Letter

Au-Catalyzed Oxidative Arylation: Chelation-Induced Turnover of ortho-Substituted Arylsilanes

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.8b02302 • Publication Date (Web): 17 Jul 2018

Au-Catalyzed Oxidative Arylation: Chelation-Induced Turnover of *ortho*-Substituted Arylsilanes

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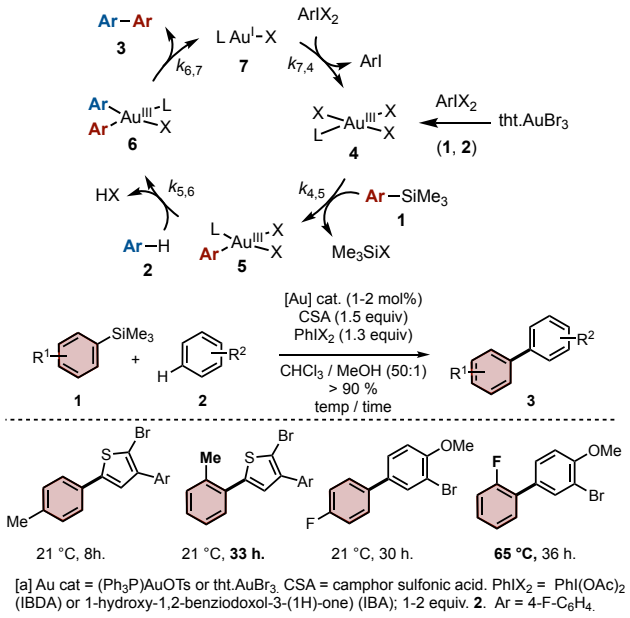
KEYWORDS Gold-catalysis, Mechanism, C–H Arylation, Rate-attenuation Analysis, Ortho-substituents

ABSTRACT: *Ortho*-substituted aryl silanes have previously been found to undergo much slower Au-catalyzed intermolecular arylation than their *m*,*p*-substituted isomers, with many examples failing to undergo turnover at all. A method to indirectly quantify the rates of C–Si auration of *o*-substituted aryl silanes, under conditions of turnover, has been developed. All examples are found to undergo very efficient C–Si auration, indicative that it is the subsequent C–H auration that is inhibited by the ortho substituent. A simple Ar-Au conformational model suggests that C–H auration can be accelerated by chelation. A series of ortho-functionalized aryl silanes are shown to undergo efficient arylation.

Introduction

Organosilanes are an attractive class of reagent for transition metal catalyzed couplings,[1] with benefits of high stability, ease of preparation, and low toxicity.[1g] The gold-catalyzed[2] direct arylation[3] of aryltrimethylsilanes (**1**) with π-rich arenes (**2**) to afford biaryls (**3**) was first reported 2012.[4] The reaction can be conducted under air, using laboratory grade solvent ($CHCl_3$/MeOH), often at ambient temperature, and around 160 examples have been published to date.[4-8] Mechanistic studies[5-7] indicate that turnover proceeds via sequential electrophilic aromatic aurations (S_EAr) of the silane ($k_{4,5}$), then the arene ($k_{5,6}$), followed by reductive elimination ($k_{6,7}$) and Au(I)/I(III) redox ($k_{7,4}$) Scheme 1. For the vast majority of cases, the turnover-rate limiting event is intermolecular C-H arylation ($k_{5,6}$), proceeding with a first-order kinetic dependence on **2** and a negative entropy of activation.[5]

Whilst the substrate scope for the coupling has proven to be reasonably broad,[4-8] ortho-substituted arylsilanes (*o*-**1**) undergo slow intermolecular coupling, requiring prolonged reaction times or elevated temperatures, Scheme 1.[4,5,8b] Indeed, a number of examples of hindered ortho-substituted arylsilanes fail to couple at all. In contrast, substituted arenes (**2**) can be efficiently coupled, even though these must also generate a sterically-hindered diaryl-gold intermediate, **6**. The slow rates of arylation of *o*-**1** also contrast other S_EAr processes, e.g. protodesilylation,[9] and mercuridesilylation,[10] where ortho-substituted arylsilanes react significantly faster than predicted based on the inductive effect of the substituents alone. Herein we analyze the reactivity of *o*-**1** in Au-catalyzed arylation and show that efficient coupling can be induced by *o*-functionalization.



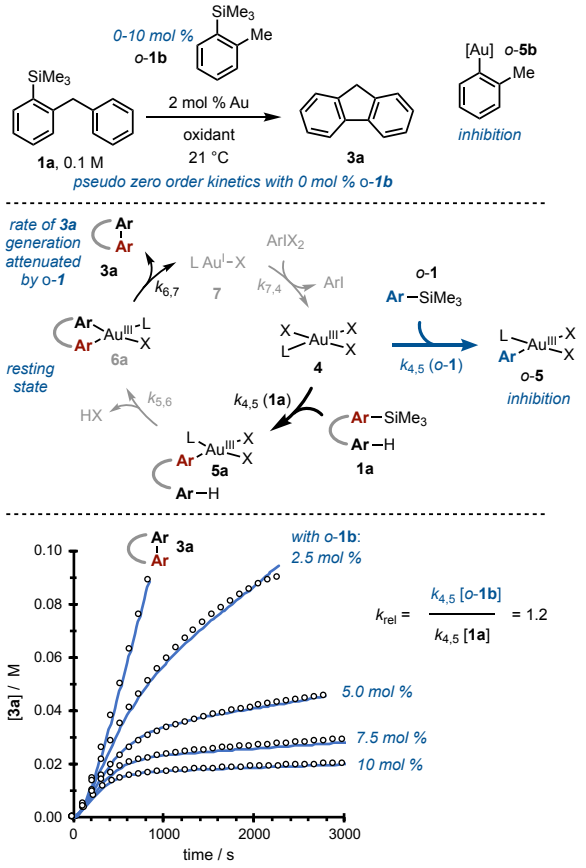
[a] Au cat = $(Ph_3P)AuOTs$ or $tht.AuBr_3$. CSA = camphor sulfonic acid. $PhIX_2$ = $PhI(OAc)_2$ (IBDA) or 1-hydroxy-1,2-benziodoxol-3-(1H)-one) (IBA); 1-2 equiv. **2**. Ar = 4-F-C_6H_4.

Scheme 1. General catalytic cycle for Au-catalyzed arylation, and comparison of conditions for arylation of *ortho*- versus *para*-$ArSiMe_3$ (*o*/*p*-**1**).[a]

Discussion

We began by testing how steric hindrance affects the C–Si auration ($k_{4,5}$) of the arylsilane, comparing the relative rates of a small series of *o*-alkyl arylsilanes (*o*-**1a-j**) under catalytic conditions. Conventional competition experiments determine relative rates (k_{rel}) for a pair of substrates by monitoring their ratio as a function of their conversion to product. However, this cannot be

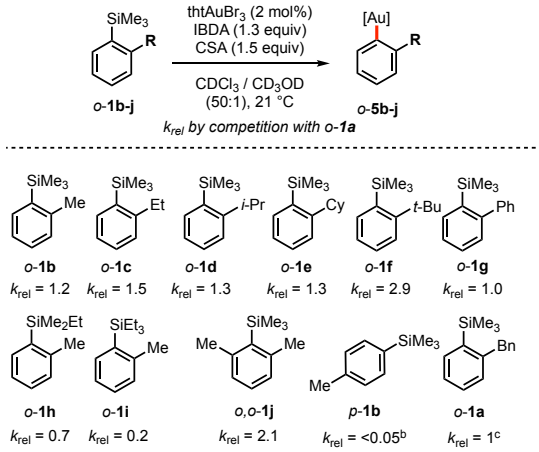
employed with the many examples of *o*-**1** that do not undergo turnover to product. We therefore developed an alternative approach that solely analyzes the effect of *o*-**1** on the kinetics of another substrate that *does* undergo turnover. The intramolecular coupling of **1a** to form fluorene (**3a**, Figure 1) proved ideal.



[a] conditions: CSA 0.15 M, $PhI(OAc)_2$ 0.13 M, $CDCl_3$ / CD_3OD (50 / 1), 21 °C. Evolution of **3a** analyzed in situ by ^1H NMR (CH_2).

Figure 1. Rate-attenuation analysis to determine k_{rel}.[a]

In the absence of competitor (*o*-**1**), the cyclization of **1a** to **3a** proceeds to completion, with clean pseudo-zero order kinetics, in about 15 minutes (2 mol% cat., 21 °C). Any factor that causes a decrease in the active catalyst concentration over the course of the reaction leads to curvature in the temporal concentration profile.[11] The rate of generation of **3a** is thus attenuated by competing C–Si auration ($k_{4,5}$) of *o*-**1**. The rate-attenuation depends on the reactivity of *o*-**1** ($k_{4,5}$) and the concentration of *o*-**1**, relative to **1a**. An example analysis for *o*-**1b** is shown in Figure 1. The onset of rate-attenuation for generation of **3a** becomes increasingly evident as the inhibitor concentration is raised (0, 2.5, 5, 7.5, 10 mol %). Kinetic simulation of the evolution of **3a**, with inclusion of pre-catalyst activation and turnover, see SI, allows extraction of the relative rates of C–Si auration ($k_{4,5}$) for the series *o*-**1b-j**, Scheme 2. It is notable that all of the examples in the series, including sterically hindered *o*-*t*Bu **1f** and 2,6-Me_2 **1j**, undergo more rapid C–Si auration ($k_{4,5}$) than unhindered *para*-**1b**.



[a] Determined by simulation of rate-attenuation for turnover of **1a** to **3a**, see Figure 1. Temporal concentrations analyzed in situ by ^1H NMR. [b] measured by competition with *o*-**1b**, see reference 5 [c] by definition, k_{rel} = 1.

Scheme 2. Relative rates of C–Si auration ($k_{4,5}$) for *o*-**1b-j**.[a]

The acceleration of aryl silane protodesilylation,[9] and mercuridesilylation,[10] by ortho-methyl substituents arises from alleviation of ground-state steric strain on approach to a pseudo-tetrahedral Wheland intermediate.[9,10,12] An analogous effect in C–Si auration ($k_{4,5}$), Figure 2A, may explain why *o*-**1b** reacts more than twenty-fold faster than *p*-**1b** (Scheme 2). The similar rates of C–Si auration of the ortho-benzyl, -methyl, -ethyl, -isopropyl, and -cyclohexyl substrates (*o*-**1a-e**) will arise from a combination of effects, including access to Ar-CHR_2 conformations that minimize steric compression with the silane (such a conformation is absent in the fastest reacting substrate *o*-**1f**), steric interaction with the incoming Au-electrophile, Figure 2B, and steric shielding of the charge-polarized Wheland intermediate from solvation. Analogous steric interactions attenuate the rate of protodesilylation of $ArSiR_3$ species with larger Si-substituents.[13] The $EtMe_2Si$ and Et_3Si substrates *o*-**1h,i** behave accordingly, Figure 2C.

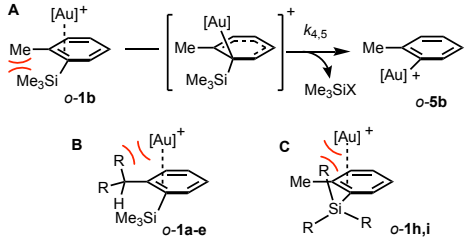


Figure 2. A. steric decompression during electrophilic auration ($k_{4,5}$) of *o*-**1b**. B. Similar reactivities of ortho methyl, ethyl, isopropyl and cyclohexyl substrates *o*-**1b-e**. C. Reduction in reactivity of $ArSiMe_2Et$ and $ArSiEt_3$ *o*-**1hi**.

Since the rate attenuation analysis (Scheme 2) shows that *all* of the *o*-arylsilanes undergo efficient C–Si auration ($k_{4,5}$), the inhibiting effect[14] of the *ortho*-substituent on the overall coupling (**1** →**6**) is therefore not manifest until the subsequent step: the C–H auration of *o*-**5** ($k_{5,6}$). In our

previous mechanistic studies on the cyclization of **1a** we found that, unusually, the turnover-rate limiting event is reductive elimination from the corresponding biaryl intermediate **6a**, leading to pseudo zero-order kinetics (Figure 1).[6] Consideration of the conformational equilibrium around the Ar-Au bond in the mono-aryl *precursor* **5a** suggests that a perpendicular arrangement of the benzyl group to the square-plane of ligands at gold (**5a**$_{per}$) will be favored, on steric grounds, over a coplanar arrangement (**5a**$_{co}$), Figure 3.

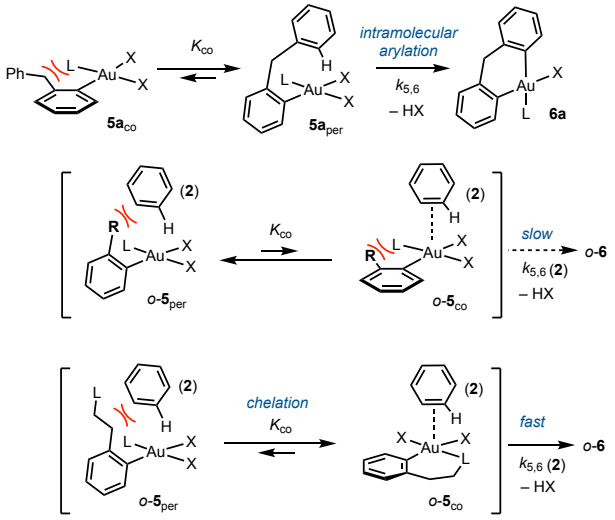
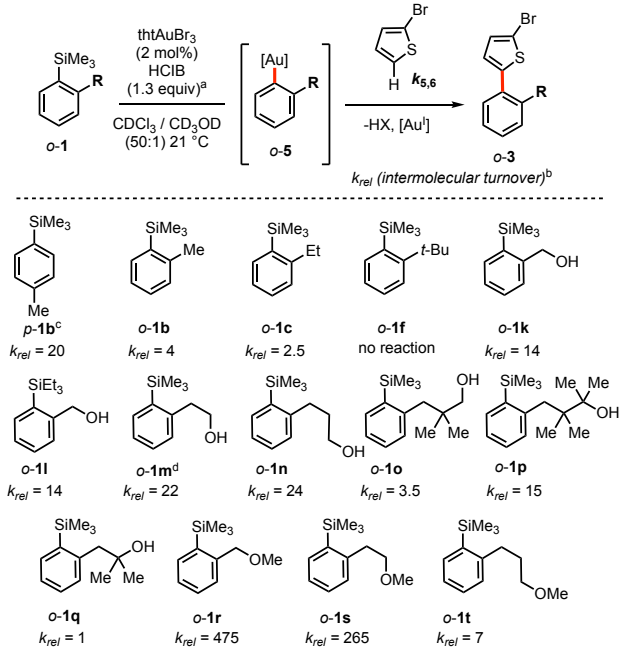


Figure 3. Conformations of Ar-Au intermediates (*o*-**5**$_{co}$ / *o*-**5**$_{per}$) leading to arylation ($k_{5,6}$) and the impact of chelation.

Arrangement **5a**$_{per}$ allows the benzyl group to undergo associative π-complexation then C-H auration ($k_{5,6}$) to access the resting state (**6a**). In contrast to **5a**, intermediates of the type **5b-f,h-j**[14] must undergo turnover-rate limiting *intermolecular* associative π-complexation to effect arylation ($k_{5,6}$).[5,6] Conformer *o*-**5**$_{per}$ will be significantly less accessible[15] to the incoming arene (**2**) than *o*-**5**$_{co}$. Thus, the more sterically imposing the *ortho*-substituent, the further the equilibrium (K_{co}) will biased toward *o*-**5**$_{per}$ and the greater the suppression of the rate of turnover. We have previously shown that the electronic influence of *m*- and *p*-arylsilane substituents on the rate of turnover is negligible (ρ = –0.2).[5] The conformational equilibrium (K_{co}), and steric shielding effect (*o*-**5**$_{per}$) thus provides a simple explanation for the five-fold faster turnover of *p*-**1b** by 2-bromothiophene compared to *o*-**1b**, Scheme 3. The rate is further suppressed by Et (*o*-**1c**), with complete inhibition of turnover by *t*Bu (*o*-**1f**), despite the latter undergoing the fastest C-Si auration (Scheme 2).

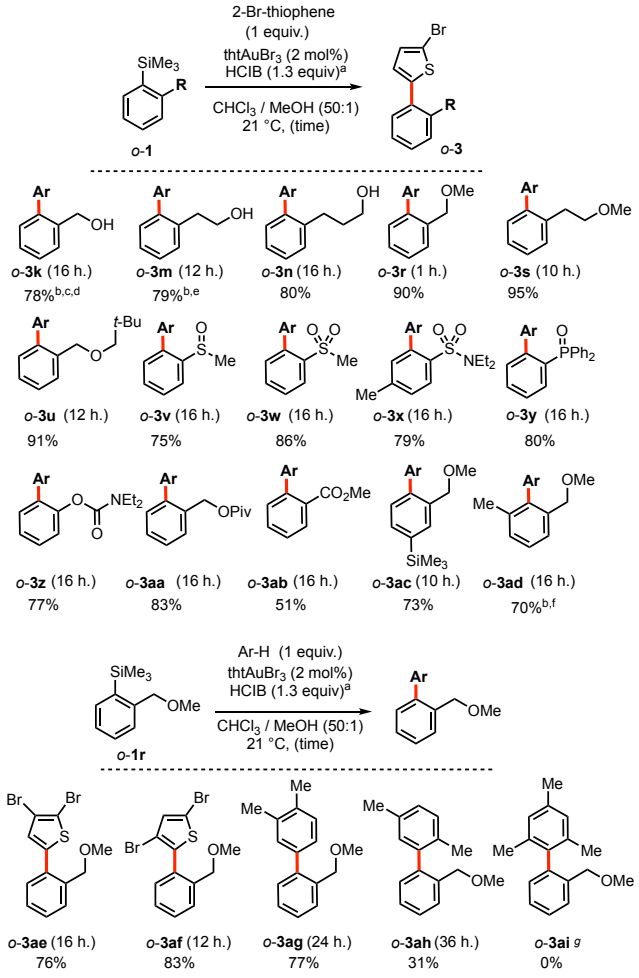
The *o*-Au-Ar conformational model[15] suggests that the rate of arylation ($k_{5,6}$), and thus net rate of turnover,[5,6] can be accelerated by using chelation to bias the equilibrium toward the reactive species, **5**$_{co}$. Introduction of *ortho*-*n*-alkylhydroxy groups (*o*-**1k-n**) resulted in an increase in turnover rate for intermolecular coupling, reacting smoothly at ambient temperature at a similar rate to *p*-**1b**, Scheme 3.



[a] [hydroxy(camphorsulfonyloxy)iodo]benzene. [b] k_{rel} estimated from initial rates: $d[\mathbf{3}]/dt = k_{5,6}[\text{Au}]_0[\text{Ar-H}]_0$. [c] data from reference 5; [d] stalled at 50 % conversion.

Scheme 3. Relative rates of intermolecular arylation ($k_{5,6}$) of *o*-**5** by 2-bromothiophene.

Unsurprisingly, the nature of the tether, e.g. coordinating ability, chelate ring size, and substitution pattern (steric effects), strongly impacts the rate of turnover. Detailed analysis is complex as the overall effect will arise though changes in chelate equilibrium (K_{co}) and the efficiency of coordination of the incoming arene ($k_{5,6}$). For example, addition of methyl substituents (*o*-**1o-q**) does not reduce turnover as much as might be anticipated, possibly due to a *gem*-disubstituent[16] effect biasing K_{co}. In contrast, the *o*-alkoxymethyl series (*o*-**1r-t**) induce a significant increase in turnover rate, with *o*-**1r** undergoing coupling >20-fold faster than *p*-**1b**. The marked difference in turnover rate between pairs of alcohols *o*-**1k**,**n** and ethers *o*-**1r**,**s** suggests that shorter tether neutral two-electron (L-type) ligation, rather than X-type, provides the greater overall activating effect (K_{co} and $k_{5,6}$). The rates for the trimethylsilyl (*o*-**1k**) and triethylsilyl (*o*-**1l**) substrates were identical, despite *o*-**1k** undergoing addition ($k_{4,5}$) to Au approximately 5-fold faster than *o*-**1l**, Scheme 2. This result is consistent with turnover-rate limiting intermolecular arylation ($k_{5,6}$), i.e. both substrates converge on the same aryl-Au intermediate (**5k** = **5l**). A selection of the more-efficient substrates from Scheme 3 (*o*-**1k**; *o*-**1mn**; *o*-**1rs**) plus a small range of other functional groups[17] were then explored for preparative arylation; isolated yields of the coupling products (*o*-**3a-ai**; 1 mmol scale) are shown in Scheme 4.



[a] [hydroxy(camphorsulfonyloxy)iodo]benzene [b] 2 equiv 2-bromothiophene; [c] With 1 equiv 2-bromothiophene 60% yield; [d] Triethylsilyl analogue *o*-**1l** gave 67% yield; [e] With 1 equiv 2-bromothiophene 54% yield; [f] Purity estimated to be 90% by ^{1}H NMR. [g] no products detected, other than initial bromodesilylation of *o*-**1r**, after 40 h.

Scheme 4. Preparative arylation of *o*-aryl silanes.

The majority of the potentially-coordinating *ortho*-substituents tested,[17] including ethers (*o*-**1u**), esters (*o*-**1aa**, *o*-**1ab**), a carbamate (*o*-**1z**), various sulfur-containing functional groups (*o*-**1v-x**), and a phosphine oxide, (*o*-**1y**) induced efficient intermolecular coupling, at ambient temperature. A small number of *ortho*-substituents that were tested underwent competing solvolysis, protodesilylation, or oxidation under the arylation conditions; see the SI for details. Hindered arenes underwent slow (*o*-**3ah**) or no reaction (*o*-**3ai**). When two silyl groups are present in the substrate (*o*-**1ac**), coupling is selective for the more-reactive *ortho*-silyl group, yielding *o*-**3ac**; the *meta*-arylated isomer could not be detected.[18]

Conclusions

In prior studies, *ortho*-substituted arylsilanes have been found to undergo slow intermolecular arylation under oxidative gold catalysis, usually requiring high temperatures and prolonged reactions times,[4-8] with some substrates failing to turn-over at all. Herein, we employed rate-attenuation analysis,[11] Figure 1, to confirm that the C-Si auration step ($k_{4,5}$) is significantly accelerated by substitution at the *ortho*-position, even with sterically-demanding substituents, Scheme 2. The effect is analogous to other S_EAr reactions of *ortho*-arylsilanes, where there is alleviation of steric strain upon formation of the Wheland intermediate.[9,10,12,13]

The marked reduction, or complete inhibition, of turnover by simple *ortho* substituents (e.g. *o*-**1f**, Scheme 3) arises from the impact of the substituent on the subsequent C-H auration step ($k_{5,6}$). A model involving two conformations of the aryl-Au intermediate **5**, with steric shielding[15] arising in the dominant conformer **5**$_{\omega}$, Figure 3, accounts for the inhibiting effect of *o*-alkyl substituents.[14] Based on the model, *ortho*-chelation should increase the population of the reactive co-planar conformer **5**$_{\omega}$. A diverse range of synthetically-useful functional groups allow the arylated products to be obtained in good yield (Scheme 4). Of the carefully selected range[17] of functional groups tested, short-chained methyl ethers, e.g. *o*-**1r-u**, induced the fastest rates of arylation.

The above observations regarding the importance of Ar-Au conformation in the Au-catalyzed oxidative arylation of aryl silanes (Scheme 1), and the ability to bias this by chelation (Scheme 3) can be applied in the analysis and development of the wide range of other catalyzed reactions involving aryl-gold intermediates.[2,19]

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Funding Sources

The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013) / ERC grant agreement n° [340163].

ASSOCIATED CONTENT

Supporting Information. Additional discussion, experimental procedures, kinetic data and simulations, substrate and product characterization data and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

We thank AstraZeneca and CatSci for support.

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(17) A number of the more orthodox 'directing' groups, such as amines, imines, thiols, etc. were not tested due to know incompatibility with the oxidative acidic and solvolytic reaction conditions ($ArIX_2$; CSA; MeOH).

(18) Complete regioselectivty for *ortho*-substituted arylsilanes has also been noted in other electrophilic desilylations: a) Bennetau, B.; Krempp, M.; Dunogues, J.; Ratton, S. Une Voie Originale et Selective de Fonctionnalisation en Position Ortho du Fluoro- ou de L'Ethylbenzene.*Tetrahedron Lett*. 1990, 31, 6179–6182; b) Bennetau, B.; Krempp, M.; Dunoguès, J.; Ratton, S. Une Voie Originale et Selective de Fonctionnalisation en Position Meta du Fluoro- et de L'Ethylbenzene. *Tetrahedron* 1990, 46, 8131.

(19) Whilst it is not clear whether an Ar-Au intermediate is involved in the gold-catalyzed oxyarylation of terminal alkenes by arylsilanes, it is of note that *o*-1m reacts more efficiently than *o*-1b, see: a) Ball, L. T.; Green, M; Lloyd-Jones, G. C.; Russell, C. A. Arylsilanes: Application to Gold-Catalyzed Oxyarylation of Alkenes. *Org. Lett* 2010, 12, 4724–4727; b) Brenzovich, Jr. W. E.; Brazeau, J.-F.; Toste, F. D. Gold-Catalyzed Oxidative Coupling Reactions with Aryltrimethylsilanes. *Org. Lett* 2010, 12, 4728.

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