

Cross-Coupling

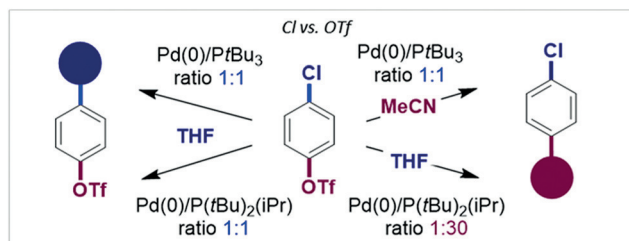
Deutsche Ausgabe: DOI: 10.1002/ange.201609635
Internationale Ausgabe: DOI: 10.1002/anie.201609635Rapid Room-Temperature, Chemoselective $C_{sp^2}-C_{sp^2}$ Coupling of Poly(pseudo)halogenated Arenes Enabled by Palladium(I) Catalysis in Air

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Abstract: While chemoselectivities in Pd^0 -catalyzed coupling reactions are frequently non-intuitive and a result of a complex interplay of ligand/catalyst, substrate, and reaction conditions, we herein report a general method based on Pd^I that allows for an a priori predictable chemoselective $C_{sp^2}-C_{sp^2}$ coupling at C–Br in preference to C–OTf and C–Cl bonds, regardless of the electronic or steric bias of the substrate. The C–C bond formations are extremely rapid (<5 min at RT) and are catalyzed by an air- and moisture-stable Pd^I dimer under open-flask conditions.

The biaryl motif is not only present in numerous drug molecules, but it is also a ubiquitous building block in materials science and complex natural products. Its substitution pattern ultimately determines the function as pharmaceutical, agrochemical, electronic device, secondary metabolite, or even privileged ligand.^[1] Consequently, the development of a synthetic repertoire to selectively access diversely functionalized arenes is of considerable interest. Owing to the relative mildness, palladium-catalyzed chemoselective cross-coupling strategies of poly(pseudo)halogenated arenes represent a strategy of considerable interest.^[2] In this context, the oxidative addition step is generally selectivity-controlling. While the relative ease of oxidative addition is frequently referred to as $C-I > C-OTf \approx C-Br > C-Cl$,^[2] these rough trends by no means allow an a priori prediction of favored coupling site. Instead, it is a result of subtle interplay between substrate (electronic/steric bias and bond strength), catalyst (ligand/ligation state), solvent, and additive effects (Figure 1).^[2,3] For example, while $[PdCl_2[P(o-tol)_3]_2]$ -catalyzed Kumada coupling of **A** gave selective C–Br functionalization, the introduction of two methyl groups *ortho* to C–Br (**B**) diminished selectivities, thus resulting in mixtures under otherwise identical reaction conditions (Figure 1).^[4] A similar substrate dependence was observed for $[Pd(PPh_3)_4]$ -catalyzed Suzuki couplings: while C–Br was the favored coupling site for **C**, analogous reaction conditions resulted in

▪ Selectivity depends on solvent, additive and ligand ratio:



▪ Selectivity depends on nature of ligand and substrate:

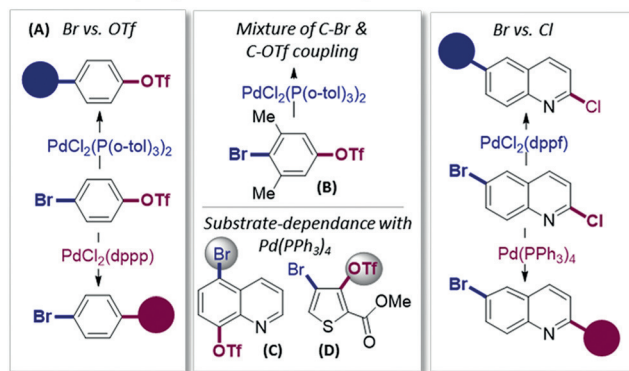


Figure 1. Examples of divergent selectivities.^[4,3] Tf = trifluoromethanesulfonyl.

preferential coupling at the C–OTf site for **D**.^[5] Although progress has been made in the development of predictive models^[6] and in the mechanistic understanding of the factors that dictate site selectivity,^[2,3,7] selective couplings frequently remain a result of rigorous screening activities. However, modern research programs not only seek for greater sustainability (i.e. less waste), but also frequently involve iterative, programmable synthetic approaches to increase chemical diversity.^[8] As such, a general and predictive coupling protocol would be highly desired, particularly if paired with operational simplicity.

Clearly, the ultimate site selectivity is strongly affected by subtle changes in substrate, ligand, or reaction conditions in the context of palladium(0) catalysis. This selectivity is likely due to modifications of the electron-richness of the active palladium(0) catalyst. Depending on the nature of the ligand and reaction conditions, multiple potentially reactive species may coexist, ranging from PdL_n to anionic $[PdL_nX]^-$ ($n = 1$ or 2)^[3,7,9] and could in turn trigger divergent selectivities.^[3d] We therefore envisioned that utilizing a different oxidation state (I), may be advantageous and potentially allow more pronounced chemoselectivities. We recently showed that the

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iodine-bridged palladium(I) dimer **1** (shown in Table 1) is an air- and moisture-stable, as well as thermally stable species which functions as an efficient catalyst for C–SCF₃, C–SeCF₃, and C–Br bond formations with aryl iodides and bromides.^[10,11] Our mechanistic data indicated that the catalysis proceeded by dinuclear palladium(I) cycles. In this context, the cross-coupling partner was employed as a nucleophile, which was incorporated as bridging unit in the Pd^I–Pd^I framework and subsequently exchanged with an aryl halide to give the functionalized arene. Whether carbon-based nucleophiles, such as aryl Grignard or organozinc species, could also function as bridges in dinuclear palladium(I) catalysis, was unclear. Our initial studies on Kumada couplings suggested that high reactivities could be achieved with **1** however.^[12] Efficient Kumada and Negishi couplings of aryl (pseudo)halides have otherwise been developed for single coupling possibilities, using air-sensitive palladium(0) [or nickel(0)] catalysis, with reaction times of several hours.^[13] Notably, Knochel and co-workers observed more rapid Negishi and Kumada cross-coupling reactions under modified palladium(0) catalysis conditions, which was ascribed to the potential involvement of radicals.^[14] A general method for the realization of chemoselective couplings has not been reported.^[15] To test whether selective cross-couplings would be possible, we subjected phenyl Grignard along with 2.5 mol% of the **1** in toluene to the densely functionalized substrate **2**, which has competitive possibilities for C–Br, C–OTf, and C–Cl couplings (Scheme 1a). All reagents were handled in air and the reaction was performed in an open flask. Pleasingly, we saw exclusive coupling at C–Br. The reaction was remarkably rapid and completed in less than 5 minutes at room temperature. In stark contrast, when we subjected other air-stable complexes based on palladium(II), we observed sluggish reactivity after 5–24 hours, thus obtaining low conversion and no pronounced selectivity under open-flask or inert reaction conditions (Scheme 1a).

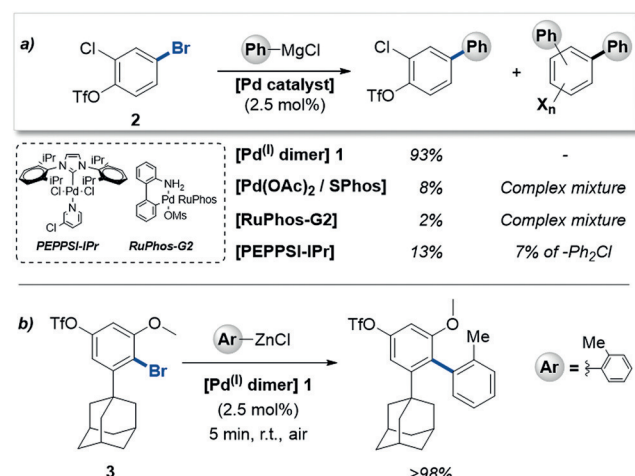
We next focused on the sterically demanding aryl bromo triflate **3** (Scheme 1b). This substrate is a stern test as it

features an electronically deactivated (by *ortho* methoxy) and sterically shielded (by *ortho* adamantyl) C–Br site in competition with an accessible C–OTf site. Despite these challenges, upon using an organozinc as the coupling partner we observed strikingly rapid and selective C–Br coupling. As such, the bromo selectivity appears general for palladium(I) catalysis, and is independent of both the steric and electronic bias of the substrate, as well as the cross-coupling partner.

We subsequently investigated a wider range of substrates for the preferred coupling selectivities, including pharmaceutically relevant heterocycles. Table 1 summarizes the

Table 1: C–Br selective Kumada cross-couplings.^[a]

<p>C–Br vs. C–OTf</p> <p>1. 95% 2. 93% 3. 96% 4. 96% 5. 96% 6. 86%^{b,e} 7. 92%^c 8. 86%^d 9. 95%</p>	<p>C–Br vs. C–Cl</p> <p>Alternative Grignards</p> <p>Ar–Br + ArMgCl → Ar–Ar' (96%)</p> <p>Y = Cl (92%) Y = F (94%)</p>



Scheme 1. Stern tests: Palladium(I) dimer performance versus alternative air-stable palladium complexes in either Kumada or Negishi couplings of challenging substrates.

[a] Reaction conditions: **1** (4.4 mg, 0.005 mmol), ArBr (0.2 mmol), PhMgCl (2 M in THF, 150 μ L, 0.3 mmol), toluene (3.0 mL). Yield is that of isolated product. [b] 5 mol% of **1** was used. [c] Used 1.8 equiv of PhMgCl. [d] Used 2 equiv of PhMgCl. [e] Used 2.5 equiv of PhMgCl.

open-flask Kumada cross-coupling reactions performed with phenyl magnesium chloride at room temperature to test for C–Br versus C–OTf and C–Br versus C–Cl selectivities. In all cases, the coupling was completely selective for C–Br, thus allowing isolation of the coupling products in good to excellent yields. This selectivity was once again found to be independent of the respective relative positioning of the potential leaving groups (*ortho*, *meta*, *para* to each other) or the presence of additional (de)activating substituents or heterocycles (**3**, **4**, **6–9**) (see Table 1). Notably, the pharmaceutically relevant quinoline **9** was previously reported to give C–Cl coupling under Pd⁰/Xantphos catalysis.^[16] In our case, orthogonal and exclusive C–Br functionalization took place. The coupling was also efficient with alternative aryl

Grignards, thus allowing the installation of additional functionality, such as either C–Cl or C–F using a Grignard (Table 1, bottom).

To further test this methodology, we also undertook a coupling reaction between PhMgCl and 2-bromophenyl triflate (see Table 1) on a 1 gram scale (3.28 mmol) using 1 mol% **1** under otherwise identical open-flask reaction conditions. The coupling reaction was found to be equally rapid and completely selective for C–Br. The corresponding coupling product was isolated in 95% yield after column chromatography, thus showcasing that these coupling reactions can also be performed under lower catalyst loadings or significantly larger scale.^[17]

We subsequently explored the generality for site-selective Negishi cross-coupling and subjected a range of polysubstituted arenes and heterocycles to the catalyst **1** under open-flask coupling conditions with *ortho*-tolyl zinc chloride in toluene/THF. Table 2 summarizes the results. Once again, we observed that the reactions were completed within 5 minutes at room temperature. In analogy to the results in Table 1, also for Negishi cross-coupling reactions, exclusive functionalizations of the C–Br bonds were seen in competition with C–Cl and/or C–OTf sites, regardless of the steric accessibility or electronic bias imposed by the substrate. Several pharmaceutically and agrochemically relevant pyridine, thiophene,

and quinoline heterocycles were also studied, and the analogous exclusive C–Br selectivity was seen in all cases.^[18] Alternative arenes (**14** and **15**) could also be introduced in an equally efficient manner. As such, this catalytic system provides consistent and predictable C–Br selectivity, thus offering orthogonal and programmable synthetic approaches of high convenience (air-stable catalyst, room temperature, rapid reaction speed, open flask).

Intrigued by the observed reactivities, we subsequently performed additional studies to shed light on the origins of the selectivity and reactivity. There is the possibility that the coupling proceeds by direct reactivity of the Pd^I dimer^[10] or, alternatively, **1** functions as a precatalyst to a highly reactive monophosphine palladium(0) complex (Pd⁰PtBu₃) upon activation by the nucleophilic organometallic coupling partner.^[12,11] While palladium(0)-based catalysis would generally be incompatible with open-flask reaction conditions because of oxidation of the catalyst/ligand, the impressive speed of the present coupling reactions may simply exceed the rates of the competing oxidation of any potentially released palladium(0) species. Our in situ ReactIR monitoring showed that the palladium(I)-dimer-catalyzed cross-coupling reaction of 4-bromoaryl triflate with *o*-tolyl-MgCl reaches completion in just over a minute (Figure 2), displaying a non-exponential pseudo-first-order growth.^[19] In contrast, when we subjected [Pd⁰(PtBu₃)₂] to air for 30 minutes, we saw a significant amount of [Pd⁰(PtBu₃)₂] remaining (as judged by ³¹P NMR data; see the Supporting Information). Interestingly, upon subsequent addition of (*n*Bu₄N)I along with PhMgCl (2 equiv relative to Pd) to the latter mixture, we observed the formation of **1** along with biphenyl.^[20] To the best of our knowledge, this is the first observation of an aerobically induced oxidation of a palladium(0) complex to a palladium(I) dimer.

These data indicate that any palladium(0) released in the reaction mixture could ultimately be reversibly transformed back into the palladium(I) dimer. On the basis of these data, neither palladium(0)- nor palladium(I)-based catalysis can be excluded. Thus, we subsequently set out to computationally study the chemoselectivities for oxidative additions at Ph–Br

Table 2: C–Br selective Negishi cross-couplings.^[a]

C–Br vs. C–Cl			
1. 91% ^c	2. 70% ^c	3. 71% ^c	4. 97%
C–Br vs. C–OTf			
5. 94%	6. 94%	7. 91%	8. 92%
9. 98%	10. 95%	11. 78% ^b	12. 92%
	Alternative ArZnX		
13. 91%			15. 86%

[a] **1** (8.7 mg, 0.01 mmol), ArBr (0.4 mmol), *o*-tolyl-MgCl (1 M in THF, 600 μ L, 0.6 mmol), ZnCl₂ (1 M in THF, 640 μ L, 0.64 mmol), toluene (1.5 mL). Yield is that of isolated product. [b] Used 1.1 equiv of ArMgCl and 1.2 equiv of ZnCl₂. [c] Used 1.3 equiv of ArMgCl and 1.4 equiv of ZnCl₂.

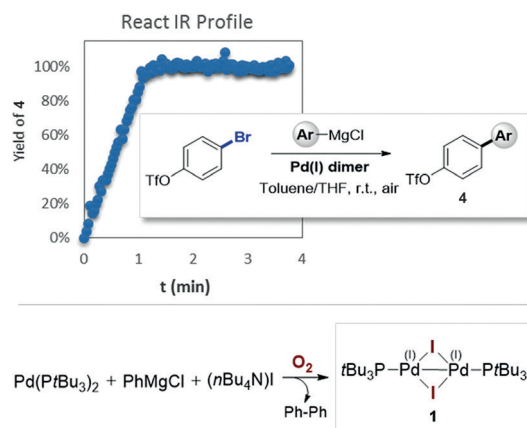


Figure 2. Top: ReactIR study of the Kumada coupling of 4-bromoaryl triflate (Ar = *o*-tol) catalyzed by **1**. Bottom: aerobic oxidation of Pd⁰ to Pd^I–Pd^I.

versus Ph–Cl versus Ph–OTf for both catalysis regimes using the method CPCM (toluene) M06/def2-TZVP// ω B97XD/6-31G(d)/SDD.^[21] The computational data suggest a clear preference for oxidative addition at C–Br for both, a monoligated $[\text{Pd}^0\text{PtBu}_3]$ and a $\text{Pd}^{\text{I}}\text{–Pd}^{\text{I}}$ derived species (by $\Delta\Delta G^\ddagger \geq 6.8 \text{ kcal mol}^{-1}$ for $[\text{Pd}^0\text{PtBu}_3]$ and $\Delta\Delta G^\ddagger \geq 3.4 \text{ kcal mol}^{-1}$ for $\text{Pd}^{\text{I}}\text{–Pd}^{\text{I}}$ relative to C–Cl). C–OTf addition is predicted to be even less favored (see the Supporting Information). In contrast, an anionic palladium(0) species $[\text{Pd}^0(\text{PtBu}_3)\text{X}^-]$ with X = halogen or aryl, which may form under conditions with nucleophilic additives,^[2a,3a,f,9] particularly Grignard reagents,^[22] is predicted to add preferentially to C–OTf (by $\Delta\Delta G^\ddagger \geq 3.5 \text{ kcal mol}^{-1}$ for X = Ph and $2.8 \text{ kcal mol}^{-1}$ for X = Cl). With monoligated $[\text{Pd}^0\text{PtBu}_3]$ and $\text{Pd}^{\text{I}}\text{–Pd}^{\text{I}}$ being formally electron-deficient species (as opposed to PdLX^-), selection occurs for the coupling site with lowest distortion energies.^[7b] Key to overall high chemoselectivities therefore appears to be the avoidance of co-existing reactive species, which are more likely encountered under prolonged reaction times.

In summary, an a priori predictable chemoselective $\text{C}_{\text{sp}^2}\text{–C}_{\text{sp}^2}$ bond formation of poly(pseudo)halogenated arenes has been developed. The coupling reactions are triggered by the bench-stable dinuclear palladium(I) complex $[(\text{PtBu}_3)\text{PdI}]_2$, and are completed in less than 5 minutes at room temperature in air.^[17] Exclusive bromo selectivity was observed in the presence of C–OTf and C–Cl sites, that is independent of any electronic or steric bias imposed by the substrate. The method proved to be compatible with heterocycles and functional groups, thus tolerating C–Cl, C–OTf, C–F, C–CN, aldehydes, esters, and sterically demanding groups (*ortho*-adamantyl) as well as both, aryl zinc, and Grignard coupling partners. The larger scale applicability of the present method was also showcased (on 1 g scale with 1 mol % catalyst loading).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chemoselectivity · density-functional calculations · heterocycles · palladium · reaction mechanisms

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- [18] Although the coupling was selective and complete, some loss of material in purifications was experienced.
- [19] This could be indicative of reductive elimination being rate determining, or a potentially autocatalytic scenario.
- [20] Subjecting [Pd⁰(PtBu₃)₂] to oxygen and (*n*Bu₄N)I did not yield Pd^I dimer **1**. However, mixing PhMgCl, [Pd⁰(PtBu₃)₂], and (*n*Bu₄N)I first under Ar (no change), followed by exposure to air, gave Pd^I dimer **1**.
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