The electrophilic aromatic substitution approach to C–H silylation and C–H borylation

Abstract: Several approaches toward electrophilic C–H silylation of electron-rich arenes are discussed, comprising transition-metal-catalyzed processes as well as Lewis-acid- and Brønsted-acid-induced protocols. These methods differ in the catalytic generation of the silicon electrophile but share proton removal in form of dihydrogen. With slight modifications, these methods are often also applicable to the related electrophilic C–H borylation.

Keywords: boron electrophiles; C–H functionalization; cooperative catalysis; electrophilic aromatic substitution; IMEBORON-16; silicon electrophiles.

Introduction

Electrophilic aromatic substitution (S_{EAr}) is established synthetic methodology for the construction of C–C (and C–Het) bonds at sufficiently nucleophilic arenes (Scheme 1, left). Friedel–Crafts alkylations proceed through Wheland intermediates II (I→II), and these convert into III by proton release (II→III). This can become an issue when the overall process is reversible, as it is the case for Friedel–Crafts alkylations and also for electrophilic C–H silylations (Scheme 1, right) [1]. In fact, the formation of Wheland intermediate IV by protonation of V is facile because IV is stabilized by the β-silicon effect. Hence, the backward reaction V to IV is favored over II from III. To avoid that protodesilylation (V→IV→I), irreversible proton removal would be the ideal solution. That means, put another way, the deliberate addition of base cannot be the solution to the problem as the resulting conjugate acid would likely be too acidic. The newly developed approaches achieve this proton removal by the generation and liberation of dihydrogen gas. With little modification, these methods are also applicable to the corresponding borylation reactions. We herein summarize our recent work on both the C–H silylation and C–H borylation by catalytic electrophilic aromatic substitution.

Ruthenium–sulfur complexes as catalysts

Dihydrogen activation at the metal–sulfur bond of the active site 1 in [NiFe] hydrogenases is likely to result in the formation of a metal hydride together with a protonated thiol ligand (Scheme 2, top) [2, 3]. Inspired by this naturally occurring example of metal–ligand cooperativity, Ohki and Tatsumi introduced rhodium(III) and iridium(III) complexes 2 and 3 (Scheme 2, bottom) [4]. The expected reactivity was indeed observed, and...
complex resulting from H–H splitting was formed at low temperature by treatment of 3 with dihydrogen (not shown). In collaboration with Ohki and Tatsumi, our group anticipated that an analogous heterolytic activation of Si–H or B–H bonds would also result in a metal hydride together with a sulfur-stabilized silylium ion and borenium ion, respectively (Scheme 2, top). This assumption was supported by a report from Stradiotto

Scheme 1: Reversibility of electrophilic aromatic substitutions with carbon and silicon electrophiles.

Scheme 2: Bioinspired concept (top) and transition-metal complexes (bottom) for the cooperative activation at metal–sulfur bonds (X = O or OH, Cys = cysteine, ArF = 3,5-bis(trifluoromethyl)phenyl).

Scheme 3: Dehydrogenative silylation of indoles 7 catalyzed by 6a.
and co-workers on rhodium(III) and iridium(III) complexes 4 and 5 with a bidentate P,S-ligand [5]. These compounds activate hydrosilanes in a cooperative fashion, and complex 4 showed also catalytic activity in the hydrosilylation of ketones (not shown). However, we observed decomplexation of the monodentate thiolate ligand upon treatment of complexes 2 or 3 with hydrosilanes [6]. This decomposition could be avoided by using ruthenium(II) complexes 6 with a bidentate thiolate ligand. This coordinatively unsaturated, cationic complex had previously been applied to dihydrogen activation by Ohki and Tatsumi with moderate efficacy [7] but emerged as a superb choice for the heterolytic splitting of the weaker Si–H bond [6, 8].

We envisioned that the sulfur-stabilized silylium ion obtained by hydrosilane activation with catalyst 6a could be sufficiently electrophilic to engage in aromatic substitution reactions with electron-rich arenes such as indoles 7 (Scheme 3). The silylated indole 8a was indeed formed when 7a was treated with 1.0 mol% of 6a in the presence of Me2PhSiH (7a→8a) [6]. In accordance with an electrophilic aromatic substitution mechanism, exclusive C3 selectivity was observed. Also, C2-substituted 7b was successfully applied (7b→8b) whereas substitution at C3 as in 7c prevented the reaction, and 8c was not formed, corroborating electronic control as the regiocontrolling factor.

The catalytic cycle of this transformation commences with cooperative Si–H bond activation across the polar metal–sulfur bond of cationic complex 6 (Scheme 4, left) [9]. Depending on the steric demand of the hydrosilane, η1 or η2 coordination of the hydrosilane to the ruthenium center in 9 precedes the heterolysis of the Si–H bond (6+Si–H→9→10). As supported by DFT calculations, the activation results in the formation of a metal hydride and a sulfur-stabilized silylium ion in 10 by way of TS1 (Scheme 4, top right). This metathesis step is significantly lower in energy compared to the alternative transition state TS2 (13.4 kJ/mol vs. 48.5 kJ/mol) that would result in the corresponding regiosymmetric complex. From 10, silyl transfer onto indole 7 results in the formation of the neutral hydride 11 (10→11). Subsequent deprotonation leads to C3-silylated 8 and dihydrogen adduct 12 (11→12). Release of dihydrogen closes the catalytic cycle concomitant with the regeneration of 6 (12→6+H2). It must be noted that all steps are reversible, and hydrogen evolution shifts the equilibrium to the side of the dehydrogenative coupling.

We were later able to adapt this dehydrogenative C–H silylation method to intramolecular reactions. It had been shown that dibenzosiloles 14 can be synthesized involving intermediate silicon electrophiles
that are accessed either stoichiometrically [10, 11] or – with limited scope though – catalytically [12]. We envisioned that 6 could also serve as suitable catalyst for the formation of dibenzosiloles 14. Ruthenium(II) complex 6b with an electron-deficient phosphine ligand turned out to be the best choice for this ring closure (Scheme 5) [13]. However, significantly higher temperatures were needed due to the lower nucleophilicity of the arenes, and the reversibility was now a serious challenge: dihydrogen activation with 6 led to incomplete conversions of the hydrosilanes 13. Key to success was microwave heating together with perforated caps to ensure the release of dihydrogen gas. Substituents such as alkyl or aryl groups as well as halogen atoms were tolerated (not shown) but the particular value of this method lies in the possibility to access dibenzosiloles 14a–c that are functionalized at both phenylene groups. Silole 15, obtained in three steps from the corresponding tert-butyldimethylsilyl-protected hydrosilane by cyclization, deprotection, and triflation, would even allow for site-selective cross-coupling. A combination of both aforementioned approaches, that is intermolecular indole C3 silylation and intramolecular benzosilole formation, enabled a facile synthesis of indole-fused benzosiloles from readily available precursors, not requiring any prefunctionalization (not shown) [14].

In analogy to the Si–H bond activation, we later showed that using a hydroborane together with catalyst 6 allows for the formation of stabilized borenium ions in 16 (6 + B–H → 16, Scheme 6, left) [15]. The corresponding B–H adduct 16 was crystallographically characterized, and we succeeded in the borylation of 7 with pinBH (7 → 17), leading for example to C3-borylated indole 17a and pyrrole 17d (Scheme 6, right). Again, the reaction of 7 proceeded with high regioselectivity and in good to excellent yields, and Lewis-basic
functionalities such as amino groups in 17e and 17f were tolerated. It is a rare example of an S$_x$Ar with pinBH; usually catBH is used in electrophilic C–H borylation followed by transesterification with pinacol.

When we applied imines 18 [16, 17] as substrates for catalysts 6 together with hydrosilanes, we expected two major reaction pathways (Scheme 7, left): ruthenium hydride 11 either serves as a reductant for the iminium-ion intermediates 19 (18→19) to yield the corresponding N-silylated amines 20 (19+11→20+6, left pathway). Alternatively, the basic sulfur atom in 11 could deprotonate at the acidified α position in 19, leading to N-silylated enamines 21 (19+11→21+6·H$_2$, right pathway). The formation of 20 was largely suppressed by performing the reaction in open vessels to ensure removal of the dihydrogen gas [16]. Hence, 21a (18a→21a, Scheme 7, right) was obtained as major product when imine 18a was treated with Me$_2$PhSiH (1 equiv) in the presence of catalyst 6c along with disilylated 22a in trace amounts. The latter results from electrophilic silylation of 21 at its nucleophilic β carbon atom and subsequent deprotonation at the same position, a reaction similar to the silylation of indoles 7 (cf. Scheme 3). Changing to the bulkier substrate 18b and applying 2 equivalents of hydrosilane resulted in the almost exclusive formation of disilylated enamine 22b (18b→22b).

We also accomplished the 1,4-hydrosilylation of pyridines 23 to dihydropyridines 24 (23→24, Scheme 8) with catalysts 6 [18]. The proposed mechanism starts again with hydrosilane activation (6+Si–H→10, Scheme 8, left). Silyl transfer from 10 onto the Lewis-basic pyridine 23a results in the formation of a pyridinium ion and ruthenium hydride 11. Regioselective hydride transfer affords the 1,4-dihydropyridine 24a exclusively, and 24a was isolated in high yield (Scheme 8, right); no 1,2-isomer or overreduced products were observed. Mono- and disubstituted dihydropyridines 24b or 24c were successfully synthesized as well.

Remarkably, and in contrast to a related work from Nikonov and co-workers [19], substituents in the C4 position of the pyridine did not thwart the reaction, and 24d was isolated in good yield.

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The dihydropyridine core in 24 resembles the structural element of two N-silylated enamines. We reasoned that electrophilic silylation in the β position of 24 (as in the disilylation of imines 18, cf. Scheme 7, right) and subsequent 1,4-dehydrosilylation of 25 would result in the formation of pyridines 26 silylated in the meta position (Scheme 9, left). As a consequence of the temporary dearomatization, the overall process can be viewed as a formal electrophilic aromatic substitution of pyridines 23. With 6c as catalyst, several silylated pyridines 26 (23→26), usually substituted with an aryl group in the ortho position as in 26a and 26b, were successfully synthesized (Scheme 9, right) [20]. Also, alkyl substituents as in 26c and 26d were tolerated, even though the products were obtained in lower yields. Deuterium-labeling as well as NMR measurements proved the stepwise sequence of 1,4-hydrosilylation, dehydrogenative silylation, and rearomatization (not shown).

**Base-metal salts and boron Lewis acids for electrophilic C–H functionalization**

Inspired by established catalysts for Friedel–Crafts chemistry, we focused on metal salts such as iron chlorides for the silylation by way of electrophilic aromatic substitution. We found that aniline derivatives 27 as electron-rich arenes are suitable for the conversion to 28 with hydrosilanes applying FeCl₂ together with NaBArF₄ as initiator (27→28, Scheme 10) [21]; 28a–c were isolated in moderate to high yields. Substitution in the para position as in 27d prevented the reaction, and 28d did not form. Other metal salts, including Fe(III), Sc(III), Co(II), Cu(II), Zn(II), Al(III), Y(III), Ce(III), Sm(III), and In(III) triflates and chlorides, were equally effective.

**Scheme 9:** C–H silylation of pyridines 23 by temporary dearomatization (left) and selected examples (right).
Even though the nature of the catalyst is unclear, we reasoned that initial borane formation from the borate counteranion caused by the metal salt could be operative; such reaction was reported with noble metal complexes of platinum(II) [22], rhodium(III) [23], and gold(I) [24]. Electron-deficient boranes are suitable catalysts for such a transformation, as independently shown by Hou and co-workers [25] who disclosed the dehydrogenative C–H silylation of anilines 27 with B(C₆F₅)₃ as catalyst. Based on that publication, also the related borylation using B(C₆F₅)₃ in catalytic amounts was recently achieved by our laboratory (Scheme 11) [26]. The mechanism involves boronium ion 29 that is formed by hydride abstraction with B(C₆F₅)₃ from catecholborane and coordination of two substrate molecules (Scheme 11, left). Decoordination leads to borenium ion 30 (29 → 30) that reacts with aniline 27a to arrive at Wheland intermediate 31 (30 → 31). Deprotonation by the substrate forms the borylated arene together with an ammonium salt. The subsequent release of dihydrogen to regenerate 29 is likely to be the rate-determining step. Dramatic rate acceleration by added alkenes is observed (not shown), even though the effect of that additive is not understood. Anilines 27 reacted in moderate to good yields to borylated 32 after transesterification with pinacol (27 → 32, Scheme 11, right). Indoles 7 participated as well (not shown) [27].

Scheme 11: Catalytic cycle for the borane-initiated borylation of anilines 27 (left) and selected examples (right).

Brønsted-acid-promoted dehydrogenative C–H silylation

A fundamentally different approach to access (stabilized) silylium ions is based on initial work by Corey and co-workers [28], in which the formation of a trialkylsilyl triflate by treatment of the corresponding hydrosilane with triflic acid was reported (Scheme 12, top left). The transfer of this procedure to aryl-substituted hydrosilanes failed due to protodesilylation; the silyltriflate was obtained together with benzene in this case (not shown) [29]. Our group succeeded in the formation of ether-stabilized, aryl-substituted silylium ions by changing to Brookhart's acid [30] as the proton source (Scheme 12, bottom left) [31].

We were also able to catalytically access the stabilized silylium ion and apply it to the conversion of indoles 7 to silylated 33 (7 → 33). Ph₂SiH₂ was chosen in order to have a handle for further functionalization at the silicon atom, and norbornene was found to be essential to secure consistently high yields. Its fate is most likely proton-induced oligomerization. Complete C3 selectivity in 33a was observed, and the C2-substituted indole 33b was also converted in high yield although indole-to-indoline reduction by dihydrogen remains a limitation for both. Again, a substituent in C3 thwarted the reaction, and 33c did not form.
Conclusion

Owing to the advances made in recent years, S$_x$Ar with silicon and boron electrophiles changed from a basic concept to a useful methodology. The advantage lies in easily available starting materials, and the formation of dihydrogen as the sole byproduct. However, limitations remain with regard to narrow functional-group tolerance, especially in case of highly electrophilic and oxophilic silicon intermediates. Furthermore, usually only electron-rich and, hence, nucleophilic arenes engage in these substitution reactions. These drawbacks, however, are the basis for further developments in this promising area.

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References