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COMMUNICATION

Ru-Catalysed C-H Silylation of Unprotected Gramines, Tryptamines and their Congeners

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Selective Ru-catalysed C2-H silylation of heteroarenes is presented. The transformation works with or without directing group assistance and requires no protecting groups. Gramines and tryptamines may be converted efficiently whilst avoiding deleterious elimination side-reactions. Mechanistic studies reveal an unusual activation of the indole C4-H bond by an electron-rich metal.

Catalytic activation of C-H bonds offers new transformations, new selectivity modes and expedited synthetic routes to various bioactive¹ and functional molecules.² Growing interest in the utility of (hetero)arylsilanes in synthesis,³ medicinal chemistry⁴ and materials science⁵ has fuelled the development of powerful C-H silylation methods,^{6,7} as exemplified by recent work on indole substrates (Figure 1). Rh-^{7b}, Ir-⁸ and even ^tBuOK-catalysed⁹ reactions have been shown to deliver C2-silylated indoles selectively, whilst C3-H silylation has been achieved using more specialised Ru complexes.¹⁰ Our interest in (hetero)arene C-H functionalisation¹¹ led us to consider a complementary strategy using the exocyclic amine substituents of naturally-occurring indole compounds to direct regioselective C-H silylation. Beyond circumventing the protecting group requirements and directing group (DG) installation,¹² such a development would open up previously intractable/under-explored substrates to catalytic C-H functionalisation.

Gramine (**1a**) is a cheap, synthetically versatile, naturally-occurring alkaloid able to deliver the indole or skatole nucleus.¹³ To the best of our knowledge, only a single report exists on its use in catalysis, which shows that in the presence of

electrophilic metal species the exocyclic amine is cleaved, making it ineffective for directing C-H bond activation.¹⁴ Tryptamine C-H functionalisation is also rare, and typically reported only on protected substrates.¹⁵ We reasoned that the use of an electron-rich metal centre could give efficient C2-H functionalisation of such unprotected substrates for the first time without inducing competitive elimination processes.

Previous work:

Hartwig:^{7a,b} cat = $[(\text{Rh}(\text{coe})_2\text{OH})_2]/\text{L1}$
Falck:^{8a} cat = $[(\text{Ir}(\text{OMe})\text{cod})_2]/\text{L2}$
Grubbs & Stoltz:⁹ cat = ^tBuOK

Oestreich, Ohki, Tatsumi and co-workers:^{10a}

This work:

Figure 1: Previous work on indole C-H silylation and the work presented herein.

To probe the feasibility of this idea, we tested the reaction between **1a** and H-SiMe₂Ph with a variety of catalyst precursors and norbornene (nbe) as the hydrogen scavenger (Table S1). No conversion was observed using the Ir-catalysed approach previously reported by Falck for 2,3-unsubstituted indoles,^{8a} or under Rh-catalysed conditions described for the C-H silylation

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of 2-arylpyridines.¹⁶ $\text{Ru}_3(\text{CO})_{12}$ was also ineffective, but $\text{Ru}(\text{II})$ precursors able to undergo reductive activation¹⁷ worked well, giving **2a** in 85% yield under optimised conditions (see Table S1 for full details). This reaction could be scaled up to 3g of **1a** without significant loss in yield (Scheme 1). Exploration of the silane scope revealed triaryl, trialkyl and mixed alkyl/aryl silanes to be effective, and afforded **2a-e** in good to excellent yields, in line with their respective steric profiles. Silane sterics were less closely correlated to the yields for other (hetero)arenes (see below). The electronic perturbation to $\text{H-SiMe}_2\text{C}_6\text{F}_5$ or $\text{H-Si}(\text{OMe})\text{Me}_2$ proved detrimental (**2f,g**). Activity did not extend to hexamethyldisilane (**2h**), nor to H-GeEt_3 (**2i**) as an analogue of H-SiEt_3 .¹⁸

Silane scope with gramine:

Scheme 1. ^a 3 g (17.2 mmol) scale of **1a**. ^b Modified conditions: $\text{Me}_3\text{Si-SiMe}_3$ used as the silane source.

Importantly, we discovered no requirement to protect exocyclic amine directing groups. Thus, **3** and C2-silylated tryptamines **4** were delivered in good to excellent yield. A longer tether (product **5**) and/or weaker¹⁹ σ -donating directing groups (products **6** and **7**) gave lower yields and led to competitive silylation at the pyrrolic nitrogen, presumably via an intermolecular pathway; a reaction between unsubstituted indole and D-SiEt_3 in the presence of HNEt_2 also resulted in indole N-silylation (see SI for details). N-methyl, N-tosyl and N-(2-pyrimidyl) indoles gave no conversion (**8a-c**); N-acetyl and N-Boc indoles gave complex mixtures (**8c-d**). Silylation at C2 therefore proceeded most efficiently with unconjugated, strong σ -donor DGs,²⁰ which presumably favours an oxidative addition by Ru species into the C-H bond.

The scope was expanded to a range of gramine derivatives (**2j-p**), although nitro and ester substituents (**2q,r**) shut down the reaction (Scheme 2B). No C-H silylation of the benzenoid ring was detected (**2r** and **9**). Silylated N-methyl tryptamine **10** and serotonin derivative **11a** were obtained in good yields. Furan, pyrrole and thiophene derivatives were also amenable to the C-H silylation (products **14** and **15**, Scheme 2B-C). A lowered temperature and extended reaction time favoured the selective formation of mono-silylated thiophene **15a**.

We also tested the undirected heteroarene C2-H silylation,^{7b, 8a} which is unprecedented in Ru catalysis. Indeed, undirected Ru-catalysed C-H functionalisation is altogether very rare.²¹ Whilst $\text{H-SiMe}_2\text{Ph}$ proved ineffective for this transformation, H-SiEt_3 gave variously substituted indoles **16b-e** and benzofuran **17a** in moderate to excellent yields (Scheme 3).

A. Directing group effects:
(Conditions as in Scheme 1)View Article Online
DOI: 10.1039/C6CC00803H B. Scope in heteroarenes:
(Conditions as in Scheme 1)

C. Regioselectivity control:

D. Undirected silylation:^e

(C3-H silylated products were not detected.)

Scheme 2. Heteroarene scope and regioselectivity control. ^a Catalyst loading = 6 mol%. ^b 4.5 mmol scale. ^c 100 °C ^d 10 equiv. HSiMe_2Ph , 10 equiv. nbe. ^e General conditions for undirected C-H silylations: $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (5 mol%), silane (10 equiv.), nbe (10 equiv.) 150 °C, 20 h. ^f Conditions: $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (5 mol%), silane (5 equiv.), nbe (5 equiv.) 135 °C, 20 h.

To date, mechanistic work on C-H silylation has been rare.^{6a} We obtained insights for our reaction from C-H/D exchange experiments. Reactions using C2-deuteroindole (**1a-d**) as the substrate and/or D-SiEt₃ as the silane gave **2e/2e-d** and 3-methylindole (**19/19-d**), as exemplified in Scheme 3 by the reaction between two deuterated coupling partners (see SI for the full details). Partial C-H/D exchange was observed at C2 in **19** and the C3-methylene/methyl positions of **2e** and **19**, as well as the C4 and C7 positions in both.

Catalytic indole C4-H activation is very rare²² and reported only for electrophilic metal species. 40% of C4-D incorporation was observed in product **2e** obtained from the reaction between **1a-d** and D-SiEt₃ (Scheme 3A). The corresponding reaction using only one deuterated substrate gave 15–19% C4-D incorporation (Table S2). These values are consistent with the intermediacy of **C** or **F** (or corresponding deuterides) in our proposed mechanism for the silylation of gramine (Figure 2). The necessarily high strain and/or steric demand in **C** and **F** also explains the absence of C4-H silylated products. No C4-H/D exchange occurred when tryptamine or indole²³ (**20_H**) was used instead of **1a**, implicating the methanamine directing group in C4-H activation in **1a**.

Catalytic indole C7-H activation is also rare.²⁴ Commonly, the corresponding functionalisation is carried out on indolines prior to their oxidation.²⁵ The extent of C7-H/D exchange was invariably greater in **19/19-d** than in **2e/2e-d** and no 2-silyl-3-methylindole was observed. This suggests C7-H activation via coordination of Ru to the pyrrolic nitrogen prior to C2 silylation; the steric bulk of a 2-silyl substituent presumably inhibits coordination to N1. Moreover, without amine DGs present on the substrate (e.g. indole, **20_H**) C7-H/D exchange was not observed, unless an amine additive was included separately (Scheme 3B). Thus, C7-H/D exchange observed in **2e** and **19** may be effected by Ru species bearing nitrogen ligands obtained from the cleavage of the methanamine DG during the formation of **19**. C7-H activation therefore seems to require unimpeded coordination to N1 and the availability of alkyl amine ligands for Ru. Finally, N-methylindole (**20_{Me}**) did not undergo C7-H/D exchange but did undergo exchange at the C2 position (see SI for more details). This supports the viability of a truly intermolecular C-H activation without any requirement for directing groups.

Disilane by-products **21** formed in the Ru-catalysed reactions, suggesting [Ru](SiR₃)₂ intermediates **G**, although at this time a metathesis mechanism involving **A** cannot be ruled out.²⁶ That hexamethyldisilane proved ineffective during our survey of silylating reagents (Scheme 1, **2h**) means Si-Si bond formation is probably irreversible under our conditions, in contrast to previously reported Rh-¹⁶ and Pd-catalysed²⁷ processes. A crossover reaction between D-SiEt₃ and H-SiMe₂Ph in the presence of [RuH₂(CO)(PPh₃)₃] led to extensive Si-H/D exchange (Scheme 3C), even at room temperature (entry 2), consistent with fast Si-H bond activation, as reported for Ir-catalysed C-H silylations.²⁸ No such exchange occurred in the absence of catalyst (entry 3).

Figure 2 shows a proposed mechanism. Insertion of Ru⁰ into the H-SiR₃ bond affords **A**, whose strongly σ-donating hydride and

silyl ligands presumably activate the metal centre towards oxidative addition into the C-H bond after substrate coordination (**B**). The formation of **D** is probably favoured over that of **C** on the basis of lower ring strain. Reductive elimination gives **E** and reduction of nbe and release of **2** restores Ru⁰. The bulky silyl group in **E** presumably forces the coordinated Ru centre towards C4-H, encouraging the formation of **F**.

Our mechanistic experiments (see SI for full details) are consistent with an analogous catalytic cycle for substrates without DGs. Thus, **A** may be active towards intermolecular C-H activation (e.g. of indole); the slightly harsher conditions for the undirected C-H silylations may result from the absence of a DG to organise the system prior to the C-H bond-breaking step.

A. C-H/D exchange using gramine:

B. C-H/D exchange using indole:

C. Si-H/D exchange in silanes:

Scheme 3: A-B: Selected C-H/D exchange experiment using gramine and indole substrates and D-SiEt₃. The full complement of combinations is described in the SI. C: Si-H/D exchange between two silanes. ^aReaction conducted at rt. ^b RuH₂(CO)(PPh₃)₃ excluded.

Figure 2. Proposed mechanism for the C2-H silylation of gramine.

In summary, we have demonstrated the selective, Ru-catalysed C-H silylation of heteroarenes, which can proceed with or without directing group assistance and no protecting groups. We also report the first C4-H activation by an electron-rich metal centre. Work on the application of this methodology in more complex synthetic contexts and more detailed mechanistic studies are ongoing.

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