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Enabling Suzuki–Miyaura coupling of Lewis-basic arylboronic esters with a nonprecious metal catalyst†

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The high cost and negative environmental impact of precious metal catalysts has led to increased demand for nonprecious alternatives for widely practiced reactions such as the Suzuki–Miyaura coupling (SMC). Ni-catalyzed versions of this reaction have failed to achieve high reactivity with Lewis-basic arylboron nucleophiles, especially pinacolboron esters. We describe the development of $(PPh_2Me)_2NiCl_2$ as an inexpensive and air-stable precatalyst that addresses this challenge. Under activation by *n*-BuMgCl, this complex can catalyze the coupling of synthetically important heteroaryl pinacolborons with heteroaryl halides. Mildly basic conditions (aqueous K_3PO_4) allow the reaction to tolerate sensitive functional groups that were incompatible with other Ni-SMC methods. Experimental and computational studies suggest that catalyst inhibition by substitution of PPh_2Me from Ni(II) intermediates by Lewis basic reactants and products is disfavored relative to more commonly employed ligands in the Ni-SMC, which allows it to operate efficiently in the presence of Lewis bases such as unhindered pyridines.

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Introduction

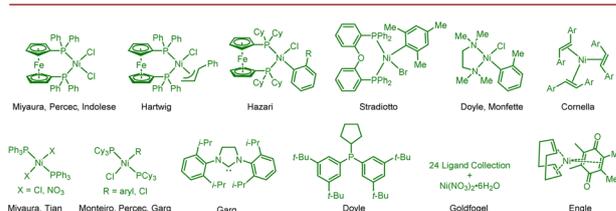
The Pd-catalyzed Suzuki–Miyaura Coupling (Pd-SMC) of aryl halides and arylboron reagents is one of the most practical catalytic methods for C(sp²)–C(sp²) bond formation.^{1–3} In the pharmaceutical industry, it ranks among the top 2–3 most widely practiced reactions in both medicinal and process chemistry groups.^{4,5} Many ligands have been identified for the Pd-SMC; however, fewer ligands for catalysis by earth-abundant metals (Ni, Cu, Co and Fe) have been developed. Given the increased emphasis on greener and more sustainable catalysis, non-precious metal alternatives for the Pd-SMC are being actively sought.⁶

The Ni-catalyzed Suzuki–Miyaura Coupling (Ni-SMC), known since the mid-1990s, is a promising alternative to Pd-SMC and even has its advantages (Scheme 1).^{7–9} For example, aryl electrophiles normally unreactive under Pd catalysis, such as carbamates, can be coupled with Ni.¹⁰ A key challenge to the wider application of the Ni-SMC, however, is the significantly reduced scope of several key heteroarylboron nucleophiles with

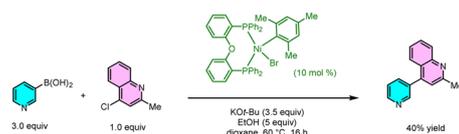
Ni vs. Pd.¹¹ Lewis-basic heteroarylborons such as pyridines are particularly problematic for Ni, possibly due to their coordinating ability.^{12–14} Furthermore, aryl BPins were the least reactive of the common SMC nucleophiles examined in a study by Percec.¹⁵

Complexes of other nonprecious metals besides Ni have also been reported as catalysts for the SMC. Fe^{16,17} and Co-

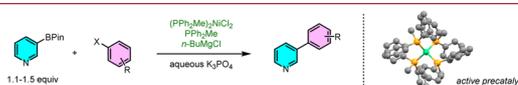
Selected ligands, catalysts, and precursors for the Nickel Suzuki–Miyaura Coupling (Ni-SMC)



State of the art Ni-SMC of Lewis basic arylboronic acid and heteroaryl halides (Stradiotto, 2018)



This research: efficient Ni-SMC of Lewis-basic aryl-BPins for biheteroaryl synthesis



Scheme 1 Catalysts for the Ni-SMC and the reaction to prepare Lewis basic heterobiaryls.

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tolyl)Cl and (TMEDA)Ni(*o*-tolyl)Cl are commercially available, they are currently more costly than common Pd sources such as Pd(OAc)₂ and Pd₂(dba)₃. Hence, we pursued the inexpensive and easily prepared (PPh₂Me)₂NiCl₂ (**Ni-1**) as a catalyst precursor. The catalyst generated from **Ni-1**, PPh₂Me and *n*-BuMgCl as an activator afforded 95% conversion of **2** to **3** after 16 h (entry 1). Omitting the *in situ* activation leads to lower conversion and the observation of significant amounts of byproducts (entries 3–4). Zn and *n*-BuLi could also be employed as *in situ* activators^{40–42} of **Ni-1**, though conversion was slightly lower than with *n*-BuMgCl (entries 5–6).

Many reported Ni-SMC methods are either sensitive to adventitious moisture or require careful control of H₂O stoichiometry. Gratifyingly, the reaction proceeded efficiently with no added H₂O through 4 : 1 v/v ratio of 2-MeTHF/H₂O (entries 7–9). We chose 5 : 1 v/v 2-MeTHF/H₂O for subsequent evaluation due to the slightly higher conversion obtained at this ratio. The conditions with less H₂O may be useful for specific applications (*i.e.*, a water-sensitive substrate). Dioxane and *t*-AmOH were also effective solvents (entries 10 and 11). Weaker bases K₂CO₃ and K₂HPO₄ were less effective than K₃PO₄ (entries 13 and 14).

Scope of the reaction

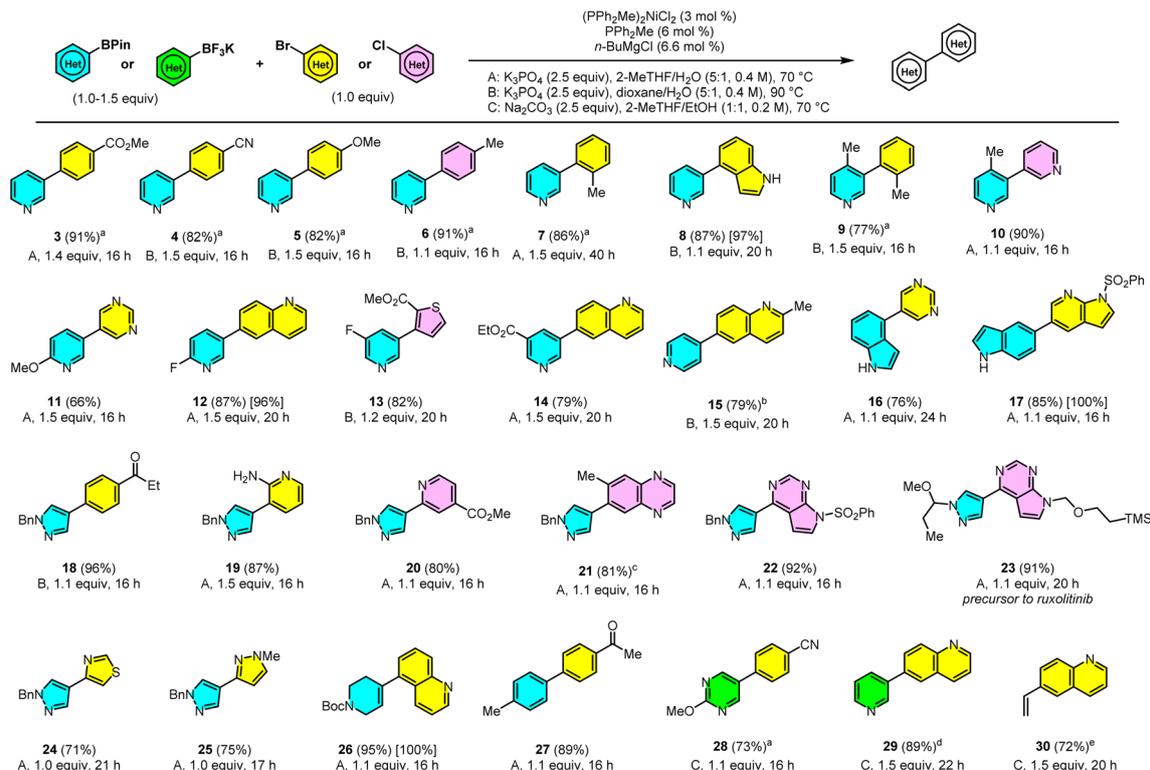
With optimized conditions in hand, we explored the scope of the reaction catalyzed by 3 mol% **Ni-1** (Scheme 3). The coupling of **1** proceeds efficiently with a range of aryl halides at 70 °C (in

2-MeTHF, bp = 80 °C) or 90 °C (in dioxane, bp = 101 °C). Electron-poor (**3** and **4**), electron-rich (**5** and **6**), and *ortho*-substituted (**7** and **9**) aryl bromides afforded the coupled products in excellent yields. Impressively, an electronically neutral aryl chloride (**6**), an unprotected bromoindole (**8**), and Lewis-basic 3-chloropyridine (**10**) also coupled in high yield.

In addition to the electron-rich pyridine-3-BPin (**11**), the previously unreported electron-poor pyridine-3-BPins coupled with heteroaryl halides (**12–14**). Even the less nucleophilic pyridine-4-BPin, an unknown substrate for the Ni-SMC and a challenging one even for the Pd-SMC, coupled efficiently at 90 °C using 5 mol% catalyst (**15**). A functionalized chlorothiophene was well tolerated as an electrophile (**13**).

Unprotected indoles are another class of heterocycles previously unreported in the Ni-SMC and were shown to be problematic in Watson's study of DPPF-Ni.¹¹ Examples **8**, **16** and **17** show the efficient coupling of unprotected indoles as both nucleophile and electrophile components. Compound **17** also demonstrates the viability of a derivatized 7-azaindole as an electrophile, a motif found in several pharmaceuticals.⁴³ Methyl/ethyl esters (**3**, **13**, **14**, and **20**), 2-fluoropyridine (**12**) and heterocyclic sulfonamides (**17** and **22**) were well-tolerated, due to the mildly basic conditions of the reaction.

Five-membered Lewis-basic arylborons represent another important class of nucleophiles that is typically difficult for the Ni-SMC. The Ni-SMC of (hetero)aryl halides with pyrazoleborons was previously unreported. Examples **18–25** show the



Scheme 3 Scope of the Suzuki–Miyaura coupling catalyzed by (PPh₂Me)₂NiCl₂ (**Ni-1**). Reactions were run on 1.0 mmol scale unless noted, isolated yield in parentheses. Equiv. given in scheme refers to the arylboron reagent. The yield in brackets represents assay yield of reaction with 1 mol% Ni on 1 g scale. (a) Reaction run on 1.0 g scale (b) 5 mol% (PPh₂Me)₂NiCl₂/10 mol% PPh₂Me/11 mol% *n*-BuMgCl (c) 3 mol% (TMEDA)Ni(*o*-tolyl)Cl/9.9 mol% PPh₂Me as catalyst (d) 90 °C (e) coupling partner was potassium vinyltrifluoroborate (1.5 equiv.).



coupling of a pyrazole-4-BPin with functionalized heteroaryl halides at 70 °C, including an unprotected aminopyridine (**18**). The pyrazolodiazaindole core of several classes of kinase inhibitors was efficiently generated in **22** and **23**.^{44,45} Diazaindole **22** is an intermediate in an enantioselective synthesis of ruxolitinib reported by Lin and coworkers at Incyte.⁴⁶ Examples **24** and **25** are notable examples of coupling two five-membered rings, which is typically more challenging than 6-membered rings for both Pd and Ni.^{47,48} An *N*-Boc containing vinyl BPin coupled to form **26** in excellent yield at 70 °C. This type of Suzuki coupling is used extensively in pharma to access 4-arylpiperidine derivatives yet was previously unknown with Ni.⁴⁹ Heteroaryl or Lewis-basic substrates are not required for the catalyst to operate efficiently, as shown by the coupling to form **27**.

Excitingly, **Ni-1** could also efficiently couple potassium organotrifluoroborates under slightly modified conditions. Both Lewis-basic heteroaryl and vinyl BF₃K derivatives coupled efficiently at 70–90 °C in the presence of Na₂CO₃/EtOH/2-MeTHF⁵⁰ (**26–28**). These examples further highlight the flexibility of this catalytic system to proceed under mild conditions.

While the scope of the reaction was explored with 3 mol% **Ni-1**, examples **8**, **12**, **17** and **26** were also conducted on gram scale with 1 mol% **Ni-1**/2 mol% PPh₂Me/2.2 mol% *n*-BuMgCl. The reactions afforded excellent assay yields in 16–24 h without any modification of the general reaction conditions, demonstrating the amenability of this system to large-scale applications. For general couplings of the arylboron nucleophile in **24**, the lowest reported catalyst loading with Pd was 1 mol%.^{51,52} In the case of the arylboron in **11**, it was 2 mol% with Pd.⁵³ Thus, our Ni catalyst can achieve efficiency on par with Pd catalysts for these more challenging substrates! Overall, the scope of the Ni-SMC

catalyzed by **Ni-1** shows broad Lewis base and functional group tolerance, while in many cases requiring only 1.1 equiv. of the aryl-BPin to afford high yield.

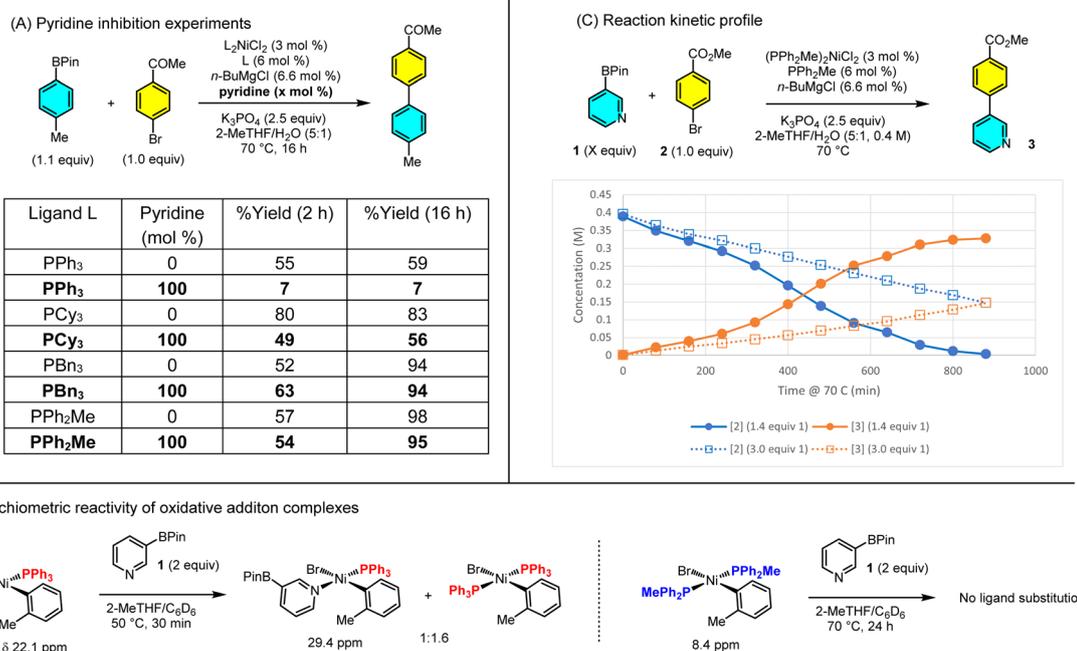
Characterization of the activated precatalyst

As noted earlier, **Ni-1**/PPh₂Me/*n*-BuMgCl showed activity comparable to (PPh₂Me)₂Ni(*o*-tolyl)Cl or PPh₂Me/(TMEDA)Ni(*o*-tolyl)Cl in our optimization studies. NMR and X-ray analysis of **Ni-1**/PPh₂Me/*n*-BuMgCl confirmed clean and rapid formation of (PPh₂Me)₄Ni, a compound known for over 50 years⁵⁴ but with few prior catalytic applications.^{55–57} Isolated (PPh₂Me)₄Ni was found to be a competent precatalyst in the Ni-SMC but had limited stability on the bench, thus *in situ* generation from **Ni-1** is preferred.

Mechanistic studies

We were intrigued by the high activity afforded by the relatively simple PPh₂Me ligand in the Ni-SMC of Lewis-basic arylboron esters, a reaction where many well-established ligands for Ni did not perform well (see Scheme 2). The most obvious challenge posed by the coupling of substrates such as **1** is their ability to coordinate to Ni, potentially displacing phosphine ligands. Indeed phosphine substitution by Lewis basic amines, including pyridine, was studied by Mizoroki and Nakamura using the related (PPh₃)₂Ni(*o*-tolyl)Br complex over forty years ago.^{58–60} Given this precedent, we wondered if the unique ability of (PPh₂Me)₂NiCl₂ in the SMC stems from a reduced tendency of the PPh₂Me ligand to be substituted by Lewis basic donors.

To test this hypothesis, we first investigated the non-heterocyclic Ni-SMC shown in Scheme 4A. With PCy₃, PPh₃, PPh₂Me, or PBN₃, the reaction proceeded to 59–98% assay yield



Scheme 4 Mechanistic experiments on the role of Lewis bases in the Ni-SMC. ^aSee ESI† for details.



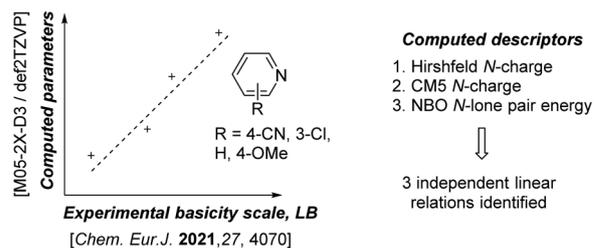
after 16 h. When 100 mol% pyridine was added, however, the reactions catalyzed by PCy₃ and PPh₃ (inactive with **1**) were significantly inhibited, as expected, while PPh₂Me and PBN₃ (active with **1**) were unaffected.⁶¹ While consistent with our hypothesis that catalyst derived from (PPh₂Me)₂NiCl₂ could be resistant to phosphine displacement, we explored this in more detail through ³¹P NMR studies.

Thus we prepared oxidative addition complexes (PPh₂Me)₂Ni(*o*-tolyl)Br and (PPh₃)₂Ni(*o*-tolyl)Br to probe the extent of phosphine substitution. We chose these complexes as (1) the ortho substituent renders them isolable as well as air-stable, and (2) 2-bromotoluene is a catalytically relevant aryl halide with PPh₂Me (Scheme 3, compounds **7** and **9**). Complex (PPh₃)₂Ni(*o*-tolyl)Br reacted with 2 equiv. **1** at 50 °C to generate a new downfield species in ³¹P NMR that is consistent with previously reported (PPh₃)(pyridine)Ni(*o*-tolyl)Br complexes (Scheme 4B).⁶⁰ By contrast, heating (PPh₂Me)₂Ni(*o*-tolyl)Br with 2 equiv. **1** at 70 °C for 24 h produced no new ³¹P NMR peaks. Hence, substitution of PPh₂Me by pyridines is disfavored relative to PPh₃. The extent of substitution of PPh₃ is significant even with only 2 equiv. of **1** relative to the Ni complex. Under typical catalytic conditions (37–47 equiv. **1** per Ni) the substitution would be expected to proceed much further.⁶² Taken together, these experiments show that addition of a Lewis basic donor such as **1** or pyridine leads to significant substitution of the phosphine ligands, which could lead to off-cycle species and thus slow or inhibit the desired SMC.

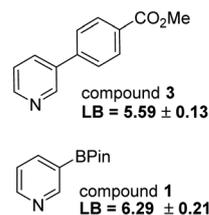
In Mizoroki and Nakamura's ligand substitution studies, sterics were the primary determinant of substitution equilibrium between PPh₃ and other ligands. Less-hindered amines and smaller cone angle phosphines displaced PPh₃ to a greater extent than larger or more hindered ones. When steric effects were held constant, however, higher basicity of the incoming ligand led to greater displacement of PPh₃. Thus, under typical reaction conditions for the SMC, we should expect a potentially different degree of substitution of the phosphine ligand as BPin **1** is converted into the biaryl product **3**. Indeed, the Lewis basicity of **1** and **3**, estimated using computed descriptors and experimental values for related pyridines (Scheme 5) show that **1** is 0.70 units more Lewis basic than **3**, which corresponds to a 5-fold greater *K*_{eq} in coordinating to a Lewis acid. If correct, we would expect the reaction to show a sigmoidal reaction profile consistent with conversion-dependent relief of inhibition. Thus, we profiled the coupling of **1** and **2** by Ni-**1** over time (Scheme 4C) and did observe the expected conversion profile. When the same reaction was conducted with a greater excess **1** (3.0 equiv. vs. 1.4 equiv.), the reaction showed overall zero-order behavior over the first 16 h, further evidence of inhibition by **1**.⁶³ An aliquot of the reaction with 1.4 equiv. **1** at 80 min (5.5% yield) was analyzed by ³¹P NMR, and showed 96% uncoordinated PPh₂Me, 1% (PPh₂Me)₄Ni, and 3% of a PPh₂Me–Ni complex.⁶⁴

The evidence described above implies that the Lewis basic Ni-SMC is governed by substantial pre-equilibrium steps involving ligand substitution between PPh₂Me, **1** and **3** (eqn (1)). While under catalytic conditions ([**1**] > [PPh₂Me]) most of the equilibrium favors the off-cycle species, enough of the on-

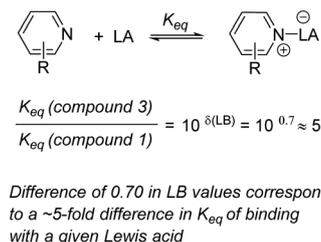
(1) Mapping Experimental Lewis Basicity Scale on Computed Parameters



(2) Computationally Estimating Lewis basicity of Target Pyridines

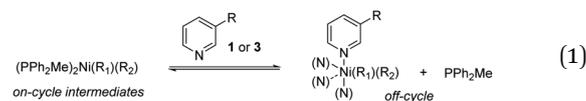


(3) Assessing relative binding propensity of pyridines



Scheme 5 Summary of the procedure used to estimate computed Lewis basicities of pyridines **1** and **3**. See ESI† for computational details, calibration of linear models and thermodynamic data.

cycle intermediates are retained with PPh₂Me to allow the reaction to proceed efficiently. Indeed, our experiments show that the commonly employed ligands PPh₃ and PCy₃ are more susceptible to substitution by pyridines than PPh₂Me and PBN₃. Mizoroki and Nakamura's studies imply that this is primarily a steric effect.



Because they are minor species in eqn (1), the PPh₂Me–Ni intermediates must also be able to promote very efficient on-cycle steps, including the potentially difficult^{65,66} transmetalation. One implication of this result for future research is to avoid using a large excess of Lewis-basic arylboron reagents when screening Ni-SMCs.

Conclusions

We have developed an effective and inexpensive catalyst system, *in situ* activated (PPh₂Me)₂NiCl₂, for the Suzuki–Miyaura coupling of Lewis basic heteroaryl BPins and BF₃Ks with (hetero)aryl bromides and chlorides. The scope and functional group tolerance of the reaction allow important Lewis-basic and biheteroaryl compounds to be prepared with a nonprecious metal catalyst for the first time. Ligand substitution of PPh₂Me by Lewis basic heterocycles is disfavored relative to more commonly studied phosphines, a key reason for its unique catalytic activity. Future research on the precise balance of steric and electronic factors that contribute to this property should



lead to the development of even more highly active ligands for Ni-catalyzed cross couplings of Lewis-basic substrates.

Author contributions

M. C. H. conceived and directed the study with contributions from S. S. and S. M. M. C. H., A. R. I., and S. S. conducted synthetic experiments. S. T. conducted the computational study. R. S., B. J. K., and J. W. conducted high-throughput experiments. A. L. W. and R. F. H. conducted HRMS and X-ray crystallography, respectively. M. C. H. and S. T. wrote the final draft manuscript. All authors contributed to the data interpretation, manuscript review, and have approved of the final version of the manuscript.

Conflicts of interest

AbbVie contributed to the design, approval, and execution of this study. M. C. H., A. R. I., S. S., R. S., B. J. K., J. W., A. L. W., and R. F. H. are current or former AbbVie employees and may own AbbVie stocks.

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- 61 Pyridine did not inhibit a non-Lewis basic Ni-SMC with DPPF in Ref 11. It seems that a different mechanistic step is problematic with this ligand.
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- 63 The analogous reaction of **2** with 1.4 equiv. PhBPin showed first-order dependence on **2**, pointing to a different rate limiting step for the Ni-SMC of non-Lewis basic arylborons. See the ESI† for details.
- 64 By contrast, ³¹P NMR of the coupling of PhBPin and **2** showed the expected mixture of PPh₂Me-Ni complexes (52–85%) and free PPh₂Me (48–15%) depending on the reaction progress. See the ESI† for details.
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