

COMMUNICATION

Ni vs. Pd in Suzuki-Miyaura sp^2 - sp^2 Cross-Coupling: A Head-to-Head Study in a Comparable Precatalyst/Ligand System

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The Suzuki-Miyaura reaction is a cornerstone method for sp^2 - sp^2 cross-coupling in industry. There has been a concerted effort to enable the use of Ni catalysis as an alternative to Pd in order to mitigate cost and improve sustainability. Despite significant advances, ligand development for Ni-catalyzed Suzuki-Miyaura cross-coupling remains underdeveloped when compared to Pd and, as a consequence, ligands for Ni-catalyzed processes are typically taken from the Pd arena. In this study we evaluate the effect of using a similar Ni and Pd precatalyst based on a common bidentate ligand (dppf) in a head-to-head format for the most common type of biaryl couplings, establishing the practical implications of direct replacement of Pd with Ni, and identifying the potential origins of these observations in a mechanistic context.

The Suzuki-Miyaura (SM) reaction is the primary method for Pd-catalyzed sp^2 - sp^2 cross-coupling, estimated to account for the majority of C-C bond constructions in the pharmaceutical industry (Scheme 1a).^{1,2} Indeed, the prevalence of the biaryl unit in marketed drugs has been attributed to the success and widespread utility of this reaction.³ While Pd remains the catalyst of choice for the SM reaction, the potential to replace Pd for less expensive transition metals has become a particularly active field of enquiry. In particular, Ni catalysis has been identified as the main alternative to Pd.⁴⁻⁶ This is based on a number of attractive attributes including, chiefly, the significantly lower cost of Ni metal vs. Pd metal (Ni is *ca.* 1000-fold less expensive than Pd)^{4,7} and the increased nucleophilicity of Ni(0) vs. Pd(0) permitting a more facile oxidative addition and therefore a wider range of electrophile.⁴⁻⁶

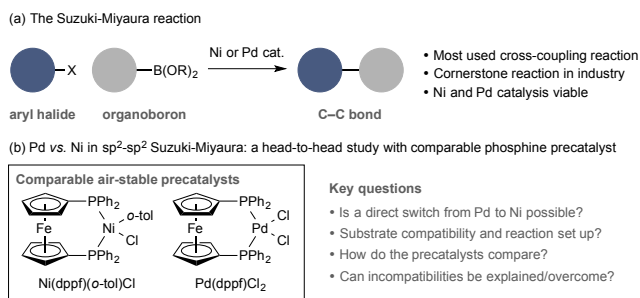
The reactivity of Ni(0) complexes (*e.g.*, Ni(cod)₂) is both an advantage and disadvantage: the enhanced nucleophilicity comes with the price of reactivity towards O₂ and H₂O.⁸ Accordingly, this has led to development of more practicable Ni(II) precatalysts that significantly simplify reaction set up.^{5-7,9-17} The choice of ligand, however, is perhaps the most difficult. The knowledge base, as well as the range of effective ligands,

for Pd catalysis is extensive to the extent that selection of a ligand to improve a particular cross-coupling has become intuitive. However, such an understanding has yet to be realized for Ni. It is widely recognized that the different properties of Ni vs. Pd require unique ligand systems; rational ligand design based on stereoelectronic considerations is at the forefront of Ni catalysis.¹⁸ In addition, several examples have shown that ligand systems for Pd can be ineffective for Ni in C-X specific bond formations.¹⁸

The development of bespoke ligands to improve the utility of Ni precatalysts has additional practical considerations: these ligands may not be commercially available and the use of proprietary ligands can obviate any economic saving afforded by the change in metal.¹⁹ This is especially pertinent on larger scale where a less effective ligand with lower overall economic cost by virtue of reduced IP barrier may be preferable to a more effective ligand.¹⁹

The use of ligands shown to be effective for Pd-catalyzed SM is therefore a common, and very practical stopgap approach. The question remains what limitations this transfer of theoretically non-ideal ligands imparts and the practical issues this may or may not cause.

Here we detail a head-to-head study of Pd vs. Ni in sp^2 - sp^2 Suzuki-Miyaura cross-coupling using a comparable and inexpensive dppf precatalyst system,²⁰ documenting the main considerations/differences in reaction set up, substrate compatibility, and observations relating to protodeboronation of sensitive organoborons.

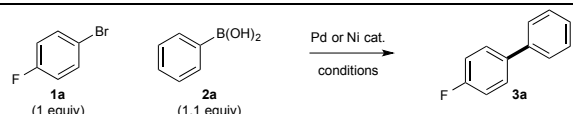


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Scheme 1. (a) The Suzuki-Miyaura reaction and (b) key questions from a head-to-head study using precatalysts derived from dppf.

Benchmark reaction and optimization. Dppf-based precatalysts were selected as Pd(dppf)Cl₂ is a highly effective, inexpensive, and routinely used precatalyst for SM cross-coupling, and dppf has been reported to be effective for specific Ni-catalyzed SM as well as other coupling processes; Ni(dppf)(*o*-tol)Cl is a comparable precatalyst that is air stable.²¹ Accordingly, this would represent a head-to-head study using precatalyst systems that are routinely used, available, and relatively well understood. The benchmark reaction with main observations (deviations from optimized conditions) is shown in Table 1.

Table 1. Main observations in a benchmark reaction.



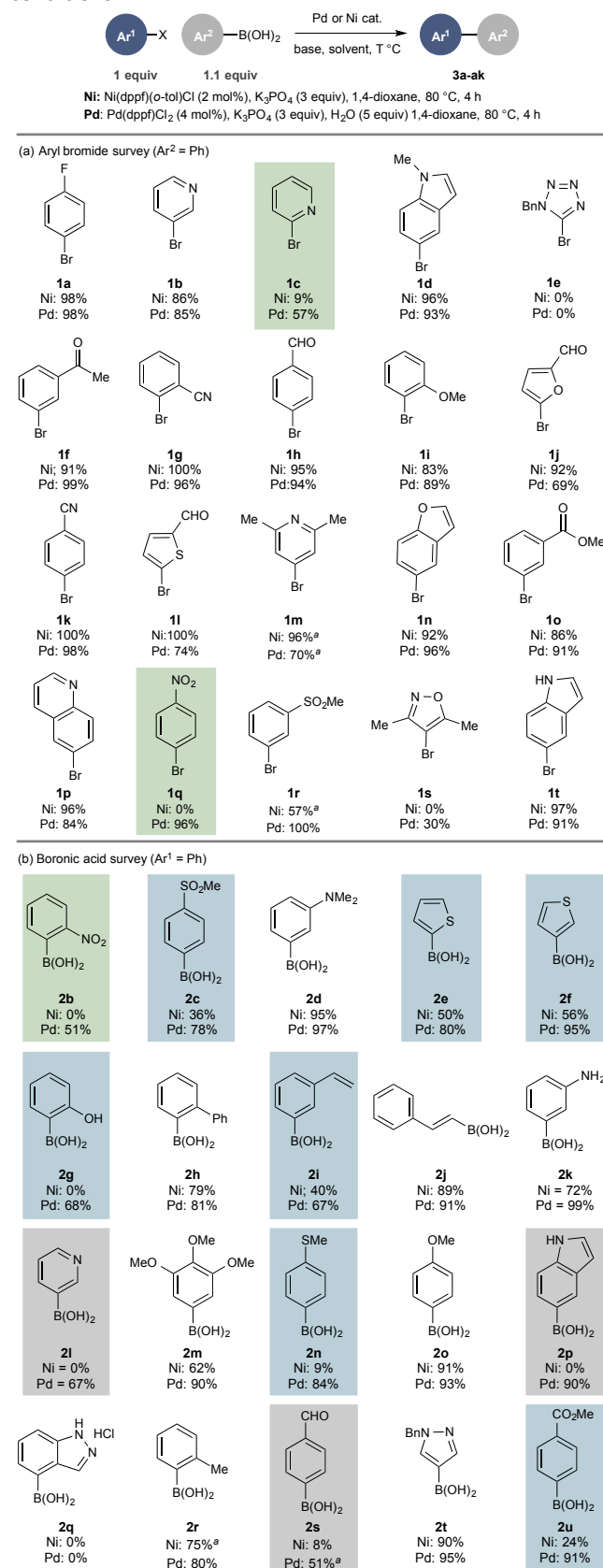
Ni: Ni(dppf)(*o*-tol)Cl (1 mol%), K₃PO₄ (3 equiv), 1,4-dioxane, 80 °C, 4 h
Pd: Pd(dppf)Cl₂ (4 mol%), K₃PO₄ (3 equiv), H₂O (5 equiv) 1,4-dioxane, 80 °C, 4 h

Entry	Deviation from 'standard' conditions	Yield (%) ^a
1	Ni method: No change	>99
2	Ni method: 4 mol% catalyst	>99
3	Ni method: 2 mol% catalyst	>99
4	Ni method: 5 equiv H ₂ O	68
5	Ni method: 50 °C	93
6	Pd method: No change	>99

^a Determined by ¹⁹F NMR analysis using an internal standard.

The optimal conditions for the simple benchmark coupling of **1a** with **2a** delivers the product **3a** in quantitative yield (entries 1 (Ni) and 6 (Pd)). The Pd system (entry 6) was based on our previous work with this and related Pd systems for SM cross-coupling where these conditions (low [H₂O] and elevated temperature)²²⁻²⁷ promote fast cross-coupling. We attribute this to promoting formation of Pd(II)(Ar)(OH)²⁷⁻³⁰ while keeping the concentration of neutral boronic acid high,²⁷⁻³¹ thereby assisting transmetalation. Translating these conditions to the Ni precatalyst system was relatively smooth with the main contrasts as follows: (1) Catalyst loading for Ni could be lowered significantly as compared to Pd, however, while 1 mol% was effective for this benchmark reaction, 2 mol% was more effective upon application to substrates with greater functionality (*vide infra*). (2) The Ni system can tolerate additional H₂O but not to the level that Pd can accommodate – the reaction remained quantitative up to a maximum of 3 equiv, with efficiency beginning to decline after this (entry 4), likely due to formation of Ni(II)(OH) dimers as proposed by Grimaud.³² Under dry conditions (*e.g.*, entry 1) boroxine is formed from the boronic acid, liberating H₂O. Indeed, many Ni-based systems use the boroxine or boronic esters to allow very dry reaction set up;⁴⁻⁶ however, this system tolerated the use of the boronic acid allowing a more practical approach. (3) Regarding temperature, Ni(dppf)(*o*-tol)Cl has been reported to allow room temperature SM of activated aryl chlorides;¹³ however, in our hands we could not take the temperature below 50 °C (no reaction at room temperature), with 80 °C being overall more efficient. In brief, however, the similar

precatalysts operated comparably effectively under very similar conditions.



Scheme 2. Substrate assessment using optimized conditions for each precatalyst. Isolated yields. ^a Determined by ¹H NMR analysis using an

internal standard. Green, expected/rationalized; blue, unexpected/rationalized; grey, unexpected/not rationalized.

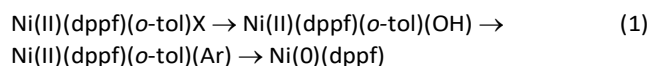
Functional group compatibility/comparison. The primary goal of this study was to determine precatalyst generality under conditions that are practically accessible and therefore more likely to be used. Important to this goal was the identification of functional groups that were problematic for either Ni or Pd. Accordingly, in a first assessment, a broad range of aryl bromide and organoboron was assessed (Scheme 2). Aryl bromides were used exclusively to allow direct comparison of the arene and avoid potential issues with oxidative addition based on variation of (pseudo)halide. Similarly, boronic acids were used as the archetypal organoboron in SM cross-coupling, and this avoids the preparation of boroxines/esters.

In terms of the electrophile, these proceeded without major incident for both Ni and Pd precatalysts, with good synthetic efficiency typically observed. The benchmark reaction using **1a** operated effectively on 0.25 and 2.5 mmol scale using both Pd and Ni systems (see Supporting Information). Bromides **1e** and **1s** were the main exceptions: **1e** was entirely unreactive and the sterically demanding **1s** impaired efficiency, especially for Ni.

Two expected observations were made regarding compatibility of **1c** and **1q** with the Ni precatalyst. Nicasio reported that Ni(II) complexes formed from oxidative addition to 2-bromopyridine (**1c**) form 6-membered dimer metalocycles that are catalytically inactive.³³ Interestingly, Hazari reports the effective use of Ni(dppf)(*o*-tol)Cl for room temperature coupling of *o*-chloroquinolines seemingly without this problem.¹³ Substrate Lewis basicity also affects the Pd system but to a lower extent. Nitroarene **1q** was unreactive with the Ni system, similar to previous findings by Percec³⁴ and possibly explained by formation of (nitroso)Ni(0) complexes, as observed by Kochi.³⁵ While **1q** was recovered, we cannot discount the formation of these complexes based on the low Ni loading. Collectively, however, the applicability of both Ni and Pd precatalysts was approximately equal for bromide electrophiles, with the exceptions noted above.

Nucleophile compatibility was a more extensive issue. Pd performed effectively, with the exceptions of known challenges mainly relating to Lewis basic substrates (**2l**, **2q**). The Ni system, however, was more significantly affected. Transmetalation is known to be more challenging for Ni than Pd and these observations may be attributable to this event.³⁴ Nitroarene **2b** experienced the same reactivity issues as the electrophile, **1q**. Several observations were worth noting, however some remain unsatisfactorily understood. (1) The lower efficiency using protodeboronation-prone boronic acids^{37,38} (e.g., **2e**, **2f**) may result from competing protodeboronation due to slow transmetalation in the Ni system (*vide infra*). (2) Specific ligating functionalities can impair reactivity either *via* Lewis basic heteroatomic sites (**2g**, **2n**) or likely η^2 coordination in the case of **2i**,³⁹ again more problematic for Ni vs. Pd. (3) The diminished reactivity of electron-deficient boronic acids (**2c**, **2l**, **2s**, **2u**) in the Ni system may result from the specific reaction conditions employed that, while effective for the benchmark reaction, could require tailoring for specific organoboron substrates.

Substituent electronic effects in Ni-catalyzed SM reactions have been recently investigated by Grimaud and can exhibit completely different electronic trends depending on the specific conditions, especially relating to the base/H₂O availability, which may explain these observations.³² Despite this, the extremely low yield for **2s** implicates additional problems with this substrate; this was reinforced by additive experiments (*vide infra*). It is important to note that sluggish transmetalation may affect precatalyst activation, which is believed to rely upon anion metathesis, transmetalation, and reductive elimination,^{13,15} *i.e.*, eqn 1.



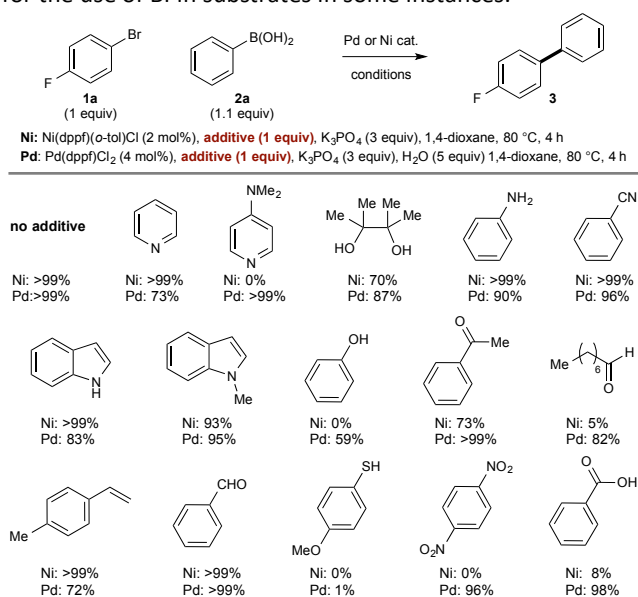
(4) The failure of **2l** in the Ni process cannot be easily explained by formation of metalocycles but seems likely to be related to catalyst coordination. (5) Finally, the major discrepancy observed with the cross-coupling of PhB(OH)₂ and 5-bromoindole (**1t**, Scheme 2a) vs. the analogous coupling of PhBr with indole-5-boronic acid (**2p**, Scheme 2b). This simple reversal in electrophile/nucleophile roles led to complete failure in catalysis using Ni despite no discernible stereoelectronic/functional group issues. (5) In all cases where conversion to product was low, the reaction profiles were highly similar containing only product, unreacted starting materials, and traces of boronic acid homocoupling. Accordingly, lower yields appear to stem from lower reactivity rather than side reactions in most cases (with the exception of boronic acids that underwent rapid protodeboronation).

Collectively, while synthetically useful yields can be obtained, the applicability of the Ni precatalyst was comparatively more problematic than the analogous Pd system and, perhaps more importantly, the issues cannot always be predicted *a priori*, even with relatively simple substrates as used here.

Robustness screen. Additional data on functional group compatibility was obtained by performing a robustness screen of the benchmark reaction in the presence of 1 equiv of a particular additive (Scheme 3).⁴⁰

As expected, the Pd system was broadly tolerant of the selected additives, with mostly relatively minor decreases in yield, except in the case of phenol, where reactivity was impeded, and thioanisole, where reactivity was completely inhibited. The impact of certain functional groups on Ni was variable and occasionally in contrast to the observations made in the substrate survey. Consistent with the substrate survey, phenol, thioanisole, and dinitrobenzene all negatively affected the reaction. Surprising results were observed with DMAP and benzoic acid, where catalysis was almost completely inhibited. The addition of indole did not have any impact on the Ni reaction in this scenario, suggesting the result observed with **1t** and **2p** is not based on the indole unit itself but on some additional interaction between substrate and Ni. Similarly, the impact of aldehyde functional groups is unclear: aryl aldehydes were not problematic in the substrate survey when on the aryl bromide (see **1h**, **1l**), however, reactivity was significantly decreased when on the boronic acid (e.g., **2s**), and addition of

octanal impeded this benchmark reaction. Finally, an important observation was the identification of a slight inhibitory impact of pinacol. While this was not severe and could be mitigated upon extending reaction times, this may have some implications for the use of BPin substrates in some instances.



Scheme 3. Robustness screen on the benchmark reaction under optimized conditions for each precatalyst. Yields determined by ¹⁹F NMR analysis using an internal standard (see ESI).

Protodeboronation. The majority of Ni-catalyzed SM reactions use excess of organoboron (typically 2 equiv),⁴⁻⁶ while in the above analyses we used a very slight excess (1.1 equiv). Based on the observations of variable efficiency with variation of the boronic acid, an assessment of the extent of protodeboronation using sensitive organoborons was conducted using both the boronic acid and BPin derivatives. Conversion to product and protodeboronation using Ni and Pd precatalysts under optimized conditions, as well as background protodeboronation is provided in Chart 1. The sulfone (**2c**, **5c**) and trimethoxy (**2m**, **5m**) organoborons were included as controls. Thiophene (**2v**, **5v**) and the fluorinated organoborons (**2x-y**, **5x-y**) are all susceptible to protodeboronation at different rates.^{35,36} Three main observations were evident: (1) the majority of protodeboronation takes place as a competing side reaction, as evinced by the control (no catalyst) reactions for each organoboron. The more stable organoborons **2/5c** and **2/5m** displayed less protodeboronation, and the extent of protodeboronation generally corresponded with the stability of the parent boronic acid. (2) In agreement with this, protodeboronation could be mitigated by using the BPin, with the caveat that cross-coupling reactivity was also slightly diminished, either as a result of slower transmetalation or hydrolysis to the parent boronic acid and subsequent transmetalation. The possibility of influence of pinacol on efficiency cannot be excluded. (3) Lastly, we cannot rule out the possibility of some on-metal or metal-assisted protodeboronation based on the slight increase in protodeboronation in certain reactions containing catalyst.

Specifically, BPins **5w**, **5x**, and **5y** all displayed noticeably more protodeboronation in the presence of both Ni and Pd than in the control reaction. However, this is a preliminary observation that will need probed more thoroughly.

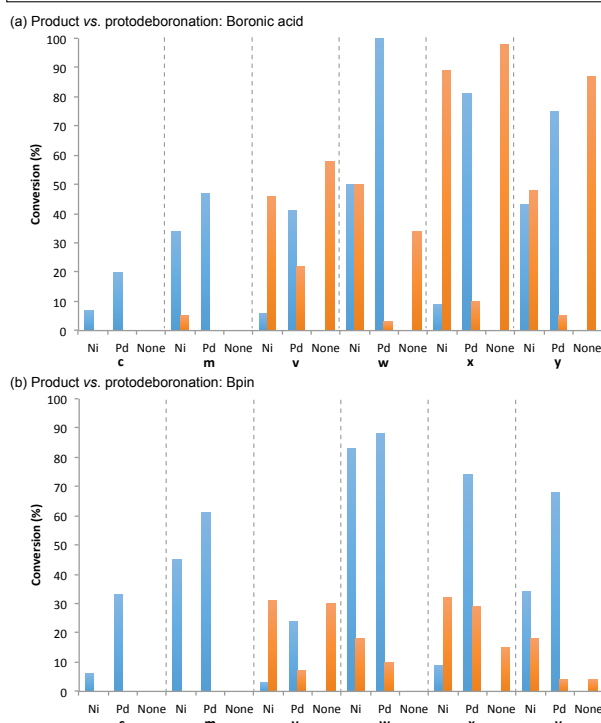
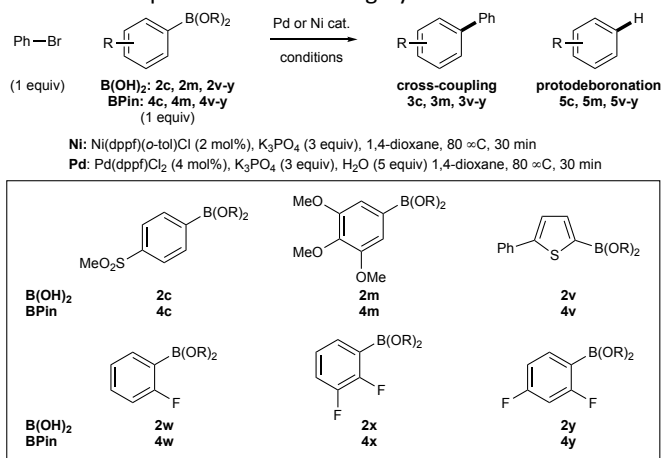


Chart 1. C–C bond formation vs. protodeboronation for Ni and Pd precatalysts using (a) boronic acids and (b) BPin. Determined by HPLC or NMR analysis using an internal standard (see ESI).

Conclusions

In summary, the practical viability of direct transfer of phosphine ligands used for effective Pd-catalyzed sp²-sp² Suzuki-Miyaura cross-coupling to a comparable Ni system has been investigated using dppf as in exemplar precatalyst systems. For electrophiles, this appears to be a relatively straightforward transfer, with the analogous Ni precatalyst delivering synthetically useful yields of products. However, significant issues can manifest with nucleophiles and some of these could not be predicted *a priori*. We hope that these results will support the development of simple and inexpensive

ligands for Ni and promote use of Ni catalysis for routine Suzuki-Miyaura cross-coupling but also encourage a balanced reasoning for the movement to Ni from Pd, as cost savings, especially on small scale, are minimal and functional group compatibility is diminished vs. Pd.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- S. D. Roughley, A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451.
- T. W. J. Cooper, I. B. Campbell, S. J. F. MacDonald, *Angew. Chem. Int. Ed.*, 2010, **49**, 8082.
- L. Yet, *Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis*; Wiley, Hoboken: 2018.
- B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.*, 2011, **111**, 1346.
- F.-S. Han, *Chem. Soc. Rev.*, 2013, **42**, 5270.
- S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature*, 2014, **509**, 299.
- J. D. Shields, E. E. Gray, A. G. Doyle, *Org. Lett.*, 2015, **17**, 2166–216.
- J. E. Dander, N. A. Weires, N. K. Garg, *Org. Lett.*, 2016, **18**, 3934.
- N. Hazari, P. R. Melvin, M. M. Beromi, *Nat. Rev. Chem.*, 2017, **1**, 0025.
- S. Ge, J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2012, **51**, 12837.
- E. A. Standley, S. J. Smith, P. Müller, T. F. Jamison, *Organometallics*, 2014, **33**, 2012.
- J. Magano, S. Monfette, *ACS Catal.*, 2015, **5**, 3120.
- L. M. Guard, M. M. Beromi, G. W. Brudvig, N. Hazari, D. J. Vinyard, *Angew. Chem. Int. Ed.*, 2015, **54**, 13352.
- J. Malineni, R. L. Jezorek, N. Zhang, V. Percec, *Synthesis*, 2016, **48**, 2795.
- M. M. Beromi, A. Nova, D. Balcells, A. M. Brasacchio, G. W. Brudvig, L. M. Guard, N. Hazari, D. J. Vinyard, *J. Am. Chem. Soc.* 2017, **139**, 922.
- J. M. Weber, A. R. Longstreet, T. F. Jamison, *Organometallics*, 2018, **37**, 2716.
- M. M. Beromi, G. Banerjee, G. W. Brudvig, D. J. Charboneau, N. Hazari, H. M. C. Lant, B. Q. Mercado, *Organometallics*, 2018, **37**, 3943.
- K. Wu, A. G. Doyle, *Nature Chem.*, 2017, **9**, 779.
- J. D. Hayler, D. K. Leahy, E. M. Simmons, *Organometallics*, 2019, **38**, 36.
- The Ni(dppf)(*o*-tol)Cl precatalyst used in this study is inexpensive to prepare; however, this is more expensive when purchased commercially (e.g., Sigma-Aldrich product code 802948).
- Ni(dppf)Cl₂ was also evaluated; however, this possible precatalyst was notably less reactive than the well-studied Ni(dppf)(*o*-tol)Cl precatalyst.
- J. W. B. Fyfe, C. P. Seath, A. J. B. Watson, *Angew. Chem. Int. Ed.*, 2014, **53**, 12077.
- J. W. B. Fyfe, E. Valverde, C. P. Seath, A. R. Kennedy, J. M. Redmond, N. A. Anderson, A. J. B. Watson, *Chem. Eur. J.*, 2015, **24**, 8951.
- C. P. Seath, J. W. B. Fyfe, J. J. Molloy, A. J. B. Watson, *Angew. Chem. Int. Ed.*, 2015, **54**, 9976.
- J. W. B. Fyfe, N. J. Fazakerley, A. J. B. Watson, *Angew. Chem. Int. Ed.*, 2017, **56**, 1249.
- C. Xu, J. W. B. Fyfe, C. P. Seath, S. H. Bennett, A. J. B. Watson, *Chem. Commun.*, 2017, **53**, 9139.
- J. J. Molloy, C. P. Seath, M. J. West, C. McLaughlin, N. J. Fazakerley, A. R. Kennedy, D. J. Nelson, A. J. B. Watson, *J. Am. Chem. Soc.*, 2018, **140**, 126.
- B. P. Carrow, J. F. Hartwig, *J. Am. Chem. Soc.*, 2011, **133**, 2116.
- A. A. Thomas, S. E. Denmark, *Science*, 2016, **352**, 329.
- A. A. Thomas, H. Wang, A. F. Zahrt, S. E. Denmark, *J. Am. Chem. Soc.*, 2017, **139**, 3805.
- M. Butters, J. N. Harvey, J. Jover, A. J. J. Lennox, G. C. Lloyd-Jones, P. M. Murray, *Angew. Chem. Int. Ed.*, 2010, **49**, 5156.
- P.-A. Payard, L. A. Perego, I. Ciofini, L. Grimaud, *ACS Catal.*, 2018, **8**, 4812.
- S. G. Rull, I. Funes-Ardoiz, C. Maya, F. Maseras, M. R. Fructos, T. R. Belderrain, M. C. Nicasio, *ACS Catal.*, 2018, **8**, 3733.
- V. Percec, J.-Y. Bae, M. Zhao, D. H. Hill, *J. Org. Chem.*, 1995, **60**, 176.
- R. S. Berman, J. K. Kochi, *Inorg. Chem.*, 1980, **19**, 248.
- A. H. Christian, P. Müller, S. Monfette, *Organometallics*, 2014, **33**, 2134.
- P. A. Cox, A. G. Leach, A. D. Campbell, G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2016, **138**, 9145.
- P. A. Cox, M. Reid, A. G. Leach, A. D. Campbell, E. J. King, G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2017, **139**, 13156.
- S. Bajo, G. Laidlaw, A. R. Kennedy, S. Sproules, D. J. Nelson, *Organometallics*, 2017, **36**, 1662.
- K. D. Collins, F. Glorius, *Nature Chem.*, 2013, **5**, 597.