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Authors: Erdem Senol, Thomas Scattolin, and Franziska Schoenebeck

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Selenolation of Aryl Iodides and Bromides Enabled by a Bench-Stable Pd(I) Dimer

Erdem Senol, Thomas Scattolin and Franziska Schoenebeck*

Abstract: Herein we report the use of an air- and moisture-stable dinuclear Pd(I) complex as an efficient catalyst for the formation of C(sp²)-SeR bonds. The privileged reactivity of the Pd(I) dimer allows the direct use of selenolates as nucleophiles in the cross-coupling. While previous methodologies suffer from catalyst poisoning through the formation of Pd-ate complexes, the mechanistically distinct dinuclear Pd(I)-catalyst circumvents this challenge. A wide variety of aryl bromides and iodides were efficiently coupled under relatively mild reaction conditions with broad functional group tolerance. Mechanistic and computational data are presented in support of direct Pd(I) reactivity.

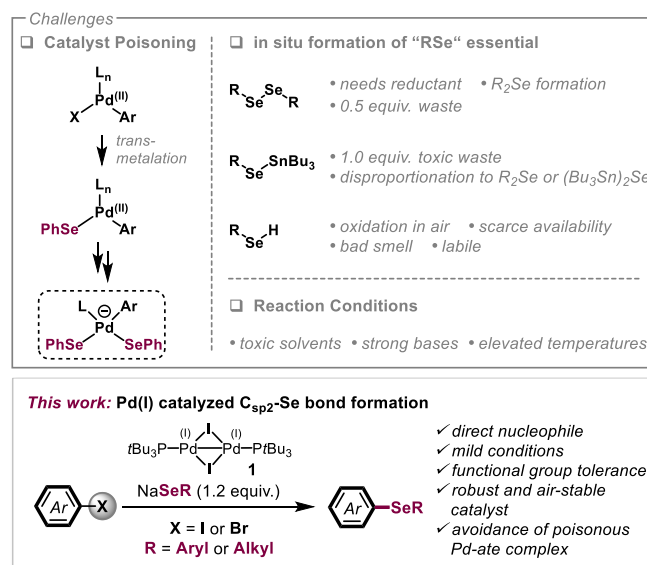
Although selenium is associated with toxicity (in larger quantities) due to its ability to replace sulfur in metabolic processes, it is also an essential nutrient,^[1] and organoselenium compounds possess valuable biological and medicinal activities, such as antioxidant, antitumor, antimicrobial and antiviral properties.^[2] In addition, organoselenium compounds also find usage as catalysts^[3] and in materials chemistry (e.g. polymers or chalcogen bonding).^[4]

In this context, only a few methods are known to construct C(sp²)-SeR bonds and even less allow access to unsymmetrical selenoethers,^[5] thus creating a high demand for novel methodology. Indirect synthetic approaches, which involve organoselenium reagents, such as toxic, unstable and unpleasantly smelling arylselenols and diselenides that require excess amounts of reducing agents, suffer from the use of polar and toxic solvents, strong bases and elevated temperatures.^[6] Furthermore, formation of (symmetrical) diselenides is commonly observed as a side process, narrowing the substrate scope due to difficulties in purifications. Methods using tin-based reagents lead to unwanted toxic by-products and side-reactions such as disproportionation.^[6-7] These drawbacks are also present in copper-catalyzed couplings.^[8]

Although palladium-catalyzed cross coupling has been the method of choice when it comes to the construction of carbon-heteroatom bonds,^[9] already low concentrations of chalcogen nucleophiles are frequently detrimental to the classical Pd⁽⁰⁾/Pd^(II) catalytic cycle due to the formation of off-cycle Pd^(II)-ate complexes.^[10] This is especially challenging for selenium-derived nucleophiles as they are roughly an order of magnitude more nucleophilic than thiolates.^[11] Moreover, the use of unstable Pd⁽⁰⁾ species under harsh reaction conditions can be difficult and frequently requires handling and storage under inert atmosphere.^[12]

Owing to the relatively high propensity of organoselenium compounds to be oxidized, a late-stage introduction of the organoselenide functionality would be highly advantageous. Thus, our objective was to develop an operationally simple and direct method that minimizes toxic by-products and unwanted side-reactions under mild conditions (Scheme 1).

Scheme 1. Key challenges in metal-catalyzed C(sp²)-Se bond formation.

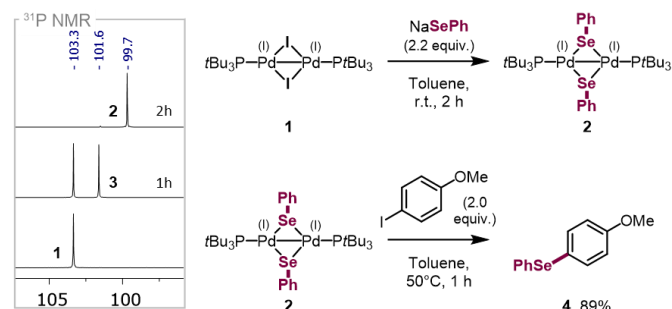


We recently showed that dinuclear Pd^(I) catalysis is a promising concept to circumvent poisonous ate complexes in catalysis.^[13] In this context, the iodide-bridged dimer **1** was shown to trigger dinuclear catalysis cycles while displaying superior stability properties: **1** is completely stable towards oxygen as a solid and can be stored on the bench.^[13-14] Our previous work indicated that Pd^(I) catalysis will be successful, if the iodide bridges are efficiently displaced by nucleophiles that are also able to stabilize the Pd-Pd core.^[14d, 14e] In this context, we previously showed that SeCF₃ nucleophiles are compatible.^[14e] For electron-rich and more nucleophilic, especially alkyl selenides, however, there is the additional challenge to potentially reduce the Pd^(I) to the corresponding Pd⁽⁰⁾. Nevertheless, if successful, this would allow for the first direct catalytic and nucleophile-based C-SeR (R = alkyl, aryl) installation.

We initially set out to test whether a RSe-bridged Pd^(I) dimer could be prepared from **1** via nucleophile exchange of the bridging moieties. To our delight, we observed the clean formation of [Pd(μ-SePh)(PtBu₃)₂]₂ **2** upon treating **1** with sodium benzeneselenolate (NaSePh) within 2 h in toluene at room temperature (Scheme 2).

[*] Mr Erdem Senol, Mr Thomas Scattolin, Prof. Dr. Franziska Schoenebeck
Institute of Organic Chemistry, RWTH Aachen University,
Landoltweg 1, 52074 Aachen (Germany).
E-mail: franziska.schoenebeck@rwth-aachen.de
Homepage: <http://www.schoenebeck.oc.rwth-aachen.de>

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Scheme 2. Formation and reactivity of SePh-bridged Pd⁽⁰⁾ dimer **2**.^a

^a³¹P NMR analysis conducted with OP(OMe)₃ as internal standard.

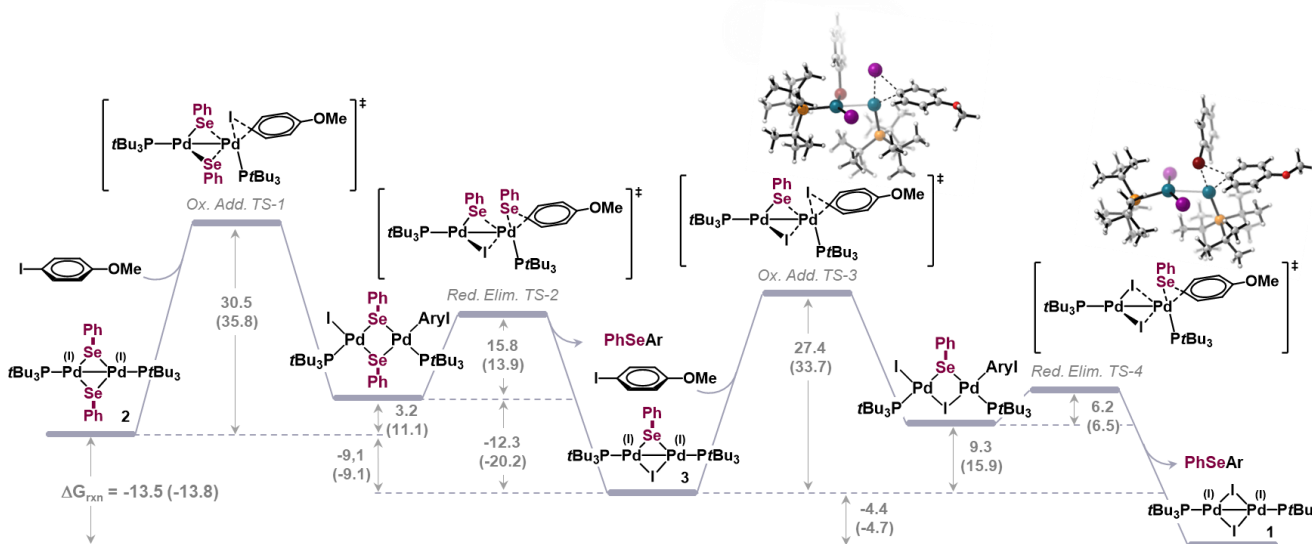
Reaction monitoring by ³¹P NMR after 1 h and 2 h showed two new resonances at 101.6 and 99.7 ppm with the complete consumption of **1** ($\delta = 103.3$ ppm) after 2 h. These signals likely correspond to the [I/SePh]-mixed dimer **3** and the doubly SePh-bridged dimer **2**, respectively.^[13, 14d, 14e, 15] We subsequently tested the ability of dimer **2** as a benzylselenolation agent by directly reacting it with an aryl iodide. By treating the SePh-bridged Pd⁽⁰⁾ dimer **2** with 2 equivalents of 4-iodoanisole at 50°C for 1 h, we observed clean formation of the corresponding SePh-functionalized anisole **4** in 89% yield (relative to 2.0 equivalents of aryl iodide). Our ³¹P-NMR monitoring indicated that SePh/I exchange had taken place with complete consumption of dimer **2** and concomitant formation of Pd⁽⁰⁾ dimer **1**. Importantly, we did not observe Pd⁽⁰⁾ or Pd^(II) species on the time scale of our monitoring, indicating that direct reactivity of the Pd⁽⁰⁾ dimer **2** with aryl iodide is likely.

To test whether the observed reactivity could be consistent with direct reactivity at Pd⁽⁰⁾-Pd⁽⁰⁾, computational studies at the CPCM(toluene) M06L/def2-TZVP level of theory were applied (Scheme 3).^[16] In analogy to our previous detailed investigation in this regard,^[13-14, 14j, 14k] we succeeded in the location of a transition

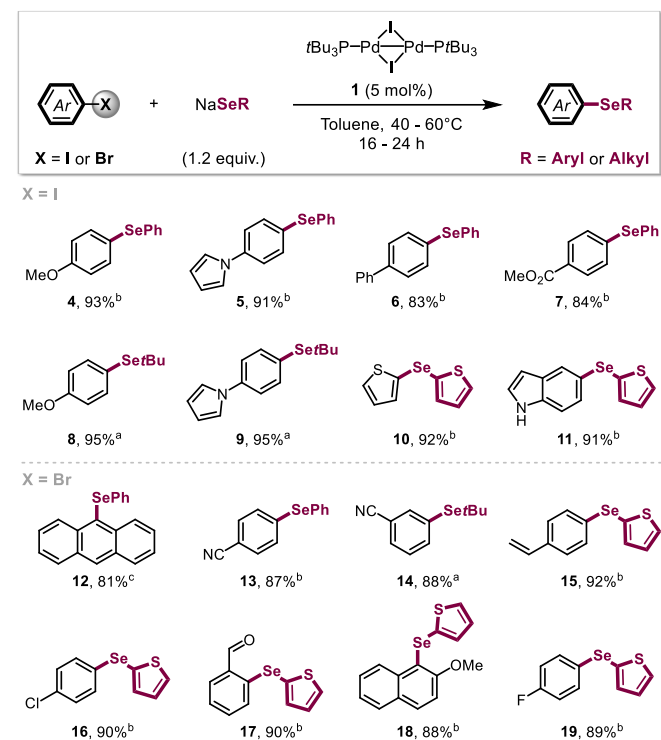
state for dinuclear oxidative addition of 4-iodoanisole at the Pd⁽⁰⁾ dimer **2** bearing two SePh-bridging units. Following the reaction pathway, subsequent oxidative addition of 4-iodoanisole to dimer **2** generates a Pd^(II) dimer species with doubly bridged SePh groups. Ultimately ArSePh is formed *via* reductive elimination along with [I/SePh]-mixed Pd⁽⁰⁾-dimer, which can subsequently undergo another exchange reaction with another molecule of 4-iodoanisole. We calculated a thermodynamic driving force of $\Delta G_{\text{rxn}} = -13.8$ kcal/mol for the process. Moreover, as for other nucleophiles, the [I/SePh]-mixed dimer is predicted to be more reactive in oxidative addition compared to dimer **2** (by $\Delta\Delta G^\ddagger \sim 3$ kcal/mol).

We subsequently explored the feasibility of dinuclear catalysis to convert aryl iodides and bromides to their corresponding selenoethers. Using 5 mol% of the Pd⁽⁰⁾-iodo dimer **1** with alkyl and aryl selenolates (1.2 equiv.) in toluene at 40-60°C, we successfully transformed a wide range of aryl iodides and bromides to their corresponding selenoethers (Table 1). In this context, our ³¹P-NMR examination of the resting state of the reaction of 4-iodoanisole with sodium benzene selenolate under Pd⁽⁰⁾ catalysis after 0.5 h, 2 h, 4 h, 8 h and 16 h reaction time indicated the presence of [(PtBu₃)Pd⁽⁰⁾(μ -SePh)]₂ **2** (99.67 ppm) as resting state.

Substrates bearing electron-rich and electron-poor functionalities on *ortho*, *meta* and *para* positions were equally effective and led to products in excellent yields. Notably, even an unprotected amine (**11**) did not hamper the efficiency of the transformation. Ether (**4**, **8**, **18**), chloride (**16**), aldehyde (**17**), ester (**7**), cyano (**13**, **14**) and vinyl (**15**) functional groups are similarly well tolerated. Moreover, given the relevance of thiophene-containing motifs in antiallergic,^[17] antibacterial,^[18] antidepressant,^[19] antidiabetic,^[20] and anti-inflammatory agents,^[21] we also coupled 2-thiophene selenolate with a range of aryl iodides and bromides. Pleasingly, high yields of the corresponding thiophene selenoethers (**10**, **11**, **16** - **20**) were isolated.^[22]

Scheme 3. Free-energy pathway of I/SePh exchange between **2** and 4-iodoanisole.^a

^a Energies (in kcal mol⁻¹ at 298K) refer to Gibbs free energies calculated at CPCM (toluene) M06L/6-311++G(d,p) [SDD for Pd,I,Se] or CPCM (toluene) M06L/def2-TZVP (in parentheses). Geometries were optimized at B3LYP-D3/6-31G(d) [LANL2DZ for Pd,I,Se].

Table 1. Scope of the Pd^(II) catalyzed formation of selenoethers from ArI and ArBr.

Reagents and conditions: Pd^(II) dimer **1** (17.4 mg, 0.02 mmol), aryl halide (0.4 mmol), NaSeR (0.48 mmol) in toluene (1.5 mL). Isolated yields are given. [a] Reactions performed at 40°C. [b] Reactions performed at 50°C. [c] Reactions performed at 60°C.

In summary, we demonstrated the direct nucleophilic selenolation of a wide range of aryl iodides and bromides with alkyl, aryl and thiophene selenolates under mild reaction conditions, enabled by a robust and air-stable Pd^(II) dimer catalyst. Experimental mechanistic and computational data support dinuclear Pd^(II) catalysis to be operative, which circumvents poisonous off-cycle Pd^(II)-ate complexes that may be encountered under typical Pd⁽⁰⁾/Pd^(II) catalysis.

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Conflict of interest

The authors declare no conflict of interests.

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