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Synthesis of chiral germanium center enabled by poly-deborylative alkylation and desymmetrization

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Ke Wang, Xin-Yuan Liu & Zhe Dong

Chiral germanium centers are historically undervalued due to their extremely limited synthetic accessibility. Although germanium shares similar chemical properties with silicon, synthesizing chiral germanium centers proves significantly more challenging. To facilitate rapid access to chiral germanium centers, we develop two synthetic strategies: deborylative alkylation of germanium chlorides and copper-catalyzed diol desymmetrization. The α-boryl carbanion is demonstrated to be an exceptional coupling partner for germanium chloride, yielding 1,3-prochiral diols, which subsequently undergo copper-catalyzed desymmetrization to afford chiral germanium centers. By combining these two synthetic methodologies, we successfully transform simple germanium tetrachloride into a chiral germanium center in merely four steps, representing a significant advancement in main-group element chirality. Additionally, this strategy efficiently facilitates the construction of chiral silicon-stereogenic centers as well. Subsequent deoxygenative cross-coupling reactions of the chiral germanium products further expand the scope of organogermanium chemistry, revealing entirely new synthetic possibilities.

Point chirality is the most common chiral elements existing in nature. Among all the different point chirality categories, tetrasubstituted carbons are the most common chiral centers occurring in nature[1]. Owing to their abundance and essential biological functions, significant progress has been made in the asymmetric synthesis of chiral carbon centers through both enantiospecific and enantioconvergent transformations[2]. A key advantage in constructing chiral carbon centers is the wide availability of structurally diverse prochiral substrates suitable for asymmetric[3]. (Fig.1a)

In sharp contrast, other group 14 elements such as silicon and germanium solely exist in the inorganic salt form[4]. Consequently, the direct transformation of inorganic silicon and germanium compounds into their corresponding organic derivatives has become an attractive synthetic goal[5]. Silicon tetrachloride and germanium tetrachloride have proven to be reactive enough for polysubstitution reactions with organolithium or organomagnesium reagents[6]. This straightforward methodology positions $SiCl_4$ and $GeCl_4$ as the principal precursors for organosilicon and organogermanium compounds[6,7]. To synthetically access the corresponding chiral silicon/germanium-stereogenic center with the same sequence, the four chloride atoms need to be distinguished site-selectively and enantioselectively. Due to the broad industrial application of organosilicons, such site-reactivity can be achieved by carefully controlling reaction stoichiometry and conditions[8]. Consequently the complex dichloro silane becomes a key intermediate for enantioselective desymmetrization[9] (Fig. 1b). Recently, catalytic enantioselective displacement of silicon chloride to access chiral silicon center was also reported by Song and coworkers[10,11]. Meanwhile, Oestreich and Wu also reported a highly controllable stepwise functionalization of polysilane's Si-H bond to provide a general and quick access to silanes with four different substitutions[12,13].

However, organogermanium compounds have proven significantly more challenging to synthesize, primarily due to the unique chemical reactivity associated with germanium tetrachloride. Unlike

Shenzhen Key Laboratory of Cross-Coupling Reactions, Department of Chemistry, Southern University of Science and Technology (SUSTech), Shenzhen 518055, China. e-mail: dongz@sustech.edu.cn

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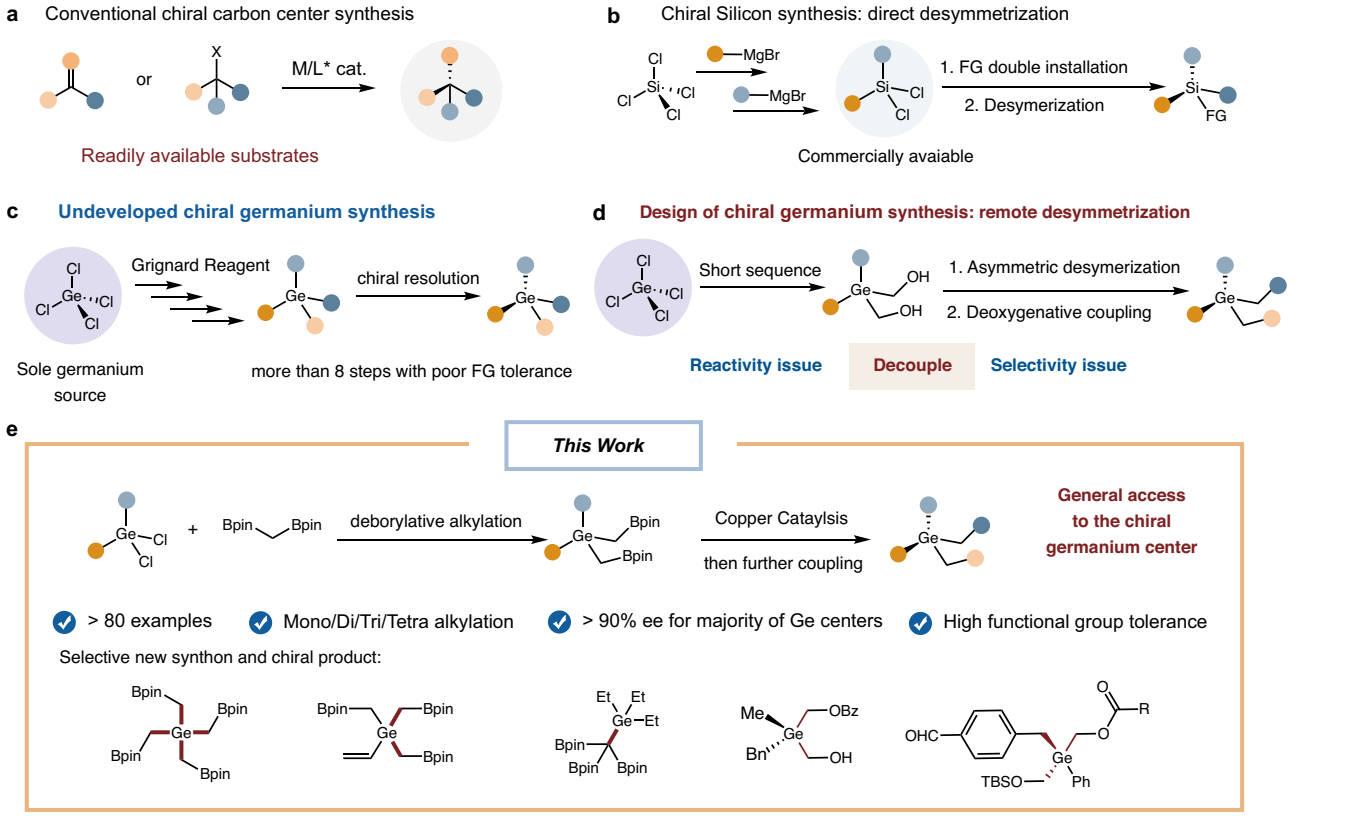

Fig. 1 | Synthesis chiral chiral group 14 element center. a Chiral carbon centers can be readily synthesized asymmetrically, primarily due to the wide availability of suitable starting materials. **b** Chiral silicon centers can be prepared by combining stepwise chloride displacement with desymmetrization strategies. **c** The reported synthetic routes for germanium centers substituted with four distinct carbon groups have thus far been limited. **d** A rapid synthesis approach for chiral germanium centers has been developed by strategically decoupling reactivity and selectivity issues. **e** Deborylative alkylation of poly-germanium chlorides, followed by copper-catalyzed enantioselective desymmetrization of prochiral 1,3-diols, has been successfully achieved. This methodology provides efficient access to synthetic intermediates and chiral germanium products characterized by high functional group tolerance and excellent enantioselectivity.

its silicon analog, reactions between $GeCl_4$ and Grignard reagents consistently yield mixtures containing varying degrees of substitution along with undesired halogen exchange as byproduct[6]. Furthermore, the nature of organometallic reagents employed restricts the functional groups that can be successfully introduced into organogermanium compounds. Consequently, achieving a general synthetic route to a racemic germanium center bearing four distinct substituents remains an unresolved challenge.

To date, all chiral germanium centers have been prepared exclusively through desymmetrization strategies or chiral resolution methods[14–16] (Fig. 1c). Zhou and He independently reported transition-metal-catalyzed desymmetrizations of dihydrogermanes, achieving high enantioselectivity[17,18]. In contrast, the enzymatic desymmetrization of germanium-containing 1,3-diols was initially reported by Tacke in 1994; however, this approach delivered only moderate enantioselectivity (50% ee) and was limited to a single substrate[19].

The lack of general access to highly enantioenriched chiral germanium centers clearly limits the understanding of the germanium element's own intrinsic chemistry[20,21] and distinct properties[22–24], such as the conformational stability of corresponding chiral germanium cations, anions, and radicals[5]. Based on previous literature, differentiating among the four chlorides in $GeCl_4$ to achieve stepwise functionalization with high chemoselectivity and enantioselectivity remains exceedingly challenging using current synthetic methodologies.

Therefore, our goal is to develop rapid and general synthetic access to highly functionalized chiral germanium centers by strategically decoupling reactivity and selectivity considerations (Fig. 1c). If global displacement of chlorides can be accomplished with pre-installed functional groups at the nucleophile site, this approach would uniquely enable late-stage differentiation and facilitate subsequent enantioselective desymmetrization. Such a concise and straightforward synthetic strategy would represent a versatile solution for constructing chiral organogermanium centers and significantly expand the chemical space accessible to main-group element chirality.

Results and discussion

We selected the phenylgermanium trichloride **1** as the standard substrate for the optimization. Organoboron compounds were chosen as coupling partners due to their structural diversity and excellent functional group compatibility[25]. Given the necessity of performing this coupling reaction three times at the germanium center, we preferred a transition metal-free coupling pathway due to its inherent robustness[26]. Unfortunately, when simple alkyl or aryl boronic esters were employed as nucleophiles, no desired products were formed. We hypothesized that the corresponding borates might not possess sufficient nucleophilicity to react with germanium chloride[27]. Inspired by the seminal work of Morken and coworkers[28], we thought α-boryl carbanion should be nucleophilic enough to react with germanium chloride[29]. The remaining boronic ester would be an ideal synthetic handle for further derivatization[30,31]. Indeed, we found that gem-diboronmethane **2** acted as an effective coupling partner, producing the desired trialkylation product **3** (Fig. 2a). A control experiment revealed that potassium tertbutoxide proved to be the optimal base for this transformation, which was particularly surprising given the oxyphilic nature of germanium chloride[6]. Our rationale was that all the tert-butoxide anions in the solution actually were tightly bonded to

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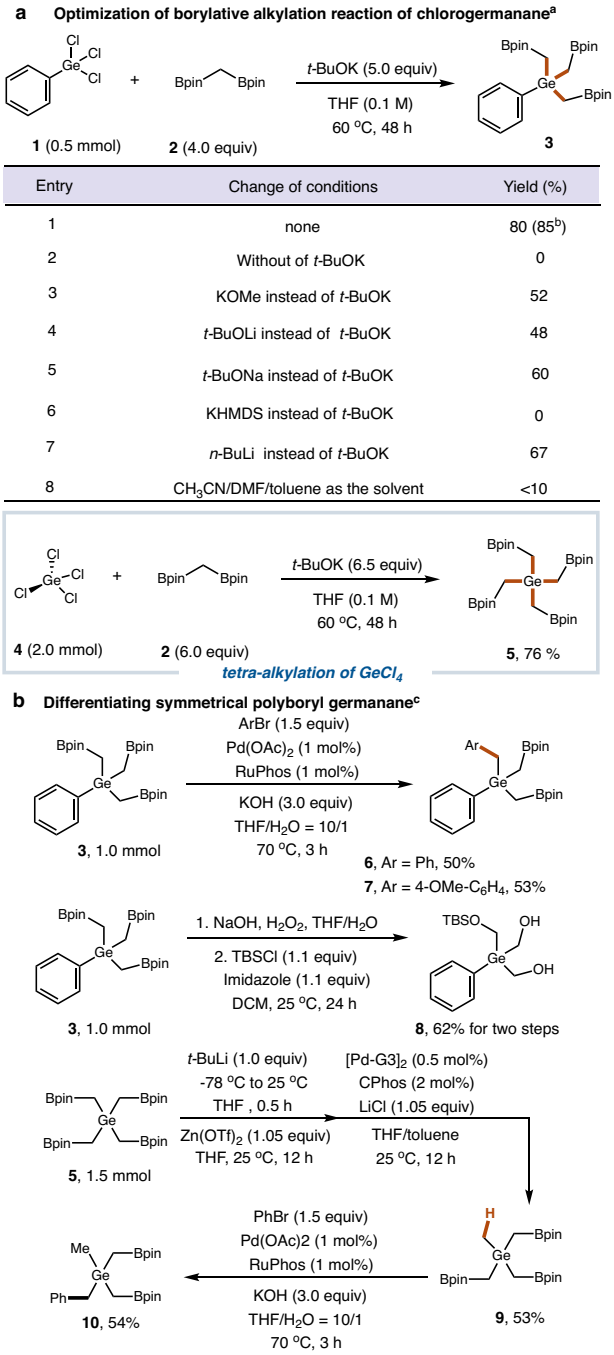

Fig. 2 | Optimization of deborylative alkylation of phenylgermanium trichloride and stepwise functionalization of remaining organoboronic ester. **a** optimized standard reaction conditions: 1 (0.5 mmol), 2 (2.0 mmol, 4.0 equiv), *t*-BuOK (2.25 mmol, 4.5 equiv) in THF (0.10 M), 48 h, under argon at 60 °C, all the yield listed were isolated yields. **b** the yield in bracket was determined by ^{1}H-NMR analysis. **c** the poly boronic esters could be differentiated by selective transmetallation; see supplementary information synthetic application for experimental details. THF, tetrahydrofuran; KHMDS, potassium bis(trimethylsilyl)amide; DCM, dichloromethane; TBSCl, *tert*-butyldimethylsilyl chloride; RuPhos, 2-dicyclohexylphosphino-2′,6′-di-i-propoxy-1,1′-biphenyl, CPhos, 2-dicyclohexylphosphino-2′,6′-bis(dimethylamino)−1,1′-biphenyl.

organoboron **2** to form the corresponding ate complex[32]. Consistent with this observation, pre-mixing the base and organoboron **2** at 60 °C significantly improved both reaction yield and reproducibility. Alternative bases and solvents provided lower coupling efficiencies. Encouraged by this trialkylation reaction, we then directly used germanium tetrachloride **4** as the electrophile. With slightly modified stoichiometry, we isolated the tetraalkylation product **5** in 76% yield, effectively converting an inorganic germanium source into an organic germanium intermediate suitable for further functionalization. Intriguingly, this methodology also efficiently transformed tin tetrachloride into the corresponding tetra-boronic esters with a yield of 66%. In stark contrast, silicon tetrachloride failed to yield any desired products. (See supporting information Figure S6 for details).

With these polyboronic ester **3** and **5** in hand, we next moved to distinguish these boronic esters to access the prochiral germanium center, which could be directly used in the enantioselective desymmetrization[33] (*vide infra*). Mono-selective Suzuki-Miyaura coupling can be achieved with palladium/RuPhos system to give mono-arylation product **6** and **7** with moderate yield[34] (Fig.2b). Alternatively, global peroxide oxidation of **3** would give the germanium-containing triol, followed by selective mono-silylation to give prochiral 1,3-diol **8**. Next, we attempted to distinguish symmetric four boronic esters in the compound **5**. However, previous Pd/RuPhos reaction conditions gave a complicated reaction mixture. We then applied Morken's method to transfer the boronic ester to organozinc via transmetallation[35], then followed by palladium/CPhos catalyzed the Negishi coupling[36]. Surprisingly, we only isolated mono-protodeborylation product **9** as the sole product. Control experiments confirmed that both zinc salts and the palladium catalyst were crucial for achieving mono-protodeborylation. Subsequent treatment of compound **9** under the Pd/RuPhos catalytic conditions smoothly produced the mono-arylation product **10** (Fig. 2b). These synthetic sequences clearly demonstrate the polyborylative product can serve as a linchpin intermediate to synthesize structurally diverse organogermanium compounds.

With the optimized reaction conditions in hand, we started to test the scope of this deborylative alkylation reaction (Fig. 3). We first started with differently substituted organogermanium trichloride (**11**-**14**) and organogermanium dichloride(**15**-**34**). We were glad to find that the alkyl (**11**-**13**), alkenyl (**14, 28**-**30**), aryl (**19**-**28, 33**), alkynyl (**31**) substitutions all work smoothly under the exact same conditions, regardless of whether they were trichlorides or dichlorides. The more hindered *ortho*-substituted arene (**25**) on the germanium site didn't hurt this transformation. This method could be easily scaled up to 80 mmol without changing any conditions (**19**). For organogermanium monochloride, we found that lithium bis(trimethylsilyl)amide gave a cleaner reaction and much higher isolation yield (**35**-**49**). More interestingly, the hydrogermanium chloride (**50, 51**) was also well-tolerated. Additionally, silicon dichloride substrates (**52**) smoothly coupled under the standard conditions. Finally, we tested the scope of alkyl boronic ester: benzyl boronic ester (**53**) smoothly yielded the benzylation product. Tertiary α-borylcarbanion (**54**) gave a quaternary carbon directly connected to quaternary germanium center, such a hindered product was quite challenging to synthesize through the traditional methods. The triborylated alkanes with different functional groups also coupled well (**55**-**62**)[37]; they can also participate in double alkylation of germanium dichloride to give tetra-boronic ester containing organogermanium (**64**). Remarkably, even tetraborylative methane underwent selective mono-deborylative alkylation with germanium chloride(**63**).

After establishing the robust and quick synthetic route to these prochiral germanium centers, our next goal was to synthesize the chiral germanium center via desymmetrization steps. Initially, applying Morken group's protocol[38] to desymmetrize 1,3-diboronic ester **19** didn't give fruitful results, mainly due to the opened transmetallation step. Motivated by previous successes in the desymmetrization of 1,3-diols[39–42], we directly converted **19** to the corresponding diol **65** via peroxide oxidation. Subsequently, we focused on the copper-catalyzed 1,3-diol desymmetrization (Fig. 4a). Although the carbon analog's desymmetrization was achieved with a copper(II) catalyst and PyBOX ligand (**L6**) before (>80% ee)[39], we found traditional PyBOX

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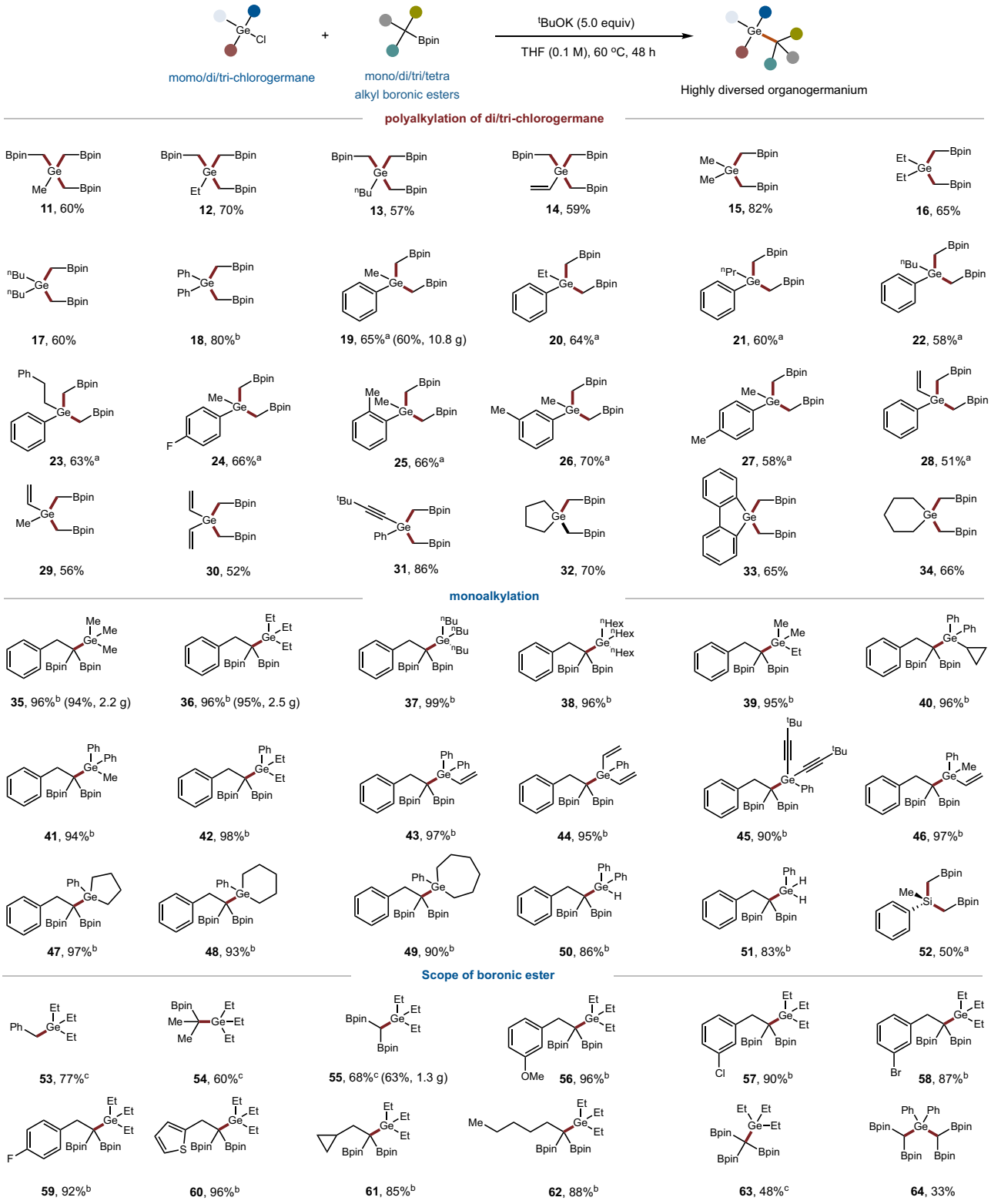

Fig. 3 | The scope of deborylative alkylation of organogermanium chloride. Mono/di/tri-germanium chlorides all can be alkylated with α-borylcarbanion. All yields are isolated unless otherwise noted. Experiments typically run with 1.0 equiv. of germanium chlorides, 4.0 equiv. of alkyl boronic ester and 4.5 equiv. of potassium *tert*-butoxide on 0.5 mmol scale. **a** Isolated as diols after $NaOH/H_2O_2$ treatment. **b** 1.5 equiv. of lithium bis(trimethylsilyl)amide was used as the base with 1.5 equiv. of germanium chlorides, 1.0 equiv. of alkyl boronic ester. **c** 1.0 equiv. of alkyl boronic ester was used as limiting reagent with 1.5 equiv. of germanium chlorides.

ligand only gave 54% ee (**L6**). This sharp loss of enantioselectivity was due to the germanium atom's large size, which directly influenced the key transition state's conformation[9]. So we further engineered the ligand from pyridine-bisoxazoline scaffold **L6** to pyridine-bisimidazoline **L8**-**L12**. We were pleased to discover that the introduction of an aryl group on the nitrogen atom of the imidazoline moiety provided an additional structural handle for tuning the ligand geometry[43], with the mesityl group providing identical steric

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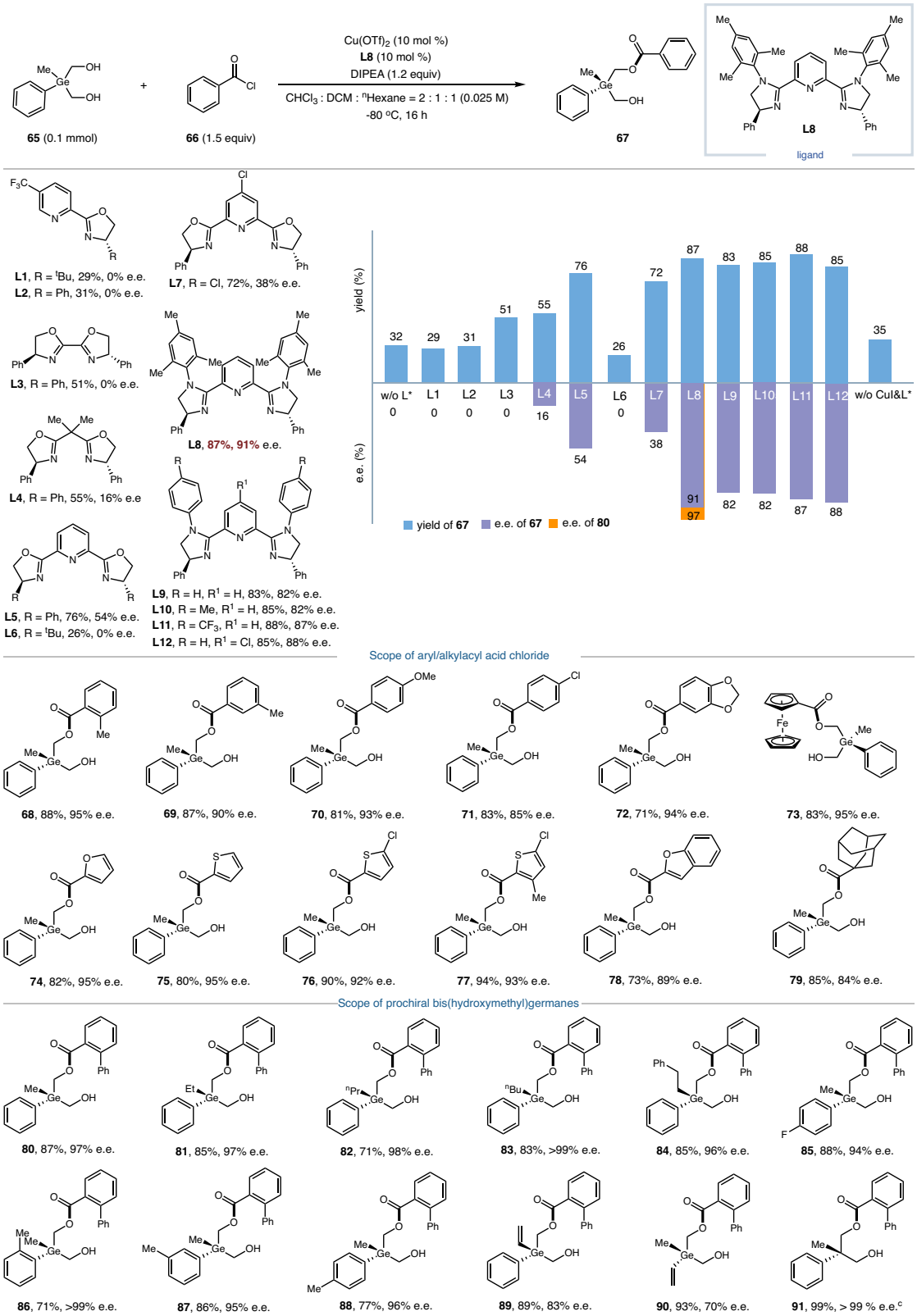

Fig. 4 | Desymmetrization of germanium containing 1,3-diols enabled copper catalysis. All yields are isolated unless otherwise noted. Enantiomeric excess was determined by chiral HPLC analysis. Experiments typically run with 1.0 equiv. of germanium containing 1,3-diol, 1.5 equiv of acid chloride and 1.2 equiv. of diisopropylethylamine on 0.2 mmol scale.

hindrance (**L8**). Mono-benzoyl-protected chiral germanium product **67** could be isolated with 87% yield and 91% ee. To further enhance enantioselectivity, we examined various acid chloride coupling partners. Electron-rich aromatic acid chlorides consistently provided higher enantioselectivity compared to their electron-deficient counterparts (**69-71**). Optimal enantioselectivity was achieved with ortho-substituted aromatic acid chlorides (**68, 80**), reaching up to 97% ee, which represents the state-of-the-art for constructing chiral

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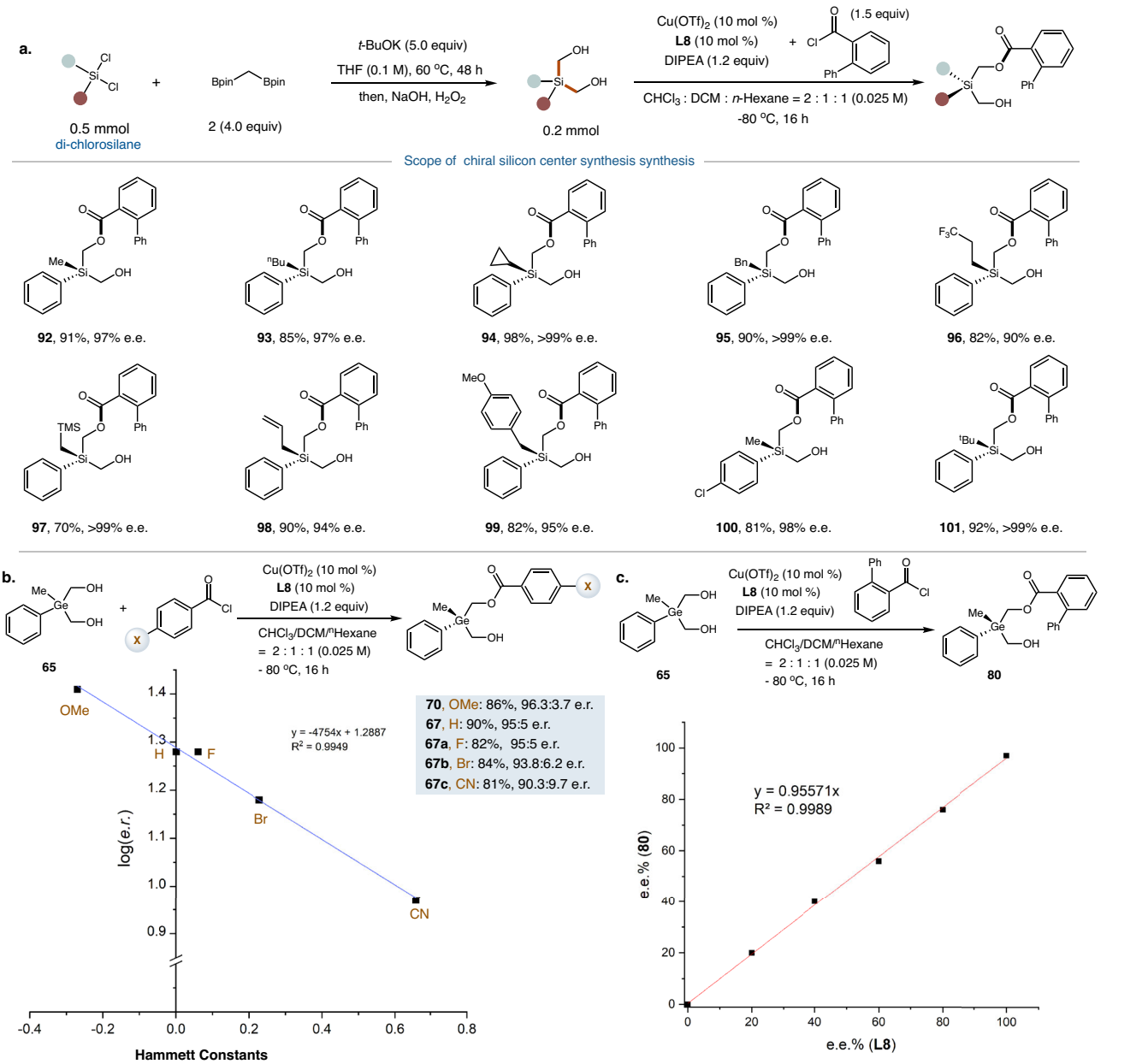

Fig. 5 | Desymmetrization of silicon containing 1,3-diols enabled copper catalysis and mechanism study of the copper catalyzed desymmetrization step. **a** The dichlorosilane could be successfully double alkylated with diboronmethane. After the hydrogen peroxide oxidation, the resulting silicon containing 1,3-diols can be desymmetrized by copper catalysis to form chiral silicon center with excellent enantioselectivity. All yields are isolated for the copper catalyzed desymmetrization step unless otherwise noted. Enantiomeric excess was determined by chiral HPLC analysis. Experiments typically run with 1.0 equiv. of silicon containing 1,3-diol, 1.5 equiv of acid chloride and 1.2 equiv. of diisopropylethylamine on 0.2 mmol scale. For deborylative 1,3-diols synthesis, see supporting information for details. **b** Hammett's linear free energy relationship study **c** nonliner effect study of the copper catalyzed desymmetrization step.

germanium centers. Conversely, alkyl carboxylic acid chloride **79** exhibited significantly lower enantioselectivity.

Next, we aimed to demonstrate the general applicability of our method in synthesizing structurally diverse germanium centers.(**80**-**89**) Both alkyl and aryl substitutions exhibited remarkably broad substrate scope. The current method consistently delivered enantioselectivity exceeding 94% ee, provided germanium-stereogenic center with one sp^2 substitution and three sp^3 substitutions, irrespective of their steric and electronic properties. Interestingly, an increase in alkyl chain length correlated positively with improved enantioselectivity (**80**-**83**), indicating that steric factors were not the sole determinants of high enantioselectivity, although they certainly played a beneficial role. When we added an *ortho* methyl substitution on the arene **86**, the ee was significantly higher than its para analog **88**. This method can even distinguish two sp^2 substitutions **89** or two sp^3 substitutions **97** with slightly decreased enantioselectivity. To provide a direct comparative reference with previously published 1,3-diol desymmetrization methods, we evaluated the analogous carbon-based substrate **91**, achieving the formation of a chiral quaternary carbon center with outstanding enantioselectivity (99% ee)[44]. To our best knowledge, this catalytic system represents a universal solution for 1,3-diol desymmetrization.

To further demonstrate the synthetic versatility of this deborylative alkylation/desymmetrization strategy, we next applied this methodology to construct chiral silicon centers (Fig. 5a). We were pleased to find that the deborylative alkylation proceeded smoothly

even with commercially available silicon dichloride, facilitating rapid access to starting materials suitable for copper-catalyzed desymmetrization. Under our optimized reaction conditions, selective differentiation of the two oxygen atoms in the prochiral 1,3-diol successfully generated silicon-stereogenic chiral centers with excellent enantioselectivity. The alkyl substitution on the silicon center exhibited broad substrate scope, ranging from methyl (**92, 101**), primary alkyl (**93, 95-99**), secondary alkyl (**94**), to tertiary alkyl (**101**). We observed a positive correlation between increased steric bulk of the alkyl substituent and higher enantioselectivity. Additionally, substituents such as cyclopropyl (**94**), allyl silane (**98**), and aryl chloride groups (**100**) were well-tolerated.

To gain deeper mechanistic insight into the copper-catalyzed desymmetrization reaction, we conducted a series of physical organic chemistry studies. To exclude the possibility of secondary kinetic resolution, we closely monitored the enantiomeric purity of the product throughout the entire reaction process. The enantiomeric excess (ee) remained constant over the full 16h reaction period, confirming that secondary kinetic resolution did not occur[45]. Further, through systematic analysis of benzoyl chloride coupling partners possessing diverse electronic characteristics (Fig. 5b), we established that the enantiomeric ratio of the desymmetrization product correlated linearly with traditional Hammett substituent constants[46].

Additionally, we performed a non-linear effect study using our newly developed pyridine-bisimidazoline ligand **L8**. Although a non-linear effect has previously been observed in Cu-PyBOX systems[47], our copper(II) triflate/pyridine-bisimidazoline ligand system surprisingly exhibited no non-linear effect under the established reaction conditions (Fig. 5c). This indicates a 1:1 stoichiometric complex between copper(II) triflate and the pyridine-bisimidazoline ligand as the catalytically active species. The observed linear free-energy relationship, coupled with its negative slope, strongly suggests an ionic pathway rather than an open-shell radical intermediate for this copper-catalyzed desymmetrization[42,48]. Based on these collective mechanistic investigations, we have proposed a detailed catalytic cycle, presented in supplementary Fig. S5.

Equipped with the deborylative alkylation and desymmetrization methods, we successfully developed a direct synthetic route from $GeCl_4$ to chiral germanium centers in four to five chemical steps. (Fig. 6a) For instance, $GeCl_4$ can be converted into 1,3-diol **102** and **103** in three chemical steps. (*vide supra*) Subsequently, copper-catalyzed desymmetrization converted these diols into chiral germanium products **104** and **105**, each with outstanding enantioselectivity (> 99% ee). A similar sequence allowed the synthesis of compound **107**, bearing four distinct sp^3 substitutions on the germanium center, in merely four steps. Alternatively, two sequential nucleophilic substitutions involving PhMgBr and *t*-BuLi would convert $GeCl_4$ to Ph*t*-Bu$GeCl_2$[49], then following our current methods, we could also access **109** with > 99% ee. (Fig. 5b) The residual alcohol functionality resulting from the desymmetrization step provided versatile handles for further derivatization via cross-coupling reactions (Fig. 5d). Utilizing MacMillan's NHC-mediated deoxygenation approach[50], we successfully incorporated sensitive functional groups, such as aldehydes (**110**) or heterocycles (**114**), thereby expanding the chemical space available for medicinal chemistry applications. Particularly noteworthy is compound **100**, whose silyl-protected alcohol group was readily amenable to subsequent deoxygenative transformations (Fig. 5c). Moreover, the alcohol group also facilitated traditional post-functionalizations, including tosylation (**101**) for potential S_{N2} substitutions, Mitsunobu reactions (**103**) for nitrogen incorporation, or Swern oxidation followed by hydrazone formation (**102**). Importantly, throughout these functionalization steps, the original high enantiomeric excess remained fully preserved. Additionally, chiral phosphate **115** was conveniently synthesized by coupling our chiral germanium-containing products with chiral phosphor chloride, further illustrating the synthetic utility of our strategy.

We successfully developed two robust synthetic methods: deborylative alkylation and copper-catalyzed diol desymmetrization—that significantly advanced the synthesis of chiral germanium centers. By merging these methodologies, rapid and general access to chiral germanium centers has become synthetically facile. These developments open avenues for the exploration and application of organogermanium chemistry, particularly regarding the stereochemical manipulation of germanium cations, anions, and radicals. Further studies into enantiospecific transformations of these chiral germanium compounds are ongoing.

Methods

General procedure of deborylative alkylation of dichlorogermanane

In an argon-filled glovebox, **2** (536.0 mg, 2.0 mmol, 4.0 equiv), potassium *tert*-butoxide (252.5 mg, 2.25 mmol, 4.5 equiv) in tetrahydrofuran (5.0 mL) were added to a 20 mL vial equipped with a magnetic stirring bar. The reaction mixture was stirred at 60 °C for 1 h. dichlorogermanane (0.50 mmol, 1.0 equiv) was added and The reaction mixture was stirred at 60 °C for 48 h. The reaction was quenched with water (20.0 mL) and, the solution was extracted with ethyl acetate (3 × 15.0 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodiumsulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford corresponding alkyl germanium compound. The alkyl germanium compound was transferred to a 25 mL round bottom flask and cooled to 0 °C (ice/water) and charged with 5 M sodium hydroxide (8.5 equiv), and 30% hydrogen peroxide (0.85 mL) and tetrahydrofuran (5.0 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was cooled to 0 °C and saturated aqueous sodium thiosulfate was added dropwise over 5 min. The reaction mixture was diluted with ethyl acetate and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20.0 mL) and the combined organics were dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford corresponding prochiral bis(hydroxymethyl)germane. (For other class of chloro-organogermanes deborylative alkylation reactions, see supporting information for detailed reaction conditions).

General procedure of desymmetrization of germanium containing 1,3-diols enabled copper catalysis

In an argon-filled glovebox, $Cu(OTf)_2$ (7.2 mg, 0.02 mmol), **L8** (12.1 mg, 0.02 mmol) in freshly distilled chloroform (2.0 mL) were added to a 20 mL oven-dried Schlenk tube equipped with a magnetic stirring bar, and then the mixture was stirred at 25 °C for 3 h. To the generated catalyst solution, a solution of the corresponding bis(hydroxymethyl) germane (0.2 mmol, 1.0 equiv) in distilled dichloromethane (2.0 mL) and distilled n-hexane (2.0 mL) was added to the above generated catalyst solution, and the mixture was stirred at 25 °C for 10 min. After cooling down the above reaction mixture to -80 °C, a solution of aryl/alkyl acyl chloride (0.3 mmol, 1.5 equiv) and N,N-diisopropylethylamine (31.0 mg, 0.24 mmol, 1.2 equiv) in distilled chloroform (2.0 mL) was finally added dropwise at -80 °C. The reaction mixture was then allowed to stir at -80 °C for 16 h. The reaction was quenched with water (20.0 mL) and, the solution was extracted with ethyl acetate (3 × 15.0 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford corresponding germanium stereoscopic compound.

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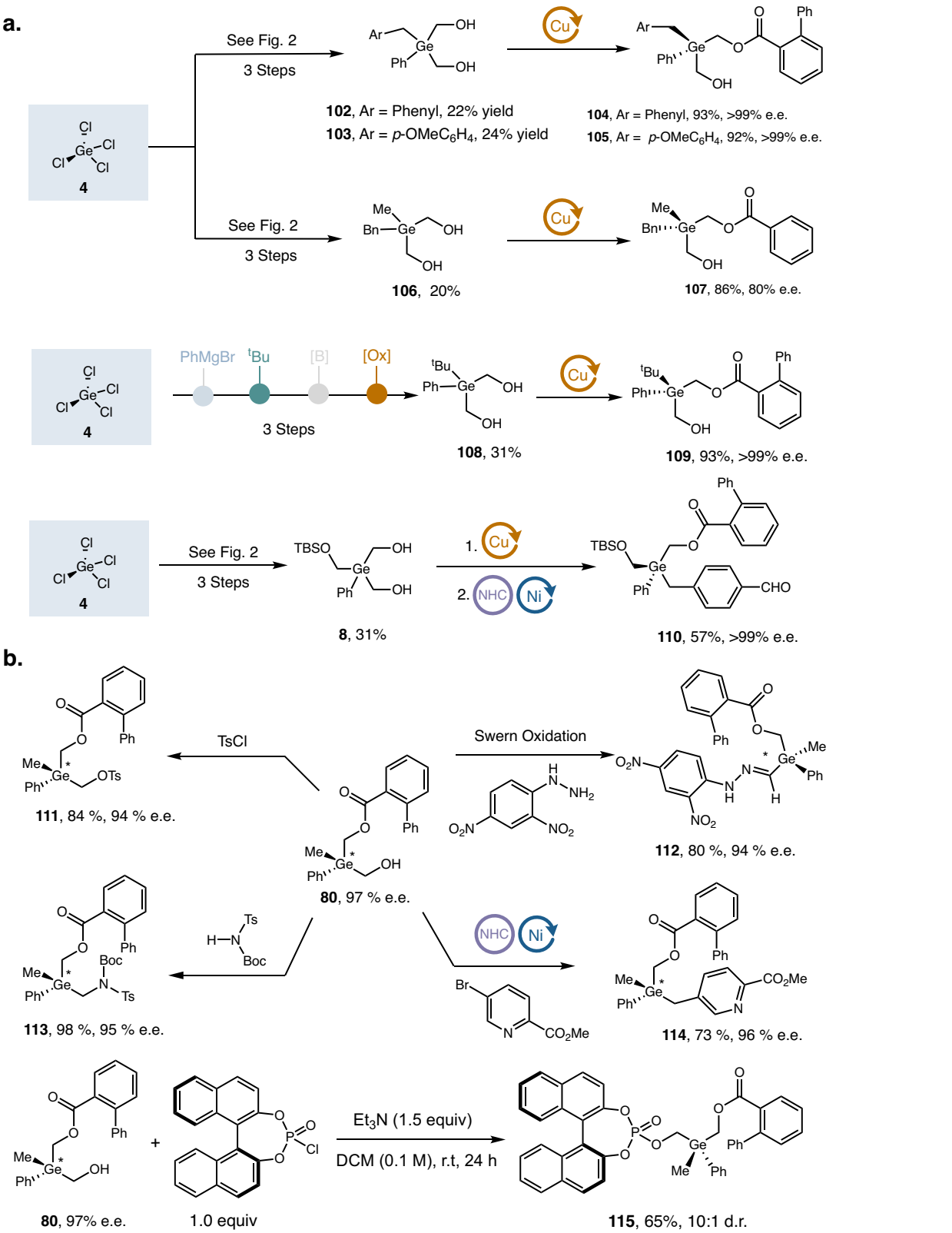

Fig. 6 | Direct synthesis of structurally diverse chiral organogermanium from simple germanium tetrachloride. a Germanium tetrachloride could be selectively functionalized using deborylative alkylation reaction illustrated in the Fig. 2. Merging those transformations with copper catalyzed the desymmetrization provided an universal approaches to access the chiral germanium center with great structure diversity. **b** Post-functionalization of the chiral germanane **80**. For detailed reaction conditions, see the synthetic application section in the supporting information.

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information. Crystallographic data are available free of charge from the Cambridge Crystallographic Database Centre (CCDC) under CCDC **2432397** (for (+)-**73** derivative). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. All data are available from the corresponding author upon request.

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Author contributions

K.W. performed and analyzed the experiments. K.W., X.-Y.L. and Z.D. designed the experiments. K.W., X.-Y.L. and Z.D. prepared this manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Zhe Dong.

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