Construction of Tetrasubstituted Silicon-Stereogenic Silanes via Conformational Isomerization and N-Heterocyclic Carbene-Catalyzed Desymmetrization

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ABSTRACT: Disclosed here is a catalytic strategy for asymmetric access to chiral tetrasubstituted silicon-stereogenic silanes. Our reaction starts with a (covalently) symmetric silane bearing two aldehyde moieties as the substrate. Single crystal structural analysis shows that the substrate exists as a racemate of two conformational enantiomers due to the presence of a Si/O weak interaction. Mechanistic studies assisted by DFT calculation indicate that the two conformational enantiomers can readily isomerize to each other, and one of the conformational enantiomers of the substrate is favorably activated by a N-heterocyclic carbene catalyst via an overall desymmetrization process to eventually afford optically enriched tetrasubstituted silicon-stereogenic silanes as the products. Our chiral silanes products can be readily transformed to a diverse set of silicon stereogenic functional molecules.

Silicon is the second most abundant element in the crust. Although natural appearance of silicon element in living systems are uncommon, incorporation of this element to organic molecules have led to impressive applications as medicines and agrochemicals[1] (Figure 1a). Examples of such silicon atom-containing medicines and pesticides include Karenitecin,[1e] Flusilazole[1a] and Silafluofen.[1b] Indeed, various molecules containing silicon element have been commercialized as pesticides, and more candidates are being developed at various stages.[2] Outside of biological applications, silicon-containing organic molecules have been found applications in many areas such as materials[3] and catalysis.[4] It has now been well recognized that replacing carbon with silicon atoms in organic molecules can lead to improved and/or alternative functions.[2a, 2b, 5] On the other side, methods for synthesis of silicon-containing moleucles remain much unmature. The synthetic challenge further increases when silicon-stereogenic centre are to be constructed. The Si-C bond is longer than the corresponding C-C bond, making it difficult to form well-organized transition states.[2b, 6] In addition, silicon can form more than four covalent bonds and thus lead to racemization of the stereogenic centre.[7] To date, the impressive yet still limited success for asymmetric synthesis of silicon-stereogenic centre-containing molecules are exclusively achieved via transition metal-catalyzed reactions[8] (Figure 1b). These methods use chiral ligand/metal complexes-catalyzed processes to form new carbon-silicon bond or selectively functionalize one of the two pro-chiral groups attached to silicon atom.[8] Enzymes and organic catalysts have found enormous applications in building carbon chiral centers. Unfortunately, in the area of silicon-stereogenic centre synthesis, few reactions are developed using enzymes[9] or organic catalysts. We believe it is worth to explore the potentials of organic catalysis to construct silicon atom chiral centers.

Here we disclose an N-heterocyclic carbene (NHC)-catalyzed[10] desymmetrization reaction for access to tetrasubstituted silicon-stereogenic silanes (Figure 1c). The overall catalytic process converts one of the two aldehyde moieties of the Si-containing dialdehyde substrate to a carboxylic ester group, leading to tetrasubstituted silicon-stereogenic silanes with high optical purities. Our experimental observations and DFT calculations on key reaction steps suggest that the addition steps and formation of Breslow intermediate between the NHC catalyst and the dialdehyde substate did not provide sufficient differentiations. Instead, stereo-determining and desymmtrization were realized during the formation of acylazuolium intermediate. Our transition metal-free catalytic reaction conditions are mild with good functional group tolerance. The optically enriched silicon-stereogenic products from our method can be readily transformed to a diverse set of molecules with the silicon stereogenic center remaining intact.

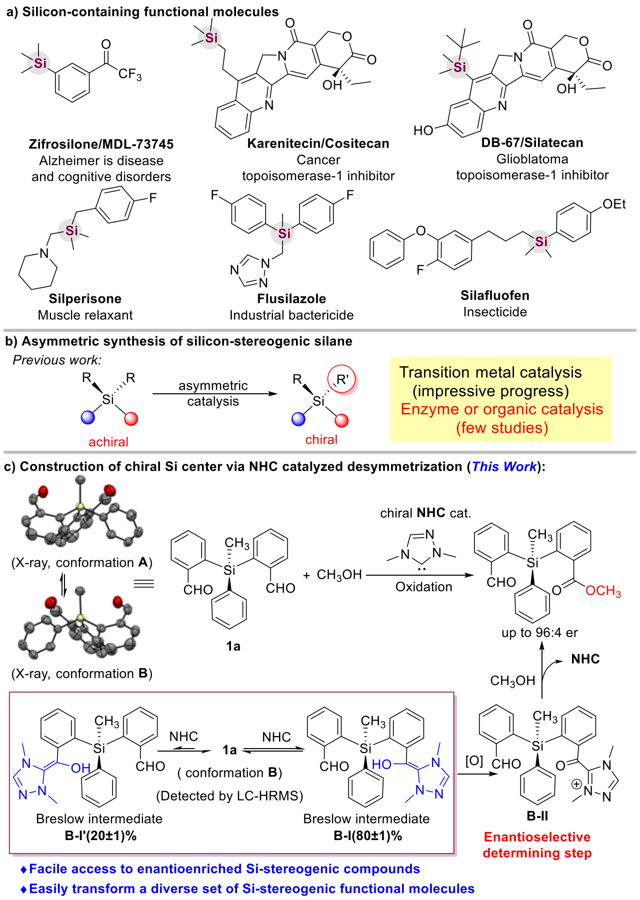
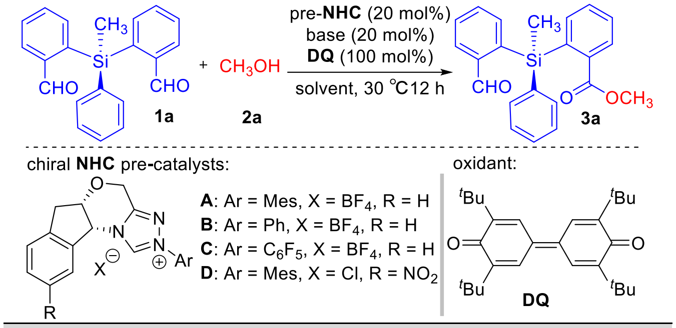


Figure 1. Silicon-containing bioactive molecules and asymmetric access to chiral silicon-stereogenic silanes

We initiated our studies on construction silicon-stereogenic centre using 2,2'-(methyl(phenyl)silanediyl)dibenzaldehyde **1a** and methanol **2a** as model substrates to search for suitable conditions, with key results summarized in Table 1. NHC pre-catalyst **A**[11] bearing an N-Mes group could promote the reaction smoothly in an enantioselective fashion and the silicon-stereogenic silane product **3a** was obtained in moderate enantioselectivity and excellent yield (Table 1, entry 1). NHC pre-catalysts **B**[12] or **C**[13] bearing N-Ph or N-C_6F_5 groups were not efficient for the reactions (Table 1, entries 2 to 3). To our delight, when NHC pre-catalyst **D**[14] bearing a nitro group was employed, the product **3a** was further improved in an 82% yield and 91:9 er (Table 1, entry 4). Therefore, we used the NHC pre-catalyst **D** for the examination of different bases in this protocol. Switching K_2CO_3 to other inorganic bases or organic bases led to drop on the product yields (Table 1, entries 5 to 9). Solvents also had a clear impact on the reaction outcomes, CH_3CN performed the best to give **3a** with 84% yield and 96:4 er (Table 1, entries 10 to 12). Further decreasing the loading of the NHC pre-catalyst **D** would result in drop on the product yield (Table 1, entry 13).

With an optimal reaction condition in hand, we explored the reaction scope of 2,2'-(methyl(phenyl)silanediyl) dibenzaldehyde **1**, different substitution patterns of **1** were examined (Scheme 1). Both electron-donating (**3b**, **3c**, **3f**) and electron-withdrawing (**3d**, **3e**, **3g**) substituents can be introduced into the 4- and 5- positions (relative to the silicon moiety) on the phenyl ring **A** of **1**, with the corresponding desired products afforded in good to excellent yields and high enantioselectivities. When the reaction time was increased from 12 h to 24 h, the desired product **3h** and **3i** can be afforded in moderate to excellent yields and high optical purities. When the electron-withdrawing group, such as Cl/CF_3 at 4- or 5- position were installed on the phenyl ring **A** of **1,** the moderate yields and er values were obtained for desired products, and the diester byproducts were found in the reactions. Subsequently, it was found that decreasing the NHC catalyst loading (5 mol%) lead to slightly improve the yields and enantioselectivities of these products (**3j-3m**). And the low NHC catalyst loading (5 mol%) was examined for all the substrates, the most substrates weren't totally converted to corresponding products after 12 hours (see SI).

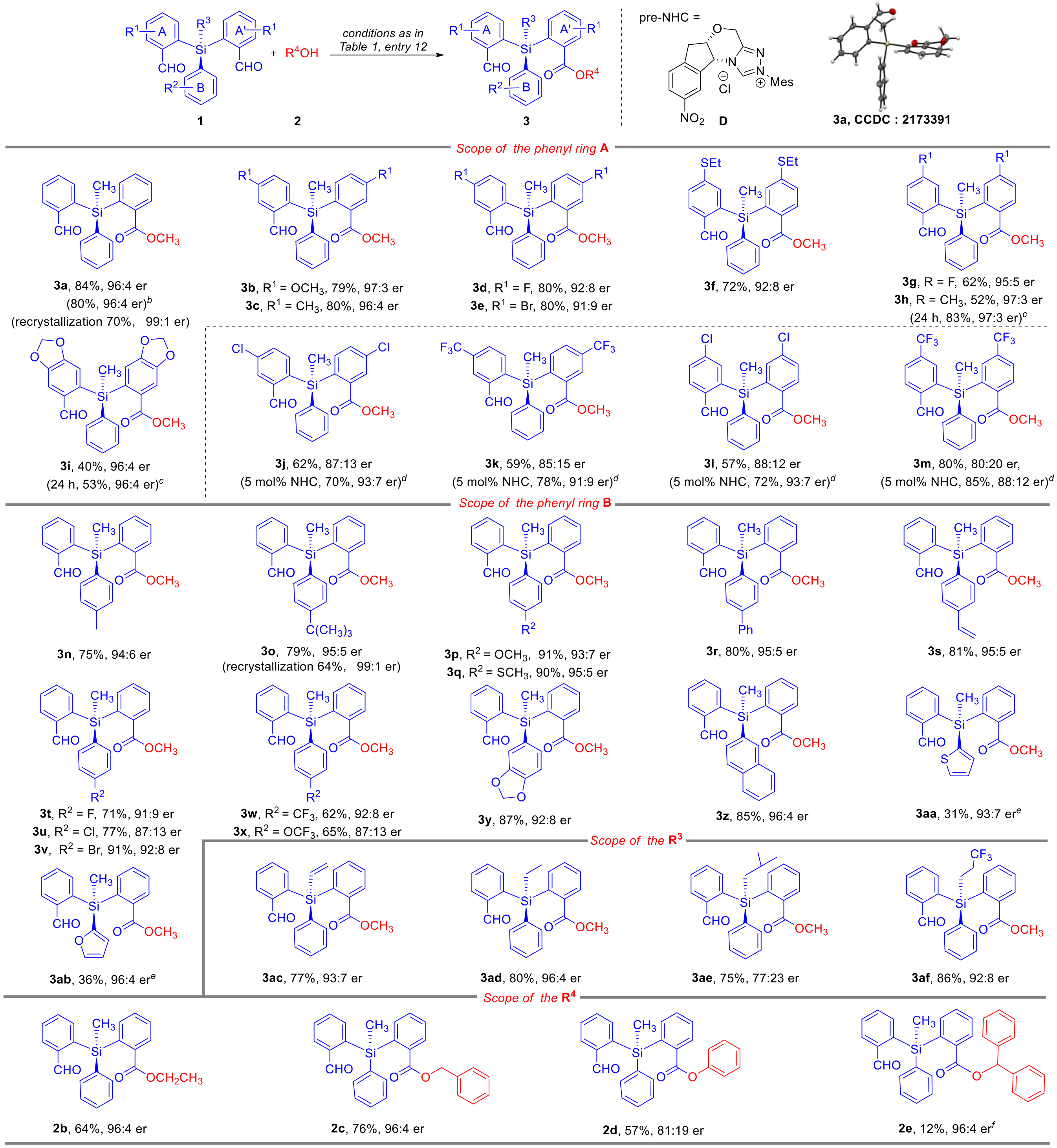
Table 1. Condition optimization[a]



Entry	Pre-NHC	Base	Solvent	Yield(%)[b]	Er[c]
1	**A**	K_2CO_3	THF	76	84:16
2	**B**	K_2CO_3	THF	58	63:37
3	**C**	K_2CO_3	THF	0	
4	**D**	K_2CO_3	THF	82	91:9
5	**D**	NaOAc	THF	30	56:44
6	**D**	Na_2CO_3	THF	61	91:9
7	**D**	Cs_2CO_3	THF	80	90:10
8	**D**	K_3PO_4	THF	43	91:9
9	**D**	DBU	THF	61	90:10
10	**D**	K_2CO_3	DMF	85	92:8
11	**D**	K_2CO_3	toluene	72	75:25
12	**D**	K_2CO_3	CH_3CN	84	96:4
13[d]	**D**	K_2CO_3	CH_3CN	30	96:4

[a]Unless otherwise specified, the reactions were carried under N_2 atmosphere using **1a** (0.10 mmol), **DQ** (0.10 mmol), **2a** (0.11 mmol), pre-NHC (0.02 mmol), base (0.02 mmol), solvent (2.0 mL), 30 °C, 12 h. [b]Isolated yield of **3a**. [c]The er values of **3a** were determined via HPLC on the chiral stationary phase, [d]0.005 mmol pre-NHC **D** was used.

Scheme 1. Scope of 2,2'-(methyl(phenyl)silanediyl)dibenzaldehyde 1[a]



[a] Reaction conditions as stated in Table 1, entry 12. Yields are isolated yields after purification by column chromatography. Er values were determined via HPLC on chiral stationary phase. [b] The reaction was carried out at 3.0 mmol scale based on **1a**, reaction time was 48 h. [c] Reaction time was 24 h. [d] The reactions were carried out using 0.005 mmol pre-NHC **D**. [e] The reaction was carried out by using THF as solvent, and reaction time was 24 h. [f] The reaction time was 24 h, the yield is determined by ^{1}H NMR using CH_2Br_2 as internal standard.

The generality of different types on the phenyl ring **B** of **1** were also examined (scheme 1). Placing different substituents on the 4-positions of the phenyl ring **B** resulted in good to excellent enantioselectivities (**3n** to **3x**). When the aromatic ring **B** was replaced by a piperonyl ring and a naphthalene ring, the desired products can be afforded in excellent yields and high optical purities (**3y** and **3z**). Only a trace amount of the target products was observed under the standard reaction condition when the heterocyclic ring was introduced to aromatic ring **B**. Switching CH_3CN to THF, the **3aa** and **3ab** can be obtained in moderate yields and excellent enantioselectivities. The methyl group of **1** was replaced with other aliphatic moieties, the corresponding products (**3ac** to **3af**) were afforded in good yields and excellent enantioselectivities. Additionally, different types of nucleophiles were also examined, the target products were also obtained (**2b** to **2e**) in moderate yields and high optical purities.

Additionally, the enantioenriched silicon stereogenic mono-carboxylate ester product **3a** was easily transformed into various derivatives through simple protocols (Figure 2). For instance, the hydrogen atom of aldehyde could be catalyzed by achiral NHC with the presence of D_2O to afford 92% deuterated **4** in 83% yield and and 96:4 er. Compound **3a** could react with Wittig reagent to give alkene **5** with 90% yield and 96:4 er. This carbon-carbon double bond of alkene **5** could also be epoxidized with *m*-CPBA to form epoxide **6** without reduction of the optical purity. The aldehyde moiety in **3a** was reduced by $NaBH_4$ to form the corresponding alcohol **7** with 98% yield and 96:4 er. The hydroxyl group in alcohol **7** was reacted with toluene sulfonyl chloride and subsequently reacted with sodium azide to form product **8** with 74% yield and 96:4 er. The product **9** could also be easily obtained in good yield and excellent enantioselectivity from alcohol **7**.

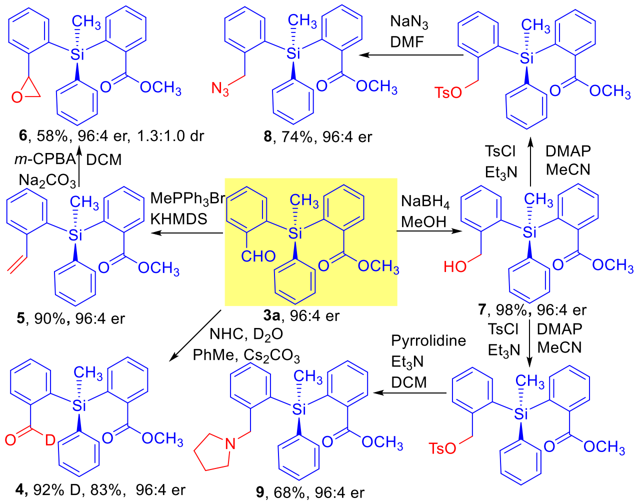


Figure 2. Synthetic transformation of **3a**

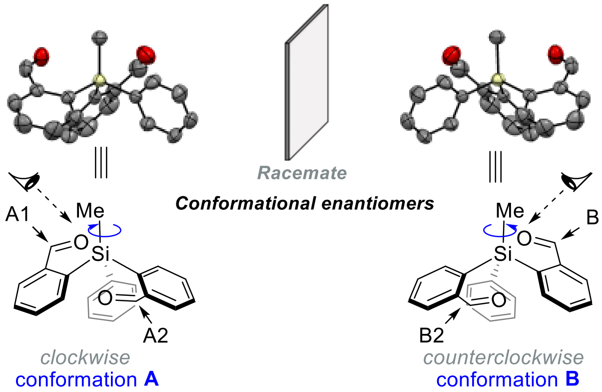


Figure 3. Unit cell analysis of **1a**

To understand the mechanism of our desymmetrization approach, single crystal structure analysis and density functional theory (DFT) calculations were performed. In the single crystal X-ray structure of **1a** (CCDC:2151740), two conformational enantiomers were found in the unit cell (Figure 3). It suggests that the presence of weak interaction between silicon and oxygen atom (bond length less than 2.90 Å). This weak interaction breaks the symmetry of **1a** and makes the entire molecule with helical chirality, therefore this symmetric silicon-bridged dibenzaldehyde is present as a racemic mixture of two conformational enantiomers. The interconversion of the two conformational enantiomers was a facile process, the conversional energy barrier is 13.56 kcal/mol (Figure 4a).

To further investigate the mechanism of the reaction, some additional experiments were performed. The ***S*-3a** (96:4 er) was employed to synthesize the single deuterium-labeled (abbreviated as D-labeled) aldehyde moiety substrate **1a(D)**, and the absolute configuration of **1a(D)** still remained intact. Then **1a(D)** was reacted with methanol (Table 1, entry 12), the D-labeled product **3a(D)** was obtained in 78% yield and 96:4 er, the reaction result was similar to non-deuterium-labeled model reaction (Figure 4a). It suggests that the D-labeled **1a(D)** can be used as model substrate to study the chemo-selectivity in reactions.

The **1a(D)** was used to react with carbene catalyst without oxidant to form two diastereoisomers Breslow intermediates **B-I(D)** and **B-I'(D)** with different molecular weight (Figure 4b). The corresponding intensity of the D-labeled and non-isotope labeled Breslow intermediates were detected and differentiated by LC-HRMS. It was found that the intensity ratio of **B-I(D)** and **B-I'(D)** was (80±1)%:(20±1)%, which means that overall the carbene addition and formation of Breslow intermediate was a enantioselective step.

Futhermore, the additions of NHC catalyst to a single aldehyde moiety in the two conformational isomers (two set of enantiomers; four possibilities for the additions) were evaluated, and the full NHC structure was employed for the DFT calculations (Figure 4c). We found that the aldehyde moieties of conformation **B** can be more easily reacted with NHC catalyst ($\Delta G^{\neq}$ = 9.10, 9.06 kcal/mol), the addition energy barriers was lower than conformation **A** ($\Delta G^{\neq}$ = 14.29, 11.28 kcal/mol). In confomation **B**, the difference of Gibbs free energy barriers ($\Delta\Delta G^{\neq}$ = 0.04 kcal/mol) between the NHC catalyst addition to the **B1**/**B2** aldehyde moiety was very small. This $\Delta\Delta G^{\neq}$ of 0.04 kcal/mol disfavors the observed enantioselectivity by 1.00:1.06 and translates to an er value of about 52.00:48.00. The transition state of **B1-TS** and **B2-TS** have lower activation barrier due to the favorable π-π stacking interactions between the aryl ring of the NHC and **1a**, which stabilize the transition state. These steric blocking are present in **A1-TS** and **A2-TS**, which lead higher energy barrier in the addition process (Figure 4d).

In summary, we have developed a NHC-catalyzed desymmetrization approach for access to enantioenriched silicon stereogenic silanes. Our reaction starts with silicon-bridged dibenzaldehyde as the substrate. The two aldehyde moieties of the substrate are symmetric in terms of covalent linkages. On the other side, X-ray structure analysis indicates that non-covalent interactions break the symmetry and the substrate is present as a racemate of two conformational enantiomers. Mechanistic studies assisted by DFT calculation suggest the reaction proceed via conformational isomerization and NHC-mediated desymmetrization to eventually afford tetrasubstituted silicon-stereogenic silanes with excellent yields and enantiomeric excesses. The chiral silanes from our reactions can be readily transformed to other molecules with the silicon-stereogenic remained. Further studies on the bioactivities of these silane compounds for agricultural applications are in progress in our laboratories. Our method and its mechanistic implications shall also stimulate further investigations on the conformational structures of silanes and their asymmetric synthesis.

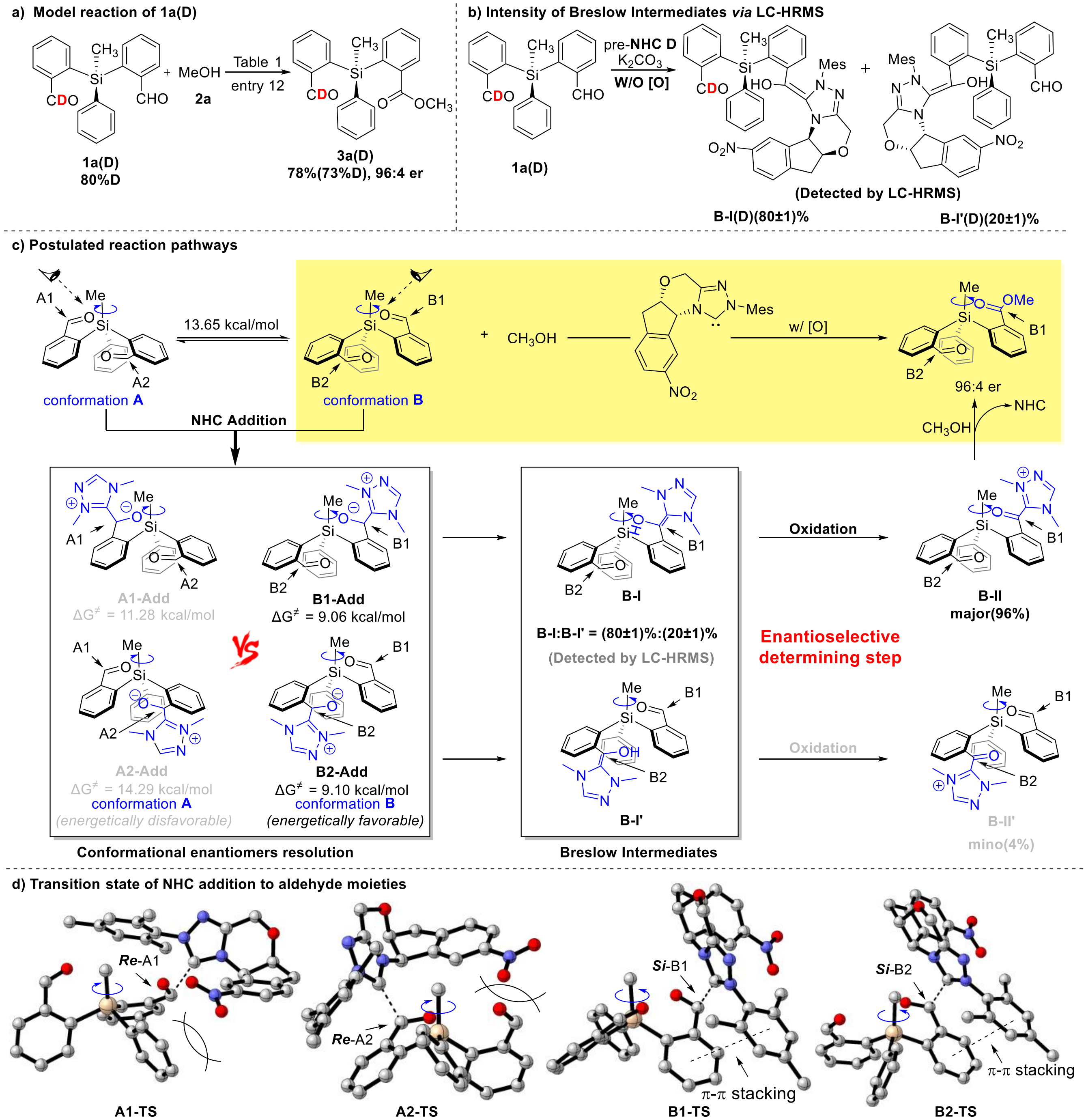


Figure 4. Postulated reaction pathways supported by control experiment and DFT calculation of key steps

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Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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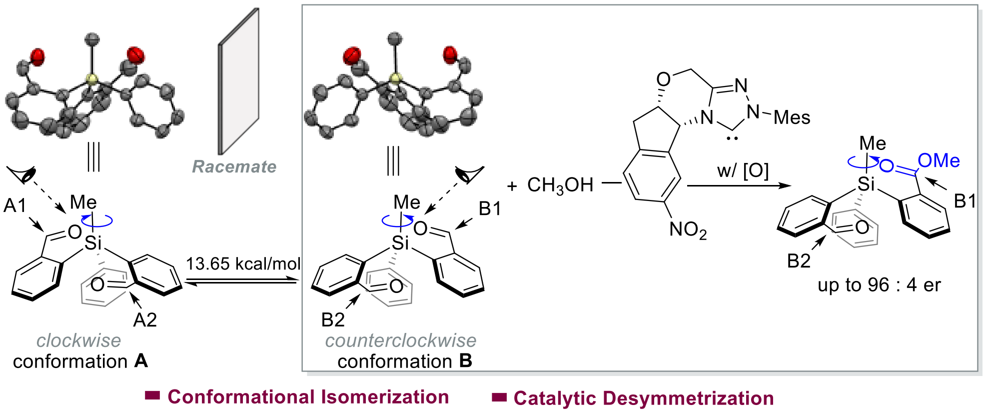
Racemate
A1
Me
O
Si
O
A2
clockwise
conformation A
13.65 kcal/mol
Me
O
Si
O
B1
B2
counterclockwise
conformation B
+ CH3OH
O
N
N
N
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NO2
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Me
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up to 96 : 4 er
Conformational Isomerization
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