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Site-Selective C-S Bond Formation at C-Br over C-OTf and C-Cl Enabled by an Air-Stable, Easy-to-Recover & Recyclable Pd$^{(I)}$ Catalyst

*Thomas Scattolin, Erdem Senol, Guoyin Yin, Qianqian Guo and Franziska Schoenebeck**

***Abstract**: This report widens the repertoire of emerging Pd$^{(I)}$ catalysis to carbon-heteroatom, i.e. 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.*

While 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** (see Figure 1).[3,4] In our previous work, we developed Pd$^{(I)}$ dimer catalyzed C_{sp2}-C_{sp2}, C_{sp2}-C_{sp3}, C-SeCF$_3$ and C-SCF$_3$ bond formations and provided mechanistic data in support of dinuclear catalysis being operative.[3,5] Aside from 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 arenas, 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, 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 sulfoxide, sulfone, sulfilimine and sulfoximine.[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 above mentioned sustainability aspects, surprisingly, site-selective thiolations of poly(pseudo)-halogenated arenes, although being a powerful handle to increase diversity and access densely functionalized arenes, has 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] Since Pd$^{(I)}$ catalyzed transformations are fundamentally different and rely on iodine/thiolate exchange at the 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 previous work indicated that the oxidation state (I) is rather privileged to achieve site-selective transformations.[5a-b]

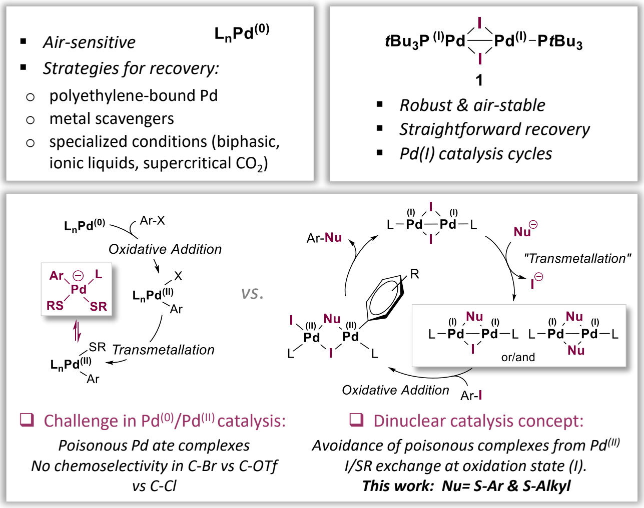

Figure 1. Mononuclear Pd$^{(0)}$/Pd$^{(II)}$ versus dinuclear Pd$^{(I)}$-Pd$^{(I)}$ catalysis.

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

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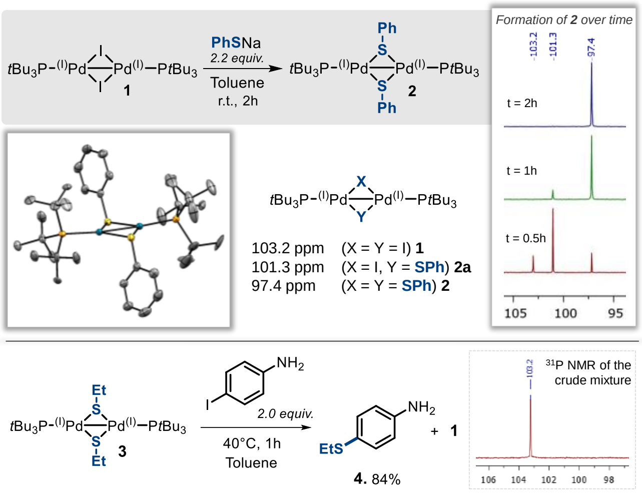
from **1**. Pleasingly, when we treated Pd$^{(I)}$-iodo dimer **1** with sodium benzenethiolate in toluene at room temperature, we observed clean exchange of the iodine bridges by SPh and formation of the new [(P*t*Bu$_3$)Pd$^{(I)}$(μ-SPh)]$_2$ **2**. Our ^{31}P NMR monitoring of the reaction at the time points 0.5, 1 and 2 hours (see SI) showed the appearance of two new signals at δ = 101.3 and 97.4 ppm in addition to the peak from the starting Pd$^{(I)}$ iodo dimer **1** (δ= 103.2 ppm) (see Scheme 1). The two new signals are consistent with the expected intermediate [I/SPh]-mixed dimer and the doubly bridged SPh dimer **2**. After 2h, 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 collected data of the Pd-Pd bond length of 2.553 Å is in the range of the previously reported Pd-Pd single bonds.[17]

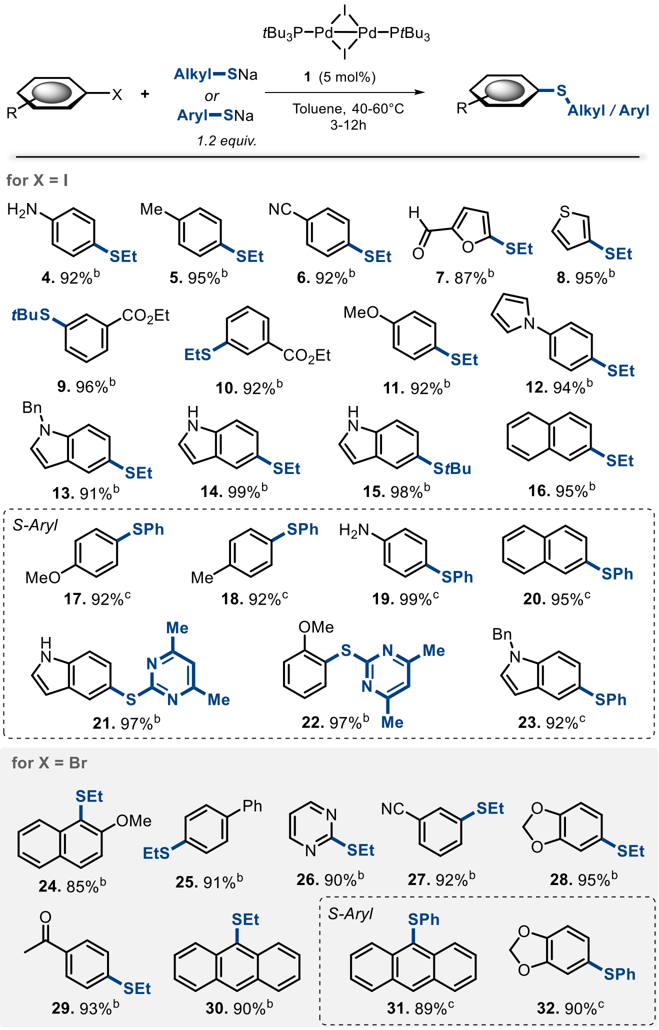


Scheme 1. Formation and reactivity of the SPh-bridged Pd$^{(I)}$ dimer **2**. ^{31}P-NMR analysis conducted with (EtO)$_3$P=O as internal standard. Xray of **2** (thermal ellipsoids are shown at 50% probability and hydrogen atoms have been omitted for clarity).

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 signal of δ = 100.6 ppm in ^{31}P-NMR 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).

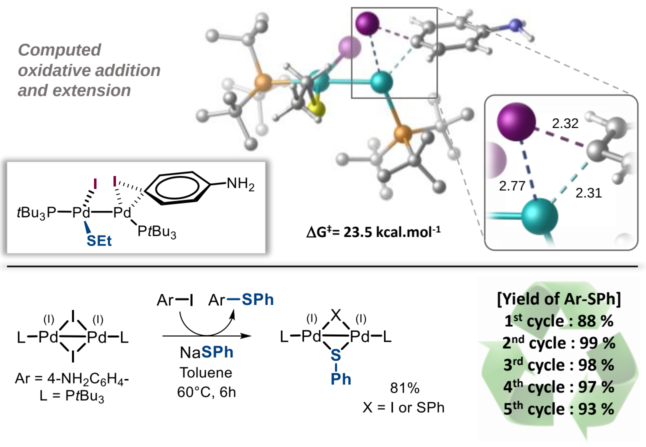
We subsequently assessed the ability of dimer **3** to undergo direct reaction with an aryl iodide. To this end, we subjected [(P*t*Bu$_3$)Pd$^{(I)}$(μ–SEt)]$_2$ **3** to 2 equivalents of 4-iodoaniline at 40°C for 1 h. We observed clean formation of the corresponding SEt-functionalized aniline **4** in 84% yield relative to 2.0 equivalents 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 SI). Importantly, we did not observe Pd$^{(0)}$ nor Pd$^{(II)}$ species, indicating that direct reactivity of the Pd$^{(I)}$ dimer **3** with the aryl iodide is likely. Moreover, we measured a 1st order kinetic dependence in 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 by 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 (TS is illustrated in Scheme 2, full pathway in SI). We calculated a strong thermodynamic driving force of ΔG$_{rxn}$ = -28.3 kcal/mol for the process. Moreover, the mixed Pd$^{(I)}$ species (with I and SEt bridge) is predicted to be more reactive in oxidative addition than the bis-SEt bridged Pd$^{(I)}$ dimer **3** (by ΔΔG‡ = 6.3 kcal/mol).

Table 1. Pd$^{(I)}$ catalyzed formation of thioethers ArSR from ArBr and ArI.[a]



[a] Conditions: Pd$^{(I)}$ dimer **1** (17.4 mg, 0.02 mmol), aryl halide (0.4 mmol), NaSR (0.48 mmol) in toluene (1.5 mL). Isolated yields are given. [b] Reactions performed at 40°C. [c] Reactions performed at 60°C.

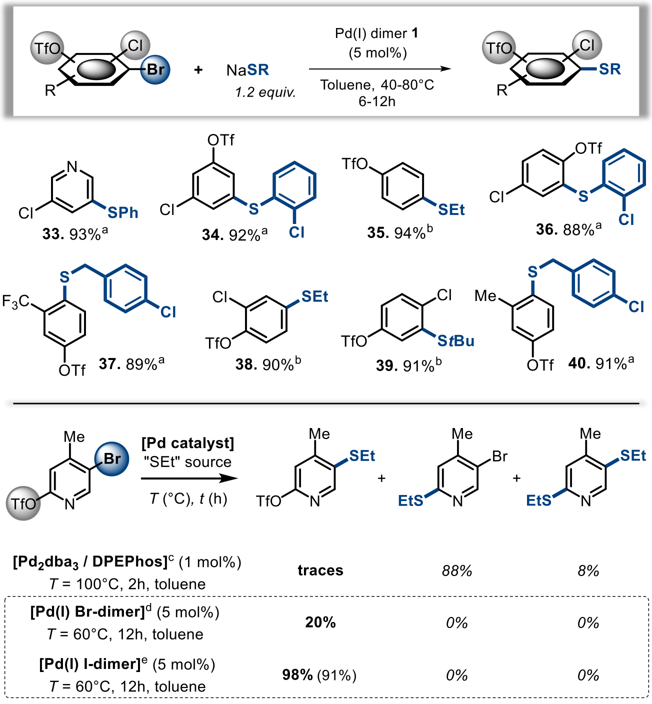
With the stoichiometric reactivity and air-stability features of the SR-bridged Pd$^{(I)}$ dimer established, we subsequently explored the potential for catalytic applications. Pleasingly, using 5 mol% of the air- and moisture stable Pd$^{(I)}$ iodo dimer **1** with alkyl and aryl thiolates (1.2 equiv.) in toluene at respectively 40°C and 60°C, we successfully coupled a range of aryl iodides and bromides to the corresponding thioethers. Electron-rich and -deficient aryl halides were equally effective. Moreover, various substituents in *ortho*, *meta* and *para* position to the site of C-S coupling were tolerated and the corresponding products isolated in excellent yields. Notably, even unprotected amines (primary amine and unprotected indole) did not impede the efficiency of the transformation. The method proved 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**) (see 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]



Scheme 2. Computed oxidative addition transition state of 4-iodoaniline (hydrogen atoms on the $PtBu_3$ ligands omitted for clarity) with extension (bond distances in Å) (top) and demonstration of the recyclability of the Pd(I) dimer species over 5 cycles (bottom).

To test whether the increasingly important demands for sustainability can also be met to some extent with our protocol, 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 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 suggest the mixed [I/SPh] Pd(I) dimer to be more reactive. We repeated the recovery/recycling cycle overall 5 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 feature of the Pd(I) dimer to be air- and moisture stable. 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 C-heteroatom bond formation, and metal catalyzed transformations more generally, is to obtain 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, *i.e.* Pd_2dba_3/DPEPhos,[21] showed functionalization at the C-OTf site (88%) in a mixture with bisfunctionalized product (8%) and remaining starting material (4%), when being challenged with 5-bromo-4-methylpyridin-2-yl trifluoromethanesulfonate (see Scheme 3, entry 1, bottom). When the air-sensitive and more labile Pd(I) bromo dimer was employed using our conditions, poor conversion to the desired product was observed (20%) with 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 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 excess of coupling partner is used, adding practicability, as little care needs to be applied in 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 protocol 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 were just as selective as the aromatic SPh nucleophile.



[Pd_2dba_3 / DPEPhos]c (1 mol%) T = 100°C, 2h, toluene	traces	88%	8%
[Pd(I) Br-dimer]d (5 mol%) T = 60°C, 12h, toluene	20%	0%	0%
[Pd(I) I-dimer]e (5 mol%) T = 60°C, 12h, toluene	98% (91%)	0%	0%

Scheme 3. Demonstration of chemoselective coupling at C-Br bonds in presence of competing C-Cl and C-OTf bonds (top) and comparison of reported efficient catalytic system in thiolation reactions[23] (bottom). [a] Reactions performed at 80°C. [b] Reactions performed at 40°C [c] Remaining starting material: 4%. [d] Remaining starting material: 80%. [e] Remaining starting material: 2%. Isolated yield is given in parenthesis.

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 build-up of densely functionalized or complex molecules ranging from pharmaceuticals to materials and a highly sought after strategy in the demand for late-stage synthetic diversification.

In summary, herein we demonstrated the versatility of the dinuclear Pd$^{(I)}$ concept in C-S bond formation, allowing avoidance 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. Due 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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[18] The geometries were optimized at B3LYP/6-31G(d) with LANL2DZ for Pd,I. Selected optimizations at ωB97XD (SDD for Pd, I) gave analogous results in terms of overall activation barrier and driving force. 6-311++G(d,p)/SDD basis set for single point energies was also tested and gave similar results. The coordinates for the optimized structures together with the energy diagram can be found in the Supporting Information.

[19] Calculations were conducted with Gaussian09, Revision E.01; Frisch M. J. et al. See Supporting Information for full reference and further computational details.

[20] a) E. Bergbreiter, P. L. Osburn, Y.-S. Liu, *J. Am. Chem. Soc.* **1999**, *121*, 9531; b) S. Phillips, P. Kauppinen, *Platinum Metals Rev.* **2010**, *54*, 69; c) H. Wong, C. J. Pink, F. C. Ferreira, A. G. Livingston *Green Chem.* **2006**, *8*, 373; d) T. Welton, *Chem. Rev.* **1999**, *99*, 2071; e) P. G. Jessop, T. Ikariya, R. Noyori, *Chem. Rev.* **1999**, *99*, 475; f) W. Leitner, *Acc. Chem. Res.* **2002**, *35*, 746; g) For an example of a recoverable Pd$^{(II)}$ cyclometallated imine catalyst applied in Heck reactions, see: M. Ohff, A. Ohff, D. Milstein, *Chem. Commun.* **1999**, 357.

[21] a) T. H. Jepsen, M. Larsen, M. Jørgensen, K. A. Solanko, A. D. Bond, A. Kadziola, M. B. Nielsen, *Eur. J. Org. Chem.* **2011**, *2011*, 53; b) B. Liu, R. S. Shetty, K. K. Moffett, M. J. Kelly, *Tetrahedron Lett.* **2011**, *52*, 1680; c) U. Schopfer, A. Schlapbach, *Tetrahedron* **2001**, *57*, 3069; d) A. Pueschl, B. Bang-Andersen, M. Joergensen, K. Juhl, T. Ruhland, K. Andersen, J. Kehler (Lundbeck & CO), WO2004087662, **2004**; e) M. Sakurai, H. Hamashima, K. Hattori (Fujisawa Pharmaceutical CO), US2004106653, **2004**; f) E. Alvira, M. J. Graneto, L. M. Grapperhaus, K. Iyanar, M. T. Maddux, W. M. Mahoney, A. M. Massa, K. R. Sample, A. M. Schmidt, E. R. Seidel, G. J. Selbo, B. M. Tollefson, A. R. E. Vonder, M. G. Wagner, S. S. Woodard (Pfizer Inc.), WO2009069044, **2009**.

[22] If the strength of the nucleophile is lowered appropriately, higher conversion to the product can be achieved. See: C. C. Eichman, J. P. Stambuli, *J. Org. Chem.* **2009**, *74*, 4005.

[23] For c) EtSH (1.0 equiv.) and KO*t*Bu (1.1 equiv.). For d) and e) NaSEt (1.2 equiv.). See Supporting Information for more details.

Layout 2:

Dinuclear Catalysis

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Site-Selective C-S Bond Formation at C-Br over C-OTf and C-Cl Enabled by an Air-Stable, Easy-to-Recover & Recyclable Pd$^{(I)}$ Catalyst