Cross-Coupling **Hot Paper**

How to cite: Angew. Chem. Int. Ed. **2021**, 60, 7007–7012
International Edition: doi.org/10.1002/anie.202014842
German Edition: doi.org/10.1002/ange.202014842

Base-Free Cross-Couplings of Aryl Diazonium Salts in Methanol: Pd^{II}–Alkoxy as Reactivity-Controlling Intermediate

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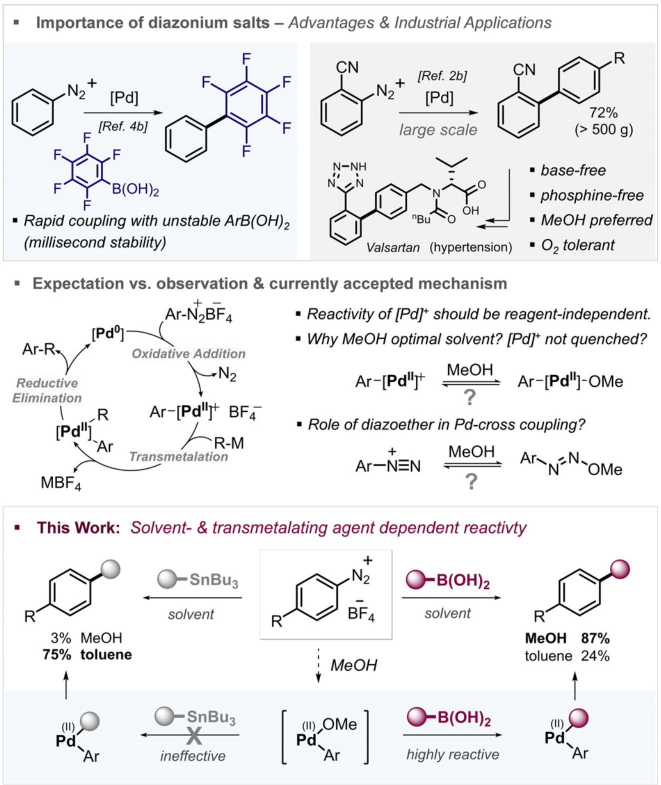
Abstract: *Pd-catalyzed cross-coupling reactions of aryl diazonium salts are generally assumed to proceed via cationic Pd^{II} intermediates which in turn would be highly reactive in the subsequent transmetalation step. Contrary to this belief, we herein report our observation and rationalization of opposing reactivities of ArN_2^+ in Suzuki (= effective) and Stille (= ineffective) cross-couplings in MeOH. Our systematic experimental and computational studies on the roles of transmetalating agent, solvent, base and the likely involvement of in situ formed diazoether derivatives challenge the currently accepted mechanism. Our data suggest that the observed solvent dichotomy is primarily due to Pd^{II}-methoxy intermediates being formed, which are unreactive with arylstannanes, but highly reactive with arylboronic acids, complementing the Suzuki "Pd-oxy" mechanism with the direct demonstration of transmetalation of a Pd^{II}-alkoxy complex. Lewis acids were found to circumvent this reactivity divergence, promoting efficient couplings regardless of the employed conditions or coupling partners.*

Owing to the highly activated nature of their C–N_2^+ bond paired with the relative ease of preparation from abundant amines, aryl diazonium salts find widespread applications in one- and two-electron-based processes in synthesis and catalysis.[1] They are also popular electrophiles in Pd-catalyzed biaryl construction,[1d] especially in large-scale industrial applications,[1d,2] as their high reactivity allows couplings in the absence of (costly) phosphine ligands, wasteful additives or bases, and under tolerance of oxygen in more environmentally benign solvents (e.g. MeOH or water), see Scheme 1.[3] Their high coupling speed also makes aryl diazonium salts privileged reaction partners for sensitive reagents, such as polyfluoroaryl boronic acids that possess only millisecond lifetimes in solution,[4] or to enable chemoselective biaryl syntheses in the presence of carbon-halogen sites.[1a,d]

In this context, the general textbook mechanism is that the reaction of Pd^0 catalysts with aryl diazonium salts proceeds via a three-centered oxidative addition under the loss of nitrogen to yield a cationic Pd^{II} intermediate (Scheme 1), which in turn would be highly reactive towards subsequent transmetalation.[1c,d,5] If this mechanism were operative, one would expect all classes of transmetalation agents to be effective in the couplings with diazonium salts. This is not the case however, and Suzuki cross-couplings by far dominate the known synthetic transformations with aryl diazonium salts. Moreover, it is somewhat surprising that the optimal solvent in couplings of aryl diazonium salts is methanol,[6] as methanol could in principle quench the cationic Pd^{II} intermediate to generate "Pd^{II}–OMe".

We herein report our observation and rationalization of the contrasting reactivities of aryl diazonium salts when varying the transmetalating reagent and solvent: much more effective cross-coupling occurs when a boronic acid is used (87%), relative to a stannane-based reagent (3%) in methanol, but the reverse trend is seen in toluene. These observations are in contrast with the proposed mechanism, as the active Pd^{II} intermediate would be expected to readily



Scheme 1. Overview of the importance and currently accepted mechanism of cross-coupling of diazonium salts (top) and our findings (bottom).

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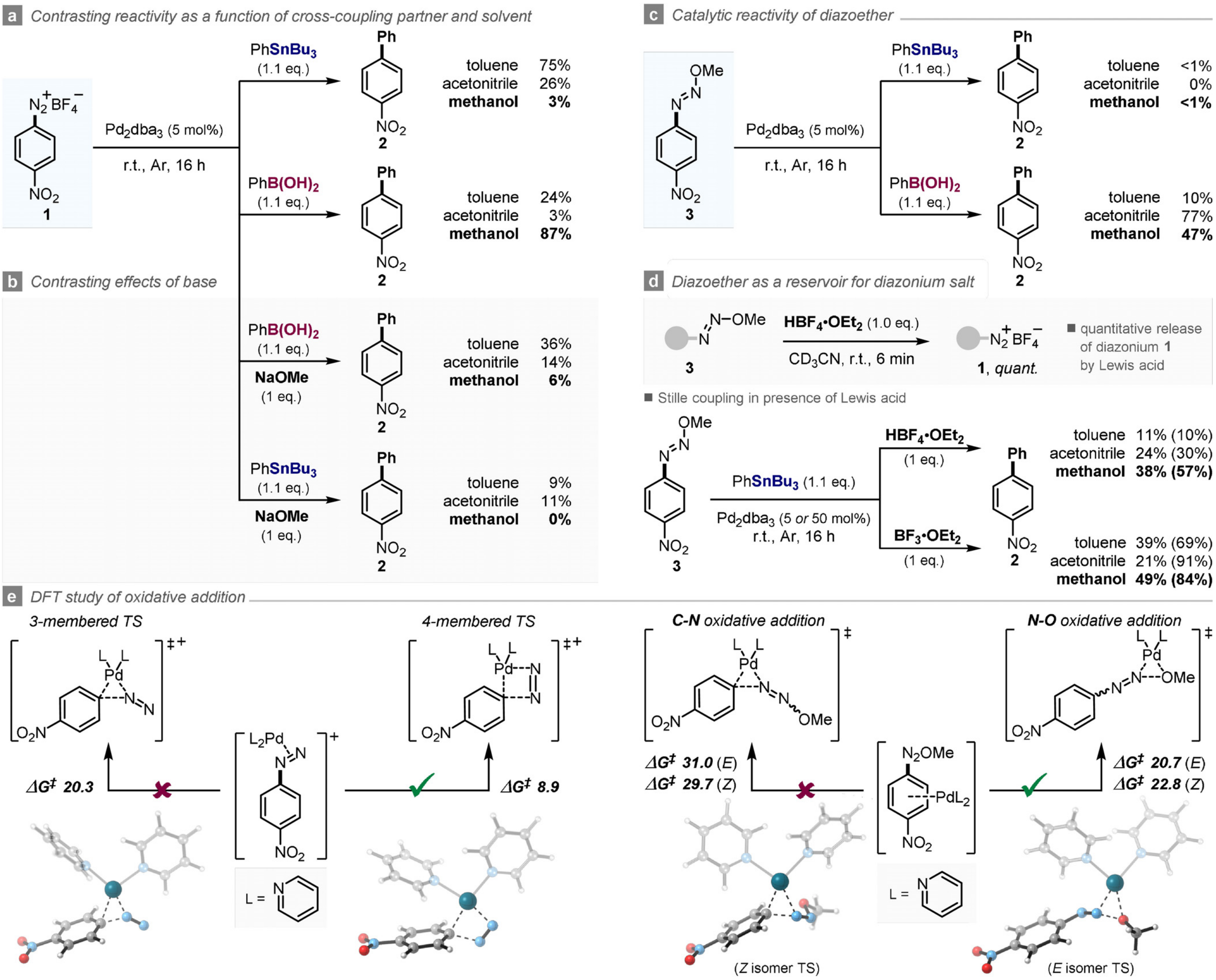
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202014842.

undergo transmetalation with both species. Our data suggest a Pd^{II}–alkoxy species as key decisive intermediate and shed light on the impacts of additives (base, Lewis acid) and the nature of the elementary steps.

As part of our mechanistic program in Pd-catalysis,[7] we had set out to investigate the solvent effects of aryl diazonium salt couplings for the representative substrate, 4-nitrobenzenediazonium tetrafluoroborate **1** (Scheme 2a). Analysis of reaction progress under Stille and Suzuki coupling conditions with $Pd_2(dba)_3$ as catalyst (5 mol%) under base-free conditions at room temperature indicated a profound solvent effect on the efficiency of the coupling. While Stille cross-coupling proceeded efficiently in toluene (75%), in MeOH only minimal product was formed (3%). In stark contrast, Suzuki cross-coupling proceeded highly efficiently in MeOH (87%), but less well in toluene or MeCN (see Scheme 2a).[8] In stark contrast to these base-free conditions, we only saw very little product formation in the $Pd_2(dba)_3$-catalyzed Suzuki cross-coupling of diazonium salt **1** in MeOH in the presence of NaOMe and of the corresponding Stille coupling in toluene with NaOMe (Scheme 2b). Intrigued by these observations, we set out to systematically investigate the mechanistic underpinning of diazonium salt cross-couplings.

In light of the contrasting effect of base in MeOH, we initially questioned whether a diazoether might be involved under either of the reaction conditions. It has previously been shown that in alcoholic media under basic conditions diazonium salts can be converted in situ to diazoethers.[9] *Z*-diazoethers, if formed, generally show lower stability to their *E*-counterparts, and may eventually fragment to aryl radicals.[9] Little is known about the direct reactivities of



Scheme 2. Reactivity comparison of diazonium salts (a,b) and diazoethers (c,d) and e) computational study (at the CPCM (toluene) PBE0-D3(BJ)/def2-QZVP//ωB97XD/6-31G(d) + LANL2DZ (for Pd) level of theory, Gibbs free energies in kcal mol^{-1}). Yields were obtained by calibrated GC-MS analyses, yields in brackets were obtained using 50 mol% Pd_2dba_3. To minimize potential errors in the computational study in relation to the conformational space of dba (and uncertainty of the speciation of Pd_2dba_3), we utilized L = pyridine in the calculations as a model, which was separately experimentally verified.[11]

diazoethers in Pd-catalysis.[10] To assess the feasibility of such a species affecting the reaction outcome, we separately prepared the corresponding diazoether **3** and studied its cross-coupling reactions under both Stille and Suzuki conditions in MeOH, MeCN, and toluene (Scheme 2c). Regardless of the solvent employed, the Pd-catalyzed cross coupling with phenylstannane was found to be ineffective. Interestingly, however, the diazoether showed high efficiency in the coupling with phenylboronic acid, giving the coupling product in 77 % yield in acetonitrile and 47 % yield in MeOH.

On the other hand, when we subjected diazoether **3** to a stoichiometric amount of $Pd_2(dba)_3$ (in toluene), we did not observe any consumption of **3**, which suggests that direct reaction of the Pd-catalyst with the diazoether may not actually be feasible.

We hypothesized that the efficient reaction under Suzuki conditions might therefore stem from the acidic nature of the boronic acid and a potential in situ "deprotection" to the diazonium salt.[9c] To examine this possibility, we repeated the experiment of diazoether **3** under Stille coupling conditions, but this time added a Lewis acid to the reaction (Scheme 2d). We hypothesized that a Lewis acid might enable a similar "deprotection" to release the "free" diazonium salt, which should then react even with the stannane. Pleasingly, the use of the Lewis acid additive, such as $BF_3{\cdot}OEt_2$, indeed promoted the Stille cross-coupling and led to notable conversion of the diazoether **3** to the cross-coupled product **2** (see Scheme 2d). Similarly, our separate subjection of diazoether **3** to $HBF_4{\cdot}OEt_2$ (1.0 equiv) in acetonitrile resulted in clean conversion to diazonium salt **1** within the time required to record a quantitative ^1H NMR spectrum (i.e. 6 minutes) at room temperature (Scheme 2d). These data strongly indicate that the diazoether is not reactive directly in $Pd_2(dba)_3$-catalyzed couplings at room temperature; it rather functions as a reservoir of the aryldiazonium salt when exposed to acidic (e.g. arylboronic acid) or Lewis acidic (e.g. $BF_3{\cdot}OEt_2$ or $HBF_4{\cdot}OEt_2$) conditions.[11]

In line with the conclusion that the diazoether is likely primarily an *inhibitor* under neutral or basic conditions, the oxidative addition to the C−N bond of a diazoether was calculated to proceed with rather high activation free energy barrier ($\Delta G^{\neq} = 31.0$ and 29.7 kcal mol^{-1}, respectively for the *E*- and *Z*-isomer, see Scheme 2e, right).[12] In fact, we found that the alternative initial addition to the distant N−O bond would be energetically preferred ($\Delta G^{\neq} = 20.7$ and 22.8 kcal mol^{-1}, respectively for the *E*- and *Z*-isomer).[13]

To put these calculated barriers into perspective, we also examined the activation barriers for the oxidative addition to the "free" aryl diazonium salt **1**. The vast majority of literature quotes a three membered transition state, similar to the geometry commonly considered for oxidative addition of aryl halides to Pd^0,[14] as preferred mechanism for oxidative addition of diazonium salts to Pd^0.[15] However, we found a four-membered TS significantly favored ($\Delta\Delta G^{\neq} = 11.4$ kcal mol^{-1}, see Scheme 2e, left). It should be noted that this is formally a σ-bond metathesis-like process, and thus no change in oxidation state occurs during C−N bond breaking. Overall, the calculations suggest that oxidative addition of a diazonium salt to Pd^0 occurs much more readily ($\Delta G^{\neq} = 8.9$ kcal mol^{-1}) than oxidative addition of a diazoether at the required Ar−N bond ($\Delta\Delta G^{\neq} > 28$ kcal mol^{-1}).

These data suggest that aryldiazonium salts are highly reactive with Pd-catalysts via a four-membered σ-bond metathesis mechanism. They may dynamically interconvert to diazoethers in alcoholic solvents under basic conditions, and were shown above to be unreactive towards the Pd-catalyst. Their mechanistic role is hence that of an *inhibitor* under basic conditions, which would be consistent with the non-productive effect of base in the cross-coupling reactions of aryl diazonium salts in MeOH. On the other hand, we identified that diazoethers can also readily release the diazonium salt in the presence of acid or Lewis acid additives.

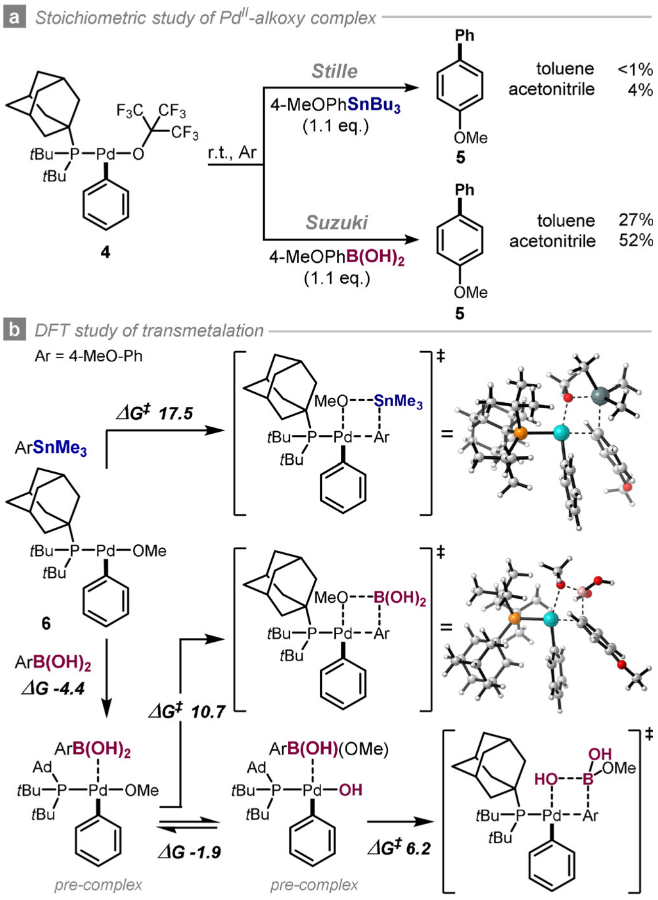
While these results could potentially explain the detrimental effects of base in MeOH,[16] the formation of a diazoether is less likely under "neutral" and base-free couplings, and therefore does not provide a rationale for the ineffectiveness of the Stille coupling of **1** in MeOH (see Scheme 2a). Indeed, when we monitored a solution of aryldiazonium salt **1** in MeOH at room temperature in the presence or absence of Bu_3SnPh over 24 hours, we saw no indication of diazoether formation.

We hypothesized that following oxidative addition of the diazonium salt to Pd^0, and subsequent extrusion of N_2, a putative cationic Pd^{II} intermediate might more rapidly react with the solvent MeOH than with the transmetalating agent. The solvent induced reactivity difference could thus potentially also arise from differences in reactivities of the transmetalating agents with a resulting Pd^{II}–OMe species. For Pd-catalyzed couplings of specialized *ortho*-substituted and in situ made aryldiazonium salts, Felpin and co-workers have previously proposed that Pd^{II}–OMe might form as an intermediate in reactions in MeOH.[6a] However, these suggestions relied primarily on mass spectrometry data; there was no direct demonstration of a transmetalation being possible. Instead, computational data was presented that suggest a prohibitively high barrier for transmetalation of Pd^{II}–OMe by $ArB(OH)_2$ of $\Delta G^{\neq} > 40$ kcal mol^{-1},[6a] which would suggest that Pd^{II}–OMe, if indeed formed, should be unreactive.

To gain unambiguous insight, we set out to synthesize Pd^{II}–alkoxy complex **4** (Scheme 3), which was chosen as it contains no β hydrogens, and therefore excludes the possibility for the β-H elimination side-reaction to occur.

The complex had previously been reported by Hartwig and co-workers, who showed that the bulky phosphine helps to avoid dimerization and maintain a mononuclear T-shaped complex as confirmed by X-ray crystallography.[17] It was shown that the complex does not undergo reductive elimination until its decomposition at 80 °C; it is therefore well suited for our intention to study transmetalation.

With complex **4** in hand, we subsequently tested the transmetalation with $PhB(OH)_2$ and $PhSnBu_3$ in toluene and acetonitrile (MeOH would lead to exchange in **4** and ambiguous side-reactions). In the context of transmetalation of Pd^{II} complexes, recent years have seen a significant increase in understanding, especially in the context of Suzuki couplings: the key pre-transmetalation Pd^{II} intermediate was identified as a boronic acid adduct, containing a Pd-



Scheme 3. a) Reactivity of Pd^{II}–alkoxy complex **4** with different transmetalating agents. Yields determined by calibrated GC-MS using mesitylene as internal standard. b) Activation free energy barriers for transmetalation of **6**, with either a boronic acid or an organostannane (calculated at the CPCM (methanol) PBE0-D3(BJ)/def-2TZVP//ωB97XD/6-31G(d) + LANL2DZ (for Pd and Sn) level of theory, Gibbs free energies in kcal mol^{-1}). ArSnMe$_3$ was employed to model ArSnBu$_3$ to minimize potential errors due to conformational effects.

O-B linkage.[18] Moreover, Pd^{II}–I or Pd^{II}–Br complexes (formed by oxidative addition to an aryl halide) were shown to be ineffective in transmetalation. Instead, compelling data was obtained for their in situ conversion to Pd^{II}–OH or Pd^{II}–F complexes, which in turn were shown to be highly reactive in transmetalation with boronic acids.[19] Information on the relative ease of direct transmetalation with a Pd^{II}–alkoxy complex in comparison to Pd^{II}–OH is scarce.[6a,20]

Our tests with complex **4** revealed that it is reactive towards a boronic acid, indicated by the formation of biaryl **5** in both acetonitrile (52 %) and toluene (27 %), while negligible reaction occurred with an organostannane (5 % of **5**) within 24 h at room temperature (Scheme 3 a). These data parallel our observations of divergent reactivity in MeOH under base-free conditions, suggesting that the intermediacy of a Pd^{II}–OMe and transmetalation-based divergency could indeed be a rationale for the observed differences. These data are of relevance also in the wider context of cross-coupling, and we therefore set out to study the transmetalation of the corresponding Pd^{II}–OMe intermediate **6** in more detail computationally [at the CPCM (methanol) PBE0-D3(BJ)/def2-TZVP//ωB97XD/6-31G(d) + LANL2DZ level of theory].

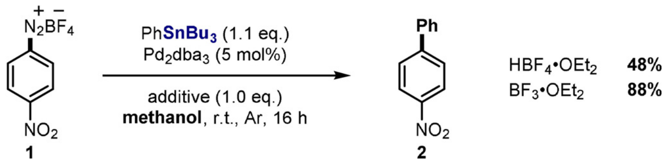
The results of our calculations are summarized in Scheme 3 b. The transmetalation pathway initially involves the formation of an adduct of the boronic acid with the *cis*-T-shaped Pd^{II} complex **6**;[18c] the corresponding stannane forms no stable pre-complex. Transmetalation in each case is favoured via a *trans*-T-shaped complex, which requires prior isomerization.[21] Our data suggest that the transmetalation at the Pd^{II}–OMe complex **6** occurs substantially more readily with a boronic acid than with an organostannane,[22] which parallels the experimental findings with **4**.

The activation free energy barrier for the direct transmetalation of the Pd^{II}–OMe species **6** is with $\Delta G^{\ddagger} = 10.7$ kcal mol^{-1} calculated to be in a similar range as that of an analogous Pd^{II}–OH complex ($\Delta G^{\ddagger} = 6.4$ kcal mol^{-1}), which has mechanistically been shown to be a key intermediate in Suzuki cross-couplings of aryl halides. There is also the possibility that a Pd^{II}–OMe complex initially converts to Pd^{II}–OH [via OH/OMe exchange with ArB(OH)$_2$], see Scheme 3 b (bottom). The latter exchange is calculated to be exergonic (by 1.9 kcal mol^{-1}), and transmetalation of the Pd^{II}–OH by PhB(OH)(OMe) is calculated to have a similarly feasible activation barrier of $\Delta G^{\ddagger} = 6.2$ kcal mol^{-1}. These data support that arylboronic acids may readily react with Pd^{II}–OMe, either directly or via prior dynamic exchange with a boronic acid to generate Pd^{II}–OH and ArB(OH)(OMe).[23]

These experimental and computational data suggest that the propensity of the transmetalating agent to react with the generated Pd^{II}–OMe intermediate could account for the divergent reactivity observed for Stille versus Suzuki cross-coupling of diazonium salts in methanol.

We speculated that in analogy to our observations with diazoethers above, an in situ formed Pd^{II}–OMe intermediate might potentially also be somewhat “deprotectable” with an appropriate Lewis acid, which in turn might allow for reaction in methanol even under Stille conditions. We therefore tested the cross-coupling of the diazonium salt **1**, under base-free Stille cross-coupling in methanol in the presence of BF$_3$·OEt$_2$, which indeed pleasingly led to 88 % yield of the coupling product **2** (Scheme 4; without BF$_3$·OEt$_2$ the yield was 3 %).

In conclusion, we discovered and mechanistically rationalized a solvent- and transmetalating agent dependent reactivity in the base-free Pd-catalyzed cross-coupling of aryl diazonium salts. Contrary to the general mechanistic proposals, the observed reactivity in MeOH is inconsistent with the reactivity of a cationic Pd^{II} intermediate, [L$_n$Pd^{II}-(Ar)]$^+$. Our experimental and computational data instead



Scheme 4. Stille cross-coupling of diazonium salt **1** using a Lewis acid additive. Yields were determined with calibrated GC-MS using mesitylene as internal standard.

suggest the intermediacy of a Pd^{II}–methoxy species, which we showed to be reactive in the direct transmetalation with arylboronic acids, but virtually unreactive with arylstannanes. Our data complement the Pd–oxy transmetalation mechanism for Suzuki couplings, suggesting that Pd–OMe is similarly competent as Pd–OH, but that a dynamic OH/OMe exchange with the boronic acid may also occur. We also examined the potential role of (in situ formed) diazoethers in catalysis, and unambiguously showed that they are not directly activated by Pd at room temperature, but will be converted to the free aryldiazonium salts with acids (e.g. arylboronic acid) or Lewis acids (e.g. BF$_3$). Our findings with Lewis acid additives enable the application of diazoethers as protected and more soluble derivatives of aryldiazonium salts, and also allow to overcome solvent- and transmetalating agent induced reactivity dependencies.

Acknowledgements

We thank the RWTH Aachen and the MIWF NRW for funding, and David Fabry for assistance and helpful discussion. Calculations were performed with computing resources granted by JARA-HPC from RWTH Aachen University under project “jara0091”.

Conflict of interest

The authors declare no conflict of interest.

Keywords: computation · cross-coupling · diazonium salts · reaction mechanism · solvent dependence · transmetalation

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[23] Our computational study of alternative Pd^{II}–OMe complexes that carry dba or pyridine ligands in place of the phosphine, gave rise to analogous results. See the Supporting Information for details.

Manuscript received: November 5, 2020
Accepted manuscript online: February 5, 2021
Version of record online: February 24, 2021