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Gold-Catalyzed C−H Functionalization with Aryl Germanes

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S *Supporting Information*

ABSTRACT: The development of orthogonal C_{sp^2}−C_{sp^2} coupling regimes to the omnipresent Pd-catalysis class would enable an additional dimension of modularity in the construction of densely functionalized biaryl motifs. In this context, the identification of potent functional groups for selective transformations is in high demand. Although organogermanium compounds are generally believed to be of low reactivity in homogenous catalysis, this report discloses the highly efficient and orthogonal reactivity of aryl germanes with arenes under gold catalysis. The method is characterized by mildness, the employment of an air- and moisture-stable gold catalyst, and robustness. Our mechanistic studies show that aryl germanes are highly reactive with $Au^{(I)}$ and $Au^{(III)}$. Our computational data suggest that the origin of this reactivity primarily lies in the relatively low bond dissociation energy and as such low distortion energy to reach the key bond activating transition state.

KEYWORDS: *gold catalysis, organogermanium, transmetalation, CH functionalization, cross-coupling*
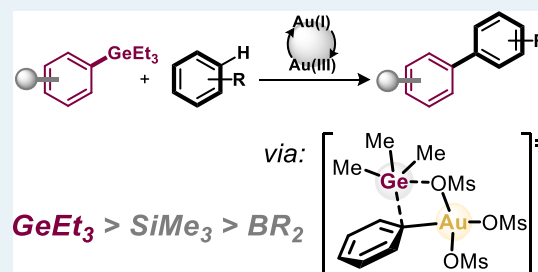
Owing to its ubiquitous presence in natural products, pharmaceuticals, and materials,[1] the biaryl motif is ideally constructed in a modular and diversifiable synthetic approach, as this would maximize opportunities for further functionalizations. Although Pd-catalyzed cross-coupling reactions of aryl halides with aryl boronic acids/esters, silanes, stannanes, or organometallic reagents are most widely applied to construct C_{sp^2}−C_{sp^2} bonds,[2] a key requirement to maximize diversity is the ability to selectively and sequentially couple at one site over all alternatives, for example, in polyhalogenated arenes. Although significant progress has been made in this direction,[3] another powerful strategy would be to devise completely orthogonal C_{sp^2}−C_{sp^2} bond-forming methodology that would not interfere with those functionalities that are so valuable in the established Pd-catalysis regime (see Figure 1). Ideally, the strategy also minimizes the requirement for prefunctionalization of arenes and allows for direct C−H arylation.[4] In this context, gold-catalyzed C−C coupling strategies are highly promising.[5] Lloyd-Jones and co-workers pioneered that biaryls can be formed under gold catalysis via coupling of aryl silanes with Ar−H bonds while tolerating aryl halides (Figure 1).[6,7] Detailed mechanistic investigations showed that the employed $Au^{(I)}$ catalyst is initially oxidized to a highly reactive noncoordinated $Au^{(III)}$. The $Au^{(III)}$ then activates the aryl silane ($ArSiR_3$), followed by activation of Ar−H.[8] Larrosa recently widened the mechanistic and synthetic repertoire and showed the direct C−H coupling of perfluorinated arenes with highly electronically activated arenes (with the help of silver).[9] Nevado and co-workers demonstrated the coupling of electron-deficient polyfluorinated aryl boronic ester derivatives (ArBPin) with Ar−H at elevated temperatures (>130 °C).[10] The ArBPin was found to also be activated at $Au^{(I)}$ (potentially forming $Au^{(I)}$−Ar prior to
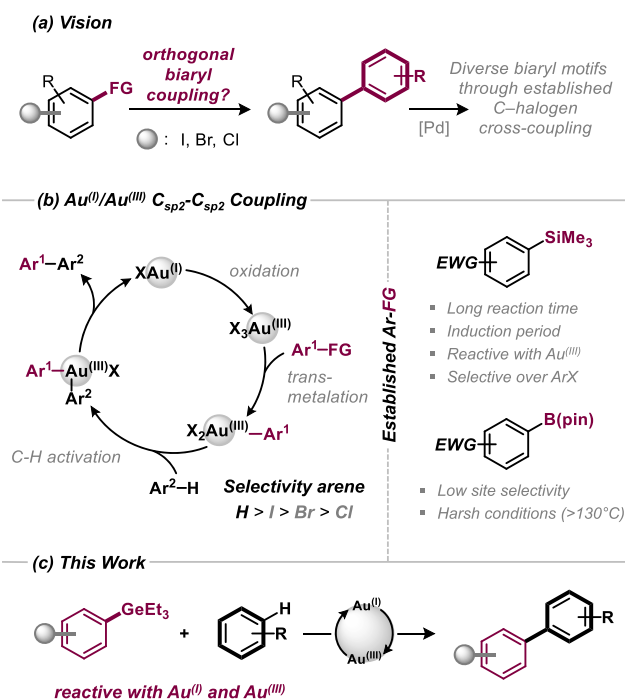

Figure 1. Gold-catalyzed C−H functionalization as potential synthetic tool for orthogonal diversification.

oxidation to the $Au^{(III)}$ intermediate).[5] Given that $ArSiR_3$ and ArBPin are valuable functionalities also for numerous other
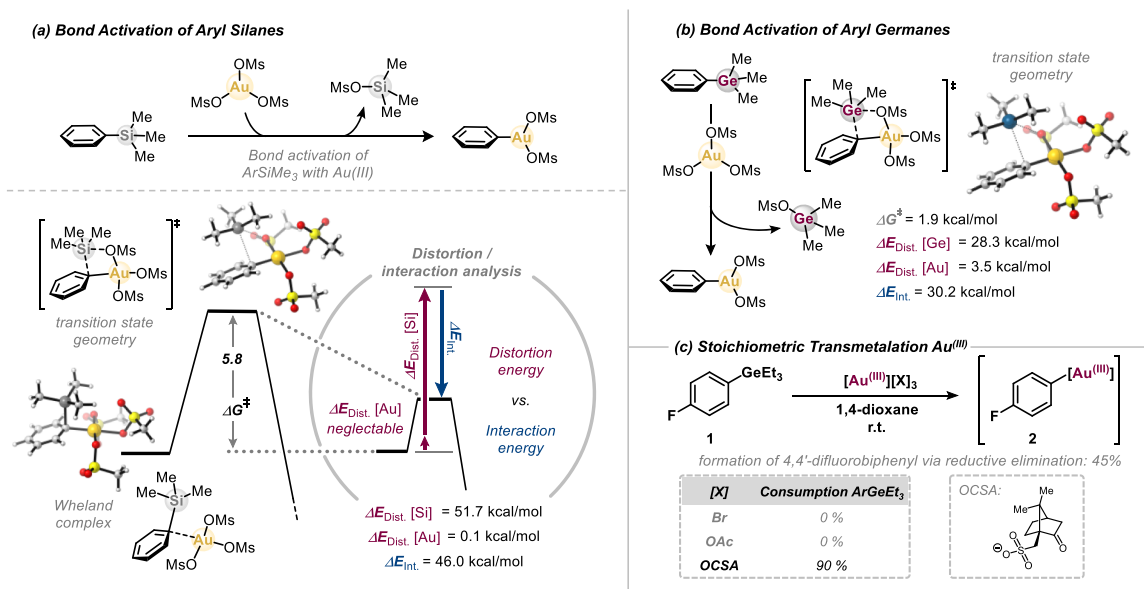
Figure 2. Computational and experimental investigation of bond activation of ArSiMe₃ and ArGeEt₃ with Au(III). Transition-state barriers were computed at the CPCM (dioxane) M06L/6-311++G(d,p)//ωB97XD/6-31G(d) [with LANL2DZ for Au] level of theory. For computational and experimental details, see the Supporting Information.[12] OCSA = camphorsulfonate.

Table 1. Scope of Gold-Catalyzed C−H Functionalization[a]
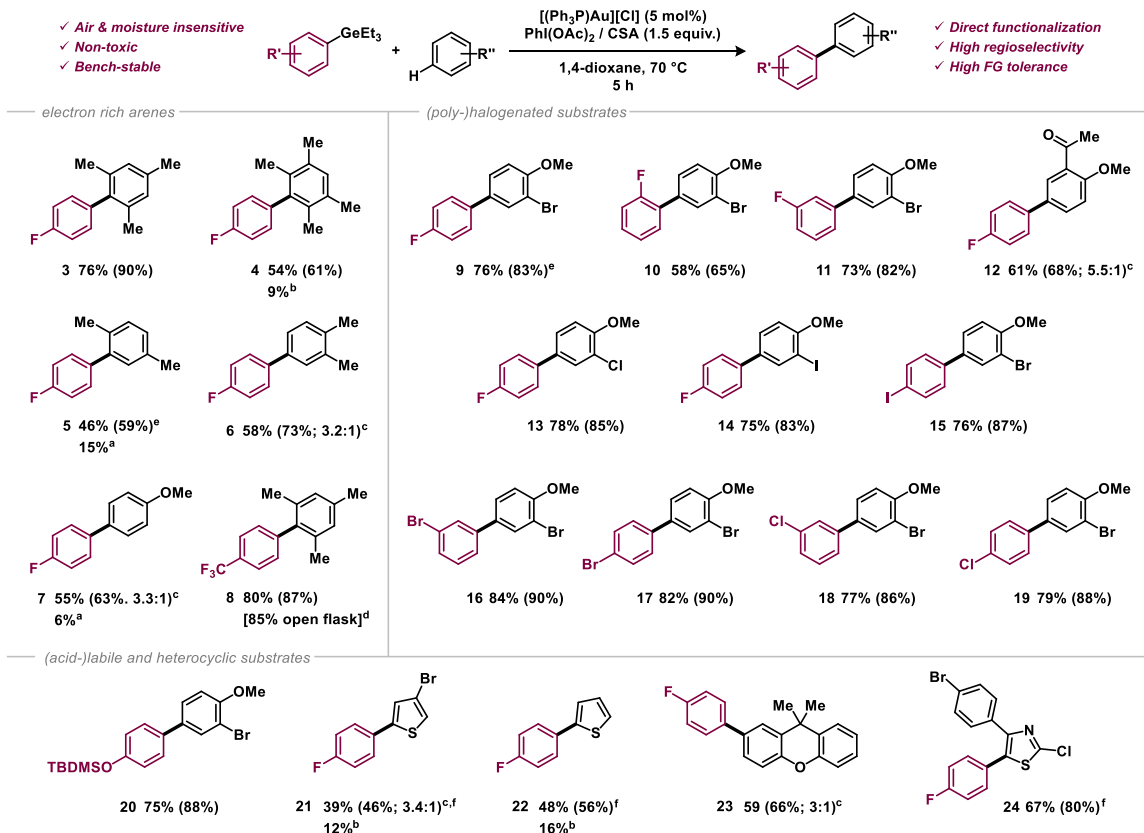
[a]Yields of isolated products are given (¹H or ¹⁹F NMR yields are given in parentheses). [b]Yield for the products of double C−H functionalization of the arene. [c]Formation of two regioisomers, ratios given in parentheses. [d]Determined by quantitative ¹⁹F NMR. [e]Reaction time: 2 h. [f]Reaction time: 16 h. For experimental details, see the Supporting Information.

bond formations,[1,2] for example, halogenation, amination, or Pd-catalyzed carbon−carbon and carbon−heteroatom bond formation, and as such are powerful handles for downstream follow-up decorations of biaryl motifs, we set out to identify

potential alternatives with a view to maximize modularity and synthetic diversity. As part of our program in chemoselective functionalizations,[3,11] we initially embarked on understanding the factors that dictate the reactivities in the activation of

ArSiR$_3$ by Au$^{(III)}$ and calculated the crucial transition state. We studied an electrophilic aromatic substitution-type reactivity, as suggested by Lloyd-Jones for ArSiR$_3$, with [Au$^{(III)}$(OMs)$_3$] as model complex.[12,13] The key bond activation is illustrated in Figure 2a; a Wheland-type intermediate was found to initially form, which then proceeds to Ar−Si bond scission. We also further analyzed the key components that dictate this step, and performed a distortion/interaction analysis, comparing the energies of geometrically distorted fragments of the transition-state structure with the corresponding structures of the preceding intermediate.[14] Interestingly, although the total distortion and interaction energies are of similarly high magnitude, the distortion energy originates nearly exclusively from the Ar−Si bending and stretching ($\Delta E_{\text{Dist.}}$ = 51.7 kcal mol^{-1}), whereas the Au$^{(III)}$ essentially remains geometrically unchanged ($\Delta E_{\text{Dist.}}$ = 0.1 kcal mol^{-1}).

Given that distortion energy usually roughly correlates with homolytic bond dissociation energies (i.e., bond strength, BDE),[15] we envisioned that a reaction partner with lower BDE, but similar interaction capability might be an excellent match for the reactivity requirements of gold.

We therefore targeted organogermanium compounds, which are characterized by lower BDEs (ΔH_{BDE} = 94.9 kcal mol^{-1} for Ph-SiMe$_3$ and 85.2 kcal mol^{-1} for Ph-GeMe$_3$).[16] Moreover, the few articles that appeared in the context of Pd-catalyzed cross-coupling of aryl halides with organogermaniums as coupling partners concluded that they are of relatively low reactivity, and certainly inferior relative to established alternatives (e.g., aryl boronic acids, -stannanes, or organometallic reagents),[17] which constitutes an advantageous feature for our goal of devising a fully orthogonal biaryl coupling system. Interestingly, our computational examination of Ar-GeMe$_3$ activation by Au$^{(III)}$ indeed predicted a roughly 70% lower barrier than for aryl silanes (Figure 2b).

Encouraged by these data, we set out to experimentally examine the reactivity of aryl germanes with Au$^{(III)}$. To the best of our knowledge, there is no precedence nor knowledge of the reactivity of aryl germanes with gold (neither stoichiometric nor catalytic). ArGeEt$_3$ are readily accessible by reaction of aryl Grignard reagents with commercially available Et$_3$GeCl. We chose the air- and moisture-stable and nontoxic PhGeEt$_3$ for our studies and tested its stoichiometric reactivity with various Au$^{(III)}$ sources (see Figure 2c). Although AuBr$_3$ or Au(OAc)$_3$ did not lead to marked reactivity, there was complete consumption of PhGeEt$_3$ 1 with [Au$^{(III)}$(OCSA)$_3$] (OCSA; formed in situ) at room temperature. As such, Ar−Ge activation by gold is indeed feasible, provided there are noncoordinating counterions at gold.

With this novel reactivity finding made, we set out to examine whether catalysis and C−H functionalization is also feasible with aryl germanes. Building on Lloyd-Jones conditions as a starting point,[6a] which involve the use of 2 mol % [(Ph$_3$P)Au$^{(I)}$(OTs)] as the catalyst and PhI(OAc)$_2$ and camphorsulfonic acid (CSA) to form the oxidant PhI(OCSA)$_2$ in situ, we tested the reactivity of aryl germane 1 with 2-bromoanisol in CHCl$_3$/MeOH (50:1). To our delight, the desired biaryl 9 was obtained in 84% yield at room temperature within 36 h.

Upon further investigation, we found that the aryl germanes are also efficiently catalyzed with commercially available gold chloride, [(Ph$_3$P)AuCl], and 1,4-dioxane as a convenient, nonprotic solvent. We subsequently set out to explore these new conditions for a wider range of arenes and aryl germanes.

Pleasingly, the C−H functionalization proceeded in a selective manner for a variety of substrates of different substitution patterns and steric hindrance (see Table 1). Although we saw complete conversion at room temperature, heating at 70 °C allowed for significantly shorter reaction times. Sterically demanding ortho, ortho-disubstitution on ArH (3, 4, and 8) was just as well tolerated as aryl halides (9−11, 13−19). The method was compatible with iodides, bromides, and chlorides on both the ArH (e.g. 10, 13, 14) and ArGeR$_3$ (15−19) reaction partners. These carbon−halogen bonds constitute powerful synthetic handles for further selective functionalization.[3] Similarly, the pharmaceutically and agrochemically important fluorine and trifluoromethyl group (8) were well tolerated. Ar−F in principle offers another diversification possibility through modern Ni-catalyzed or base-mediated coupling strategies.[18]

Other functional groups, such as the TBDMS-protected phenol 20 and pharmaceutically relevant heterocycles (i.e., xanthene 23) could be tolerated under the applied reaction conditions (Table 1). Moreover, thiazole 24, derivatives of which have been reported to exhibit physiological activity as COX-1 inhibitors,[19] was similarly formed in high yield, showcasing the applicability of this methodology in the synthesis of high-value biaryl motifs. Notably, aryl silanes were previously shown to display excellent functional group tolerance in such biaryl syntheses;[6a] the scope with aryl germanes is similar. As all reaction components, including the employed catalyst [(Ph$_3$P)AuCl], are air- and moisture-stable, we also tested the reaction to make hindered biaryl 8 open to air. We saw essentially the identical reaction outcome as under exclusion of oxygen, suggesting that just like for silanes,[6a,8] the gold-catalyzed coupling of aryl germanes is tolerant to oxygen and moisture also.

We next investigated the relative reactivity of ArGeR$_3$ compared to ArBpin or ArSiR$_3$ under our reaction conditions. It has previously been shown that the relative reactivity of ArSi versus ArBR can in principle be modulated through appropriate modification of conditions.[10] Intermolecular competition experiments under our catalysis conditions gave full consumption of ArGeEt$_3$ (25), whereas ArSiMe$_3$ (26) and ArBpin (27) were fully recovered after 12 h (Figure 3),[20] in accord with the observed relative speed of conversion over time ArGe > ArSi ≫ ArBR (see Figure 3a).[21]

There was no induction period; the aryl germane is consumed from the beginning and transformed to the biaryl product in a relatively rapid fashion (see Figure 3). Given the observed high reactivity with Au$^{(III)}$, we wondered about the feasibility of aryl germanes to potentially also react with the less activated oxidation state (I) of gold. Eventually this might offer additional opportunities and flexibility for catalysis developments in terms of employed oxidants and conditions, being less dependent on the relative kinetics of oxidation versus transmetalation. Aryl silanes were previously shown to be unreactive with Au$^{(I)}$,[8] whereas ArBPin is reactive with Au$^{(I)}$ as long as acetate is present as counterion to the gold cation.[10,22]

Pleasingly, we found that subjecting aryl germane 28 to [(Ph$_3$P)Au$^{(I)}$(OMs)] at room temperature resulted in full consumption of 28 (see Figure 4), showcasing that aryl germanes—although no ideal partner in homogeneous Pd$^{(0)}$/Pd$^{(II)}$ catalysis—are an optimal match for gold (Figure 4). In line with these findings, our DFT studies suggest a relatively facile activation by [(PPh$_3$)Au$^{(I)}$OMs]. A $\Delta\Delta G^{\ddagger}$ = 8.8 kcal
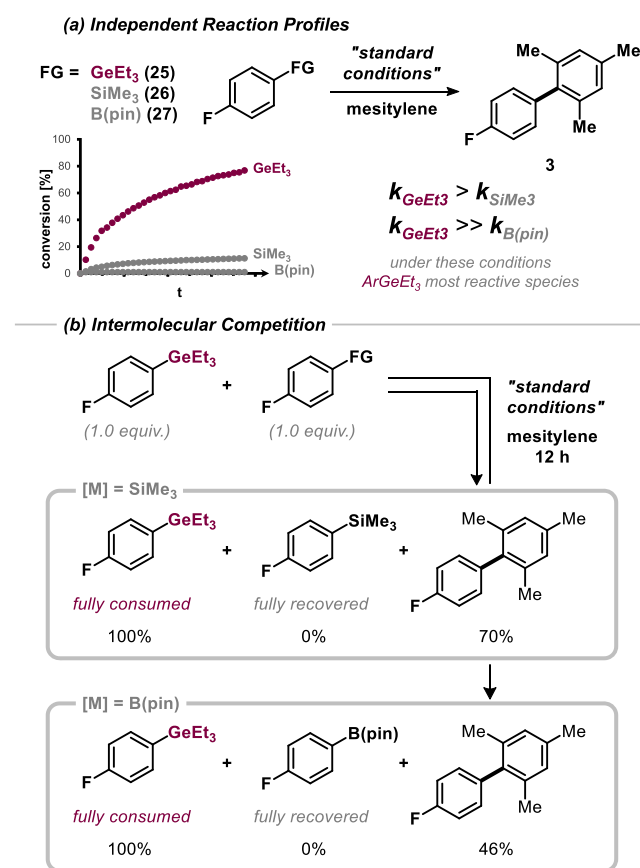
(a) Independent Reaction Profiles

FG = GeEt$_3$ (25)
   SiMe$_3$ (26)
   B(pin) (27)

"standard conditions"
mesitylene

$k_{GeEt3} > k_{SiMe3}$

$k_{GeEt3} \gg k_{B(pin)}$

under these conditions
ArGeEt$_3$ most reactive species

(b) Intermolecular Competition

+

(1.0 equiv.)   (1.0 equiv.)

"standard conditions"
mesitylene
12 h

[M] = SiMe$_3$

fully consumed   *fully recovered*

100%   0%   70%

[M] = B(pin)

fully consumed   *fully recovered*

100%   0%   46%

Figure 3. ArGeEt$_3$, under these conditions most reactive site compared to ArSiMe$_3$ and ArB(pin). Standard conditions: [(Ph$_3$P)-Au][Cl] (5.0 mol %), PhI(OAc)$_2$ (1.5 equiv), CSA (1.5 equiv) in 1,4-dioxane (0.3 M) at 70 °C. Quantification by ^{19}F NMR analysis.

(a) Bond Activation Au$^{(I)}$

$\Delta G^{\ddagger}$ = 14.9 kcal/mol
$\Delta E_{Dist.}$ [Ge] = 67.3 kcal/mol
$\Delta E_{Dist.}$ [Au] = 7.1 kcal/mol
$\Delta E_{Int.}$ = 61.2 kcal/mol

transition state geometry

(b) Stoichiometric Transmetalation Au$^{(I)}$

[Au$^{(I)}$][X]

1,4-dioxane
r.t.

28

formation of anisol via protodeauration: 96%

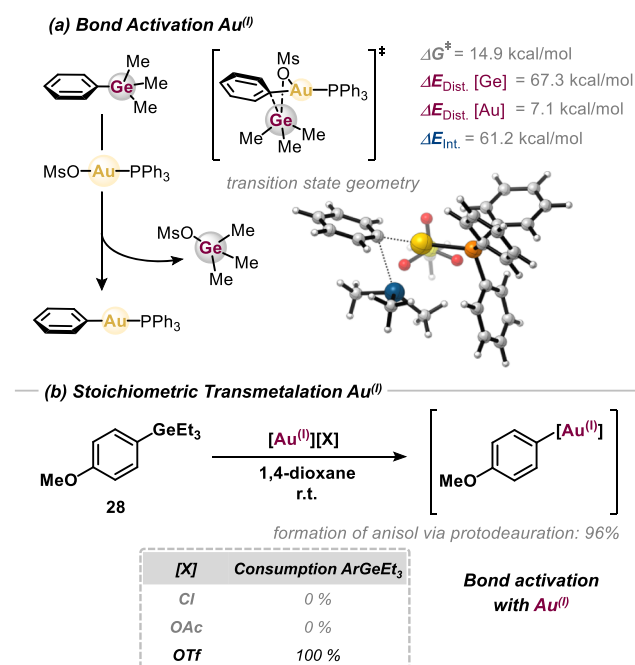| [X]	Consumption ArGeEt$_3$	
Cl	0 %	**Bond activation**
OAc	0 %	**with Au$^{(I)}$**
OTf	100 %	

Figure 4. Computational and experimental investigation of bond activation of ArGeEt$_3$ with Au$^{(I)}$. Energies calculated at the CPCM (dioxane) M06L/6-311++G(d,p)//ωB97XD/6-31G(d) [LANL2DZ for Au] level of theory.

mol^{-1} lower activation free-energy barrier was calculated for PhGeMe$_3$ than for PhSiMe$_3$, in line with the experimental observations that showed no bond activation with silanes.[23]

Our further studies revealed that aryl germanes undergo activation with a variety of Au$^{(I)}$ complexes, as long as the counterion of gold is noncoordinating: [(Ph$_3$P)Au$^{(I)}$][X] with X = OTf or BF$_4$ were all found to efficiently react with Ar-GeR$_3$ **28** (see Figure 4 and the Supporting Information for details). By contrast, the bond activation of boronic ester derivatives on Au(I) proceeds exclusively with the OAc– counterion; other boronic acid derivatives typically require OH– or F– counterions.[10,23,24] Ultimately, in catalysis, the employed oxidant will end up as counterion on Au$^{(I)}$. As such, the tolerance of different counterions might offer possibilities to develop and employ different catalysis conditions to modulate selectivity and/or substrate scope.

In conclusion, aryl germane—long thought to be of low reactivity in catalysis and C–C coupling reactions—presents itself as a versatile, nontoxic, air- and moisture stable reaction partner in gold-catalyzed couplings with arenes. As opposed to silanes, aryl germanes are reactive with both Au$^{(I)}$ and Au$^{(III)}$, much like the corresponding boron reagents, albeit under milder conditions and with different gold counterions. Our computational studies identified relatively low distortion energy as a consequence of the lower BDE as the primary origin of high reactivity of aryl germanes with gold, allowing for efficient couplings with arenes and offering a new reactivity mode in the toolbox of selectivity and cross coupling.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b02841.

> Computational details and data, experimental procedures, and spectroscopic data for compounds including ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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