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Research Article

# Halide Salts Alleviate TMSOK Inhibition in Suzuki–Miyaura Cross-Couplings

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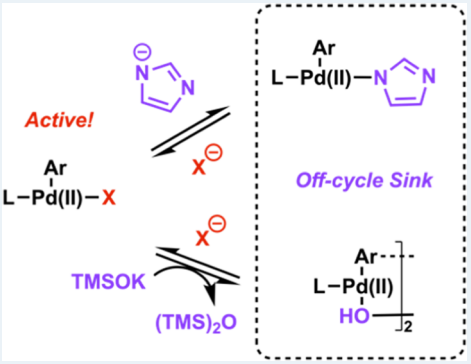
**ABSTRACT:** The Suzuki–Miyaura cross-coupling (SMC) remains one of the most widely used transformations available to chemists. Recently, robust new conditions achieving rapid reactivity under homogeneous aprotic conditions enabled by the use of potassium trimethylsilanolate (TMSOK) as a base were reported. However, the strong inhibitory effect of TMSOK restricts the generality of such conditions. Moreover, the basic nature of TMSOK impedes the use of protic heterocycles as substrates, as these latter anionic species are even more potent catalyst inhibitors. Herein, we report a thorough mechanistic study of these novel SMC conditions. Halide salt additives were found to provide a dramatic rate acceleration and mitigate the inhibitory effect of TMSOK. NMR experiments revealed that this is largely achieved by impacting the unexpected formation of inactive $[LnPd(Ar)(\mu-OH)]_2$, favoring the formation of active LnPd(Ar)(X) instead. These findings enabled an impressive substrate scope even at low catalyst loadings (0.1 mol %). Finally, halide additives were observed to enable the use of protic heterocyclic substrates, which could otherwise completely inhibit reactivity.




**KEYWORDS:** *Suzuki–Miyaura cross-coupling, mechanistic study, halide additive, potassium trimethylsilanolate, catalyst speciation*

## INTRODUCTION

The Suzuki–Miyaura cross-coupling (SMC) remains among the most important reactions available to chemists to forge C–C bonds.[1] The remarkable versatility of the SMC arises from exhaustive investigations into its underlying mechanism,[2] enabling the judicious design of catalysts and reagents that effectively promote the key elementary steps (i.e., oxidative addition, transmetalation, reductive elimination) while circumventing common detrimental pathways.[3] For instance, protodeboronation of the nucleophilic organoboron species is a common competitive reaction, especially prominent with the use of heterocyclic and polyfluorinated organoboron derivatives. This led to the development of several strategies enabling the use of such substrates and limiting this undesirable pathway.[4] Significant efforts have also been dedicated to the design of ligands such as dialkybiaryl phosphines,[5] bulky trialkylphosphines,[6] and *N*-heterocyclic carbenes.[7] These privileged ligand classes typically combine significant steric bulk with strong sigma donicity, promoting the formation of highly reactive monoligated Pd species.[3a] These advancements have played key roles in enabling SMCs to achieve efficient reactivity with complex heterocyclic coupling partners, which are otherwise prone to both degradation[4] and catalyst inhibition.[8] Despite these advancements, the use of unprotected, acidic, heterocyclic species in SMCs remains challenging, typically requiring extensive screening of conditions and high loadings of the organoboron derivative and of the palladium catalyst.[9]

The Denmark group has made a number of seminal contributions toward the mechanistic understanding of SMCs.[10] This culminated in the development of innovative conditions that facilitate SMCs under homogeneous aprotic conditions.[11] These conditions offer distinct advantages over conventional SMC conditions: (1) significant rate accelerations can be achieved over literature precedence; (2) the aprotic nature of the system can limit competitive protodeboronation; (3) the homogeneous nature of the system can eliminate the impact of particle size or mixing effects which are otherwise difficult to control. However, trimethylsilanolate (TMSOK) also exerts a potent inhibitory effect under these conditions. Without tight control over its concentration, the reaction may be completely inhibited, leading to poor reproducibility. Furthermore, substrates bearing protic heterocycles have yet to be reported under such conditions, likely due to the basicity of the reaction conditions leading to significant catalyst inhibition.[9h] Herein, we report the use of halide salts as key additives under homogeneous TMSOK-based conditions, drastically increasing reaction rates and expanding the substrate scope of such conditions. A thorough mechanistic

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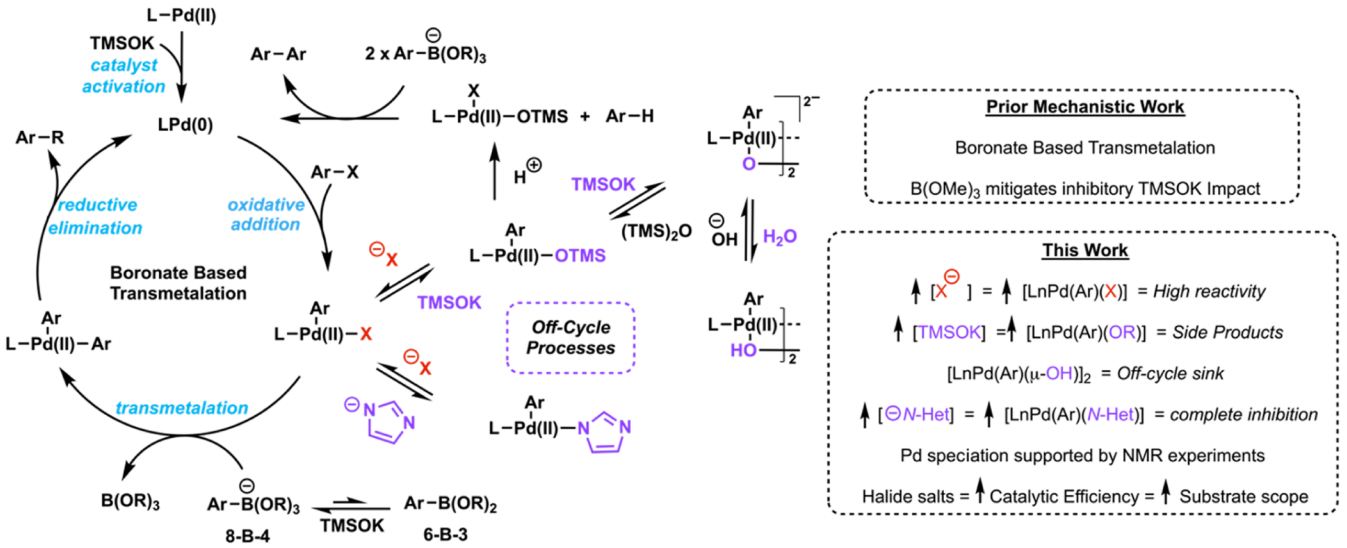


**Figure 1.** Proposed mechanistic cycle for the SMC under aprotic homogeneous conditions studied herein.

study revealed that this behavior arises from the impact of the halide on catalyst speciation (Figure 1). Specifically, under standard reaction conditions, the catalyst is brought off-cycle through the unexpected formation of $[LnPd(Ar)(\mu-OH)]_2$. This species has limited activity under the TMSOK-based condition due to the minimal presence of 6-B-3 boron species in these settings. The addition of halide salts favors the formation of LnPd(Ar)(X), which promotes the dominant pathway to transmetalation with the 8-B-4 boronate nucleophile. The ability of halide salts to favor the formation of the active LnPd(Ar)(X) species was further demonstrated in the presence of substrates bearing acidic heteroatoms, which, in the absence of halide additives, could completely inhibit reactivity.

## RESULTS AND DISCUSSION

Our laboratory has maintained a longstanding interest in the mechanistic study of complex organic transformations.[12] This enduring pursuit culminated in our development of an

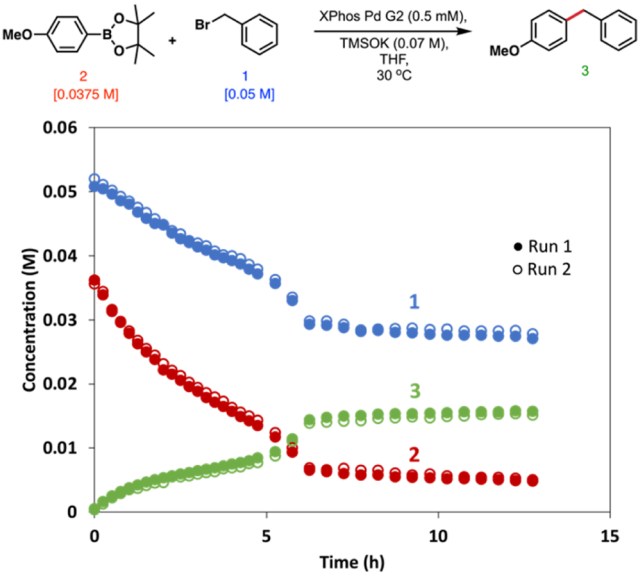


**Figure 2.** Probing the reproducibility of our model reaction.

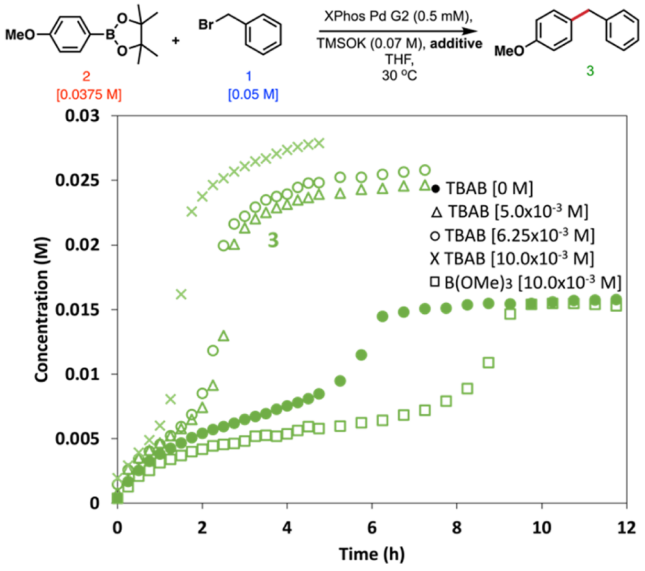


**Figure 3.** Time course data probing the impact of increasing concentrations of TBAB.

automated sampling platform coupled with direct injection to high-performance liquid chromatography-mass spectrometry (HPLC-MS) for reaction analysis.[12c] Recently, we conducted a detailed mechanistic study of the SMC coupling under biphasic reaction conditions and reported a significant rate enhancement with the addition of tetrabutylammonium (TBA) halide salts.[13] This rate enhancement stemmed from the ability of TBA salts to increase the organic phase concentration of both the eight-electron four-coordinate boronate (8-B-4) nucleophile, as well as the halide-bound oxidative addition complex (LnPd(Ar)(X)). This resulted in a shift in the dominant mode of transmetalation from an oxo-palladium-dominated system to a boronate-dominated pathway. Recent results by Denmark et al. suggested that their TMSOK-based conditions are dominated by the boronate pathway.[11c] Consequently, they proposed that the potent TMSOK inhibition observed was a result of the formation of LnPd(Ar)(OTMS). We hypothesized that halide additives may significantly alleviate the inhibitory impact of TMSOK


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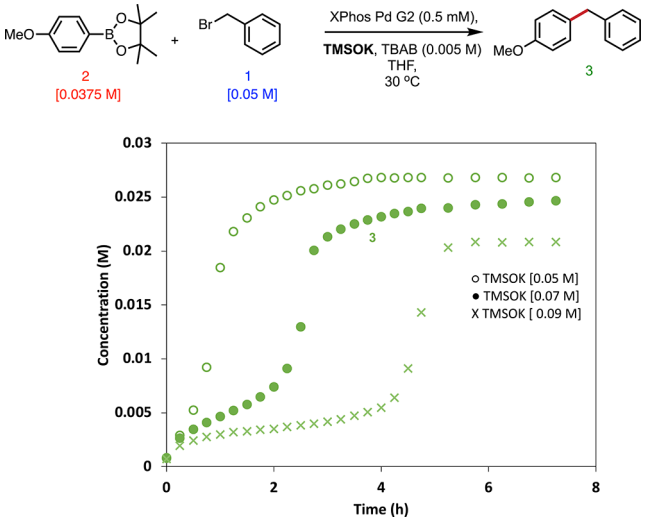


**Figure 4.** Time course data probing the impact of increasing concentrations of TMSOK.

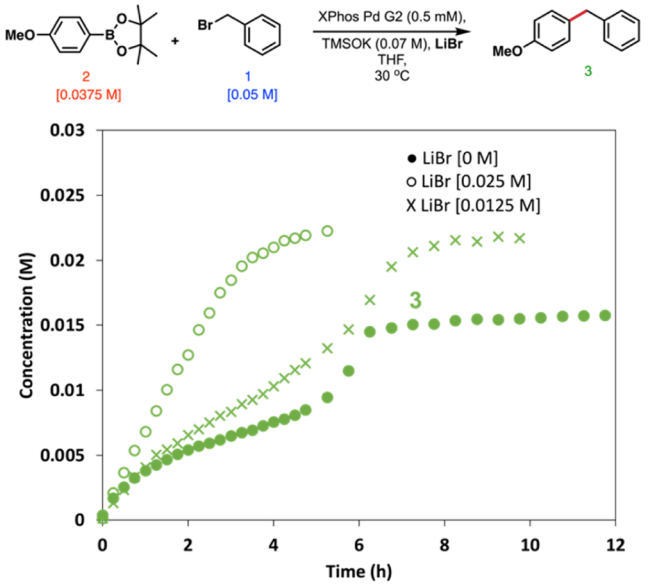


**Figure 5.** Time course data probing the impact of increasing concentrations of LiBr.

observed under such conditions by favoring the formation of LnPd(Ar)(X) instead.

To begin our study, we needed to identify a model system. We chose to work with the same benzylic halide SMC that had been the target of our prior investigations. Denmark et al. reported that TMSOK loadings of one equivalent relative to the aryl boron nucleophile can result in significant inhibition.[11] In such cases, the portion-wise addition of the TMSOK significantly limits this undesired reactivity.[11a] Notably, TMSOK loadings were kept below that of the aryl boron nucleophile during their kinetic studies, likely due to simplifying the kinetic regime (vide infra). In contrast, we wanted to target a system that suffered significant inhibition to probe the impact of halide salts. Consequently, we chose to study this system with a significant excess of TMSOK relative to that of the aryl boron nucleophile. With our model system in hand, we began our study by probing the reproducibility of our sampling platform. Excellent overlay was achieved when monitoring our model system under standard reaction conditions (Figure 2). Notably, the kinetic regime of the reaction system clearly changes several times over the course of the reaction, suggesting that steady-state kinetic analyses will not be amenable to this system.

We hypothesized that the root cause of this complex kinetic behavior results from significant shifts in catalyst speciation throughout the course of the reaction. During the initial stages of the reaction, TMSOK is present in high concentration with a limited halide salt byproduct, favoring the formation of off-cycle LnPd(Ar)(OTMS). However, this changes in the latter parts of the reaction, where TMSOK has largely been consumed while the concentration of the halide byproduct increases, favoring the formation of on-cycle LnPd(Ar)(X). Consequently, we reasoned that the addition of halide salts to the reaction would improve reactivity by counteracting the negative impact of TMSOK and shifting catalyst speciation. Pleasingly, when targeting our standard reaction conditions with increasing TBAB loadings, a significant reduction in the length of the induction period was observed. This increase in reactivity occurred alongside a shift in selectivity away from the two major side products, homocoupling of **2** and dehalogenation of **1** (see Supporting Information Figure S3), resulting in a much higher overall yield of **3** (Figure 3).

We also probed the use of trimethyl borate ($B(OMe)_3$) as an additive under the reaction conditions. This additive was recently reported by Denmark et al. to drastically increase the scope of this methodology by (1) solubilizing the in situ-generated boronate complex, (2) limiting catalyst poisoning by heteroaromatic units, and (3) buffering the inhibitory effect of excess TMSOK.[11b] However, this additive had a minimal impact on the reactivity of our standard reaction conditions (Figure 3).

To further validate this theory, a similar set of experiments was targeted while using different concentrations of TMSOK. If Pd speciation lies at the root of the induction behavior, not only would one expect the addition of halide salts to diminish such behavior but also one would expect increasing TMSOK loadings to prolong the induction period. Thus, a set of different excess reactions varying the concentration of TMSOK in the presence of the halide additive was carried out (Figure 4). Notably, the length of the induction period was observed to be proportional to the concentration of TMSOK.

During our prior work, the TBA cation was observed to play a crucial role as a phase transfer catalyst under biphasic conditions. However, under the targeted conditions herein, we believe that the cation plays a limited role except for ensuring the solubility of the halide anion in the organic solvent. Toward this end, we probed the impact of LiBr as an alternative soluble halide source. Significant rate accelerations were observed with increasing concentrations of lithium salts (Figure 5). This suggests that the halide plays a key role in increasing reactivity under the reaction conditions. A control reaction using TBAOTf further confirms the impact of the cation to be minimal under the targeted conditions (see Supporting Information Figure S4).

The use of lithium salts presented an excellent opportunity to probe the turnover-limiting steps. In contrast to the use of TBAB, which continues to display complex kinetic behavior even at increased loadings, LiBr results in a simpler kinetic regime, which lends itself to standard kinetic analysis using the same and different excess reactions. A series of different excess reactions revealed a zeroth order reaction in electrophiles,


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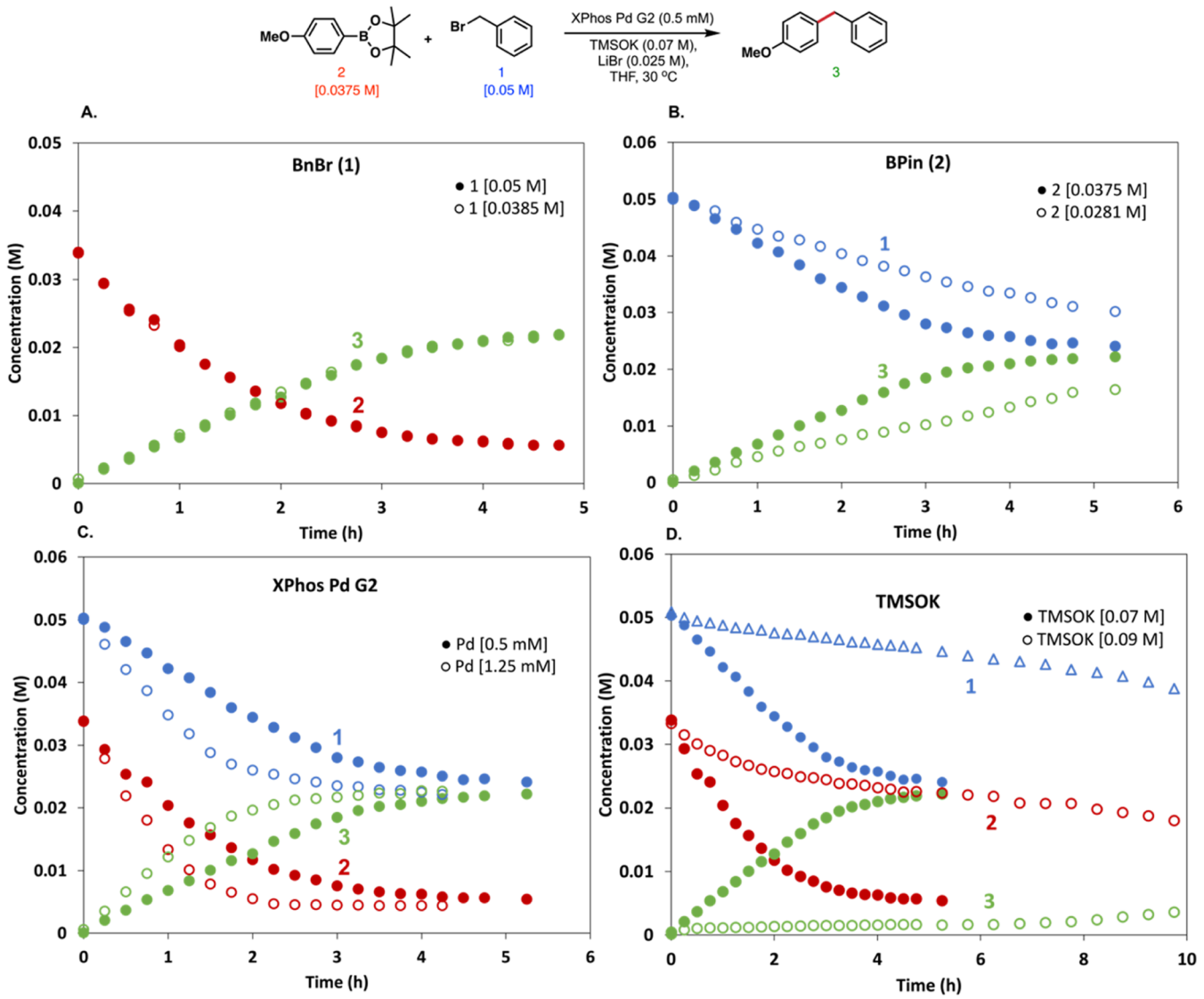


**Figure 6.** Different excess experiments probing the impact of **1**, **2**, XPhos Pd G2, and TMSOK.

positive orders in both the catalyst and nucleophiles, and a negative order in base (Figure 6). These data are consistent with turnover-limiting transmetalation. The negative order in TMSOK can be rationalized through its ability to shift the Pd resting state from the active LnPd(Ar)(X) to the off-cycle LnPd(Ar)(OTMS), in line with Denmark's prior investigation. Finally, the same excess experiments in the presence of LiBr also revealed a lack of catalyst degradation (see Supporting Information Figure S13).

To substantiate the role of added halide salts on catalyst speciation, we targeted stoichiometric NMR experiments. Difficulties associated with the synthesis of the benzylic oxidative addition complexes led us to target a C($sp^2$)-based system. The use of SPhos was targeted, as the ligand SPhosPd(Ph)(Cl) had been employed in similar speciation experiments by our group[13] and others.[9h] Control reactions confirmed that the catalytic impact of halide salts is active for the targeted model system (see Supporting Information Figure S21). Thus, SPhosPd(Ph)(Cl) was exposed to 10 equiv of TMSOK (Figure 7). The disappearance of the original phosphine peaks (**4** and **5**) was observed with the appearance of a single new phosphine resonance (**6c**) initially thought to be SPhosPd(Ph)(OTMS). Single crystals suitable for X-ray diffraction analysis were obtained and revealed instead $[SPhosPd(Ph)(\mu{-}OH)]_2$ (see Supporting Information Figure S24). The presence of hydroxide is a known impurity in commercial samples of TMSOK that could explain the formation of $[SPhosPd(Ph)(\mu{-}OH)]_2$. However, the TMS group can be labile under basic conditions and could also lead to the formation of the requisite hydroxide. $^{29}$Si NMR experiments of the reaction solution revealed the formation of TMS-O-TMS, thus suggesting that the formation of hydroxide occurs in situ (see Supporting Information Figure S26). Given the lack of formation of TMS-O-TMS in the absence of palladium, we propose the formation of SPhosPd(Ph)(OTMS) in situ as an intermediate species leading to the formation of both TMS-O-TMS and the $[SPhosPd(Ph)(\mu{-}OH)]_2$. This is in line with observations from both Denmark et al.[11c] and this work (see Supporting Information Figure S25), where ratios of TMSOK to Pd lower than 2:1 result in the presence of several different species.

With the major Pd species present under the reaction conditions identified, we moved forward to probe the impact of the addition of halide salts to this mixture. Upon the


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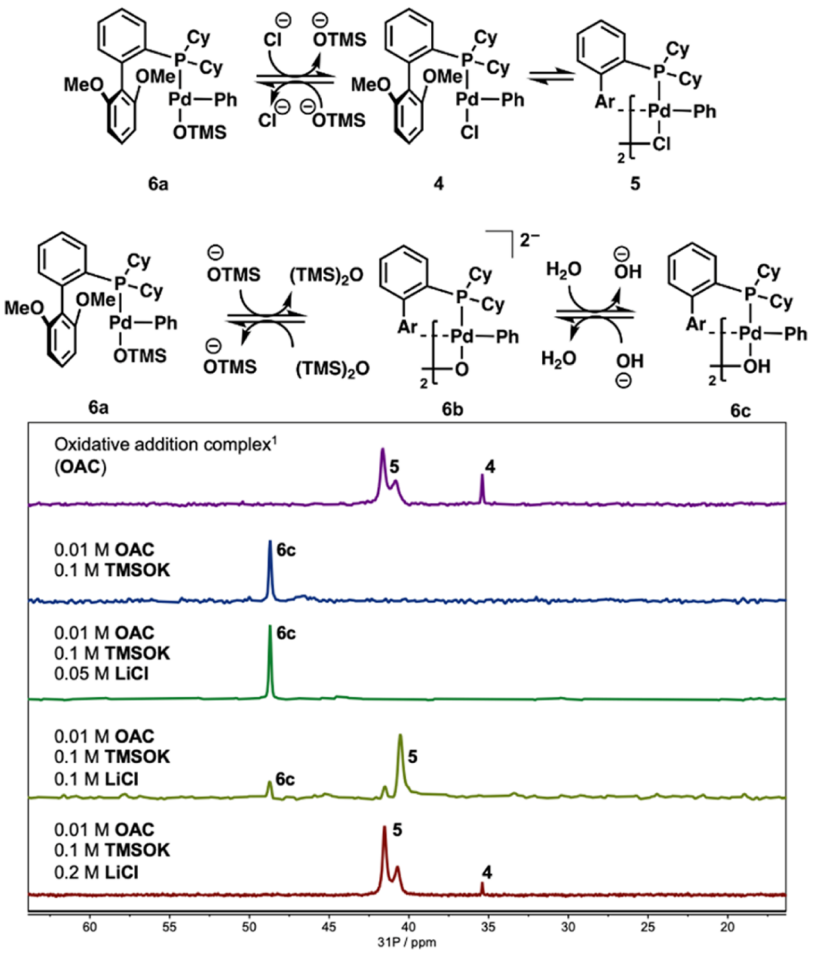


**Figure 7.** Overlay of $^{31}$P NMR study probing the impact of TMSOK and LiCl on Pd speciation. [1] OAC was synthesized according to the prior literature procedure.[9h]

addition of increasing equivalents of LiCl (Figure 7), the resurgence of the original SPhosPd(Ph)(Cl) signals was observed (see Supporting Information S22). Notably, when both TMSOK and LiCl were present in equivalent ratios, SPhosPd(Ph)(Cl) bridge dimers (**5**) dominated the NMR spectra. Further increasing the LiCl loading led to [SPhosPd-(Ph)(OH)]$_2$ signals falling below the limit of detection. Taken together, these data strongly support the idea that TMSOK and added halide salts have an antagonistic effect on palladium catalyst speciation, with the latter favoring the formation of LnPd(Ar)(X), the active species under the targeted conditions.

The inactivity of [SPhosPd(Ph)(OH)]$_2$ under the TMSOK-based reaction conditions is worthy of further comment. Palladium hydroxide species have previously been shown to transmetalate rapidly with 6-B-3 boron species.[14] Thus, one may wonder why the formation of [LnPd(Ar)(OH)]$_2$ is shown to be an off-cycle species in this work. Palladium hydroxide catalyst has been found to be inactive toward transmetalation with 8-B-4 boron species,[11c,14d] which dominate the reaction solution under TMSOK-based conditions (see Supporting Figure S19.).[11c] Consequently, the addition of halide salt favors the formation of on-cycle LnPd(Ar)(X) under TMSOK-based homogeneous conditions. These results highlight how one may leverage insight into catalyst and nucleophile speciation to inform the optimization of SMCs.[13,14c]

We now turned our attention to substantiating the practical significance of these findings by probing the impact of halide salt additives in a variety of C(sp$^2$)−C(sp$^3$) couplings. During our previous work, we had conducted an extensive literature search for the SMC coupling of benzylic electrophiles, which revealed two major issues: (1) the use of heterocyclic coupling partners was limited; (2) when heterocycles are present, catalyst loadings of 1.0 mol % or greater were necessary. We went on to show the use of TBAB as an additive under otherwise standard biphasic reaction conditions enabled a broad substrate scope even at catalyst loadings of 0.1 mol %.[13] We chose to compare a portion of our prior substrate scope with our novel conditions at the same catalyst loadings to enable a direct comparison of the conditions. It is worth noting that a single example of SMC with a benzylic electrophile under anhydrous TMSOK-based conditions was reported and required an increased catalyst loading from 2 to 4 mol %.[11a] To our delight, both reaction conditions performed exceptionally similarly on most substrates (Scheme 1); however, the TMSOK-based conditions did provide increases in yield (>10%) for a few selected substrates (**3ga**, **3ja**, **3la**, **3na**). Moreover, control reactions without the halide additive were conducted for several substrates (**3aa**, **3ga**, **3la**, **3ma**, **3na**, **3pa**, **3ac**, **3ae**), and significant reductions in yield were observed in all cases (range = 15−72%, average = 33%). These results highlight the key role of TBAB under the targeted conditions, enabling reactivity at such low catalyst loadings. To our knowledge, these are the lowest reported catalyst loadings to date for homogeneous TMSOK-based SMCs.


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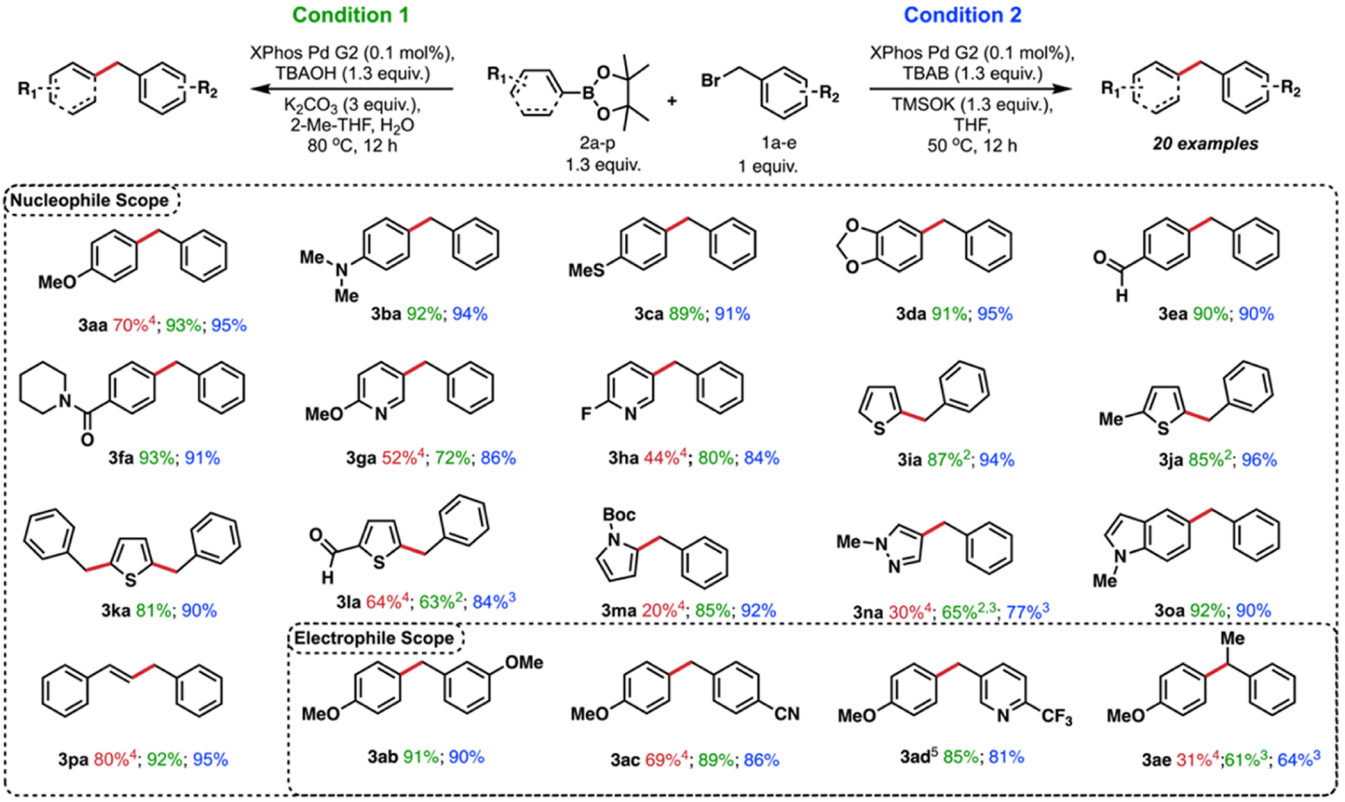
**Scheme 1. Reaction Scope**[1]




[2]TBAB was added. [3]1.0 mol % XPhos Pd G2. [4]Reactions were run under condition 2 without TBAB additive. [5]Chloride-based electrophile was used. [1]Reactions were run on a 0.375 mmol scale; HPLC yields were reported.

We next hypothesized that halide additives may enable the use of protic heterocycles as substrates under TMSOK conditions. This substrate class continues to be a particularly difficult substrate to engage in SMCs more broadly.[9] Buchwald and co-workers have reported that the strength of the inhibitory effect increases with the decreasing p$K_a$ of the protic heterocycle. This arises from an increased concentration of the anionic heterocycle under the reaction conditions. The increased basicity of TMSOK relative to standard SMC conditions is likely to exacerbate this effect, resulting in potent catalyst inhibition. This may explain the conspicuous absence of such substrates under TMSOK conditions thus far. Overcoming such a limitation will prove vital to expanding the scope of application of these new reaction conditions.

To confirm the presence of this inhibitory behavior, we again turned to NMR experiments to probe the ability of added halide salt to limit undesired Pd speciation (Figure 8). Dosing 2-bromoimidazole (8) to a solution of TMSOK and SPhosPd(Ph)(Cl) resulted in the formation of a single new signal determined by $^{31}$P NMR assigned as **7** (Figure 8). 2D-NMR experimentation supports the formation of the imidazole-bound palladium complex (see Supporting Information Figures S30−S33). Furthermore, following the procedure of a prior report, synthesizing a related indazole-derived Pd complex generates the same species.[9h] Upon the addition of increasing equivalents of LiCl, the reformation of SPhosPd-(Ph)(Cl) was observed. However, **7** remained detectable even at loadings as high as three equivalents of LiCl relative to TMSOK. These results suggest that heterocyclic species such as imidazole can form off-cycle species more thermodynamically favored than that observed with TMSOK alone.

With our theory supported by NMR experiments, we gathered a handful of protic heterocyclic substrates to probe the practical significance of halide salts in achieving reactivity in such settings. We chose to expand our additive screen to include both LiBr and TBAB. Despite both providing a source of halide for the reaction, both these additives display slightly disparate reactivity. TBA salts are susceptible to degradation in the presence of excess TMSOK, which is necessary under such conditions due to the acidic nature of the targeted substrates (see Supporting Information Figure S18). We further included the use of $B(OMe)_3$, as we reasoned that a larger impact may be observed in these settings given the presence of various heterocyclic derivatives.[11b] Finally, we chose to study $C(sp^2)$−$C(sp^2)$ couplings due to rapid, competitive substitution reactions by protic heterocyclic derivatives observed with benzylic electrophiles.

To our delight, a variety of substrates showed drastic benefits when in the presence of halide salts, trimethyl borate, or combinations of both (Scheme 2). Both 2-bromoimidazole (**3ai**) and benzimidazole (**3qj**) showed a complete lack of product formation in the absence of additives, with TBAB performing the best in both cases. 4-bromoimidazole (**3ak**) also exhibited complete inhibition of the reaction conditions; however, the combination of trimethyl borate and TBAB proved to be the most efficient for this substrate. Both phenol (**3an**) and carbazole (**3am**) derivatives showed partial or complete inhibition, where LiBr proved to be the most effective additive for these substrates. Finally, trimethyl borate ($B(OMe)_3$) proved to be the most effective additive for several substrates (**3af**−**3ah**). Denmark et al. had previously shown that the mild Lewis acidity of $B(OMe)_3$ limits the catalyst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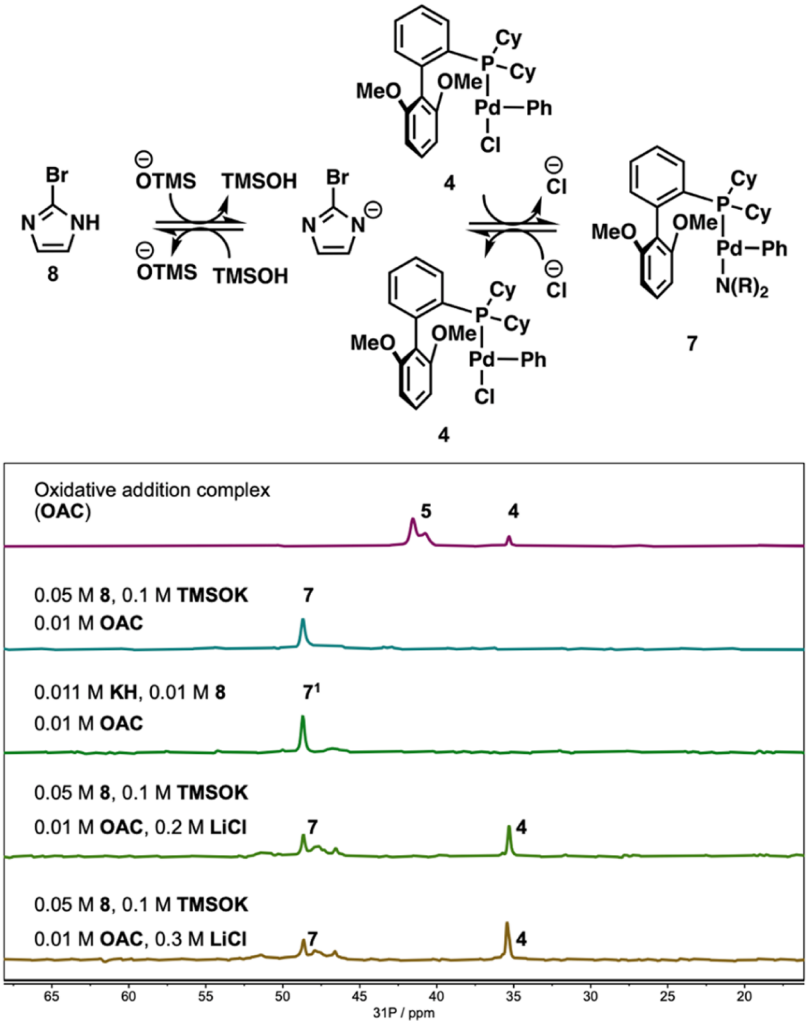


**Figure 8.** Overlay of $^{31}$P NMR experiments probing the inhibitory behavior of 2-bromoimidazole. [1] 7 was synthesized according to the prior literature procedure on a similar compound.[9h]

inhibition exhibited by pyridyl-type nitrogen, such as those in **3af** and **3ag**. Moreover, Denmark et al. reported that competitive $S_NAr$ with TMSOK can be problematic for electron poor substrates such as benzothiazole and benzoxazole.[11b] In fact, we observed significant amounts of this undesired $S_NAr$ in the absence of $B(OMe)_3$, while its presence significantly reduces this detrimental side reaction (see Supporting Information Figure S36). We were surprised at the minimal impact halide salts had on the reactivity of **3ah** despite the presence of a protic nitrogen atom. However, NMR experiments revealed that added halide salts had no ability to impact catalyst speciation from the off-cycle species toward the SPhosPd(Ph)(Cl) (see Supporting Information Figure S34–S35). It was previously shown by Buchwald et al. that indazole derivatives strongly deactivate Pd catalyst in SMCs by forming off-cycle bridged dimers through both nitrogens of the indazole heterocycle, which could explain the limited impact of added halide salt.[9h] The Lewis acidity of $B(OMe)_3$ may account for its greater performance in this setting, as it would be expected to significantly impact this speciation. Overall, these results suggest that both halide additives and $B(OMe)_3$ will play key roles in increasing the scope and efficiency of these novel SMC conditions.

In conclusion, we discovered that halide salts have profound impact on the reactivity of SMC under homogeneous TMSOK-based reaction conditions. A thorough mechanistic investigation of this phenomenon revealed that this impact predominantly arises by promoting the formation of LnPd(Ar)(X) from off-cycle reservoirs such as $[LnPd(Ar)(\mu\text{-}OH)]_2$ or LnPd(Ar)(N-Het). These latter species not only display diminished reactivity but also lead to side-product formation, such as reductive dehalogenation and homocoupling. The practical significance of these findings was showcased by achieving a broad substrate scope using the lowest catalyst loadings for SMC under the TMSOK-based conditions reported to date. Furthermore, the halide effect was further leveraged to enable the use of substrates bearing acidic heterocycles, which could otherwise completely inhibit reactivity.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c02407.

Additional experimental details including the automated sampling platform setup; characterization of the products, and detailed kinetic data (PDF)



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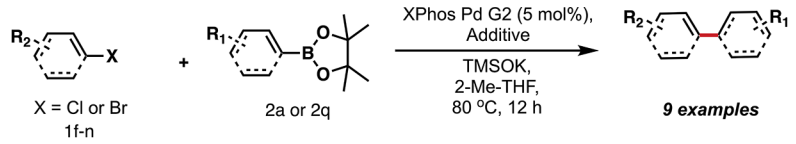
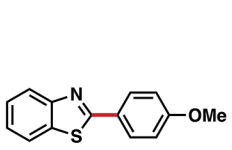
**Scheme 2. Probing the Impact of Additives on the Use of Acidic Heterocyclic Electrophiles**[1]

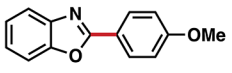



| | Condition A | Condition B | Condition C | Condition D | Condition E |
|---|---|---|---|---|---|
| Additive | - | 1.0 equiv. TBAB | 0.5 equiv. LiBr | 3.0 equiv. $B(OMe)_3$ | 0.5 equiv. LiBr; 3.0 equiv. $B(OMe)_3$ |



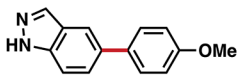

3af[2,5]

| | |
|---|---|
| A | trace |
| B | 24% |
| C | 32% |
| D | 73% |
| E | 61% |



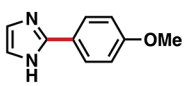

3ag[2,5]

| | |
|---|---|
| A | trace |
| B | trace |
| C | trace |
| D | 64% |
| E | trace |



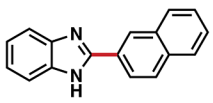

3ah[3,6]

| | |
|---|---|
| A | 20% |
| B | 26% |
| C | 25% |
| D | 72% |
| E | 36% |



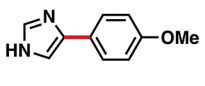

3ai[3,6]

| | |
|---|---|
| A | 0 |
| B | 70% |
| C | 0 |
| D | 18% |
| E | 15% |



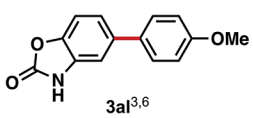
3qj[3,5]

| | |
|---|---|
| A | 0 |
| B | 48% |
| C | 10% |
| D | 35% |
| E | 30% |



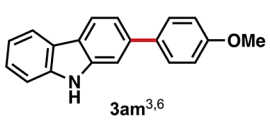

3ak[3,4,6]

| | |
|---|---|
| A | 0 |
| B | 44% |
| C | 33% |
| D | 41% |
| E | 54% |



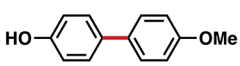

3al[3,6]

| | |
|---|---|
| A | 76% |
| B | 54% |
| C | 85% |
| D | 60% |
| E | 41% |




3am[3,6]

| | |
|---|---|
| A | 0 |
| B | 0 |
| C | 84% |
| D | 39% |
| E | 28% |




3an[3,6]

| | |
|---|---|
| A | 42% |
| B | 77% |
| C | 88% |
| D | 65% |
| E | 73% |

[2]Conditions: **2a** (1.0 equiv), **1f–h** (1.3 equiv), TMSOK (1.0 equiv), and additive. [3]Conditions: **2a**(**2q**) (1.0 equiv), **1i–n** (1.3 equiv), TMSOK (2.0 equiv), and additive. [4]RuPhos Pd G4 was used. [5]Chloride-based electrophile was used. [6]Bromide-based electrophile was used. [1]Reactions were run on a 0.375 mmol scale; HPLC yields were reported.

## Accession Codes

Crystallographic data for structure **6c** reported in this article has been deposited at the Cambridge Data Center under deposition number 2362061.

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## Author Contributions

Y.S. conducted all experimental work. Y.S., J.S.D., and J.E.H. contributed to devising the project and the experimental design and analysis. S.M.G. helped acquire the NMR data. B.O.P. helped X-ray diffraction data collection. Y.S. and J.S.D. contributed to the preparation of the manuscript and the



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### Notes

The authors declare no competing financial interest.

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## ■ ABBREVIATIONS

SMC, Suzuki−Miyaura coupling; TMSOK, potassium trimethylsilanolate; TBA, tetrabutyl ammonium; NMR, nuclear magnetic resonance; HPLC, high performance liquid chromatography

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