
Peer reviewed version

Link to published version (if available):
10.1039/C6CC00803H

Link to publication record in Explore Bristol Research

PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via RSC at http://pubs.rsc.org/en/Content/ArticleLanding/2016/CC/C6CC00803H#!divAbstract. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
http://www.bristol.ac.uk/pure/about/ebr-terms
This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
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)aryl silanes 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). RhIB, Ir8 and even BuOκ-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.

To probe the feasibility of this idea, we tested the reaction between 1a and H-SiMe3Ph 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,8u or under Rh-catalysed conditions described for the C-H silylation
of 2-arylpipyrirines. Ru(CO)$_2$ was also ineffective, but Ru(II) precursors able to undergo reductive activation 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 H-SiMe$_2$C$_6$H$_5$ or H-Si(OH)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$_3$.

Importantly, we discovered no requirement to protect exocyclic amine directing groups. Thus, 3 and C$_2$-silylated tryptamines 4 were delivered in good to excellent yield. A longer tether (product 5) and/or weaker $\sigma$-donating directing groups (products 6 and 7) gave lower yields and led to competitive silylation at the pyrrolic nitrogen, presumably via an intramolecular pathway; a reaction between unsubstituted indole and D-SiEt$_3$ in the presence of HNEt$_2$ also resulted in indole $\text{Si}$-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 (8d-c). Silylation at C$_2$ therefore proceeded most efficiently with unconjugated, strong $\sigma$-donor DGs, 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 C$_2$-H silylation, which is unprecedented in Ru catalysis. Indeed, undirected Ru-catalysed C-H functionalisation is altogether very rare. Whilst H-SiMe$_2$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).
To date, mechanistic work on C-H silylation has been rare. We obtained insights for our reaction from C-H/D exchange experiments. Reactions using C2-deuterogramine (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 rare 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 intermecan 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 indole (20h) was used instead of 1a, implicating the methanamine directing group in C4-H activation in 1a.

Catalytic indole C7-H activation is also rare. Commonly, the corresponding functionalisation is carried out on indolines prior to their oxidation. 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, 20h) 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 an unimpeded coordination to N1 and the availability of alkyl amine ligands for Ru. Finally, N-methylindole (20me) 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. 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- and Pd-catalysed 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. 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-free 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 C4-H silylations may result from the absence of a DG to organise the system prior to the C-H bond-breaking step.

Figure 2. Proposed mechanism for the C2-H silylation of gramine.
In summary, we have demonstrated the selective, Ru-catalysed C-H silylation of heteroaromatics, 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.

We thank the Swedish Research Council (Vetenskapsrådet) for funding and Dr Johanna Larsson for manuscript proof-reading.

Notes and references


Published on 01 April 2016. Downloaded by University of Bristol on 01/04/2016 13:22:00.