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Modifications to the Aryl Group of dppf-Ligated Ni σ–Aryl Precatalysts: Impact on Speciation and Catalytic Activity in Suzuki–Miyaura Coupling Reactions

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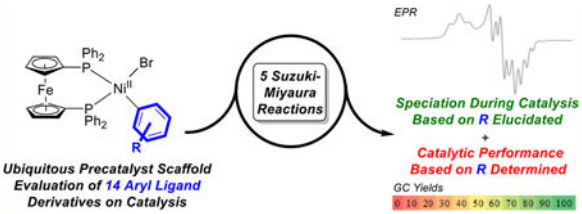
Abstract

There is currently significant interest in the development of efficient nickel precatalysts for cross-coupling. In this work, 14 nickel(II) precatalysts of the form (dppf)Ni(aryl)(X) (dppf = 1,1′-bis(diphenylphosphino)-ferrocene, X = Cl, Br) were synthesized. In particular, both the electronic and steric properties of the aryl group were modified to understand how this affects precatalyst activation. Using EPR spectroscopy, it was demonstrated that the amount of off-cycle nickel(I) species which are formed via comproportionation during precatalyst activation varies depending on the nature of the aryl group. For example, sterically bulky aryl groups reduce comproportionation. Additionally, the catalytic activity of the family of precatalysts was evaluated in five different Suzuki−Miyaura coupling reactions. The results from these catalytic studies provide information about how precatalyst structure affects catalytic efficiency, which may be useful for the rational design of improved nickel precatalysts for cross-coupling.

GRAPHICAL ABSTRACT



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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00589.

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CCDC 1860562−1860572 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Notes

The authors declare no competing financial interest.

INTRODUCTION

Cross-coupling is one of the most powerful synthetic methods and is commonly used to synthesize pharmaceuticals, agro-chemicals, ligands for metal complexes, and precursors for materials chemistry.[1] In recent years, the development of nickel-catalyzed cross-coupling reactions has attracted significant interest.[1j,2] In comparison to traditional cross-coupling reactions, which use palladium catalysts, nickel-based systems could provide cost-effective and sustainable alternatives. Additionally, in some cases nickel catalysts can promote reactivity that is not possible with palladium-based systems. For example, nickel catalysts can promote reactions using sp^3-hybridized substrates[3,4] and aryl ether and ester electrophiles.[5] Nevertheless, despite the intense research aimed at developing systems for nickel-catalyzed cross-coupling, in general these reactions are hindered by the need for high catalyst loadings, long reaction times, and elevated temperatures.[1j,6] This can limit the synthetic utility of nickel-catalyzed cross-coupling reactions.

At this stage, the procedures for most nickel-catalyzed cross-coupling reactions generate the catalytically active species by mixing a nickel(II) salt or a nickel(0) precursor, such as $Ni(COD)_2$ (COD = 1,5-cyclooctadiene), with free ligand in situ.[2] In contrast, many modern procedures for palladium-catalyzed cross-coupling use well-defined precatalysts, in which the ligand is already bound to the metal.[1h,j,7] The use of precatalysts limits the formation of off-cycle species which contain more than the desired number of ligands bound to the metal and as a consequence improves catalytic efficiency. Additionally, there are practical advantages associated with utilizing precatalysts, as they are typically bench stable and easy to use in high-throughput experimentation methods, which can aid in ligand screening or reaction optimization. Therefore, it is likely that the design and development of nickel-based precatalysts instead of in situ based systems will increase the utility and efficiency of nickel-catalyzed cross-coupling reactions.

To date there are relatively few examples of well-defined bench-stable nickel precatalysts for cross-coupling reactions (Scheme 1).[8] One of the most popular and active families of precatalysts comprises complexes of the type (L)Ni(aryl)(X), where L is an ancillary ligand and X is a halide ligand (usually Cl or Br).[1j] These complexes are typically air-stable solids that can be synthesized readily from nickel(II) salts, which means that, unlike other nickel precatalysts, an expensive nickel(0) source, such as $Ni(COD)_2$, is not required for their preparation.[9] Known aryl substituents for this precatalyst scaffold include 1-naphthyl,[10] 4-trifluoromethylphenyl,[11] 4- methoxyphenyl,[12] phenanthryl,[13] and anthracenyl[13] ligands, which are competent for Suzuki−Miyaura reactions and Buchwald−Hartwig aminations. Additionally, Jamison and co-workers recently described (L)Ni(aryl)(X) type precata- lysts, which feature a pendant olefin on the aryl ligand.[14] These complexes activate via an intramolecular Heck reaction and are active for carbonyl-ene coupling reactions. However, the most common aryl group in precatalysts of the type (L)Ni(aryl)(X) is an *o*-tolyl ligand. Precatalysts containing an *o*-tolyl ligand have been used with both NHC and phosphine ligands, as well as with recently developed ancillary ligands such as JosiPhos and PAd-DalPhos.[1j,9a,15] To date it has been demonstrated that (L)Ni(*o*-tolyl)(X) precatalysts can facilitate Suzuki−Miyaura coupling reactions with heteroaryl chloride and sulfamate electrophiles,[16] the benzylation of terminal alkenes,[17] carbonylene reactions,[9a] and

Buchwald−Hartwig amination reactions with heteroaryl halide and pseudohalide substrates.[15c,18] Additionally, this precatalyst scaffold is one of the few nickel-containing precatalysts that can be used for rapid screening of ancillary ligands when it is ligated by the more labile TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) ligand, which can be substituted by a variety of monodentate and bidentate phosphine and NHC ligands in situ.[19]

Even though precatalysts of the type (L)Ni(*o*-tolyl)(X) are often used in catalysis,[1j] there are relatively few detailed studies exploring their activation.[13c,b,16b] Previously, we described mechanistic studies on the nickel-catalyzed Suzuki−Miyaura cross-coupling of aryl chlorides and sulfamates using (dppf)-Ni(*o*-tolyl)(X) (dppf = 1,1′-bis(diphenylphosphino)ferrocene, X = Cl, Br).[16] We determined that, during the activation of the precatalyst, there is a competing comproportionation process between the active nickel(0) catalyst and unreacted nickel(II) precatalyst that siphons nickel from the catalytic cycle in the form of catalytically inactive nickel(I) species (Scheme 2). Furthermore, in subsequent work, we isolated one of the nickel(I) products and determined that the rate of disproportionation, the reverse process to comproportionation during activation, can be inhibited by increasing the steric bulk on the aryl group of the nickel(I) species.[20] On the basis of these results, we hypothesized that we could control the extent of comproportionation during precatalyst activation through modification of the (dppf)Ni(aryl)(X) scaffold. Herein, we have prepared 14 different compounds of the type (dppf)Ni-(aryl)(X) with sterically and electronically diverse aryl groups. The effects of the aryl group on both comproportionation and catalytic performance in Suzuki−Miyaura reactions are described. This work provides insight into the factors that control speciation during the activation of the precatalyst, which may lead to improved systems for nickel-catalyzed cross-coupling.

RESULTS AND DISCUSSION

Precatalyst Synthesis.

Fourteen precatalysts of the form (dppf)Ni(aryl)(X) containing aryl groups with different steric and electronic properties were synthesized to compare with the literature compounds **1-Cl, 1-Br,** and **16** (Figure 1).[9a,16b,20] In our series of complexes, trends based on steric effects can be assessed by comparing precatalysts **2, 3, 6, 11, 14,** and **16.** Additionally, for most groups of precatalysts with similar steric properties, representative complexes with both electron- withdrawing and electron-donating substituents on the aryl group were prepared; for example, within the family of 2,4- substituted precatalysts a complex with an electron-deficient aryl group, **8,** and a complex with an electron-rich aryl group, **9,** were synthesized for comparison with the parent complex 6.

Except for complex **7,** the precatalysts were synthesized via transmetalation of (dppf)$NiBr_2$ (**17**) with the appropriate arylmagnesium bromide Grignard reagent (Scheme 3a). These reactions proceeded with modest to good yields (see the Supporting Information). The choice of bromide as the halide ligand instead of chloride greatly simplified the synthesis of the precatalysts, as arylmagnesium bromide reagents can easily be prepared if they are not commercially available. Additionally, the bromide ligand provides a useful handle for the identification of paramagnetic bromide-containing species by EPR spectroscopy, as bromide

has two relatively abundant spin-active isotopes (^{79}Br, I = 3/2, 50% abundance; ^{81}Br, I = 3/2, 50% abundance) (vide infra). All precatalysts are stable over several months as solids on the benchtop. It is noteworthy that at least one ortho substituent is required on the aryl group to generate species that are stable in solution and can be isolated. We were unable to prepare (dppf)Ni^{II}(Ph)(Br), as the transmetalation reaction between **17** and phenylmagnesium bromide immediately resulted in the formation of a black, intractable mixture. Similarly, synthesis of the chloride analogue (dppf)Ni^{II}(Ph)(Cl) via oxidative addition of chlorobenzene to a nickel(0) source is known to yield the paramagnetic comproportionation product (dppf)Ni^{I}Cl (**19-Cl**) instead of the desired nickel(II) complex.[21] Furthermore, the attempted preparation of (dppf)Ni^{II}(2-naphthyl)(Br) via transmetalation resulted in the formation of an unstable species, which suggests that meta and para substitution by itself is not sufficient to generate stable σ-aryl precatalysts using this ancillary ligand.

Complex 7, which contains a 2-methyl-4-nitrophenyl ligand, could not be synthesized using the Grignard-based route, as it is not possible to prepare the appropriate Grignard reagent. Instead, 7 was synthesized by oxidative addition of 2-bromo-5-nitrotoluene to (dppf)Ni^{0}(C_2H_4) (**18**) (Scheme 3b). In this case, the oxidative addition reaction between the aryl halide and the nickel(0) source is presumably fast enough to outcompete comproportionation reactions between the nickel-(II) product and unreacted starting material that generate nickel(I) species. However, this is not a general phenomenon (vide infra) and as a consequence this route cannot always be used to prepare σ-aryl type precatalysts.

The ^{1}H NMR spectra of the singly ortho substituted aryl species 2−10 are not fluxional and are consistent with the complexes having C_1 symmetry. For example, they contain eight distinct resonances for the cyclopentadienyl protons of the dppf ligand at both room temperature and low temperature. In contrast, the ^{1}H NMR spectra of species **11** and **13−16,** containing symmetric diortho substitution on the aryl ring, are fluxional (see Figure 2 for a representative example). In these complexes, at room temperature one broad signal is observed for both of the methyl groups in the ortho position of the aryl ligand, whereas at low temperature, two distinct signals are present. The peaks associated with the aromatic protons directly bound to the aryl group are also broad at room temperature but sharp at low temperature. We propose that the fluxionality arises because of restricted rotation of the Ni−C_{aryl} bond, which is slow on the NMR time scale at low temperature but rapid at room temperature. A consequence of this restricted rotation is that at room temperature only four broad, but distinct, resonances are present for the eight cyclopentadienyl protons of the dppf ligand, whereas at low temperature eight distinct signals are observed for these protons. Effectively, the rapid rotation about the Ni−C_{aryl} bond renders the cyclopentadienyl protons C_2 symmetric on the NMR time scale. A special case of the restricted rotation occurs in complex **12,** which contains asymmetric diortho substitution on the aryl ligand. At room temperature the ^{1}H NMR spectrum of **12** is broad and difficult to interpret. However, the spectrum at −50 °C is sharp and contains twice the expected number of signals, indicating that two chemically distinct species are present. The ratio between the two species is approximately 2:1. We propose that in this case restricted rotation of the Ni−C_{aryl} bond results in the presence of two chemically distinct rotamers in solution due to the asymmetric substitution of the aryl group. In complexes **11** and **13−16,** which contain symmetric diortho

substitution on the aryl ring, the corresponding rotamers are chemically equivalent and lead to one set of resonances in the NMR spectrum. Consistent with this hypothesis, the ^{31}P NMR spectrum of **12** at −50 °C contains two sets of doublets in approximately a 2:1 ratio due to the presence of the rotamers. At room temperature, the ^{31}P NMR spectrum contains only two broad peaks, indicating that interconversion between the rotamers is rapid on the NMR time scale. The ^{19}F NMR spectrum of **12** also shows a 2:1 ratio of rotamers, and disorder resulting from the rotation of the aryl group is observed in the solid-state structure, as determined by X-ray crystallography (see the Supporting Information). Apart from **12,** the room-temperature ^{31}P NMR spectra for all other complexes contain two well-resolved resonances, consistent with a cis-ligated dppf ligand with each phosphorus atom in a different chemical environment (one phosphorus atom is trans to the aryl group, while the other is trans to the bromide). For complexes **1−3, 5−11,** and **13−16,** both of the resonances in the ^{31}P NMR spectra are doublets, while in the case of **4,** one of the phosphorus signals appears as a doublet of quartets due to coupling to the trifluoromethyl group on the aryl ring.

X-ray-quality single crystals of complexes **2−8, 10,** and **12−14** were obtained either from concentrated solutions in THF layered with pentane or concentrated solutions in dichloromethane layered with hexanes at −15 °C. In all cases the structures indicate a square-planar coordination geometry around the nickel center with a cis-ligated dppf ligand, consistent with the symmetry indicated by ^{31}P NMR spectroscopy. Comparison of the structures of **4, 5, 6, 8,** and **14** provides insight into the effect of varying the steric and electronic properties of the aryl group on the precatalyst structure (Figure 3). Complex **4** has an electron-withdrawing trifluoromethyl group in the 2-position of the aryl group, while complex **5** contains an electron-donating methoxy group in the same position. Nevertheless, there is little difference in the solid-state structures of the two complexes. The Ni−C_{aryl} bond lengths are the same within error, and the Ni−P_{trans} (where P_{trans} denotes the phosphorus atom trans to the aryl group on the precatalyst) bond length of **4** is only an average of 0.015 Å shorter than that of **5.** Similarly, the structures of **6** and **8,** which have the same electron-withdrawing and –donating substituents in the 4-position of the aryl ligand, are essentially identical. In contrast, steric factors have a large influence on the Ni−C_{aryl} bond length, and in our series of complexes as steric bulk of the aryl group increases the Ni−C_{aryl} bond length increases (Table 1). For example, the Ni−C_{aryl} bond length of 1.960(7) Å in **16**[20] is significantly longer than the Ni−C_{aryl} bond length of 1.906(6) Å in the next-smallest analogue, **14** (Table 1). While the Ni−C_{aryl} bond length increases with increasing steric bulk on the aryl ligand, the Ni−P_{trans} bond length decreases. A comparison of the bond lengths for Ni− C_{aryl} and Ni−P_{trans} in **6** and **14** indicates that a lengthening of approximately 0.02 Å occurs in Ni−C_{aryl} with a subsequent reduction in length of approximately 0.03 Å in Ni −P_{trans}. The exception to this trend is **16,** where, presumably, the very bulky ortho substitution prevents the shortening of Ni−P_{trans} that would otherwise coincide with the lengthening of Ni−C_{aryl} bond. There is also a trend in the size of the dppf bite angle as the sterics on the aryl group increases. The most sterically congested analogues, **14** and **16,** have bite angles of approximately 100°, which is contracted by about 2° in comparison to that of the less sterically hindered **6.** All synthesized analogues have bond and angle metrics that deviate minimally from those seen in the state of the art precatalyst **1-Cl.**[18]

Speciation of Precatalysts during Activation via EPR Spectroscopy.

In Suzuki−Miyaura coupling reactions, it is proposed that activation of the σ-aryl precatalysts occurs through transmetalation of the halide ligand with boronic acid and base to generate a nickel(II) bis-aryl species.[9a,16b] This nickel(II) bis-aryl species then reductively eliminates the biaryl organic product to form a nickel(0) species, which enters the catalytic cycle. We have previously shown that a competing comproportionation reaction can occur between the zerovalent nickel species and unreacted nickel(II) precatalyst to yield off-cycle nickel(I) halide and aryl species, which lowers the selectivity of activation (Scheme 2). To examine the selectivity of precatalyst activation on the basis of the properties of the aryl group, a selection of the precatalysts prepared in this work were utilized in Suzuki−Miyaura reactions between naphthalen-1-yl sulfamate and 4-methoxyphenylboronic acid (Figure 4). As the steric bulk on the aryl group increased, there was a decrease in the yield of the cross-coupled product. Control experiments suggest that this is due to a decrease in the rate of activation as the size of the aryl group was increased. For example, at room temperature only 34% of **16** was activated in comparison to 87% for the standard **1-Br.** When the temperature was raised to 50 °C, 64% of **16** was activated, and after 4 h a quantitative yield of cross-coupled product was obtained. The effect of varying the electronic properties of the aryl group on the yield of cross-coupled product is less pronounced, as both the electron-deficient 8 and electron-rich **9** operate as efficiently in catalysis as the parent species **6.** Furthermore, there is only a slight difference (~10%) in precatalyst activation between **8** and **9**—nevertheless, catalytic efficiency is not greatly affected by this difference in the amount of activated nickel.

The tendency of the nickel(II) precatalysts to form nickel(I) during activation was probed using EPR spectroscopy. When the reaction between naphthalen-1-yl sulfamate and 4-methoxyphenylboronic acid is catalyzed by **1-Br** and **11** (Figure 4), we see clear evidence for the formation of (dppf)Ni^{I}Br (**19-Br**) (by comparison of the EPR spectra of the catalytic reaction mixtures with authentic **19-Br**).[16b] This strongly suggests that in these systems precatalyst activation is not selective and off-cycle nickel(I) species are formed. When the same reaction is catalyzed by **6, 14,** and **16,** an EPR-active species is detected. However, this species does not have bromide hyperfine coupling and is not **19-Br,** which indicates that no significant quantity of nickel(I) is formed during activation. Instead, the EPR spectra are consistent with the formation of (dppf)NiI(sulfamate), which we have previously characterized using EPR spectroscopy.[16b] This species forms as a result of comproportionation during oxidative addition, which is a well-documented process.[16b,21,22] Furthermore, the amount of nickel(I) formed in the cases of **14** and **16** is significantly less than that of **6,** suggesting that less nickel is in an inactive form when the sterically bulky precatalysts are used. These EPR results also indicate that electronic factors do not have a drastic effect on the speciation of nickel during catalysis. Electronically distinct precatalysts **8** and **9** appear to behave similarly to that of their structural analogue **6—**that is, there is no comproportionation occurring during the activation process, and the only nickel(I) seen by EPR is (dppf)-Ni^{I}(sulfamate). When these determinations are taken together, it appears that ortho and para substitution is sufficient to prevent comproportionation during the activation process, regardless of the identity and size of the para substituent. Our results indicate that, although increasing the steric bulk on the aryl group increases the selectivity of activation by

decreasing the formation of nickel(I) species, it can result in less active catalysts because the overall rate of precatalyst activation is significantly slower. Furthermore, electronic factors appear to minimally affect activation and speciation during catalysis for the specific reaction examined in this set of experiments; rather, the steric properties of the aryl group of the precatalysts dictate speciation.

Catalytic Performance of the Full Precatalyst Family.

Given that steric and to a lesser extent electronic effects have an effect on the yield of cross-coupled product for a prototypical Suzuki−Miyaura reaction (vide supra), we evaluated the catalytic performance of the full family of precatalysts in a series of Suzuki−Miyaura coupling reactions with different electrophiles and nucleophiles, as shown in Figure 5a. The goal was to determine if a precatalyst could be found that was generally superior to the commonly used **1-Cl.** The five different reactions all represent challenging Suzuki− Miyaura reactions for nickel catalysts and were chosen to evaluate different aspects of precatalyst performance. Reaction A is a standard coupling reaction between naphthalen-1-yl sulfamate, a substrate that readily undergoes oxidative addition, and 4-methoxyphenylboronic acid, a nucleophile that is relatively activated for transmetalation. It is the same reaction we used to study precatalyst activation and connects our activation studies with catalysis (vide supra). Variation in the number of equivalents of boronic acid and base used in this reaction (A′ and A′′) provides a method to evaluate the effect of nucleophile concentration on the performance of the precatalyst family. Reaction B differs from reaction A because a more electron deficient boronic acid, 4-trifluoromethylphenyl- boronic acid, is used. This allows us to assess the effect of a less nucleophilic transmetalation partner, which could affect precatalyst activation. The effect of a less nucleophilic transmetalation reagent is also probed in reaction C; however, in this system, a relatively activated chloride electrophile, naphthalen-1-yl chloride, is employed. This system explores if there are differences in relative precatalyst performance based on use of a chloride electrophile in comparison to a sulfamate electrophile. In reaction D, the effect of an electrophile, 4- trifluoromethylphenyl sulfamate, which does not readily undergo oxidative addition was evaluated, while in reaction E the effect of heteroatoms on both the electrophile and nucleophile are probed. The yields for each of the precatalysts for all five reactions are presented in Figure 5b. It is noteworthy that **1-Cl** and **1-Br** perform comparably in all five reactions, indicating that the identity of the halide ligand does not greatly affect catalytic activity. It also suggests that the trends elucidated for our family of bromide-containing precatalysts are also likely relevant for chloride-containing systems.

The majority of the precatalysts evaluated gave the cross-coupled product in 90% or greater yield for the standard reaction A. This activity is comparable to that obtained with the state of the art precatalysts **1-Cl** and **1-Br.** The exceptions are precatalysts **7, 12,** and **16,** which performed poorly. In fact, the poor performance of 7, 12, and 16 is general to all reactions studied, except for reaction **E** (vide infra). In the cases of precatalysts **12** and **16** yields of around 50% are obtained in reaction A, and we propose that activation is hindered by the steric bulk of the aryl groups, which lowers catalytic efficiency. For **7,** which contains a nitro substituent, the reasons for the poor catalytic performance are unclear; however, it is possible that the highly reactive nitro group may undergo unproductive side reactions that

cause decomposition of the catalyst. For example, nickel(0) complexes are known to undergo oxygen atom transfer reactions with nitro groups, which, in this case, would siphon active nickel out of the catalytic cycle.[23] Further support for the hypothesis that the nitro group interferes in catalysis is provided by an experiment in which 1 equiv of 3-nitrotoluene (relative to the catalyst) is added to reaction A catalyzed by **1-Br.** In this case, no cross-coupled product is formed (see the Supporting Information).

When the amounts of boronic acid and base are reduced to 1.5 and 2.5 equiv, respectively (reaction A′), all precatalysts except **7, 12,** and **16** formed the cross-coupled product in 80% or greater yield, performing only slightly worse than in reaction A. However, both precatalysts **12** and **16** produced only approximately 10% yield in reaction A′, which is a 30−40% lower yield in comparison with reaction A. When the amounts of boronic acid and base are reduced even further to 1.05 and 2 equiv, respectively (reaction A′′), there are differences in the efficiency of the precatalysts that had performed well in reactions A and A′. Notably, five precatalysts still generated cross-coupled product in 80% yield or greater: **2, 5, 9, 10,** and **15.** The yield of cross-coupled product in each of these cases is significantly higher (~15−20%) than that of **1-Cl** and **1-Br,** highlighting their efficiency for this catalytic reaction. Although there does not appear to be a common structural connection among all five of these precatalysts, it is interesting to note that all three of the methoxy-functionalized precatalysts **5, 9,** and **15** evaluated are contained within this high-performing group.

The excellent performance of the methoxy-functionalized precatalysts **5, 9,** and **15** relative to other precatalysts in reaction A′′ does not apply in the case of reaction B, in which 4-trifluoromethylphenylboronic acid was coupled with naphthalen-1-yl sulfamate. **5, 9,** and 15 did not produce more than 30% of the cross-coupled product over 8 h, in comparison to 57% for the standard precatalyst **1-Cl.** A potential explanation for these results may be related to the relative difficulty in transmetalating a nickel center containing an aryl ligand with an electron-rich methoxy group with a relatively weakly nucleophilic boronic acid.[24] Consistent with this hypothesis, complexes **2** and **10,** which contain less electron rich aryl groups, performed slightly better than **1-Cl,** although this difference (~10% above **1-Cl**) is much less pronounced than the difference between methoxy-substituted species and **1-Cl** (20−40% below **1-Cl**). Our results indicate that, when a relatively deactivated boronic acid is used as the nucleophile, a more electron deficient nickel center is preferable, most likely because this leads to easier activation.

In reaction C, 1-chloronaphthalene was paired with a relatively deactivated nucleophile, 4-trifluoromethylphenylbor-onic acid. In this reaction, two precatalysts achieved yields significantly higher than that of **1-Cl** namely, the 2,4,6-aryl- substituted complexes **13** and **14.** Given that reaction C requires a long reaction time (16 h) and that **13** and **14** both contain very large aryl groups, the increased efficiency of these precatalysts may be related to the fact that a larger amount of nickel likely enters the catalytic cycle. This is because systems with more sterically bulky aryl groups form fewer off-cycle nickel(I) complexes (vide supra). In a slower reaction the rate of activation presumably becomes relatively less important and the amount of nickel that eventually enters the catalytic cycle is more important. Nevertheless, with the most sterically bulky precatalyst **16,** almost no product is obtained. We suggest that this is because the slow rate of precatalyst activation means that a

significant amount of nickel(0) is never generated in the reaction. In general, for reaction C, apart from the almost universally poorly performing **7, 12,** and **16** and the high performance of **12** and **13,** all other precatalysts gave comparable performance. This includes the methoxy-functionalized precatalysts **5, 9,** and **15.**

In reaction D, an electrophile that is difficult to oxidatively add, 4-trifluoromethylphenyl sulfamate, was coupled with an electron-rich boronic acid, 4-methoxyphenylboronic acid. For this reaction all precatalysts performed poorly. The only precatalyst able to achieve greater than a 50% yield of cross-coupled product was **1-Cl.** There are no obvious trends in the performance of other precatalysts, and the exact reasons **1-Cl** gives better activity are unclear. The results from reaction E are perhaps the most surprising. In this case all precatalysts gave approximately 35% yield, even the precatalysts that were unable to catalyze reactions **A−D.** One explanation for these results may be that the presence of coordinating heteroatoms generates common intermediates that undergo slow elementary steps; this scenario negates any differences in the rates of activation that arise from different structural features on the precatalyst. For example, pyridyl electrophiles are known to generate off-cycle, pyridyl-bridged Ni(II) dinuclear complexes in Buchwald−Hartwig amination reactions after oxidative addition.[25] In this reaction, the 2-chloroquinoline electrophile may result in similar off-cycle species and the catalytic activity may be governed by the rate at which this off-cycle species, which will be the same regardless of the initial structure of the precatalyst, re-enters the catalytic cycle.

In several of our test reactions, we hypothesize that the differences in yields are related to the rate at which a precatalyst activates and the amount of unproductive comproportionation that occurs. For reactions requiring longer reaction times, we propose that bulkier precatalysts may be superior because they activate more slowly and do not undergo as much comproportionation during activation, resulting in an increased lifetime in catalysis. To probe the lifetime of the active catalyst as a function of the steric bulk of the precatalyst, we devised a spiking experiment. In this experiment, we performed reaction A as previously described but then added an additional 1 equiv of electrophile after 4 h. The reaction was then allowed to proceed for another 4 h (so that the experiment lasted 8 h in total), after which the yield of cross-coupled product was analyzed (Figure 6). This experiment was conducted using precatalysts **1-Br, 6, 11, 14,** and **16,** which are similar electronically but have different steric properties. The bulkiest precatalyst, **16,** is able to produce the highest total yield of cross-coupled product after spiking, in contrast to our original results from reaction A. In fact, the yield of cross-coupled product in the reaction catalyzed by **16** is approximately 20% higher than that of any of the other precatalysts tested. These data are consistent with our model in which **16** is activated more slowly and does not comproportionate, leaving more unreacted precatalyst available in the second 4 h to activate and couple the freshly added electrophile. In contrast, the relatively small precatalysts are proposed to activate rapidly during the first 4 h and undergo significant decomposition, leaving no viable catalyst to couple the additional electrophile added in the second segment.

Overall, there are several conclusions that can be made on the basis of our catalytic data. (1) None of the aryl ligands tested in this work are more efficient than the *o*-tolyl ligand in the state of the art **1-Cl/Br** system across the entire suite of catalytic reactions performed. (2)

The performance of each precatalyst is reaction-dependent; this is exemplified, for example, in the nature of the nucleophile having a drastic effect on the performance of the methoxy-substituted species (reaction A versus reaction B) and the fact that the use of heteroaryls as the electrophile and nucleophile (reaction E) resulted in similar performance from all precatalysts, even those that did not work for previous reactions. Additionally, attempts to correlate the performance of our precatalyst family with quantifiable properties, such as percent buried volume[26] or Hammett parameters,[27] did not lead to meaningful associations (see the Supporting Information). (3) As indicated by the results from reaction C, it may be advantageous to use bulkier precatalysts for more challenging reactions where the rates of the elementary steps are slower. In these reactions, the fact that more sterically bulky precatalysts form fewer off-cycle nickel(I) species is more important than the fact that they also activate more slowly. However, at this stage there is a tradeoff between rapid activation and the selectivity of activation. Unfortunately, our results suggest that it is unlikely that there is a “universal” aryl ligand which is optimal for all reactions; rather, within a given set of design rules (for example, sterically bulky aryl ligands result in slower activation) the aryl group may need to be optimized on a case by case basis for each individual reaction. Furthermore, in many cases significant improvements in catalyst performance will not be possible by changing the aryl ligand.

CONCLUSIONS

In this work we have prepared a family of precatalysts for cross-coupling of the form (dppf)Ni(aryl)(Br) with electronically and sterically diverse aryl groups. In most cases these species can be formed readily through the reaction of (dppf)$NiBr_2$ with the appropriate Grignard reagent. Studies using EPR spectroscopy indicate that the nature of the aryl group influences the selectivity of precatalyst activation in a prototypical Suzuki−Miyaura reaction. More sterically bulky systems are less likely to form off-cycle nickel(I) species; however, there is a tradeoff, as these precatalysts activate more slowly, which can lead to a less efficient catalytic system. When the performance of our family of precatalysts was compared for a diverse variety of Suzuki−Miyaura reactions, general trends which indicate that a particular aryl group is more desirable than another were not observed. In fact, our results show that precatalyst performance is highly variable depending on the nature of both the electrophile and nucleophile and that precatalysts which give poor performance in comparison to other systems with one set of substrates can give very good performance with a different set of substrates. For example, precatalysts containing a more sterically bulky aryl group are generally better for substrates which undergo slow elementary reactions because they increase the amount of nickel that is in an active form during catalysis. However, they are less desirable for substrates which undergo rapid elementary steps because they activate slowly. Given the complex dependence of precatalyst performance on the nature of the aryl group and our inability to find a universally better system, we conclude that the original **1-Cl/Br** system is an excellent choice for initial investigations aimed at finding a precatalyst to perform a particular reaction, especially given its commercial availability.[5b,28] If further optimization of a reaction is required, modifying the aryl group of **1-Cl/Br** could lead to an improved system, but in most cases it will be difficult to predict which modification will result in better performance. It is also unclear if the results described in this work will be

general to precatalysts containing other ancillary ligands, for example if the ancillary ligand is changed to bipyridine instead of dppf, and further research is required to address this issue.

EXPERIMENTAL SECTION

General Methods.

Experiments were performed under an atmosphere of dinitrogen in an MBraun glovebox or using standard Schlenk techniques, unless specified otherwise. Purging of the glovebox atmosphere was not performed between uses of pentane, benzene, toluene, diethyl ether, and THF; as such, trace amounts of the solvents may have been present in the box atmosphere and intermixed in the solvent bottles. All chemicals were used as received unless otherwise stated. Air- or moisture-sensitive liquids were transferred using stainless steel cannulas on a Schlenk line or in a glovebox. Solvents were dried via passage through a column of activated alumina and subsequently stored under dinitrogen. Deuterated solvents were obtained from Cambridge Isotope Laboratories. Powdered K_3PO_4 was purchased from Acros Organics, finely ground using a mortar and pestle, heated in an oven at 120 °C for at least 24 h, and stored in a glovebox. NMR spectra were recorded on Agilent 400, 500, and 600 MHz spectrometers at ambient probe temperatures unless otherwise stated. Chemical shifts are reported in ppm with respect to residual internal protio solvent for ^{1}H and ^{13}C NMR spectra and $^{31}P\{^{1}H\}$ NMR spectra are referenced via the ^{1}H resonances based on the relative gyromagnetic ratios. Gas chromatography was performed on a ThermoFisher Trace 1300 GC apparatus equipped with a flame ionization detector and a Supelco fused silica capillary column (5 Å molecular sieves, 30 m × 0.53 mm) using the following parameters: flow rate 1.23 mL/min constant flow, column temperature 50 °C (held for 5 min), 20 °C/min increase to 300 °C (held for 5 min), total time 22.5 min. GC yields were calculated on the basis of calibration curves generated using the independently synthesized biaryl product of interest. Naphthalen-1-yl sulfamate and 4-trifluoromethylphenyl sulfamate were prepared according to literature procedures.[29] **1-Cl,**[9a] **1-Br,**[9a] and **16**[20] were prepared following literature procedures. X-band EPR spectra were recorded on a Bruker ELEXSYS E500 EPR spectrometer equipped with an SHQ resonator and an Oxford ESR-900 helium-flow cryostat with the following settings: microwave frequency, 9.4 GHz; modulation frequency, 100 kHz; modulation amplitude, 10 G; sweep time, 84 s; conversion time, 41 ms; time constant, 20 ms. One millimolar solutions of the samples of interest were prepared in the glovebox using toluene for a total of 200 μL of solution per tube. The tubes were sealed in the glovebox and immediately frozen in liquid nitrogen. Robertson Microlit Laboratories, Inc., performed the elemental analyses (inert atmosphere).

General Procedure for the Synthesis of Nickel(II) Precatalysts via Transmetalation.

All compounds, except for 7, were synthesized by modification of the previously described literature method for the preparation of **1-Br.**[9a,16b] (dppf)$NiBr_2$ (17; 100 mg, 0.129 mmol) was placed in a 100 mL Schlenk flask containing a stir bar. A 10 mL portion of THF was cannula-transferred into the flask, and the contents were stirred until dissolution. The flask was cooled to 0 °C in an ice bath, after which the appropriate arylmagnesium bromide Grignard reagent (0.129 mmol) was added dropwise using a gastight syringe. The solutions

turned from dark green to orange in all cases by the end of the addition. The flask was warmed to room temperature, after which the THF was removed under vacuum to yield an orange residue. A 5 mL portion of methanol was placed in the flask, and the heterogeneous mixture was sonicated for 3 min until a uniform suspension was obtained. The flask was cooled in an ice bath for 15 min, and the resulting bright yellow solid was isolated by vacuum filtration and analyzed by ^{1}H, ^{31}P, ^{13}C, and ^{19}F (if applicable) NMR spectroscopy as well as elemental analysis. The synthesis of 7 is detailed in the Supporting Information, along with characterization data and yields for compounds **1**−**6** and **8**−**15.**

Crystallographic Information.

Single crystals of precatalysts were grown from a concentrated THF solution layered with pentane or a concentrated dichloromethane solution layered with hexanes at −15 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku SCX Mini diffractometer coupled to a Rigaku Mercury275R CCD with Mo Kα radiation (λ = 0.71073 Å). The diffraction images were processed and scaled using Rigaku CryAlisPro software.[30] The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL.[31] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). See the Supporting Information for more information about the structures solved in this work.

General Procedure for EPR Spectroscopy.

A stock solution containing naphthalen-1-yl sulfamate (0.266 mmol), naphthalene (0.133 mmol), and precatalyst (2.5 mol %, 0.00665 mmol) in 2 mL of toluene was prepared. 4-Methoxyphenylboronic acid (50.0 mg, 0.333 mmol) and K_3PO_4 (127.2 mg, 0.599 mmol) were weighed into a 1 dram vial containing a stir bar. A 1 mL portion of the stock solution was placed via micropipet in the vial. The vial was tightly capped and removed from the glovebox. The vial was then placed in an aluminum heating block with a thermocouple at room temperature, and the contents were stirred for 4 h. In order to record an EPR spectrum, 61 μL of the reaction mixture was removed from the catalytic reaction in a glovebox and placed in an EPR tube along with 139 μL of toluene. The tube was sealed, removed from the glovebox, and immediately frozen in liquid nitrogen. The EPR spectrum was then recorded. The presence of bromide-ligated nickel(I) species was verified by the septet hyperfine splitting pattern in $g_{\perp}$.

General Procedure for Catalysis for Reactions A, A′, A′′, B, and D.

A stock solution containing aryl sulfamate (0.266 mmol), naphthalene (0.133 mmol), and precatalyst (2.5 mol %, 0.00665 mmol) in 2 mL of toluene was prepared. Boronic acid and K_3PO_4 were weighed into a 1 dram vial containing a stir bar. A 1 mL portion of the stock solution was placed via micropipet in the vial. The vial was tightly capped and removed from the glovebox. The vial was then placed in an aluminum heating block with a thermocouple at room temperature, and the contents were stirred for the appropriate amount

of time. In order to prepare a GC sample, the reactions were quenched by exposure to air, after which 100−200 μL of the reaction mixture was placed on an ~5 cm plug of silica and eluted with ethyl acetate. The yield of cross-coupled product was determined by gas chromatography, referenced to the naphthalene internal standard. All reactions were performed in duplicate, and the reported yields are the average of two runs.

General Procedure for Catalysis for Reactions C and E.

A stock solution containing aryl chloride (0.4 mmol), naphthalene (0.2 mmol), and precatalyst (2.5 mol %, 0.01 mmol) in 680 μL of 1,4- dioxane and 320 μL of benzene was prepared. Boronic acid (0.4 mmol, 2 equiv) and K_3PO_4 (0.8 mmol, 4 equiv) were weighed into a 1 dram vial containing a stir bar. A 500 μL portion of the stock solution was placed via micropipet in the vial. The vial was tightly capped and removed from the glovebox. The vial was then placed in an aluminum heating block with a thermocouple at room temperature, and the contents were stirred for the appropriate amount of time. In order to prepare a GC sample, the reactions were quenched by exposure to air, after which 50−100 μL of the reaction mixture was placed on an ~5 cm plug of silica and eluted with ethyl acetate. The yield of cross-coupled product was determined by gas chromatography, referenced to the naphthalene internal standard. All reactions were performed in duplicate, and the reported yields are the average of two runs.

General Procedure for Spiking Experiments.

A stock solution containing naphthalen-1-yl sulfamate (66.6 mg, 0.266 mmol), naphthalene (16.8 mg, 0.133 mmol, 0.5 equiv), and precatalyst (2.5 mol %, 0.00665 mmol) in 2 mL of toluene was prepared. 4- Methoxyphenylboronic acid (49.9 mg, 0.333 mmol, 2.5 equiv) and K_3PO_4 (127.2 mg, 0.599 mmol, 4.5 equiv) were weighed into a 1 dram vial containing a stir bar. A 1 mL portion of the stock solution was placed via micropipet in the vial. The vial was tightly capped and removed from the glovebox. The vial was then placed in an aluminum heating block with a thermocouple at room temperature, and the contents were stirred for 4 h. Another stock solution was prepared, containing naphthalen-1-yl sulfamate (66.6 mg, 0.266 mmol) in 1 mL of toluene. After 4 h, the vial was brought back into the glovebox, after which 500 μL of the stock solution containing only naphthalen-1-yl sulfamate was added. The vial was capped tightly and removed from the glovebox, and the contents were stirred in the aluminum heating block at room temperature for another 4 h. In order to prepare a GC sample, the reactions were quenched by exposure to air, after which 50−100 μL of the reaction mixture was placed on an ~5 cm plug of silica and eluted with ethyl acetate. The yield of cross-coupled product was determined by gas chromatography, referenced to the naphthalene internal standard. All reactions were performed in duplicate, and the reported yields are the average of two runs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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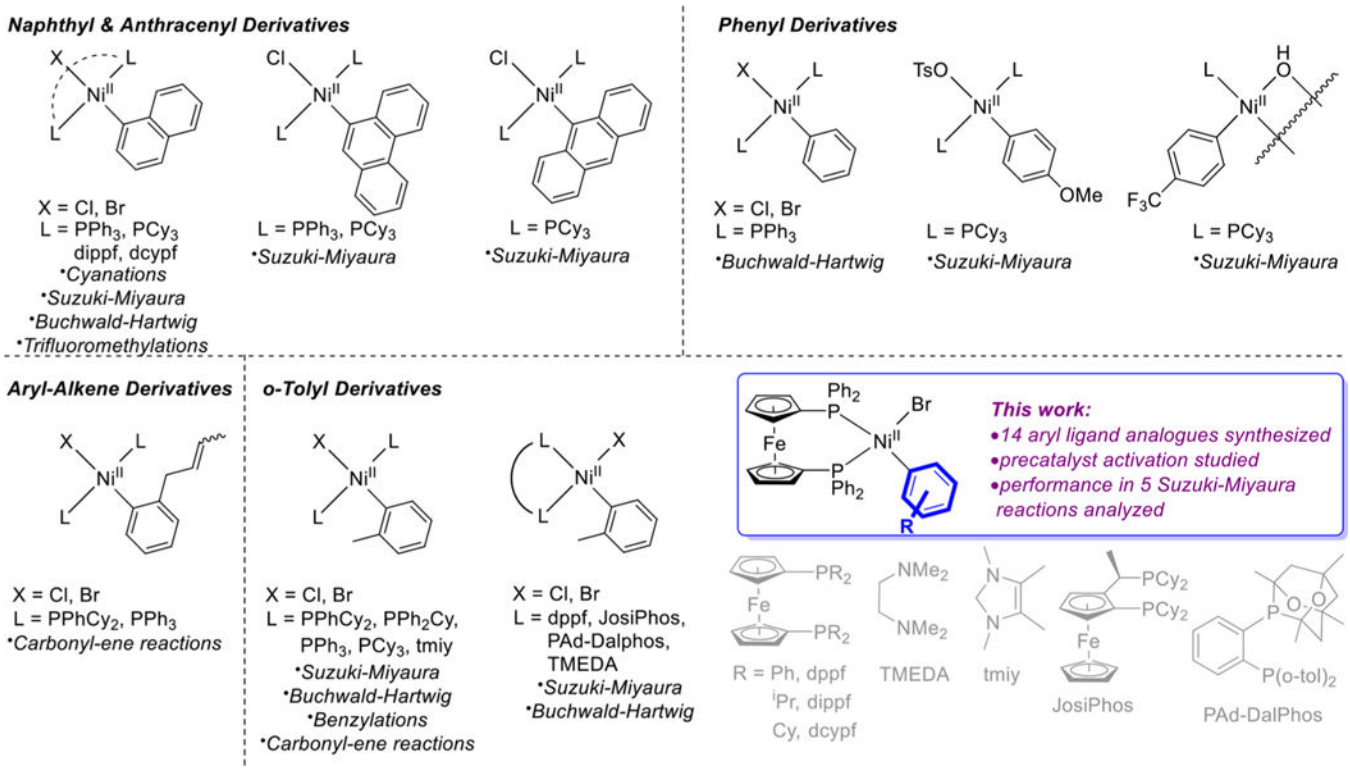
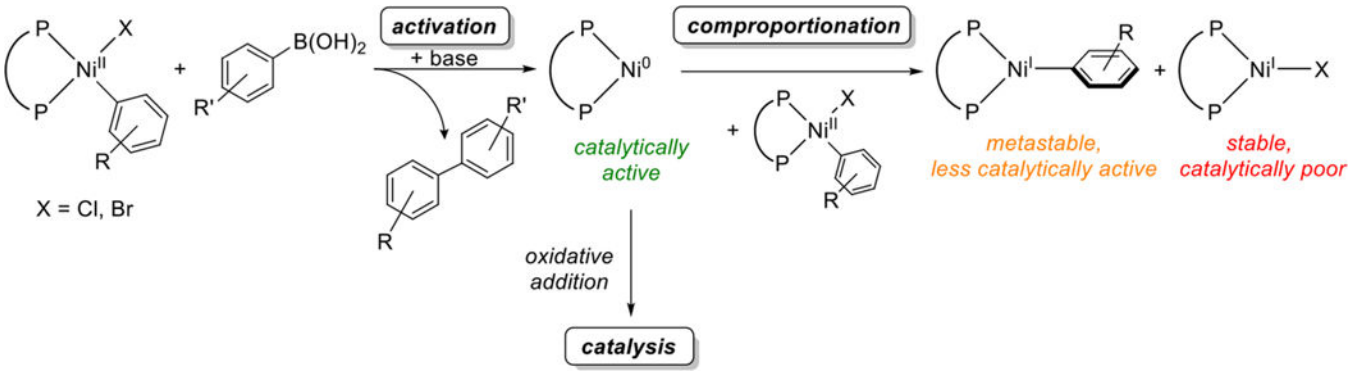


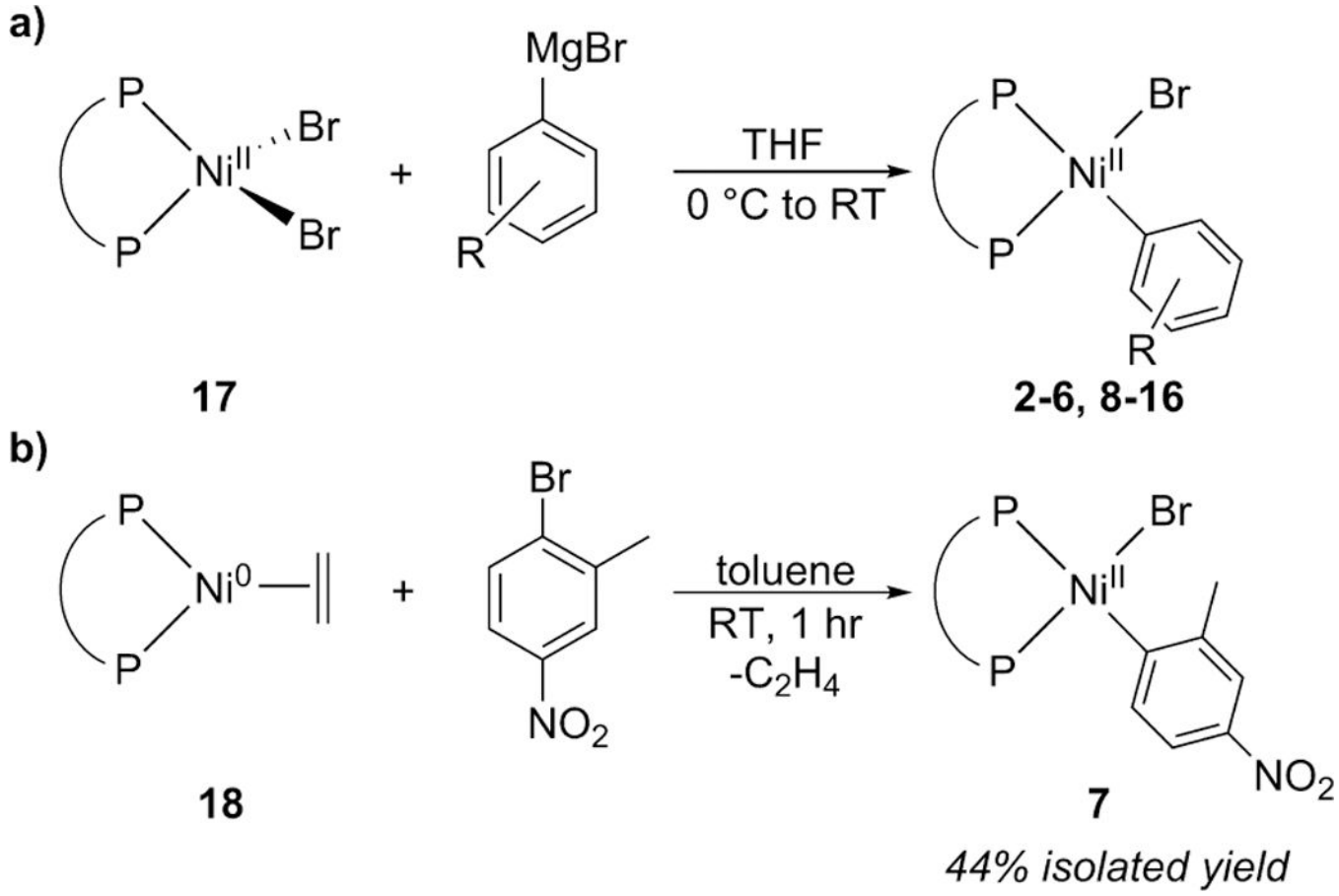
Scheme 1.

Previous Examples of Ni(II) σ-Aryl Precatalysts and Summary of the Present Work



Scheme 2.

Summary of Previous Work Exploring Comproportionation during the Activation Process To Form Catalytically Inactive Nickel(I) Complexes



Scheme 3.

(a) Generic Synthesis of Precatalysts from Transmetalation of 17 with Arylmagnesium Bromide Grignard Reagents[a] and (b) Synthesis of 7 via Oxidative Addition of 2-Bromo-5-nitrotoluene to 18

[a]Specific reaction conditions for each precatalyst are given in the Supporting Information.

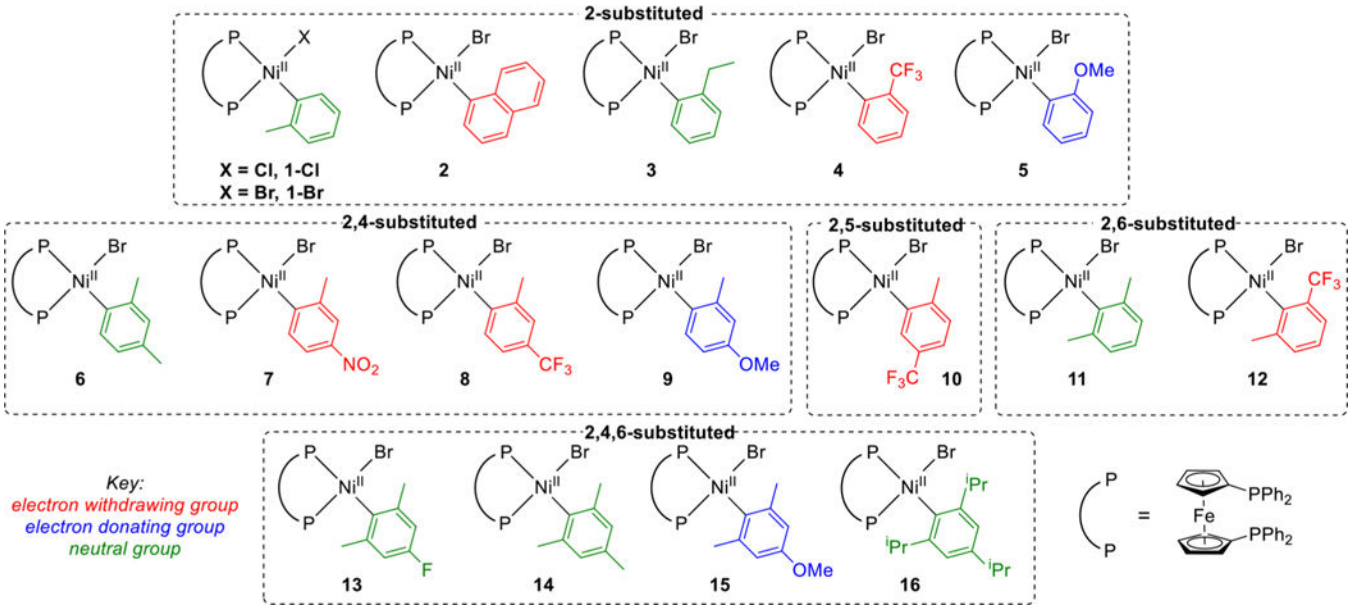


Figure 1.
Precatalysts examined in this work.

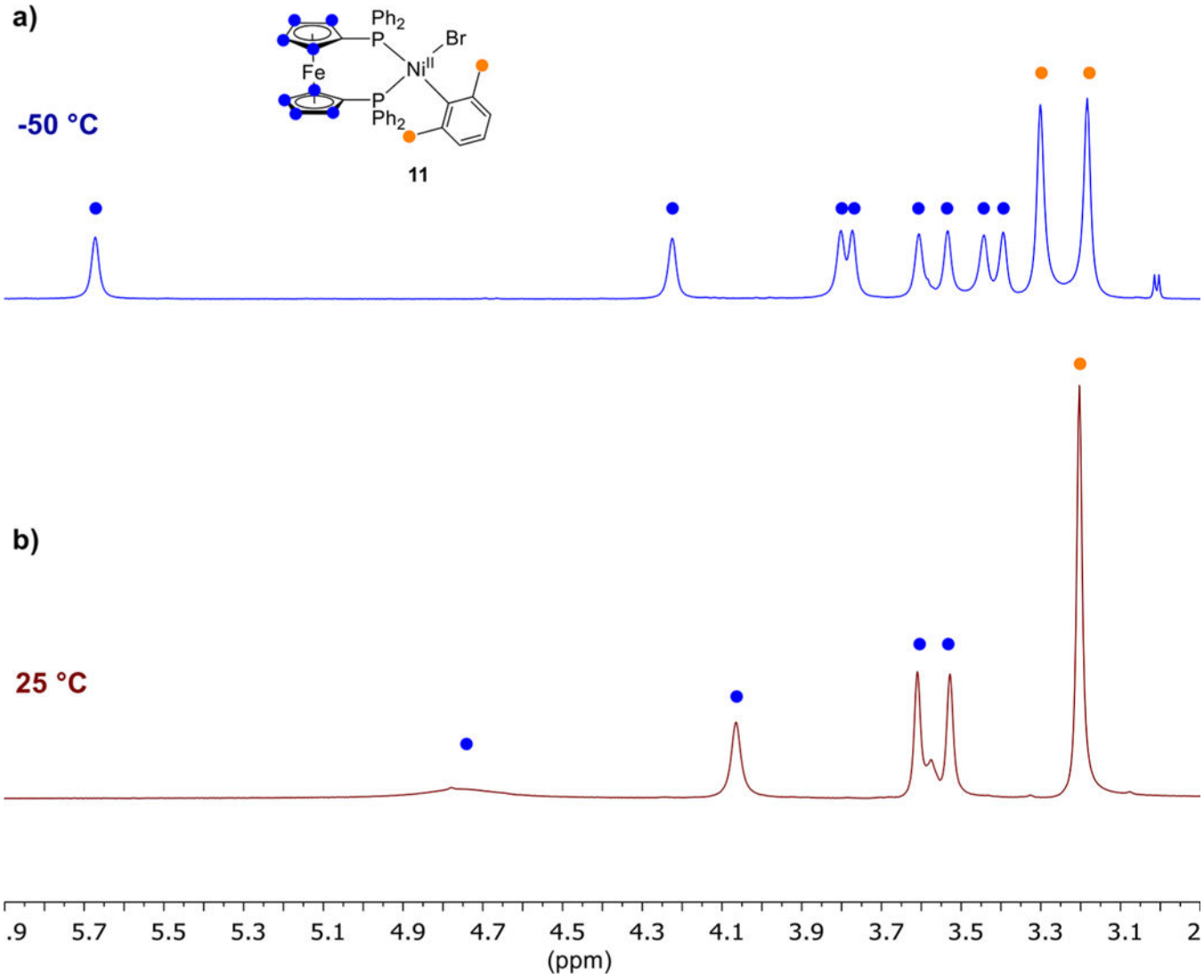


Figure 2.

^{1}H NMR spectra of the region containing the cyclopentadienyl resonances for precatalyst **11** at (a) 25 °C and (b) −50 °C.

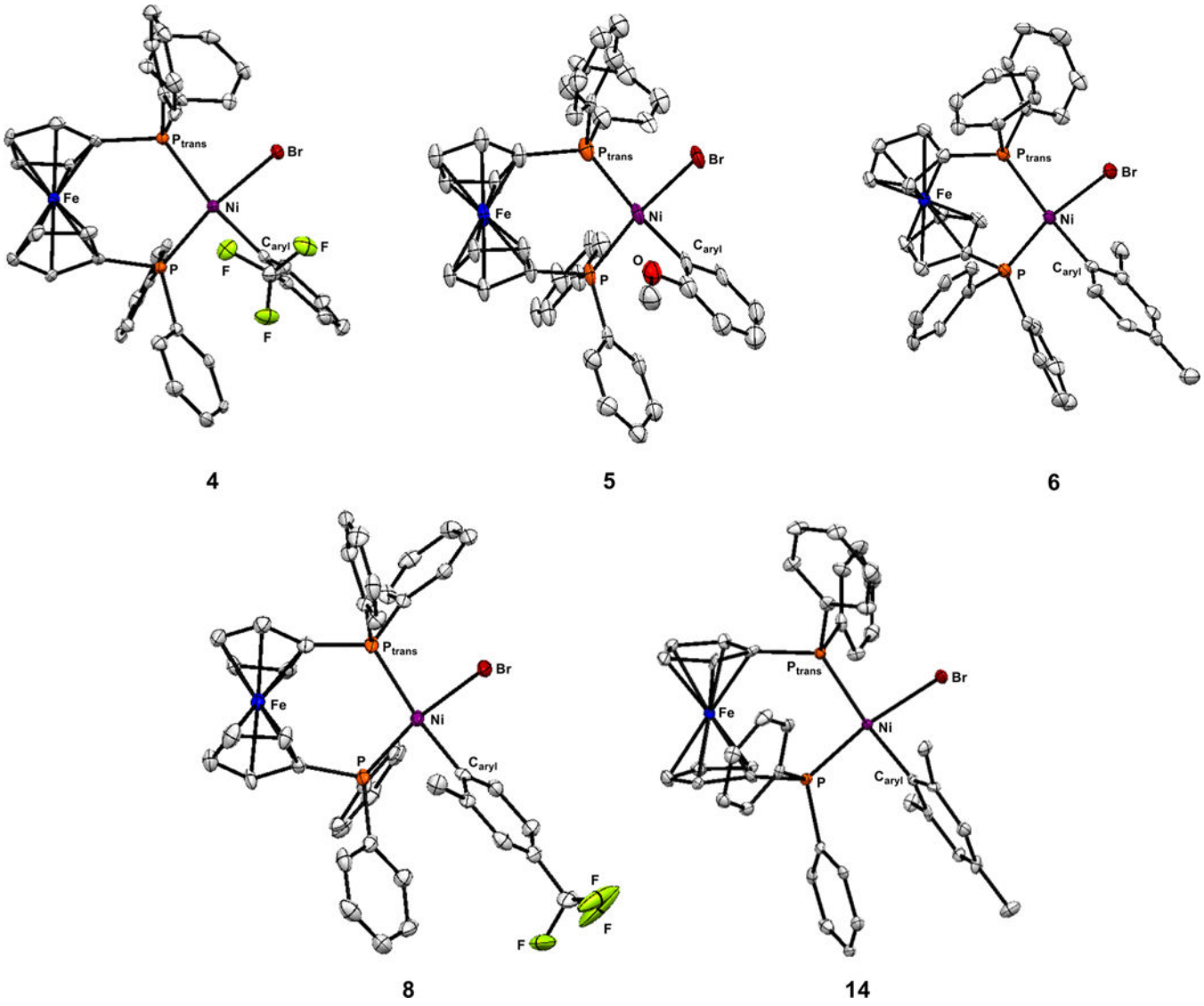


Figure 3.

ORTEP drawings of **4, 5, 6, 8,** and **14.** Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms and solvent of crystallization have been omitted for clarity. Only one of the structures is shown in the case of **5,** in which there are two independent molecules in the unit cell.

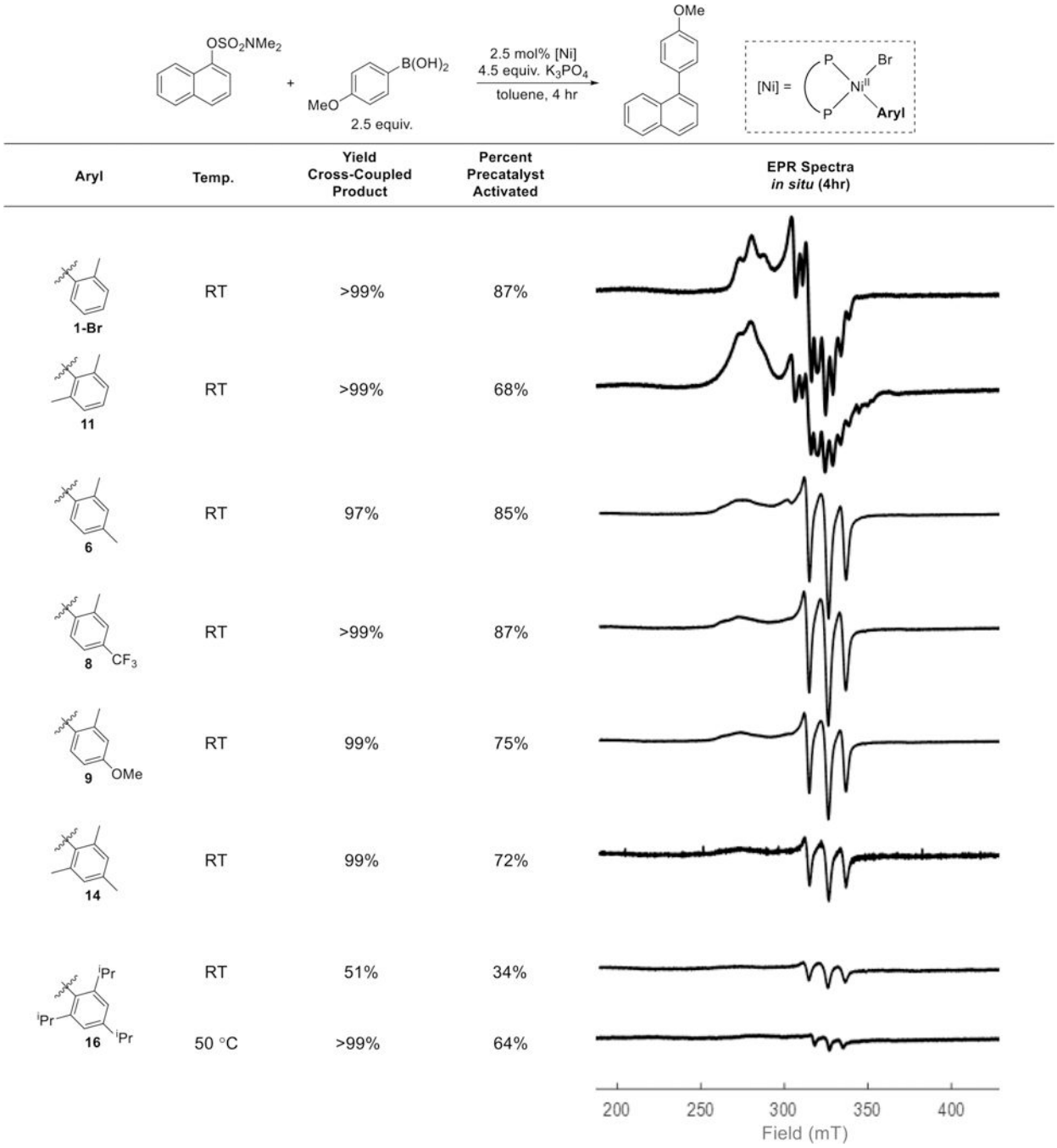
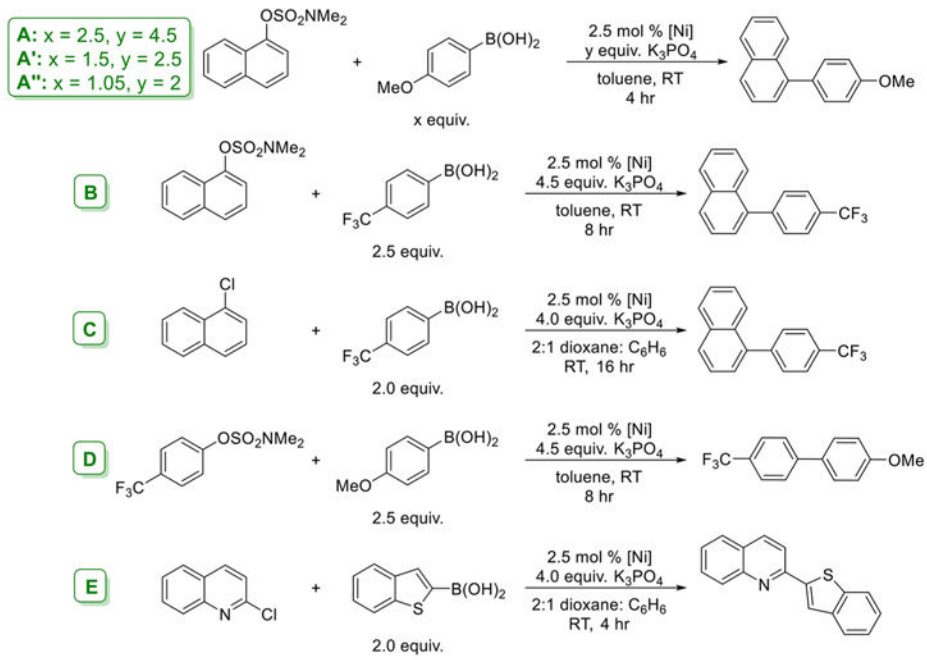


Figure 4.

Yields and in situ low-temperature, X-band EPR spectra for the reaction of naphthalen-1-yl sulfamate with 4-methoxyphenylboronic acid catalyzed by precatalysts of the form (dppf)Ni^{II}(aryl)(Br).

a)



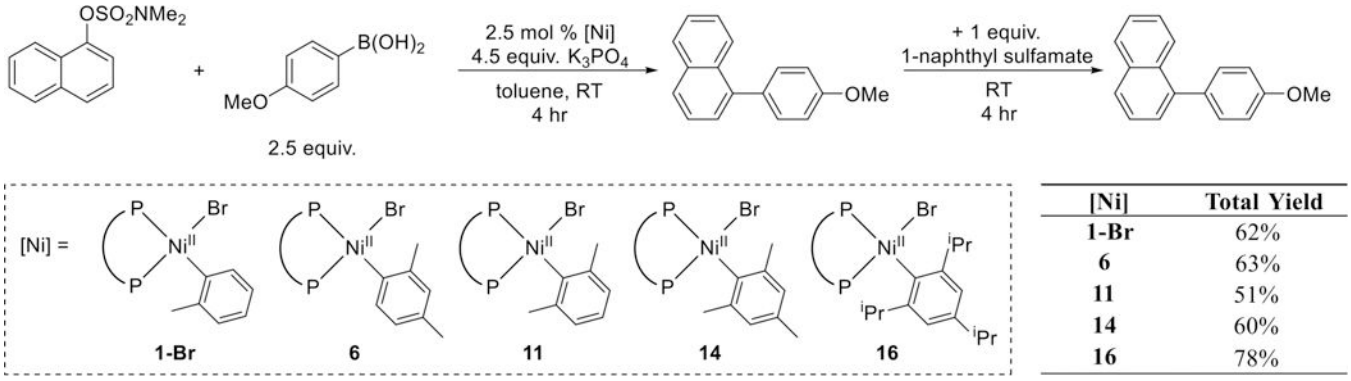
b)

Precatalyst	Aryl Group	Reaction A	A'	A''	B	C	D	E
1-Cl	*o*-tolyl	100	92	68	57	62	53	38
1-Br	*o*-tolyl	100	84	69	63	53	44	35
2	1-naphthyl	99	90	83	71	65	23	34
3	2-ethylPh	99	90	71	58	71	36	33
4	2-CF_3Ph	92	89	74	62	64	43	30
5	2-OMePh	90	91	82	30	71	30	30
6	2,4-xylyl	97	92	68	69	59	36	35
7	2-Me-4-NO_2Ph	5	0	0	15	0	0	30
8	2-Me-4-CF_3Ph	100	89	70	66	53	42	26
9	2-Me-4-OMePh	99	94	80	2	70	36	35
10	2-Me-5-CF_3Ph	100	93	84	71	63	37	35
11	2,6-xylyl	99	87	75	50	70	39	30
12	2-CF_3-6-MePh	43	13	19	15	7	3	26
13	2,6-Me-4-FPh	99	80	70	53	82	27	32
14	mesityl	99	85	74	46	85	42	32
15	2,6-Me-4-OMePh	99	86	89	15	71	42	24
16	2,4,6-$^{i}Pr_3$Ph	51	4	3	8	0	0	31

Key
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

Figure 5.

(a) Reactions screened in this work. (b) Heat map of cross-coupled product yield as a function of precatalyst and reaction screened. The values in the cells correspond to GC yields of cross-coupled product, reported as the average of at least two runs. The variability between runs was typically between 0 and 10%. Specific conditions for each reaction are provided in the Supporting Information.



[Ni]	Total Yield
1-Br	62%
6	63%
11	51%
14	60%
16	78%

Figure 6.

Yield of cross-coupled product for catalytic reactions in which reaction A was spiked with additional electrophile after 4 h. Reaction conditions: 0.133 mmol of naphthalen-1-yl sulfamate, 0.333 mmol of 4-methoxyphenylboronic acid, 0.599 mmol of K_3PO_4, 0.00333 mmol of precatalyst, 0.0665 mmol of naphthalene (internal standard), 1 mL of toluene. Catalysis was run for 4 h, after which another 0.133 mmol of naphthalen-1-yl sulfamate in 500 μL of toluene was added. Reactions were run in duplicate, and yields are reported as the average of two runs. Yields are reported relative to the total amount of electrophile added to the reaction.

Table 1.

Selected Bond Lengths and Angles of the Crystallized Precatalysts

Species	Ni−C_{aryl}(Å)	Ni−P_{trans}(Å)	P−Ni−P (deg)
1-Cl[a]	1.922(10)	2.2874(3)	102.02(1)
4	1.897(6)	2.2564(17)	101.39(6)
5[b]	1.896(18), 1.898(17)	2.274(6), 2.263(5)	100.08(19), 100.09(19)
6	1.890(7)	2.278(2)	102.54(8)
8	1.891(9)	2.280(3)	101.77(10)
14	1.906(6)	2.2460(17)	100.11(6)
16[c]	1.960(7)	2.290(2)	99.81(8)

[a]Data obtained from ref 17.

[b]Two sets of geometric parameters are included because there are two independent molecules in the unit cell.

[c]Data obtained from ref 19.