Stereoselective C−B and C−H Bonds Functionalization of polyBorylated Alkenes

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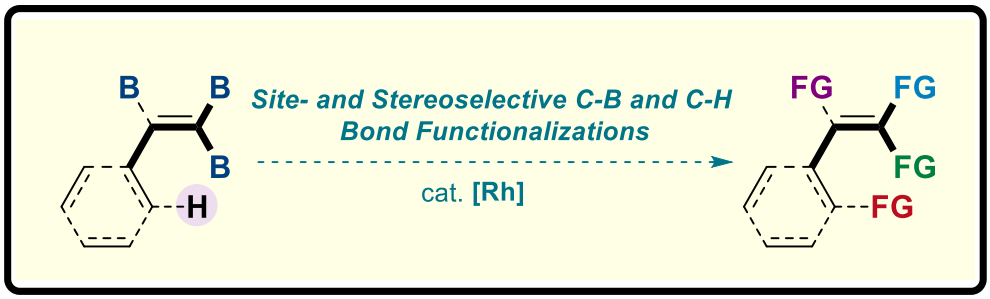

Abstract

Alkenes are fundamental functional groups which feature in various materials and bioactive molecules; however, efficient divergent strategies for their stereodefined synthesis are difficult. In this regard, numerous synthetic methodologies have been developed to construct carbon–carbon bonds with regio- and stereoselectivity, enabling the predictable and efficient synthesis of stereodefined alkenes. In fact, an appealing alternative approach for accessing challenging stereodefined alkenes molecular frameworks could involve the sequential selective activation and cross-coupling of strong bonds instead of conventional C–C bond formation. In this study, we introduce a programmed site- and stereoselective strategies that capitalizes on the versatile reactivity of readily accessible polymetalloid alkenes, through a tandem cross-coupling reaction, which is catalyzed by an organometallic Rh-complex to produce complex molecular scaffolds. By merging selective C–B and remote C–H bond functionalization, we achieve the generation of polyfunctional C(sp^2)-nucleophilic species intermediates. These species can be further modified by selective coupling reactions with various C-based electrophiles, enabling the formation of C(sp^2)–C(sp^3) bond for the generation of even more complex molecular architectures using the readily available starting polyborylated-alkenes.

Introduction

Polysubstituted olefins are essential functional groups that serve as the building blocks for a diverse array of materials and bioactive molecules.[1-3] They possess remarkable versatility as starting materials in the synthesis of various compounds, including those utilized in pharmaceuticals and materials science. Moreover, they are prevalent in numerous natural products. The double bond of alkenes, characterized by electron density and high energy, imparts distinctive properties, making them pivotal for a multitude of organic transformations.[1-5]

However, achieving the synthesis of alkenes with diverse (all-carbon) multisubstituents through stereodefined methods i.e. when aiming for *Z/E* stereoselectivity control, often demands the development of intricate synthetic routes.[1-4] Classical double bond-forming methods such as the Wittig and Horner-Wadsworth-Emmons reactions encounter serious problems of generality and stereoselectivity when used to form polysubstituted double bonds.[4,6] Consequently, alternative approaches have been devised to synthesize geometrically defined polysubstituted olefins.[7,8] Among the widely recent used techniques, diverse alkynyl carbometallation strategies dominate the field as the primary means of achieving polysubstituted olefins.[4,5,7] Another commonly employed approach involves the modification of existing olefins, with cross-coupling reactions being a prominent method in this regard.[4,9] In this realm, modern organic chemistry has embraced a new paradigm by utilizing alkenes that incorporate functionalizations and cross-coupling of strong bonds in both close proximity and remote positions relative to the double bond.[10-12]

Motivated by environmental and economic considerations, there is a growing emphasis on the discovery of novel reactions that facilitate direct derivatization of existing olefins. This pursuit encompasses direct diversification of carbon-boron (C−B) and carbon-hydrogen (C−H) bonds, which are prevalent in a wide array of organic compounds and reagents. In the later scenario, the 1,*n*-Metal shift is an elegant alternative approach enabling the functionalization of remote C–H bonds from alkenes precursors.[13-18] We postulate that the synergistic polyfunctionalization of C−B and (remote) C−H bonds can unlock fresh avenues for constructing intricate polysubstituted alkenes. In this context, we envision that polyborylated alkenes **III-1,2** hold great potential as a starting point for exploring the polyfunctionalization of C−B and C−H bonds, thereby enabling the synthesis of stereodefined alkenes (Figure 1d).[14]

Polyborylated alkenes **III**,[19-25] which comprise molecules with more than one single C–B bond, serve as valuable polymetalloid reagents in contemporary organic synthesis, facilitating a broad range of transformations that encompass the construction of multiple C–C and C–heteroatom bonds, through boron-selective transformations.[19-21,23,26,27] Chemoselective reactions on the poly C(sp^2)–B sites have

attracted great research interest since they provide an efficient and flexible platform to construct molecular diversity.[24-26,28,29] Utilizing these polyborylated alkene motifs in the context of tandem C−B and C−H bond functionalization is rarely discussed, yet holds the potential to enhance structural diversity and unlock novel transformations.[14,22,23,25,28] Furthermore, the presence of multiple C–B bonds offers the opportunity for customizable synthesis of olefins, enabling the production of both *E*- and *Z*-olefins by precisely controlling the site selectivity of the activated C–B through adjustment of reaction conditions.[22,23] While the literature provides numerous methods for synthesizing either *Z*-alkenes or *E*-alkenes, the availability of adaptable synthesis approaches for generating divergent geometric isomers (*E* and *Z*-alkenes) remains limited.[22,24,25]

In fact, our research group,[20] along with others,[24] has been extensively involved in studying the selective chemistries of polyborylated alkenes, including *gem*-diborylalkenes.[20,21,24,25,30,31] For instance, in 2019, Meek introduced a highly efficient catalytic enantioselective conjugate addition of α-boryl-C(sp^2) nucleophiles for synthesizing 1,4-ketoalkenylboronate esters (Figure 1b).[32] This reaction utilized readily available 1,1-diborylalkenes (**III**) and exhibited excellent yields and *E*-selectivity.[32] In 2022, Fernandez discovered a clever coupling methodology involving the site-selective activation of 1,1-diborylalkenes (**III**) catalyzed by a copper complex (Figure 1c).[33] The formation of energetically preferred (*Z*)-α-borylalkenyl copper **Z-[Cu]** species, followed by the coupling reaction with allyl bromides, dictated the stereoselectivity by alleviating the steric repulsion of the cis pinacolboryl alkene substituent (Figure 1c).[33] Looking back to 2012, Hayashi reported significant advancements in the field, specifically regarding the pioneering work on the 1,4-Rh shift through C–H activation, followed by 1,4-addition of the only substrate (*E*)-1,2-diphenylethenylboronic acid (**I**) to enones.[14] This process exhibited high selectivity in the presence of a Rh-catalyst (Figure 1a).[14]

Inspired by these elegant transformations involving borylated alkenes **I**, **III** (Figure 1a-c),[14,33] we envisioned a complementary approach that merges these processes into a single catalytic system for the simultaneous functionalization of synergetic C–B and remote C–H bonds in *gem*- and polyborylated alkene precursors **III-1,2** (Figure 1d-e).[14] This innovative approach would enable divergent synthesis of stereodefined alkenes. (Figure 1d-e).

This work presents a series of programmed strategies involving four designed pathways employing Rh-catalysis. These pathways result in divergent reactivity of polyborylated alkenes (Figure 1e). Path A illustrates the stereoselective generation of the *Z*-Rh species, which can undergo C(sp^2)–C(sp^3) bond coupling reactions with C(sp^2)-electrophiles i.e. enones and aldehydes (Figure 1e).

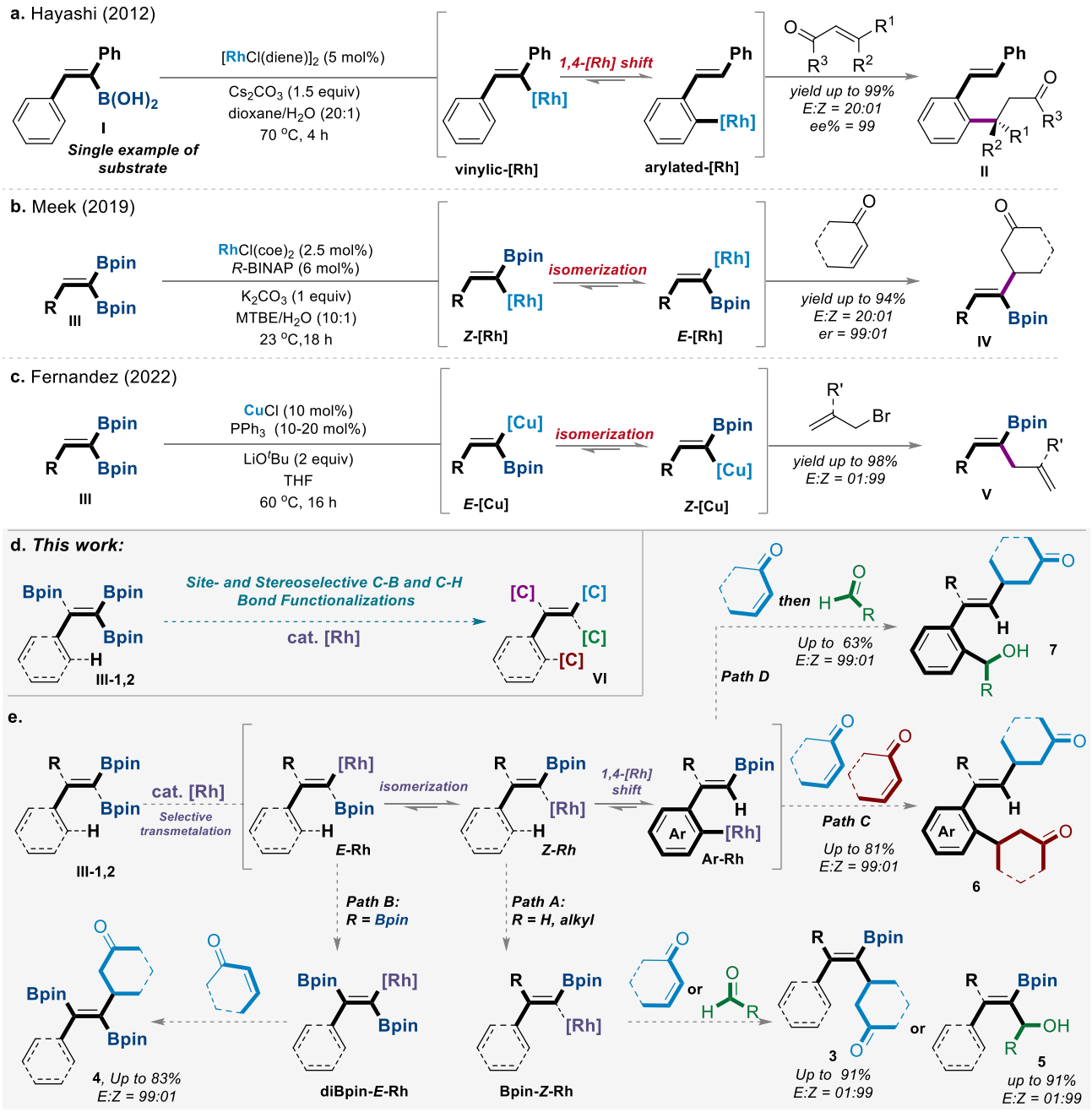

Figure 1. Prior art methods and general scheme of the work. a. 1,4-Rh migration from vinyl to aryl position via C-H bond activation using vinylboronic acid (**I**). **b** Rh-catalyzed *E*-selective C–B bond alkylation of *gem*-Diborylalkenes (**III**). **c** Cu-catalyzed *Z*-selective C–B bond alkylation of *gem*-diborylalkenes (**III**). **d** This work: Programmed Rh-catalyzed stereoselective C–B and distant C–H bond functionalization of polyborylated alkenes (**III-1,2**). **e** Stereo-divergent generation and reactivity of C(sp^2)-Rh species toward their stereospecific functionalization. **Path A**: *Z*-selective C–B functionalization through Rh-transmetalation and intercepting *Z*-alkenyl-Rh specie. **Path B**: *E*-selective C–B functionalization of triborylated alkenes via Rh-transmetalation and functionalization of the *E*-alkenyl-Rh specie. **Path C**: Rh-catalyzed (Domino) C–B and remote C–H bond functionalization of *gem*-diborylalkenes. **Path D**: Sequential C–B and C–H bond functionalization of *gem*-diborylalkenes using enones and aldehydes as electrophiles. B = boron group, M = metal, Bpin = pinacolato-boron, [Rh] = rhodium complex.

Path B outlines the exclusive formation of the *E*-Rh intermediate from triborylated alkenes **III-1,2**, subsequently functionalized by enones in a stereospecific manner.

The knowledge obtained from these two processes led us to design the merging of selective C–B and remote C–H bond functionalization through the 1,4-Rh shift,[13] as described in Paths C and D. These pathways facilitate the generation of polyfunctional C(sp^2)-nucleophilic species intermediates. These Rh-species can be further modified through selective (sequential) coupling reactions with various C-based electrophiles, such as enones or aldehydes, enabling the formation of multiple C(sp^2)–C(sp^3) bonds.

However, there are several potential challenges associated with these reactions, including the site-specific transmetalation of the boron groups, precise control of alkenyl-Rh geometry (*Z* or *E*), the prevention of protodeboration of the boryl moieties, and allowing the system to go until the 1,4-Rh migration via the C–H bond activation step.[14] We envision that the discovery of appropriate reaction conditions will aid in overcoming these complications (Figure 1d-e).

Notably, our comprehensive divergent programme offers an efficient synthetic approach to generate families of highly potent stereodefined (borylated) alkenes **3-7** (Figure 1e). This approach exhibits exceptional site-selectivity and precise stereocontrol, enabling selective subsequent modifications of these compounds leading to the stereodefined poly substituted alkenes this also include the synthesis of the stereodefined all-carbon tetrasubstituted olefin[2,3] e.g., **11** **3-7** and **VI,** respectively.

Results and discussion

The stereoselective coupling of polyborylated alkenes (III-1,2) with enones

Despite notable progress in the transition-metal-catalyzed C–B functionalization of *gem*-diborylalkenes (**III**), the precise control of *Z*-selectivity remains a significant and challenging issue.[24] Recently, Meek made a significant advancement in this area with an elegant study involving Rh-complexes catalyzed that selectively functionalize the *E*-pseudo C–B bond of the diborylated unit.[32] In their work, they elucidated the formation of the *Z*-α-borylalkenyl Rh-complex intermediate ***Z*-[Rh]**, which undergoes rapid isomerization to the more thermodynamically stable *E*-α-borylalkenyl Rh-complex (Figure 1b).[32] This outcome inspired us to consider the possibility of achieving Rh-*Z*-selectivity by manipulating this isomerization process.[24,32]

To explore this concept further, our research focused on identifying a Rh-catalytic system capable of effectively suppressing the isomerization step while selectively activating the *Z*-pseudo C–B bond of *gem*-diborylalkenes (**III**).[24,32,33] Subsequently, we aimed to facilitate the cross-coupling functionalization of this *Z*-α-borylalkenyl Rh complex intermediate (***Z*-[Rh]**) before the isomerization event takes place (blue box, Figure 2b).[33] By successfully achieving this objective, we anticipate a

significant advancement in controlling *Z*-selectivity in the functionalization of *gem*-diborylalkenes.[32,33]

To initiate our investigation, we conducted a model reaction involving the coupling of *gem*-diborylalkenes **III-1a** with cyclohexenone **eno-1a**. Through an extensive reaction screening process, we identified the optimal reaction conditions, which entail using the $[Rh(COD)Cl]_2$/BINAP catalytic system, K_2CO_3 as the base, and a solvent mixture of dioxane/H_2O (further details can be found in the supporting information on pages xx to xx).[32]

Remarkably, this catalytic system exhibited exceptional efficiency, resulting in the conversion of *gem*-diborylalkene **III-1a** to the desired product **3a** with excellent **Z**-selectivity and a high yield of 80%. To further validate the outcome, the relative **Z**-configuration of product **3a** was unambiguously confirmed through X-ray crystallographic analysis (see X-ray structure of **3a** in Figure 2b).

Next, we explored the reaction scope by investigating various coupling partners of enones **eno-1a-e** and *gem*-diborylalkenes **III-1a-j** (Figure 2b). The reaction exhibited good tolerance towards a range of cyclic enones, such as cyclopentenone **eno-1b**, and cycloheptenone **eno-1c**, leading exclusively to the formation of the corresponding *Z*-borylated alkene products **3b-c** in moderate yields. We also examined heterocyclic enones, including *N*-methylmaleimide (**eno-1d**) and dihydropyranone (**eno-1e**), which efficiently yielded the desired products **3d-e**, respectively. Also, various arylated *gem*-diborylalkenes (**III**), featuring both electron-donating and electron-withdrawing substituents on the aryl moiety, were examined to successfully yielding the *Z*-alkylated products **3f-j** in good yields. This also includes the anthracene-derived *gem*-diborylalkene **III-1g** which demonstrated viability and proceeded with high *Z*-coupling selectivity (in **3k**). Aliphatic *gem*-diborylalkenes were also applied to obtain products **3l** and **3m** (Figure 2b).

The observed *Z*-selectivity can be rationale by two key factors, in which ensures a temporal sequence to the formation of the *Z*-α-borylalkenyl Rh intermediate ***Z*-[Rh]** (blue box, Figure 2b).[32,33] Firstly, the likelihood occurrence of kinetically favored B/Rh transmetalation step of the *Z*-pseudo Bpin group compared to the *E*-pseudo Bpin group plays a crucial role. This preference is likely driven by the necessity to relieve the 1,2-aryl Bpin strain that sterically builds up between the bulky Bpin group and the aryl on the *gem*-diborylalkene (**III**).[32,33] Secondly, the addition reaction to the enone occurs prior to the isomerization of the Rh-complex (blue box, Figure 2b).[32] These suggestions are also supported by the recent observations of Fernandez coupling methodology involving the Z-selective copper-catalyzed activation of *gem*-diborylalkenes (Figure 1c).[33]

Finally, the fully-substituted *gem*-diborylalkenes (**III-1j**) demonstrated exclusive mono-selective functionalization, resulting in the formation of borylated product (**3n**) with a 73% yield.

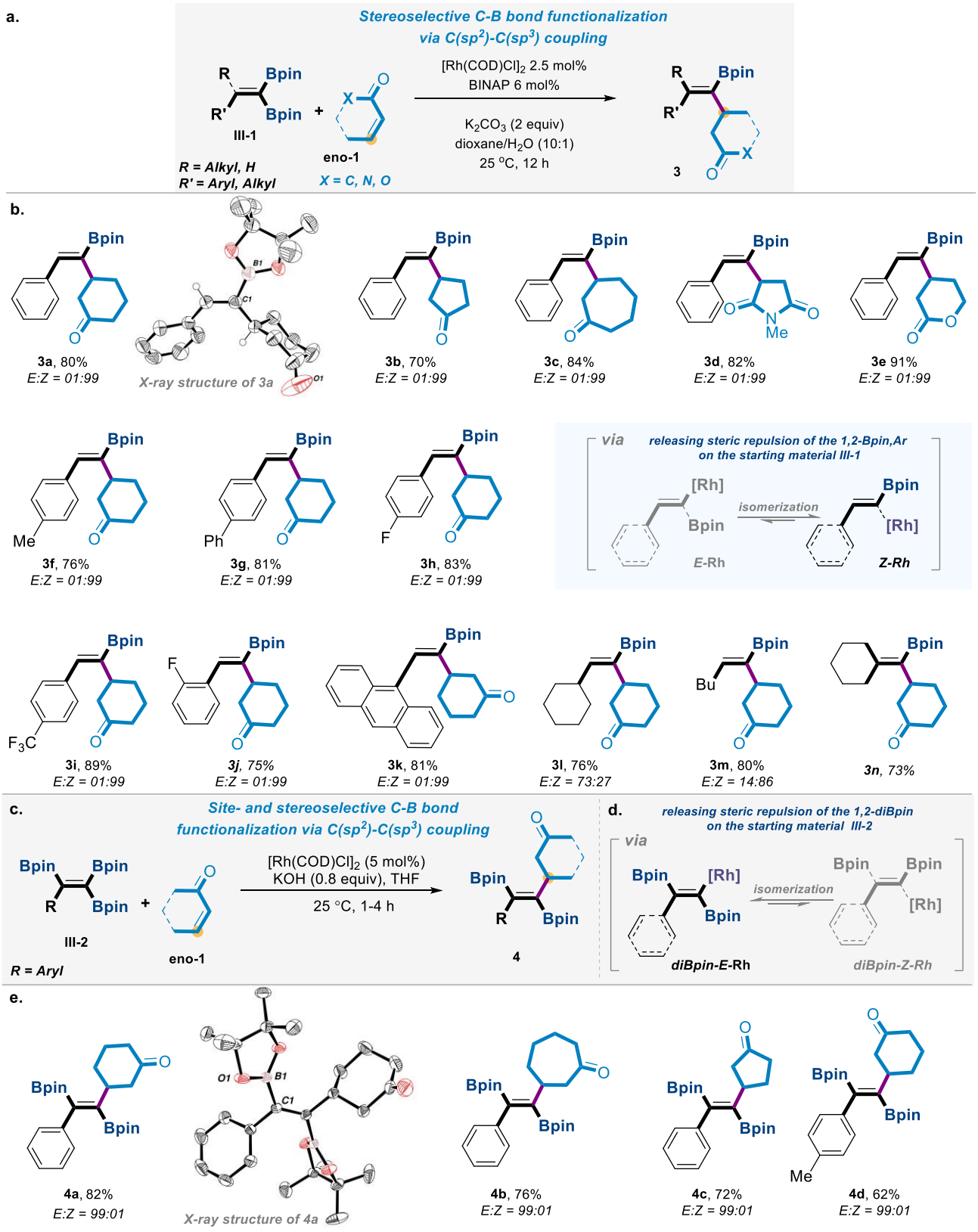

Figure 2. Stereoselective C-B bond functionalization via enone coupling. a. General Scheme of the Rh-catalyzed *Z*-selective C–B bond alkylation of the *gem*-diborylalkenes **III-1**. **b.** Scope of the Rh-catalyzed *Z*-selective C–B bond functionalization of the coupling reaction of *gem*-diborylalkenes (**III-1**) and enones (**eno-1**). **c.** General Scheme of the Rh-Catalyzed *E*-selective C–B alkylation of triborylated alkenes (**III-2**). **d.** Selectivity rational. **e.** Scope of the Rh-catalyzed C–B functionalization bond of triborylated alkenes (**III-2**). Bpin = pinacolato-boron, [Rh] = Rhodium complex. Yields of isolated products are given.

Next, we sought to expand the scope of our method to more complex polyborylated alkenes structures, specifically triborylated alkenes **III-2** (Figure 2c-e).[22,24,25,34] The main question we aimed to address was whether we could achieve precise control over site- and stereoselectivity in this system.[34] Undoubtedly, this presented a significant challenge since we now have three C–B bonds that potentially can undergo transmetalation with the Rh-complex (Figure 2c-d). Managing the selectivity in this intricate setting required careful consideration and innovative approaches.[22,25]

To probe this new reactivity, we carried out a reaction using tri-borylated[24,34] alkenes **III-2a** and cyclohexanone **eno-1a**, implementing minor adjustments to the reaction conditions. Remarkably, the reaction proceeded smoothly, leading to the exclusive formation of the *E*-selective product **4a** with a yield of 82%. The *E*-configuration of product **4a** was confirmed through X-ray crystallographic analysis, providing solid evidence for the achieved selectivity (See x-ray structure of **4a** in Figure 2e). Once again, the observed site and *E*-selectivity aligns well with our proposed rationale, which involves the relief of 1,2-strain that accumulates the bulkier 1,2 diBpin groups on the borylalkene substrates (Figure 2e).

Expanding the scope further, we explored the use of additional cyclic enones, such as cycloheptenone **eno-1c** and cyclopentenone **eno-1b** which also proved to be effective in this transformation, affording intriguing stereodefined diborylated olefins **4b-c** in good yields. Additionally, we tested the reactivity of para-methyl substituted tri-borylalkenes under standard conditions, and this reaction proceeded efficiently, yielding the desired product **4d** in a respectable 62% yield (Figure 2e).

The stereoselective coupling of *gem*-diborylalkenes (III) with aldehydes

Encouraging by these obtained results, we are now motivated to explore further possibilities of expanding the Rh-catalyzed stereoselective functionalization of the *gem*-diborylalkene **III** by introducing new C(sp^2)–C(sp^3) bond coupling reactions.[35,36] By analogy to the previous *Z*-selectivity addition reaction to cyclic enones, this can be envisioned by employing the in-situ generated *Z*-Rh-borylated alkene intermediate (***Z*-Rh**) in conjunction with other C(sp^2)-based electrophiles. Nevertheless, to ensure the desired outcome and the success of the process, it is crucial to bear in mind that the addition reaction step to the electrophile must take place prior to the isomerization of the Rh-complex (Figure 3b).

To address this goal, we anticipated that utilizing aldehydes as possible C(sp^2)-based electrophiles, could offer a new versatile synthesis method, enabling the creation of a relatively rare class of stereodefined *Z*-2-Bpin-allylic alcohols **5** (Figure 3a).[25,35]

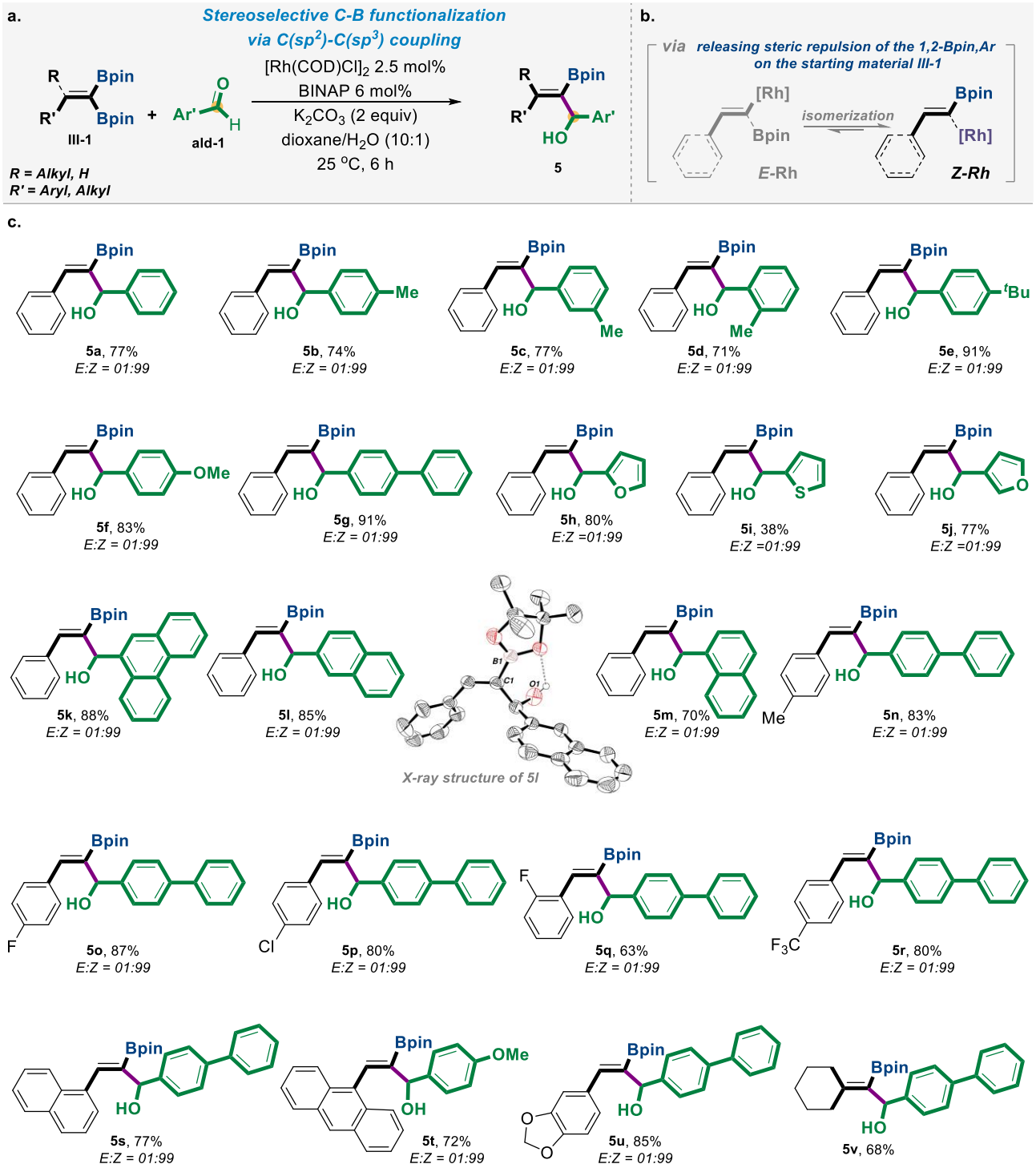

Figure 3. Stereoselective C-B bond functionalization via aldehyde coupling. a. General Scheme of the Rh-catalyzed *Z*-selective C(sp^2)–C(sp^3) coupling of the *gem*-diborylalkenes (**III-1**) with aldehydes **ald-1**. **b.** Stereoselectivity proposed model. **c.** Reaction scope with respect to *gem*-diborylalkenes (**III-1**) and aldehydes (**ald-1**). Bpin = pinacolato-boron, [Rh] = Rhodium complex. Yields of isolated products are given.

In this regard, it is worth mentioning that Walsh has reported the stoichiometric $ZnMe_2$-promoted nucleophilic addition of the in-situ generated *gem*-Zinc,boryl alkenes to aldehydes at -78 °C, resulting

in *E*-selective allylic alcohol derivatives.[36] To the best of our knowledge, the catalytic synthesis of *Z*-selective functionalization of *gem*-diborylalkenes **III** using aldehydes has not been reported, yet making it a highly appealing and promising area for further exploration.[36] [25]

To this end, we started our investigations by conducting a model Rh-catalyzed reaction utilizing phenyl-*gem*-diborylalkene **III-1a** and benzaldehyde **ald-1a** under the optimized conditions. The reaction result showed, that the desired borylated-allylic alcohol product **5a** was formed as a single *Z*-stereoisomer with a yield of 77% (Figure 3c).

After establishing the optimized Rh-catalyzed reaction conditions, we proceeded to broaden the substrate scope by introducing diverse *gem*-diborylalkenes **III**, coupling them with various aryl aldehydes **ald-1**. We observed that aldehydes bearing electron-donating or electron-withdrawing groups at the para, meta, and ortho positions on the aryl ring were highly relevant precursors, yielding products **5b-g** with exclusive *Z*-selectivity and good yields. Furthermore, the reaction exhibited compatibility with aldehydes bearing heteroarenes, such as furan **ald-1h** and thiophene-derived aldehydes **ald-1i**, leading to stereodefined allyl alcohol derivatives **5h-j** in good yields. Moreover, various polyaromatic aldehydes, including phenanthrene aldehyde **ald-1k**, α-naphthalene carboxaldehyde **ald-1l**, and β-naphthaldehyde **ald-1m**, effectively participated in the reaction, furnishing the desired 2-Bpin-allylic alcohols **5k-m** with excellent stereoselectivity and satisfactory yields as well. Notably, the relative *Z*-configuration of product **5l** was unambiguously confirmed through X-ray crystallographic analysis (See X-ray structure of **5l**, Figure 3c).

Subsequently, we explored different arylated *gem*-diborylalkene substrates **III-1b-m** under the established optimal Rh-catalyzed reaction conditions. *Gem*-diborylalkenes **III** containing both electron-donating and electron-withdrawing groups at the aryl moiety demonstrated excellent tolerance in the transformation, affording stereodefined alcohols **5n-r** in good to excellent yields. Additionally, anthracene (**III-1g**), naphthalene (**III-1i**), and dioxol-derived *gem*-diborylalkenes **III-1m** proved to be viable substrates, providing the desired products **5s-u** with good yields and excellent stereocontrol. Importantly, the tetrasubstituted *gem*-diborylalkenes (**III-1j**) exclusively underwent mono-selective functionalization, delivering product (**5v**) with a 68% yield, showcasing remarkable compatibility and selectivity (Figure 3c).

The stereoselective tandem C–B and C–H bonds functionalization

Based on these promising outcomes, we are now filled with confidence that we can successfully generate the *Z*-Rh specie, a crucial and customizable intermediate essential for the proposed distal C–H bond rhodation process via 1,4-Rh shift (Figure 4b).[13-17] We questioned whether it is plausible for

a single metal complex to be engaged in a series of domino sequential reactions, involving activations of three bonds (C–B and C–H bonds), two transmetalations, migration of the metal to a distal position, and ultimately modifying three sites (Figure 4a-b).[13] Moreover, we aimed to ascertain whether all these functionalizations occur in a site- and stereoselective manner? In order to explore these inquiries, we considered the possibility that the system of *Z*-Rh species could be influenced, by fine-tuning the reaction conditions, allowing the 1,4-Rh shift (Figure 4).[13-17 18]

To test our hypothesis, we conducted a campaign of optimizations on reaction conditions (for additional information, refer to supporting information, pages xx-xx). Our findings demonstrate that employing KOH as a strong base, THF as a solvent, and elevating the reaction temperature up to 60 °C efficiently resulted in the formation of the difunctionalized product **6a**, in extraordinary stereoselectivity. This suggests that the *gem*-diborylalkene underwent a Hayashi-type 1,4-Rh shift facilitated by selective C–H bond activation (Figure 4a-b).[13,14,16,17]

Having these optimized conditions, we next investigated the scope of this tandem reaction (Figure 4a, 4c). The reaction was found to be tolerant for various substituted aryl groups on the *gem*-diborylalkene **6a-d**. Furthermore, the reaction exhibited compatibility with a variety of in-situ added electrophilic enones, such as cyclopentenone **eno-1b**, and cycloheptenone **eno-1c**, allowing the synthesis of the desired difunctionalized products **6e-g** as the exclusive *E*-stereoisomer in satisfactory yields. Remarkably, the reaction shows excellent stereoselectivity when fully substituted Me, Ph-*gem*-diborylalkene **III-1n** have been subjected to the reaction conditions, obtaining the *E*-difunctionalized products **6h** in good yield (Figure 4c).

Based on the obtained results, we have proposed two mechanistic pathways for the sequential C–B/C–H functionalizations (Figure 4b, 4d).[13,14] In Path A, the process begins with a selective *E*-pseudo C-B bond alkylation, followed by a B/Rh transmetalation involving the second boron group located *syn* to the aryl group, forming an intermediate (***Z*-Rh**). This intermediate ***Z*-Rh** then undergoes a 1,4-Rh shift, leading to the second functionalization of the C(sp^2)–Rh bond of the arylrhodium species **Ar-Rh**. In Path B, the initial step involves the Rh-mediated transmetalation of the *Z*-pseudo C-B bond, which IS located *syn* to the aryl group, leading to a 1,4-Rh shift and functionalization at the ortho position of the aryl moiety.[17] Subsequently, the remaining C–B bond on the *E* position undergoes functionalization in this way (Figure 4d).[13,14]

Although in this stage we cannot determine which pathway is the dominant among both paths A-B (Figure 4d). We think that it might be a mix between these two pathways. Yet, the desired product obtained as designed via a 1,4-Rh swap.[13-15,17,18]

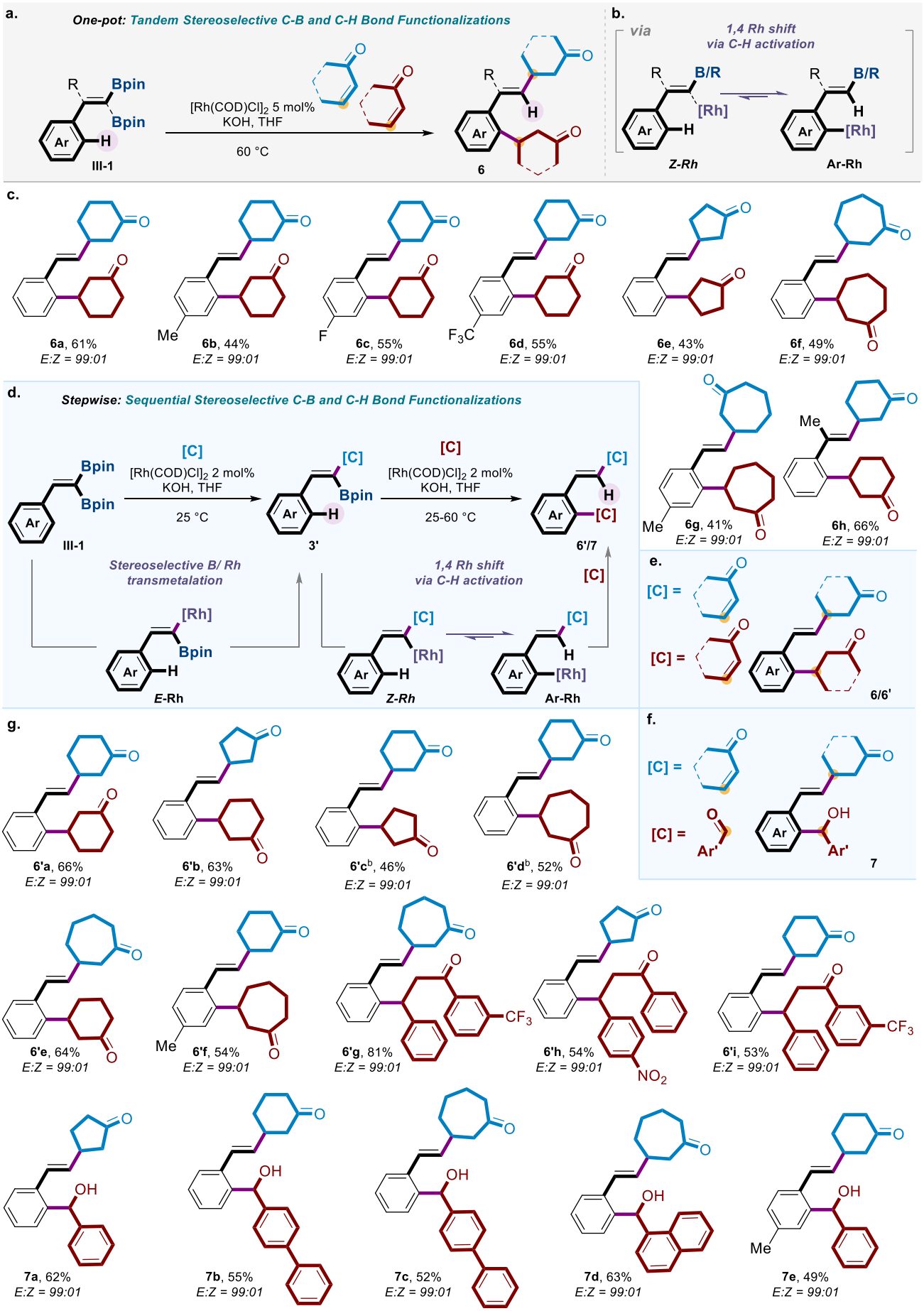

Figure 4. Sequential Stereoselective C-B and C-H Bond Functionalizations. **a.** The programmed one-pot Rh-catalyzed tandem C–B and C–H bond difunctionalization of *gem*-diborylalkenes (**III-1**). **b.** Proposed Ar-Rh species generations via 1,4-Rh migration. **c.** Reaction scope of stereoselective tandem C–B bond and C–H bond functionalization via coupling reaction of *gem*-diborylalkenes (**III-1**) and Enones. **d.** The stepwise Rh-catalyzed stereoselective C–B bond and C–H bond transformations. **e.** Representative [C]-enone-based electrophiles for the stepwise C–B and *ortho* C–H functionalization. **f.** Representation of the [C]-based electrophiles e.g. enones and aldehydes for C–B and C–H functionalization. **g.** The reaction scope for the stepwise functionalization through the coupling reaction of *gem*-diborylalkenes with to aldehydes and Enones. [C] = C(sp^2)-based electrophile, Bpin = pinacolato-boron, [Rh] = Rhodium complex. The Diastereomeric ratio (d.r.) values for all examples are 1:1 which were determined by NMR analysis. Yields are given for the isolated products of the C–H functionalization step.

Nevertheless, through this Rh-catalyzed one-pot approach, we successfully achieve selective functionalization of two different distal positions utilizing the same electrophile (Figure 4a, 4c). To introduce two different electrophiles into the system, we envisaged that a programmed stepwise Rh-catalyzed reaction might enable us to achieve this objective as described in Figure 4d.

As per our strategy, we initiated the process by functionalizing the *E*-pseudo C–B bond of *gem*-diborylalkene **III-1** with the first electrophilic enone **eno-1**, resulting in the exclusive formation of the *E*-borylated alkene product **3'**, in which we actually achieve stereodivergent complementation of the *Z*-selective products **3** in Figure 2 (Figure 4d-g). Subsequently, the borylated alkenes **3'** underwent a second Rh-catalyzed reaction with the second electrophile, leading to the successful generation of the difunctionalized products **6'**,**7** through C–B/C–H bond activation via a C–B/Rh transmetalation/migration /addition reaction (Figure 4d-g).[14] This method allowed us to synthesize a diverse array of *E*-difunctionalized products (**6'a-i**) using two distinct electrophiles (Figure 4g). Notably, the second electrophile can encompass cyclic-enones **eno-1**, aldehydes **ald-1**,[35] or acyclic-enones **eno-2**, leading to the formation of new C-C bonds with various functional groups (**7a-e**, Figure 4e-g). It is worth emphasizing that 1,4-Rh migration followed by alkylation using aldehydes as an electrophile, is quite elusive.[17,18] This flexibility opens up possibilities for creating compounds with diverse and unique functionalizations **6'** and **7** (Figure 4e).

Synthetic utility of borylated-alkenes (3-5) and products (7)

Next, we explored the potential applications of the borylated alkenes **3-5** and the difunctionlized products **7b** by utilizing them on the C-C bond forming reactions to construct more complex structures of stereodefined polysubstituted alkenes (Figure 5).[25] To this end, various representative arylation coupling reactions for applications were conceived for some of these valuable alkene products **3**, **4a**, **5** as depicted in Figure 5a-d. For instance, we conducted a selective Suzuki–Miyaura cross-coupling

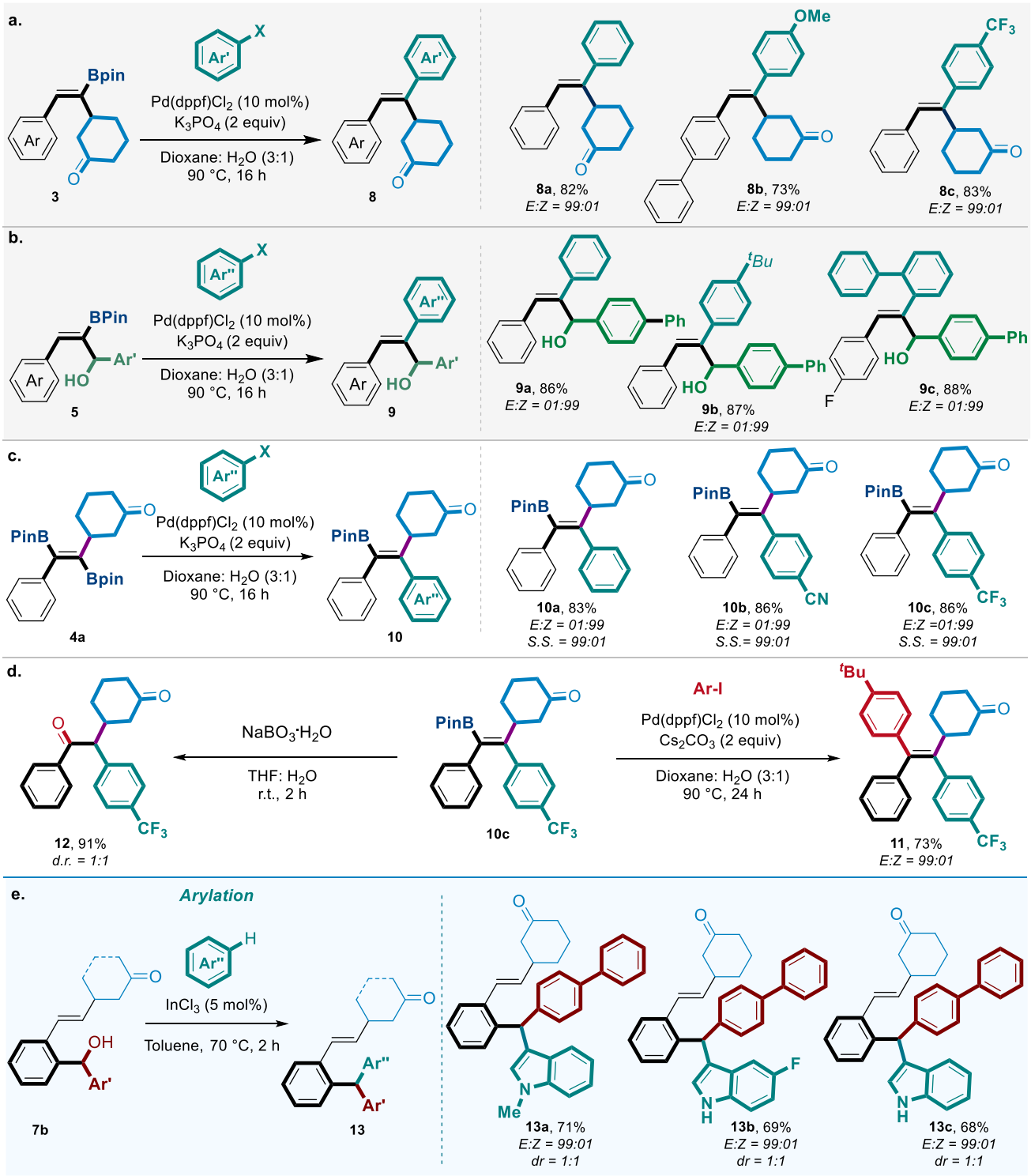

Figure 5. General scheme of the representative applications. a. Selected examples of Suzuki–Miyaura Coupling of (**3**). **b.**Selected examples of Suzuki–Miyaura Coupling of borylated allylic alcohol alkene **5**. **c.** Examples of the Suzuki–Miyaura Coupling of *tran*-diborylated alkene (**4a**). **d.** Example of oxidation reaction and Suzuki–Miyaura Coupling of alkenes (**10c**). **e.** Friedel-Crafts arylation-type reaction of difunctionalized alcohol alkenes **7b**. Site selectivity ratio (S.S.). Yields are given for the isolated products of the C–H functionalization step. The stereo-structure of **10** was determined by HMBC NMR study and by the outcome of the oxidation reaction resulting in ketone **12**. Bpin = pinacolato-boron.

reaction, of borylated alkenes **3**, **5** and *anti*-diborylated alkenes **4a**, with aryl-halides providing desired cross-coupling product **8-10** respectively in very good yields (Figures 5a-c).

Moreover, the new *trans*-diborylated alkene **10c** underwent further Suzuki–Miyaura cross-coupling reaction affording the stereodefined all-carbon tetrasubstituted olefin[2] **11** (Figure 5c) in a highly selectivity fashion. Importantly, borylatedalkene **10c** can be converted to ketone product **12** through the oxidation reaction as described in Figure 5d.

Finally, we explored the application of difunctionalized alcohol products **7b** in the Friedel-Crafts arylation-type reaction catalyzed by $InCl_3$, successfully producing the indole-based triarylmethanes **13a-c** (Figure 5e).[37,38] These findings highlight the promising potential of borylated alkenes and their difunctionalized derivatives in constructing complex and highly functionalized alkenes.

Conclusions

This paper describes a set of complementary programmed strategies aimed at tackling the enduring obstacle of achieving site- and stereoselective synthesis of stereodefined polysubstituted alkenes. This was achieved by introducing four stereoselective Rh-catalyzed protocols, which facilitate the utilization of polyBpin-containing alkenes as Rh-transmetallating active groups. These protocols generate divergent reactive nucleophilic-type alkenyl-Rh and aryl-Rh intermediates, enabling diverse stereoselective C–C bond forming reactions. To the best of our knowledge, this study explores the generation and application of the ***Z*-Rh** species from polyborylated alkenes, for the first time. This in-situ generated *Z*-borylated-Rh ***Z*-Rh** can then be selectively functionalized through addition reactions to enones and aldehydes. Moreover, this ***Z*-Rh** complex plays a key customizable intermediate for the distal C–H bond activation process via 1,4-Rh migration. In overall, this leads to the one-pot stereoselective sequential functionalizations of C–B and C–H bonds, resulting in the formation of difunctionalized products **6**. Notably, a Rh-catalyzed stepwise approach for *gem*-diborylalkenes has also been devised, allowing the introduction of two different electrophiles in a highly site- and stereoselective manner as in **6',7**.

The obtained products, many of which serve as valuable building blocks, are achieved with high yields and exceptional chemo-, site-, and diastereoselectivity. Additionally, these products demonstrate successful application in selective C–C bond forming reactions, exhibiting excellent chemo- and stereoselectivity. Remarkably, they were demonstrated in the synthesis of the stereodefined all-carbon tetrasubstituted olefin e.g., **11**. Given its simplicity and versatility, these Rh-designed reactions present a general and efficient method for converting polyborylated alkenes into stereodefined polysubstituted alkenes, a class of compounds previously lacking efficient synthetic access. This approach offers

flexibility, versatility and hold great promise in creating compounds with diverse and unique functionalizations, paving the way for novel synthesis strategies and applications.

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information. Details about materials and methods, experimental procedures, characterization data, NMR spectra are available in the Supplementary Information. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2237709 (**3a**), 2284057 (**5l**), 2284058 (**4a**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/ .

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Competing interests

The authors declare no competing interests.

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