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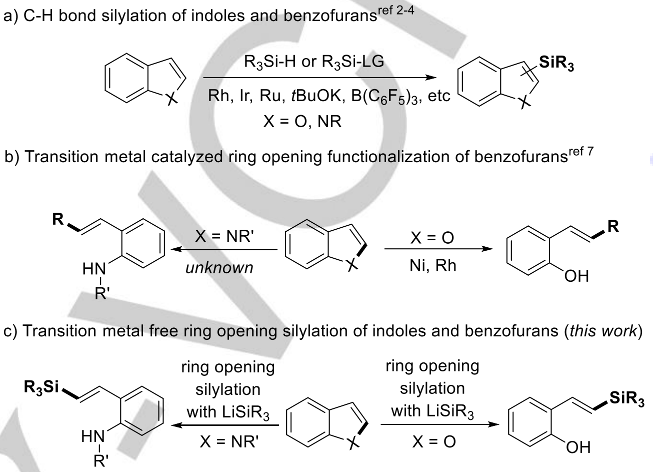
Transition-Metal-Free Ring Opening Silylation of Indoles and Benzofurans with (Diphenyl-*tert*-butylsilyl)lithium

Pan Xu, Ernst-Ulrich Würthwein, Constantin G. Daniliuc and Armido Studer*

Abstract: A practical method for ring opening of various indoles and benzofurans with concomitant stereoselective silylation using readily generated (diphenyl-*tert*-butylsilyl)lithium to provide *ortho*-β-silylvinyl anilines or phenols is presented. Dearomatization of the heteroarene core proceeds in the absence of any transition metal catalyst via silyl anion addition and subsequent stereoselective β-elimination. DFT calculations provide insights into the mechanism. Functionalizing C-X bond cleavage in heteroarenes is rare and generally requires transition metal catalysis.

Due to the importance of Si-based compounds in materials science, for biomedical applications and as intermediates/reagents in synthesis, organosilane chemistry has attracted considerable attention.[1] Heteroarylsilanes occupy a prominent role and the direct introduction of silyl groups into heteroarenes such as indoles and benzofurans has been intensively investigated. Recent reports focus on the direct C-H bond silylation that complement conventional silylation of a preformed metalated heteroarene. Friedel-Crafts type,[2] transition-metal (Rh, Ir, Ru) catalyzed[3] and KO*t*Bu catalyzed C–H silylation[4] have to be mentioned along these lines (Scheme 1a).

Arenes express high stability due to their resonance stabilization. The typical transformation at an arene being radical or ionic in nature proceeds *via* temporary disruption of the arene resonance with subsequent rearomatization. Compared to such widely studied arene functionalizations, much less attention has been devoted to the ring opening functionalization of aromatic compounds.[5] Whereas C-H functionalization of indoles has been widely explored,[6] indole C-N bond ring opening functionalization is unknown (Scheme 1b). However, benzofurans are known to undergo C(2)-O bond cleavage/functionalization using Ni- or Rh-catalysis (Scheme 1b).[7] Yorimitsu reported a Ni-catalyzed ring-opening/insertion borylation of benzofurans,[7e] where the arene core is destructed via oxidative addition of a Ni-complex into the C(2)-O bond. However, such a mechanistic option is not offered in transition metal free approaches and the development of arene ring opening functionalization in the absence of any transition metal remains challenging. We disclose herein transition metal free ring opening silylation of indoles and benzofurans through C(2)-N/O bond cleavage by a silyl anion (Scheme 1c). Product vinyl silanes, that are versatile synthetic intermediates, are obtained with moderate to excellent stereoselectivity.


a) C-H bond silylation of indoles and benzofurans$^{\text{ref 2-4}}$

b) Transition metal catalyzed ring opening functionalization of benzofurans$^{\text{ref 7}}$

c) Transition metal free ring opening silylation of indoles and benzofurans (*this work*)

Scheme 1. C-H bond silylation and ring opening functionalization of indoles and benzofurans

Silyllithium compounds react efficiently with various organic electrophiles,[8] but their reactivity towards arenes and heteroarenes has not been well explored. Rossi investigated the nucleophilic aromatic silylation using the highly reactive (trimethylsilyl)lithium.[9] Likely due to the fact that Me_3SiLi is too reactive and not readily generated, this area has remained unexplored. We decided to study the reaction of various arylsilyllithium reagents with *N*-phenylindole **1a** as a model substrate. The silyllithium reagents were readily generated from the corresponding silyl chlorides by reductive lithiation with elemental lithium in THF. Reactions were generally conducted at room temperature for 24 h and the silyl-Li reagent was systematically varied. With $Me_2PhSiLi$, $MePh_2SiLi$ and Ph_3SiLi the corresponding ring opening silylation products were not formed (Table 1, entries 1-3) and traces of C(2)-H bond silylation were identified by GC mass spectrometry. Pleasingly, the targeted **2a** was isolated in 57% yield with high *E*-selectivity using *t*$BuPh_2SiLi$ (Table 1, entry 4). Yield further increased to 80% upon raising temperature to 50 ^{o}C but *E*/*Z* selectivity slightly decreased. Attempted generation of *t*$BuPh_2SiNa$ failed and large amounts of *t*$BuPh_2SiSiPh_2$*t*Bu were observed. Reaction with *t*$BuPh_2SiK$ resulted in a complex mixture and the target **2a** was not identified (Table 1, entry 6). (*t*$BuPh_2Si)_2Zn$ did also not react with **1a** to **2a** (Table 1, entries 7, 8).

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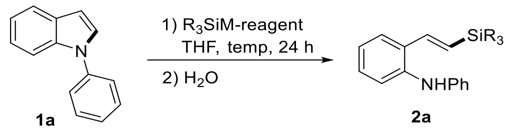
Table 1. Reaction optimization.

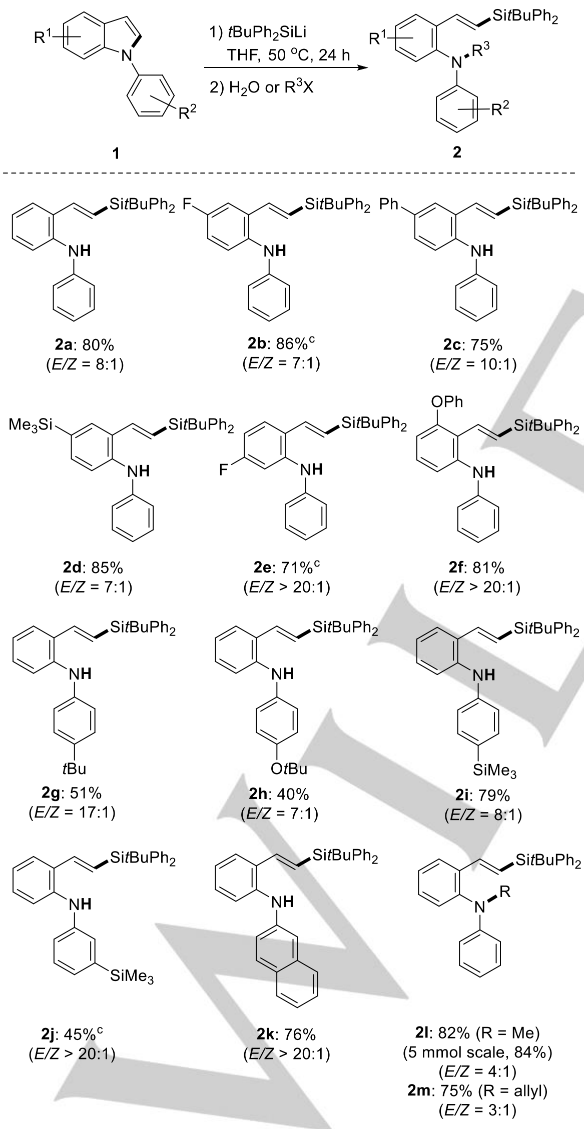


1a **2a**

entry[a]	Si-reagent (2 equiv)	temp	ratio (*E/Z*)[b]	yield (%)[c]
1[d]	Me$_2$PhSiLi	rt	-	0
2[d]	MePh$_2$SiLi	rt	-	0
3	Ph$_3$SiLi	rt	-	0
4	*t*BuPh$_2$SiLi	rt	>20:1	57
5	***t*BuPh$_2$SiLi**	**50 °C**	**8:1**	**80**
6	*t*BuPh$_2$SiK	rt	-	0
7	(*t*BuPh$_2$Si)$_2$Zn	rt	-	0
8[e]	(*t*BuPh$_2$Si)$_2$Zn[e]	rt	-	0

[a] Reaction condition: **1a** (0.2 mmol, 1.0 equiv), Si-reagent (0.4 mmol, 2.0 equiv), THF (1 mL). [b] *E/Z* isomer ratio determined by 1H NMR. [c] Isolated yield. [d] Traces of the C(2)-H bond silylation product were identified by GC mass spectrometry. [e] CuI (0.01 mmol, 0.05 equiv) was added.

Table 2. Ring opening silylation of various indoles.[a,b]



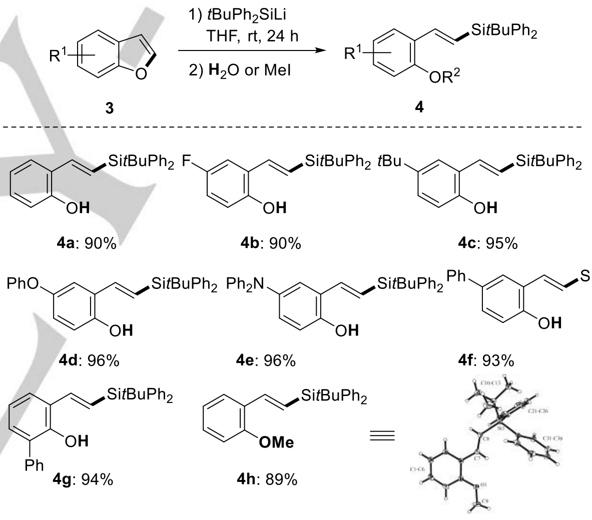
2a: 80% (*E/Z* = 8:1)
2b: 86%[c] (*E/Z* = 7:1)
2c: 75% (*E/Z* = 10:1)
2d: 85% (*E/Z* = 7:1)
2e: 71%[c] (*E/Z* > 20:1)
2f: 81% (*E/Z* > 20:1)
2g: 51% (*E/Z* = 17:1)
2h: 40% (*E/Z* = 7:1)
2i: 79% (*E/Z* = 8:1)
2j: 45%[c] (*E/Z* > 20:1)
2k: 76% (*E/Z* > 20:1)
2l: 82% (R = Me) (5 mmol scale, 84%) (*E/Z* = 4:1)
2m: 75% (R = allyl) (*E/Z* = 3:1)

[a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv), *t*BuPh$_2$SiLi (0.4 mmol, 2.0 equiv), THF (1 mL), 50 °C, 24 h. [b] Yield corresponds to isolated yield. [c] Conducted at rt.

With optimized conditions in hand, we next investigated scope and limitations of this novel indole ring opening (Table 2). Effects exerted by indole substituents were investigated first. The 5-F, 6-F, 5-Ph, 5-Me$_3$Si, and 4-OPh substituted *N*-phenyl indoles **1b**-**1f** worked well and the vinyl silanes **2b**-**2f** were isolated in 71-86% yield. *E/Z*-selectivity varied from 7:1 to >20:1. The *N*-phenyl group could be replaced by substituted phenyl groups (see **2g**-**2j**) and also the *N*-naphthyl indole **1k** underwent ring opening to provide **2k** in 76% yield. Selectivity varied in this series without identifying any trend. Unfortunately, *N*-methylindole did not provide the corresponding vinylsilane (not shown). We assume that the anion stabilizing effect of the aryl group at the nitrogen atom to be of key importance. Reaction did also not work for N-phenyl pyrrole as an acceptor and *n*-BuLi or *t*-BuLi did not ring-open **1a** under the same conditions.

If reaction is quenched with methyl iodide or allyl bromide in place of water, the *N*-atom could be directly methylated or allylated. The corresponding products **2l** and **2m** were isolated in good yields but moderate *E/Z*-selectivity. Successful gram scale synthesis of **2l** without any loss in yield demonstrated the robustness and practicability of the transformation.

Table 3. Ring opening silylation of various benzofurans.[a,b]



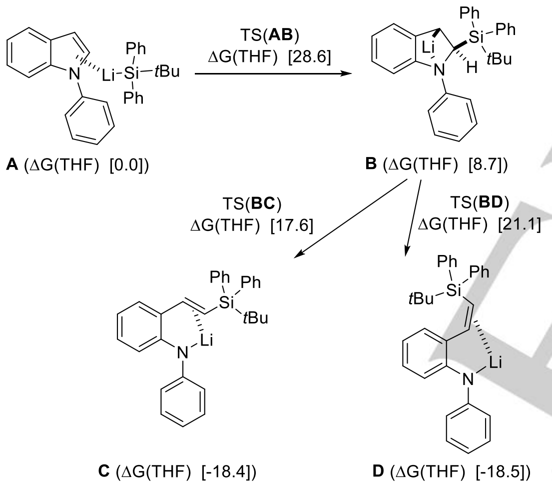
4a: 90%
4b: 90%
4c: 95%
4d: 96%
4e: 96%
4f: 93%
4g: 94%
4h: 89%

[a] Reaction conditions: **3** (0.2 mmol, 1.0 equiv), *t*BuPh$_2$SiLi (0.4 mmol, 2.0 equiv), THF (1 mL), 25 °C, 24 h. [b] Yield corresponds to isolated yield.

We then turned our attention to the ring opening of benzofurans and found that the parent **3a** reacted efficiently at room temperature with *t*BuPh$_2$SiLi in 90% yield and complete *E*-selectivity to vinyl silane **4a** (Table 3). Me$_2$PhSiLi and MePh$_2$SiLi also worked, but lower yields were obtained in these cases. The 5-F, 5-*t*Bu, 5-PhO, 5-Ph$_2$N, 5-Ph, and 7-Ph substituted benzofurans **3b**-**3g** reacted with *t*BuPh$_2$SiLi to **4b**-**4g** in excellent yields (90-96%) and excellent selectivity (*E/Z* > 20:1). The phenolate could be directly alkylated with MeI to give the methyl ether **4h**. The structure of **4h** was confirmed by X-ray crystallographic analysis.[10]

The suggested mechanism for the indole ring opening silylation based on DFT calculations (TPSS/def2-TZVP-PCM(THF)), for details see the Supporting Information) is depicted in Scheme 2. The silyl lithium compound first interacts with the five-membered ring of indole via Lewis acid/base interaction to give complex **A**. The Si-anion then adds at the 2-position via TS(**AB**) to give a benzylic anion **B**. The Li-ion is located syn to the bulky Si group and interacts also with the dihydroindole N-atom. We found a low barrier (TS(**BC**)) for β-elimination to give the major *E*-complex **C**.[11] Formation of the *Z*-isomer **D** via TS(**BD**) is less favored but feasible, as observed in the experiments. Interestingly, isomers **C** and **D** are very close in energy. N-protonation or N-alkylation eventually provides **2** (not shown).

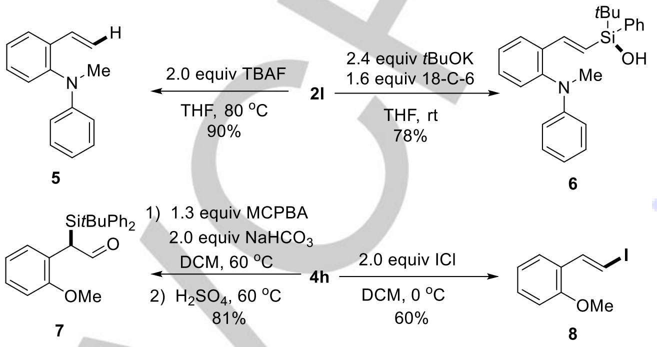
For benzofuran **3a**, a similar addition-elimination mechanism is suggested (see SI). To exclude that reaction proceeds via α-lithiation of benzofuran,[11a,b] 2-deuterated benzofuran **3a-D** was reacted with tBuPh$_2$SiLi and the deuterated vinylsilane **4a-D** was obtained without any loss in deuterium content (see SI), clearly showing that deprotonation is not occurring. In addition, DFT calculations (TPSS/def2-TZVP-PCM(THF)) were also conducted on **3a** (see SI). We found the barrier for tBuPh$_2$SiLi-addition to **3a** to lie at 21.53 kcal/mol (298 K) and addition to be exothermic by 2.02 kcal/mol. The TS for β-elimination to the *E*-isomer lies at 6.25 kcal/mol and for the *Z*-isomer at 8.40 kcal/mol. β-Elimination is highly exothermic for both isomers (*E*-isomer: -42.93 kcal/mol; *Z*-isomer: -43.20 kcal/mol). We also repeated the calculations of **3a** with tBuPh$_2$SiLi including two THF molecules complexed at the Li-atom and found similar energies (see SI).



Scheme 2. Structures of intermediates for reaction of **1a** with tBuPh$_2$SiLi and calculated free energies (kcal/mol at 298 K) for intermediates and transitions states.

To demonstrate the synthetic value of the method, we investigated follow-up chemistry on vinylsilanes **2l** and **4h** (Scheme 3). Reaction of **2l** with TBAF at 80 °C provided the *ortho*-vinylaniline **5** in 90% yield.[12] Vinylsilane **2l** was easily converted to silanol **6** with tBuOK and 18-crown-6 in wet THF.[13] Epoxidation of the *E*-vinylsilane **4h** with *meta*-chloroperbenzoic acid (MCPBA) and subsequent acid-catalyzed rearrangement gave the α-silyl aldehyde **7**.[14d] α-Silylaldehydes are valuable intermediates in organic synthesis.[14] Stereospecific iodinolysis of the C−Si bond in **4h** with ICl provided vinyl iodide **8**.[15]

In summary, we have demonstrated a practical method for ring opening silylation of various indoles and benzofurans. Whereas the benzofuran C(2)-O bond cleavage functionalization has previously been achieved using transition metal catalysis the analogous process on indoles is unprecedented. The method introduced herein uses readily generated tBuPh$_2$SiLi and does not require any transition metal catalyst. Transformations proceed under mild conditions and indole derived products are obtained in moderate to excellent yields with generally very high *E*-selectivity. For benzofurans, all transformations occurred with excellent yields and complete *E*-selectivity. Importantly, vinyl silanes obtained as products are valuable building blocks in synthesis.



Scheme 3. Follow-up chemistry

Acknowledgements

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Keywords: dearomatization • benzofuran • indole • transition-metal-free • silylation

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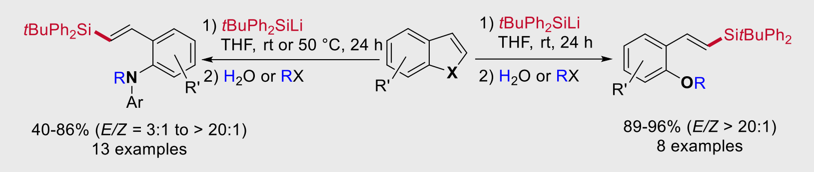

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Transition-Metal-Free Ring Opening Silylation of Indoles and Benzofurans with (Diphenyl-*tert*-butylsilyl)lithium

Ring opening silylation of various indoles and benzofurans using diphenyl-tert-butylsilyllithium to provide ortho-β-silylvinyl anilines or phenols is presented. Dearomatization of the heteroarene core proceeds in the absence of any transition metal catalyst via silyl anion addition and subsequent stereoselective β-elimination.