysis using naphthalene as the internal standard. a) Ligands (15 mol%), and the yields were determined by NMR using CH_2Br_2 as the internal standard. e.r. was determined by chiral HPLC analysis.



Scheme 3. Mechanistic studies. Unless otherwise specified, all reactions were carried out using **1** (0.25 mmol), B_2pin_2 (3.0 equiv.), ^{i}PrMgCl (3.0 equiv.), $ZnCl_2$ (10 mol%), ligands (25 mol%) at -10 °C for 12 h. a) These yields were determined by NMR using CH_2Br_2 as the internal standard. b) Yields of isolated products. All energies were calculated at the (U)ωB97XD/6–311 + G(d,p)/SMD(THF)//(U)B3LYP-D3(BJ) /6–31 + G(d)/SMD(THF) level of theory.

Then, the influence of different α-ester groups (**1ae**–**1al**) on the enantioselectivity of the product was evaluated. As shown in Scheme 4, substrates with α-alkyl ester groups have been tested. Along with the ester group changed from methyl (**1ae**), ethyl (**1af**), and isopropyl (**1ag**) to *tert*-butyl (**1ah**), there was a decreasing trend of enantioselectivity of the product (**3ae**–**3ah**, Scheme 4). There was also a general trend that introducing substituents on phenyl group leads to relatively lower enantioselectivity of the product (**1ai**–**1al**). For example, with one methyl substituent (**1ai**), the enantioselectivity dropped to 91:9 e.r. (**3ai**). With 2,4,6-trimethyl substituents (**1aj**), the enantioselectivity further dropped to 79:21 e.r. (**3aj**). Substrates with electron-withdrawing trifluoromethyl (**1ak**) and electron-donating methoxyl (**1al**) substituents also afforded reduced enantioselectivity (**3ak**, 85:15 e.r., **3al**, 88:12 e.r.). Therefore, under standard experimental conditions, the benzoyl group was identified as the most effective auxiliary group.

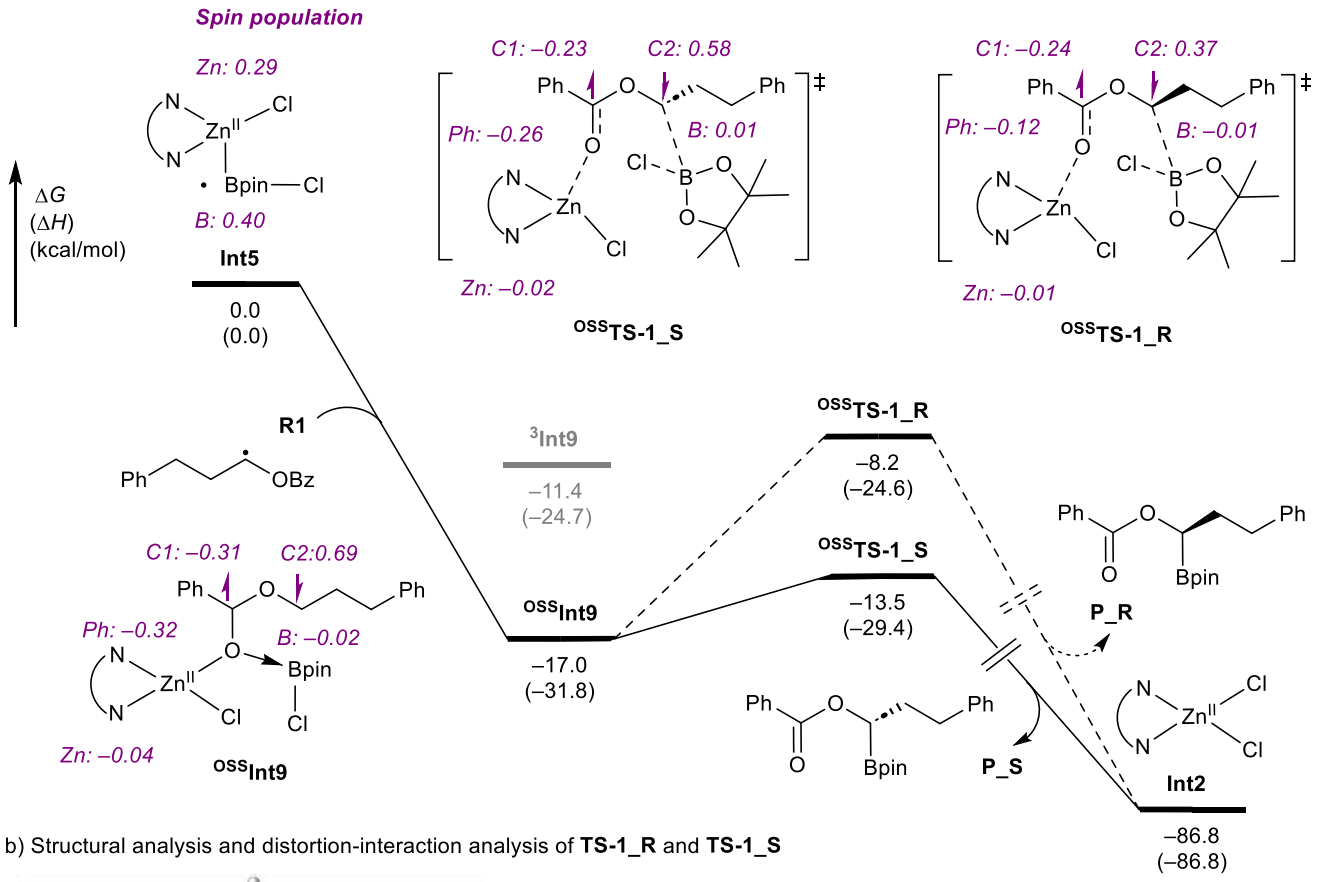
Subsequently, DFT calculations were conducted to investigate the C–B bond formation of stereoselectivity between Zn(II) complex **Int5** and radical **R1** (Scheme 5). It is noteworthy that **Int5** is also a radical species, wherein most of the spin locates at the zinc atom and boron atom. The combination of radical **R1** with **Int5** generates a stable open-shell singlet (OSS) complex ^{OSS}**Int9** (ΔG = -17.0 kcal mol^{-1}). The corresponding triplet structure is less stable by 5.6 kcal mol^{-1}. Theoretical analysis of ^{OSS}**Int9** suggests that the carbonyl moiety of **R1** is bound to the Zn center and the spin density (purple numbers in Scheme 5a) mainly concentrates on two carbon atoms adjacent to oxygen and the Ph moiety of **R1** fragment. These results imply the ester group is critical for stabilizing the radical centers and bring them closer to the chiral center. The corresponding Mulliken atomic spin density located on the zinc atom is negligible, which indicates that the valence state of Zn remains to be two. Then the radical triggered C–B bond formation prefers to occur via ^{OSS}**TS-1_S** ($\Delta G^{\ddagger}$ = 3.5 kcal mol^{-1}), generating the (*S*)-product and Zn(II) catalyst. The formation of (*R*)-product through ^{OSS}**TS-1_R** ($\Delta G^{\ddagger}$ = 8.8 kcal mol^{-1}) turns out to be kinetically disfavored. The distortion-interaction analysis was performed to clarify the energy difference between ^{OSS}**TS-1_R** and ^{OSS}**TS-1_S**. Based on the data of



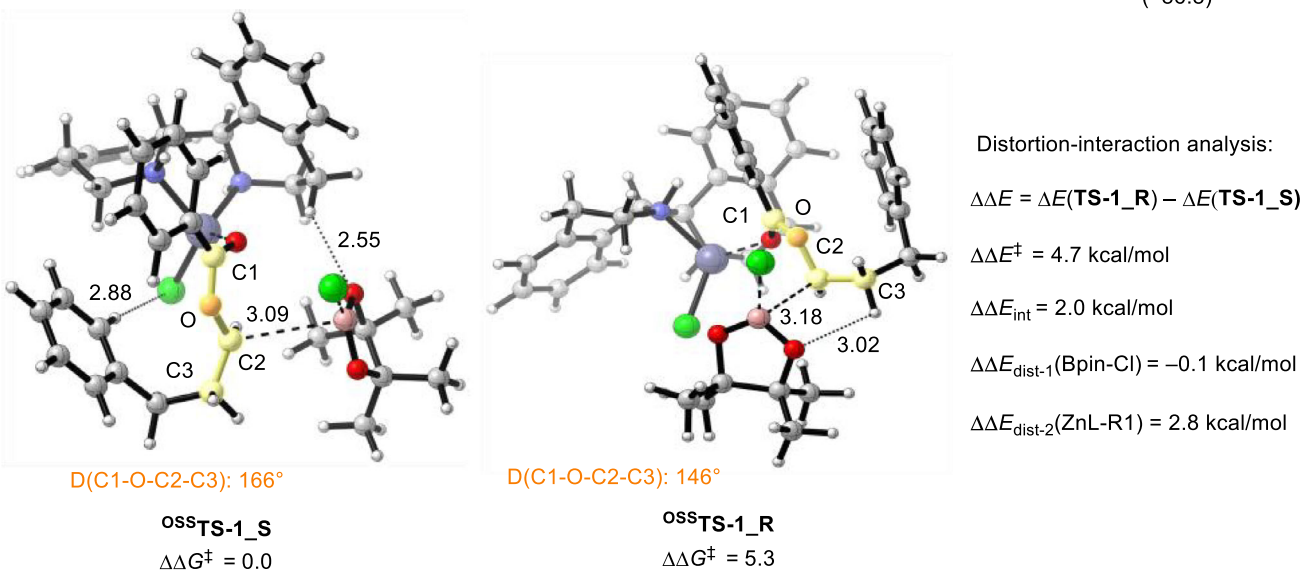
Scheme 4. Effect of the R′ substituent on product enantioselectivity. All reactions were carried out using **1** (0.25 mmol), B_2pin_2 (3.0 equiv.), ^{i}PrMgCl (3.0 equiv.), $ZnCl_2$ (10 mol%), ligands (25 mol%) at -10 °C for 12 h. Yields are isolated yields.

distortion-interaction analysis of ^{OSS}**TS-1_R** and ^{OSS}**TS-1_S**, the origin of enantioselectivity is attributed to the difference of both distortion and interaction energy, 2.7 and 2.0 kcal mol^{-1}, respectively. Structural analysis shows the dihedral angle of C1—O—C2—C3 (orange numbers in Scheme 5b) in ^{OSS}**TS-1_R** is smaller than that in ^{OSS}**TS-1_S** (166°) by 20°, which weakens the stability of radical by turning it from planar geometry into pyramid one and thus increases the distortion energy. The greater distortion in ^{OSS}**TS-1_R** originates from the large steric repulsion. As for the interaction energy, there is significant O–H interaction (2.55 Å) in ^{OSS}**TS-1_S** while the O–H interaction (3.02 Å) is weaker in ^{OSS}**TS-1_R**. The computational results suggest that the chiral diamine ligand and zinc catalyst create relatively wider space for *Si*-attack (the less steric repulsion in ^{OSS}**TS-1_S**), thereby enables the Zn(II)-catalyzed enantioconvergent borylation of

a) Free energy profile of the enantioconvergent C-B bond formation

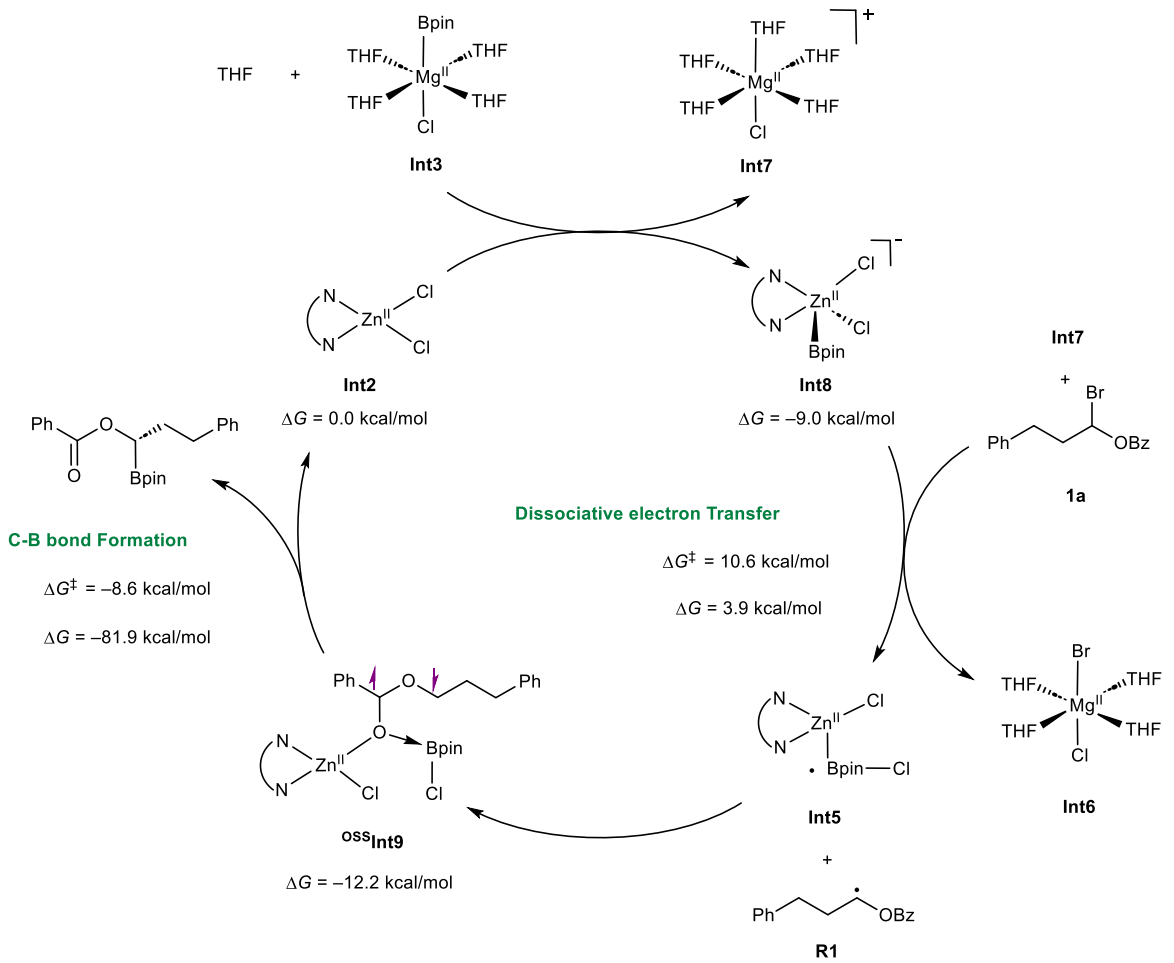


b) Structural analysis and distortion-interaction analysis of **TS-1_R** and **TS-1_S**



Scheme 5. DFT study of the origin of stereoselectivity. All energies were calculated at the (U)ωB97XD/6–311 + G(d,p)/SMD(THF)//(U)B3LYP-D3(BJ)/6–31 + G(d)/SMD(THF) level of theory. The bond lengths are in angstroms. The italicized purple numbers denote the Mulliken atomic spin densities at certain atoms.

racemic alkyl bromides. Spin and frontier molecular orbital (FMO) analyses along the intrinsic reaction coordinate (IRC) of **ossTS-1_S** show that the variation of spin state from open-shell singlet to closed-shell singlet occurs when the distance of C─B bond is shortened from 3.09 (**ossTS-1_S**) to 2.89 Å (**irc_7**). (Figure S6, see Supporting Information for details) Moreover, the spin density on the boron atom is maintained nearly zero during C─B bond formation. These results indicate that the C─B bond formation is achieved through a polar nucleophilic addition mechanism, and this process results in the annihilation of the radical property.



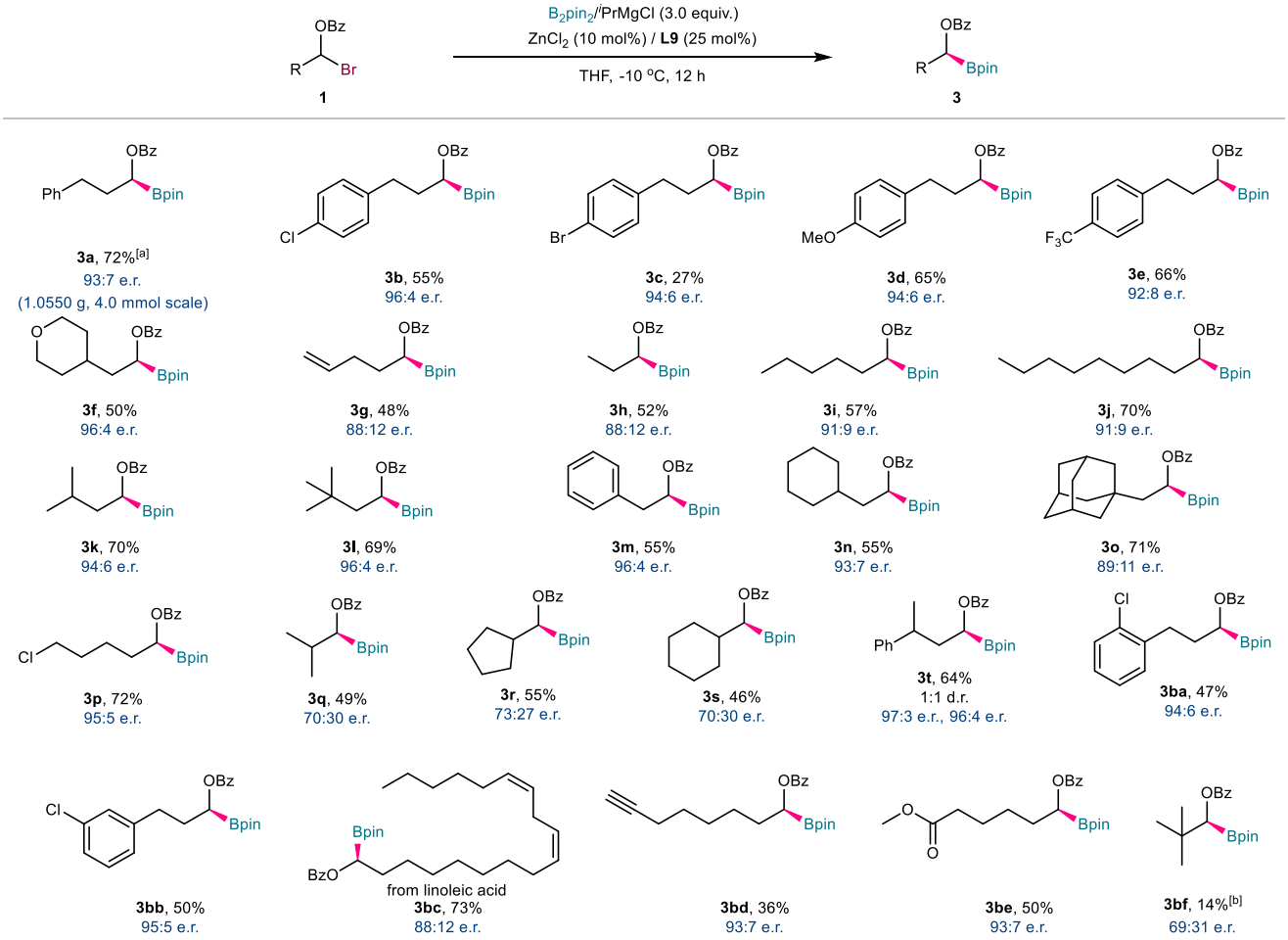
Scheme 6. Proposed catalytic cycle.

Based on the experiments described above and complemented by DFT calculations, we proposed a potential mechanism for this reaction (Scheme 6): First, the Bpin group of **Int3** transfers to Zn(II) complex **Int2**, generating THF stabilized Mg (II) cation **Int7** and anionic complex **Int8**. Subsequently, the dissociative electron transfer occurs from **Int8** to **1a** to give radical **R1**, complex **Int5** and $\mathbf{Br^-}$, followed by combination of **Int7** and $\mathbf{Br^-}$ to generate **Int6**. Then the carbonyl moiety of **R1** combinates with the zinc atom of **Int5** to form an open-shell singlet Zn(II) intermediate **Int9**, and the C—B bond formation within **Int9** occurs quickly to release the product and regenerate **Int2**.

Substrate Scope

Based on the above results, the scope of enantioconvergent borylation was investigated by using racemic 1-bromoalkyl benzoates (**1**) as substrates (Scheme 7). The catalytic system showed good compatibility with substrates. Chloro (**1b**), bromo (**1c**), methoxyl (**1d**), and trifluoromethyl (**1e**) groups on the aromatic ring all provided corresponding products with high enantioselectivity. When the para position of the phenyl ring was substituted by bromine, a low yield of product was obtained (**3c**, 27%). Ether substrate (**1f**) provided product (**3f**) with moderate yields and high e.r. The reaction also exhibited good compatibility with substrates containing highly reactive functional groups, such as alkenyl (**1g**) groups, no borylation of carbon-carbon double bonds were detected during the reaction, proving the exclusiveness of the catalytic system.

The effect of alkyl chain steric hindrance on the product e.r. was subsequently examined. There is a moderate increase in the enantioselectivity of the product when appropriately increasing the carbon chain length and the steric hindrance on the substrates (from **3h**, 88:12 e.r. to **3m**, 96:4 e.r.). When the substituents are the cyclohexylmethyl (**1n**) and adamantylmethyl (**1o**) groups, the e.r. of the product shows a marginal decrease (**3n**, 93:7 e.r. and **3o**, 89:11 e.r.). However, when the α-substituent of the substrate were isopropyl (**1q**), cyclopentyl (**1r**) or cyclohexyl (**1s**) further steric hindrance leads to a significant decrease in the enantioselectivity control. For substrates containing chlorine atoms, the chlorine atoms were retained during the reaction, and the product was obtained in high isolated yield (72%) and enantioselectivity (95:5 e.r., **3p**), which provided an opportunity for further functionalization of the C—Cl bonds. For substrate containing two chiral centers (**1t**), the resulting product has a d.r. value of approximately 1:1 (as determined by NMR), with 97:3



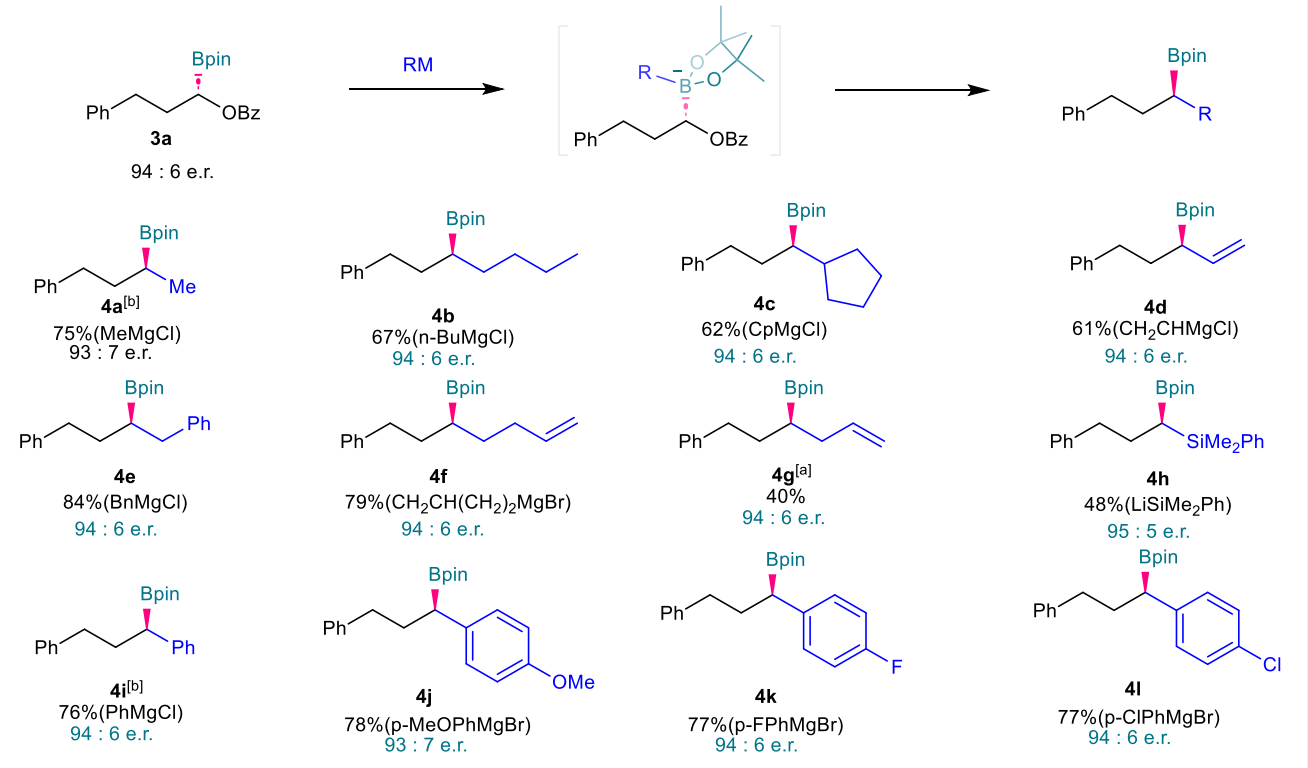
Scheme 7. Scope of enantioconvergent borylation. Reaction conditions: **1** (0.25 mmol), $ZnCl_2$ (10 mol%), **L9** (25 mol%), B_2pin_2 (3.0 equiv.), ^{i}PrMgCl (3.0 equiv.), THF (2.5 mL), -10 °C for 12 h; yields of isolated products. a) **1a** (4 mmol), $ZnCl_2$ (10 mol%), **L9** (25 mol%), B_2pin_2 (2.5 equiv.), ^{i}PrMgCl (2.5 equiv.), THF (45 mL). e.r. was determined by chiral HPLC. b) Yields were determined by NMR analysis.

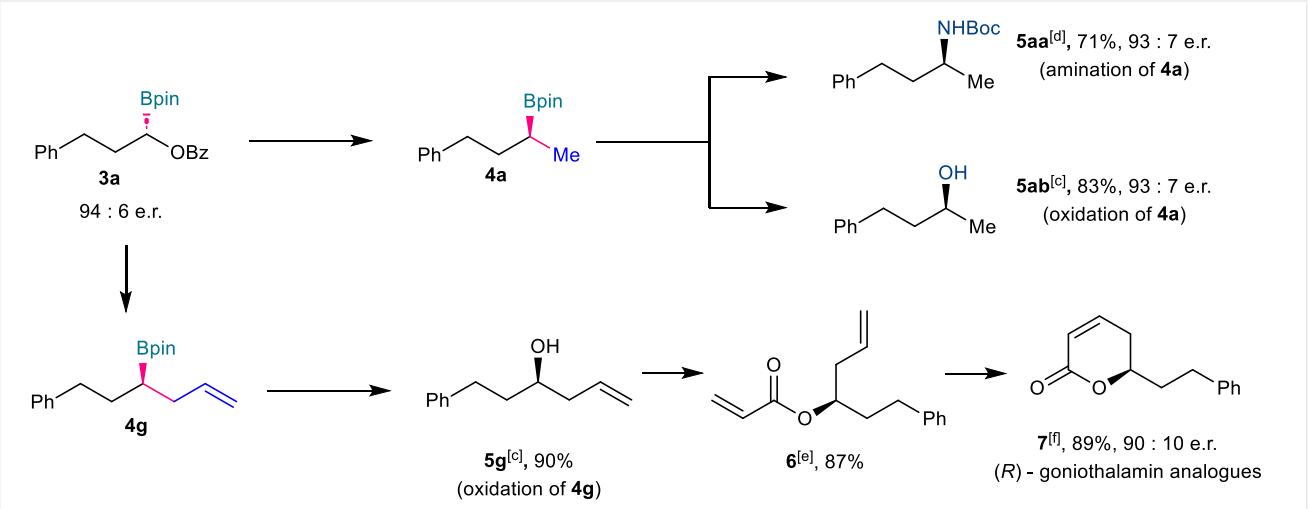
e.r. and 96:4 e.r. Furthermore, this reaction enables the synthesis of borylation products on a gram scale, obtaining the target product **3a** with an isolated yield of 72% and 93:7 e.r. (Scheme 7). For substrates bearing ortho- or meta-substituted phenyl groups, the desired products (**3ba**, **3bb**) were obtained in moderate yields with high e.r. The reaction was also effective for a substrate derived from the natural product linoleic acid, affording **3bc** in 73% isolated yield. Moreover, the reaction could tolerate substrates containing alkynyl (**3bd**) or multiple ester functionalities (**3be**) albeit in relatively low yields. In contrast, substrates with tertiary alkyl groups exhibited low conversion, likely due to steric hindrance (**3bf**).

Synthetic Utility

Chiral secondary alkyl boronic esters are highly versatile intermediates in synthesis, providing a ready source of chirality for the construction of chiral functional molecules.[76] Among the existing synthetic approaches for the synthesis of chiral secondary alkyl boronic esters,[77–79] the enantioselective borylation of alkenes and C(sp^3)—H bonds is hindered by challenges in regioselectivity control,[70,80–90] while the asymmetric borylation of halides requires substantial steric differentiation between substituents for effective chiral discrimination, typically yielding chiral benzyl boronic esters as major products.[31,56,91,92] Conversely, asymmetric transformations of boron-containing substrates and 1,2-metalate rearrangements of boronic ester complexes have been identified as highly efficient strategies for synthesizing chiral secondary alkyl boronic esters.[93–106] Notably, chiral boron compounds with α-leaving groups[70,99,101,105,107,108] serve as ideal precursors for constructing chiral secondary boronic esters via the 1,2-metalate rearrangement of boronic ester complexes as they readily undergo transformation using commercially available nucleophiles without requiring metal catalysts. Nevertheless, synthetic methods for preparing such chiral boron compounds with α-leaving groups remain scarce, with zinc catalysis emerging as a practical solution for their preparation.

To illustrate the further synthetic potential of the enantioconvergent borylation, transformations of **3a** were conducted (Scheme 8). Enantiomerically enriched long-chain





Scheme 8. Synthetic applications. Reaction conditions: **3a** (0.20 mmol), RM (1.1 equiv.), toluene (2 mL), -30 °C, 30 min, then 100 °C, 6 h; yields of isolated products. a) LiOTf (1.0 equiv.), RM (1.1 equiv.), THF (2 mL), -78 °C, 1 h, then 100 °C, 6 h; yields of isolated products. b) -30 °C, 30 min, then 80 °C, 3 h; yields of isolated products. c) NaOH(aq.), H_2O_2, r.t., 3 h. d) MMN-NH_2 (1.2 equiv.), KO^{t}Bu (1.2 equiv.), THF, 80 °C, 1 h, then $(Boc)_2O$ (2 equiv.), 80 °C, 1 h. e) Add Et_3N (1.5 equiv.), DMAP (0.1 equiv.) and acryloyl chloride (1.1 equiv.) to a solution of **5g** (0.29 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C. Warming the reaction mixture to 25 °C and stir for 4 h. f) Grubbs' II catalyst (10 mol%), CH_2Cl_2 (2.5 mL), 6 h at 50 °C. e.r. was determined by chiral HPLC.

sec-alkylboronic esters could be conveniently obtained by reacting chiral compound **3a** with different long-chain alkyl metal reagents (**4b**-**4g**, Scheme 8). Similarly, the use of silicon–lithium reagents allowed for the straightforward synthesis of chiral *sec*-silicon–boronates (**4h**, Scheme 8). Additionally, the use of aryl metal reagents also yielded chiral benzylboronic esters (**4i**–**4l**, Scheme 8). It is important to note that the selective synthesis of chiral *sec*-alkylboronic esters is challenging due to the inherent difficulty in controlling the regioselectivity of olefin, alkyne, and C–H bond borylation.[77,79,91,97] To our delight, the stereospecific 1,2-rearrangement facilitated by tetracoordinated boron species[70,79,95,97–101,107,109–117] enables the rapid and convenient synthesis of chiral *sec*-alkylboronic esters.

The product from our enantioconvergent borylation possesses two convertible functional groups (ester group

and boron group), enabling the synthesis of a broader range of compounds by transforming both functional groups (Scheme 8). For example, **3a** could be first converted into a chiral secondary alkyl borate **4a**, followed by an amination reaction[118,119] to obtain a chiral secondary amine **5aa** or oxidation to yield chiral secondary alcohol **5ab**. It worth mentioning that (*R*)-goniothalamin analogue (**7**) was successfully synthesized in a few steps by using **3a** as a raw material, which has potential applications in medicinal research.[120,121] These synthetic examples demonstrate the immense potential of this class of chiral α-boryl benzoates in synthesizing enantiomerically enriched compounds.

Conclusion

In summary, we have developed a zinc-catalyzed method for the enantioconvergent borylation of alkyl halides. We further elucidated the radical reaction mechanism through experiments and DFT calculations: The formation of anionic Zn(II)-Bpin complex through the transmetalation of Bpin group is the critical step for initiating the radical process; the ester group in the substrate and its interaction with the catalyst plays decisive role for chiral control in this radical-involved reaction process. Zn(II) retains its original oxidation state throughout the catalytic cycle. This method represents the first successful use of zinc catalysts for the enantioconvergent borylation of alkyl halides and exhibits excellent substrate compatibility. Particularly, the reaction system showed the retention of alkenyl groups, which is challenging in asymmetric borylation reactions of olefins. The chiral α-boryl benzoates show tremendous potential in synthetic applications, offering new pathways and choices for the synthesis and transformation of chiral compounds.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Alkyl halides · Borylation · Enantioconvergent synthesis · Zinc catalysis

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