LETTER

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Silylation of C–H bonds in aromatic heterocycles by an Earth-abundant metal catalyst

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Heteroaromatic compounds containing carbon–silicon (C–Si) bonds are of great interest in the fields of organic electronics and photonics[1], drug discovery[2], nuclear medicine[3] and complex molecule synthesis[4–6], because these compounds have very useful physicochemical properties. Many of the methods now used to construct heteroaromatic C–Si bonds involve stoichiometric reactions between heteroaryl organometallic species and silicon electrophiles[6,7] or direct, transition-metal-catalysed intermolecular carbon–hydrogen (C–H) silylation using rhodium or iridium complexes in the presence of excess hydrogen acceptors[8,9]. Both approaches are useful, but their limitations include functional group incompatibility, narrow scope of application, high cost and low availability of the catalysts, and unproven scalability. For this reason, a new and general catalytic approach to heteroaromatic C–Si bond construction that avoids such limitations is highly desirable. Here we report an example of cross-dehydrogenative heteroaromatic C–H functionalization catalysed by an Earth-abundant alkali metal species. We found that readily available and inexpensive potassium tert-butoxide catalyses the direct silylation of aromatic heterocycles with hydrosilanes, furnishing heteroarylsilanes in a single step. The silylation proceeds under mild conditions, in the absence of hydrogen acceptors, ligands or additives, and is scalable to greater than 100 grams under optionally solvent-free conditions. Substrate classes that are difficult to activate with precious metal catalysts are silylated in good yield and with excellent regioselectivity. The derived heteroarylsilane products readily engage in versatile transformations enabling new synthetic strategies for heteroaromatic elaboration, and are useful in their own right in pharmaceutical and materials science applications.

Heteroarylsilanes are important motifs in medicinal chemistry and drug discovery[2,3], advanced materials and polymer synthesis[1,10], and various biomedical applications[3,11]. In addition, they are emerging as one of the most versatile heteroaryl metal species for complex molecule synthesis owing to the high natural abundance and low toxicity of silicon[4–6]. At present, the most common approach to heteroaromatic C–Si bond construction involves the interception of heteroaryl lithium or magnesium reagents with silicon electrophiles (Fig. 1a, route A). However, this method is often limited in scope and requires prefunctionalization of heteroarenes by using pyrophoric organometallic species in stoichiometric quantities[7]. Powerful heteroaromatic functionalization strategies, such as Minisci-type radical substitutions[12] and Friedel–Crafts reactions[13,14], have been of limited use for C–Si bond construction owing to the difficulty of generating the corresponding silyl radicals and silylium ions. An efficient and regioselective sila-Friedel–Crafts reaction to access C3-silylated indoles was recently described[15], although the catalysis required a precious metal ruthenium (Ru) species for activation of the hydrosilane.

Thus far, only complexes based on precious metal elements, namely rhodium (Rh) and iridium (Ir), have been demonstrated to catalyse the intermolecular C–H silylation of heteroarenes with hydrosilanes[16] (Fig. 1a, route B). Two examples have been reported: an $[Ir(OMe)(cod)]_2$ precatalyst with a 4,4′-dtby ligand, used at 80 °C (ref. 9), and a $[Rh(coe)_2(OH)]_2$ precatalyst in combination with a MeO-BIPHEP ligand[8] (Me, methyl; cod, 1,5-cyclooctadiene; 4,4′-dtby, 4,4′-di-tert-butyl-2,2′-dipyridyl; coe, *cis*-cyclooctene.) Excess quantities of a sacrificial hydrogen acceptor were necessary for catalyst turnover in these systems. Although these are both important silylation methods, they rely on catalysts derived from rare and expensive precious metals, which can be a significant limitation, particularly for large-scale syntheses. Moreover, substrates containing Lewis-basic nitrogen functionalities are notably absent in both reports, limiting the use of these methods in pharmaceutical science and other biomedical applications. Thus, the development of a general catalytic method for heteroaromatic C–Si bond formation remains a considerable challenge in the broader field of C–H functionalization. Here we report that inexpensive and commercially available

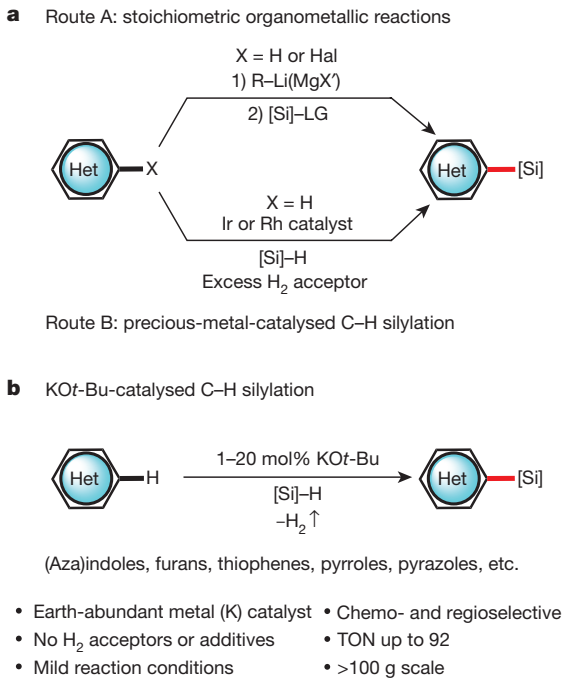

Figure 1 | Approaches to the silylation of heteroarenes. a, Route A, classical synthesis of heteroaryl silanes by reaction of organometallic species with silicon electrophiles. The organometallic species is typically prepared by deprotonation of heteroarenes or by lithium–halogen exchange of heteroaryl halides. X′ = Cl or Br; Hal, halogen; LG, leaving group. Route B, recently emerging direct, transition-metal-catalysed C–H activation/silylation. Excess amounts of hydrogen acceptors are required. **b**, A departure from the transition metal catalysis paradigm: KO*t*-Bu-catalysed, acceptorless, cross-dehydrogenative heteroaromatic C–H silylation with hydrosilanes. TON, turnover number.

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potassium tert-butoxide (KO*t*-Bu) catalyses the acceptorless, cross-dehydrogenative coupling of aromatic heterocycles with hydrosilanes to generate heteroarylsilanes under mild conditions (Fig. 1b). The alkali metal catalyst is compatible with a range of functional groups including pyridines, piperidines and amines, making this novel C–H silylation method immediately applicable to medicinal chemistry and alkaloid natural product synthesis.

In a recent report, we described the reductive cleavage of C–O bonds in aryl ethers using stoichiometric quantities of alkali metal alkoxides to activate hydrosilanes at elevated temperatures[17]. We were surprised to observe minor by-products derived from *ortho*-silylation with dibenzofuran as the substrate. Considering prior reports of Lewis-base activation of hydrosilanes[18], we questioned whether these unanticipated silylation by-products could be pointing to a more general reaction manifold. Thus, with 1-methylindole as a model substrate, an extensive optimization exercise was conducted (Supplementary Information). We observed that the combination of a bulky basic anion (that is, O*t*-Bu, trimethylsilanolate or bis(trimethylsilyl)amide) and, importantly, a potassium countercation led to the desired C–Si bond formation. KO*t*-Bu proved to be the ideal catalyst, furnishing synthetically useful C2-silylated indole **2a** in good yield and with >20:1 regioselectivity under mild conditions. The reaction can be optionally performed under solvent-free conditions, which in certain cases leads to improved selectivity. Experiments and analyses to rule out catalysis by adventitious transition metal residues were carefully conducted (Supplementary Information).

A variety of indoles with Me, ethyl (Et), benzyl (Bn), phenyl (Ph) and the readily cleavable methoxylmethyl and 2-[(trimethylsilyl)ethoxy]methyl groups on nitrogen all lead to regioselective C2 silylation in moderate to good yields (Fig. 2, **2a–2f**). We then explored the influence of substituents at various positions of the indole nucleus and found that Me, OMe, OBn, CH_2OMe and Ph are all compatible, giving the desired products **2g–2n** in 48%–83% yield. Several hydrosilanes were examined and the silylation products (**2o–2x**) were obtained in good yield. A diverse range of N-, O- and S-containing heteroaromatics[19] (Fig. 3), including pyridine-containing scaffolds (**4a–4g** and **4j–4l**), undergo the reaction with high regioselectivity. Reactions at decreased catalyst loadings (1–3.5 mol%; **4j**, **4m** and **4n**) and on a large scale (**4h** and **4n**) demonstrate the robustness and preparative scale utility of the process. The reaction scaled to greater than 100 g without loss of catalyst activity under procedurally convenient conditions[20] (Fig. 4a).

In general, the reaction proved to be selective for electron-neutral and electron-rich heterocycles; indoles possessing electron-withdrawing groups are unreactive. To further probe the functional group tolerance of the method, a comprehensive robustness evaluation was performed[21].

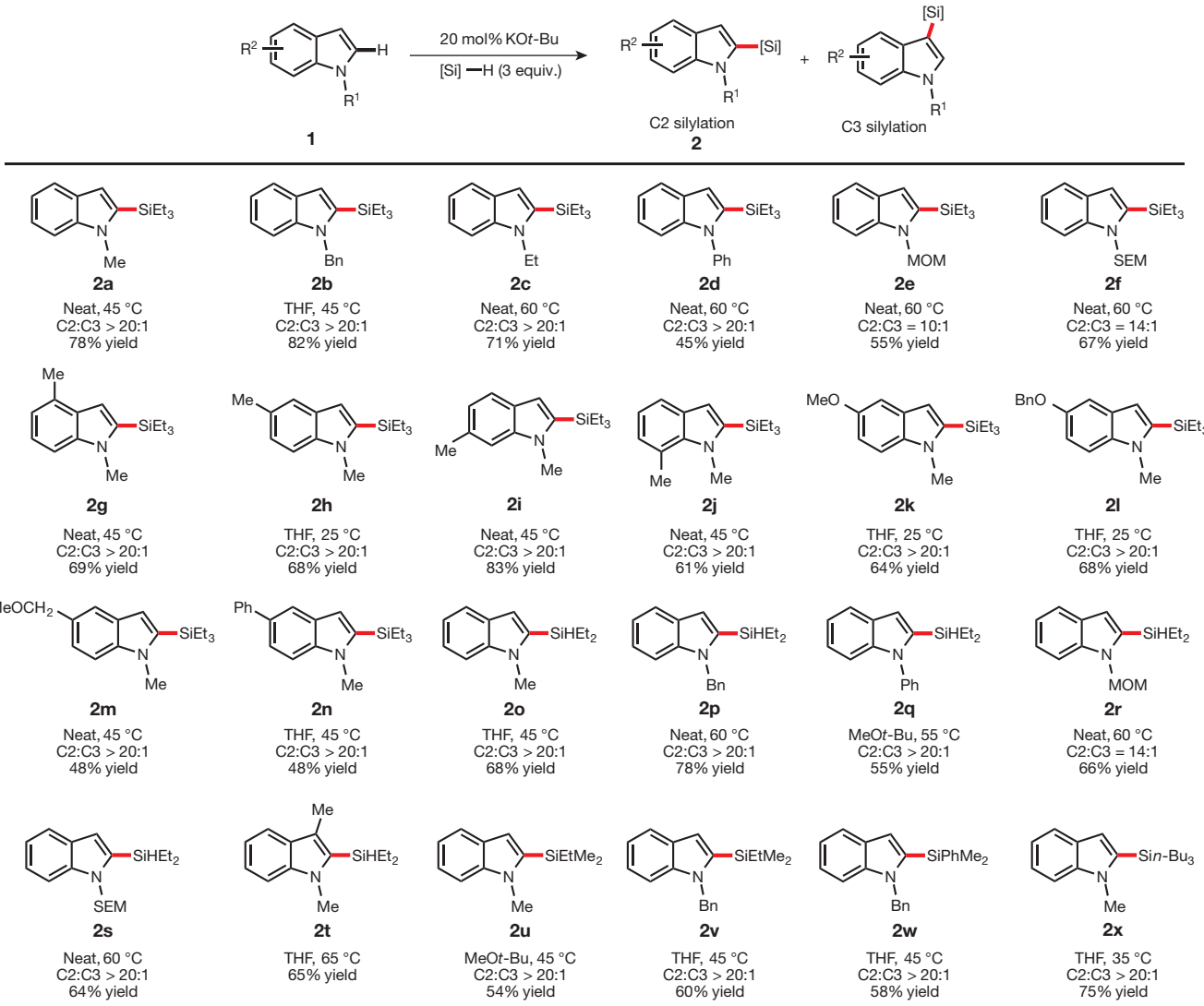

Figure 2 | Scope of the KO*t*-Bu-catalysed silylation of indoles. For the reactions of **2g** and **2i**, silylation on the benzylic methyl group was observed with tetrahydrofuran (THF) as solvent; solvent-free conditions often led to improved regioselectivity and yield. For the reaction of **2k**, silylation at C6 was observed as a by-product in THF. The reactions of 1,3-dimethyl indole with Et_3SiH and $PhMe_2SiH$ were sluggish, probably owing to steric congestion at C2. For the reaction of **2o**, bisindolyldiethylsilane was isolated as a by-product. See Supplementary Information for details. [Si]–H = Et_3SiH, Et_2SiH_2, $EtMe_2SiH$, $PhMe_2SiH$ or *n*-Bu_3SiH. MOM, methoxylmethyl; SEM, 2-[(trimethylsilyl)ethoxy]methyl.

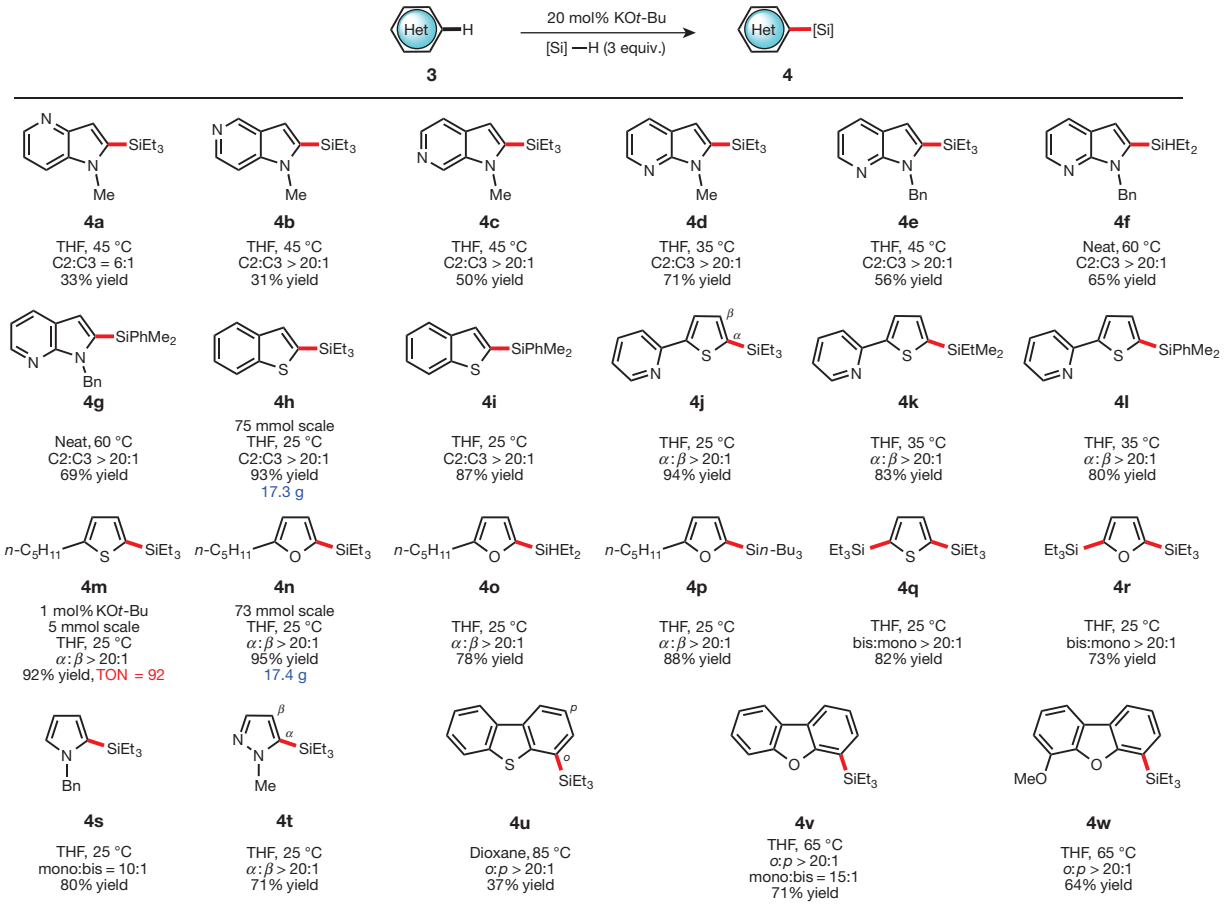

Figure 3 | KO*t*-Bu-catalysed silylation of N-, O- and S-containing heteroarenes. Multigram-scale syntheses were presented for **4h** and **4n**. Catalyst loadings can be reduced to 1 mol% with a TON of 92 (**4m**). For **4j**, with 3.5 mol% KO*t*-Bu, TON = 23 (82% yield); for **4n**, with 1.5 mol% KO*t*-Bu, TON = 61 (91% yield). Bisfuranyldiethylsilane was isolated as a by-product in the reaction of **4o**. Unsubstituted thiophene and furan favoured 2,5-bis-silyation (**4q** and **4r**). See Supplementary Information for details. [Si]–H = Et_3SiH, Et_2SiH_2, $EtMe_2SiH$, $PhMe_2SiH$ or n-Bu_3SiH.

The results showed that carbonyl groups in general are not tolerated, but are compatible if protected as the corresponding acetal. Ar–Br, Ar–I, Ar–CN, and Ar–NO_2 also shut down the reaction. However, Ar–F, Ar–Cl, Ar–CF_3, epoxide, *N*-alkyl aziridine, *cis*- and *trans*-olefins, acetylene, pyridine, and tertiary amine and phosphine moieties are all compatible with the silylation chemistry. Even free OH and NH groups are tolerated to some extent, apparently owing to a fortuitous silylative protection of the heteroatom *in situ*[18] (Supplementary Information).

Preliminary mechanistic investigations suggest the involvement of radical species. However, an elementary silyl radical generation-substitution mechanism seems to be unlikely owing to poor reactivity with electron-deficient heteroarenes[12,22]. Moreover, the rate of silylation is greater in sulphur-containing heteroarenes than in oxygen-containing heteroarenes, and is greater in oxygen-containing heteroarenes than in nitrogen-containing heteroarenes, as observed in an internal competition study, which provides complementary reactivity to electrophilic substitutions[14,15] and Minisci-type reactions[12,22]. These observations point to an underlying mechanism that is distinct from known heteroaromatic C–H functionalization reactions (Supplementary Information).

Heteroarylsilane derivatives are known to undergo a variety of powerful synthetic transformations; a number of representative examples are demonstrated here (Fig. 4b). For example, C2 Si-directed Suzuki–Miyaura cross-coupling by the method of Zhao and Snieckus[23], or Hiyama–Denmark cross-coupling[5] via heteroarylsilanol **6**[24], furnishes 2-arylated indole **5**. An unusual direct C7 functionalization of benzothiophene to give boronate esters **7** and **8** was achieved by using a blocking group strategy from silylated precursor **4h**[25].

Organosilicon has been extensively investigated in the development of advanced materials owing to silicon's unique physical and chemical properties[1,26]. To demonstrate the utility of our method in possible materials science applications, we prepared sila-heterocycle **9** in one step directly from the commercially available unfunctionalized heteroarene by an unprecedented double C–H functionalization involving intermolecular silylation followed by intramolecular silylation[10,16,27] (Fig. 4c). A high-yielding bis-silylation of thiophene oligomer **10** furnishes the starting material for an entirely transition-metal-free catalytic route to alternating copolymers[26]. Finally, the monoselective silylation of the 3,4-ethylenedioxythiophene monomer provides a potential strategy for the modification of polythiophene-derived materials (Fig. 4c, **11**).

Sila-drug analogues have garnered much attention from medicinal chemists because they can offer improved stability, solubility and pharmacokinetic properties compared with the parent all-carbon compounds[3]. Moreover, the installed organosilicon functionality can serve as a synthetic handle for subsequent elaboration, facilitating library synthesis and enabling structure–activity relationship studies. As a result, organosilicon-containing small molecules are of growing interest in pharmaceutical science, and the direct silylation of lead compounds would thus represent a new and potentially powerful tool in drug discovery[2]. To evaluate our method for such late-stage C–H functionalization applications, we subjected the antihistamine thenalidine and the antiplatelet drug ticlopidine to our catalytic silylation conditions. The reactions proceeded smoothly in the case of both active pharmaceutical ingredients, yielding the Si-containing target compounds **12** and **13a–c** in 56%–68% yield with excellent chemo- and regioselectivity (Fig. 4d). The

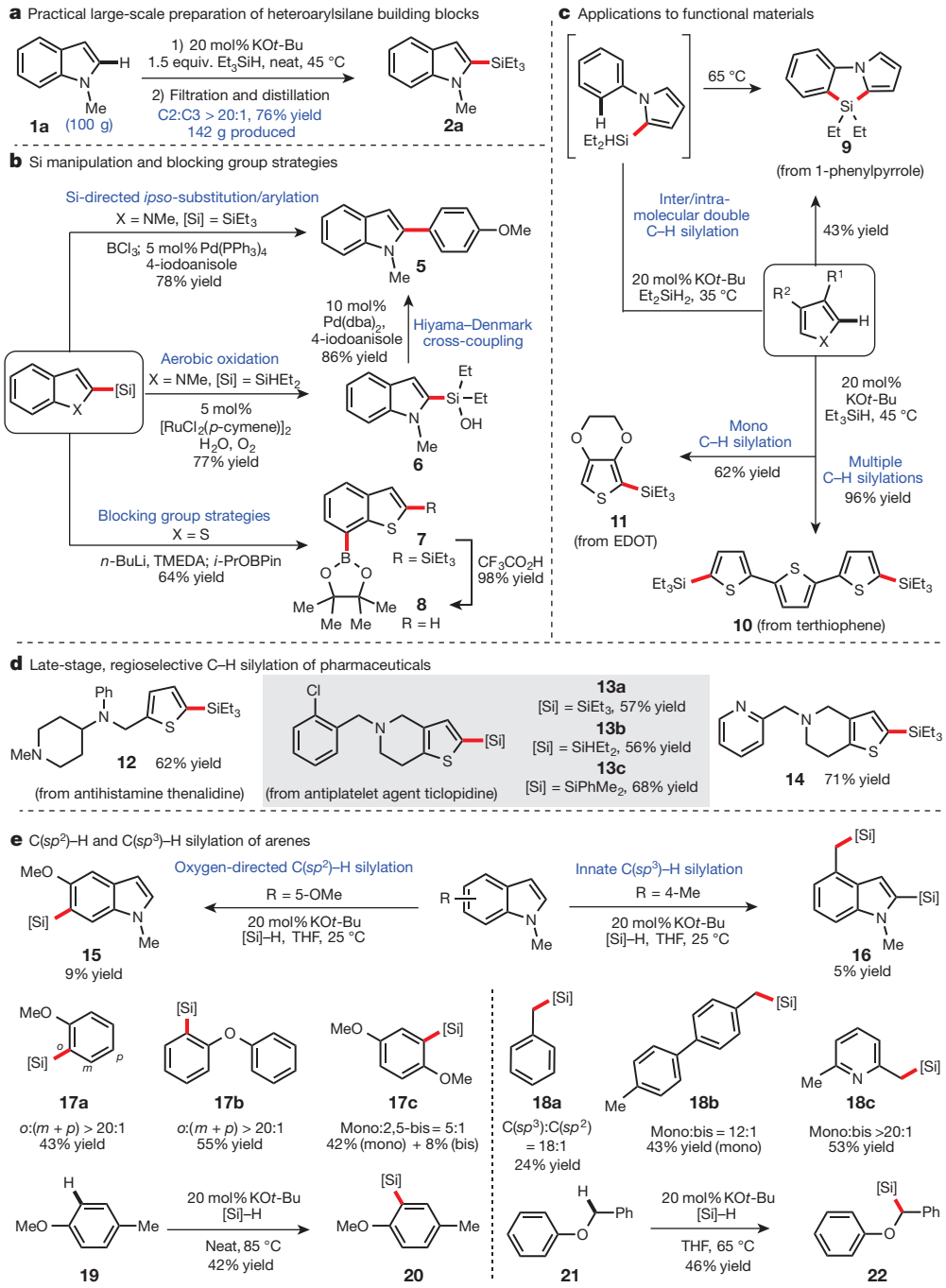

Figure 4 | Synthetic applications of the KO*t*-Bu-catalysed C–H silylation. **a**, Preparation of 142 g of C2-silylated indole building block **2a**. **b**, Application of heteroarylsilanes in cross-coupling and a formal C–H borylation at C7 of benzothiophene. **c**, Synthesis of precursors to advanced materials and polymers. **d**, Late-stage chemo- and regioselective modification of active pharmaceutical ingredients. **e**, KO*t*-Bu-catalysed functionalization of arenes by oxygen-directed sp^2, and innate benzylic sp^3 C–H silylation. See Supplementary Information for details. [Si] = Et_3Si; *i*-Pr, isopropyl; dba, dibenzylideneacetone; Bpin, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane; TMEDA, tetramethylethylenediamine; EDOT, 3,4-ethylenedioxythiophene.

piperidines, aniline, benzylic C–H bonds and aryl chloride moieties were all tolerated without any observed side reactions. Silylation of aza-analogue **14** also proceeded well, demonstrating the compatibility of our method with pyridine-containing complex molecules of potential pharmaceutical importance.

Finally, during our investigations we had observed minor amounts of sp^2 and sp^3 C–H silylation by-products at ambient temperature in the cases of methoxy- and methyl-substituted indoles, respectively (that is, **15** and **16**; Fig. 4e). This led us to consider whether simple arenes would react analogously. The *ortho*-silylation of anisole[28] and the directing-group-free C(sp^3)–H silylation of toluene[29,30] were discovered, furnishing silylated derivatives **17a** and **18a**, respectively. Four additional examples were demonstrated, providing silylarenes (**17b** and **17c**) and benzylsilanes (**18b** and **18c**) with excellent selectivity. Of particular note is the C(sp^3)–H silylation of 2,6-lutidine, providing an example of C–H silylation in an electron-deficient system. Interestingly, methoxy toluene **19** and benzyl ether **21**, both containing potentially reactive sp^2 and sp^3 C–H bonds, are silylated with opposite selectivities to yield **20** and **22**. In the case of **22**, the reaction introduces a Si-substituted chiral centre. Optimization and further elaboration of these substrate classes is currently ongoing.

We have reported sp^2 and sp^3 C–H silylation reactions catalysed by KO*t*-Bu, which is abundant, inexpensive, commercially available and bench stable. The transformation has been applied to an array of privileged heteroaromatic scaffolds and to a number of carbocyclic aromatic moieties. The potential for late-stage functionalization has been demonstrated by the direct silylation of active pharmaceutical ingredients. The extension of this work to non-aromatic systems is in progress, and detailed mechanistic investigations by experimental and computational methods are under way.

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Supplementary Information is available in the online version of the paper.

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