The Development and Application of SPSiBox Ligands: Cu-Catalyzed Enantioselective Carbene Insertion of Ge–H Bonds

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A class of C_2-symmetrical bisoxazoline ligands with a flexible chiral pocket has been developed, which could be readily prepared in three steps from enantiopure SPSiOLs. This type of ligands presented high level of enantioselectivity for the Cu-catalyzed asymmetric carbene insertion of Ge–H bonds with α-trifluoromethyl diazo compounds, thus providing an efficient method for the preparation of enantioenriched α-trifluoromethyl ogranogermanes. This reaction features a broad substrates scope, mild reaction conditions, excellent enantioselectivity, and low catalyst loading. Preliminary mechanistic studies unveiled that this Cu-catalyzed Ge–H insertion might undergo a concerted mechanism, and computational studies unveiled the origin of chiral induction of this reaction with SPSiBox ligand.

C_2-Symmetric chiral bisoxazoline ligands have significantly contributed to the evolution of the catalytic methods for the construction of optically relevant molecules, which are privileged in pharmaceuticals, agrochemicals and materials.[1] For several decades, tremendous effort has been devoted to the development of chiral bisoxzaline ligands in order to achieve high enantioselectivity and reactivity for transition-metal catalysis, and a series of C_2-symmetric bisoxazoline ligands[1-7], including BOX[2], Py-Box[3], BiOx[4], TOX[5], SpiroBox[6] etc. have been prepared and widely applied in many hot areas (Scheme 1a). In the design of chiral bisoxazoline ligands, the structure of the backbone normally plays a crucial role, because it could not only provide a supported chiral scaffold, but also serve as a key factor to alter the steric and electronic properties of the metal-catalyst by adjusting the bite angle and stereo-environments. As a result, to further

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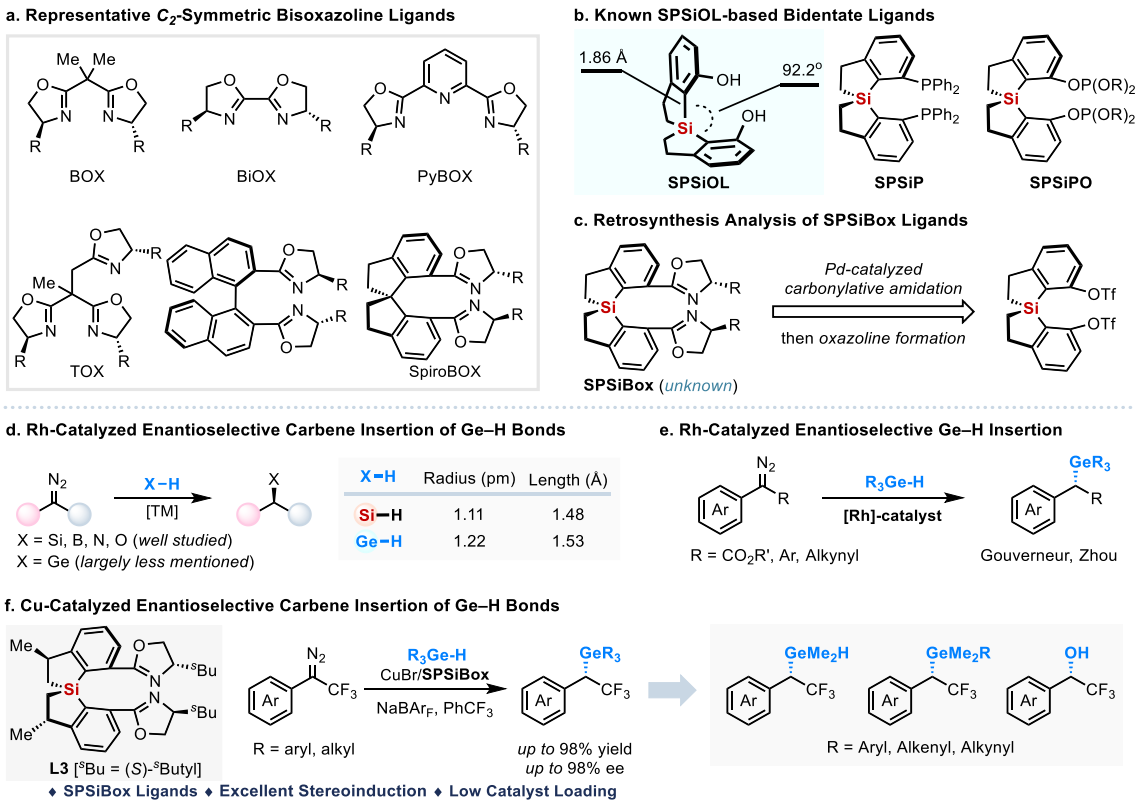
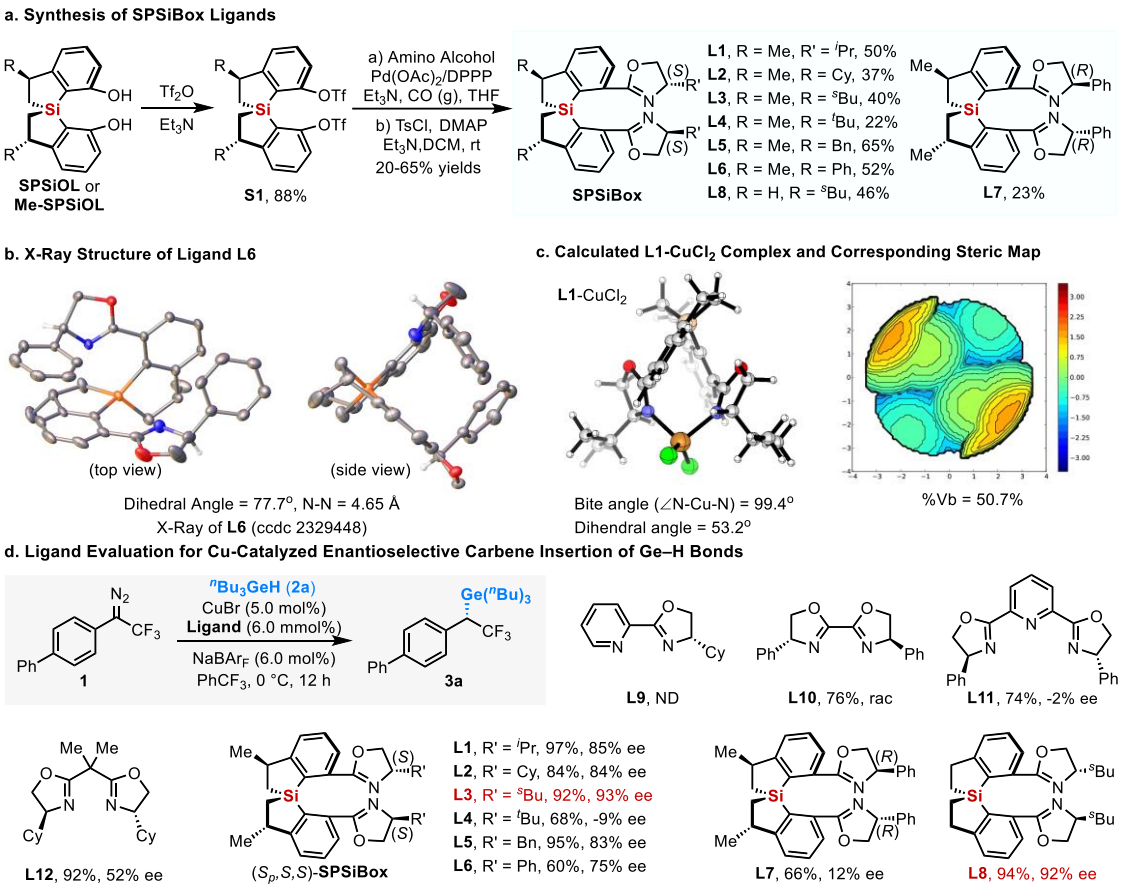
develop novel chiral bisoxazoline ligands with novel chiral scaffold is highly desired, which might lead to visible impacts in many enantioselective processes requiring the use of bisoxazoline ligands with different metal catalysts. Recently, we have demonstrated that the chiral spirosilacycle-based scaffold, including SPSiOL and SPOSiOL, could serve as novel chiral platforms for the development of new chiral bidentate ligands with a large bite angle, which presents superior performance in transition metal asymmetric catalysis.[8] Further studies indicate SPSiOL-scaffold possesses a flexible and variable "chiral pocket" as the dihedral angle of this ligand scaffold could deform from 92.2° to 36.2° due to the long C–Si bond (a weaker sigma bond in comparison to C–C bond)[8a]. Given the bite angle between the two coordination sites and the dihedral angle of the scaffold are crucial to the reactivity and stereoenvironment of the metal catalyst, we thus hypothesized the SPSiOL-based bisoxazoline (SPSiBox) ligands might provide a tunable "chiral pocket" in the transition metal complexes, and could be potentially employed in many unsolved asymmetric reactions (Scheme 1b).



Scheme 1. Synopsis for the Development of C_2-Symmetric Bisoxazoline Ligands and Cu-Catalyzed Enantioselective Carbene Insertion of Ge–H Bonds.

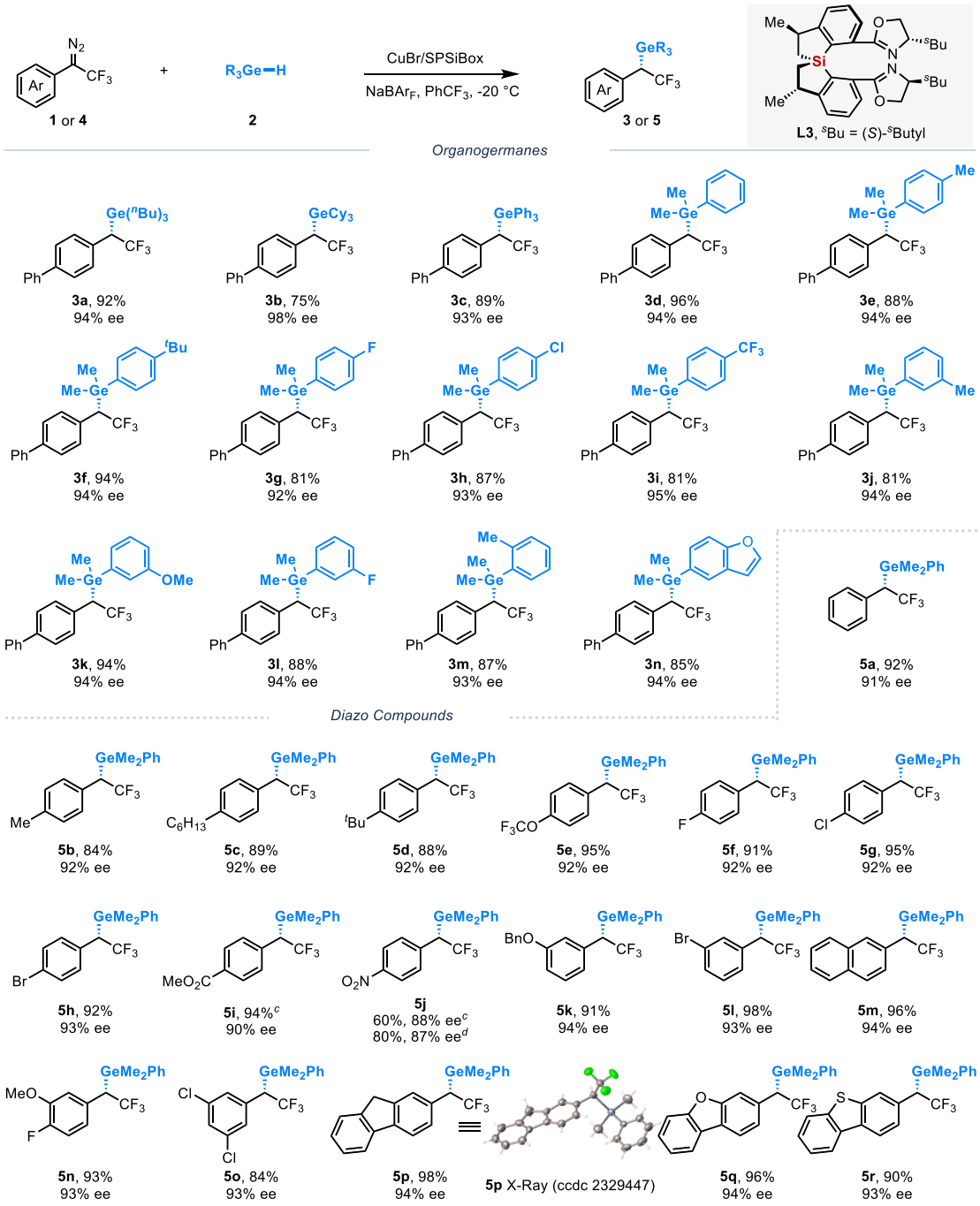
Transition metal catalyzed X–H (X = N, O, Si, B etc.) insertion reaction represented one of the most efficient ways to access chiral molecules possessing C–X bonds.[9-13] In this area, significant progress has been made in Si–H,[10] B–H,[11] N–H,[12] O–H[13] insertion reactions (Scheme 1c). However, the insertion of Ge–H bonds with metal carbene species for the efficient preparation of chiral organogermanes is largely unexplored, despite of the increasing importance of organogermanes as a versatile linchpin in coupling reaction[14], bioactive drug candidates, organic light-emitting diodes, and plastic electronics[15]. In comparison to its congener Si, Ge has a larger atom radius (Ge vs Si, 1.22 pm *vs* 1.11 pm), and the Ge–H bond is slightly longer than Si–H bond (Ge–H *vs* Si–H, 1.53 Å *vs* 1.48 Å). The structural properties of Ge–H bond might result in a flabby transition state in the transition metal-catalyzed carbene insertion event. In addition, the strong reductive ability of Ge–H bond also inhabits the development of asymmetric Ge–H insertion reaction, which might lead to the incompatibility with known catalytic systems. Despite of those challenges, Gouverneur group[16a] reported one case of enantioselective Ge–H insertion reaction with Rh_2(*S*-*tert*PTTL)$_4$ as the catalyst. Very recently, Zhou and coworkers[16b] have demonstrated an elegant example of enantioselective Ge–H insertion reaction with both donor-accepter and donor-donor carbene precursors by using chiral dirhodium phosphate catalyst (Scheme 1e). Notably, the enantioselective Ge–H insertion reaction with cheap Cu-catalyst has not been disclosed to date. Here, we report the design, synthesis of SPSiOL-based bisoxaline ligands (SPSiBox), and the application of this type of ligands in the Cu-catalyzed enantioselective Ge–H insertion reaction (Scheme 1f). Employing α-trifluoromethyl diazo compounds as the carbene precursor, a number of enantioenriched α-trifluoromethyl organogermanes were prepared in high yields and excellent enantioselectivities. This protocol features mild reaction conditions, excellent chiral induction, and the catalyst loading could be lowered to 0.5 mol%. Notably, our catalytic system is not sensitive to the steric hindrance on both diazo compounds and monohydrogermanes, probably due to the flexible and tunable "chiral pocket" with SPSiBox ligand. As the trifluoromethyl group is privileged in many pharmaceuticals and materials[17], this protocol also provides a new method for the preparation of trifluoromethyl-containing chiral molecules, which is highly synthetic useful in pharmaceutical industry and drug discovery.



Scheme 2. Synthesis of SPSiBox Ligands and Condition Optimization.

With those chiral SPSiBox ligands in hand, we commenced our studies by investigating the asymmetric Ge–H insertion of *α*-trifluoromethyl diazo compounds with a Cu catalyst (Scheme 2d). Although the pyridine-oxazoline ligand **L9** cannot afford the desired product, bisoxazoline ligand **L10** and Py-Box **L11** could gave the desired product in high yields albeit without chiral induction. Notably, the Box ligand **L12** gave the desired *α*-trifluoromethyl organogermane **3a** in 92% yield and 52% ee. To our great delight, our SPSiBox ligand **L1** gave the desired product in 97% yield and 85% ee. Following this lead, systematically evaluation of the structures of SPSiBox ligands was carried out. Further increase the steric hindrance of the substitute provided inferior chiral induction (**L4**). The benzyl substituted SPSiBox ligand **L5** and phenyl substituted SPSiBox ligand **L6** resulted in 83% ee and 75% ee, respectively. To clarify the role of chiral oxazoline ligand, we further checked the ligand with (*R*)-phenyl substituent, which provided the desired product in a slightly higher yield and inferior ee values. This outcome indicated that both the chiral backbone and chiral oxazoline fragment are crucial for the high enantioselectivity. Notably, the methyl

group on the chiral backbone didn't significantly alter the chiral induction, giving similar outcomes (**L8**, 92% ee vs **L3**, 93% ee).



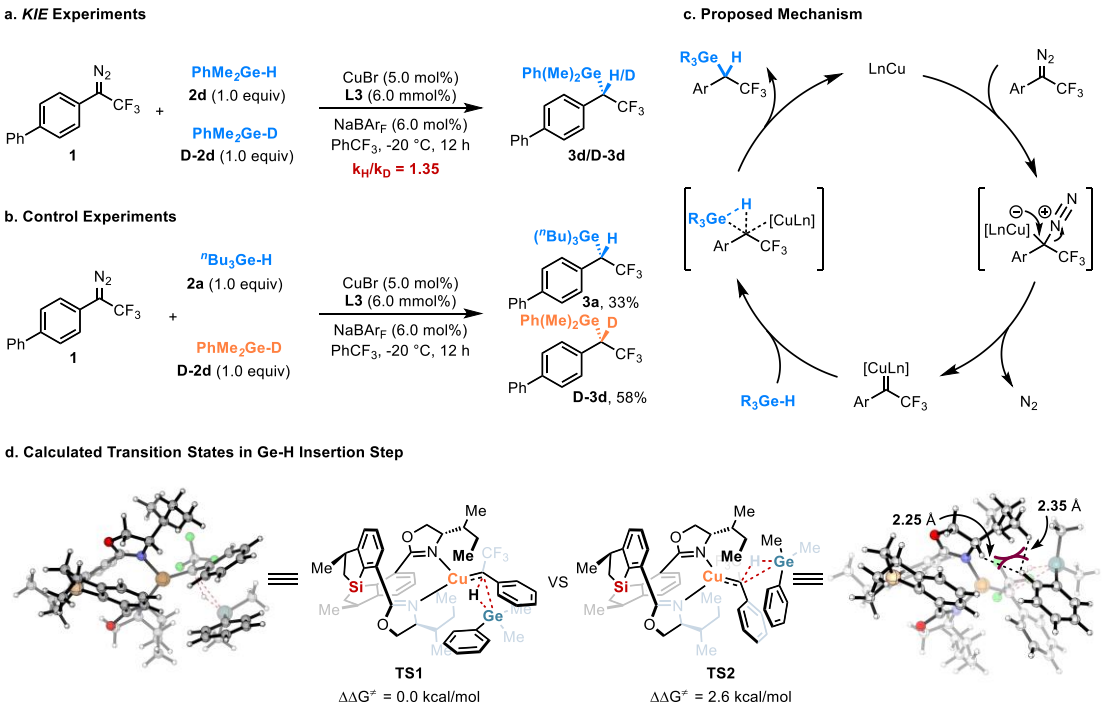
Scheme 3. Substrate Scope of Cu-Catalyzed Enantioselective Carbene Insertion of Ge–H Bonds[a,b]. [a]Reaction conditions: **1** or **4** (0.2 mmol, 1.0 equiv), **2** (0.2 mmol, 1.0 equiv), CuBr (5.0 mol%), SPSiBox **L3** (6.0 mol%), NaBAr$_F$ (6.0 mol%), PhCF$_3$ (2.0 mL), -20 °C, N$_2$, 12 h. [b]Isolated yield, and the enantioselectivity was determined by chiral HPLC. [c]The reaction was conducted at 0 °C for 24 h. [d]The reaction was conducted at 9 °C for 24 h.

Under the optimal conditions, the breadth of this SPSiBox ligand-enabled enantioselective Ge–H insertion reaction was evaluated. As showed in Scheme 3, a wide range of monohydrogermanes bearing various functional groups, including alkyl (**1a-b**), aryl (**1c**), methoxy (**1k**), fluoro (**1g, 1l**), chloro (**1h**), trifluoromethyl (**1i**) etc. are well tolerated, delivering the desired products in high yields and excellent enantioselectivities. Notably, both trialkyl (**1a-b**) and triaryl (**1c**) monohydrogermanes are compatible with this protocol, providing the desired products in 75-93% yields and 93-98% ee. The evaluation of substituents on aryl group of the dimethylaryl monohydrogermanes (**1d-n**) all gave similar reactivities and enantioselectivities, which is not normal in the transition metal catalyzed asymmetric reactions. This observation might be explained by the tunable "chiral pocket" the SPSiBox ligands possessed.

We next turned to evaluate the scope of *α*-trifluoromethyl diazo compounds, using dimethyl(phenyl)germane **2d** as the model substrate. Again, the substituents on the aryl group didn't significantly affect the outcomes, and a wide range of functional groups are well tolerated, delivering the desired *α*-trifluoromethyl organogermanes in good to excellent yields and excellent enantioselectivities. It is noteworthy that both electron-deficient and electron-rich substituents at *para*- and *meta*- positions on the aryl group in *α*-trifluoromethyl diazo compounds are suitable carbene precursors for this Ge–H insertion reaction. A wide range of functional groups, including alkyl (**4b-d**), methoxy (**4n**), trifluoromethoxy (**4e**), fluoro (**4f**, **4n**), halo (**4g**, **4h**), ester (**4i**), nitro (**4j**) etc., are all tolerated, providing the desired products 88-96% ee values. Notably, this protocol also showed high level of compatibilities with multiple substituted substrates (**4n-p**) and heterocyclic substrates (**4q**, **4r**), giving the desired products in high yields and excellent enantioselectivities. The stereo-configuration of the enantioenriched *α*-trifluoromethyl organogermanes was determined by the analysis of crystal structure of enantiopure compound **5p**, disclosing a (*S*)-configuration.

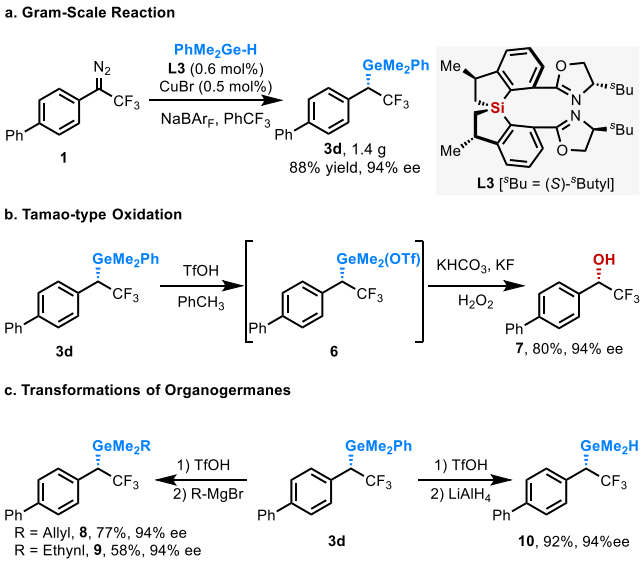
To further understand this Ge–H insertion reaction, the competitive KIE experiments were conducted, indicating the Ge–H cleavage might not be involved in the rate-determining step (Scheme 4a). The control experiments with deuterium-labelled $PhMe_2Ge$–D (**D-2d**) and $^{n}Bu_3Ge$–H (**2a**) in one pot gave the corresponding products in 58% and 33% yield, respectively (Scheme 4b). The cross-over phenomena of

deuterium was not observed, unveiling that this Cu-catalyzed Ge–H insertion reaction might undergo a concerted mechanism, similar to Cu-catalyzed Si–H insertion[9g]. According to the known reports and our preliminary mechanistic studies, we thus hypothesized that this reaction might undergo the formation of Cu-carbene species, concerted Ge–H insertion along with the regeneration of Cu(I) species (Scheme 4c). To further understand the stereoinduction model of this reaction with our newly developed SPSiBox ligand, preliminary computational studies on the transition states of Ge–H insertion step via a concerted mechanism have been performed. The energy barrier in the transition state via (*Re*)-face insertion is 2.6 kcal/mol higher than that via (*Si*)-face insertion, which is consistent with our experimental results (Figure 1d). The steric repulsion between the *s*-butyl group and the substituents on organogermane has been proven as the key factor to provide high enantioselectivity. Further analysis of the transition state and the Cu-carbene intermediate disclosed that the dihedral angle in the transition state (**TS1**) is slightly compact in comparison to that in the Cu-carbene intermediate (49.5° for **TS1** *vs* 51.9° for Cu-carbene). The aforementioned preliminary computational results further confirmed our SPSiBox ligand might have a tunable "chiral pocket" (For details, see supporting information).



Scheme 4. Mechanistic Studies and Stereoinduction Model.

The scalability of this newly developed process has been demonstrated by conducting this reaction on gram scale. Notably, the catalyst loading of CuBr could be reduced to 0.5 mol%, without observation of a decrease of efficiency and enantioselectivity (Scheme 5a). The further derivations of chiral α-trifluoromethyl germane have been demonstrated using **3d** as the model substrate. The dimethylphenyl germane could be stereospecific oxidized to corresponding chiral *α*-trifluoromethyl benzyl alcohol **7** in 80% yield and 94% ee upon the activation of TfOH (Scheme 5b). In addition to the transformation of C(sp^3)–Ge bond, the C(sp^2)–Ge bond could also be converted via the same intermediate **6** via nucleophilic substitution or reduction, thus providing corresponding enantioenriched allylic organogermane **8**, alkynyl organogermane **9** and monohydrogermane **10** in high yields and high ee values (Scheme 5c). The development of efficient transformations of chiral organogermane not only demonstrates the synthetic value of current methods in the preparation of chiral molecules, but also paves a new avenue for the construction of various Ge-containing functional molecules.



Scheme 5. Gram-Scale Reaction and Synthetic Applications.

In summary, we have developed a series of SPSiOL-based bisoxazoline ligand, which could be efficiently preparation in three steps starting from optical pure SPSiOL. With the newly developed SPSiBox ligand, a Cu-catalyzed enantioselective Ge–H insertion reaction with *α*-trifluoromethyl diazo compounds has been realized for the first time. This reaction features low catalyst loading, a broad substrate scope, and

excellent enantioselectivity. Further development and application of spirosilacycle-based chiral ligands and catalysts are underway in our laboratory.

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