Au-catalyzed Biaryl Coupling to Generate 5- to 9-membered Rings: Turnover-Limiting Reductive Elimination versus π-complexation

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ABSTRACT: The intramolecular gold–catalyzed arylation of arenes by aryltrimethylsilanes has been investigated from both a mechanistic and preparative aspect. The reaction generates five to nine membered rings, and of the 44 examples studied, ten include a heteroatom (*N, O*). The tethering of the arene to the arylsilane not only provides a tool to probe the impact of the conformational flexibility of Ar–Au–Ar intermediates, via systematic modulation of the length of aryl-aryl linkage, but also the ability to arylate neutral and electron-poor arenes - substrates that do not react at all in the intermolecular process. Rendering the arylation intramolecular also results in phenomenologically simpler reaction kinetics, and overall these features have facilitated a detailed study of linear free energy relationships, kinetic isotope effects, and the first quantitative experimental data on the effects of aryl electron-demand and conformational freedom on the rate of reductive elimination from diaryl gold(III) species. The turnover-limiting step for the formation of a series of fluorene derivatives is sensitive to the electronics of the arene and changes from reductive elimination to π-complexation for arenes bearing strongly electron-withdrawing substituents (σ >0.43). Reductive elimination is accelerated by electron-donating substituents ($\square$ = –2.0) on one or both rings, with the individual σ-values being additive in nature. Longer and more flexible tethers between the two aryl rings results in faster reductive elimination from Ar-Au(X)-Ar, and to the π-complexation of the arene by Ar-AuX$_2$ becoming the turnover-limiting step.

Introduction

Transition metal-catalyzed cross-coupling has revolutionized synthesis,[1] with the biaryl motif a major focal point for research in this area.[2] The union of aryl-(pseudo)halides and aryl-metallic reagents have been extensively studied, and there is now substantial interest in more step- and atom-economic variants. In this regard, the reaction of arenes with aryl-metallic reagents, one class of the so-called 'direct arylation' reaction, has received significant attention.[3] Catalysis by gold is emerging as a powerful synthetic tool.[4] We recently reported a gold-catalyzed *intermolecular* arylation of electron-rich arenes by aryltrimethylsilanes (Scheme 1).[5]
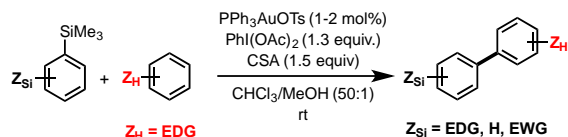
Scheme 1. Au-catalyzed intermolecular arene-arylsilane oxidative coupling, as initially reported (2012).[5] CSA = camphorsulfonic acid. For further advances, see references 6-8.

The process is operationally simple, proceeds under air, often at room temperature, at low catalyst loadings (1-2 mol%), and with broad functional-group tolerance. In subsequent developments, Itami and Sagewa demonstrated that pyridylidene Au-complexation facilitates arylation of isoxazoles, indoles and benzothiophenes,[6] Jeon applied Au-

catalyzed arylation to functionalize *ortho*-silyl aryl triflates generated via Rh/Ir-catalyzed traceless *ortho*-CH silation,[7] and we reported that silane and oxidant modification allows arylation of a range of heterocycles.[8]

Major advances have also been made towards understanding the unique reactivity and selectivity of catalytic reactions proceeding via Au(I) and Au(III) intermediates.[6,9] Nonetheless, in comparison to many transition metal catalyzed processes, overall mechanistic understanding of homogeneous gold catalysis remains less well developed. In 2014 we reported our initial mechanistic investigations into the gold-catalyzed *intermolecular* arylation (Scheme 1).[9h] Study of the pre-catalyst activation process revealed that during an approximately 2 hour-long induction period, the Au(I)-phosphine complex was oxidized to yield PPh$_3$O and the active gold catalyst: a solvated AuX$_3$ species (X = CSA, OTs). By changing to a thtAuBr$_3$ pre-catalyst (tht = tetrahydrothiophene) we were able to reduce the induction period to around 300 seconds; again liberating a solvated 'ligand-free' AuX$_3$ species. Using this pre-catalyst system and a specifically tailored substrate (arylthiophene 1, Scheme 2, upper) the reaction kinetics were sufficiently tractable to allow us to determine the empirical rate law by ^{19}F NMR, and to deduce that intermolecular Au(III)-arene π-complexation is the turnover-limiting step.[9h] However, our conclusions were predominantly based on detailed study of this *single* well-behaved model system. Information on some of the

other steps in the cycle was less clear, being gained indirectly, from competition experiments, literature precedent, and model stoichiometric reactions.

Gaining mechanistic insight to other steps in the cycle has become an important goal. However, to date the process has been limited to π-rich arenes and some heterocycles. Neutral or electron-poor arenes act solely as spectators to the competing homocoupling of the aryl trimethylsilane. This substantially limits the range of arenes that can be explored in, for example, linear free-energy relationships, even by way of analysis of relative rather than absolute rates.
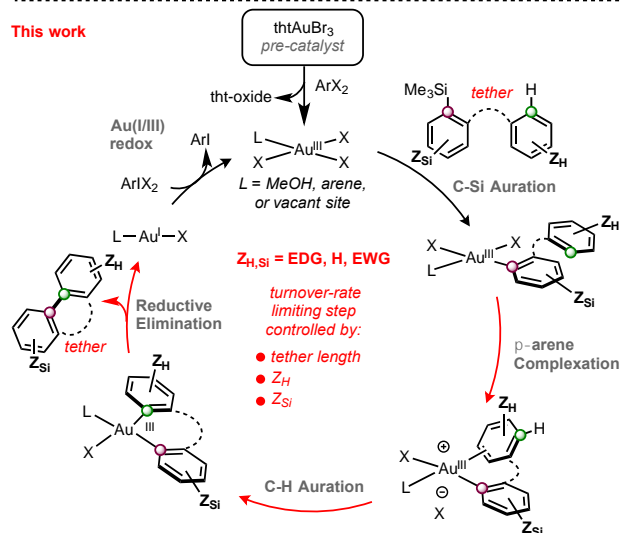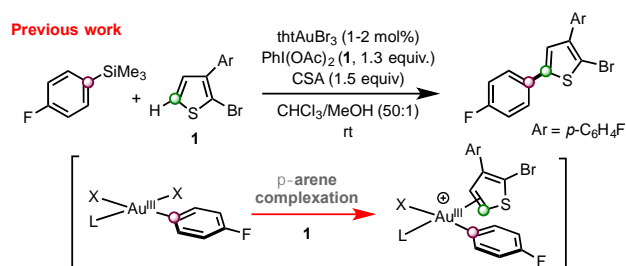

Scheme 2. Mechanistic studies of Au-catalyzed arene-arylsilane oxidative coupling. tht = tetrahydrothiophene. CSA = camphorsulfonic acid. L, X = unspecified neutral and anionic ligands. The intermolecular process[9h] is limited to π-rich arenes.

Herein we report on the *intramolecular* process (Scheme 2, lower). Conducting the arylation intramolecularly induces a number of useful changes to the system: i) in contrast to the intermolecular reaction, the reactions proceed with very reproducible and, in the main, phenomenologically-simple kinetics, *vide infra*; ii) a very broad range of arenes, including highly electron-deficient examples, can be arylated without competing arylsilane homocoupling; and iii), the tether between the arene and the aryl silane can be used to systematically perturb arene-Au conformational flexibility, and to modulate the effective molarity of arene,

in the catalytic intermediates. Overall the intramolecular system allows substitution patterns (Z_{Si} and Z_H) and tether lengths to be tuned to provide the reactivity and kinetic regulation requisite for elucidation of mechanistic features that are *not accessible in the intermolecular version*. Using this platform we have gain insight into arene auration, Wheland intermediate generation and, uniquely, reductive elimination.

Results and Discussion

Preparative Arylation We began by exploring preparative cyclization, using 'HCIB' (**2**) or 'PIFA', (**3**) as the oxidant, and the rapidly-activating pre-catalyst thtAuBr$_3$ (*vide supra*)[9h] in CHCl$_3$/MeOH at 27 °C. A series of 35 aryl-TMS substrates (Table 1) were cyclized, affording 5- to 9-membered rings in good to excellent isolated yields.
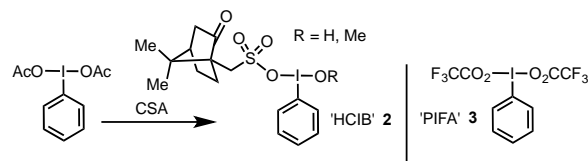

The structures of the largest rings (**5ah**, **5ai**, entries 17,18) were confirmed by single crystal X-ray diffraction. Although a number of other intramolecular direct arylation strategies have been reported,[10] the gold-catalyzed cyclization displays excellent functional group tolerance, proceeds at low reaction temperatures, uses readily prepared TMS-bearing starting materials, and yields 5-9 membered ring products bearing a diverse range of substitution patterns, from CF$_3$ to highly electron donating (Scheme 2). For the majority of examples, 1-2 mol% Au allowed complete conversion, at 27°C in a reasonable timescale; with some substrates substantially lower loadings were possible. For example cyclization of **4n** (Table 1, entry 3) was complete in under 10 minutes using 1 mol% Au (95% yield) and at 0.06 mol% Au still afforded dimethylfluorene **5n** in 80% yield, with formal turnover number of 1330. In contrast, the cyclization of **4ah** (Table 1, entry 17) to generate 8-membered **5ah** required 4 mol% Au, and 9-membered **5ai** (Table 1, entry 18), required heating to 50 °C (52% yield). Although the formation of 8- and 9- membered rings *via* metal catalyzed direct arylation has been reported,[11] examples involving simple aryl rings (no directing groups) are rare.

HCIB (**2**)[12] reacts directly with electron-rich arenes to generate diaryliodonium salts *via* an S$_E$Ar mechanism.[13] This competing process, which is not Au-catalyzed, severely reduced the yield with certain examples, in particular anisyl and naphthyl substrates **4a**, **4i** and **4s**. Changing from HCIB (**2**) to PIFA (**3**) largely eliminated diaryliodonium formation, allowing **5a**, **5i** and **5s** to be obtained in 80-88% yields. The impact of oxidant is exemplified in the cyclization of **4a**, Table 2.

Table 2. Effect of oxidant (**2**, **3**) on the cyclization of **4a**.
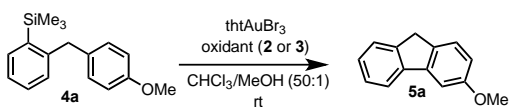
thtAuBr₃	Conversion of **4a** to **5a**	
	HCIB (**2**)[a]	PIFA (**3**)[b]
0.25 mol%	11%	85%
0.5 mol%	17%	90%
1 mol%	33%	88%
2 mol%	42%	90%

[a] generated in situ from PhI(OAc)₂ (1.1 equiv) + CSA (1.3 equiv). [b]PIFA (**3**, 1.1 equiv). Conversion by ^{1}H NMR using internal standard (CH₂Br₂).
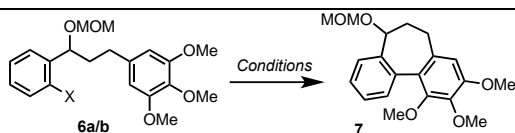
6a: X = SiMe₃: thtAuBr₃ (5 mol%), **3** (1.2 equiv), CHCl₃/MeOH (50:1), 2.5 h, 27 °C, 75%
6b: X = Cl: Pd(OAc)₂ (10 mol%), K₂CO₃ (2 equiv), DMA, 14 h, 145 °C, 69%[11f]

Scheme 3. Au / Pd catalyzed direct arylation of **6a** / **6b**.

Suppression of the background diaryliodonium formation using PIFA (**3**) allows substantially lower catalyst loadings to be employed.[14] The beneficial effect of replacing HCIB (**2**) with PIFA (**3**) was further explored by conversion of **6a** (X = TMS) to **7**, Scheme 3, requiring arylation of a highly electron-rich trimethoxy benzene ring.[15] Thus, whilst HCIB (**2**) led to a complex mixture, due to diaryliodonium salt generation *and* acid-mediated *in situ* MOM deprotection, use of PIFA (**3**) afforded the 7-membered ring allocolchinoid skeleton[15] **7** in 75% yield, with the MOM group intact. An analogous Pd-catalyzed process using **6b** (X = Cl) requires substantially more forcing conditions (145 °C).[11f]

Table 1. Preparative gold-catalyzed cyclizations (35 examples) of **4a**-**4ai** to **5a**-**5ai** at 27 °C.[a]

Entry	Substrate	Product	(Yield, Time)		Entry	Substrate	Product	(Yield, Time)
1	**4a-g** (SiMe₃)	**5a-g**	R = OMe (88%, 2 h)[b] **5a** H (94%, 1 h) **5b** *t*-Bu (81%, 1 h) **5c** Cl (90%, 4 h) **5d** OPiv (81%, 6 h) **5e** CF₃ (80%, 15 h) **5f** OTf (92%, 16 h)[c] **5g**		10	**4x-z** (SiMe₃)	**5x-z**	R = H (72%, 1 h) **5x** Cl (91%, 1 h)[c] **5y** CF₃ (82%, 16 h)[c] **5z**
2	**4h-m** (SiMe₃)	**5h-m**	R = Me (95%, 1 h)[d] **5h** OMe (80%, 1 h)[b,d] **5i** F (85%, 2 h)[d] **5j** Cl (90%, 3 h)[d] **5k** CF₃ (88%, 16 h)[d,e] **5l** OTf (78%, 15 h)[d] **5m**		11	**4aa-ab** (SiMe₃)	**5aa-ab**	R = H (86%, 2 h)[c,f] **5aa** *t*-Bu (60%, 1 h)[c,f] **5ab**
3	**4n-p** (SiMe₃, Me)	**5n-p**	R = H (95%, 10 min) **5n** F (89%, 15 min) **5o** Cl (91%, 1 h)[c] **5p**		12	**4ac** (SiMe₃, Me)	**5ac**	(86%, 1 h)[e,c,f]
4	**4q** (SiMe₃, F)	**5q**	(87%, 16 h)		13	**4ad** (SiMe₃)	**5ad**	(85%, 15 h)[c]
5	**4r** (SiMe₃, Me, F)	**5r**	(89%, 5 h)		14	**4ae** (SiMe₃, N-Ms, benzyl)	**5ae** (Ms-N)	(73%, 16 h)[c]
6	**4s** (SiMe₃)	**5s**	(80%, 1 h)[b]		15	**4af** (SiMe₃)	**5af**	(76%, 16 h)[c,e]
7	**4t** (SiMe₃, Me, Me)	**5t**	(76%, 1 h)		16	**4ag** (SiMe₃, Me, F)	**5ag**	(82%, 15 h)[c]
8	**4u** (Me₃Si, Me, Me)	**5u**	(79%, 1 h)[b,c,d]		17	**4ah** (SiMe₃)	**5ah**	(75%, 14 h)[g]
9	**4v-w** (SiMe₃)	**5v-w**	R = H (87%, 30 min) **5v** R = CH₂NPhth (94%, 1 h) **5w**		18	**4ai** (SiMe₃)	**5ai**	(52%, 16h)[e,g,h]

[a]Unless otherwise stated: **4** (0.50 mmol), thtAuBr₃ (1 mol%), PhI(OAc)₂ (0.55 mmol), CSA (0.65 mmol) in CHCl₃/MeOH (50:1, 0.1 M).[b]PhI(OCOCF₃)₂ **3**, (0.55 mmol) replaces **1**/CSA. [c]thtAuBr₃ (2 mol%). [d]Ratio of 2-/4-regioisomers: **5h** (95:5), **5i** (88:12), **5j** (97:3), **5u** (97:3) and 3-/1-regioisomers: **5ac** (89:11). [e]CSA (1.0 mmol). [f]0.05 M **4**. [g]thtAuBr₃ (4 mol%). [h]50 °C. Phth = phthalimido. Piv= t-BuCO₂.

Mechanistic Study The intramolecular arylation, particularly the examples generating substituted fluorene products[16] (entries 1-8, Table 1), proved ideal for mechanistic study. Firstly, as noted above, the intramolecular process tolerates a very much larger range of arene substituents than the intermolecular version, where only electron rich arenes are tolerated. This key feature has allowed detailed analysis of linear free energy relationships - both for the silane and the arene. Secondly, the reactions tend to proceed with reproducible and (phenomenologically) simple

kinetics, often pseudo zero-order *vide infra*, without significant side-product formation. In contrast, the intermolecular system display complex kinetic profiles and often suffers from competing aryl silane homocoupling. Thirdly, deuterium labels can be readily installed at strategic positions to analyze for KIEs at key steps. And finally, the tether length between the arenes is readily varied, allowing the kinetics of intramolecular arene capture to be modulated. Overall, in combination with earlier data,[9h] the system allows a more holistic analysis of the catalytic cycle.

Kinetics and Activation Parameters In our previous investigation of the *intermolecular* reaction (Scheme 2, upper), arene π-complexation was found to be the turnover-limiting step, leading to pseudo first-order kinetics.[9h] By tethering the arene to the arylsilane, and thus in turn to the arylgold, the effective molarity of the arene is raised, potentially leading to the turnover limiting step being driven to a later or earlier stage in the cycle. Monitoring of the reaction of **4b** by ^{1}H NMR spectroscopy revealed the expected[9h] induction period (approx 300 seconds) during which the catalyst is converted to the tht-free active species $LAuX_3$, where L = MeOH, arene, or vacant site; X = CSA, and up to one Br. After completion of the induction period, catalytic turnover proceeds with clean pseudo-zero order kinetics, turning-over for the full reaction evolution at a formal frequency of 0.07 s^{-1} at 27 °C (Figure 1, top).
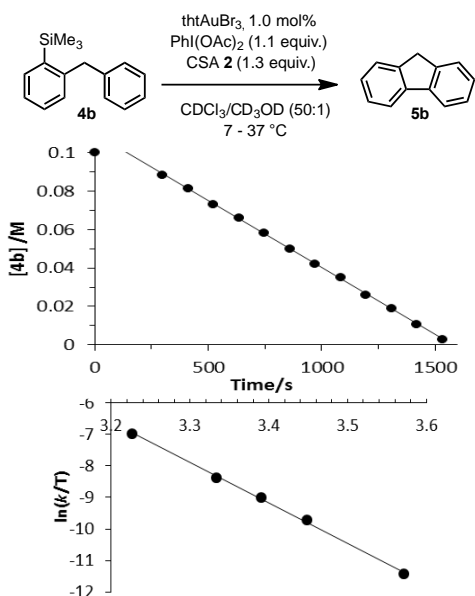

Figure 1. Top: Pseudo-zero order kinetics for consumption of **4b** in Au-catalyzed cyclization at 27 °C; d[**4b**]/dt = $-k_{obs}$t; where k_{obs} = 7×10^{-5} Ms[−1]; R² = 0.99. Bottom: Eyring analysis for cyclization of **4b** (0.1 M) with 1 mol% Au, ln(k/T) = 34.54 − (12.86 × 10³/T); R² = 1.00; ⧄$H^{\ddagger}$ = **+26** kcal mol^{−1} and ⧄$S^{\ddagger}$ = +21 e.u.

The pseudo-zero order kinetics preclude an intermolecular turnover limiting step, or an intermolecular pre-equilibrium, and thus cannot involve Au(I/III) redox by PhIX₂, or C-Si auration (Scheme 2). In a general sense, this confines the turnover-rate limiting step to being one of: intramolecular

π-complexation, C-H auration, reductive elimination, or another process, prior to Au(I/III) redox.

Eyring analysis, between 7 and 37 °C, afforded ⧄$S^{\ddagger}$ = **+21** e.u (Figure 1, lower); opposite in sign to the intermolecular arylation (Scheme 2 upper) where turnover-rate limiting π-complexation induces a strongly negative ⧄$S^{\ddagger}$.[9h] Although interpretation of activation parameters must be taken with care, the results suggest that the turnover-rate limiting step for the *intramolecular* system occurs *after* π-complexation, which would be expected to induce a small but negative ⧄$S^{\ddagger}$. Further experiments were performed to deduce which process prior to Au(I/III) redox, including C-H auration and reductive elimination, is turnover-rate limiting.

Deuterium Kinetic Isotope Effects In order to probe events before and after the turnover-limiting step, a range of deuterated substrates were deployed in intramolecular arylation, Scheme 4, equations 1-4. Control experiments confirmed that there is no deuterium-protium exchange before, during, or after cyclization, indicating that overall C–H / C–D cleavage is irreversible. The absolute rates of turnover of **4b** versus d_5-**4b** (Scheme 4, equation 1) were experimentally indistinguishable (k_H/k_D = 1.0). Thus the perdeuterated phenyl ring induces no significant primary or secondary kinetic isotope effect (KIE) on the overall rate of catalytic turnover. This eliminates C-H cleavage from consideration as the turnover-rate limiting step.
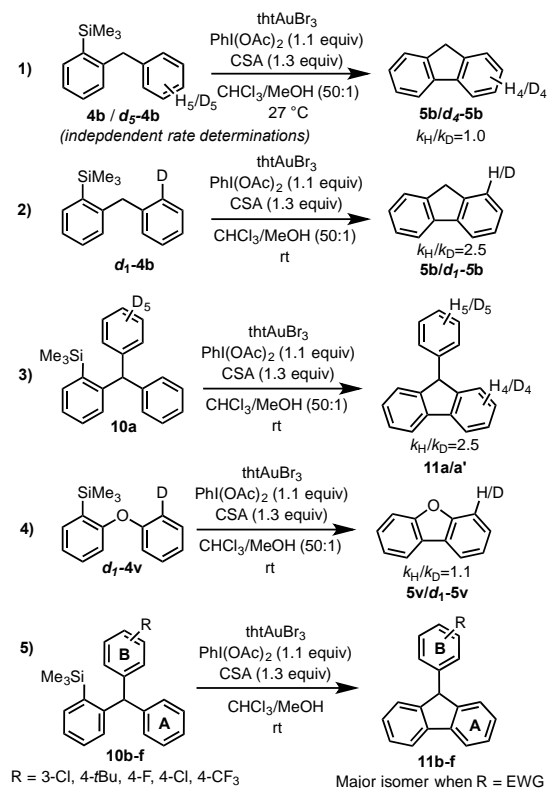
Scheme 4. KIEs (1-4) and substituent partitioning (5) for intramolecular Au-catalyzed arylation.

As noted by Schmidbaur, "η²-coordination to unsaturated and aromatic hydrocarbons is the key step in gold-catalyzed organic transformations",[17] and gold(III) has a long history of interacting with arenes. For example, it has been known for over 80 years that anhydrous $AuCl_3$ reacts readily with aromatic hydrocarbons leading C-H auration of the arene.[18] However, to date, all attempts to experimentally prepare stable molecules demonstrating Au•arene interactions have been unsuccessful.[17] Nonetheless, such η²-arene gold(III) π-complexes species have been explored computationally,[19] and are implicated as precursors to C-H auration. In our previous studies,[9h] this *intermolecular* π-complexation event was deduced to be turnover-rate limiting, and the relative rates of arylation a series of arenes shown to correlate with known stabilities of reference, Ag-π-arene complexes and HF/BF_3 Wheland-intermediates.[9h] However, there was no indication from any of the data obtained, whether prior to irreversible C-H auration, the arene π-complexation by Au is reversible, or not.

In contrast, this aspect can be tested with the intramolecular cyclization. Thus although no KIE is exhibited intermolecularly (**4b** versus d_5-**4b**), an intramolecular competition reaction employing d_1-**4b** was found to elicit a significant KIE (k_H/k_D = 2.5, equation 2) on the product distribution. In order for the primary KIE arising from C-H cleavage to impact on the product distribution (**5b** versus d₁-**5b**), the isotopomeric precursor η²-complexes (**8** and **9**, Scheme 5) must be able to equilibrate prior to irreversible, i.e. product-determining, C–H / C–D cleavage. Equilibration could occur within discrete Au-arene complexes (pathway **A**) or by reversible η²-complexation (pathway **B**). The same primary KIE (k_H/k_D = 2.5) was obtained with bis-arene d₅-**10** (Scheme 4, equation 3) confirming that Au-arene π-complexation is reversible, with C–H / C–D cleavage being product-determining, but not turnover-rate limiting (no KIE, Scheme 4 equation 1).
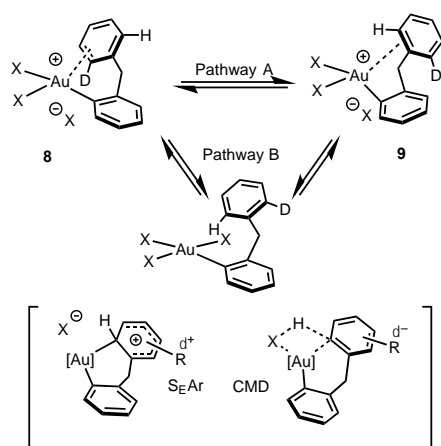
Scheme 5. η²-arene π-complexes and C-H auration mechanisms.

The KIEs outlined in equations 1-3 are consistent with both a concerted metalation-deprotonation (CMD) pathway,[20] and an aromatic electrophilic substitution (S_EAr)

pathway,[9h,18,21] both stemming from a presumed precursor η²-complex, Scheme 5. When the methylene bridge in d_1-**4b** is replaced with an *O*-atom linker, d_1-**4v**, the primary KIE is nearly eliminated (Scheme 4, equation 4), suggesting that the aryl-ether is able to sufficiently stabilize the π-complex (CMD), or the Wheland intermediate (S_EAr) such that one of these two steps, rather than the C–H / C–D cleavage, becomes product-determining.

C-H Auration via S_EAr versus CMD   Having established that, for **4b** and **10a**, C-H cleavage is irreversible and thus product-determining (Scheme 4, equations 1-3), we studied intramolecular competition (**10b**-**f**) between electronically biased pairs of arenes, equation 5. This allows distinction of reaction *via* a monoaryl gold Wheland intermediate (S_EAr) from C-H deprotonation of a π-complex (CMD), both leading to the same diaryl gold intermediate. A large negative ρ value was obtained (ρ = –3.7; see SI). In a concerted metalation-deprotonation (CMD) the acidity of the proton would be of importance[20b] and the net (negative) inductive effects of substituents will likely dominate, leading to a complex but overall *positive* ρ-correlation, which is not observed. In contrast, stabilizing (positive) inductive and resonance effects of substituents are expected to be of importance in an S_EAr process, leading to a *negative* ρ/ρ⁺-correlation.[22]

Turnover-limiting Reductive Elimination   Reaction rates (Ms⁻¹) were determined under standard conditions (0.1 M substrate, 2 mol% thtAuBr₃) for a series of 18 substrates in which the arene (**4a**-**m**) or arylsilane (*iso*-**4i**-**m**) or bears a substituent that is *meta* or *para* to the site of coupling in **5a**-**m**, Figure 2. In addition to singly substituted substrates, bis-silyl **12** and doubly-substituted **4t** / **13** were also tested. The kinetics were analyzed by way of a linear free-energy relationship (LFER) using the standard Hammett σ-function, affording a reaction constant (ρ) of –2.0.
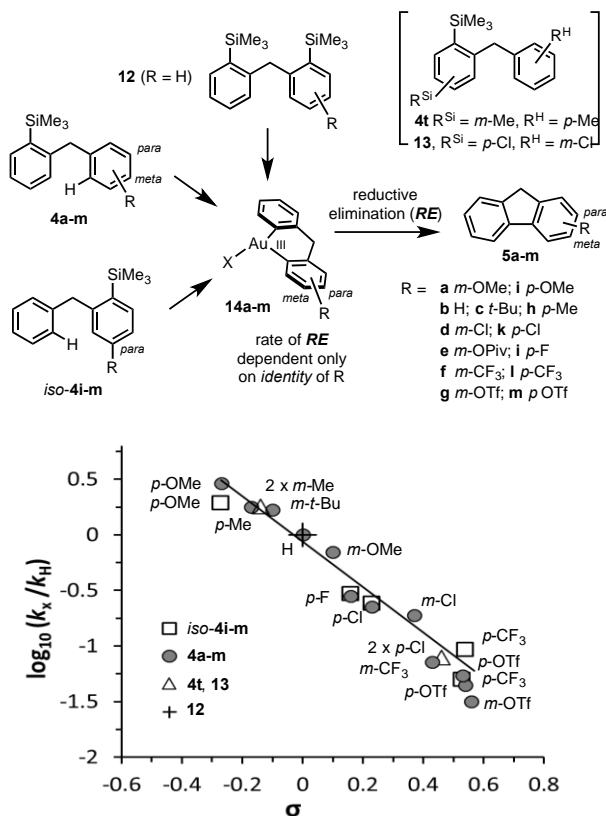
Figure 2. LFER analysis of rates of catalytic turnover during cyclization of **4a-m**; **4t**, *iso*-**4i-m**, **12**, and **13**; $\log_{10}(k_X/k_H) = -2.0\sigma\sigma - 0.06$;[23] σ-values are additive for **4t/13**. Conditions: substrate (0.05 mmol), thtAuBr$_3$ (2 mol%), 2-bromothiophene (0.5 mmol),[24] PhI(OAc)$_2$ (0.055 mmol), CSA (0.065 mmol), CDCl$_3$/CD$_3$OD (50:1, 0.1 M).

The correlation indicates that the impact of a substituent on the rate of catalytic turnover is independent of its provenance; *i.e.* whether it was initially on the arene (**4a-m**), the aryl-silane (*iso*-**4i-m**), or on both (**4t**, **13**). This requires that the substrates converge on a common intermediate, at, or prior to, the turnover-rate limiting step. This condition can be satisfied at any point *after* C-H cleavage to generate a diaryl-gold intermediate **14**. Further evidence for convergence at a common intermediate arises from the identical rates of turnover of *bis*-TMS **12** and *mono*-TMS **4b** (R = H), both of which generate **5b**, *via* the same intermediate (**14b**, R = H). Reaction of *bis*-TMS **12** thus involves a *second* C-Si cleavage, rather than C-H cleavage, at the stage of the mono-aryl-gold intermediate. The selective intramolecular C-Si versus C-H auration is again consistent with an S$_E$Ar process, with TMS-stabilization of the σ-cation in the Wheland intermediate being favored.[9h]

The pseudo zero-order kinetics observed for of *bis*-TMS **12** and *mono*-TMS **4b** limit the possibilities for the unimolecular turnover-rate limiting step to one of: ligand dissociation, or reductive elimination from a diaryl gold intermediate, e.g. **14**; a processes involving substantial reorganization or isomerization would not be consistent with the

large $\Delta S^{\ddagger}$ value.[25] Reductive elimination is rarely the turnover limiting step in C(sp^2)-C(sp^2) cross-coupling.[26] In most cases, oxidative addition or transmetalation is rate-limiting. Indeed, as a consequence of this, there has been a reliance on *stoichiometric* studies to indirectly investigate reductive-elimination in catalytic systems.[9g,9i,9j,27] Details relating to the kinetics and structures involved in reductive elimination of a biaryl moiety from diarylgold species are very sparse. There are very few examples of isolated diaryl gold complexes in which the aryls groups are simple, *i.e.* non-chelating.[9h,28] Nevado was able to isolate and characterize (X-ray)[9jk] the neutral biaryl complex [Ar$_2$Au(PPh$_3$)Cl] where Ar = C$_6$F$_5$, and found that forcing forcing conditions were required to trigger reductive elimination of perflurobiphenyl (150 °C, 20 h).[9j]

Pioneering studies by Kochi on trialkyl and dialkylgold phosphine complexes R$_3$Au(PPh$_3$) and R$_2$Au(PPh$_3$)X (where R = Me, Et; X = Cl, TFA, NO$_3$, OTf), revealed that that dissociation of PPh$_3$, leading to high-energy T-shaped species R$_3$Au and R$_2$AuX, precedes reductive elimination of R-R.[29] In most cases, reductive elimination was slow (k_{obs} = 10^{-6} to 10^{-7} s^{-1} at 45- 80 °C) and the liberated PPh$_3$ progressively inhibited reaction by disfavoring the dissociative pre-equilibrium required for reductive elimination. The exception to this trend was Me$_2$Au(PPh$_3$)OTf, which reductively eliminated very rapidly (k_{obs} >10s^{-1} at 25 °C). Notably, the possibility of an additional pathway for reductive elimination involving triflate ionization to generate *cationic* [Me$_2$Au(PPh$_3$)]+, rather than phosphine dissociation, could not be discounted.[29b]

More recently, Toste has confirmed that, for specific cases, phosphine dissociation is not necessary for reductive elimination to occur.[9g] The neutral complex [Ar$_2$Au(PPh$_3$)Cl], where Ar = *p*-C$_6$H$_4$F, was generated *in situ*, and found to more efficiently undergo reductive elimination (k_{obs} = 10^{-4} s^{-1} at −32 °C) than the analogous perfluoroaryl complex studied by Nevado.[9j] In contrast to the inhibiting effects of added phosphine noted by Kochi, addition of PPh$_3$, to generate the cationic bisphosphine complex [Ar$_2$Au(PPh$_3$)$_2$]$^+$, resulted in substantial rate enhancement (k_{obs} = 0.2 s^{-1} at −52 °C). This process is "among the fastest observed C–C bond-forming reductive couplings at any transition metal centre."[9g] The high reaction velocity is ascribed to a combination of Au(III)-destabilization by the formal cationic charge at the gold, and the driving force provided by steric decompression of the bulky triphenyl phosphine ligands as the biaryl elimination proceeds.[9g] Thus overall, a very wide range of rates have been determined for reductive R-R elimination from gold (III) species, with a number of factors, including coordination number, formal charge, steric demand of ligands, and the electron demand by the Ar / alkyl groups undergoing elimination, all contributing. The turnover-rates of the intramolecular Au-catalyzed process considered herein (up to 1 s^{-1}, 27 °C, **4n**, Table 1) are significantly slower than that of the stoichiometric reductive elimination from cationic [Ar$_2$Au(PPh$_3$)$_2$]$^+$, but not

dissimilar to that for the neutral complex [Ar$_2$Au(PPh$_3$)Cl].[9g,30]

On further investigation of the kinetics of the catalytic intramolecular arylation, the rate was found to be first-order dependent on [Au], with a complex inverse dependency on [MeOH]. The latter effect was explored in detail with **4b** (Figure 3) and it is unusual in that whilst the methanol acts as an inhibitor, it only does so in a partial sense: catalytic turnover still proceeds, albeit slowly, at very high methanol concentrations. Conversely, at very low methanol concentrations, or by replacing methanol with trifluoroethanol, a significant increase in reductive-elimination rate is observed for (Figure 3, $k_1 = 0.6$ s^{-1}, 27 °C; see SI for full details).
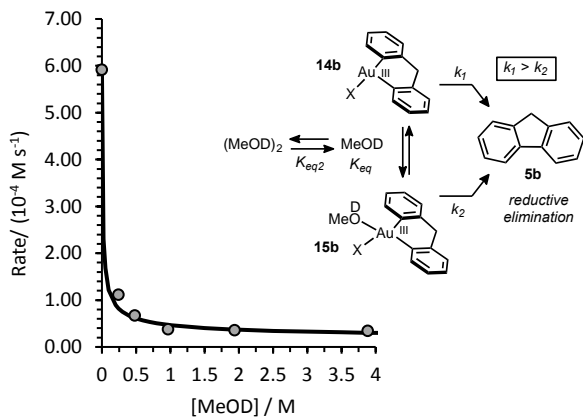

Figure 3. Effect of [MeOD] on the pseudo zero-order rate of catalyst turnover, k[Au] = (k_1[**14b**] + k_2[**15b**]); [Au] = 0.001 M, 27 °C. Circles: experimental data. Solid line: simulation based on catalytic rate law (see SI) for scheme shown, with $k_1/k_2 \geq 17$. Methanol is extensively dimerized in CHCl$_3$;[31] For $x = 0$, trifluoroethanol (0.27 M) replaces MeOD.

The phenomenon can be interpreted by analogy to the alkylgold phosphine complexes studied by Kochi, in that fast reductive elimination proceeds from a three-coordinate intermediate (**14b**) that is in equilibrium with a MeOH-complexed four-coordinate intermediate (**15b**). The difference here being that the four-coordinate intermediate (**15b**) can still undergo reductive elimination, albeit less efficiently ($k_1/k_2 \geq 17$; Figure 3). The analysis indicates that at under the standard reaction conditions (Table 1, Figure 1) where [MeOH] = 0.5 M, the catalyst resting state should be diarylgold complex **15b**, with the turnover-rate limiting process being a mixture of direct and indirect reductive elimination, from **15b** and **14b**, respectively.

Careful ^{1}H NMR spectroscopic analysis of the Au-catalyzed intramolecular arylation of **4b** in CDCl$_3$ / CD$_3$OD at 27 °C revealed that a transient low-intensity methylene signal, not attributable to either **4b** or **5b**, or to traces of a Ph$_2$CH$_2$ impurity, could be detected at a constant intensity, but only *during* turnover (see SI for full details). The signal is tentatively assigned to the ^{1}H nuclei in the –CH$_2$– tether in the catalyst resting state **15b**. Integration against an internal standard allowed analysis of the temporal concentration of

15b during catalytic arylation of **4b** conducted at three different Au-loadings (1.0, 1.5 and 2.0 mol%), Figure 4.
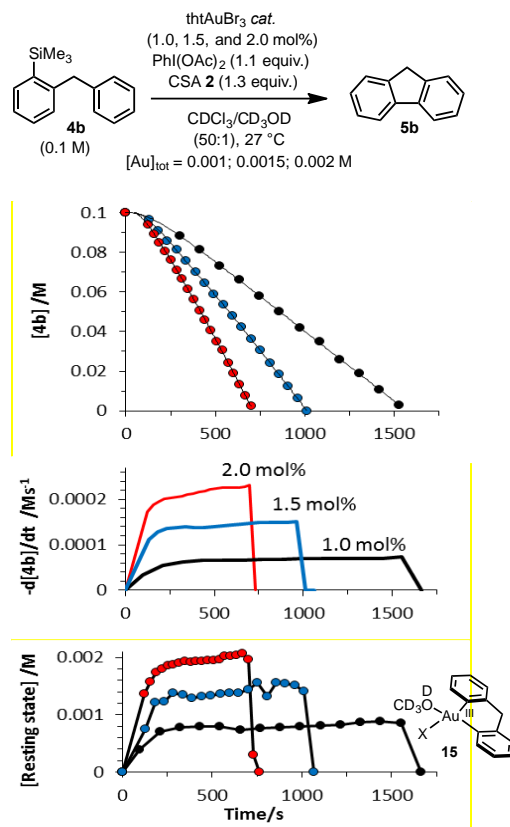

Figure 4 Top: Pseudo-zero order kinetics (after induction period, approx. 300 sec.)[9h] for Au-catalyzed intramolecular arylation of **4b** using 1.0, 1.5 and 2.0 mol % Au. Middle: temporal turnover-rate of **4b** /M s^{-1}. Bottom: temporal concentration of catalyst resting state (tentatively assigned as **15b**, see Figure 3).

Analysis of the steady-state maximum concentration of the transient species (resting state, **15b**; Figure 4, bottom) confirmed that it accounts for >90% of [Au]$_{tot}$. Moreover, the concentration of **15b** can be correlated with the temporal changes in turnover-rate (–d[**4b**]/dt, Ms^{-1}), Figure 5, middle. Thus the during the induction period (approx 300 sec.) the concentration of **15b** rises from zero to reach the steady-state, which is maintained throughout the pseudo zero-order phase of turnover. On complete consumption of substrate **4b**, the concentration of **15b** rapidly decays to zero.

Effect of aryl electron-demand and aryl-Au conformations on Reductive-Elimination rates The acceleration of reductive-elimination by electron-donating substituents (⌑ = – 2.0; Figure 2) is partially consistent with literature precedent for other Ar$_2$[M] complexes (M = Pt, Pd), where electron-withdrawing substituents are found to strengthen the ground-state metal-carbon bonds.[27b,32] Hartwig showed,

from LFER analyses, that reductive elimination from Ar$_2$[Pt] "is faster from complexes with a larger difference between the electron-donating properties of the two aryl groups."[27b,32] In other words, the electronic effects of substituent on reductive elimination rates *are not simply additive*. In contrast, a recent computational study on reductive elimination from *cis*-[AuPPh$_3$(Ar^1)(Ar^2)] complexes suggests that the electronic effect of aryl substitution is additive.[33] This is now experimentally confirmed: disubstituted compounds **4t** and **13** generate diarylgold intermediates (**14/15**) that reductively eliminate at the rates predicted by the sum of their ⌐-values (Figure 2).

Calculations on reductive elimination from unconstrained[28] [(Ar^1)(Ar^2)Au(PPh$_3$)Cl] and [(Ar^1)(Ar^2)Au(PPh$_3$)]$^+$ complexes also show that the lowest energy transition state for involves Au-Ar conformations in which the two aryl rings are oriented face-to-face.[33] If this arrangement is made less energetically accessible, e.g. by strain, tethering or chelation,[28] then reduced rates of reductive elimination will result. The methylene tether present in intermediates of type **14b/15b** (Figure 3) can provide exactly such a condition, Figure 5. Longer, non-rigid, tethers are expected to allow greater Au-Ar conformational mobility and thus a lower energetic barrier to the attainment of the requisite face-to-face orientation of the two aryl rings. As such, as the tether length is increased, the effective molarity of the arene available for the precursor C-H auration step would be reduced, whilst the rate of reductive elimination would increase. Such a situation would eventually lead to a change in the turnover-rate limiting step, *vide infra*.
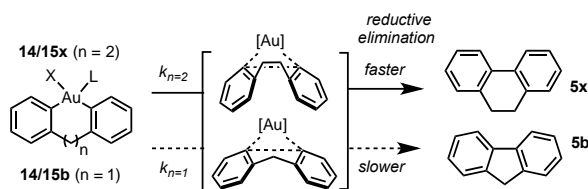

Figure 5. Effect of tether length (*n*) and flexibility on Ar–Au–Ar conformers from which developing Ar-Ar ⌐-facial interaction[28,33] can facilitate reductive elimination.

Reductive-Elimination versus ⌐-Complexation Whilst most cyclizations gave pseudo-zero order profiles (e.g. Figures 2), the two slowest-reacting examples (**4l**, **4g, Figure 2**), where the arene ring is substituted by electron-withdrawing CF$_3$ / OTF groups *meta* to the reacting C-H, showed distinct curvature.[34] The curvature was traced to autocatalysis by CSA, which grows in concentration as the oxidant is consumed.

Notably, CSA-dependent turnover was previously found in the intermolecular reaction,[9h] where it accelerates arene ⌐⌐-complexation to the aryl-gold(III) resting state. This suggested that for intramolecular examples where the arene ring is strongly electron-deficient at the site of C-H cleavage, the turnover-rate limiting step is arylation of a mono-aryl-

gold(III) (e.g. **17l**, Figure 6) rather than reductive elimination from diaryl-gold(III) (e.g. **14/15l**) . To test this hypothesis, we intermolecularly intercepted **17l** with a ⌐-rich arene, resulting in co-generation of biaryl **16**.[35] Towards the end of reaction of **4l**, when the CSA concentration is high, the rate of turnover approaches that of the pseudo zero-order kinetics of *iso*-**4l**, Figure 6. This is consistent with a partial transition of the resting state for cyclization of **4l** back towards the diaryl gold common intermediate (**14/15l**)
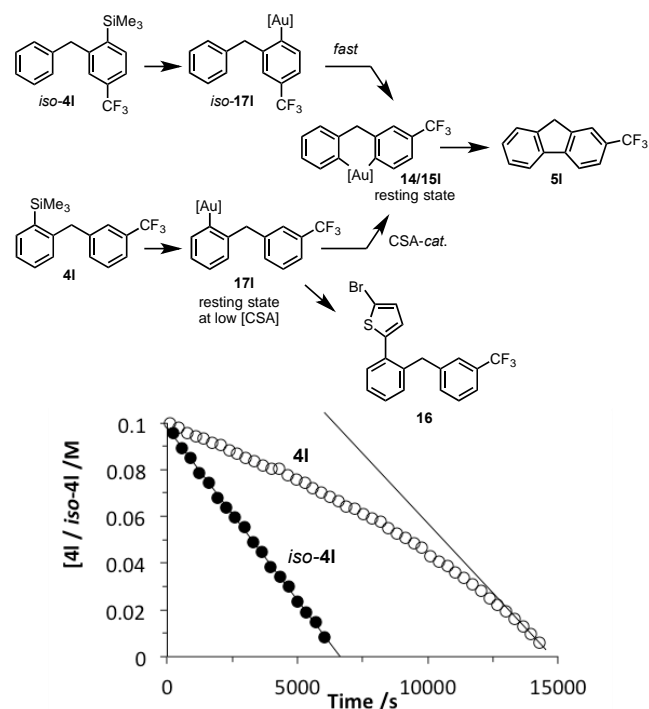

Figure 6. Kinetic profiles for of Au-catalyzed reactions of arenes **4l** and *iso*-**4l**; see text for full discussion. Conditions: **4l** /*iso*-**4l** (0.05 mmol), thtAuBr$_3$ (2 mol%), PhI(OAc)$_2$ (0.055 mmol), CSA (0.065 mmol), CDCl$_3$/CD$_3$OD (50:1, 0.1 M), 2-bromothiophene (0.5 mmol), 27 °C. See SI for an analysis of **5l** / **16** partitioning as a function of conversion for further evidence in support of a transition from a mono-arylgold (**17l**) to a diarylgold (**14l**) resting state.

Au-Ar conformational mobility The hypothesis that short tether lengths between the aryl rings restricts the Au-Aryl conformations available for reductive elimination from the diarylgold (**14/15**) resting state was tested by comparing the kinetics of a system containing a –CH$_2$– tether (**4b**) with a –CH$_2$CH$_2$– tether (**4x**). In the latter case, increase of the tether length by one methylene unit results in a kinetic profile (Figure 7) similar to that of **4l** (Figure 6). Thus, as reaction proceeds, the rising concentration of CSA (liberated from **2**) accelerates turnover rate. For **4x**, the rate rises to the point where, for the latter half of reaction, it is substantially faster than that observed in the pseudo-zero order profile of **4b**, for which reductive-elimination is turnover-rate limiting. In other words, the intrinsic rate of reductive-elimination in the longer –CH$_2$CH$_2$– tethered intermediate **14/15x**, must be *faster* than in the shorter –CH$_2$– tethered

intermediate **14/15b** (Figure 5).[36] A normal primary KIE of 1.9 was obtained on intramolecular competition using d_1-**4x**, indicative that Wheland intermediate generation is partially reversible (Scheme 6). Once again, stabilization of the Wheland intermediate by replacing the CH₂ linker by oxygen (d_1-**4aa**) eliminates the KIE.
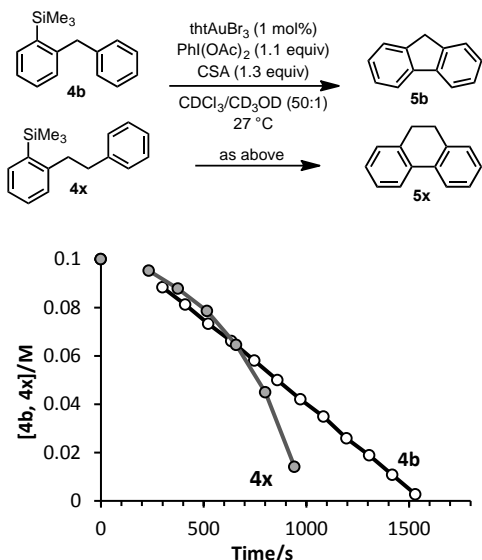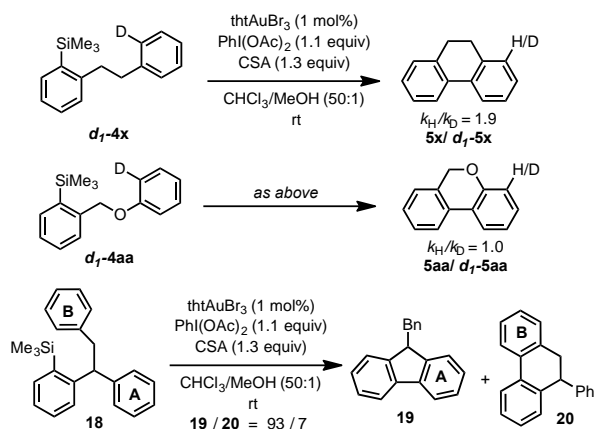

Figure 7. Turnover to generate 5- versus 6- membered rings. Initial concentration of **4b** and **4x** 0.1 M.

Scheme 6. KIEs for 6-membered ring cyclization of **4x** and **4aa**, and intramolecular competition (**A** versus **B**) to generate 5-membered (**19**) versus 6-membered (**20**) rings.

The impact of tether length (n = 1, 2) was further explored by intramolecular competition using **18** (Scheme 6). The 5-membered ring cyclization outcompetes the 6-membered ring forming process by a factor of 13, consistent with *selectivity-determining*, *i.e.* irreversible, C-H cleavage after Wheland intermediate generation by ring **A**.[37]

Conclusions

In 2012 we introduced a gold-catalyzed intermolecular direct arylation reaction that uses arylsilanes to generate highly electrophilic Ar-Au intermediates capable of arylating arenes at ambient temperature.[5] The reaction has proven to be a high-yielding, mild and efficient process for the coupling of a wide variety of arylsilanes with electron rich arenes, and heteroarenes.[5-8] In the study reported herein, an intramolecular arylation has been developed, both as a preparative process, and as a vehicle for mechanistic study. Using a standard set of conditions, 44-examples of annelated-biaryls, with ring sizes ranging from 5- to 9-membered, including heteroatoms and a diverse range of arene substituents, have been prepared under mild conditions at ambient temperature (Table 1).[38] Whilst the majority of the reactions proceed with minimal side-product generation, some highly electron-rich substrates, are susceptible to an direct reaction with the *in situ* generated HCIB oxidant (**2**), resulting in diaryliodonium salts. In such cases, PIFA (**3**) can be used as a milder oxidant to bypass this undesired side reaction. This is effect is unique to the intramolecular process, and facilitates the clean arylation use very electron-rich arenes such as the trimethoxy phenyl system found in the allocholochinoid (allocolchinoid)skeleton **7**,[15] Scheme 3.

Rendering the arylation process intramolecular also induces a number of useful features for mechanistic investigation. Firstly, unlike the intermolecular system, the vast majority of the intramolecular substrates undergo turnover with simple and reproducible kinetics, without complications from side reactions such as direct arene oxidation or arylsilane homocoupling. Secondly, only electron rich arenes can be employed in the intermolecular reaction, limiting the range of arene substituents that can be explored in linear free-energy relationships. In contrast, the intramolecular system tolerates a wide range of arene substituents, and the kinetics for substrates bearing substituents with σ-values ranging from −0.3 to +0.6 have been determined. Thirdly, relative to all of the other steps in the intermolecular catalytic cycle other than the Au(I)/Au(III) redox, reductive elimination from diaryl gold(III) is a fast process. This means that it has not previously been possible to acquire kinetic data to reveal the influence of substituents on the rate of the key C-C bonding forming process. In contrast, the intramolecular system allows two effects to be used in concert: high effective molarity of the arene raises the velocity of the C-H auration step, whilst close-tethering of the aryls can decrease the velocity of the reductive elimination. In certain cases these two effects have been sufficient to move the catalyst resting state to the diaryl gold(III) intermediate, allowing a detailed analysis of the influence of substituents on the rate of reductive elimination step. Using the unique features of the intramolecular variant of the arylation process, we have been able to deduce the following new mechanistic information:

i) Electron-donating substituents accelerate reductive elimination and rate predicted by sum of sigma values.

ii) Reductive elimination can be *via* a fast reacting 3-coordinate species or slow reacting 4-coordinate species.

iii) Data consistent with S$_E$Ar mechanism, not CMD.

iv) a key mechanistic outcome

In summary, the investigation of catalytic reaction mechanism plays an important role of the discovery and development of new synthetic methodology. It can lead to useful generalizations and principles for in the design, optimization and application of reactions. However, it is often found that mechanistic studies are inherently limited to a small collection of well-behaved substrates, or to a narrow range of accessible reaction conditions. In such cases, the mechanistic information that is elucidated must be extrapolated with caution, even if it is applied to what may appear to be a closely related system: the assumption that the same parameters and constraints apply, may not hold. The results presented herein demonstrate exactly such a situation. Even small changes in the substrate structure lead to quite different mechanistic behaviors. Thus by changing a single aryl substituent from being mildly electron-withdrawing to mildly electron-donating, or by varying the length of the tether between the aryl silane and the arene by one methylene unit, the turnover-rate limiting step can switching from one side of the catalytic cycle to the other (see red arrows, Scheme 7).
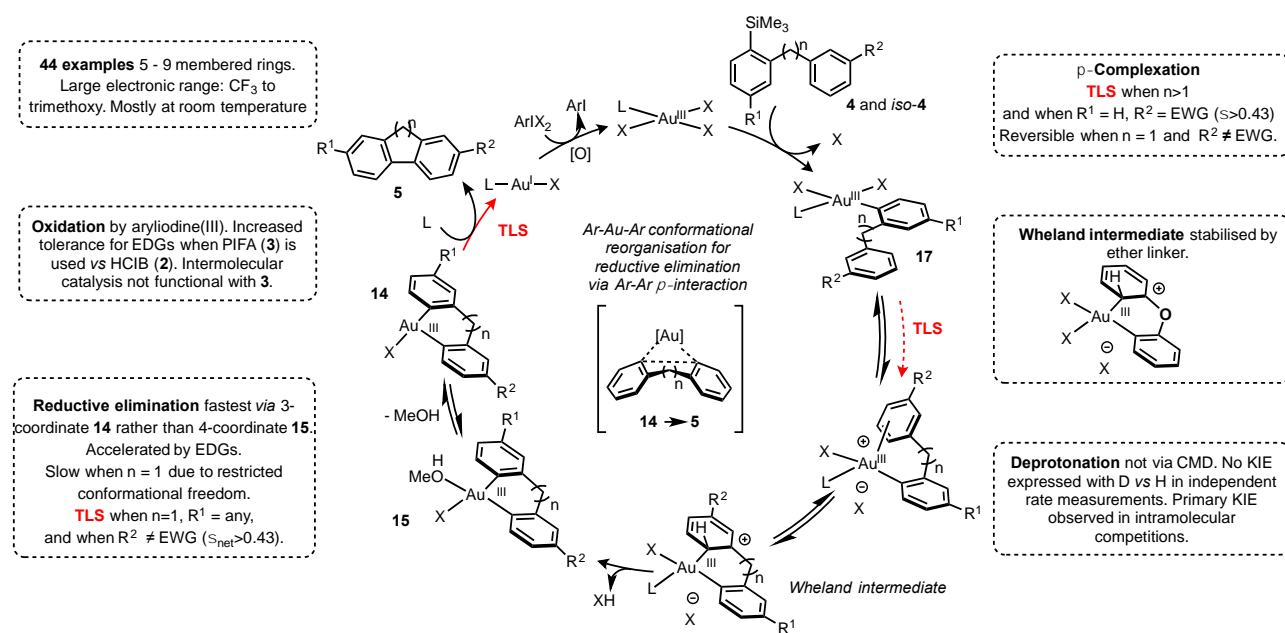
Scheme 7. NEEDS EDITING Mechanism of Au-catalyzed cyclization, **4** → **5**, with turnover-rate limiting step (TLS) proceeding *via* a mono-aryl (**17**) or diaryl (**14**) gold resting state, depending on tether-length (*n*), and electronic influence of substituents (R^1,R^2)

ASSOCIATED CONTENT

Additional discussion, experimental procedures, kinetic data, characterization data, and NMR spectra. This material is available free of charge via the internet at

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Notes The authors declare no competing financial interest.

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(22) A 'normal' ρ value would be expected for π-complexation, whereas a ρ$^+$ value would be expected for Wheland intermediate generation, see reference 9h. The KIEs obtained with **10a** indicate π-complexation is reversible for simple phenyl rings. However, the rate data do not give an ideal linear correlation, and the electronically biased rings in **10b-f** may shift the process away

(23) from Curtin-Hammett control such that the ratios begin to reflect the equilibrium population.

(23) Standard Hammett ⊡-values were employed (Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev*. **1991**, *91*, 165– 195) except for the value for *p*-F where, in our experience, ⊡$_p$ = 0.15 (Shulgin, A. T.; Baker, A. W. *Nature*, **1958**, *182*, 1299) is better parameterized *for reactions in non-aqueous media*, as compared to the standard value of ⊡$_p$ = 0.06 which was determined in water.

(24) Kinetic profiles obtained with electron deficient arylsilanes were partially non-linear, this was resolved by addition of 2-bromothiophene. The detailed kinetics of this phenomenon are currently under investigation. Arenes **4l** (p-CF$_3$) and **4g** (m-OTf) also gave curved kinetic profiles (i.e. imperfect pseudo zero order kinetics) that were not linearized by addition 2-bromothiophene. The rate averages were employed for the correlation, and are slightly lower than predicted by $\log_{10}(k_X/k_H) = -2.0⊡ - 0.06$. See Figure 6 and associated text for more detailed discussion, and SI for rate limits.

(25) It should be noted that because the kinetic analyses were performed at a methanol concentration where this process is not saturated (see Figure 3), the Eyring analysis and associated enthalpy and entropy of activation may be affected by a pre-equilibrium involving methanol and therefore not fully reflect the true activation barriers for reductive elimination.

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(28) Reductive elmination from chelated Ph-Au(X)-(Ar-*N*-donor) complexes requires addition of PPh3 to displace the *N*-donor: Vicente, J.; Dolores Bermudez, M.; Escribano, J. *Organometallics* **1991**, *10*, 3380–3384; see also reference 9i

(29) a) Komiya, S.; Albright, T. A.; Hoffmann, R.; Kochi, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 7255–7265; b) Komiya, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 7599–7607; c) Tamaki, A.; Magennis, S. A.; Kochi, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 6140–6148.

(30) Use of the reported activation parameters (ref 9g) for Ar$_2$Au(PPh$_3$)Cl, indicates that the rate of reductive elimination of this system at 27 °C is about 5 s^{-1}.

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(32) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936–1947.

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(34) The curvature does not arise from a longer induction period; pre-catalyst activation is complete in around 300 seconds[9h] (based on analysis of Ar-Br co-products, see SI) this being less than 2% of the time taken for complete turnover of the substrate.

(35) Control experiments confirmed that the pseudo-zero order rate profile for cyclization of *iso*-**4l** is *independent* of CSA concentration, consistent with turnover of *iso*-**4l** via reductive elimination from the normal diaryl gold **14/15l** resting state. For systems bearing a –CH_2– tether, the transition between mono and diarylgold resting states is only observed for examples **4l** and **4g**, where the arene ring bears strongly electron-withdrawing groups (Σ_{net} ≥0.43). The analogous bromothiophene-trapped products were not obtained with any substrates where Σ_{net} <0.43.

(36) At this stage we cannot assess how much faster the reductive elimination to the 6-membered ring is, as the change in kinetic profile also suggests a change in the TLS; thus turnover-rate may be limited by π-complexation or reductive elimination, or both, at different stages in the reaction evolution.

(37) This selectivity may arise from the differential developing strain in 6-membered versus 7-membered aurocycles generated from rings **A** / **B** respectively.

(38) This aplies to all but **4ai** (Table 1, entry 18) which required heating to 50 °C.