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Generation and Application of (Diborylmethyl)zinc(II) Species: Access to Enantioenriched *gem*-Diborylalkanes by an Asymmetric Allylic Substitution

Yeosan Lee, Jinyoung Park, and Seung Hwan Cho*

Abstract: We report the successful generation of (diborylmethyl)zinc species by transmetallation between isolable (diborylmethyl)lithium and zinc(II) halide (X = Br, Cl) and their application in the synthesis of enantioenriched *gem*-diborylalkanes bearing a stereogenic center at the β -position of the diboryl groups by an asymmetric allylic substitution reaction. The reaction has a broad substrate scope, and various enantioenriched *gem*-diborylalkanes can be obtained in good yields with excellent enantioselectivity. Further elaboration of the enantioenriched *gem*-diborylalkanes provides access to a diverse set of valuable chiral building blocks.

The preparation of novel multi-organometallics is one of the most important tasks in modern chemistry because they provide access to synthetically valuable compounds by chemoselective carbon-carbon bond-forming reactions.^[1] In particular, the preparation of new types of gem-diborylalkanes has gained considerable attention in recent years^[2] owing to the widespread use of these compounds in several transition-metal-catalyzed^[3-5] and transition-metal-free^[6] transformations (Scheme 1a). Alternatively, gem-Diborylalkanes have also been used to generate (gem-diborylalkyl)lithiums by treatment with a sterically hindered amide base (Scheme 1b).^[7] These lithium species was known to undergo Boron-Wittig reaction with carbonyl compounds via four-membered cyclic boronate intermediates.^[8] Meek et al. disclosed a highly stereoselective addition of generated (diborylmethyl)lithium to enantioenriched epoxides to obtain fivemembered cyclic boronates and their practical use in the coppercatalyzed stereospecific deborylative coupling with allylic electrophiles.^[9] More recently, the group of Pattison reported a convenient method to generate boron enolates by reacting esters with (gem-diborylalkyl)lithiums, which could be trapped by an electrophile to afford α, α -difunctionalized ketones.^[10] Despite this progress, the current utilization of (gem-diborylalkyl)metallics relies primarily on the use of in situ generated (gemdiborylalkyl)lithiums. Such reagents are useful for reactions with organo electrophiles, but there have been problems in developing catalytic asymmetric reactions due to their high reactivity. Therefore, the development of an efficient and operationally simple protocol for the preparation of other (aemdiborylalkyl)metallics and application of these species to catalytic asymmetric reactions is highly desirable.

Herein, we report a convenient approach to generate (*gem*diborylalkyl)zinc(II) species, comprising two identical boron

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Scheme 1: Utilization of gem-Diborylalkanes. Pin = pinacol.

groups and zinc species at the same sp³ carbon center, by transmetallation of isolated (diborylmethyl)lithium with ZnX_2 (X = Br, Cl). This newly prepared organometallic reagent was applied in metal-catalyzed asymmetric allylic substitution reaction (Scheme 1c)^[11] to afford a broad range of enantioenriched *gem*-diborylalkanes in high yields with excellent enantioselectivity. The obtained enantioenriched *gem*-diborylalkanes can be elaborated to various synthetically valuable chiral building blocks via appropriate stereospecific transformations, highlighting the synthetic utility of these new compounds.

Transition-metal-catalyzed asymmetric allylic alkylation (AAA) reactions are among the most efficient and reliable tools to prepare enantioenriched allylic compounds, which are useful building blocks in organic synthesis.^[12] Recent progress in this field includes the development of efficient protocols for the introduction of a range of nucleophiles to the branched position of allylic electrophiles with excellent enantioselectivity.^[13,14] Based on these substantial advances, we assumed that an iridium-catalyzed AAA reaction with (diborylalkyl)metallics^[14] would offer a convenient platform for a rapid accessing of enantioenriched



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Scheme 2: (a) *In situ* generation of (diboryImethyl)zinc(II) species from isolable (diboryImethyl)lithium and application to the synthesis of enantioenriched *gem*-diborylalkane via iridium-catalyzed AAA. (b) Reaction of **3a** with *in situ* generated **2a**.

gem-diborylalkanes.

Before commencing our study, we first attempted to establish a method for the isolation of diborylmethyl)lithium (2a). In previous reports, 2a has been typically generated in situ from diborylmethane (1a) in the presence of a sterically hindered amide base, such as lithium diisopropylamide (LDA) or lithium tetramethylpiperidide (LiTMP); however, this approach was accompanied by the formation of an amine after deprotonation of the α -C-H bond of **1a**, which might lead to the formation of an undesired allylic amination product during the iridium-catalyzed AAA process.^[15] Therefore, we deemed the isolation of 2a was essential to efficiently achieve our proposed transformation while avoiding the problematic, competing allylic amination pathway. To the best of our knowledge, 2a has never been isolated and indeed, we successfully isolated 2a in 95% yield with 95% purity^[16] as a white solid from the reaction of 1a (30 mmol) with LDA in THF and subsequent filtration inside a glove box [Eq. (1)].^[17]

To examine the feasibility of our proposed reaction, we initially employed 2a as a potential nucleophile for the iridium-catalyzed AAA reaction (Scheme 2a). No reaction occurred when Bocprotected racemic allylic alcohol (3a) and 2a were reacted in the presence of 2.0 mol % [{Ir(cod)Cl}₂] and 8.0 mol % phosphoramidite ligand (L), one of the most frequently used ligands for the asymmetric allylic substitution of branched allylic alcohols or carbonates,^[18] in DME/toluene at room temperature, and all of the starting materials were decomposed after 12 h. However, the addition of ZnCl₂, as an additive, did furnish the enantioenriched homoallylic gem-diboronate 4a in 81% yield and 99% ee. This result indicated that the (diborylmethyl)zinc(II) species^[19] generated in situ served as a nucleophile under the reaction conditions.^[20,21] A higher yield of 90% was obtained when ZnBr₂ was employed instead of ZnCl₂, but the addition of Znl₂ deteriorated the reactivity.^[17] Note that the reaction of 3a with 2a generated in situ from diborylmethane and LDA in the presence of ZnBr₂ did not afford the enantioenriched product 4a, instead, provided allylic amine 5a as a single product in 35% yield and 86% ee (Scheme 2b). This result clearly suggests that the use of isolated 2a is crucial to achieve the present transformation. The absolute configuration of 4a was assigned to be R by further derivatization of 4a to homoallylic boronate ester 6 (vide infra)



^[a] Reaction conditions: **2** (1.1 equiv), **3** (0.20 mmol), ZnBr₂ (1.2 equiv), [{Ir(cod)Cl}₂] (2.0 mol %), **L** (8.0 mol %), and DME/toluene (1.0 mL, v/v = 1:1) at room temperature for 12 h. ^[b] Isolated yields are given. ^[c] Enantiomeric excess was determined by HPLC. ^[d] 4.0 mol % of [{Ir(cod)Cl}₂] and 16 mol % **L** was used. ^[e] Runs at 50 °C. Ts = *p*-toluenesulfonyl.

and comparison of its optical rotation with that in the literature. $\ensuremath{^{[5f,g],[17]}}$

Having achieved this result, the scope of allylic electrophiles was immediately investigated (Table 1). The reactions of allylic electrophiles bearing electron-donating (4b and 4c) and electronwithdrawing (4d) substituents at the C4-position on the arene ring provided the corresponding enantioenriched gem-diborylalkanes in moderate to good yields with excellent enantioselectivity, although 4d required increased catalyst loading and elevated temperature (50 °C) to give a synthetically acceptable yield. The reaction condition was compatible with substrates bearing halides (4e and 4f) or an ester (4g). Racemic allylic electrophiles containing substituents at the C3- or C2- position on the arene ring afforded the products 4h and 4i with high enantioselectivity, although the use of an allylic electrophile bearing a substituent at the C2-position of the arene ring (4j) led to decreased yield. The reaction conducted with an allylic carbonate containing a naphthyl group furnished 4k in good yield and enantioselectivity. The analogous reactions with heteroaryl allylic carbonates containing 3-furanyl, 3-thienyl, and 3-indolyl groups yielded enantioenriched gem-diborylalkanes 4I-4n with good to excellent efficiency and enantioselectivities. In the presence of 4.0 mol % [{Ir(COD)CI}2] and 16 mol % L at 50 °C, an aliphatic allylic carbonates also underwent the reaction and provided the product 40 in moderate vield and enantioselectivity. When (gem-diborylpropyl-3phenyl)lithium (2b) was subjected to the optimized reaction conditions, no desired product (4p) was obtained, indicating the current limitation of the developed process.

A gram scale reaction was conducted to demonstrate the practicality of the current methodology (Scheme 3a). When 5.0 mmol of **3a** and **2a** were subjected to the reaction conditions, the product **4a** was obtained in 82% yield (1.57 g) without compromising the enantioselectivity. Given the broad applicability

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Scheme 3: Transformations of the enantioenriched **4a**: Reaction conditions: [a] NaOtBu, MeOH, THF, rt, 6 h. [b] quinoline-*N*-oxide, NaOMe, toluene, 120 °C, 3 h. [c] *cat.* Pd/C, H₂, MeOH, rt, 2 h. [d] H₂O₂, NaHCO₃, THF/H₂O, 0 °C to rt, 1 h. [e] LDA, 3-phenylpropyl bromide, THF, 0 °C to rt, 6 h. [f] LDA, CH₂I₂, THF, 0 °C to 60 °C, 48 h. [g] NaBO₃·4H₂O, THF/H₂O, 0 °C to rt, 3 h. [h] *cat.* Pd(PPh₃)₄, 4-iodoanisole, NaOH, 1,4-dioxane/H₂O, 100 °C, 6 h.

of the gem-diborylalkanes and usefulness of the enantioenriched allylic compounds in synthetic chemistry, we elaborated 4a to various enantioenriched compounds (Scheme 3b). The protodeboronation of 4a by treatment with NaOtBu and MeOH in THF at room temperature afforded homoallylic boronate ester 6 in 82% yield and 99% ee. The base-promoted, direct C2-selective alkylation of 3a with quinoline N-oxide formed 7 in 71% yield without affecting the enantioselectivity upon treatment with NaOMe in toluene at 120 °C.[6c],[22] The hydrogenation of an olefin moiety of 4a using Pd/C in MeOH at room temperature, followed by the oxidation of diboron groups in the presence of H2O2 and NaHCO₃ in THF/H₂O furnished the corresponding aldehyde 8 in 67% yield (2 steps) in 98% ee. Treatment of 4a with LDA in THF and subsequent trapping of the generated (gem-diboryl)lithium intermediate with 3-phenylpropylbromide yielded internal gemdiborylalkane 4p in 94% yield, respectively, without erosion of the enantiomeric excess (99% ee). In view of the poor reactivity of (gem-diborylalkyl)zinc bromide in the iridium-catalyzed AAA reaction (Table 2, 4p), this approach provided an alternative route for the synthesis of enantioenriched internal gem-diborylalkanes. Following olefin hydrogenation of 4a, the reaction of (gemdiborylalkyl)lithium with diiodomethane afforded enantioenriched 1,1-disubsituted vinylboronate 9 (75% in 2 steps from 4a) under slightly modified Morken's conditions.[8a] The obtained product 9 converted to enantioenriched acyclic a-substituted ketone 10 (97%, 99% ee) by Bpin oxidation. Compound 9 was also used in a Suzuki-Miyaura cross-coupling with 4-iodoanisole catalyzed by Pd(PPh₃)₄ to afford product **11** in 80% and 99% ee.

In summary, we have developed an efficient protocol for the generation of (*gem*-diborylmethyl)zinc(II) species from isolable (*gem*-diborylmethyl)lithium with zinc(II) halides and demonstrated the successful application of this novel muti-organometallic reagents for the synthesis of enantiomerically enriched *gem*-diborylalkanes by an iridium-catalyzed asymmetric allylic

alkylation reaction. The reaction provides a broad range of enantioenriched *gem*-diborylalkanes in good yields and excellent enantioselectivity. Synthetic applications of the obtained products are also demonstrated, and they represent useful enantioenriched compounds in organic synthesis. Further efforts to generate other (*gem*-diborylalkyl)metallic species and develop metal-catalyzed chemoselective and stereoselective transformations are ongoing in our laboratory.

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We report a facile generation of (diborylmethyl)zinc(II) species by transmetallation between isolable (diborylmethyl)lithium and zinc(II) halides and application to the synthesis of enantioenriched *gem*-diborylalkanes via iridium-catalyzed asymmetric allylic alkylation reaction.

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