Site-Selective C−S Bond Formation at C−Br over C−OTf and C−Cl Enabled by an Air-Stable, Easily Recoverable, and Recyclable Palladium(I) Catalyst

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Abstract: *This report widens the repertoire of emerging Pd^I catalysis to carbon–heteroatom, that is, C−S bond formation. While Pd^0-catalyzed protocols may suffer from the formation of poisonous sulfide-bound off-cycle intermediates and lack of selectivity, the mechanistically diverse Pd^I catalysis concept circumvents these challenges and allows for C−S bond formation (S–aryl and S–alkyl) of a wide range of aryl halides. Site-selective thiolations of C−Br sites in the presence of C−Cl and C−OTf were achieved in a general and a priori predictable fashion. Computational, spectroscopic, X-ray, and reactivity data support dinuclear Pd^I catalysis to be operative. Contrary to air-sensitive Pd^0, the active Pd^I species was easily recovered in the open atmosphere and subjected to multiple rounds of recycling.*

Whereas palladium-catalyzed coupling reactions have developed into ubiquitous synthetic tools of significant industrial and societal impact,[1] the vast majority of these coupling reactions rely on air-sensitive mononuclear Pd catalysts that are either used directly under inert conditions or formed in situ from suitable precursors.[1,2] As such, the recovery of the active Pd species is frequently challenging under routine laboratory conditions, ultimately resulting in the disposal of the Pd. In this context, the emerging concept of dinuclear Pd^I catalysis has shown promise in displaying features of air stability, robustness, and recoverability in applications employing the iodine-bridged dinuclear Pd^I complex **1** (Figure 1).[3,4] In our previous work, we developed Pd^I dimer catalyzed C$_{sp^2}$−C$_{sp^2}$, C$_{sp^2}$−C$_{sp^3}$, C−SeCF$_3$, and C−SCF$_3$ bond formations and provided mechanistic data in support of dinuclear catalysis being operative.[3,5] Aside from
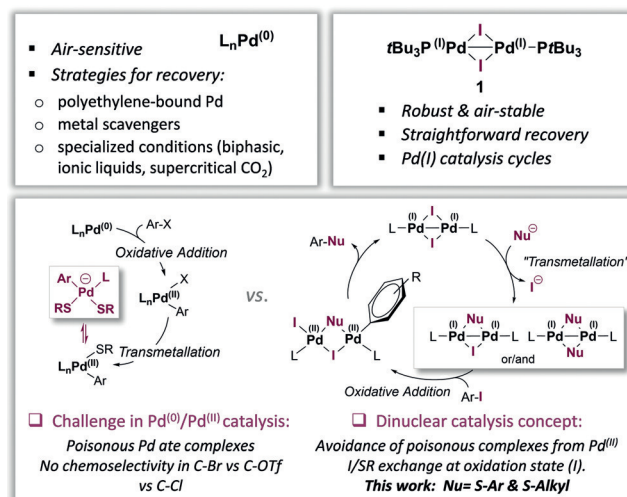

Figure 1. Mononuclear Pd^0/Pd^{II} versus dinuclear Pd^I−Pd^I catalysis.

the mentioned specialized fluorinated examples, to date, carbon–heteroatom bond formation is clearly underdeveloped in the Pd^I arena, but would benefit from widening of the repertoire. Thiolation reactions (to make aryl or alkyl sulfides) are of importance in the pharmaceutical and agrochemical industry as the C−S bond is widely encountered in bioactive molecules.[6] To name a few, the thioether motif is featured in agents to fight Alzheimer, Parkinson's disease, HIV, and cancer,[7] but is also of importance in materials chemistry (e.g., polymerization).[8] Thioethers are also key precursors in the synthesis of highly relevant functional groups such as sulfoxides, sulfones, sulfilimines, and sulfoximines.[9] While catalytic methods involving Ni or Cu catalysts can in principle be used for thiolations,[10] Pd^0-catalyzed processes have become the method of choice owing to their relative mildness, functional group tolerance, and generality.[11] Yet, challenges still remain: aside from the abovementioned sustainability aspects, surprisingly, site-selective thiolations of poly(pseudo)halogenated arenes, albeit a powerful handle to increase diversity and access densely functionalized arenes, have not been accomplished for a broad set of substrates.[12] Moreover, traditional Pd^0/Pd^{II} cycles may suffer from poisonous off-cycle Pd^{II} ate complexes that are assumed to form in the presence of thiolate nucleophiles (Figure 1).[13] As Pd^I-catalyzed transformations are fundamentally different and rely on iodine/thiolate exchange in oxidation state I prior to oxidative addition to the aryl halide (see Figure 1), we envisioned that we should be able to circumvent these mechanistic limitations. Moreover, our

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previous work indicated that the oxidation state I is rather privileged in achieving site-selective transformations.[5a,b]
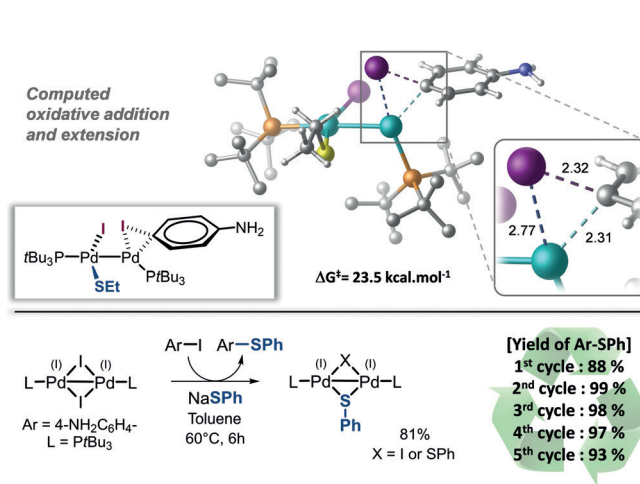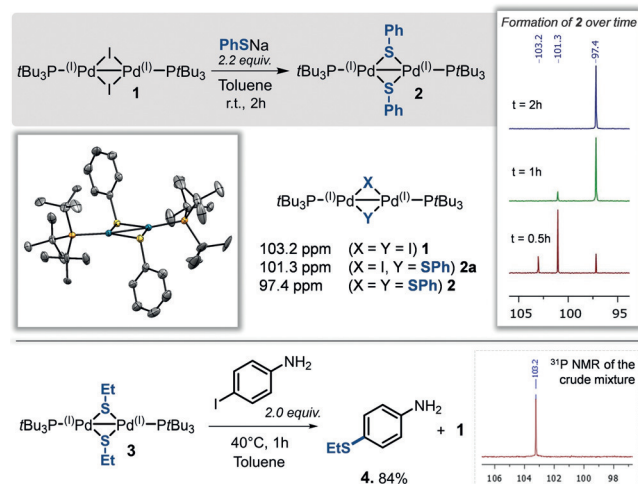
Our previous work in the area of Pd^I catalysis indicated that the key to efficient dinuclear Pd^I catalysis is the effective displacement of the iodine bridge by the employed nucleophile along with the ability of the nucleophile to function as a stabilizing unit of the dinuclear entity.[3a,b] In this context, electron-rich nucleophiles could potentially also compete in formally reducing the Pd^I entity to Pd^0,[14] and as such, alkyl and aryl thiolates present a significantly greater challenge than the electron-deficient SCF$_3$ nucleophile. A handful of dinuclear Pd^I complexes with a single SR bridge have been prepared and characterized to date,[15] but were never investigated for their reactivity or catalytic potential. Thus we first set out to test whether a RS-bridged Pd^I dimer could be prepared from **1**. Pleasingly, when we treated Pd^I iodo dimer **1** with sodium benzenethiolate in toluene at room temperature, we observed clean exchange of the iodine bridges by SPh and formation of the new [(PtBu$_3$)Pd^I(μ-SPh)]$_2$ complex (**2**). Our ^{31}P NMR monitoring of the reaction at the time points 0.5, 1, and 2 h (see the Supporting Information) showed the appearance of two new resonances at $\delta = 101.3$ and 97.4 ppm in addition to the resonance from the starting Pd^I iodo dimer **1** ($\delta = 103.2$ ppm; Scheme 1). The two new resonances are consistent with the expected intermediate [I/SPh]-mixed dimer and the doubly bridged SPh dimer **2**. After 2 h, only species **2** remained, which was further unambiguously characterized by X-ray crystallographic analysis.[16] The two SPh groups are oriented in an *anti* configuration to each other in the solid state (see Scheme 1, middle). The determined Pd—Pd bond length of 2.553 Å is in the range of the previously reported Pd—Pd single bonds.[17]

Similarly, we found alkyl thiolates (such as sodium ethanethiolate) to be equally effective in forming stable Pd^I entities under these conditions, displaying a characteristic resonance at $\delta = 100.6$ ppm in the ^{31}P NMR spectrum for the fully SEt-bridged Pd^I dimer **3**. These newly formed Pd^I dimers

were found to be completely stable to air and moisture (time of examination: 12 months).

We subsequently assessed the ability of dimer **3** to undergo direct reaction with an aryl iodide. To this end, we subjected [(PtBu$_3$)Pd^I(μ-SEt)]$_2$ (**3**) to 2 equiv of 4-iodoaniline at 40 °C for 1 h. We observed clean formation of the corresponding SEt-functionalized aniline **4** in 84 % yield relative to 2.0 equiv of ArI (see Scheme 1, bottom). Our ^{31}P NMR monitoring indicated that clean SEt/I exchange had taken place, with complete disappearance of dimer **3** and concomitant appearance of Pd^I iodo dimer **1** (see the Supporting Information). Importantly, we did not observe Pd^0 or Pd^{II} species, indicating that direct reaction of the Pd^I dimer **3** with the aryl iodide is likely. Moreover, we measured a first-order kinetic dependence on Pd^I dimer **3**. We also studied the feasibility of direct reactivity computationally, using the M06L level of theory in combination with the implicit solvation model CPCM (to account for toluene) and the basis set def2TZVP.[18] In analogy to our previous detailed investigations in this regard,[3a,b] we succeeded in the location of a transition state for dinuclear oxidative addition of the Pd^I dimer **3**, bearing two SEt bridging units, to 4-iodoaniline.[19] Following the reaction pathway, ultimately ArSEt will be formed along with the [I/SEt]-mixed Pd^I dimer, which can subsequently undergo another exchange reaction with another molecule of ArI (the TS is illustrated in Scheme 2; instead, see the Supporting Information for the full pathway). We calculated a strong thermodynamic driving force of $\Delta G_{rxn} = -28.3$ kcal mol^{-1} for the process. Moreover, the mixed Pd^I species (with an I and a SEt bridge) is predicted to be more reactive in oxidative addition than the doubly SEt-bridged Pd^I dimer **3** (by $\Delta\Delta G^{\ddagger} = 6.3$ kcal mol^{-1}).
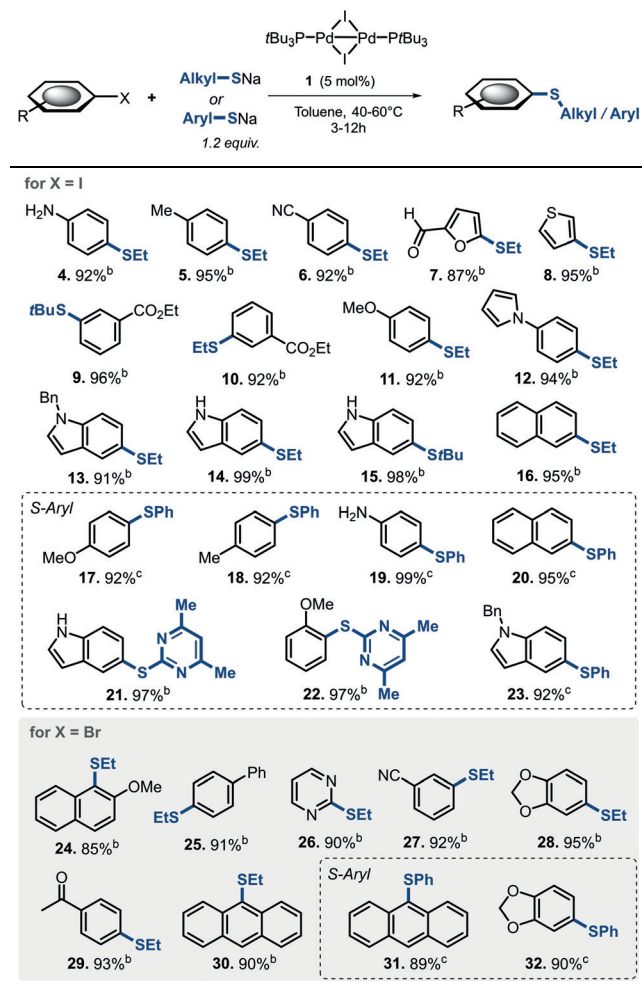
With the stoichiometric reactivity and air-stability features of the SR-bridged Pd^I dimer established, we subsequently explored its potential for catalytic applications. Pleasingly, using 5 mol % of the air- and moisture-stable Pd^I iodo dimer **1** and alkyl and aryl thiolates (1.2 equiv) in toluene at 40 °C and 60 °C, respectively, successfully transformed a range of aryl iodides and bromides into the corresponding

Scheme 1. Formation and reactivity of the SPh-bridged Pd^I dimer **2**. ^{31}P NMR analysis conducted with (EtO)$_3$P=O as the internal standard. X-ray crystal structure of **2** (thermal ellipsoids set at 50 % probability; hydrogen atoms omitted for clarity).

Scheme 2. Top: Computed oxidative addition transition state of 4-iodoaniline (hydrogen atoms on the PtBu$_3$ ligands omitted for clarity) with extension (bond distances in Å). Bottom: Demonstration of the recyclability of the Pd^I dimer species over five cycles.

thioethers. Electron-rich and -deficient aryl halides were equally effective. Moreover, various substituents were tolerated in the *ortho*, *meta*, and *para* positions to the site of C–S coupling, and the corresponding products were isolated in excellent yields. Notably, even unprotected amines (primary amine and unprotected indole) did not impede the efficiency of the transformation. The method proved to be compatible with ether (**11**, **17**, **22**, and **24**), ketone (**29**), aldehyde (**7**), ester (**9** and **10**), and cyano (**6** and **27**) functional groups. Moreover, pharmaceutically and agrochemically important heterocycles, such as furan, thiophene, indole, and pyrimidine, gave rise to equally high yields of the corresponding sulfide coupling products as standard aromatic or polyaromatic substrates (**7**, **8**, **21**, **22**, and **26**; Table 1). For example, **33** is the final intermediate towards key bioactive compounds, shown to have strong affinity for nicotinic acetylcholine receptors with potential relevance in the treatment of Alzheimer's disease.[7]

To test whether the increasingly important demands for sustainability can also be met to some extent with our procedure, we next explored the ease of recoverability and recyclability of the Pd[I] entity. Pleasingly, following the Pd[I]-

catalyzed reaction of 4-iodoaniline with sodium benzenethiolate, we were able to recover 81% of the dinuclear Pd[I] species (almost exclusively as the [I/SPh]-mixed dimer **2a**), using simple column chromatography on silica gel under standard laboratory conditions in open atmosphere. Submission of the isolated Pd[I] species to another transformation of 4-iodoaniline was highly effective, which is in line with the computational data that suggested the the mixed [I/SPh] Pd[I] dimer to be more reactive. We repeated the recovery/recycling cycle overall five times and saw no decay in product yields or catalytic performance of the Pd[I] species (see Scheme 2, bottom). The ease of recovery and recycling is due to the exquisite air and moisture stability of the Pd[I] dimer. Standard Pd[0] catalysts are not generally air-stable and usually require specialized recovery techniques, such as polymer-bound catalysts, use of metal scavengers, or specialized reactions conditions (biphasic, ionic liquids, supercritical CO_2).[20]

A remaining challenge in carbon–heteroatom bond formation, and in metal-catalyzed transformations more generally, is to achieve site selectivity in couplings of poly-(pseudo)halogenated arenes. While isolated examples exist,[12] there is a lack of generality in substrate. Subtle variations in steric or electronic features frequently lead to diminished or abolished selectivities.[5b] In line with this, our test of one of the most employed Pd[0]-derived thiolation catalysts, Pd_2dba_3/DPEPhos,[21] showed functionalization at the C–OTf site (88%) in a mixture with difunctionalized product (8%) and remaining starting material (4%) when 5-bromo-4-methylpyridin-2-yl trifluoromethanesulfonate was

Table 1: Pd[I]-catalyzed formation of thioethers ArSR from ArBr and ArI.[a]
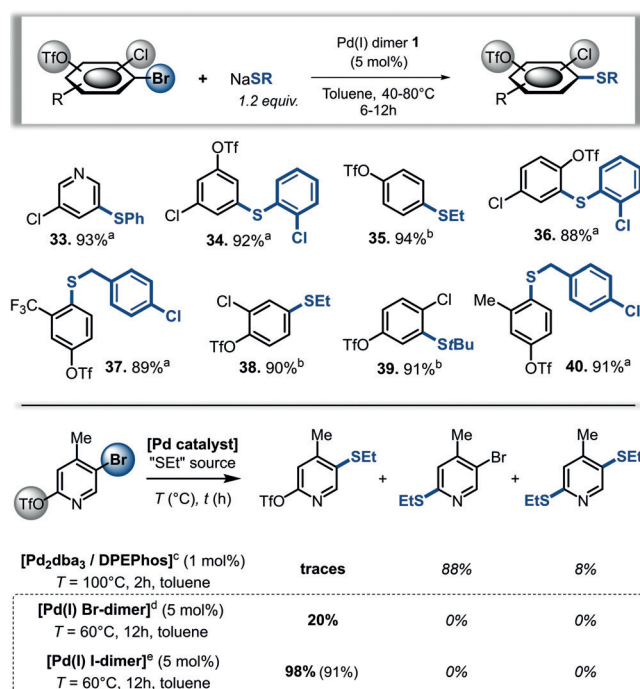
Scheme 3. Chemoselective couplings at C–Br bonds in the presence of competing C–Cl and C–OTf bonds (top) and comparison of reported efficient catalytic system in thiolation reactions[23] (bottom). [a] At 80°C. [b] At 40°C. [c] Remaining starting material: 4%. [d] Remaining starting material: 80%. [e] Remaining starting material: 2%. Yields of isolated products given in parentheses.

[a] Conditions: Pd[I] dimer **1** (17.4 mg, 0.02 mmol), aryl halide (0.4 mmol), and NaSR (0.48 mmol) in toluene (1.5 mL). Yields of isolated products are given. [b] At 40°C. [c] At 60°C.

used (see Scheme 3, entry 1, bottom). When the air-sensitive and more labile Pd^I bromo dimer was employed under our conditions, poor conversion into the desired product was observed (20%), with a significant amount of starting material remaining. This suggests that the Pd^I bromo dimer might behave as a precatalyst, releasing Pd^0 species in situ, which might subsequently be trapped as Pd^{II} ate complexes by the sulfur nucleophile (see Scheme 3, entry 2, bottom) or alternatively be deactivated.[22] By contrast, employing Pd^I iodo dimer **1** led to the exclusive functionalization of the C–Br position in the presence of C–OTf, regardless of the electronic or steric bias in the substrate (see Scheme 3, entry 3). Notably, the complete selectivity for the C–Br bond is also retained if an excess of coupling partner is used, adding practicability, as little care needs to be applied in the weighing or handling of the coupling partner. Standard Pd^0-based reactivity trends usually refer to the relative reactivities of C–OTf vs. C–Br as being roughly the same and highly dependent on the steric or electronic influence by the substrate.[5b] By contrast, Pd^I catalysis proves to be completely Br-selective also for C–S bond formation, in accord with our previous observations in C–C bond formations.[5a,b] As such, the reaction is a priori predictable and completely substrate-independent. The selectivity was also independent of the nature of the sulfide that was installed. Electron-rich and hindered S*t*Bu was just as selective as the aromatic SPh nucleophile.

To the best of our knowledge, this is the first general and a priori predictable chemoselective C–S bond formation in the presence of competing potentially reactive C–OTf and C–Cl sites (see Scheme 3). Such chemoselective strategies are of considerable value in the generation of densely functionalized or complex molecules ranging from pharmaceuticals to materials.

In summary, we have demonstrated the versatility of the dinuclear Pd^I concept in C–S bond formation, avoiding the generation of poisonous Pd ate complexes that may be encountered under Pd^0 catalysis. We achieved thiolations of a wide range of aryl iodides and bromides, even selectively in the presence of C–OTf and/or C–Cl for the first time for a broad set of substrates. We provided X-ray, computational, and reactivity data in support of direct Pd^I–Pd^I catalysis. Owing to their air and moisture stability, the Pd^I species generated were easily recovered using standard laboratory purification methods (chromatography on silica gel). In multiple rounds of recycling, there was no loss in catalytic activity or efficiency.

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