Single-Atom Ligation of Four Different Alcohols at One Silicon Center: Methodology Development and Proof of Concept

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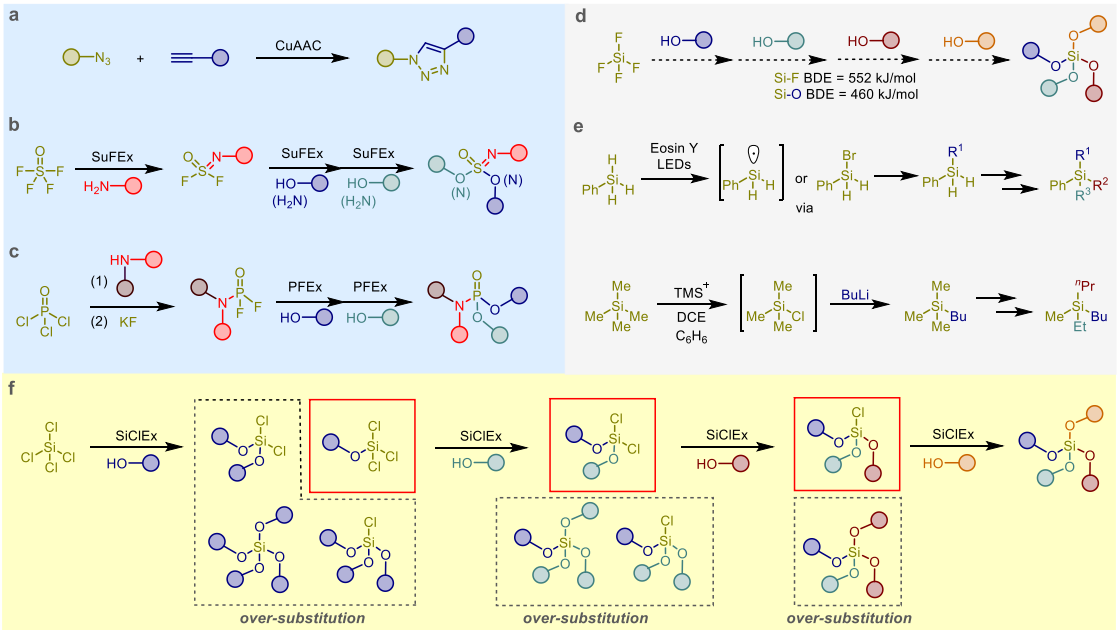
Abstract

Click chemistry[1] continues to impact the chemistry and biology community, with the most well-known being the CuAAC click chemistry[2]. Topologically, the CuAAC click chemistry only ligated two fragments in a two-dimensional manner. While the SuFEx[3-15] and PFEx[16] chemistry could ligate fragments three-dimensionally, maximally three fragments (amine/alcohol) could be clicked together for now. Herein, we report the three-dimensional single-atom ligation of four different fragments (alcohols) at one silicon center using triphenylchlorosilane as the ligation hub in an iterative, controllable, and programmable fashion. To fulfill the mission, we established a new silicon-phenyl exchange reaction with alcohols. A broad spectrum of alcohols could be ligated using various types of phenylchlorosilanes as ligation hubs, affording a library of mixed-dialkoxysilanes, trialkoxysilanes, and tetraalkoxysilanes. Notably, fully heteroleptic tetraalkoxysilanes were barely known in literature and extremely difficult to access in a selective fashion from a

retrosynthetic viewpoint. Our protocol thus provided a robust solution to materials of such nature. To highlight the application potential, four different biologically relevant alcohols, representing four different functions, were successfully ligated to one Si(IV) center as fully heteroleptic tetraalkoxysilane. More importantly, the four alcohols could be released and recovered via silicon-alkoxy exchange of the stable yet cleavable Si-O bonds.



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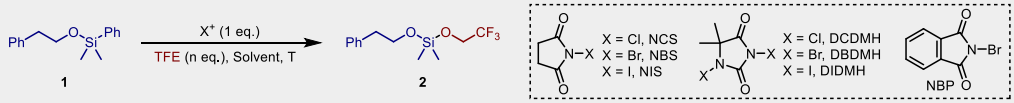

Entry	Solvent	X+	T	Yield (1)	Entry	Solvent	X+	TFE (n eq.)	T	Yield (1)
1	TFE	NCS	rt	decomposition	8	EtOAc or acetone	DBDMH	30	rt	NR
2	TFE	DCDMH	rt	decomposition	9	MeCN or THF	DBDMH	30	rt	decomposition
3	TFE	NBS	rt	57%	10	benzene	DBDMH	30	rt	83%
4	TFE	NBP	rt	decomposition	11	DCM	DBDMH	30	rt	81%
5	TFE	DBDMH	rt	82%	12	DCM	DBDMH	10	rt	85%
6	TFE	NIS	rt	decomposition	13	DCM	DBDMH	5	rt	85%
7	TFE	DIDMH	rt	decomposition	14	DCM	DBDMH	10	50 °C	90%

Fig. 1 | Research background and the proposed alcohol ligation at silicon. a, CuAAC: ligation via triazole formation. **b**, SuFEx: ligation via S-F exchange. **c**, PFEx: ligation via P-F exchange. **d**, The infeasible ligation of four different alcohols using SiF_4 via Si-F exchange. **e**, Examples of iterative and step-by-step substitution at silicon. **f**, The impracticable ligation of four different alcohols using $SiCl_4$. **g**, Our proposed single-atom ligation of four different alcohols using triphenylchlorosilane as the connective hub. **h**, Key reaction development.

Click chemistry[1] is a synthetic concept introduced by K. Barry Sharpless in 2001, which has revolutionized the way people practiced chemistry as well as biology in the past two decades. Its profound impact was recognized by the Nobel Prize in Chemistry in 2022. In 2014, Sharpless pushed it to a new level by launching the groundbreaking sulfur-fluoride exchange (SuFEx) based click chemistry[3]. Unlike the CuAAC (copper-catalyzed azide-alkyne cycloaddition) click chemistry[2] where the azide and alkyne functionalities usually had to be pre-installed to the two linking fragments prior to ligation (Fig. 1a), the SuFEx chemistry could directly ligate two or three free alcohols (mainly phenols) or amines, which are fundamental and much more common functionalities than azides and alkynes (Fig. 1b). Another key feature is that the two or three fragments branched three-dimensionally from the sp^3-hybridized S(VI) center while the traditional CuAAC chemistry only linked the two fragments two-dimensionally on the planar triazole ring. Undoubtedly, this pioneering technology already triggered tremendous advancement in the field of click chemistry[4-15]. Notably, in 2023, Moses and Sharpless further extended the sulfur-fluoride exchange chemistry to the phosphorus fluoride exchange (PFEx) version[16], where three amines and alcohols could be sequentially

ligated at one P(V) center (Fig. 1c). However, the state-of-the-art SuFEx and PFEx chemistry only ligated maximally three amines and alcohols through fluoride exchange, although theoretically the quadruple ligation is possible since the sp^3-hybridized S(VI) and P(V) require four ligands on them. We envisioned that Si(IV) might be ideal for the single-atom ligation of four amines and alcohols, especially four alcohols for the following considerations. First of all, silicon is an oxophilic element with the Si-O bond energy as high as 460 kJ/mol while the bond energy for P-O is 410 kJ/mol and 364 kJ/mol for S-O, which ensures the ligation of alcohols to silicon a favorable process. Secondly, in fully heteroleptic tetraalkoxysilanes, the four different alkoxy fragments would occupy the four vertices of a Si(IV)-centered tetrahedron to branch three-dimensionally. Finally, the four alcohols are attached to Si(IV) via the same Si-O single bond, thus making the iterative and programmable ligation viable simply through four repeated Si-O bond forming reactions.

Unfortunately, imitation of the SuFEx and PFEx chemistry to ligate alcohols using SiF_4 via silicon-fluoride exchange would lead to nowhere due to the extremely strong Si-F bond (552 kJ/mol) (Fig. 1d). The most straightforward candidate would be $SiCl_4$ since the Si-O bonds are most frequently constructed via silicon-chloride exchange with alcohols[17,18]. However, one imminent and critical issue with the $SiCl_4$ hub is the highly probable yet unpredictable over-substitution of the multiple chlorines when ligating the first three alcohols (Fig. 1f), not mentioning the sensitive nature of the chlorosilane intermediates and the tedious separation of them from the over-substituted by-products. In silicon chemistry, although alternative silicon precursors and methodologies have been developed to achieve iterative and step-by-step

substitution at silicon (Fig. 1e)[19-21], maximally three iterations have been realized and these iterations only enabled repeated Si-C bond instead of Si-O bond formations, thus affording silanes with three or four different carbon-substituents instead of fully heteroleptic tetraalkoxysilanes ligating four different alcohols. Surprisingly, while homoleptic tetraalkoxysilanes such as tetramethoxysilane were already prepared more than one hundred years ago and have been widely utilized ever since, fully heteroleptic tetraalkoxysilanes were barely known in literature, not mentioning the selective synthetic strategies. Therefore, for the ligation of four different alcohols at one silicon center, both ligation hubs and techniques need to be developed.

We proposed to employ the commercial triphenylchlorosilane (Ph_3SiCl) as the ligation hub to fulfill the above mission. As shown in Fig. 1g, the first alcohol could be reliably linked to the Si(IV) center as triphenylsilyl ether. Then, an *ipso* electrophilic halogenation[22] of the Si-Ph bond of the triphenylsilyl ether would first generate the Wheland-type cationic intermediate (σ-complex) **A**[23], which might undergo either a silicon cation[24] formation/alcohol addition mechanism (**B**) or a non-silicon cation mechanism (**C**) to ligate the second alcohol. Over-substitution was envisioned disfavored since the dialkoxydiphenylsilane product would be less electron rich compared to the monoalkoxytriphenylsilane starting material, thus less reactive towards X^+. Further iterations of this proposed silicon-phenyl exchange methodology would accomplish the ligation of four different alcohols at one silicon center.

Key reaction development and scope study

To setoff, we first probed the prospect of the above proposed key reaction using

dimethylphenylsilyl (DMPS) protected 2-phenylethanol as model substrate (Fig. 1h). 2,2,2-Trifluoroethanol (TFE) was initially added as solvent to maximize the interception of any cationic species. A series of commercial electrophilic halogenation reagents were tested. Although the Cl^+ and I^+ ones all caused decomposition to 2-phenylethanol (entry 1,2,6,7), N-bromosuccinimide (NBS) smoothly promoted the desired reaction, ligating TFE with 2-phenylethanol as mixed-dialkoxysilane **2** (entry 3). Further screening of the Br^+ reagents revealed the optimal 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (entry 5). Delightfully, the loading of TFE could be reduced to 5 equivalent by using DCM as solvent (entry 13). Benzene was also a suitable solvent (entry 10), while EtOAc or acetone led to no conversion (entry 8) and MeCN or THF caused decomposition (entry 9). The yield could be further enhanced to 90% with drastically shortened time at slightly elevated temperature (50 ºC) (entry 14).

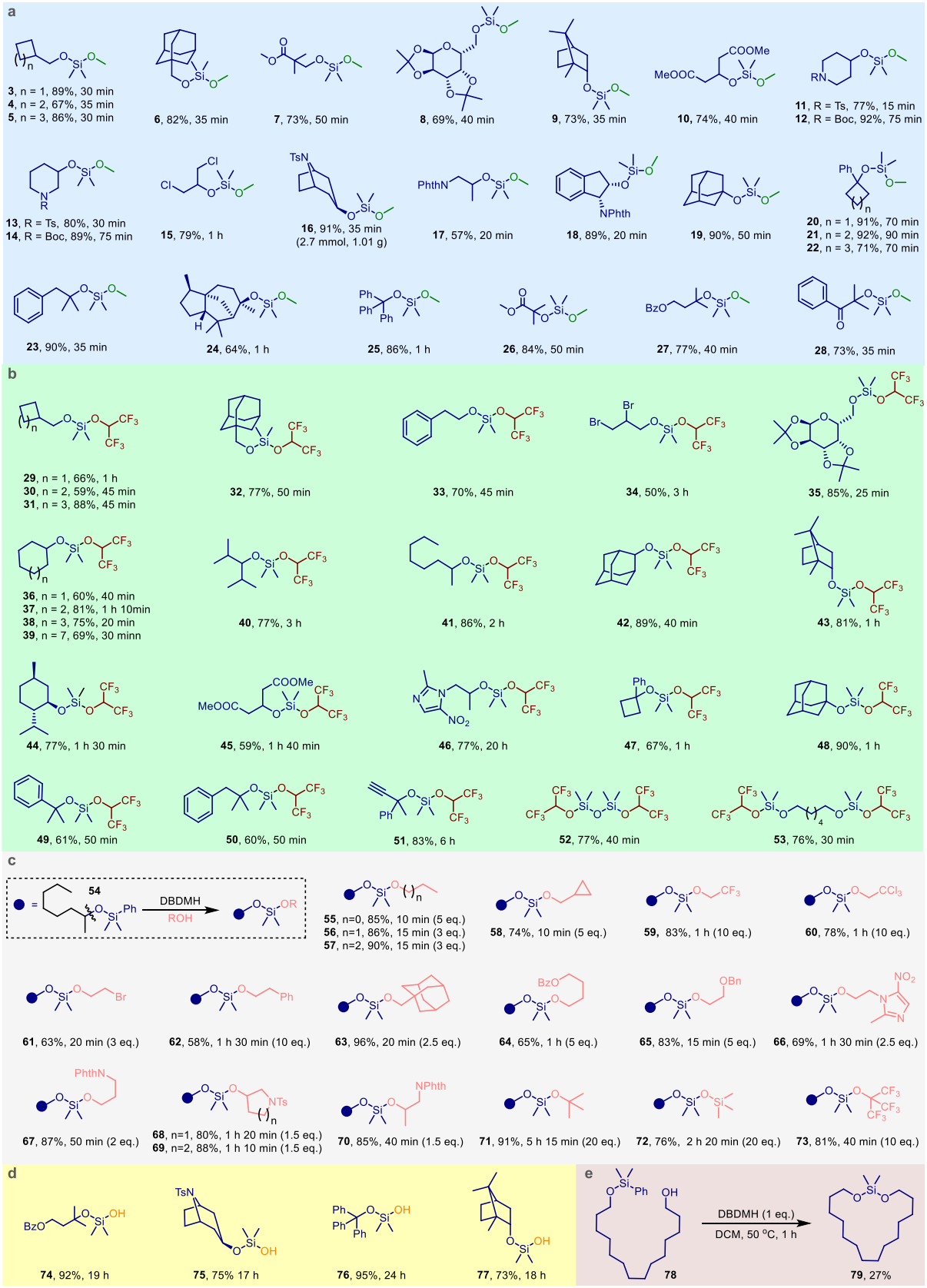

Fig. 2 | Substrate scope of alcohols. a, Ligation of MeOH with various types of ROH via $ROSiMe_2Ph$. **b**, Ligation of HFIP with various types of ROH via $ROSiMe_2Ph$. **c**, Ligation of

other types of free alcohols with 2-octanol using $Me_2PhSiCl$ as the connective hub. **d**, Ligation of H_2O with various types of ROH via $ROSiMe_2Ph$. **e**, Macrocyclization.

The alcohol scope for the above key reaction was then systematically investigated (Fig. 2). First of all, various primary, secondary, and tertiary alcohols were linked to DMPS group. It turned out the ligation of these DMPS-capped alcohols with free methanol worked well regardless of their steric and electronic properties (Fig. 2a). Notably, the DMPS ethers derived from tertiary alcohols (**19**-**28**), especially the triphenylmethanol one (**25**), survived the standard conditions from decomposition since HBr or Br_2 might be formed from potential side reactions[25,26]. Then, the ligation of the DMPS ethers was performed with free 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which represents the type of alcohols opposite to methanol: sterically bulky, poorly nucleophilic, and strongly hydrogen bond-donating[27]. Again, the ligations worked with various types of substrates, including the sterically bulky or acid sensitive ones (Fig. 2b). In addition to methanol and HFIP, other types of free alcohols including primary, secondary, and tertiary ones could be directly ligated to silicon center as well (Fig. 2c). Intriguingly, the extremely bulky, electron deficient, and poorly nucleophilic perfluoro-*tert*-butanol could be effortlessly ligated (**73**), even faster than HFIP (**41**) and the parent *tert*-butanol (**71**). Moreover, water could be ligated, affording the alkoxydimethylsilanols **74**-**77** in medium to excellent yields (Fig. 2d). Finally, the silicon-phenyl exchange reaction could be conducted intramolecularly for the macrocyclization of mono-DMPS protected 1,14-tetradecadiol **78** (Fig. 2e). While the backbone was completely flexible with no Thorpe-Ingold effect, the macrocyclic silyl ether **79** could still be obtained in

a serviceable 27% yield.

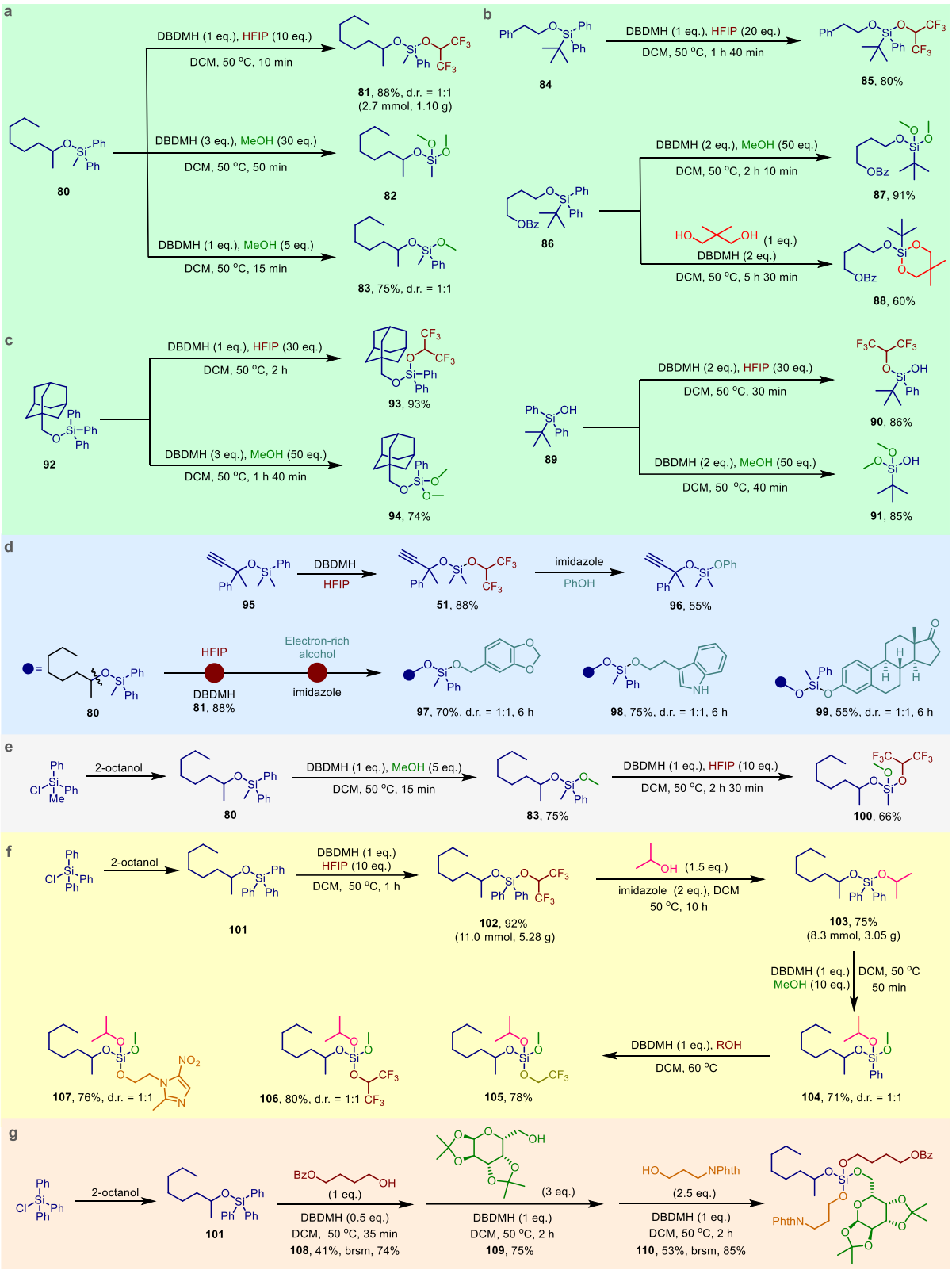

Fig. 3 | Other phenylchlorosilane hubs, two-step ligation, and the ligation of multiple different alcohols. a, $Ph_2MeSiCl$ as the connective hub. **b**, $^tBuPh_2SiCl$ as the connective hub.

c, Ph_3SiCl as the connective hub. **d**, Two-step ligation. **e**, Ligation of three different alcohols at one silicon center. **f**,**g** Ligation of four different alcohols at one silicon center.

One advantage employing chlorosilanes as ligation hubs for alcohols is their widely availability both commercially and synthetically[28,29], such as the diphenylmethylsilyl chloride (DPMSCl), *tert*-butyldiphenylsilyl chloride (TBDPSCl), and triphenylsilyl chloride (TPSCl). It turned out the silicon-phenyl exchange reaction was also applicable to the DPMS, TBDPS, and TPS ligated alcohols (Fig. 3a-c). For the DPMS ligated 2-octanol **80**, selective coupling of one or two methanol could be achieved by controlling the loading of DBDMH and methanol (**82**,**83**). Interestingly, **89** could only ligate with one HFIP as **90** even with excess amount of DBDMH and HFIP, presumably due to the steric shielding and inductively deactivating effect from the 1,1,1,3,3,3-hexafluoro-2-propoxy group on the remaining phenyl group of **90**. Unfortunately, the dr for **81** and **83** was near 1:1 using 2-octanol as auxiliary. The mono-specific ligation of HFIP was also true for the TBDPS ether **84**, TBDPSOH **89**, and TPS ether **92**, yielding **85**, **90**, and **93** respectively. Such reliable and predictable mono-exchange of triphenylsilyl group's three phenyl rings laid the foundation for the ultimate goal of iterative, controllable, and programmable ligation of four different alcohols at one silicon center. Interestingly, besides the ligation of two free methanol (**82**,**87**,**91**,**94**), neopentyl glycol could be ligated to silicon center to afford the dioxasilinane **88** via two consecutive inter- and intramolecular silicon-phenyl exchange reactions.

Two-step ligation technique and the ligation of three or four different alcohols

One drawback for the above DBDMH-promoted silicon-phenyl exchange was the

incompatibility with highly electron rich systems, such as phenols and indoles. Fortunately, such sensitive alcohols could still be ligated to the Si(IV) center via a two-step ligation technique (Fig. 3d). For instance, the DPMS-ligated 2-phenyl-3-butyn-2-ol **95** was first ligated with HFIP as the mixed-dialkoxysilane **51**. Then, the 1,1,1,3,3,3-hexafluoro-2-propoxy group of **95** could be facilely substituted by phenol to furnish the desired ligation product **96** with the terminal alkyne intact, which could be utilized for another CuAAC click chemistry. Similarly, the DBDMH-sensitive piperonyl alcohol, indole-3-ethanol, and estrone were respectively ligated to 2-octanol via the two-step ligation technique as **97**, **98**, and **99** in modest to good yield.

With the key methodology to ligate two different alcohols established, we proceeded towards the ultimate goal of ligating four different alcohols at one silicon center. Along the way, we also realized the ligation of three different alcohols using DPMSCl as the connective hub. As shown in Fig. 3e, the first alcohol (2-octanol) was connected to the silicon center via routine silicon-chloride exchange reaction (**80**). The second and third alcohols (MeOH and HFIP) were then directly ligated via two consecutive silicon-phenyl exchange reactions to furnish the mixed-trialkoxysilane **100**. Ultimately, we touched on the issue of single-atom ligation of four different alcohols using TPSCl as the connective hub (Fig. 3f). 2-Octanol and isopropanol were first ligated as the mixed-dialkoxysilane **103** via the two-step ligation technique. Methanol was then ligated to give the mixed-trialkoxysilane **104**. Subsequently, TFE, HFIP, and metronidazole were directly coupled with **104** to afford the fully heteroleptic tetraalkoxysilanes **105**, **106**, and **107** respectively, thus proving the concept and feasibility of iterative, controllable,

and programmable ligation of four different alcohols to one silicon center. Furthermore, starting from TPSCl, we also realized the selective ligation of four different alcohols in just 4 steps (Fig. 3g), which represented the theoretically shortest synthesis of fully heteroleptic tetraalkoxysilanes. It is worth highlighting that, from a retrosynthetic point view, fully heteroleptic tetraalkoxysilanes are extremely difficult to access in a selective fashion. Our protocol thus provided a robust solution to materials of such nature, including the less challenging mixed-dialkoxysilanes and -trialkoxysilanes.

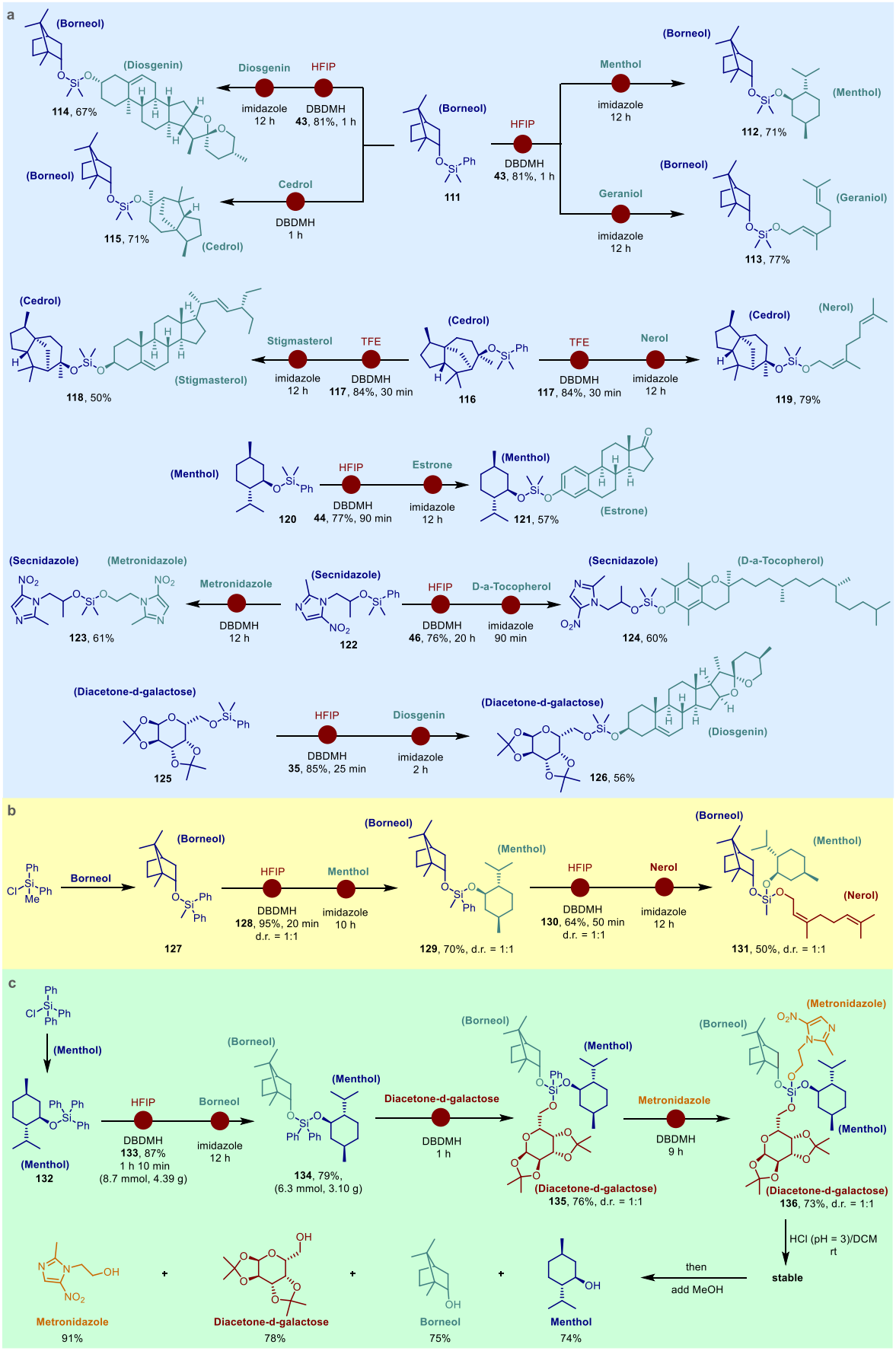

Fig. 4 | Ligation of two (a), three (b), or four (b) biologically relevant alcohols.

To demonstrate the application potential for functional molecule engineering and discovery, we moved forward to ligate two, three, or even four natural products, drugs, or other biologically relevant alcohols using the silicon strategy. As shown in Fig. 4a, a broad spectrum of biologically relevant alcohols, such as borneol, menthol, geraniol, diosgenin, cedrol, nerol, stigmasterol, estrone, secnidazole, metronidazole, d-α-tocopherol, and diacetone-d-glacatose, could be facilely conjugated to Si(IV) as mixed-dialkoxy(arenoxy)silanes (**112**-**126**). Moreover, borneol, menthol, and nerol were conjugated together as mixed-trialkoxysilane **131** using DPMSCl as the connective hub (Fig. 4b). Ultimately, borneol, menthol, diacetone-d-glacatose, and metronidazole were ligated to one Si(IV) center as mixed-tetraalkoxysilane **136** (Fig. 4c) in just five steps from Ph_3SiCl, highlighting the potential of this protocol for covalent drug or hybrid drug development[30-32]. It was worth mentioning that the above four biologically relevant alcohols were ligated to the Si(IV) center via stable yet cleavable Si-O bonds, which might find applications for precise and concerted delivery of multiple drugs to targeted area[33,34]. Surprisingly, the mixed-tetraalkoxysilane **136** in DCM was rather stable when treated with aqueous HCl. After the addition of methanol, it was fully hydrolyzed and the borneol, menthol, diacetone-d-glacatose, and metronidazole were recycled in 75%, 74%, 78%, and 91% yield respectively under this unoptimized hydrolysis condition.

Mechanistic studies

To shed light on the reaction mechanism, we first conducted one reaction in $CDCl_3$ and monitored it using NMR and could indeed identify same amount of bromobenzene along with the product **42** (Fig. 5a). We then investigated the nature of the above silicon-phenyl exchange

reaction, i.e. the halodesilylation reaction. Firstly, control experiments on **139** showed that no reaction occurred without the external alcohol **140** (Fig. 5b), which was in drastic contrast to the well-known additive-free halodesilylations of phenylsilanes using Br_2 or ICl to give phenylhalides and silylhalides. Therefore, in the current work, the proposed cationic Wheland intermediate **A** was unlikely formed, which otherwise would most likely be trapped by the corresponding hydantoin anion. The racemic substrate **139** was then subjected to HPLC separation to get the two enantiomers **139-enantiomer-1** (>99% ee) and **139-enantiomer-2** (<-99% ee). Interestingly, the silicon-phenyl exchange reactions of these two enantiomers afforded products **141-1** and **141-2** in 34% ee and -34% ee respectively (Fig. 5c), thus ruling out both the S_N1-like and S_N2-like mechanism (Fig. 1g). On the other hand, the enantiomeric purity of the two recovered starting materials remained >99% ee and <-99% ee (Fig. 5c).

Based on the above observations, a plausible mechanism was depicted in Fig. 5d. First of all, DBDMH reversibly complexed with the phenylsilane substrate as **D**, thus partially activating the silane substrate. Then, the external alcohol (Nu) approached **D** from ten possible trajectories: the 4 faces and 6 edges of the hypothetical tetrahedron[35,36]. The six trajectories in the upper box (Fig. 5d) would result in the retention of the silicon center's configuration, while the other four in the lower box would lead to inversion of configuration[37]. It is worth highlighting that the 34% ee (67:33 er) for product **141-1** and the -34% ee (33:67 er) for product **141-2** unambiguously evidenced that both retention and inversion of configurations could occur in the halodesilylation reactions. As a comparison, for the traditional Br_2 or ICl-promoted alcohol free halodesilylation reactions, the retention of configuration was not conclusive from the

minor amount of retention product, which might originate from the inversion of the predominant inversion product due to the labile nature of the silylhalide products[38-41].

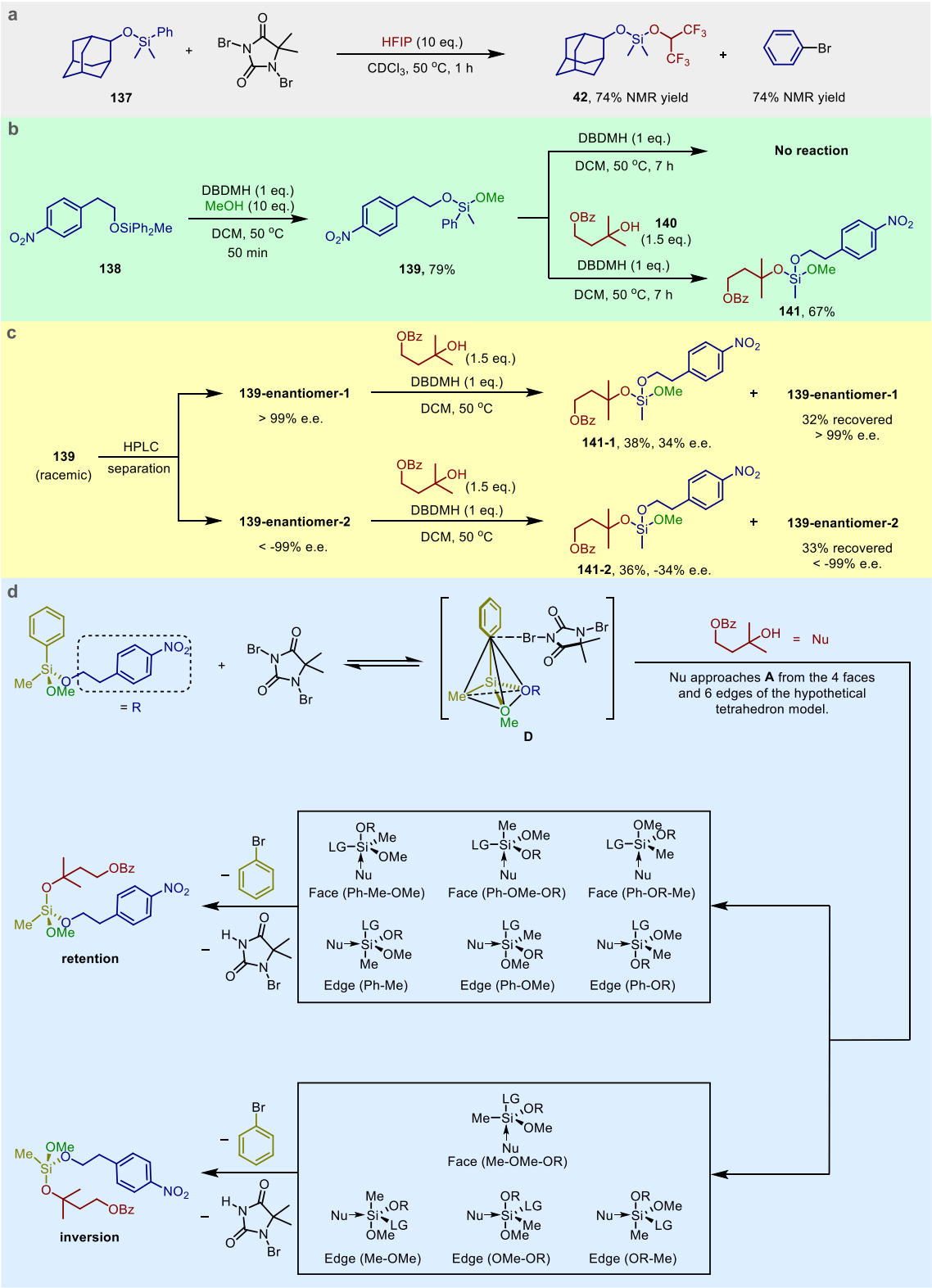

Fig. 5 | Mechanistic studies. a, NMR study. **b**, Preparation of racemic materials and control

experiment. **c**, Study on the retention/inversion of silicon's configuration. **d**, Proposed mechanism.

Conclusion

In summary, we have established a new silicon-phenyl exchange reaction to connect alcohols to silicon centers. A broad spectrum of alcohols could be directly ligated except the highly electron rich ones, which could be accomplished via a two-step ligation technique using HFIP or TFE as the mediator. Various types of phenylchlorosilanes were demonstrated as effective ligation hubs for two, three, or even four alcohols. The mission of iterative, controllable, and programmable single-atom ligation of four different alcohols was realized based on this new ligation reaction. The four alcohols ligated to the silicon center could be released and recovered via silicon-alkoxy exchange of the stable yet cleavable Si-O bonds. We believe this work will open up new chemical space for novel functional molecule development and discovery. The construction of chiral silicon centers based on the silicon-phenyl exchange reaction and the application of the 2,2,2-trifluoroethoxysilanes and 1,1,1,3,3,3-hexafluoroisopropoxysilanes as new types of silylation reagents are underway.

Methods

Direct silicon-phenyl exchange: A 8 mL glass vial was charged with DCM (2 mL). Then, (cyclobutylmethoxy)dimethyl(phenyl)silane (0.50 mmol), MeOH (5 mmol, 0.21 mL), and DBDMH (0.50 mmol, 0.14 g) were successively added into the vial. The reaction mixture was stirred at 50 ^{o}C for 30 min. Then, it was filtrated through a short pad of silica gel. The solvent was removed under reduced pressure with the aid of a rotary evaporator and the crude residue was purified by silica gel column chromatography to give compound **3** (77.6 mg, 89% yield).

Two-step ligation using HFIP or TFE as the mediator: A 8 mL glass vial was charged with DCM (2 mL). Then, methyl(octan-2-yloxy)diphenylsilane (0.50 mmol), HFIP (5 mmol, 0.53 mL) and DBDMH (0.50 mmol, 0.14 g) were successively added into the vial. The reaction mixture was stirred at 50 ºC for 10 min. Then, it was filtrated through a short pad of silica gel. The solvent was removed under reduced pressure with the aid of a rotary evaporator and the crude residue was purified by silica gel column chromatography to give compound **81** (183.3 mg, 88% yield, 1:1 d.r.).

A 8 mL glass vial was charged with DCM (2 mL). Then, piperonyl alcohol (1.5 eq., 0.75 mmol), imidazole (2 eq., 1 mmol), and ((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(methyl)(octan-2-yloxy)(phenyl)silane **81** (1 eq., 0.50 mmol) were successively added into the vial. The reaction mixture was stirred at 50 ºC for 6 h. Then, it was filtrated through a short pad of silica gel. The solvent was removed under reduced pressure with the aid of a rotary evaporator and the crude residue was purified by silica gel column chromatography to give compound **97** (140.2 mg, 70% yield, 1:1 d.r.).

Data availability

The data supporting the findings of this study are available within this article and its Supplementary Information.

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Author contributions

Y.W. designed and conceived the project. C.W., X.X., X.Z., H.L., and P.M.A. carried out the reactions. C.W. and Y.W. wrote the manuscript with input from all authors. All authors analyzed the data and discussed the results.

Competing interests

The authors declare no competing interests.