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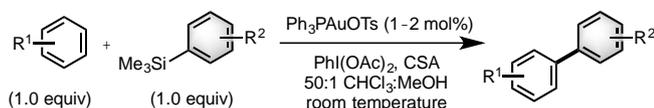
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Room Temperature Gold-Catalysed Arylation of Heteroarenes: Complementarity to Palladium Catalysis

Alexander J. Cresswell^[a] and Guy C. Lloyd-Jones^{*[a]}

Abstract: Tailoring of the pre-catalyst, the oxidant and the arylsilane enables the first room temperature, gold-catalysed, innate C–H arylation of heteroarenes. Regioselectivity is consistently high and, in some cases, distinct from that reported with palladium catalysis. Tolerance to halides and boronic esters, in both the heteroarene and silane partners, provides orthogonality to Suzuki-Miyaura coupling.

We recently reported a new route to biaryls *via* oxidative cross-coupling of moderately electron-rich arenes with aryltrimethylsilanes.^{1,2} This gold-catalysed reaction exploits the innate S_EAr -type reactivity of the arene partner, rather than a directing group, and proceeds under mild and convenient conditions (Scheme 1).



Scheme 1. Gold-catalysed C–H arylation.^{1,2} CSA = camphorsulfonic acid.

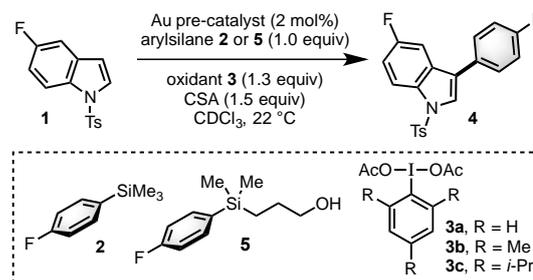
However, although many substituents are tolerated, including esters, aldehydes, alcohols, and (pseudo)halides, the only heteroarenes we were able to efficiently arylate under our original conditions were 2-bromothiophenes.^{1,2} By stabilising the Au(III)² catalyst with a strongly electron donating 2-pyridylidene ligand, Itami and Segawa *et al.* showed that arylation of other heteroarenes was feasible.³ However, the range was still limited (four isoxazoles, one indole, and one benzothiophene) the yields moderate (13–54%), and the reaction rather slow (5 mol% Au, 65 °C, 18–48h).³ Larrosa *et al.* have also reported a gold-catalysed *polyfluoroarylation* of π -rich heteroarenes *via* double C–H activation (5 mol% Au, 35 mol% Ag, 110 °C).⁴

The area of metal-catalysed, innate C–H arylation of heteroarenes^{5,6} remains dominated by palladium catalysis, with a frequent requirement for highly elevated temperatures (often >100 °C), an excess of one coupling partner, stoichiometric Ag or Cs additives, or inert conditions. In this respect, we were motivated to explore the potential of our gold-catalysed arylation methodology¹ to address these issues, and perhaps even enable C–H arylations which are not currently possible with palladium.

Initial investigations focused on the arylation of indole **1** with Ar-TMS **2** to give **4** (Figure 1). Using our originally-reported conditions,¹ arylated indole **4** was produced in only 16% yield, with the remainder of the indole **1** being consumed by competing (uncatalysed) oxidative decomposition. Using *tht*AuBr₃ as a

more rapidly-activating pre-catalyst² improved conversion (40% of **4**), but interaction of **1** with the *in situ* iodine(III) oxidant¹ remained a problem. However, by sterically-encumbering the oxidant (**3b-c**), the undesired oxidation was reduced, and **4** could be obtained in 87% yield over 2.5 hours using oxidant **3c**.⁷ Because the methanol co-solvent¹ is known to be a catalyst inhibitor,² we tested whether the arylation of **1** could be accelerated using methanol-free conditions. However, despite a faster initial rate, the generation of **4** ceased after approximately 35% conversion of **2**,⁸ with unreacted indole **1** then being slowly consumed in a non-productive oxidation (Figure 1, left-hand plot).

Having found that removal of the methanol causes reaction stalling, we tested whether a silyl-tethered alcohol could act as a methanol surrogate.⁸ Accordingly, replacing aryl-TMS **2** with arylsilane **5**, bearing a 3-hydroxypropyldimethylsilyl (HPDMS) group,⁹ resulted in much more efficient arylation (>90% conversion of **5** in under an hour, Figure 1 right-hand plot) allowing isolation of **4** in 87% yield. Notably, the addition of one equivalent of methanol to **2** is not an effective substitute for **5**: the generation of **4** ceases after 40% conversion of **2** (see SI).



entry	pre-catalyst	oxidant	ArSiR ₃	MeOH	time (h)	4
1	Ph ₃ PAuOTs	3a	2	2%	2.3 ^a	16%
2	<i>tht</i> AuBr ₃	3a	2	2%	1.5 ^a	40%
3	<i>tht</i> AuBr ₃	3b	2	2%	2.0 ^a	62%
4	<i>tht</i> AuBr ₃	3c	2	2%	2.7 ^a	87%
5	<i>tht</i> AuBr ₃	3c	2	none	0.3 ^b	29%
6	<i>tht</i> AuBr ₃	3c	5	none	1.0 ^b	87%

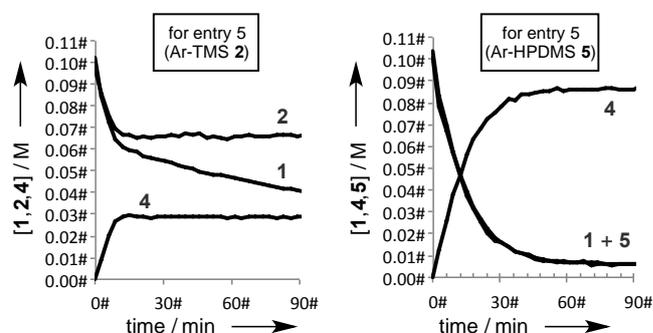
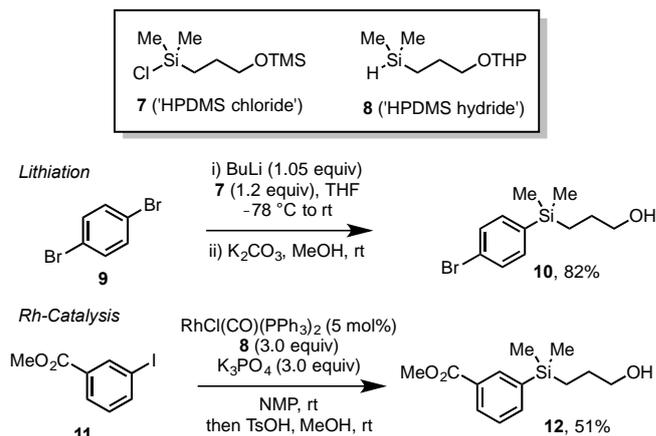


Figure 1. Identification of conditions for efficient C–H arylation of indole **1**. All yields are calculated by ¹⁹F NMR against an internal standard. ^aTime at which **1** is fully consumed. ^bTime at which arylation ceases. Ar = 4-fluorophenyl; CSA = camphorsulfonic acid; *tht* = tetrahydrothiophene; Ts = 4-toluenesulfonyl.

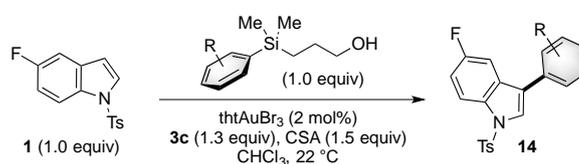
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Having established a rapid and efficient arylation process, concise routes for Ar-HPDMS synthesis were next designed. Reagents **7** and **8**, easily prepared *via* alkene hydrosilylation in one or two steps without chromatography (see SI), can be conveniently applied in one-pot processes (Scheme 2). For example, 'HPDMS chloride' **7** adds to the aryllithium derived from **9** to afford Ar-HPDMS **10** after O-desilylation, and adapting the trialkylsilylation procedure of Yamanoi and Nishihara,¹⁰ 'HPDMS hydride' **8** silylates iodoarene **11** to give Ar-HPDMS **12** after cleavage of the THP protecting group. Although the latter procedure suffers from competing reduction (protodeiodination)¹⁰ this method does tolerate functionality that would otherwise be incompatible with lithiation-silylation approaches (e.g. -CO₂Me). With convenient routes to Ar-HPDMS reagents in hand, their performance in heteroarene C-H arylations was evaluated next.



Scheme 2. Ar-HPDMS preparation. HPDMS = 3-hydroxypropyldimethylsilyl; NMP = *N*-methylpyrrolidinone; TMS = trimethylsilyl; THP = tetrahydropyranyl; Ts = 4-toluenesulfonyl.

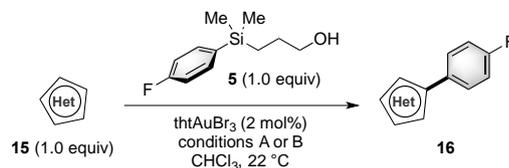


HPDMS arylsilane	Time	Product	Yield
	1.5 h		87%
	1 h		89%
	14 h		43% ^a
	0.5 h		69%
	2 h		85%
	2 h		80%
	1 h		73% ^b
	2 h		89%
	5 h		80%
	-		0%
	-		0%
	1.5 h		65%
	2 h		67%
	1.5 h		73%

Scheme 3. Isolated yields from arylation of indole **1** followed by ¹⁹F NMR at 22 °C. tht = tetrahydrothiophene; Piv = pivaloyl; Ts = 4-toluenesulfonyl. ^aStalled at 65% conversion of **13b**. ^bStalled at 75% conversion of **13f**

With respect to the arylsilane (Scheme 3), the process is compatible with a range of useful spectator functionalities, including carboxyl (**14f**), boryl (**14m**), silyl (TMS) (**14k,l**) and halogen (Br) groups (**14d**). Paralleling earlier work with Ar-TMS reagents (e.g. **2**) for C–H arylation,^{1,2,3} Ar-HPDMS **13b** bearing *ortho*-substitution led to slow and inefficient arylation (43% yield), whereas silanes **13i-j** bearing highly electron-withdrawing

substituents proved unreactive. The generality of the C–H arylation protocol with respect to the heteroarene partner is also good (Scheme 4), with regioselectivity essentially quantitative (>95%) in all but one case (i.e. **16r**, ≥80%). Again, the reaction tolerates a range of functionalities on this partner, including carboxyl (**16b-d,l-n**), boryl (**16k**), and halogen (Br, Cl) groups (**16a,d,f-i,l,o-q**).



Heteroarene	Conditions	Time	Product	Yield	Heteroarene	Conditions	Time	Product	Yield
	A	1 h		56%		A	1 h		53% ^b
	A	3 h		62%		B	10 h		45%
	A	1.5 h		60% ^a		B	9 h		72%
	A	5 h		64%		B	3 h		57% ^c
	A	0.5 h		85%		B	2 h		74%
	A	1.5 h		86%		B	2 h		76%
	A	2.5 h		82%		B	17 min		71%
	A	1.5 h		89%		A	10 min		46% ^d
	A	1.5 h		76%		A	1.7 h		78% ^e
	A	12 min		80%		A	33 h		67% ^e

Scheme 4. Isolated yields from room temperature arylation of **15a-t**, followed by ¹⁹F NMR at 22 °C. Conditions: A = **3c** (1.3 equiv) + CSA (1.5 equiv); B = Ph(OH)OTs (1.3 equiv). Ar = 4-fluorophenyl; pin = pinacolato; Ts = 4-toluenesulfonyl. ^aContaminated with 8% diarylated product. ^bStalled at 72% conversion of **15k**. ^c5.0 equiv of **15n**. ^d88:12 C(3):C(5). ^e4 mol% of thtAuBr₃

In most cases we employed the sterically-encumbered oxidant **3c** (conditions A) developed for the arylation of indole **1**, but for slower-reacting **15l-q**, commercially-available Koser's reagent [PhI(OH)OTs] proved superior (conditions B), leading to increased arylation rates.¹¹ Some heteroarenes (including isoaxazole, for which the Itami-Segawa catalyst³ is successful) proved unsuitable, either due to a lack of reactivity, or because they gave complex mixtures of products (see SI for full details)

It is particularly instructive to compare and contrast our new methodology with prior art in metal-catalysed, innate C–H arylation of heteroarenes. For example, indoles **4**, **15f-k** have not previously been used in C–H arylation, and the only other “low” temperature (<100 °C) methods for the β -arylation of indoles (as opposed to α -arylation)¹² include a Cu-catalysed protocol with diaryliodonium salts (35 °C)¹³ and an oxidative, Pd-catalysed process with arylboronic acids (80 °C).^{6c} The successful α -arylation of brominated pyrrole **15a** and furan **15l** are also significant, as there are no other published examples of C–H arylation of these or other ring-halogenated pyrroles/furans. The regioselective arylation of brominated thiophenes **15o-p**¹⁴ and benzo[*b*]thiophenes **15q**¹⁵ and **15r** under such mild conditions is also likely to find application in the preparation of functional organic materials.^{16,17}

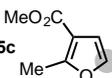
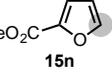
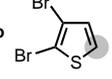
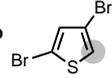
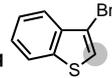
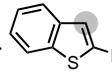
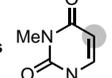
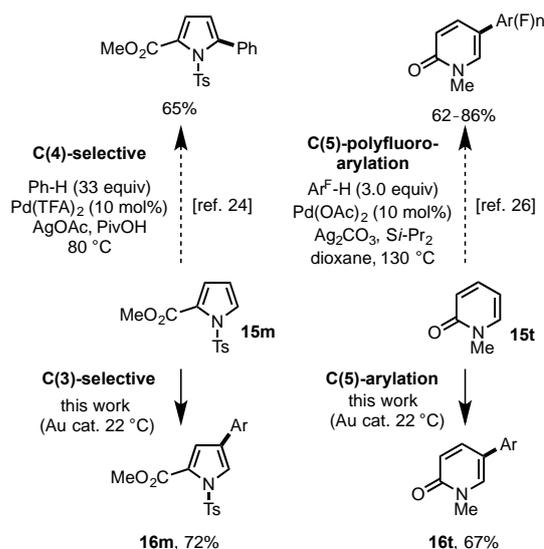
Heteroarene (and arylation site)	Examples & Yields	Ar-H:Ar-X Ratio	Pd Loading	Ag or Cs Additives	Temp	Inert?
	[>10 publications]	2 : 1	0.01-1 mol%	-	150 °C	argon
	13 examples (58–78% wrt Ar-X)	4 : 1	0.5-1 mol%	-	130 °C	argon
	5 examples (67–87% wrt Ar-X)	1.2 : 1	5 mol%	AgNO ₃	100 °C	argon
	1 example (65% wrt Ar-X)	1.2 : 1	5 mol%	AgNO ₃	100 °C	argon
	24 examples (8–88% wrt Ar-X)	1.5 : 1	0.5 mol%	-	80 °C	argon
	1 example (16%)	1 : 2	9.4 mol%	Cs ₂ CO ₃	150 °C	air
	6 examples (42–80% + 7–20% a-isomer)	1 : 2	5 mol%	Cs ₂ CO ₃	160 °C	argon

Table 1. State-of-the-art in Pd-catalysed C–H arylation of selected heteroarenes with aryl halides (see main text for references).

As a further illustration of practical advance, the state-of-the-art in Pd-catalysed C–H arylation of some of the heteroarenes employed in the current work are presented in Table 1 (i.e. for **15c**,¹⁸ **15n**,¹⁹ **15o,p**,¹⁴ **15q**,¹⁶ **15r**,²⁰ and **15s**.²¹)²² Although catalyst loadings in some cases are <1 mol%, all of the procedures require an excess of one coupling partner (typically

the heteroarene), elevated temperatures (80–160 °C), and, almost invariably, an inert atmosphere. By contrast, all of these heteroarenes can be arylated at ambient temperature, under air, in ≤ 3 hours under our gold-catalysed conditions, typically employing 2 mol% Au and 1:1 coupling partner stoichiometry. Complementarity to Pd catalysis is also apparent for the β -selective²³ arylation of pyrrole **15m**, which contrasts with the α -arylation of **15m** reported with Pd(TFA)₂ as the catalyst (Scheme 5, left).²⁴ Similarly, the β -arylation of pyridone **15t** is the first example of C–H arylation²⁵ at this position that does not require polyfluorinated arene partners (Scheme 5, right).²⁶



Scheme 5. Complementarity to Pd catalysis: β -arylations of pyrrole **15m** and pyridone **15t**. Ar = 4-fluorophenyl; Ar^F = perfluoroaryl; TFA = trifluoroacetate; Piv = pivaloyl; Ts = 4-toluenesulfonyl.

In summary, we have developed the first room temperature, gold-catalysed, innate C–H arylation of heteroarenes, proceeding with high chemo- and regioselectivity. The process is facilitated by use of a rapidly activating thtAuBr₃ pre-catalyst,² the exclusion of methanol as co-solvent, and the use of tailored oxidants and arylsilane partners.

Complementarity to Pd catalysis is apparent not only from the exceptionally mild and non-inert reaction conditions, but also the ability to effect certain arylations which are currently not possible with Pd catalysts. Moreover, as far as we are aware, this work provides the first examples of boryl spectator functionality (pinB) in *both* coupling partners in a metal-catalysed C–H arylation (i.e. **14m** and **16k**).²⁷ Together with halides **14d** and **16a,d,f-i,l,o-q**, these products highlight the orthogonality of gold-catalysed C–H arylation to Suzuki-Miyaura cross-coupling.

Experimental Section

Preparation of 14a. A 30 mL vial equipped with a stirrer bar was charged with **13a** (194 mg, 1.00 mmol, 1.0 equiv), **1** (289 mg, 1.00 mmol, 1.0 equiv), thtAuBr₃ (10.5 mg, 0.02 mol, 2 mol%), and CHCl₃ (10 mL). The mixture was stirred for ca. 1 min to fully dissolve the thtAuBr₃ pre-catalyst,

resulting in a deep red-orange solution. Taking no precautions to exclude air or moisture, **3c** (583 mg, 1.30 mmol, 1.3 equiv) and CSA (356 mg, 1.50 mmol, 1.5 equiv) were added simultaneously in a single portion, and the vial sealed with a screw cap. Over approximately 1 min, the solution changed to a clear pale-yellow solution, signifying pre-catalyst activation. After 1 h, ¹⁹F NMR indicated no further reaction and Celite (ca. 4 g) was added. The volatiles were allowed to evaporate to give a free-flowing powder. Purification via flash column chromatography (100 g SiO₂, 40 mm Ø, 60:40 hexane/toluene, ca. 14 mL fractions) gave **14a** as a clear, colorless gum (332 mg, 89%).

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Keywords: gold catalysis • C–H functionalisation • arylation • heteroarenes • silicon

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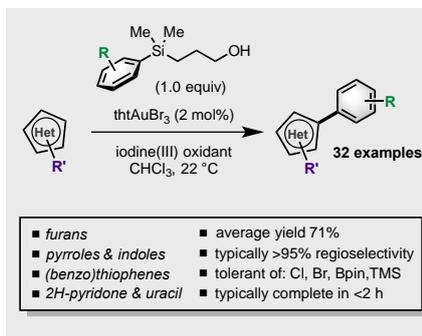
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Gold-catalysed, room temperature, C–H arylation of heteroarenes provides a mild and practical synthetic protocol compatible with a range of functional groups, including boronic esters and halides



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Room Temperature Gold-Catalysed
Arylation of Heteroarenes:
Complementarity to Palladium
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