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Gold-Catalyzed Oxidative Coupling of Arylsilanes and Arenes: Origin of Selectivity and Improved Precatalyst

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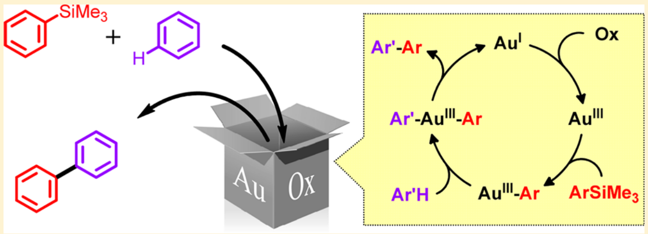
S *Supporting Information*

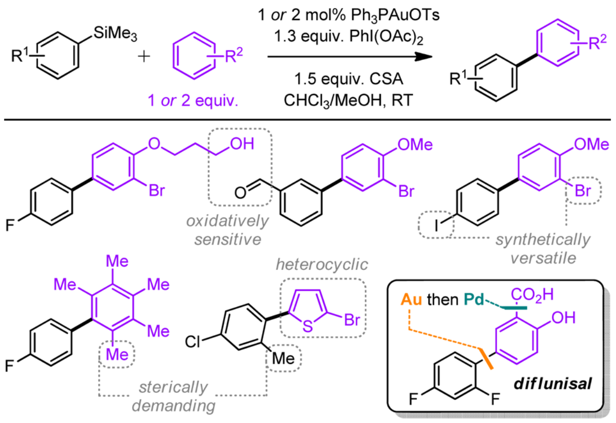


ABSTRACT: The mechanism of gold-catalyzed coupling of arenes with aryltrimethylsilanes has been investigated, employing an improved precatalyst (thtAuBr$_3$) to facilitate kinetic analysis. In combination with linear free-energy relationships, kinetic isotope effects, and stoichiometric experiments, the data support a mechanism involving an Au(I)/Au(III) redox cycle in which sequential electrophilic aromatic substitution of the arylsilane and the arene by Au(III) precedes product-forming reductive elimination and subsequent cycle-closing reoxidation of the metal. Despite the fundamental mechanistic similarities between the two auration events, high selectivity is observed for heterocoupling (C−Si then C−H auration) over homocoupling of either the arylsilane or the arene (C−Si then C−Si, or C−H then C−H auration); this chemoselectivity originates from differences in the product-determining elementary steps of each electrophilic substitution. The turnover-limiting step of the reaction involves associative substitution en route to an arene π-complex. The ramifications of this insight for implementation of the methodology are discussed.

■ INTRODUCTION

Advances in synthetic methodology benefit from mechanistic insight. In cross-coupling this has allowed rational design of both catalyst[1] and reagent;[2] in direct arylation,[3] a potential alternative to classical cross-coupling, experimental and computational investigations have illuminated the main modes of reactivity,[4] in particular the C−H activation step. We recently reported the gold-catalyzed arylation of arenes by aryltrimethylsilanes (Scheme 1).[5] The reaction exhibits high regio- and chemoselectivity, without reliance on ortho-directing groups, and proceeds under mild and convenient conditions (low loading of a relatively benign metal catalyst,[6] room temperature, aerobic atmosphere, reagent-grade solvents, and near-equal stoichiometries of coupling partners/oxidant). The oxidative nature of the reaction and the passivity of the arylsilane coupling partner tolerate a broad range of functionality, including not only esters, aldehydes, and primary alcohols but also arylhalides and triflates, rendering the methodology orthogonal to traditional cross-coupling.

Scheme 1. Representative Scope of Au-Catalyzed Arene−Arylsilane Oxidative Coupling[5]



Since Periana's seminal report in 2004,[7] the field of oxidative gold catalysis has expanded to encompass a diverse spectrum of C−C and C−X bond-forming reactions.[8] However, for such processes, there is generally little evidence regarding the oxidation states of the metal that are accessed,[9] and only an empirical appreciation of the factors affecting reaction rates. Thus, it is widely appreciated[8b,c] that further developments will benefit from a deeper understanding of the elementary reactivity involved.[10] For the process outlined in Scheme 1, both the relative reactivity of the arene and the regioselectivity of its arylation are consistent with the established rules of electrophilic aromatic substitution (S$_E$Ar).[5] Similar observations have been made in stoichiometric auration of simple arenes by Au(III),[11] and in their Au-catalyzed oxidative functionalization.[12] In contrast, the interaction of Au(I) cations with arenes results in either labile complexes[13] or benzylic C−H activation.[14] Given this precedent, and the well-documented ipso S$_E$Ar reactivity of aryltrimethylsilanes, we envisaged that *net* C−H and C−Si auration[15] by an electrophilic Au(III)

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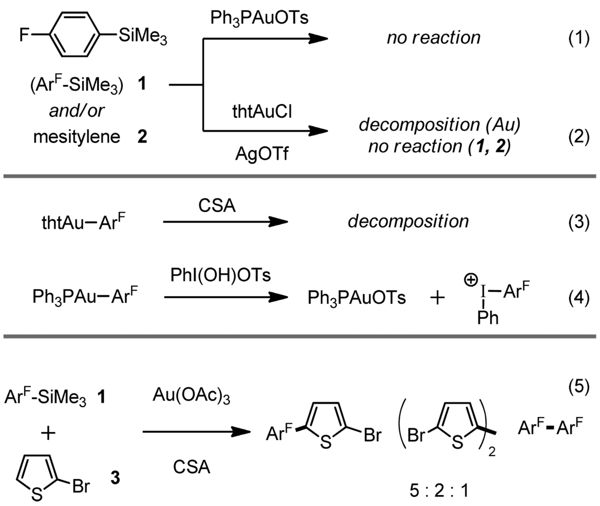
species may constitute key elementary steps in the cycle.[16] Herein, we report a mechanistic investigation into Au-catalyzed arylation, with the aim of elucidating the origin of the chemoselectivity that results in heterocoupling of the arylsilane with the arene, rather than homocoupling of either species.

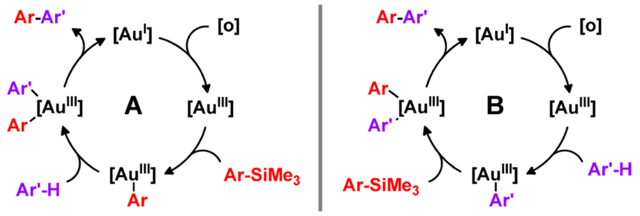
RESULTS AND DISCUSSION

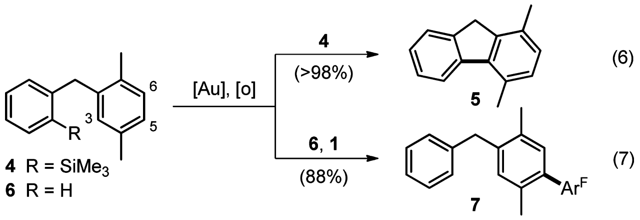
Preliminary Studies. Our initial mechanistic hypotheses were based on prior observations[5] and were reinforced by preliminary stoichiometric studies. Treatment of (4-fluorophenyl)trimethylsilane (Ar^FSiMe_3, **1**) and/or mesitylene (**2**), with $Ph_3PAuOTs$ resulted in no change in either the Au(I) complex or the aromatic substrates ($^{31}P\{^1H\}$, ^1H, ^{19}F NMR) (eq 1).[17] Attempts to generate a more-electrophilic, phosphine-free Au(I) species *in situ* by addition of AgOTf to thtAuCl (tht = tetrahydrothiophene) resulted in deposition of metallic gold and no reaction of either **1** or **2** (eq 2).[14]As the lack of reactivity of Au(I) toward **1** and **2** (eqs 1 and 2) does not preclude intermediacy of aryl–Au(I) species, their involvement was tested under catalytically relevant conditions (eqs 3 and 4). $thtAuC_6H_4F$ decomposed in the presence of acid,[18] as did $thtAuC_6F_5$,[19] while $Ph_3PAuC_6H_4F$ reacted with excess PhI(OH)OTs to give $Ph_3PAuOTs$ and the corresponding diaryliodonium salt.[20] Finally, stoichiometric reaction of **1** and 2-bromothiophene **3** in the presence $Au(OAc)_3$ and camphorsulfonic acid (CSA) afforded both hetero- and homocoupling products (eq 5). Together, these observations disfavor a catalytic cycle involving auration by Au(I), and/or the involvement of discrete aryl–Au(I) intermediates, and demonstrate the feasibility of aryl–aryl bond formation mediated by Au(III). The operation of a Au(I)/Au(II)-dimer redox cycle, as proposed for olefin heteroarylation,[10a] was discounted following isolation of reactive intermediates (*vide infra*).



We were thus able to outline a catalytic cycle in which oxidation of Au(I) by iodine(III) generates a reactive Au(III) species capable of aurating both the arylsilane C–Si bond and the arene C–H bond. Subsequent, product-forming reductive elimination from the diaryl Au(III) intermediate closes the catalytic cycle. However, this initial hypothesis (Scheme 2) raises the question of whether C–Si auration precedes C–H auration, or *vice versa* (cycle A vs cycle B). Discrimination between these two scenarios was achieved by subjecting tethered substrate **4** to the standard coupling conditions,[5] which afforded fluorene-derivative **5** as the sole product (eq 6). Operation of cycle B with *irreversible* C–H auration would require reaction to occur with exceptional selectivity for C-3, despite the fact that C-5 is similarly electronically activated and more sterically accessible. Indeed, arylation of des-silyl analogue **6** afforded **7** as a single regioisomer (eq 7). Alternatively, C–H auration may be reversible, with rapid protodeauration of a monoarylgold species allowing formal migration of the metal: once C-3 is reached, C–Si auration and reductive elimination would afford **5**. Conducting cyclization of **4** with CD_3OD as cosolvent, however, resulted in no isotopic enrichment of either **5** or residual **4** (at ~90% conversion). In contrast, initial C–Si auration renders a single aromatic C–H bond (C-3) accessible in a subsequent intramolecular C–H auration, consistent with the quantitative formation of **5**. These observations point to C–Si auration preceding C–H auration in **4**, as illustrated in cycle A.

Scheme 2. Dichotomous Au-Catalyzed Arylation Cycles





After screening a wide range of fluorinated reactants[19] as candidates for *in situ* ^{19}F NMR kinetic studies, we selected a combination of fluorophenylsilane **1** and thiophene **8** with a fluorinated oxidant (F-IBDA, 4-fluoroiodobenzene diacetate). Although arylation proceeds cleanly to form **9** as a single regioisomer within an appropriate time frame, an induction period of ~45 min (Figure 1, left) complicated analysis. The origin of this induction period was investigated, *vide infra*, to

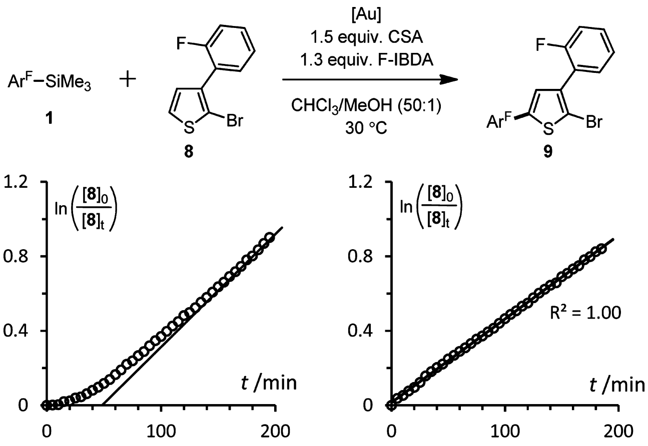


Figure 1. Representative first-order log-plots with $Ph_3PAuOTs$ (left) and $thtAuBr_3$ (right) as precatalyst.

allow its circumvention and ultimately facilitate a more thorough treatment of reaction kinetics (Figure 1, right).

Induction Period. *Origin of the Induction Period.* Sulfonic acids react with iodobenzene(dicarboxylates) to generate the more reactive [hydroxy(sulfonyloxy)iodo]benzene oxidants.[21] However, reaction of F-IBDA with CSA to generate hydroxy(camphorsulfonyloxy)iodo]fluorobenzene (F-HCIB), or a similar species,[19] is complete upon mixing (^{19}F NMR). Furthermore, an identical induction period is observed when arylation is conducted with preformed F-HCIB, suggesting that formation of an active catalyst from $Ph_3PAuOTs$ is instead responsible for the induction period.[22] Under catalytically relevant conditions, but in the absence of **1** or **8**, treatment of $Ph_3PAuOTs$ with F-IBDA/CSA led to consumption of 2 equiv of oxidant over ~120 min (Figure 2, left).

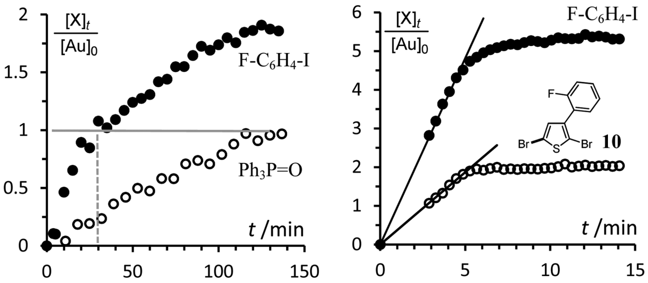
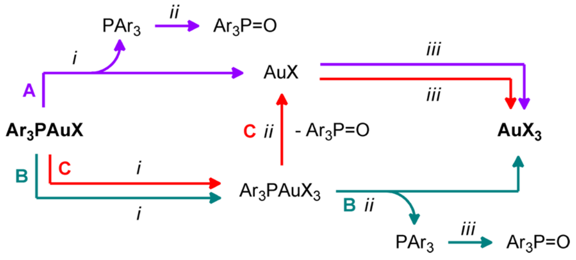


Figure 2. Reaction of $Ph_3PAuOTs$ (left), and $thtAuBr_3$/**8** (right), with F-IBDA/CSA at 30 °C in $CDCl_3/CD_3OD$. 4-Fluoroiodobenzene was monitored as a proxy for oxidant consumption.

Monitoring the process by $^{31}P\{^1H\}$ NMR revealed quantitative formation of Ph_3PO.[23] The induction period is thus associated with the net two-electron oxidation of both the metal *and* the ligand. Pathways for liberation of a phosphine-free catalyst from $Ph_3PAuOTs$ (Scheme 3) include: dissociation of PPh_3 from Au(I) prior to independent oxidation of each component (path A), oxidation of phosphine-ligated Au(I) to Au(III), followed by either dissociation and oxidation of PPh_3 (B), or reductive elimination of phosphorus(V)[24] and reoxidation of Au(I) (C). Rapid initial consumption of one equivalent of oxidant (relative to [Au]) is accompanied by formation of only ~0.2 equiv of Ph_3PO (Figure 2, left). Slower, subsequent consumption of the second equivalent of oxidant occurs at a rate that parallels formation of Ph_3PO. It follows that the initial burst of oxidant consumption corresponds to oxidation of Au(I) which, taken with the observation that free PPh_3 is oxidized very rapidly under the reaction conditions,[19] suggests that path A is not a major contributor to catalyst activation.

Scheme 3. Liberation of a Phosphine-Free Catalyst



For a series of precatalysts, $(p\text{-}RC_6H_4)_3PAuOTs$, the duration of the induction period increases as R = Me < H < CF_3. As more strongly donating ligands facilitate metal oxidation[25] and retard ligand dissociation, the observed trend disfavors path A. In contrast, if B_i and C_i are fast, the induction period associated with paths B and C will depend differently on ligand basicity: while phosphine dissociation (B_{ii}) is expected to be slower for R = Me than for R = CF_3, reductive elimination of a phosphonium salt (C_{ii}) is expected to be accelerated by a more nucleophilic phosphine.[26] Path C is thus most consistent with the observed dependence of the induction period on R.

Changing from tri(*p*-tolyl)phosphine to tri(*o*-tolyl)phosphine resulted in lengthening of the induction period to ~3 h, consistent with the more sterically demanding phosphine[27] disfavoring the geometry change (linear to square-planar) that accompanies oxidation of the Au(I) center (steps B_i and C_i).[25] With this insight it is now possible to rationalize the ligand-dependence observed during initial reaction development:[5] $(p\text{-}RC_6H_4)_3PAuOTs$ precatalysts gave uniformly high yields and selectivities, suggesting that the same active catalyst is formed, independent of ligand. With bulkier ligands, including NHCs,[19] very slow release of the active catalyst results in greatly diminished yields.

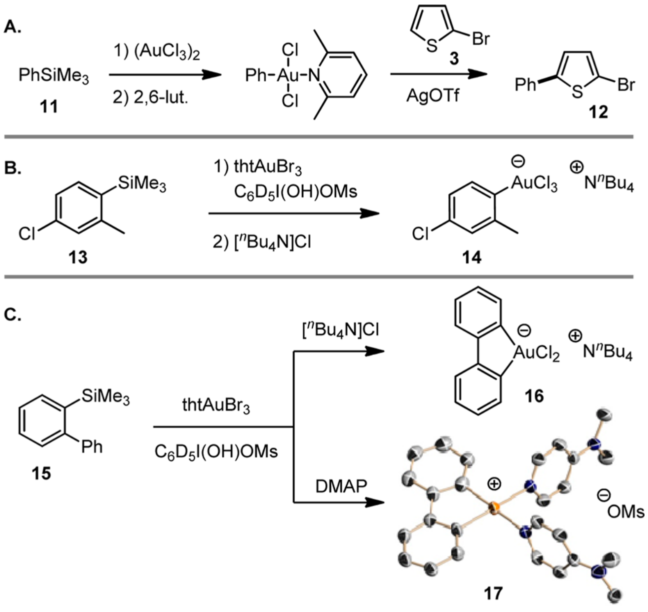
Development of an Improved Precatalyst. Having established that phosphine oxidation occurs during the induction period, a range of 'ligand-free' Au(I) and Au(III) species was tested as arylation precatalysts. $AuBr_3$ was identified as a source of highly active catalyst that initiated turnover without induction,[19] although the hygroscopicity and limited solubility of the salt rendered its use inconvenient. Through further precatalyst screening[19] we found that $thtAuBr_3$ also led to high catalyst turnover without a discernible induction period (Figure 1, right). In addition to simplifying kinetic analyses, $thtAuBr_3$ is conveniently soluble in organic media and stable toward air, light, and moisture. Couplings between a diverse range of partners exhibited chemo- and regioselectivities identical to reactions performed with $Ph_3PAuOTs$ as precatalyst.[5]

The high selectivity for heterocoupling (leading to **9**) with $thtAuBr_3$, thtAuBr, or $Ph_3PAuOTs$, contrasts strongly with the reduced activity and selectivity obtained with chloride-based precatalysts such as Ph_3PAuCl or thtAuCl.[19] The origins of these differences became apparent upon detailed analysis of the crude reaction mixtures. Aromatic bromination products were detected in reactions employing $thtAuBr_3$ as precatalyst,[28] the net loss and oxidation of bromide resulting in the *in situ* formation of a gold sulfonate (*vide infra*). The ancillary sulfide is also rapidly and quantitatively oxidized on addition of F-IBDA/CSA, forming tetrahydrothiophene 1-oxide and a product of ring opening.[19] The same ratio of tht-derived byproducts[19] is observed under stoichiometric and catalytic conditions and is independent of the presence of substrates. Monitoring the reaction of $thtAuBr_3$ with F-IBDA/CSA in the presence of thiophene **8** indicated that, relative to [Au], formation of 2 equiv of bromination product **10**, and consumption of 5 equiv of oxidant, accompanies catalyst activation (Figure 2, right). In contrast, chlorination side products were not observed with thtAuCl as precatalyst, and the only tht-derived byproduct was the sulfoxide.[29]

Reaction of **8** with $[^nBu_4N]Br$ under the conditions of Scheme 1, but in the absence of gold, led to clean bromination.[30] In contrast, $[^nBu_4N]Cl$ did not chlorinate **8**, suggesting that the chloride in Ph_3PAuCl and thtAuCl remains available to ligate gold. This was corroborated by addition of catalytic [^{n}Bu$_4$N]Cl to a thtAuBr$_3$-catalyzed coupling of **1** and **8** ([Cl]/[Au] = 1), which resulted in a substantial drop in selectivity and activity, analogous to that observed with both of the AuCl-based precatalysts.[19]

Stoichiometric Studies. With the insight that precatalyst activation affords 'ligand-free' Au(III), we conducted stoichiometric reactions (Scheme 4) to confirm the viability of the sequential C−Si/C−H auration of cycle A (Scheme 2). The isolation of discrete Au−C σ-bonded species, and the absence of products arising from benzylic activation, provided support for ionic, rather than SET-type mechanisms.[31]

Scheme 4. Stoichiometric Experiments



While the auration of simple arenes by Au(III) was documented by Kharash as early as 1931,[11a] the corresponding auration of arylsilanes has not been reported. By analogy to Fuchita's modification[11d] of the original C−H auration procedure,[11a] reaction of phenyltrimethylsilane **11** with (AuCl$_3$)$_2$, and addition of 2,6-lutidine, afforded *trans*-AuPhCl$_2$(lut.) as evidence of C−Si auration by a well-defined Au(III) precursor (Scheme 4A). The same species was isolated from a thtAuBr$_3$-catalyzed reaction following addition of 2,6-lutidine and its HCl salt.[19] Phenylthiophene **12** was obtained upon addition of AgOTf to *trans*-AuPhCl$_2$(lut.) and 2-bromothiophene **3** in CDCl$_3$/CD$_3$OD, thereby demonstrating that further arylation of a coordinatively unsaturated intermediate, and subsequent reductive elimination, are also feasible (cf. eq 5).[32]

Although thtAuBr$_3$ itself does not react with either coupling partner, formation of an active Au(III) species under catalytically relevant conditions and its reactivity toward arylsilanes were confirmed by treating the precatalyst with C$_6$D$_5$I(OH)OMs in the presence of arylsilane **13** (Scheme 4B). Addition of excess [^{n}Bu$_4$N]Cl allowed trichloroaurate **14** to be characterized *in situ* (^{1}H NMR and HR ESI-MS). Alternatively, the product of sequential C−Si/C−H auration could be generated from (*o*-biphenyl)trimethylsilane **15** under analogous conditions (Scheme 4C). Addition of either [^{n}Bu$_4$N]Cl or 4-(dimethylamino)pyridine (DMAP) allowed isolation of the dibenzoaurole as anion **16** or cation **17**, respectively. That arylation of biphenyl with **1** occurs solely at the 4-position,[19] while (*o*-biphenyl)silane **15** is aurated at the 2′-position, is again consistent with C−Si auration preceding C−H auration. The acceleration of C−Si auration by steric decompression (*vide infra*) and the stability of the resulting dibenzoaurole toward reductive elimination render **15** a powerful catalyst poison.[19]

Reaction Kinetics. *Catalytic Rate Law; Activation Parameters.* Having identified thtAuBr$_3$ as an efficient precatalyst, the coupling of fluorophenylsilane **1** and thiophene **8** was investigated in detail by *in situ* ^{19}F NMR, allowing formulation of an empirical rate law (Figure 3, left). The rate of arylation exhibits first-order dependence on the concentrations of thtAuBr$_3$, arene **8**, and CSA[34] and is independent of silane **1** and F-IBDA. The clean first-order dependence of rate on [thtAuBr$_3$] over an 8-fold concentration range strongly suggests a monomeric, and presumably mononuclear, catalyst. In addition to acting as an essential cosolvent and sequestering the TMS moiety liberated upon C−Si auration, monomeric MeOH is an inhibitor.[35] Analysis over the temperature range 25−55 °C afforded apparent activation parameters of ΔH = 15.2 ± 0.5 kcal mol^{-1} and ΔS = −26.5 ± 0.5 cal K^{-1} mol^{-1} for arylation of **8** with **1** (Figure 3, right).[36] The large, negative value of ΔS is consistent with a significant increase in order during the turnover-limiting event, although care should be taken in the interpretation of this value, due to the possibility of contributions to ΔS from several elementary steps.

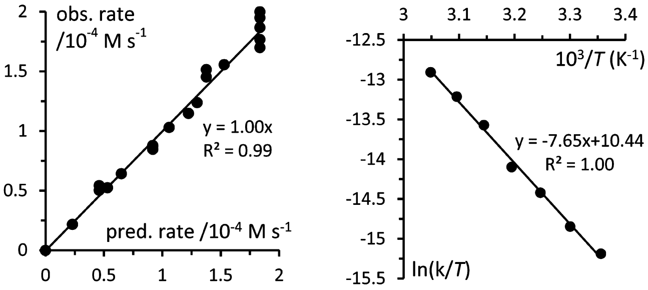
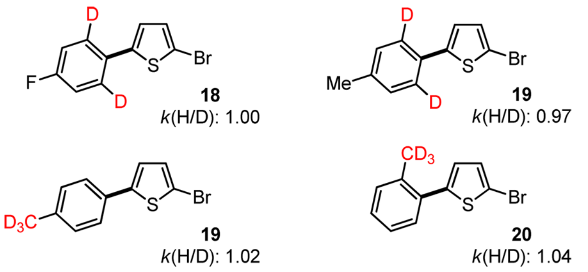


Figure 3. Predicted vs experimentally observed rates (left, $d[\mathbf{9}]/dt = k_{obs}[\mathrm{thtAuBr_3}][\mathbf{8}][\mathrm{CSA}]/[\mathrm{MeOH}]^{0.5}$; k_{obs} = 3.09 M$^{-1.5}$s^{-1}), and Eyring analysis (right), of the arylation of **8** with **1** (Figure 1).

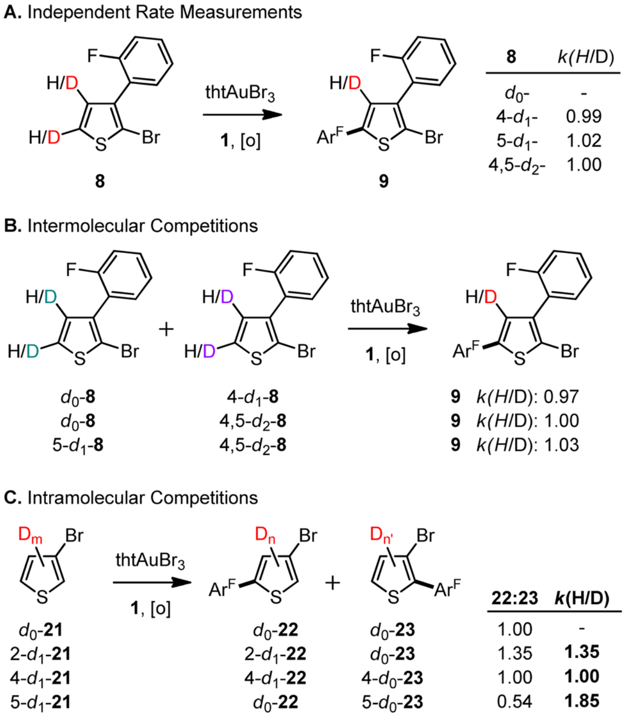
Deuterium Kinetic Isotope Effects (KIEs). Measurement of absolute rate, as well as a series of intra- and intermolecular competitions, afforded KIEs for both the arylsilane and the arene. There was no detectable (^{1}H NMR) transfer of ^{1}H/^{2}H between substrates/products and the cosolvent (CD$_3$OD or MeOH). Arylation of 2-bromothiophene **3** with mixtures of either d_0-**1**/2,6-d_2-**1** (→**18**) or d_0- and 2,6-d_2-(*p*-tolyl)-trimethylsilane (→**19**) gave no significant β-SKIE (Chart 1), suggesting that a substantial change in hybridization β to Si does not occur on approach to the product-determining transition state (TS) for C−Si auration. Negligible SKIEs were also observed for arylation of **3** with mixtures of d_0- and α,α,α-d_3-(*p*-tolyl)trimethylsilane (→**19**), or d_0- and α,α,α-d_3-(*o*-tolyl)trimethylsilane (→**20**).

The absolute rate of arylation of thiophene **8** with silane **1** proved insensitive to isotopic substitution at either the 4- or 5-positions of the thiophene (Scheme 5A). Similarly, intermolecular competitions between isotopologues of **8** for **1** yielded no significant KIE (Scheme 5B). Intramolecular competitions were performed by reaction of a single isotopomer of 3-

Chart 1. SKIEs for C–Si Bond Auration (Intermolecular Competition)



Scheme 5. PKIEs for C–H Bond Auration



bromothiophene **21** with **1**; in contrast to the previous experiments, small normal PKIEs were observed (Scheme 5C). Together, these results indicate that the turnover-limiting elementary step of C–H auration involves neither C–H/D cleavage nor a change in hybridization/geometry and that C–H/D cleavage is product determining only in the partitioning that leads to regioisomers.

Linear Free Energy Relationships (LFERs). *Arylsilane.* Hammett plots derived from analysis of both absolute rates of arylation (single arene/single silane; A, Figure 4), or from competition between two arylsilanes for a single arene (B, Figure 4), correlated against *standard* σ-values. This confirms the absence of direct resonance interaction between the aromatic substituent and the reaction center in the product-determining TS; a similar observation has been made for mercuridesilylation.[37] Since the silane does not appear in the empirical rate equation, the dependence of k_{obs} on the identity of the arylsilane was, as expected, negligible ($\rho = -0.2$). In contrast, partitioning between competing arylsilanes confirmed that C–Si auration is accelerated by electron-releasing substituents ($\rho = -1.6$).

Arene. The absolute rates of arylation of 2-substituted-9,9-dimethylfluorenes gave a good correlation against σ (Figure 5).

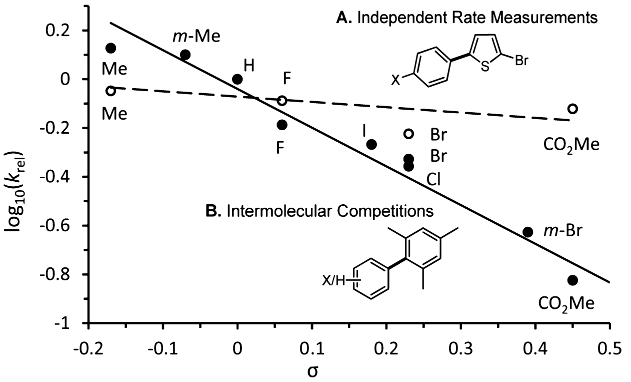


Figure 4. Hammett plot for silanes derived from absolute rates of arylation of **3** and relative rates of arylation of mesitylene **2**.

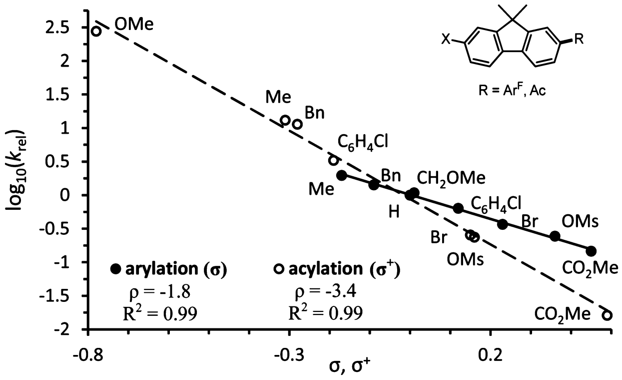


Figure 5. Hammett plot of rates of arylation (vs σ) and rates of acylation (vs σ^+) of 2-substituted-9,9-dimethylfluorenes.

While arylation is accelerated by electron-releasing substituents, the magnitude of the reaction constant ($\rho = -1.8$) is relatively small due to the insulating effect of the fluorene system.[38] In comparison, Friedel–Crafts acylation of the same fluorenes gave $\rho^+ = -3.4$,[19] 2.7-fold less than the ρ^+ value reported for acylation of simple arenes under the same conditions ($\rho^+ = -9.1$).[39] Scaling by the same factor thus gives $\rho \approx -4.9$ for Au-catalyzed arylation of simple arenes, similar to the value ($\rho = -4.7$) found for electrophilic, benzylic auration of para-substituted toluenes.[40] Comparable reaction constants (all based on σ^+) have been reported for electrophilic aromatic metalation by Hg ($\rho^+ = -4.0$ to -6.4),[39] Rh ($\rho^+ = -4.5$),[39] and Ru ($\rho^+ = -4.4$).[41] In contrast, a negligible reaction constant is observed for stoichiometric C–H activation *via* σ-bond metathesis (σBM) at Sc,[42] while Ru-mediated C–H activation *via* σBM is predicted to have a positive reaction constant ($\rho = 2.6$ to 3.2).[43] The significance of the reaction constant for Au-catalyzed arylation is discussed in later sections.

Alkylbenzenes. *Wheland Intermediate and π-Complex Stability.* For S_EAr reactions, the Hammond postulate suggests that, if the relative rate of reaction of a series of arenes correlates with the relative stability of the intermediate π-complexes, then the rate-limiting TS resembles a π-complex; similarly, correlation against Wheland Intermediate (WI) stability suggests rate-limiting formation of a WI.[39] In practice, the relevant π-complexes/WIs cannot usually be observed directly, and thus model complexes with *e.g.*, silver cations, HCl, or Br_2 (model π-complex), or superacids (model WI) are employed. Relative rates of Au-catalyzed arylation of a series of methylbenzenes with silane **1** were derived from absolute rate data and were analyzed as a function of the relative stabilities of the π-complexes (Figure 6, left) or WIs (right) formed by the same arenes with $AgNO_3$[44] or HF/BF_3,[45] respectively.

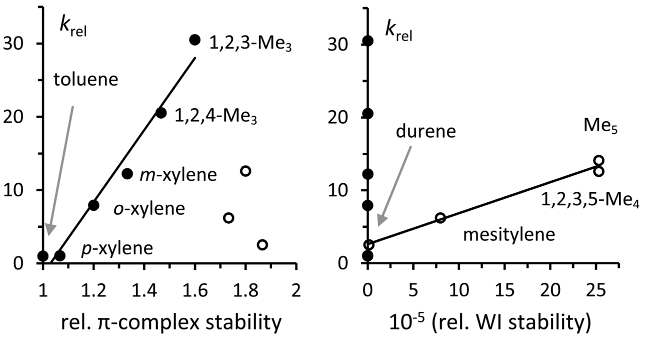


Figure 6. Absolute rates of arylation of polymethylbenzenes with **1** vs relative stabilities of the corresponding π-complex (left; $R^2 = 0.97$) and WI (right; $R^2 = 0.99$). Rates are plotted as k_{rel} with respect to toluene; see Supporting Information [SI] for details.

The rates of arylation of substrates with one or no methyl substituents ortho to the reacting C−H bond correlate against π-complex stabilities, suggesting that the turnover-limiting elementary step proceeds *via* a TS resembling a π-complex. The converse is true of substrates with methyl substituents at both positions ortho to the reacting site. Within the context of S_EAr, this can be rationalized by considering that evolution from a π-complex to a WI requires the electrophile (in this case Au) to move toward the aryl plane, which would be met by an increasing steric penalty as the number of methyl groups ortho to the reactive site increases. A similar phenomenon has been noted in electrophilic mercuration, for which the barrier to metalation of di-ortho-substituted arenes is greater than twice that for mono-ortho-substituted arenes, an effect that is amplified by buttressing between adjacent substituents.[38a] By analogy to electrophilic mercuration and thallation,[31b] the steric component of the energy barrier to π-complex formation is largely unchanged by increasing methylation, such that the overall π-complexation barrier would decrease with increasing arene methylation (*i.e.*, π-basicity). In contrast, the stability of the WI would show significant sensitivity to steric factors, with the energy barrier to WI formation exceeding that associated with π-complexation in di-ortho-methylated substrates.

Baker−Nathan Reactivity. The relative rates of Au-catalyzed arylation of monoalkylbenzenes (PhR) decrease as R = Me > Et > ^{i}Pr > ^{t}Bu, opposing the increasing arene activation by induction/hyperconjugation. A similar trend is observed for stoichiometric electrophilic mercuration,[46] with k_{rel}(arylation) correlating linearly with k_{rel}(mercuration) (A, Figure 7). The Baker−Nathan order arises from increasing hindrance by R to the solvation of a charged Ar−R intermediate,[47] suggesting that some positive charge does develop on the arene during the turnover-limiting event.

In contrast to the arene, the relative rates of C−Si auration in the competition between a series of p-$R'C_6H_4SiMe_3$ for **8** are almost insensitive to the nature of R′ (B, Figure 7); similarly, mercuridesilylation also shows smaller dependence on R′ than does mercuration on R (in PhR).[48] It has been proposed that, due to the high S_EAr reactivity of arylsilanes, the TS for electrophilic mercuration is early and resembles the reactants, such that there is little electronic demand on ring substituents.[48] The observed trend suggests that: (1) auration of the arylsilanes is insensitive to minor electronic changes in R′, (2) there is minimal charge delocalization in the product-determining step, or (3) the opposing electronic and solvation effects cancel.

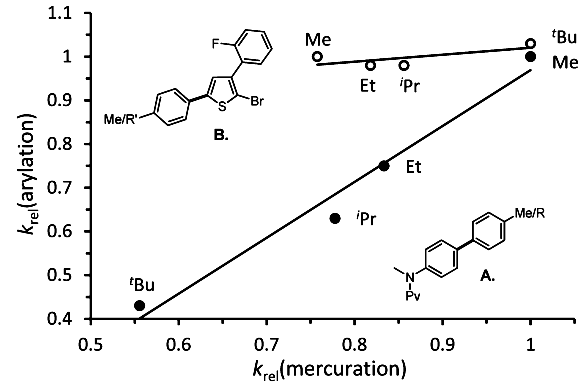
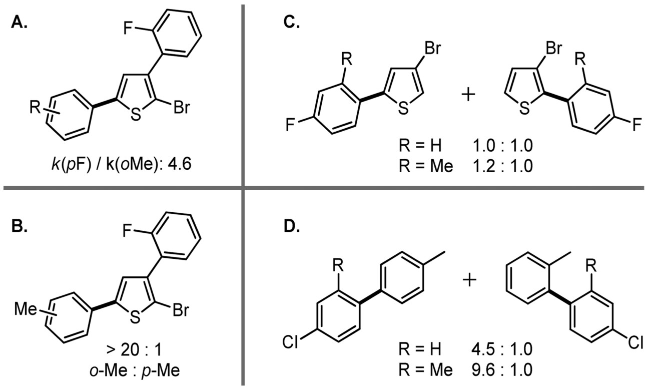


Figure 7. Relative rates of Au-catalyzed arylation of alkylbenzenes with 4-TMS-(N-Me-N-Pv)aniline vs relative rates of mercuration (A), and of thiophene **8** with (p-alkylphenyl) silanes vs relative rates of mercuridesilylation (B). Pv = pivaloyl.

o-Methyl Arylsilanes. Comparison of the absolute rates of reaction of thiophene **8** with either (4-fluorophenyl)silane **1** or (o-tolyl)trimethylsilane revealed that arylation with the less electron-rich arylsilane occurred some 4.6 times faster (Chart 2A); given the low sensitivity of k_{obs} to the electronic nature of the arylsilane (Figure 4), this can largely be attributed to steric effects in the turnover-limiting auration of thiophene **8**. In contrast, *competition* between o- and p-tolylsilanes for **8** resulted in substantial partitioning in favor of the more sterically congested ortho-isomer (Chart 2B). Ortho-methylation of arylsilane **1** resulted in a small increase in regioselectivity for arylation of 3-bromothiophene **21** (Chart 2C); a more appreciable increase in regioselectivity was observed for arylation of toluene with 4-chloro-2-methylphenyltrimethylsilane **13** relative to (4-chlorophenyl)trimethylsilane (Chart 2D). Thus, introduction of a methyl substituent ortho to the silyl moiety results in an increase in both the *relative* reactivity of the arylsilane and the regioselectivity with which the arene is arylated, while the overall rate of catalytic turnover is decreased.

Chart 2. Reactions of *o*-Methyl Arylsilanes



Proposed Mechanism. The data presented above and in the SI, taken with the discussion below, allow a more detailed catalytic cycle to be proposed (Figure 8). Following precatalyst activation, electrophilic auration of the arylsilane by 'ligand-free' Au(III) species **I** affords, *via* **II** and **III**, the catalyst resting state

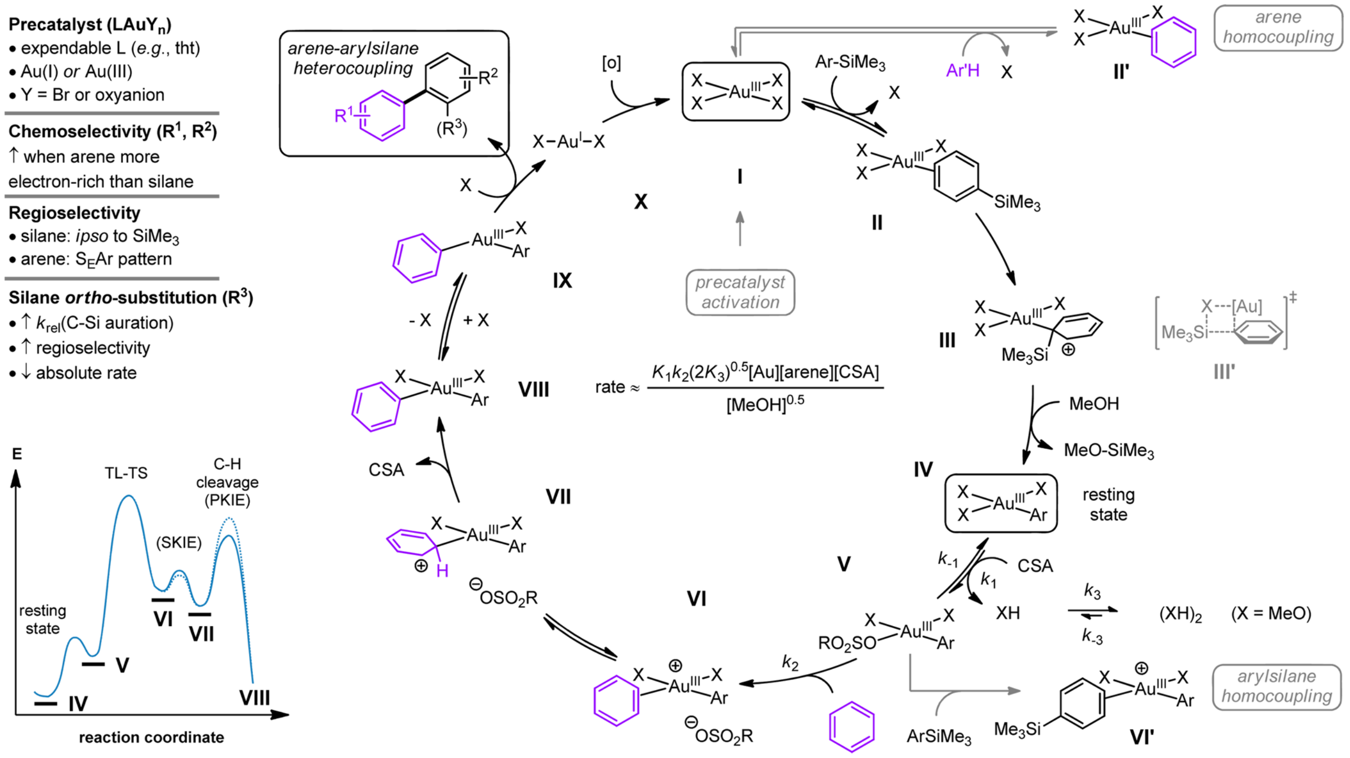


Figure 8. Overall catalytic cycle proposed for Au-catalyzed arylation of arenes with aryltrimethylsilanes. [‘X’ = undefined ligand(s), likely comprising a mixture of MeOH/CSA and conjugate bases. The identity of ‘X’ and its protonation state is expected to change during the cycle in response to electronic and steric requirements of the catalyst, in turn determining the stereochemistry and net charge of the complex. Inset: qualitative reaction coordinate for C−H auration of **8** (solid line) and 4,5-d_2-**8** (dashed line).]

IV. Exchange of methoxide in **IV** for camphorsulfonate in **V** provides a more electrophilic metal, which undergoes turnover-limiting, associative substitution by the arene to afford π-complex **VI**. This species evolves to WI **VII**; for certain substrate classes (e.g., 3-bromothiophene **21**), formation of **VII** is reversible (or the Au fluxional), such that C−H cleavage is regioselectivity determining. Collapse of **VII** to **VIII** precedes ligand dissociation, with reductive elimination from three-coordinate diaryl−Au(III) intermediate **IX** releasing the biaryl product. Oxidation of the resulting Au(I) species **X** regenerates **I**, thereby closing the cycle.

Catalyst Speciation. Precatalyst activation proceeds with irreversible loss of the supporting phosphine/sulfide. A corollary is that, while neither the selectivity nor activity of the catalyst can be modulated by tuning the ancilliary ligand, substrate-specific precatalysts are not required. Identification of the active Au(III) species that is liberated from the precatalyst is challenging due to the dynamics of ligand exchange. Indeed, the nature of the supporting ligands/anions (e.g., MeOH, CSA, AcOH, methoxide, camphorsulfonate, acetate, π-bound arene, etc.), the net charge of the complex, and its geometry will likely change in response to the different electronic and steric requirements of the metal at various stages of the cycle. Nonetheless, we suggest that camphorsulfonate anions, and up to one methoxide/hydroxide, are associated with the Au(III) center, alongside datively bound methanol/water.[19]

C−Si Auration. Precedent exists for transmetalation of aryl moieties to Au(III) from various organometallic reagents[33,49]—including boroxines[50]—although no mechanistic studies have been reported to date. While formation of Au−CF$_3$ species via reaction of Au(I) and Au(III) phenoxides with TMS-CF$_3$ has been proposed to proceed via σBM,[51] a large body of data supports reactivity of arylsilanes via S$_E$Ar, including arylation of late transition metals such as Pd(II) and Pt(II).[52]

Protodesilylation of arylsilanes exhibits an inverse β-SKIE,[53] typical for an S$_E$Ar reaction with rate-limiting formation of a WI. The absence of a SKIE in intermolecular competition between d_0-/2,6-d_2-arylsilanes (Chart 1) suggests that there is little rehybridization β to Si, and the absence of a normal SKIE for arylation of 2-bromothiophene **3** with the CH$_3$/CD$_3$ isotopologues of tolyltrimethylsilanes implies that there is little delocalization of charge onto the aromatic system during the product-determining step of C−Si auration.[54] Furthermore, the low sensitivity of the reaction rate to the identity of p-alkyl substituents (B, Figure 7) may also be indicative of minimal charge delocalization in the rate-limiting step of C−Si auration. That the Hammett reaction constant ($\rho = -1.6$) is significantly smaller than values for typical S$_E$Ar substitutions ipso to silicon[55] and that good correlation is found against σ rather than σ$^+$ (Figure 4) are also consistent with small electronic demands being made of the arylsilane.

The increase in relative reactivity upon ortho-methylation (Chart 2B) of the arylsilane arises from steric decompression, a phenomenon observed in other S$_E$Ar processes, including mercuridesilylation[56] and protodesilylation.[57] Steric interactions that destabilize the arylsilane in the ground state are reduced upon formation of a WI, in which the TMS moiety moves out of the aryl plane. Thus, for the Au-catalyzed process, the product-determining event must involve distortion of the arylsilane from planarity.

Three general scenarios can be envisaged in which the rate of C−Si auration, and selectivity for C−Si over C−H, is controlled by (a) π-complexation of the arylsilane (**I** → **II**), (b) cleavage of the C−Si bond via σBM (**II** → **III**′ → **IV**),[58] or

(c) formation of a WI on an S_EAr pathway (**II** → **III**). Scenario (a) is consistent with the small, negative reaction constant (and the correlation against σ), the insensitivity to the nature of *p*-alkyl substituents and the lack of KIEs. However, it fails to account for the accelerating effect of silane ortho-methylation, and provides no explanation for the selectivity between the silane and the arene (*i.e.*, chemoselectivity; *vide infra*). As an alternative, scenario (b) fails to account for both the accelerating effects of ortho-methylation and the reaction constant (a negligible or positive ρ value is expected for σBM),[42,43] although invoking a reaction manifold fundamentally different from that operating for C−H auration offers a clear basis for chemoselectivity. Finally, rate-limiting formation of a WI, scenario (c), accounts not only for the accelerating effect of ortho-methylation but also, in the limit of an early TS,[48] for the absence of KIEs, the insensitivity to the nature of alkyl substituents, and the magnitude/direction of the reaction constant. Thus, when taken with the high ipso-factors of arylsilanes,[39] an S_EAr mechanism with rate-limiting formation of a WI (**III**) (scenario (c)) is the preferred pathway for C−Si auration.[40]

C−H Auration. The empirical rate law (Figure 8) is consistent with rate-governing generation of a π-complex between the arene substrate and the catalyst.[59] The first-order dependence on the concentration of CSA, and inhibition by MeOH, implies a pre-equilibrium between methoxide resting state **IV** and camphorsulfonate **V**, with the fractional dependence on the concentration of MeOH resulting from the extensive dimerization of MeOH in $CHCl_3$.[60] Following turnover-limiting formation of the π-complex **VI**, evolution to **VIII** can nominally occur *via* σBM, concerted metalation−deprotonation, or S_EAr, pathways, although the latter is preferred (*vide infra*).[61]

That **V** → **VI** is the turnover-limiting step is corroborated by the KIEs determined for reactions of deuterated thiophenes (Scheme 5). The absence of any KIE on the absolute rate suggests that the turnover-limiting step does not involve cleavage of the C−H bond (**VII** → **VIII**) or significant rehybridization en route to WI **VII**.[62] The absence of KIEs in intermolecular competition is consistent with irreversible substrate coordination being both turnover limiting and product determining.[63] The observation of small PKIEs (Scheme 5C) in intramolecular competition indicates that cleavage of the C−H bond (*i.e.*, collapse of **VII** to **VIII**, *via* an early and/or nonlinear TS) controls regioselectivity, which in turn requires that formation of the WI is formally reversible and that π-complex **VI** is fluxional.[59] Figure 8 includes a qualitative reaction coordinate diagram illustrating these points; however, this does not necessarily extend to other substrates, as the strong resonance stabilization of a thiophene-derived WI will significantly lower the energy of the TS by which it is formed. Such an effect will be absent in toluene, for example, so that formation of the WI may become irreversible and regioselectivity determining. In hindered substrates, *e.g.*, mesitylene **2**, the energy of the WI may be raised sufficiently for its formation to become both product determining and turnover limiting (*vide supra*).

The increase in regioselectivity observed upon arylation of 3-bromothiophene **21** or toluene with ortho-substituted arylsilanes (Chart 2C and D) cannot be used to distinguish between scenarios in which formation of WI **VII** is either irreversible and product determining, or reversible, although KIEs support the latter. In the first case, a more sterically demanding gold center may be more discriminating during formation of **VII** from fluxional π-complex **VI**. In the second case, if formation of **VII** is rapidly reversible, the regioselectivity of auration will depend on the rate of collapse of **VII** to **VIII**, which will be influenced by the steric requirements of the metal center as it moves into the aryl plane. The Baker−Nathan reactivity (A, Figure 7) suggests that charge develops on the arene (*e.g.*, formation of a WI) during the turnover-limiting TS, contrary to the small reaction constant (σ rather than σ^+, Figure 5). However, the effect can also be rationalized in terms of steric hindrance to formation of **VI** *via* π-complexation. The generation of **VI** has the characteristics of an associative process:[64] the rate is first order in arene ($\rho = -1.8$) with a large apparent negative entropy of activation (Figure 3, right). Orientation of the silane-derived aryl ring perpendicular to the square plane of **V** results in one axial site of the metal being blocked;[65] as such, the approach of the arene en route to formation of **VI** is hindered, and the turnover rate is reduced with ortho-methyl arylsilanes (Chart 2A).

Origin of Chemoselectivity. The high selectivity for hetero- over homocoupling (Scheme 1) requires a high degree of discrimination between the arene and the silane in two superficially similar S_EAr processes. An explanation is, however, provided by considering how the coupling partners are able to meet the different demands made by the metal during the two chemoselectivity-determining steps. Thus, while the high ipso factor of the silyl moiety activates the arylsilane toward formation of a WI (**III**) by stabilizing the TS leading to it, activation of the ground state through donation of electron density into the π-system of the arylsilane is minimal. This is reflected in the low resonance-effect parameter and substituent constant of the TMS moiety ($R = -0.08$, $\sigma_p = -0.07$), as compared to *e.g.*, MeO ($R = -0.56$, $\sigma_p = -0.27$) or Me ($R = -0.18$, $\sigma_p = -0.17$).[66] In contrast, the arene is unactivated toward substitution ipso to H; the substrates employed, however, all feature functionality that increases π-electron density (*i.e.*, π-basicity). Thus, if the first auration proceeds *via* chemoselectivity-determining formation of a WI (**III**), the silane will generally out-compete the arene. In this model rapid equilibrium between arene and arylsilane π-complexes (**II**′ ↔ **II**) prior to the first auration is inconsequential. The converse is true for the second auration, in which irreversible π-complexation by the most π-basic arene provides the second stage of chemoselectivity, *i.e.*, formation of **VI** outcompetes formation of **VI**′. The steric bulk of the TMS moiety may augment this selectivity by destabilizing π-complex **VI**′, comparable to the Baker−Nathan selectivity observed for the arene, thereby accounting for the suppression of homocoupling observed with the triethylsilyl analogue of **1**.[5] The overall selectivity is thus controlled by two different elementary processes in the sequential auration events. This shift in the selectivity-determining step requires a change in the Au(III) electrophile in the second auration, as provided by the silane-derived σ-bonded aryl. Chemoselectivity begins to break down in the limits of π-basic arylsilanes, or less π-basic arenes (*e.g.*, benzene, fluorobenzene). Both situations result in the silane competing effectively in the second auration event (**VI**′) and thus homocoupling; the impact of chloride is discussed in the SI.

Reductive Elimination. Investigations into C−C bond-forming reductive elimination from a Au(III) center have found generation of a coordinatively unsaturated intermediate to be rate limiting.[67] The conditions developed for gold-catalyzed arylation[5] thus favor reductive elimination: ancillary ligands are removed by oxidation during the induction period, a polar, but poorly coordinating, solvent system is employed, and weakly coordinating sulfonate anions are introduced through both the acid additive and the precatalyst.

Oxidant Speciation. A key requirement of oxidative arylation is the regeneration of a Au(III) species *via* iodine(III)-mediated oxidation of Au(I). Despite the frequent invocation of such a transformation in oxidative gold catalysis[8] and its regular stoichiometric exploitation,[68] the intimate mechanism of the redox event has yet to be elucidated. Indeed, the mechanism for the analogous oxidation of Pd(II) to Pd(IV) has only very recently been investigated (DFT).[69] Thorough investigation of Au(I) oxidation is hampered by the distribution of iodine(III) species in solution;[19] we anticipate that insight into this elementary step will prove central to further development of the field.

CONCLUSIONS

The investigation reported herein has provided preliminary insight into the mechanism of Au-catalyzed coupling of arenes with aryltrimethylsilanes, from initial activation of the precatalyst and the general structure of the catalytic cycle, to the nature of some of the key elementary processes and the origins of chemoselectivity and regioselectivity. A mechanistic proposal that is consistent with all of our experimental observations is illustrated in Figure 8, together with points for consideration during practical application of the methodology.

Kinetic analysis shows that PR_3-ligated precatalysts are associated with long induction periods, which are extended by sterically demanding and/or less basic phosphines. This allows not only *a posteriori* rationalization of previously observed ligand-dependence, but also facilitates *a priori* prediction of precatalyst suitability. In this regard, $thtAuBr_3$ catalyzes arylation without an observable induction period, and is both conveniently stable (air, moisture, and light) and soluble. Rapid activation of $thtAuBr_3$ is accompanied by generation of bromination byproducts. The analogous *in situ* anion exchange does not occur for gold chlorides, and this appears to be the basis of the lower reactivity and selectivity obtained with these precatalysts.[19] Similar active species are generated from $Ph_3PAuOTs$ and $thtAuBr_3$ precatalysts *via* an oxidative process, accounting for the empirical use of excess iodine(III) reagent. The on-cycle metal is essentially 'ligand-free', improving economy and making for simple precatalyst selection, albeit at the expense of ligand-based catalyst tuning. The extent to which 'ligand-free' conditions apply to related oxidative gold-catalyzed processes[8] remains to be fully explored.

Elucidation of the empirical catalytic rate law suggests that the originally reported conditions[5] (2 mol% Au and 1 equiv arene vs 1 mol% Au and 2 equiv arene) are equivalent in terms of reaction kinetics (but not necessarily in terms of selectivity). The rate of arylation depends on the arene concentration, but not on the silane concentration, validating use of the latter as the limiting reagent. However, an excess of arylsilane may be valuable in some circumstances, such as in the reaction of strongly activated arenes with deactivated arylsilanes. The effects of ortho-substitution of the arylsilane must also be considered in synthetic strategy: although C−Si auration is accelerated *via* steric decompression, and the regioselectivity of C−H auration improved, the overall turnover frequency is reduced. It is also important to note that *o*-biphenylsilanes sequester the catalyst *via* generation of a stable cycloaurate. MeOH is found to perform three roles, acting as cosolvent, TMS-scavenger and inhibitor. Given the inhibitory effect of the alcohol, there is a practical benefit to performing reactions at lower MeOH concentration, which is facilitated by use of a more-soluble oxidant (generated with CSA rather than TsOH, for example). Although reactions can be run under air, catalytic turnover is suppressed by adventitious water.[19] Inhibition by Brønsted- and Lewis-bases arises from the dependence of rate on CSA concentration, and the possibility of coordinative saturation of the electrophilic metal center. The chemoselectivity results from electrophilic C−Si and C−H auration in which formation of a Wheland Intermediate and a π-complex, respectively, are selectivity determining, allowing informed retrosynthetic disconnection to an electron-poor arylsilane and an electron-rich arene; this insight may also facilitate extension of the methodology to other arylating agents/coupling partners.

Finally, we note that the evidence in support of a Au(I)/Au(III) redox cycle suggests that this manifold may also function in other oxidative, Au-catalyzed protocols employing iodine(III) oxidants. This insight may facilitate informed development of new catalysts and new catalytic cycles, leading ultimately to alternative, more efficient oxidants.

ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

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(16) Transmetalation *via* a siliconate is unlikely as electronegative substituents on Si and/or basic additives are required. We are aware of one example of Si to Au aryl transmetalation employing aryl*siloxane* and Au(I): (a) Dupuy, S.; Slawin, A. M. Z.; Nolan, S. P. *Chem.—Eur. J.* **2012**, *18*, 14923. For aryltrimethylsilanes in cross-coupling, see: (b) Funaki, K.; Kawai, H.; Sato, T.; Oi, S. *Chem. Lett.* **2011**, *40*, 1050. (c) Funaki, K.; Sato, T.; Oi, S. *Org. Lett.* **2012**, *14*, 6186.

(17) Stoichiometric arylation of Au(I) has been reported in the presence of base using electron-deficient arenes (a) Lu, P.; Boorman, T. C.; Slawin, A. M. Z.; Larrosa, I. *J. Am. Chem. Soc.* **2010**, *132*, 5580, boronic acids (b) Partyka, D. V.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 8188. (c) Partyka, D. V.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Inorg. Chem.* **2012**, *51*, 8394. See also ref 10f), and siloxanes (ref 16a), in the absence of base using tetraaryl borates (d) Weber, S. G.; Zahner, D.; Rominger, F.; Straub, B. F. *Chem. Commun.* **2012**, *48*, 11325, and stannanes (e) Meyer, N.; Sivanathan, S.; Mohr, F. *J. Organomet. Chem.* **2011**, *696*, 1244.

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(19) See SI.

(20) Control experiments detailed in ref 5 indicate diaryliodonium salts to be unreactive. See also ref 10g.

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(24) Initially formed Ph$_3$PX$_2$ will rapidly solvolyze to Ph$_3$PO.

(25) For example, oxidation of R$_3$PAuI with I$_2$ occurs for PR$_3$ = PMe$_2$Ph but not PMePh$_2$ or PPh$_3$, and for PMe$_3$ but not P^{t}Bu$_3$. See: (a) Schneider, D.; Schier, A.; Schmidbaur, H. *Dalton Trans.* **2004**, 1995.

(26) Reductive elimination of Ar$_3$P$^+$-O$_2$CCF$_3$ from Pd is accelerated by basic phosphines, as the TS resembles nucleophilic attack by Ar$_3$P on the trifluoroacetate oxygen. The converse is true for Pd(OAc)$_2$. See: (a) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818. (b) Amatore, C.; Jutand, A.; Lemaitre, F.; Ricard, J. L.; Kozuch, S.; Shaik, S. *J. Organomet. Chem.* **2004**, *689*, 3728.

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(29) Two equivalents of oxidant are consumed in the reaction of thtAuCl with F-IBDA/CSA. See SI.

(30) For nonmetal-mediated oxidative bromination, see: Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Synlett* **2004**, 461.

(31) For examples of benzylic activation during electrophilic metalation, see: (a) Kochi, J. K.; Tang, R. T.; Bernath, T. *J. Am. Chem. Soc.* **1973**, *95*, 7114. (b) Lau, W.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 6720. Reduction of Au(I) in the presence of silver salts results in benzylic activation (ref 14).

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