Ruthenium-catalyzed C-H Functionalization of (Hetero)arenes

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Abstract

This thesis concerned about the Ru-catalyzed C-H functionalizations on the synthesis of 2-arylindole unit, silylation of heteroarenes and preparation of aryne precursor.

In the first project, we developed the Ru-catalyzed C2-H arylation of N-(2-pyrimidyl) indoles and pyrroles with nucleophilic arylboronic acids under oxidative conditions. Wide variety of arylboronic acids afforded the desired product in excellent yield regardless of the substituents or functional group electronic nature. Electron-rich heteroarenes are well suited for this method than electron-poor heteroarenes. Halides such as bromide and iodide also survived, further derivatisation of the halide is shown by Heck alkenylation. In order to find catalytic on-cycle intermediate extensive mechanistic experiments have been carried out by preparing presumed ruthenacyclic complexes and C-H/D exchange reactions. It suggested that para-cymene ligand is not present in the catalytic on-cycle intermediate and we suspect that metalation occurs with electrophilic ruthenium center via S_E_Ar mechanism.

In the second project, we developed the Ru-catalyzed silylation of gramine, tryptamine and their congeners using silanes as coupling partner. The transformation worked well with many different silanes. Regarding directing group, nitrogen atom containing directing groups are more favoured than the oxygen containing directing groups. Wide range of gramines and tryptamines also yielded the desired product in poor to excellent yield. At higher temperature, albeit in low yield, undirected silylation occurred. In order to get some insights about the reaction pathway of the silylation C-H/D exchange experiments were performed, and it revealed the possibility of C4-H activation of gramines by an electron rich metal- Si-H/D experiments showed Si-H activation by Ru is easy.

In the final project, we presented the closely related aryne precursors from arylboronic acids via Ru-catalyzed C-H silylation of arylboronates and their selective oxidation. Worthy of note, the aryne capture products obtained from arylboronic acids in a single purification.

Keywords: catalysis, C-H activation, heterocycles, ruthenium, aryne precursor, silylation, gramine

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Dedicated to my parents and the Pilarski research group.
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals. Reprints appear herein with permission from the respective publishers.


The following publications are not included as part of this thesis:

IV  E. Demory, K. Devaraj, A. Orthaber, P. J. Gates, L. T. Pilarski

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Abbreviations

**Abbreviations**

- aam: anthranilamido
- aamH2: anthranilamide
- BOC: butyloxy carbonyl
- CMD: concerted metalation deprotonation
- cod: 1,5-cyclooctadiene
- coe: cyclooctene
- Cp: cyclopentadienyl
- Cp*: 1,2,3,4,5-pentamethylcyclopentadienyl
- DG: directing group
- DMF: dimethylformamide
- dtbpy: 4,4′-di-tert-buty1-2,2′-dipyridyl
- eq.: equivalent
- h: hour
- HMDS: hexamethyldisilazane
- iPrOH: isopropanol
- MTBE: methyl tert-butyl ether
- MS: molecular sieves
- Nf: nonafluorobutanesulfonfyl
- nbd: 2,5-norbornadiene
- nbe: norbornene
- NMR: nuclear magnetic resonance
- PG: protecting group
- phen: 1,10-phenanthroline
- pym: 2-pyrimidyl
- SeAr: electrophilic aromatic substitution
- SnAr: nucleophilic aromatic substitution
- TBAB: tetrabutylammonium bromide
- t: time
- Temp.: temperature
- Tf: trifluoromethanesulfonfyl
- THF: tetrahydrofuran
- TM: transition metal
- TMS: trimethylsilane
- Ts: 4-methylbenzenesulfonfyl
1. Introduction

1.1 Background

1.1.1 C-H bond functionalization

Organic compounds are made up of carbon skeletons, which contain many C-H bonds, and functional groups. Traditional organic reactions make new bonds by manipulating the available functional groups. However, the rest of the free or untouched C-H bonds of organic compounds are generally not used or even considered as functional groups. It is even common to omit C-H bonds for clarity when drawing organic compounds. However, the ability to activate these ‘unreactive’ C-H bonds and transform them can enable us to build up organic molecules in new ways, often more directly than is typical using established approaches. The field encompassing their transformation using the transition metals is mostly called C-H activation or C-H functionalization.

1.1.2 C-H activation versus functionalization

The specific use and meaning of the term “C-H activation” has been the subject of some discussion.[1] Generally, the use of a transition metal catalyst in the substitution of a C-H bond for a different functional group may be broadly termed “C-H functionalization”. This may proceed via different pathways in which C-TM intermediates (where TM = transition metal) are formed and subsequently converted to products. Subsets of C-H functionalization reactions are reactions that proceed via “C-H activation”, a term which has some more specific mechanistic meanings. The conversion of a C-H bond to a C-TM bond may occur via reactivity of which the substrate is ordinarily in some way already capable (e.g., SEAr for the case of an electron rich aromatic substrate and an electrophilic metal center), or via a pathway made possible by the specific properties of the metal species and, perhaps, other additives, such as ligands. An example of the latter may be an oxidative addition of an electron-rich metal center into the C-H bond. The C-H to C-TM bond conversion depends on the properties of the TM complex is C-H activation. However, C-H activation may not necessarily lead to a C-H functionalization. It is possible that the C-H bond is activated reversibly, but no new functional group is installed. Various mechanistic possibilities for C-H activation are discussed below in Section 1.4.
1.1.3 Selected pioneering work

In the last few decades, intensive research efforts have been made to achieve the selective C-H bond functionalization of various substrates to afford synthetically valuable products. It is very hard to summarize all of the work in this field in a short introduction. However, the following three studies are representative of the developments in the field.

In 1963, Kleiman and Dubeck showed that the ortho-C-H bond of azobenzene can be activated through the addition of a stoichiometric amount of dicyclopentadienylnickel. The result was the formation of a five membered nickelacycle 1 (Scheme 1).[2]

![Scheme 1. Early example of transition metal-promoted C-H bond cleavage.](image1.png)

The first example of C-H bond functionalization of arenes using ruthenium was shown by Chatt and Davidson in 1965. In their study, the treatment of zero-valent ruthenium species 2 with naphthalene afforded the C-H activated ruthenium complex 3 (Scheme 2).[3]

![Scheme 2. Example of C-H bond functionalization of an arene.](image2.png)

Although there are many examples of stoichiometric C-H bond cleavage by various metals, catalytic versions remained undeveloped for a long time. In 1993 Murai et. al reported a breakthrough discovery in this field by showing the Ru-catalyzed, efficient and selective C-H bond functionalization of aromatic ketones with olefins (Scheme 3).[4]
Scheme 3. Ruthenium-catalyzed C-H bond functionalization of aromatic ketones.

This initial catalytic C-H bond functionalization of aromatic ketones led to the significant development of economically feasible processes for C-C,[5] C-Si,[6] C-B,[7] C-N[8] and many other bond forming reactions. A huge number of reactions have thus been reported, including recent advances in milder conditions.[9]

1.2 Advantages of C-H bond functionalization

The formation of new C-C bonds is of central importance in organic chemistry, including the synthesis of bi(hetero)aryl motifs. In the 1970s, the cross-coupling reactions between aryl halides and nucleophilic reagents for the construction of C-C bonds was discovered using transition metal catalysts (Scheme 4a). However, such reactions need pre-functionalized starting materials. The functionalization of C-H bonds provides an attractive alternative for the cross coupling reactions by using arenes as the coupling partner (Scheme 4b). In addition to efficiency and producing less waste, this approach offers alternative disconnections and new reactivity to form new bonds.[10]

Scheme 4. Traditional cross-coupling versus C-H arylation.
1.3 Overcoming the challenges of C-H bond functionalization

Transition metal-catalyzed C-H functionalization reactions are a key development in organic synthesis.\cite{11} They offer transformations that are otherwise difficult or even impossible to achieve, new chemo- and regioselectivities and streamlined syntheses.\cite{12} However, despite all the progress up to now, the development of C-H functionalization methods remains an enormous challenge, partly because of the diversity of C-H environments that it is desirable to transform and also because converting the C-H bond to a different, specific functional group can pose complications. Catalytic C-H functionalization addresses these challenges through the formation of metalated intermediates. One of the most successful and widely adopted strategies to achieve regioselective C-H bond functionalization involves coordination of the transition metal species to a Lewis basic heteroatom (or ‘directing group’). This positions the transition metal center over a specific C-H unit. This approach is most commonly used to activate C-H bonds ortho\cite{13} to the directing group. However, more recent work has shown that directing groups can be used in the selective functionalization of meta,\cite{14} and even para\cite{15} positions of (hetero)aromatic substrates (see Figure 1 for examples). In addition, much effort has been put into the development of removable or even ‘traceless’\cite{16} directing groups, which can be cleaved at the end of the synthesis to reveal valuable functional groups.

Regioselectivity can be determined by directing group strategies or aspects of the mechanism, such as the C-H bond’s acidity, the nucleophilicity of the position, its steric environment and so on.

![Figure 1. Example of directed ortho, meta and para C-H functionalizations.](image)
1.4 Mechanisms of C-H bond activation

Over the last decades, many research groups have studied the mechanisms of C-H activation.\textsuperscript{[17]} These studies have shown that C-H activation can occur through different kinds of mechanisms. Four of the most commonly invoked mechanisms are shown in Scheme 5.

Generally, an electrophilic activation (Scheme 5a) occurs with electrophilic late transition metal species, whereas oxidative addition pathways are seen more commonly with electron-rich transition metal centers (Scheme 5b). Base-assisted C-H activation is a complex range of reactions. The field has been strongly influenced in recent years by the emergence of many reactions based on assistance by a carboxylate or carbonate base via a six-membered transition state (Scheme 5c). This is sometimes termed “concerted metatation deprotonation”, or CMD.\textsuperscript{[18]} The final example, σ-bond metathesis (Scheme 5d), is perhaps rarely used approach for organic synthesis. It is known to occur for metals with a d\textsuperscript{0} electronic configuration. It is worth noting that not all of these mechanisms are considered to fulfill the stricter definition of “C-H activation” (as discussed above). For example, S\textsubscript{E}Ar is considered not to be an activation in the same sense that, for example, an oxidative addition pathway might be because the C-H bond is broken after the Wheland intermediate forms. By contrast, only a specific transition metal species might be able to carry out an oxidative addition into a C-H bond (e.g., the C-H bond is activated by the metal). In reality, C-H functionalizations can exist on a spectrum of mechanistic possibilities and may even proceed by a variety of pathways, conceivably even in the same reaction flask.

1.5 Aim of this thesis

The development of C-H activation methodology has seen rapid recent advances. The most versatile transition metal-based systems for synthetically useful C-H functionalizations emerged from an early focus on Pd- and Rh-based systems.\textsuperscript{[19]} Equivalent versatility based on Ru-based catalysts has been slower to emerge.\textsuperscript{[20]} The work in this thesis addresses a need to develop more competent, tolerant and useful Ru-catalyzed C-H activation systems for organic synthesis. This includes the need to enhance mechanistic understanding of Ru-catalyzed C-H functionalizations, which can proceed via a variety of pathways.
2. Ru-Catalyzed C-H arylation of indoles and pyrroles with boronic acids: Scope and mechanistic studies

2.1 Introduction

Indoles and pyrroles are present in various biologically and medicinally active compounds.\textsuperscript{[21]} The development of methods for their efficient derivatization is an important area of research. This chapter concerns a new, Ru-catalyzed C2-H arylation of indoles and pyrroles using arylboronic acids as the coupling partner under oxidative conditions.

2.1.1 Pioneering transition metal-catalyzed arylation of indoles

The C2 arylation of indoles has been reported several times using aryl (psuedo)halides as the arylation reagents (Scheme 6a).\textsuperscript{[22]} Early work in this area included that of the Sanford and Gaunt groups, who reported the arylation of indole using Pd and Cu catalysts with diaryliodonium salt electrophiles (Scheme 6b).\textsuperscript{[23]} Later, Shi and Zhan also independently showed that arylboronic acids\textsuperscript{[24]} and arylsiloxyxanes\textsuperscript{[25]} can be used as a aryl coupling partners in the oxidative arylation of indoles under acidic conditions using Pd (Scheme 6c).

\textbf{Scheme 6.} Examples of indole C2-H arylation using electrophilic coupling partners.
2.1.2 Transition metal-catalyzed arylation of \( N \)-(2-pyrimidyl) indoles

Ackermann and co-workers demonstrated the Ru-catalyzed C2 selective arylation of indole by using a removable pyrimidyl directing group (Scheme 7a).\(^{[26]}\) The group of Xu and Loh developed the Rh-catalyzed selective arylation of indoles using arylsiloxanes as coupling partners (Scheme 7b).\(^{[27]}\) Even though significant advances have been made in indole arylation methodology, methods using nucleophilic arylating reagents and an external oxidant have received less attention. No Ru-catalyzed methods under oxidative conditions were known at the time we undertook this work. Moreover, the Ackermann group’s method consumed valuable aryl halide functional groups, whereas Rh catalysts and siloxane reagents can be very expensive. In this context, we chose to investigate cheaper Ru-based systems with arylboronic acids as the coupling partners (Scheme 7c). The notable advantages of arylboronic acids are their low toxicity, stability, diversity, commercial availability and low cost.\(^{[28]}\)

![Scheme 7. Examples of C2-H arylation of \( N \)-(2-pyrimidyl)indoles and pyrroles.](image)

2.2 Results and discussion

2.2.1 Reaction optimization

Encouraged by the previous work of Ackermann, we started our investigation by testing the reactions of \( N \)-(2-pyrimidyl)indole 4a with 4-tolylboronic acid, 2.5 mol\% of \([\{\text{RuCl}_2(p\text{-cymene})\}_2]\), 0.12 eq. of AgSbF\(_6\) and 1.5 eq. of Ag\(_2\)O in THF (Table 1, entry 1). This gave 5a in 37\% yield. Moving from Ag\(_2\)O to Cu(OAc)\(_{2}\)·H\(_2\)O as the oxidant enhanced the yield to 64\% and including water raised the yield further to 84\% (Table 1, entries 2 and 3). Reducing the amount of Cu(OAc)\(_{2}\)·H\(_2\)O to 0.5 eq. led to the desired product in a lower yield, even in the presence of oxygen (Table 1, entry 4). The examination of additives showed that KPF\(_6\), AgPF\(_6\) and AgBF\(_4\) gave lower yields.
than did AgSbF₅ (Table 1, entries 5-7). The desired transformation did not occur with a combination of KOAc and water (Table 1, entry 8). Interestingly, replacing the THF/H₂O solvent system with ³PrOH led to superior conversion, (Table 1, entry 10 vs. 3). This is presumably due to the in situ formation of alkoxylboronates which would likely give improved solubility and maybe discourage protodeborylation.[28] Moving from [{RuCl₂(p-cymene)}₂] to [{Ru(OAc)₂(p-cymene)}₂] or the more expensive [{Cp*RhCl₂}₂] gave the desired product in a lower yield (Table 1, entries 11 and 12). Finally, control experiments confirmed the desired transformation did not occur in the absence of Ru catalyst, oxidant or silver additive.

2.2.2 Selected unsuccessful heteroarene substrates
Indoles with other N-substituents, such as H, Me, C(O)Me and C(O)NMe₂ (6a-d, Figure 2) failed to give the corresponding C₂-H-arylated product. We also tested the substrates 6e-h. None of these afforded the corresponding arylation products under the conditions derived from our optimization studies using 4a as shown in Table 1, entry 10.

![Figure 2](image_url)

Figure 2. Substrates that did not undergo arylation under the optimized conditions.
Table 1. Selected results from optimization studies.\[a\]

![Chemical structure diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Oxidant (eq.)</th>
<th>Additives (eq.)</th>
<th>Solvent</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2.5)</td>
<td>Ag$_2$O (1.5)</td>
<td>AgSbF$_6$ (0.12)</td>
<td>THF</td>
<td>37$^c$</td>
</tr>
<tr>
<td>2</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2.5)</td>
<td>Cu(OAc)$_2$•H$_2$O (1.0)</td>
<td>AgSbF$_6$ (0.12)</td>
<td>THF</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2.5)</td>
<td>Cu(OAc)$_2$•H$_2$O (1.0)</td>
<td>AgSbF$_6$ (0.12) H$_2$O (4.4)</td>
<td>THF</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2.5)</td>
<td>Cu(OAc)$_2$•H$_2$O (0.5) O$_2$ (balloon)</td>
<td>AgSbF$_6$ (0.12) H$_2$O (3.7)</td>
<td>THF</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2.5)</td>
<td>Cu(OAc)$_2$ (1.5)</td>
<td>KPF$_6$ (0.12) H$_2$O (3.7)</td>
<td>THF</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2.5)</td>
<td>Cu(OAc)$_2$ (1.5)</td>
<td>AgPF$_6$ (0.12) H$_2$O (3.7)</td>
<td>THF</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2.5)</td>
<td>Cu(OAc)$_2$ (1.5)</td>
<td>AgBF$_4$ (0.12) H$_2$O (3.7)</td>
<td>THF</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2.5)</td>
<td>Cu(OAc)$_2$•H$_2$O (1.0)</td>
<td>AgSbF$_6$ (0.12) KOAc (1.0) H$_2$O (3.7)</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2.5)</td>
<td>Cu(OCCF$_3$)$_2$ (1.0)</td>
<td>AgSbF$_6$ (0.12)</td>
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<td>89</td>
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<td>10</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2.5)</td>
<td>Cu(OAc)$_2$•H$_2$O (1.0)</td>
<td>AgSbF$_6$ (0.12)</td>
<td>tPrOH</td>
<td>98</td>
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<tr>
<td>11</td>
<td>[Ru(OAc)$_2$(p-cymene)$_2$] (2.5)</td>
<td>Cu(OAc)$_2$•H$_2$O (1.0)</td>
<td>AgSbF$_6$ (0.12)</td>
<td>THF</td>
<td>53</td>
</tr>
<tr>
<td>12</td>
<td>[Cp*RhCl$_2$] (2.5)</td>
<td>Cu(OAc)$_2$•H$_2$O (1.0)</td>
<td>AgSbF$_6$ (0.12) H$_2$O (3.7)</td>
<td>THF</td>
<td>52</td>
</tr>
</tbody>
</table>

[a] Conditions: 4a (0.15 mmol), arylboronic acid (0.45 mmol), solvent (0.5 mL). [b] $^1$H NMR yield with respect to 1,3,5-trimethoxybenzene (0.05 mmol) standard added after the end of the reaction. [c] Yield of the isolated product.
2.2.3 Arylboronic acid substrate scope

With the optimized reaction condition in hand, we next explored the scope in arylboronic acids. Arylboronic acids with both electron-donating and electron-withdrawing groups led to products in moderate to excellent yield. The scope of this protocol is, to the best of our knowledge, the most flexible with respect to the substitution of the incoming aryl group for indole substrates. The reaction tolerates methoxy (5c), ester (5h) and ferrocenyl (5n) groups, which rarely or never appear in the scope of related or previous studies. It is particularly significant that C-Cl (5d), C-Br (5l), and C-I (5e) bonds on the arylboronic acid could be tolerated under these conditions, as these groups are usually consumed in protocols developed by other groups. To the extent of our knowledge, at the time of writing, this C-H arylation was the only example of transition metal-catalyzed indole C-H arylation that tolerated C-I bonds. These are important advances because methodological development aims at enabling new synthetic routes and broad functional group tolerance can make syntheses much more convenient. Arylboronic acids with an ortho substituent delivered the corresponding arylated indole (5j) in lower yields, for which steric hindrance seems the most likely explanation.

2.2.4 Heteroarene substrate scope

The scope of this transformation with respect to heteroarenes was next evaluated using the optimized conditions (Scheme 8). Substituent groups on the indole coupling partner affected the reactivity of this transformation more than did those on the arylboronic acids. Indoles containing electron-withdrawing groups (7b, 7c and 7f) gave lower yields compared to the arylations of indoles with electron-donating groups (7d and 7k). This suggests the importance of the nucleophilicity of the indole substrate, in keeping with our observations for substrates (6c-h, 6g and h) (Figure 2). Halogen substituents on the indole substrate led to moderate but still synthetically useful yields (7i and 7j).
Scheme 8. Scope of the boronic acids in the Ru-catalyzed indole C2-H arylation reaction (the yields given are for the isolated products). Conditions: 4a (0.5 mmol), boronic acid (1.5 mmol), \([\{\text{RuCl}_2(p\text{-cymene})\}_2]\) (2.5 mol%), AgSbF₆ (12 mol%), Cu(OAc)₂·H₂O, ¹PrOH, 120 °C, 18 h. [a] = 4 h, 100 °C. [b] Solvent system: THF (1.5 mL + 3.7 eq. water). [c] t = 3 h. [d] 2 mmol boronic acid was used.
Scheme 9. Scope of the indoles and boronic acids (the yields are for the isolated products). Conditions as in Scheme 8, except for [a] t = 6 h.

2.2.5 Selective derivatization of aryl halide

To demonstrate the synthetic flexibility given by the tolerance towards aryl halide substituents, we derivatized product 7l further through a chemoselective Heck reaction (Scheme 10). This shows that the incoming aryl group of the C-H arylation reaction may be further functionalized, and that the commercial availability of the initial arylboronic acid is not a limitation. Also, the C4-Br group of product 8 remains as a chemical handles for further transformations.

Scheme 10. Selective derivatization of the aryl halide functionality.
2.2.6 Arylation of pyrrole derivatives

Next, we tested the protocol on pyrrole derivatives (Scheme 11). 2-Pyrimidyl-substituted pyrrole was converted into separable mono- (10e) and diarylated (10e’) products in 42% combined yield. 2-Ethylpyrrole derivative treated with both electron-rich and electron-poor arylboronic acids gave the corresponding products 10a-c in moderate to excellent yields. The 2-methoxycarbonyl substituted pyrrole did not afford any of the desired product 10d. As we saw for indole derivatives, electron-withdrawing substituents on the heteroarene are detrimental to the arylation. This is consistent with nucleophilicity of the heteroarene playing an important role in the reaction.

Scheme 11. Arylation reaction using pyrrole derivatives. Conditions: 9 (0.5 mmol), boronic acid (1.5 mmol), [RuCl\(_2\)\((p\text{-cymene})\)]\(_2\) (2.5 mol%), AgSbF\(_6\) (12 mol%), Cu(OAc)\(_2\)\(\cdot\)H\(_2\)O (0.5 mmol), PrOH (120 °C, 16 h). [a] Mono- and diarylated products were separated by chromatography.
2.3 Mechanistic studies

2.3.1 Synthesis of presumed ruthenacyclic intermediates

Previously, rhodacycle 11 (Scheme 12) was synthesized by Lan and co-workers as part of a set of mechanistic experiments. They found out that its treatment with benzothiophene gave the coupled product 12 in 72% yield, which suggested that 11 could be a possible intermediate in the catalytic cycle they were studying.\[29\]

![Scheme 12. Rhodium-catalyzed arylation of benzothiophene.](image)

Similarly, Dixneuf and co-workers, as well as other research groups, have proposed para-cymene-containing complexes as catalytic intermediates in related Ru-catalyzed reactions. However, it is established that in the presence of strongly electron-donating ligands, the para-cymene ligand can be displaced.\[30\]

In order to investigate the possible intermediates in our catalytic system, we prepared a range of previously unreported ruthenacyclic complexes, analogous to Rh species 11. The reaction of 4a with \([\text{RuCl}_2(p\text{-cymene})_2]\) afforded the cyclometalated Ru(II) complex \([13]\)Cl in 78% yield. Complex \([13]\)Cl was converted to \([13]\)OAc in 80% yield and \([13-\text{OH}_2]\)SbF$_6$ was obtained and characterized \textit{in situ} (Scheme 13). These species were chosen on the basis that a) the starting pre-catalyst \([\text{RuCl}_2(p\text{-cymene})_2]\) contains chloride ligands, b) acetate is present in our optimized catalytic reaction (from the Cu(OAc)$_2$·H$_2$O oxidant) and c) the presence of silver salts is routinely used to remove halides from transition metal centers and is present in our optimized system.
We tested complexes 13 as replacements for [{RuCl2(p-cymene)}2] under our optimized reaction conditions for the arylation of indoles. Thus, [13]Cl, [13]OAc and [13-OH2]SbF6 led to the desired product 5b in 86%, 60% and 40% spectroscopic yields. This suggests that these complexes are either catalytically active or transformed into catalytically active complexes under the reaction conditions. However, the large difference in yields between these species is not easily explained.

2.3.2 Transmetalation experiments

The treatment of complexes [13]Cl, [13]OAc and [13-OH2]SbF6 with 4-tolylboronic acid did not afford the transmetalated product [13]tol, either in the presence or absence of Cu(OAc)2·H2O (Table 2). This indicated that these species might not be intermediates in the catalytic cycle. In the absence of Cu(OAc)2·H2O complex [13]OAc gave 15% of 5a, whilst [13-OH2]SbF6 gave traces of 5a. This suggests that some transmetalation and reductive elimination might be viable for Ru(II) complexes of this type and that perhaps a Ru(0)/Ru(II) is operating. Dixneuf and co-workers previously proposed the oxidative addition of Ru(II) intermediates to Ru(IV) aryl species as the rate-limiting step in the arylation of phenyl pyridines. Thus, a Ru(II)/Ru(IV) cycle seems to be less likely.
Table 2. Transmetalation experiments

![Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Complex</th>
<th>Cu(OAc)$_2$•H$_2$O</th>
<th>[13]tol</th>
<th>5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[13]Cl</td>
<td>yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>[13]Cl</td>
<td>no</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>[13]OAc</td>
<td>yes</td>
<td>-</td>
<td>traces</td>
</tr>
<tr>
<td>4</td>
<td>[13]OAc</td>
<td>no</td>
<td>.[a]</td>
<td>15%</td>
</tr>
<tr>
<td>5</td>
<td>[13-OH$_2$]SbF$_6$</td>
<td>yes</td>
<td>-</td>
<td>traces</td>
</tr>
<tr>
<td>6</td>
<td>[13-OH$_2$]SbF$_6$</td>
<td>no</td>
<td>-</td>
<td>traces</td>
</tr>
</tbody>
</table>

[a] A symmetrical complex of the type [RuX$_2$(p-cymene)] was observed by $^1$H NMR at the end of the reaction.[31]

2.3.3 Importance of the para-cymene ligand

In Ru-catalyzed C-H functionalization, intermediates with a Ru-cymene unit have been considered as reasonable catalytic intermediates. However, it is also known that strong nitrogen donor ligands can displace $\eta^6$-arene ligands from Ru.[30b] We ran the arylation of 4a under our optimized conditions at 120 °C for 10 min instead of 18 h, after which it was cooled to room temperature. We observed 5 mol% of free para-cymene in the crude mixture by $^1$H NMR spectroscopy. At this point, conversion to 5b was 50%. The reaction mixture was reheated to 120 °C for a further 7 h to see if having the para-cymene ligand in the Ru coordination sphere affected the formation of 5b. The amount of 5b increased from 50% to 67%, suggesting that coordinated para-cymene is not necessarily present on the catalytically active Ru species.
Scheme 14. The catalytic arylation of 4a continued despite the loss of para-cymene ligand from the Ru centre.
2.3.4 Discussion of the mechanism

On the basis of our current experimental studies and previous reports, a plausible mechanism is suggested in Scheme 15. First, the treatment of 4a with [{RuCl₂(p-cymene)}₂] and AgSbF₆ gives the cyclometalated ruthenium species A. Species A acts as a precursor rather than as a catalytic intermediate. The dissociation of the para-cymene ligand from the ruthenium coordination sphere has previously been observed by Jutand and co-workers.³⁰b We also propose in our catalytic system the conversion of A to B, displacement of the para-cymene ligand occurs by 4a (or the product 5b) as these contain multiple nitrogen donor units and are present in the mixture in excess. In our experiments, we observed the following: 1) the electron-rich
heteroarenes are more reactive than electron-poor heteroarenes; 2) silver additives provide higher yields, presumably by increasing the electrophilicity of Ru through halide abstraction. All these suggest that possibly the transformation from A to B might follow an electrophilic aromatic substitution mechanism. Transmetalation from arylboronic acid gives C and reductive elimination gives D. The desired product 5b is lost from the Ru coordination sphere. Finally, the Ru(II) is regenerated by Cu(OAc)$_2$·H$_2$O to complete the catalytic cycle. The order in which oxidation by Cu(OAc)$_2$·H$_2$O and reductive elimination occur is not certain, although a Ru(0)/Ru(II) mechanism (e.g., with reductive elimination first) is suggested by our experiments with complexes 13.

2.4 Conclusion

In this project, we have demonstrated a versatile Ru-catalyzed C2-H arylation of indoles and pyrroles with arylboronic acids under oxidative conditions. This transformation furnished the desired arylated products in moderate to excellent yields, and applied to a notably broad functional group scope. The mechanistic experiments indicated that the on-cycle intermediates do not possess the para-cymene ligand. Our results are accounted for most efficiently by an electrophilic aromatic substitution mechanism, rather than a ‘true’ C-H activation. However, it must be stressed that alternative pathways may also be operating. For example, the presence of acetate in the mixture may promote a CMD-type C-H activation, for which precedent exists on other substrates.[32]
3. Ru-Catalyzed C-H silylation of unprotected gramines, tryptamines and their congeners

3.1 Introduction

Recent years have seen a rapid growth of interest in C-H silylation methodology,\[^{[33]}\] and the use of arylsilanes in synthesis more generally.\[^{[34]}\] The silylation of aromatic C-H bonds serves as a valuable method for the preparation of arylsilanes, which can be used as versatile building blocks in organic synthesis.

3.1.1 Stoichiometric organometallic reactions

Generally, silyl substituents have been introduced by the treatment of organo-lithium or -magnesium reagents to Si electrophiles. For instance, Snieckus and co-workers showed the reaction of 14 with tert-BuLi and trimethylsilylchloride led to product 15 in excellent yield.\[^{[35]}\] Such methods are reliable but need stoichiometric amounts of the organometallic reagent and often a directing group approach.

![Scheme 16. Indole C2-H silylations based on stoichiometric metalation.](image)

3.1.2 Metal-catalyzed C-H silylation of indoles

In 2008, the Ir-catalyzed C-H silylation of indole was demonstrated by Falck and co-workers.\[^{[36]}\] [{Ir(OMe)(cod)}\(_2\)] precatalyst with 4,4’-dtbpy (L1) and norbornene in THF at 80 °C led to regioselective C2-H-silylated indoles in excellent yields. In 2014, Hartwig and co-workers showed that C2-H-silylation of indoles could be achieved in mild conditions, using expensive [{Rh(OH)(coe)}\(_2\)] as the catalyst, L2 as the ligand, 2 eq. of silane and 2 eq. of cyclohexene (a hydrogen acceptor) in THF at 45 °C (Scheme 17).\[^{[37]}\] In early 2015, Grubbs and Stoltz reported that tert-BuOK, which is considerably cheaper than Rh-based salts, catalyzed the C-H silylation of heteroarenes
without the need for a hydrogen acceptor.\textsuperscript{[33a]} However, owing to the strongly basic nature of tert-BuOK, unprotected amine groups were not tolerated.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure1.png}
\caption{Scheme 17. Recently reported approaches to catalytic C-H silylation.}
\end{figure}

### 3.1.3 Friedel-Crafts-type intermolecular C-H silylation

In contrast to most transition metal-catalyzed C-H silylations in which the metal center activates a C-H bond, Oestreich and co-workers recently developed a C3-H selective silylation of indoles with a catalytically generated silicon electrophile.\textsuperscript{[38]} In the proposed mechanism, the silane, H-SiR\textsubscript{3}, is added across the Ru-S bond of complex 16. Nucleophilic attack by the indole substrate gives the silylated product.
3.1.4 Exploration of C-H silylation of gramines and tryptamines

Even though indoles are well explored in C-H functionalization, the exocyclic alkyl amine groups of naturally-occurring indoles, such as gramines and tryptamines, have remained essentially unused. This is unfortunate because several of these could potentially be considered as naturally-occurring directing groups. Tryptamines are interesting because their derivatives play important roles in biological systems; gramines are cheap and synthetically versatile and give access to the indole unit in various syntheses. Gramines can be functionalized at C4 via directed ortho metalation and at C3 via retro-Mannich reactions. However, only a single report existed on the use of gramines in catalysis. The reported transformation proceeds by the coordination of an electrophilic Rh(I) center to the exocyclic amine group of gramine (17), leading to an elimination to give the cationic intermediate 18. This may either undergo further attack by indole, or otherwise be intercepted by Rh-aryl species generated from arylboronic acids. In either case, the electrophilicity of the Rh(I) center is sufficient to give 20 and 21. Elimination from intermediates of type 18 may have hindered attempts at developing catalytic gramine C-H functionalizations.

Scheme 18. Catalytic indole C3-H silylation reported by Oestreich and co-workers using a Ru complex.
Previously, Murai and co-workers reported a single example of a Ru\(^0\)-catalyzed mono-selective C-H ortho-silylation of \(N,N\)-dimethylbenzylamine. The reaction of \(N,N\)-dimethylbenzylamine with triethylsilane, norbornene as a hydrogen acceptor and \([\text{Ru}_3(\text{CO})_{12}]\) as a catalyst gave the desired product 22 in 58% yield.\(^{41}\) We reasoned that, as this process probably involves mainly electron-rich transition metal centers, it might not lead to the difficulties with elimination of the exocyclic amine in gramine substrates described in Scheme 19. Electron-rich transition metal centers are also less likely to participate in \(\beta\)-H elimination. With this in mind, we pursued the Ru-catalyzed C-H silylation of gramines, tryptamines and their congeners.

**Scheme 19.** Rh-catalyzed conjugate addition to indoles.

3.2 Results and discussion

3.2.1 Reaction optimization

In an initial reaction between gramine and HSiMe\(_2\)Ph, in the presence of 5-mol\% of \([\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]\) and norbornene in toluene at 135 °C, the corresponding ortho-silylated product 23a formed in 85% yield (Table 3, entry 1). By contrast, neither \([\text{Ru}_3(\text{CO})_{12}]\) nor \([\text{RhCl}(\text{PPh}_3)_3]\) gave the desired silylated product (Table 3, entries 2 and 3). However, the latter afforded 3-methylindole in 35% yield, which showed that Rh(I) can indeed cleave the amino group. Changing from \([\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]\) to \([\text{RuH}_2(\text{PPh}_3)_4]\) lowered the yield to 56% (Table 3, entry 4). Under Falck’s \([\{\text{Ir}(\text{OME})(\text{cod})\}_2]\)-catalyzed conditions,\(^{36}\) no silylated product was formed (Table 3, entry 5).
The desired transformation did not occur without norbornene and fewer equivalents of norbornene gave the product in only moderate yield (Table 3, entries 6 and 7). The reason for this is possibly the disfavored formation of Ru(0) and the failure in the reductive elimination of hydrogen. Lowering the catalyst loading to 2.5 mol% decreased the yield to 71% (Table 3, entry 8).

Table 3. Selected optimization results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Silane (eq.)</th>
<th>Norbornene (eq.)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[RuH₂(CO)(PPh₃)₃] (5.0)</td>
<td>5.0</td>
<td>5.0</td>
<td>85(83)[a]</td>
</tr>
<tr>
<td>2</td>
<td>[Ru₃(CO)₁₂] (5.0)</td>
<td>5.0</td>
<td>5.0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>[RhCl(PPh₃)₃] (5.0)</td>
<td>5.0</td>
<td>5.0</td>
<td>0 (34)[b]</td>
</tr>
<tr>
<td>4</td>
<td>[RuH₂(PPh₃)₄] (5.0)</td>
<td>5.0</td>
<td>5.0</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>[(Ir(OMe)cod)₂] (2.5)</td>
<td>5.0</td>
<td>5.0</td>
<td>0[c]</td>
</tr>
<tr>
<td>6</td>
<td>[RuH₂(CO)(PPh₃)₃] (5.0)</td>
<td>5.0</td>
<td>5.0</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>[RuH₂(CO)(PPh₃)₃] (5.0)</td>
<td>5.0</td>
<td>0.0</td>
<td>traces</td>
</tr>
<tr>
<td>8</td>
<td>[RuH₂(CO)(PPh₃)₃] (2.5)</td>
<td>5.0</td>
<td>5.0</td>
<td>71[d]</td>
</tr>
</tbody>
</table>

Modification of conditions: [a] 3 g (17.2 mmol) scale of 17a. [b] 3-methylindole formed in 34% yield. [c] 4,4′-di-tert-butylbipyridine ligand (10 mol%), THF, 80 °C, 24 h. [d] Reaction performed under air in m-xylene as solvent.

3.2.2 Silane scope

With the optimized conditions in hand, we investigated the scope of this reaction with respect to a variety of hydrosilanes. The reaction of gramine with dimethylphenyl-, methyldiphenyl-, triethyl- and triphenyl silanes afforded the corresponding products in good to excellent yields (Scheme 21). There is literature precedent for triethylsilane acting an excellent coupling partner in direct C-H silylations but, unfortunately, in our case the expected product 23e was observed only in 50% yield. The use of H-SiMe₂C₆F₅ and H-Si(OMe)Me₂ failed to give the desired product. Finally, the use of hexa-
methyldisilane and H-GeEt₃, the analogue of H-SiEt₃, resulted in no reaction. Notably, hexamethyldisilane has been used in Pd-catalyzed C-H silylations.[42] Its failure here suggests that Ru species activate the Si-H bond more readily than Si-Si.

Scheme 21. Silane scope of the gramine C₂-silylation. [a] Me₃Si-SiMe₃ used as the silane coupling partner.

3.2.3 Directing group effects

Following these results, we explored the effect of different directing groups on the silylation (Scheme 22). The optimized silylation conditions used with gramine also were effective on unprotected amino group-containing compound (1H-indol-3-yl)methanamine to give the silylated product 24 in 80% yield. Unprotected tryptamine, which has a longer alkyl amine side chain than does gramine, proved to be very effective in silylation, giving 25a and 25b in 79% and 93% yields, respectively. Very few literature procedures have been reported in which a C-H activation/functionalization takes place on unprotected tryptamine substrates,[43] despite the high interest in indole C-H functionalization methodology and the biological importance of tryptamines. The homologous substrate 3-(1H-indol-3-yl)propan-1-amine exclusively afforded the N-silylated product 26 in 30% yield, thus indicating the formation of seven-membered ruthenacycles is disfavoured. We suspect that the N-silylated product could have formed via an intermolecular pathway. Changing from nitrogen to oxygen-based directing groups led to significantly lower yields (products 27 and 28). No silylation occurred with N-methyl,
N-benzyl, N-tosyl or N-(2-pyrimidyl) indoles. N-Acetyl and N-Boc indoles provided an intractable complex mixture of indole-containing species.

Scheme 22. Directing group effects on the Ru-catalyzed C-H silylation of indoles.

3.2.4 Substrate scope of gramine and tryptamines

After establishing the optimized reaction conditions, we carried out the silylation of substituted gramine and tryptamine derivatives (Figure 3). Electron-rich 5-methoxy substituted gramine afforded the desired products 29a-c in moderate to excellent yields. The yield improved as the number of phenyl substituents on the silane was increased. An extended aromatic system on the indole 6-membered ring with different silanes yielded the desired product 29d and 29e in 37% and 88% yield, respectively. Halogen-substituted gramines and tryptamines gave lower yields (29f and 29g). Electron-withdrawing substituents such as ester and nitro on the indole backbone were detrimental to the catalysis, resulting in no formation of the silylated products (29h and 29i). O-Benzyl and O-methylserotonin derivatives and 2-(5-methyl-1H-indol-3-yl)ethan-1-amine gave 30a in 38% yield and 30b 76%. Using 2-(1H-indol-3-yl)-N-methylethan-1-amine instead of tryptamine lead to a diminished yield of the silylated product 30f, compared to compound 25b, which was isolated in 58% yield (Scheme 22). This might be due to the unfavorable steric effects exerted by the additional methyl group on the exocyclic nitrogen.
3.2.5 Substrate scope of heteroarene

An expanded heteroarene scope was investigated next. Benzothiophene derivative 31 was isolated in 75% yield. Having the directing group at C2 of benzofuran, and therefore aiming at C3-H activation, gave the corresponding C2-H-silylated product 32 in substantially lower yield compared to substrates in which C2-H is activated. Also, their gramine’s 7-azaindole analog failed to give 33. It is likely that the coordination of the pyridine-type nitrogen to Ru inhibits catalytic activity. Furan and the pyrrole were converted to their silylated derivatives 34-36 in lower yields.

Figure 3. Substituted gramines and tryptamines in Ru catalyzed C-H silylation.
3.2.6 Regioselective directed silylation of thiophene derivative

Previously, Suginome and co-workers developed the silylation of thiophene using directing groups based on boronates protected using 2-pyrazol-5-ylaniline\textsuperscript{[44]} and anthranilamide.\textsuperscript{[45]} With that in mind, we tried the silylation of thiophene derivative 37. At lower temperatures and with longer times compared to the standard reaction conditions, 37 converted to a separable mixture of mono- and di-silylated products (38a and 38b) in a 3.6:1 ratio (Table 4, entry 1). Additional equivalents of silane and norbornene at higher temperature yielded the products in 93% combined yield with a 1:1.4 ratio of 38a:38b (Table 4, entry 2).

\textbf{Table 4. Directed C-H silylation of thiophene derivative 37.}

<table>
<thead>
<tr>
<th>Entry</th>
<th>HSiMe\textsubscript{2}Ph (eq.)</th>
<th>Norbornene (eq.)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>38a:38b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
<td>100</td>
<td>168</td>
<td>79</td>
<td>3.6:1</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>10</td>
<td>135</td>
<td>48</td>
<td>93</td>
<td>1:1.4</td>
</tr>
</tbody>
</table>

\textbf{Scheme 23.} Substrate scope of heteroarene. [a] Reaction conducted at 100 °C.
3.2.7 Undirected Silylation

Falck,[36] Hartwig,[37] Oestreich,[38] Grubbs and Stoltz[33a] have all reported systems for the undirected C-H silylation of heteroaromatic substrates. Prior to this work, no undirected C2-H silylations were known using Ru catalysis. We reasoned that this ought to be possible by adapting our conditions to overcome the lack of a directing group. Indeed, in the absence of a directing group no silylation was observed when the optimized reaction conditions were directly used on the heteroarene substrates, such as benzothiophene, benzo furan or indole. We found that simply increasing the temperature to 150 °C led to the corresponding silylated products when triethylsilane was used as the coupling partner (Scheme 24). Benzo furan afforded 40 in excellent yield, and benzothiophene led to no conversion. Substituents on the heteroarenes generally lowered the yield. However, using 5-aminoindole as the substrate gave the product 39f in 33% yield. This is an interesting result because it shows the viability of using an unprotected aniline-type amine in the catalysis. Therefore, our method is able to convert substrates with primary, secondary and tertiary amine groups as well as aniline-type and pyrrolic nitrogens.

![Scheme 24. Undirected silylation of heteroarene substrates](image)

- 39a: [Si] = SiMe2Ph, 0%
- 39b: [Si] = SiEt3, 40%, 72%
- 39c: 40%
- 39d: 53%
- 39e: R = OMe, 47%
- 39f: R = NH2, 33%

**Scheme 24.** Undirected silylation of heteroarene substrates [a] Conditions: [RuH2(CO)(PPh3)3] (5 mol%), HSiEt3 (5 eq.), norbornene (5 eq.), toluene, 150 °C, 20 h. [b] 22% of N1-silylated product observed.
3.3 Mechanistic insights

To gain extra insights, we undertook C-H/D exchange investigations (Scheme 25). Treating 17a-d with D-SiEt3 gave C2-H silylated product 23e-d with 40% of deuterium incorporation at C4. 3-Methylindole (42/42-d) was also obtained as a side-product with 15% deuterium incorporation at C4 and 79% at C2. Replacing D-SiEt3 with H-SiEt3 in otherwise the same reaction, led to lower deuterium incorporation: 15% at C4 in 23e/23e-d and 72% at C2 of 3-methylindole. C4-H/D exchange in the latter remained very similar. These results point to an easier activation at C2 than C4. The lower C4 deuterium incorporation in 3-methylindole is consistent with that process being directed by the amine group. Transition metal-catalyzed C4-H functionalization of indoles is particularly rare. \[46\] This process is the first observed instance of C4-H activation occurring at electron-rich transition metal centers. A mechanistic proposal consistent with these observations is described below.

Next, silane crossover experiments were performed to gain insight into the activation of the silane substrate. The reaction of D-SiEt3 with H-SiMe2Ph in presence of [RuH2(CO)(PPh3)3] as a catalyst at 135 °C incorporated 45% of deuterium into the dimethylphenylsilane (Table 5, entry 1), and the extent of deuterium incorporation lowered to 19% at room temperature. This implies that the H/D exchange can occur easily, so we suspect that the insertion of the Ru into the Si-H bond might be the first step in the catalytic cycle (Table 5, entry 2). No deuterium incorporation occurred among silanes in the absence of catalyst (Table 5, entry 3).

![Scheme 25. Selected C-H/D exchange experiments.](image-url)
Table 5. H/D exchange reactions with silanes

<table>
<thead>
<tr>
<th>Entry</th>
<th>[RuH₂(CO)(PPh₃)₂] (mol%)</th>
<th>Temp (°C)</th>
<th>Extent of deuterium incorporation (%)</th>
<th>Et₃Si-H/D</th>
<th>D/H-SiMe₃Ph</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>135</td>
<td></td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
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<td>rt</td>
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<tr>
<td>3</td>
<td>0</td>
<td>135</td>
<td></td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

3.4 Plausible mechanism

On the basis of our experimental studies, a plausible mechanism for the C-H silylation is shown in Scheme 26. Initially, the [RuⅡ]H₂ catalyst precursor is reduced via the hydrogenation of norbornene. The resulting Ru⁰ species then undergoes oxidative addition into the Si-H bond of a silane substrate to give intermediate A. The facile Si-H/D scrambling described above suggests that this process is fast and reversible. Subsequent oxidative addition to a second silane equivalent would give intermediate G, which can reductively eliminate disilane and return a [RuⅡ]H₂ complex. During our work on the reaction scope, varying quantities of disilane by-products were isolated, which is consistent with this proposal. Alternatively, intermediate A could undergo coordination of the heteroarene B and oxidative addition into the C₂-H bond to give intermediate D. Reductive elimination E and loss of the product from the Ru coordination sphere yields 23 and regenerates [RuⅡ]H₂ to close the catalytic cycle. The observed C₄-H/D exchange described above is presumably explained by oxidative addition of Ru into the C₄-H bond to give intermediates such as C or F. As more silylated C₄-D product was observed, it is likely that the steric bulk in intermediate F pushes the Ru center towards the C₄ position after C₂ silylation has already taken place.
3.5 Conclusion

In summary, we have developed a new method to obtain C2-H silylated heteroarenes using ruthenium as a catalyst. This method worked well without the protection of pyrrolic or exocyclic NH groups. A key discovery was that the process also works for Ru without directing group assistance. With respect to the mechanism, H/D exchange experiments revealed first C4-H activation of gramine by electron-rich transition metal centers. Si-H/D exchange experiments indicated that Si-H activation by Ru occurs easily. Our method uses a comparatively inexpensive system to achieve both directed and undirected C-H silylation of the indole core and other heterocycles. Future mechanistic understanding will hopefully lead to milder systems.

Scheme 26. Plausible mechanism for the Ru-catalyzed C-H silylation of gramine.
4. Aryne precursors via Ru-catalyzed C-H silylation

4.1 Introduction

4.1.1 Do arynes really exist?

Arynes are electrophilic, short-lived intermediates that contain a highly-strained C≡C triple bond in the aromatic ring, formally obtained from removing two neighboring hydrogen atoms from arenes.

The history of arynes dates back to 1902 when Stoermer and Kahlert proposed 2,3-benzofuranyne intermediate 43a to explain unexpected selectivity in the reaction between 3-bromobenzofuran and ethoxide (Scheme 27).[47] Both products 44a and 44b were obtained but a SNAr mechanism would lead only to 44b. Stoermer and Kahlert tried but failed to isolate 43a. Today, five-membered arynes are understood to be considerably less stable than their six-membered counterparts.[48]

![Scheme 27. Early proposal of 2,3-benzofuranyne.](image)

In later decades debate arose about whether arynes are viable intermediates that could explain the outcome of related reactions.

For example, they seemed to account for various unusual selectivities (e.g., as above) but were not seen to react as strained alkynes. However, in the 1950s, Roberts and co-workers reported evidence in support of the intermediacy of benzyne (Scheme 28a).[49] The reaction of $^{14}$C labelled chlorobenzene with potassium amide led to a 1:1 mixture of anilines 45a and 45b. In addition to this, Wittig’s conversion of 46 to 47 (Scheme 28b) is consistent with a [4+2] cycloaddition of furan to benzyne, further suggesting that arynes are real.[50]
Scheme 28. Selected studies related to the formation of aryne intermediates.

Very recently, in 2015, Pavliček, Peña and co-workers isolated and observed aryne intermediates directly on an ultrathin insulating film surface using scanning tunneling microscopy and atomic force microscopy.\[^{51}\]

4.1.2 Generation of arynes

Since Roberts and co-workers used the deprotonative method for benzyne generation (Scheme 29, path a), many more synthetic methods have been reported to generate aryne intermediates. In the 1950s Wittig reported the use of 1,2-dihalo arenes as aryne precursors (Scheme 29, path b).\[^{50}\] The treatment of 1,2-dihalo arenes with a stoichiometric amount of strong base, e.g., Mg/Li, led to halogen metal exchange prior to 1,2-elimination to form the aryne intermediate. This method offers an advantage over that using the mono-halogenated arenes because it provides regioselectivity control. In 1963, Lester and co-workers reported that cheap and readily available anthranilic acid can be used as an aryne precursor (Scheme 29, path c).\[^{52}\] Slow addition of anthranilic acid to amyl nitrite in an aprotic medium generates a zwitterionic intermediate. This intermediate fragments on heating to the corresponding aryne, nitrogen and carbon dioxide. This is an efficient and clean method for generating arynes but amyl nitrite is explosive. Hence, handling these compounds requires considerable care. Alternatively, \(^{48}\) may be used to generate arynes by heating. This generates nitrogen, sulfur dioxide and the corresponding aryne (Scheme 29, path d).\[^{53}\] However, precursors \(^{48}\) undergo gradual decomposition and are therefore less than ideal for long-term storage.
Scheme 29. Selected historic methods of the generation of arynes.

4.1.3 Fluoride-activated aryne precursors

In 1973, Cunico and Dexheimer showed that the treatment of ortho-tosyl arylsilanes 49a with fluoride led to the generation of benzene intermediates (Scheme 30).\cite{54} Fluoride is understood to attack the silyl substituent leading to elimination of the leaving group (tosylate in this case). Cunico and Dexheimer’s precursor design underwent gradual improvements, most notably by Kobayashi and co-workers who used triflate as the leaving group in 1983.\cite{55} Their work was ignored in the literature for the best part of 15 years. However, at the turn of the century, the convenience of their approach to arynes began to be recognized. Several research groups undertook exploring the use of Kobayashi’s precursor design for the generation of arynes under mild conditions, particularly with respect to the development of new synthetic transformations.\cite{56} In 1995, Kitamura showed that aryliodonium substituents could act as powerful leaving groups.\cite{57}

Scheme 30. Generation of benzene from various precursors.

Since then, 49b and a handful of its very simple derivatives have been commercialized and several publications have addressed their efficient synthesis. Notable amongst these is Peréz and Guitián’s procedure starting from 2-bromophenol (Scheme 31).\cite{58} Reaction of 50 with hexamethyldisilazane (HMDS) and treatment of intermediate 51 with n-BuLi at -100 °C to -80 °C
gives 52 via lithium-halogen exchange. Triflation gives the Kobayashi-type precursor 49b.

![Scheme 31](image)

**Scheme 31.** Modified procedure for the synthesis of ortho-trimethylsilylphenyl triflate.

In another development, Akai and co-workers showed that arynes could be generated from ortho-silylaryl nonaflates 54 by a domino process (Scheme 32), where 54 is prepared in situ by the reaction of phenols 53 with NfF, followed by the attack of produced fluoride ion on the trimethylsilyl group led to the formation of benzyne.\(^{[59]}\) This method has an advantage over the established Kobayashi’s approach: NfF is cheaper than Tf₂O and that the arynes can be generated from the ortho-silylphenol intermediates directly means that one less step is required compared to the Kobayashi approach.

![Scheme 32](image)

**Scheme 32.** In situ generation of benzyne from an ortho-silylphenol.

4.1.4 Arynes and their precursors via C-H activation

Presently, whether more highly substituted precursors of the type 49b or 53 may be used depends on the specific case and, in particular, access to the corresponding ortho-bromophenol. Unfortunately, very few variants may be purchased or prepared conveniently. Often, precursors with even slightly more complex R groups (53, R ≠ H, Me, OMe, Br, etc.) are difficult to access. One potential approach to this limitation is the development of C-H functionalization methods that install two neighboring groups able to release an aryne. To the best of our knowledge, however, only one publication describing such an approach appeared prior to our work in this area. Greaney and co-workers showed the generation of arynes directly from cheap benzoic acids via Pd-catalyzed ortho C-H activation (Scheme 33).\(^{[60]}\) However, the highest yield of the corresponding capture products obtained by this method
is only 47%, it requires a complex reaction mixture and the range of transformations is limited to [2+2+2] cycloadditions. Moreover, the procedure requires a complex reaction mixture and was not demonstrated to work on a wide range of benzoic acids.

Scheme 33. Generation of benzyne from benzoic acid via C-H activation

In mid-2016, after our work had already started, Jeon and co-workers published a method based on Ir and Rh catalysis in which aryl acetates were converted to ortho-silylphenols (Scheme 34). A diverse range of R groups was shown to survive the protocol. However, whilst the transformation of the ortho-silylphenols to diverse products was explored, the authors did not focus on aryne generation, showing only one example. Nevertheless, in principle, the method provided a strong solution to the challenge of ortho-silylphenol synthesis.

Scheme 34. Jeon and co-workers’ route to ortho-silylphenols from aryl acetates.

4.2 The inspiration

Our group’s interest in catalytic C-H functionalization, boronates, C-H silylation and aryne chemistry led us to imagine an alternative disconnection of leading back to arylboronic acids (Scheme 35). As starting materials for aryne precursor synthesis, arylboronic acids would offer a significant advantage over the ortho-halophenols: a large variety of arylboronic acids is commercially available and even cheap, largely due to their use in well-established coupling methodology, such as the Suzuki-Miyaura and Chan-Lam reactions. Arylboronic acids are most commonly prepared from the parent haloarenes, rather than halophenols, so the overall prefunctionalization requirement would also be reduced.
Key to our approach is the work of Suginome and co-workers, who reported a novel C-H silylation reaction based on the use of aryl anthranilamidoboronates, ArB(aam) (56), as substrates (Scheme 35a). We reasoned that selective oxidation of the boronate residue could, in principle, lead us from the arylboronic acid to the ortho-silylphenol – or even arynes and their adducts themselves – in a single, simple operation.

![Scheme 35. a) Suginome’s C-H silylation of boronate derivatives; b) Our envisioned approach to ortho-silylphenols compared to established routes.](image_url)

4.3 Results and discussion

4.3.1 Substrate scope of ortho-silylphenol

At the outset of our studies, the reaction of PhB(aam) with dimethylphenylsilane in the presence of catalytic [RuH2(CO)(PPh3)3] and norbornene as a hydrogen scavenger at 135 °C in toluene gave the desired ortho-silylated product in quantitative yield. In the same reaction flask, the resulting crude mixture was reacted with an excess of H2O2 under basic conditions in EtOH, to give 58a in 81% after column chromatography, the only required purification (Scheme 36). Replacing the dimethylphenylsilane with trimethylphenylsilane lowered efficiency: 58b was obtained in 47% yield. Arylboronic
acids with either an electron-donating or electron-withdrawing substituent led to the corresponding ortho-silyl phenol products in moderate to excellent yields. Arylboronates with two inequivalent ortho C-H units were silylated preferentially at the sterically less hindered position (e.g., 58k and 58i). The ortho-fluoro substituted boronate gave corresponding product 58j in 42% yield. The reaction was also useful for synthesizing the fluorene-based derivative 58m. The carbazole 58n was also tolerated, which bodes well for the application of this method to the synthesis of aryne precursors in more challenging chemical environments. However, this substrate required the use of NH₂OH·HCl instead of H₂O₂ as the oxidant.

**Scheme 36.** Reagents and conditions: i) arylboronic acid (0.5 mmol), anthranilamide (0.5 mmol), toluene; ii) hydrosilane (2.5 mmol), [RuH₂(CO)(PPh₃)₃] (6 mol%), norbornene (2.5 mmol), toluene, 135 °C, 20 h; iii) Na₂CO₃ (0.5 mmol), H₂O₂ (5 mL), EtOH (20 mL), rt. Isolated yield over 3 steps. Modified conditions: [a] HSiMe₂Ph (5.0 mmol), 150 °C. [b] step ii) HSiMe₂Ph (5.0 mmol), [RuH₂(CO)(PPh₃)₃] (10 mol%), norbornene (5.0 mmol), toluene, 150 °C, 20 h. iii) NH₂OH·HCl (0.75 mmol), NaOH (1.0 mmol), EtOH (11 mL).
4.4 Aryne capture reactions

4.4.1 One-pot benzyne capture directly from phenylboronic acid

After the preparation of various ortho-silyl phenols, we explored the generation of the corresponding arynes and their capture reactions. In particular, we were interested in converting the starting arylboronic acid directly to the product of an aryne capture reaction in a one-pot sequence, thus going around the need to isolate or store ortho-silyl phenol or aryl triflate precursors. We chose the well-established [4+2] cycloaddition reaction with furan. Substrate 55 underwent steps i-iii (Scheme 36) followed by a simple aqueous work-up. To the solution of the concentrated organic phase were added NfF, Cs₂CO₃, 18-crown-6 and furan, leading to the generation of benzyne in situ and the [4+2] cycloaddition product 47, which was isolated in 70% yield (91% average yield per step).


4.4.2 Derivatization of a fluorene-based aryne precursor

Fluorene derivatives are versatile building blocks for a wide range of organo electronics. The derivatization of the fluorene core is therefore a worthwhile pursuit. We sought to demonstrate that aryne reactivity can be used to generate previously unavailable fluorene-based derivatives. The reaction of 58m with NfF in the presence of NaH base gave the nonaflate 60 in 85% yield. With this precursor in hand, we explored the generation and trapping of the corresponding aryne with N-Boc-pyrrole (a [4+2] cycloaddition) as well as its insertion into molecular iodine, previously develop by Peréz, Guixtian and co-workers (Scheme 38). The desired bridged bicyclic adduct 61 was obtained in 94% yield when 60 was exposed to N-Boc-pyrrole and CsF in acetonitrile at 60 °C; the second reaction gave diiodoarene 62 in 77% yield under similar conditions using I₂ as the trapping reagent. These reagents highlight the value and versatility of the aryne triple bond generated in a new context.
4.5 Conclusion

We have demonstrated the generation of ortho-silylphenols as aryne precursors in an expedient way from diverse, commercially available boronic acids. The transformation is very simple from an experimental point of view: the three step sequence uses a broad variety of arylboronic acids as the starting materials and requires only one chromatographic purification to deliver the ortho-silylphenols in synthetically useful yields. Moreover, the aryne can also be generated directly without isolating the ortho-silylphenol intermediate, which is a significant advance in convenience and cost reduction as arylboronic acids are abundant and cheap, whereas chromatography is expensive and time-consuming. We expect this method will be useful in the preparation of other, more complex aryne precursors in the future.
Svensk Sammanfattning

Avhandlingen avser nya syntesmetoder med syftet att uppnå effektivare och tidigare omöjliga transformationer inom organisk kemi. De nya metoderna som presenteras i avhandlingen berör katalytisk C-H funktionalisering, d.v.s. metoder vilka direkt byter ut C-H bindningen i molekylen mot en önskad funktionell grupp. Detta är i princip en av de mest direkta metoderna tillgängliga för att bygga upp komplexitet i organiska molekyler. Fokus ligger framför allt vid rutenum-katalyserade metoder för derivatisering av aromatiska föreningar.

1. Ru-katalysrad C-H arylering av indoler och pyrroler
2. Ru-katalyserad C-H silylering av graminer, tryptaminer och deras analoger


![Diagram of Ru-catalyzed C-H silylation](image)

3. Syntes av arynprekursorer från arylborsyror via Ru-katalyserad C-H silylering


![Diagram of synthesis of arynprecursors](image)
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References


A doctoral dissertation from the Faculty of Science and Technology, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Science and Technology. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Science and Technology”.)