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Microwave-Assisted Heterogeneous Cross-Coupling Reactions Catalyzed by Nickel-in-Charcoal (Ni/C)

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Dedicated to Professor Harry H. Wasserman on the occasion of his 85th birthday

Abstract: A study involving the relatively rare combination of heterogeneous catalysis conducted under microwave conditions is presented. Carbon–carbon bond formation, including Negishi and Suzuki couplings, can be quickly effected with aryl chloride partners by using a base metal (nickel) adsorbed in the pores of activated charcoal. Aminations were also studied, along with cross-couplings of vinyl alanes with benzylic chlorides as a means to stereodefined allylated aromatics. Reaction times for all these processes are typically reduced from several hours to minutes in a microwave reactor.

Keywords: aryl halides · cross-coupling · heterogeneous catalysis · microwaves · nickel

Introduction

Transition-metal-based heterogeneous catalysis has been broadly embraced by industrial labs, perhaps for obvious reasons.[1] Ease of reaction workup, catalyst removal, recovery, and (often) recycling offer significant economic benefits as well as positive outcomes with regard to environmental issues (Figure 1). Less common, however, are metal-mediated cross-couplings,[2] which have been developed mainly under homogeneous conditions. In other words, the vast majority of carbon–carbon and carbon–heteroatom bond constructions, usually reserved for Group 10 (in particular Ni and Pd) or 11 (mainly Cu) metals, take place in solution rather than on (or within) a solid support. Given the extraordinary popularity of palladium chemistry,[3] documented recently by monumental works such as Negishi's *Handbook of Organopalladium Chemistry*[4a] and Tsuji's updated monograph on this subject[4b] (among other valued contributions), it is curious that relatively few alternatives exist for carrying out these now commonplace reactions in a heterogeneous fashion.[5] Until recently, nickel, an obvious potential alternative with a rich history in organometallics,[6] had no counterpart to, for example, Pd/C as a heterogeneous catalyst. As nickel is a base metal (as opposed to the classification of palladium as a "precious" metal; Figure 2), there is considerable incentive to develop a source of active nickel(0) that could be used in a heterogeneous context in key cross-couplings. This reasoning led us to develop nickel-in-charcoal (Ni/C; Scheme 1),[7] shown to be capable of catalyzing several important reactions (Negishi,[8a] Suzuki,[8b] Kumada,[8c]

Heterogeneous Catalysis	
Benefits:	workup
	recycling
	environment
	economics
Disadvantages:	reaction rates

Figure 1. Benefits and drawbacks of heterogeneous catalysts.

Representative Base Metals	Examples of Precious Metals
Mo, Pb, Al, Zn, Co	Rh, Ir, Pd, Pt
Ni Cu	Ag, Au

Figure 2. Base and precious metals.

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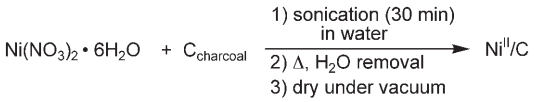


Scheme 1. Formation of nickel-in-charcoal.

amination,[8d] and reduction;[8e] Figure 3) by using aryl chlorides as substrates. Although each reaction type is of reasonable generality and proceeds in synthetically useful yields,

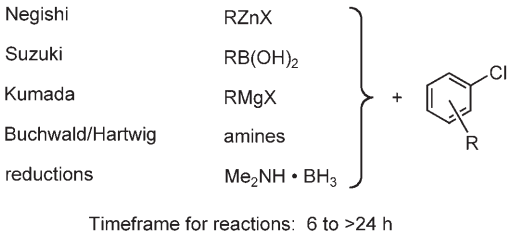


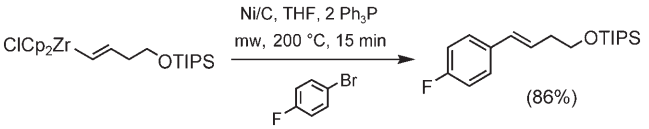
Figure 3. Couplings catalyzed heterogeneously by Ni/C with conventional heating.

reaction rates are lowered relative to the corresponding homogeneous-catalysis versions, as might be expected from their heterogeneous nature. To address this remaining characteristic issue, use of microwave irradiation[9] to thermally enhance reaction rates was considered. To our knowledge, there are no reports on heterogeneous sources of nickel in cross-couplings assisted by microwave conditions.[9d] Herein, the dramatic influence of microwaves on Ni/C-catalyzed reactions is discussed.

Results and Discussion

From the outset, it was far from obvious to us that organometallics commonplace to cross-couplings would tolerate microwave irradiation, a largely thermal phenomenon.[10] Reagents such as organozinc halides and organozirconocenes are rarely utilized in refluxing ethereal or chlorinated media, let alone at the far-higher temperatures (and pressures) attainable in a microwave reactor. Moreover, anticipation that the nickel in our Ni/C would remain impregnated within the charcoal matrix at such thermal extremes had no literature-based support.

Having tested the concept with alkenylzirconocenes derived in situ,[11] which were surprisingly robust in their Ni/C-catalyzed cross-couplings with aryl halides under microwave conditions even at 200 °C (Scheme 2),[12] we studied four additional types of reaction: Negishi couplings with organozinc reagents, Suzuki couplings, aminations, and couplings between benzylic chlorides and vinyl alanes prepared in situ.

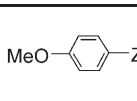
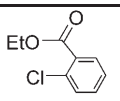
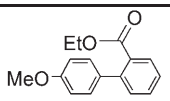
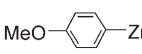
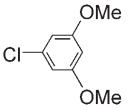
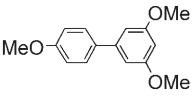
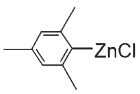
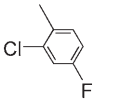
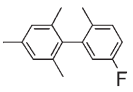
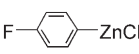
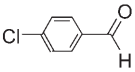
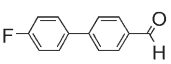
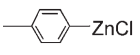
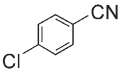
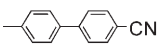
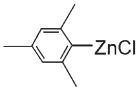
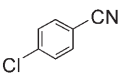
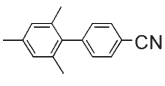
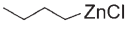
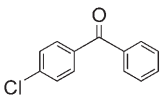
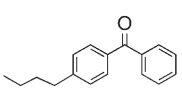
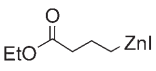
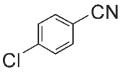
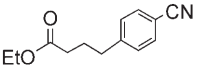


Scheme 2. Ni/C-promoted vinyl zirconocene cross-coupling with aryl halides under microwave irradiation. Cp = cyclopentadienyl, TIPS = triisopropylsilyl, mw = microwave.

Negishi Couplings

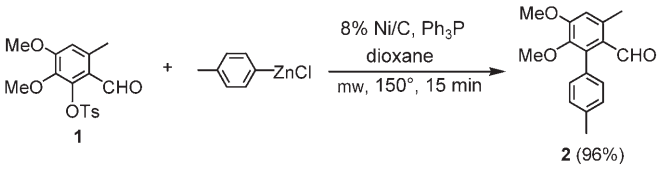
Although organozinc halides tend to be sensitive to moisture and limitations exist regarding their preparation in the presence of some functional groups, they are still among the most useful coupling partners.[13] Indeed, the facility with which they undergo transmetalation from zinc to Group 10 metals leads to enhanced reaction rates under mild (usually room) temperatures. With catalysis by Ni/C,[8a] typical conditions require refluxing THF over a 12–24-h period. Under the influence of microwave irradiation, however, reaction times drop to 15–30 min (Table 1). Most couplings can be effected in the 150–200 °C range, whether involving biaryl formation (Table 1, entries 1–6) or alkyl-substituted aromatics

Table 1. Negishi couplings catalyzed by Ni/C under microwave irradiation.

Entry	Organozinc halide	Aryl chloride	Product	Ni/C [%]/ Ph_3P [%]	t [min]	T [°C]	Yield [%][a]
1				8:30	15	150	94
2				8:40	30	200	75
3				8:30	15	150	90
4				8:30	30	150	80
5				8:30	15	150	95
6				8:30	15	150	95
7				8:30	15	150	91
8				8:30	30	70	85

[a] Isolated, chromatographically purified material. [b] Used 3 equivalents in this reaction.

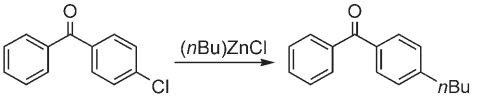
(Table 1, entries 7 and 8). The electronic nature of the zinc reagent appears to play a minor role, as both electron-rich and -poor ArZnCl readily participate. Both activated and deactivated substituted aromatic chlorides afford good yields of biaryls. In addition to the aryl chlorides used in this study, the highly substituted tosylate **1** was also found to react smoothly to give biaryl **2** within 15 min in close to quantitative yield (Scheme 3).



Scheme 3. Ni/C-promoted Negishi coupling under microwave irradiation. Ts = *p*-toluenesulfonyl.

Normally, complete reduction of the catalyst to active Ni^0/C is done by using *n*BuLi in THF at room temperature prior to introduction of the coupling partners. However, we have found that with zinc reagents this is unnecessary, as direct use of Ni^{II}/C in a microwave-assisted coupling (e.g., Table 1, entry 7) gave excellent results under otherwise identical reaction conditions (Table 2). Interestingly, a third alternative that invoked ultrasonication for mixing purposes (no microwave irradiation, with pre-reduced Ni^0/C, bath temperature up to only 40 °C) afforded the same high yield of *n*-butylated product.

Table 2. Study on pre-reduction of Ni^{II}/C in Negishi couplings.

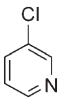
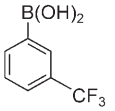
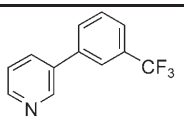
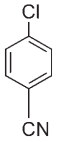
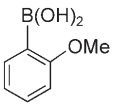
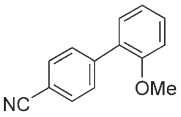
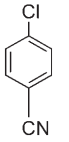
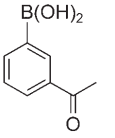
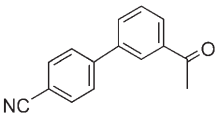
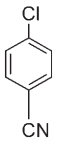
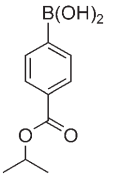
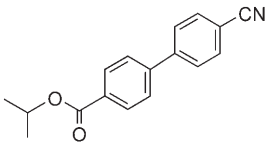
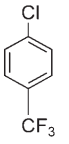
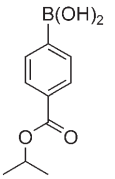
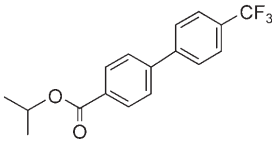
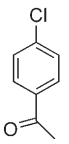
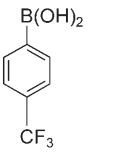
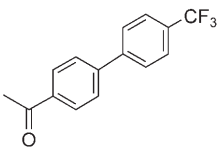
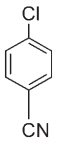
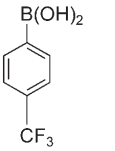
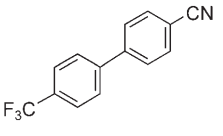


Conditions	Yield [%]
1) Pre-reduced Ni^0, mw, 150 °C, 115 min	91
2) Ni^{II}/C, mw, 150 °C, 115 min	92
3) Ultrasound + Ni^0/C, ≈40 °C, 18 h	95

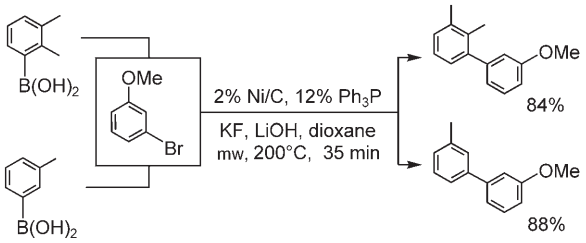
Suzuki Couplings

Owing, in part, to the remarkable tolerance to functionality present in either the aryl boronic acid or aryl halide or pseudohalide, Pd-catalyzed Suzuki couplings are usually regarded as the method of choice for biaryl constructions,[14] especially in the total synthesis of complex molecules.[15] Heterogeneous versions are becoming more popular as new technologies are developed for these and related reactions (e.g., Heck reactions),[16] although reliance on palladium (e.g., Pd/C) is still maintained. These highly valued cross-couplings have also been shown to be subject to Ni/C catalysis (7–10%), employing conventional heating in toluene or dioxane[8b] with reaction times on the order of up to one day. When an aryl boronic acid and aryl

Table 3. Microwave-assisted Ni/C-catalyzed Suzuki couplings.[a]

Entry	Aryl halide	Boronic acid	Product	Base	*t* [min]	*T* [°C]	Yield [%][b]
1				3 equiv KF, 3 equiv LiOH	30	200	90
2				3 equiv KF, 3 equiv LiOH	30	200	91
3				3 equiv KF, 3 equiv LiOH	30	200	86
4				3 equiv KF, 3 equiv LiOH	35	200	81
5				3 equiv KF, 3 equiv LiOH	35	200	80
6				3 equiv KF	40	180	80
7				3 equiv KF, 3 equiv LiOH	30	180	91

[a] Reactions were performed with Ni/C (2%), Ph_3P (12%), and boronic acid (1.5 equiv) in dioxane. [b] Yield of isolated product. [c] With Ni/C (3%). [d] Boronic acid (2 equiv) was used.



Scheme 4. Ni/C-promoted Suzuki coupling of aryl bromides under microwave irradiation.

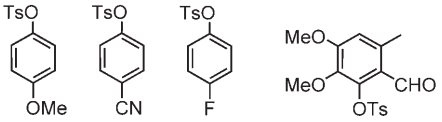


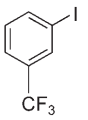
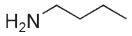
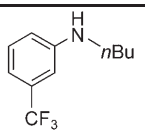
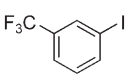
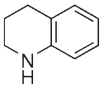
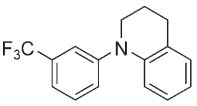
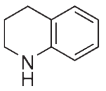
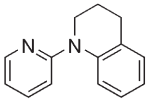
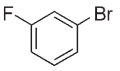
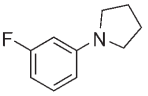
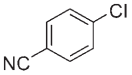
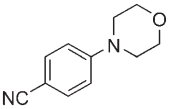
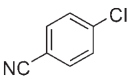
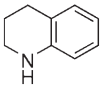
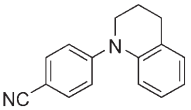
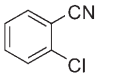
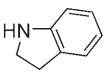
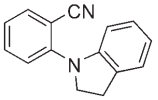
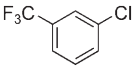
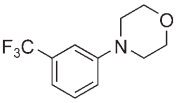
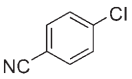
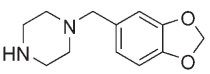
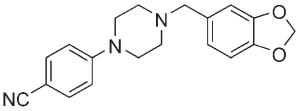
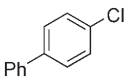
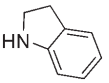
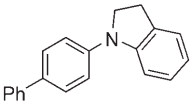
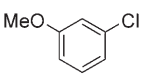
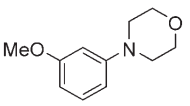
Figure 4. Aryl tosylates that failed to undergo Suzuki-like couplings. Ts = *p*-toluenesulfonyl.

chloride are exposed to microwave heating at 180 °C (Table 3), with only 2 % Ni/C (pre-reduced to Ni^0/C with *n*BuLi), reaction times can be significantly decreased to 40 min or less. The best results are observed when KF (3 equiv) is present, which possibly generates in situ fluoroborate salts as the active species undergoing transmetalation.[17] In most cases, inclusion of LiOH (3 equiv) led to improved levels of conversion. While activated aryl chlorides coupled readily, electron-rich cases were disappointingly not reproducible despite extensive efforts to track the source of the observed highly variable levels of conversion. Switching to the corresponding bromide (Scheme 4) gave clean biaryl couplings in good yields. As with the Negishi reaction (Scheme 3), aryl tosylates were examined (Figure 4). In all cases, even at 200 °C and independent of the substitution pattern on the ring (i.e., activating or not), little or no coupling (< 20 %) was observed; the recovered mass was mainly the starting tosylate. Use of KF in the absence of LiOH also led to low levels of conversion. These unexpected results, however, may present unique opportunities to use Ni/C for substitutions of halides, while tosylates (and mesylates) may then, in tandem, be susceptible to nickel-on-graphite-catalyzed chemistry.[18]

Aminations

As illustrated in Table 4, the combination of Ni/C and microwave irradiation can be very effective for generating aryl amines from precursor iodides (Table 4, entries 1 and 2),

Table 4. Aminations of aryl halides catalyzed by Ni/C under microwave irradiation.[a]

Entry	Aryl halide	Amine	Product	Ni/dppf[b]	*t* [min]	Yield [%][c]
1				5:2.5	10	80
2				5:2.5	10	88
3				5:2.5	15	91
4				5:2.5	10	92
5				10:5	10	95
6				10:5	10	84
7				10:5	10	92
8[d]				10:5	15	82
9				10:5	15	89
10				10:5	20	91
11				10:10	40	86

[a] Reactions were performed in dioxane at 200 °C. [b] Mol % with respect to substrate; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene. [c] Yield of isolated product. [d] Performed in toluene at 200 °C.

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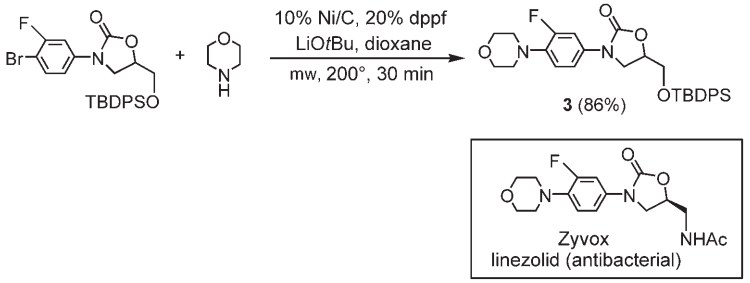
bromides (Table 4, entries 3 and 4), and chlorides (Table 4, entries 5–11). As anticipated, activated chlorides reacted most rapidly (within 15 min; Table 4, entries 5–9), while less-activated (Table 4, entry 10) or electron-rich (Table 4, entry 11) substrates took up to 40 min to reach completion of reaction. In the absence of catalyst, no amination took place. Aryl chlorides required 10% Ni/C, whereas bromides and iodides reacted to completion with half this amount of catalyst. Only in the case of *m*-chloroanisole (Table 4, entry 11) was an additional ligand (dppf) relative to Ni/C needed: a 1:1 rather than 1:0.5 ratio was essential. Substrate concentration is also an important variable; the optimum concentration to achieve rapid and complete conversion while maintaining safety requirements is 0.33 M (see below). Pre-reduction of the Ni^{II}/C with *n*BuLi at room temperature is necessary prior to amination. Prior work[8d] had shown that under conventional conditions over time, in situ conversion of Ni^{II}/C to active Ni^{0}/C occurs. However, the shortened reaction time in the microwave vial allows for only about 25% conversion (e.g., Table 4, entry 5). At 200 °C, use of either dioxane or toluene as solvent led to similar results. These data parallel earlier findings realized under conventional refluxing conditions,[8d] except for reaction times, which previously took several hours or even days with deactivated substrates. This cross-coupling technology can be applied to the preparation of trisubstituted aromatic **3**, a precursor to the oxazolidinone antibacterial linezolid,[19] in good yield within 30 min in a microwave reactor (Scheme 5).



Scheme 5. Ni/C-promoted amination reaction resulting in a precursor to linezolid. TBDPS = *tert*-butyldiphenylsilyl.

Aryl chlorides that bear aldehyde, ketone, and ester functionalities (e.g., **4**–**6**; Figure 5) are incompatible with the amines used in this high-temperature coupling, presumably due to the presence of electrophilic centers. Each educt was consumed, although none of the desired aniline could be detected.

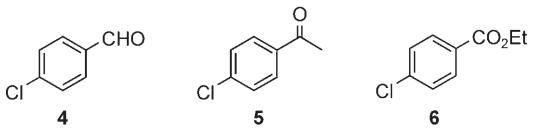
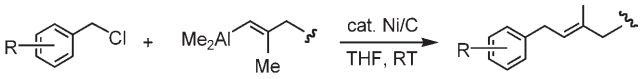


Figure 5. Substrates that are incompatible with Ni/C-catalyzed aminations.

Benzylic Chlorides and Vinyl Alanes

In a previous study, we showed that Ni/C is a viable catalyst for bond construction between a variety of benzylic chlorides and vinylalanes formed in situ from alkynes through Negishi carboalumination (Scheme 6).[20] Although these

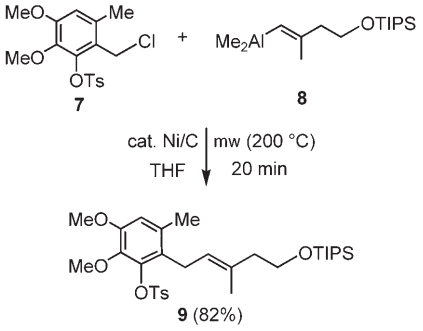


Scheme 6. Ni/C-promoted cross-coupling of benzylic chlorides with vinyl alanes.

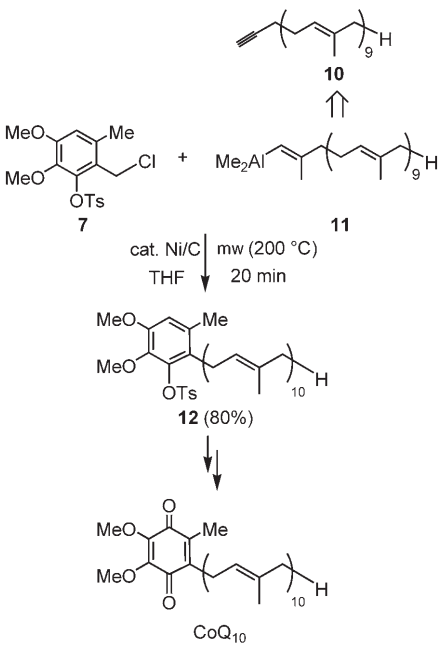
couplings proceeded at ambient temperatures (0.33 M in THF) and in high yields, times on the order of 10–15 h were to be expected. In the light of the potential for Ni/C catalysis to serve as mediator of this key coupling reaction en route to coenzyme Q_{10} (CoQ_{10}),[21] an effort was made to hasten these couplings. Microwave irradiation applied to the reaction between the tailor-made CoQ_{10}-related educt **7**[22] and model vinyl alane **8** led to rapid formation of product **9** in good yield (Scheme 7). Under identical conditions, the "real" coupling partner **11**, derived from alkyne **10**,[23] underwent conversion to the fully fashioned CoQ_{10} precursor **12** in 80% yield (Scheme 8). Subsequent two-step processing to arrive at the increasingly important dietary supplement CoQ_{10} (removal of Ts with *n*BuLi followed by [Co(salen)]-catalyzed autoxidation; salen = *N*,*N*′-ethylenebis-(salicylideneiminato)) is well-established.[24]

Sample Manipulation for Microwave Reactor

All reactions were performed in microwave vials that fit the chamber of an Emrys Optimizer.[25] They required proper handling to maximize conversion given their heterogeneous



Scheme 7. Ni/C-promoted coupling resulting in a CoQ_{10}-related adduct. Yield quoted is of isolated product.



Scheme 8. Ni/C-promoted coupling of "real" CoQ_{10} educts and subsequent conversion to the natural product. Yield quoted is of isolated product.

state. Each vial contained a magnetic stirrer bar; however, the effectiveness was variable depending on the nature and amount of additives present. Thus, although conventional heating at reflux maintains all solids within a solvent-bathed reaction mixture, this may not be the case (at least initially) in a microwave experiment. For solid materials visible above the solvent level, they are likely not to be involved in the desired chemistry. Moreover, since the magnetron emits microwave radiation that can be absorbed directly by solids (e.g., salts) situated above a reaction medium, overheating can easily occur, leading to generation of pinhole(s) within the glass vessel and, therefore, leakage. In extreme cases the vials can crack or even shatter. By covering all solids simply through the expedient adding of solvent to wash down the sides of the vial, these potential pitfalls are averted. Figure 6a illustrates the appearance of a representative Ni/C-catalyzed reaction mixture, while Figure 6b shows an insufficient volume of solvent present and the protruding solids. These factors played a major role in our choice of conditions for the Ni/C-catalyzed Suzuki cross-couplings described herein (see above). Thus, rather than using bases of higher molecular weight such as K_3PO_4, along with salts such as

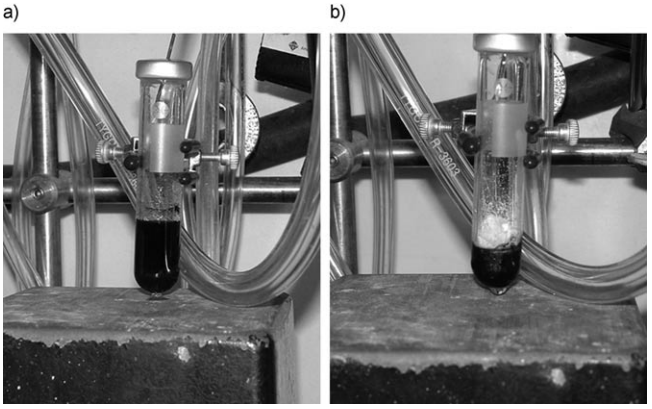
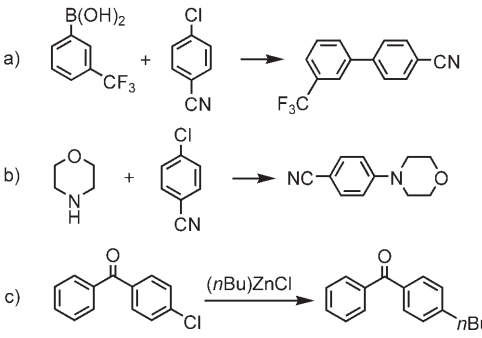


Figure 6. a) Properly prepared reaction mixture with all solids covered by solvent; b) insufficient solvent volume leaving solids exposed.

LiBr to decrease homocoupling, alternative (lower-weight) combinations such as KF/LiOH were developed.

ICP-AES Analyses of Nickel Bleed: Conventional versus Microwave Reactions

To investigate the extent of nickel bleed from the solid support under conditions of microwave irradiation, inductively coupled plasma-atomic emission spectrometry (ICP-AES) analyses[26] were applied to a representative Suzuki cross-coupling (Scheme 9a). With each analysis run in duplicate, the data (Table 5) obtained upon completion of the reaction followed by filtration establish that only 0.24% of the nickel (2%) used in the reaction was in solution. This corresponds to a substrate/nickel ratio in solution of >20000:1, which is



Scheme 9. ICP-AES analyses of a) Suzuki coupling, b) amination, and c) Negishi coupling.

Table 5. ICP-AES data for reactions performed under microwave versus conventional heating conditions.

	Ni/C (microwave irradiation)						Ni/C (conventional heating)				
Reaction	Ni [ppm]	Trial 1 [μg Ni]	Trial 2 [μg Ni]	Average [μg Ni]	Average % Ni of Ni/C in solution	Reaction	Ni [ppm]	Trial 1 [μg Ni]	Trial 2 [μg Ni]	Average [μg Ni]	Average % Ni of Ni/C in solution
1	0.0296	1.10	1.94	1.52	0.24	1	0.1186	6.96	5.25	6.11	0.94
2	0.2781	14.37	16.18	15.28	0.35	2	0.8456	41.16	45.92	43.56	1.00
3	0.7298	24.93	42.31	33.62	0.57	3	0.9009	45.68	47.43	46.56	1.06
Ni/C + base	–	0.01	0.42	–	0.01	Ni/C + base	–	0.01	0.72	–	0.02

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far below the amount of nickel necessary for this reaction to proceed. The same reaction performed with conventional heating (analyses again run in duplicate) showed that leaching was also minimal (0.94%), but approximately four times greater than under microwave irradiation (corresponding to a substrate/nickel ratio of >5300:1). This unforeseen result led us to question whether the same trend would be observed with aromatic aminations (Scheme 9b). Results similar to the Suzuki cross-couplings were indeed found, indicating that aromatic aminations under conventional heating conditions afforded approximately three times more leaching of nickel into solution than with the corresponding microwave-assisted method. Nonetheless, the leaching in each case is still quite low (0.35% of the nickel (10%) used in the microwave, 1% of the nickel (10%) used under conventional heating conditions).[27]

For the Negishi cross-coupling reaction (Scheme 9c), heating under conventional reaction conditions led to twice as much leaching as the microwave-irradiated process (1.06% vs. 0.57%), in line with the trend. The control reaction, in the absence of coupling partners, suggested that although the level of bleed was extremely low, conventional heating led to twice as much leached nickel in solution compared to microwave heating (0.02% vs. 0.01%). Thus, under microwave-irradiation conditions, the much-shorter times are likely due to higher reaction temperatures and not a result of greater amounts of leached nickel into the macroscopic medium. It therefore appears that these heterogeneous Ni/C-catalyzed cross-couplings that employ microwave irradiation not only proceed significantly faster than conventionally heated reactions, but also result in lower levels of metal bleed from the charcoal.

Handling and Safety of Ni/C

The reagent as prepared from commercially available activated charcoal and $Ni(NO_3)_2$ is routinely stored in an inert atmosphere to maximize shelf life, which is on the order of several months. Exposure to air over time decreases activity, even after reduction to the more active Ni^0 state. The reagent that has been reduced to presumably Ni^0/C, as is true for Ni^{II}/C, remains intact when left open in air for short periods of time, suggesting that neither is pyrophoric to any extent. Ni^0/C also tested negative for shock sensitivity.

Summary and Outlook

Nickel-in-charcoal (Ni/C) when used in a conventional sense is an inexpensive and effective heterogeneous catalyst for several types of C–C and C–heteroatom cross-coupling reactions, but heat applied in the form of microwave irradiation has been found to enhance greatly the rates of these processes. Although conducted on a relatively small scale (i.e., milligrams), recent advances in microwave technology have led to reactors that are capable of larger-volume reactions under fully controlled, safe conditions (e.g., Advancer, Biotage). Thus, heterogeneous catalysis by Ni/C together with microwaves can be considered a plausible combination for bond construction at both the discovery and process development levels.

Experimental Section

General

Reactions were performed in oven-dried glassware with a teflon-coated stirrer bar and dry septum under argon atmosphere. THF and 1,4-dioxane were freshly distilled from Na/benzophenone ketyl prior to use. Ni/C was stored and weighed out as a black powder in a glove box. All coupling reagents were obtained commercially and used as received. All microwave experiments were performed with a Personal Chemistry (now Biotage) Emrys Optimizer in pyrex reaction vessels (2–5 mL) that were flame-dried under argon atmosphere. Each contained a teflon stirrer bar and teflon-coated reaction vessel cap. ICP-AES analyses were performed on a Thermo Jarrell Ash IRIS plasma spectrometer. GC analyses were carried out with an HP-5 capillary column (0.25 μm, $\xi = 30$ m; cross-linked 5% PH ME siloxane) and a time program beginning with 5 min at 50 °C, followed by a ramp at 20 °C min^{-1} to 280 °C, then 20 min at this temperature. Column chromatography was performed with Davisil Grade 633 Type 60 A silica gel. TLC analyses were performed on commercial Kieselgel 60 F_{254} silica-gel plates. NMR spectra were obtained on Varian Inova systems using $CDCl_3$ as solvent, with proton and carbon resonances at 400 and 100 MHz, respectively. FTIR spectra were obtained on an ATI Mattson Infinity series spectrometer with neat samples on NaCl plates and are reported in cm^{-1}. Mass-spectral data were acquired on a VF Autospec or an analytical VG-70–250 HF instrument.

Preparation of Ni^{II}/C

Darco KB (100 mesh) activated carbon (5.00 g, 25% H_2O content) was added to a 100 mL round-bottomed flask containing a stirrer bar. A solution of $Ni(NO_3)_2 \cdot 6H_2O$ (727 mg, 2.30 mmol; Aldrich catalogue #24,407-4; Ni content by ICP determination: 92%) in deionized H_2O (35 mL) was added to the activated carbon, and deionized H_2O (40 mL) was added to wash down the sides of the flask. The flask was purged under argon, the contents stirred vigorously for 1 min, then the flask was submerged in an ultrasonic bath under a positive argon flow for 30 min. The flask was then attached to an argon-purged distillation setup and placed in a preheated (175–180 °C) sand bath over a stir plate. As the distillation ended, the flask temperature rose automatically but was held below 210 °C for a further 15 min. Upon cooling to room temperature, the black solid was washed with H_2O (2×50 mL) under argon into a pre-dried evacuated course-fritted funnel (150 mL). The H_2O used to wash the Ni/C was removed by rotary evaporation and analyzed for any remaining nickel. The fritted funnel was turned upside down under vacuum for 3 h until the Ni/C fell from the frit into the collection flask. The collection flask was then dried in vacuo at 100 °C for 18 h. Using these specific amounts, all of the nickel was mounted onto the support, which corresponds to 0.552 mmol Ni^{II}/g catalyst, or 3.2% Ni/catalyst by weight.

Representative Procedure for Ni/C-Catalyzed Negishi Coupling

(4-butylphenyl)phenylmethanone (Table 1, entry 7): Ni^{II}/C (135 mg, 0.08 mmol, 0.59 mmol g)$^{-1}$ and PPh_3 (78 mg, 0.30 mmol) were added to a flame-dried Biotage process vial (2–5 mL) under argon at room temperature. Dry dioxane (1 mL) was added by syringe, and the slurry was stirred for 20 min. *n*-Butyllithium (62 μL, 2.5 M in hexanes, 0.16 mmol) was then added dropwise with swirling. After 5 min, 4-chlorobenzophenone (216 mg, 1.0 mmol) in THF and *n*-butylzinc chloride (1.50 mmol, in dry THF) were added by cannula. The resulting heterogeneous mixture was then heated in an Emrys Optimizer with the following settings: temperature: 150 °C, time: 900 s, fixed hold time: on, sample absorption: normal, pre-stirring: 10 s. After cooling to room temperature, the crude reaction mixture was filtered through celite, and the filter cake was further rinsed with ethyl acetate. The filtrate was collected, the solvent was removed

with a rotary evaporator, and the residue was purified by flash chromatography on silica gel with hexanes/EtOAc (9:1) to yield the pure product (216 mg, 91%) as an oil. The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with spectral data already reported.[28]

Procedure for Ni^{II}/C-Catalyzed Negishi Coupling without Prior Reduction of Ni/C

(4-butylphenyl)phenylmethanone: Ni^{II}/C (135 mg, 0.08 mmol, 0.59 mmol g)$^{-1}$ and PPh_3 (78 mg, 0.30 mmol) were added to a flame-dried Biotage process vial (2–5 mL) under argon at room temperature. Dry dioxane (1 mL) was added by syringe, and the slurry was stirred for 20 min. 4-Chlorobenzophenone (216 mg, 1.0 mmol) in THF and *n*-butylzinc chloride (1.50 mmol, in dry THF) were added by cannula. The resulting heterogeneous mixture was then heated in an Emrys Optimizer with the following settings: temperature: 150 °C, time: 900 s, fixed hold time: on, sample absorption: normal, pre-stirring: 10 s. After cooling to room temperature, the crude reaction mixture was filtered through celite, and the filter cake was further rinsed with ethyl acetate. The filtrate was collected, the solvent was removed with a rotary evaporator, and the residue was purified by flash chromatography on silica gel with hexanes/EtOAc (9:1) to yield the pure product (218 mg, 92%) as an oil.

Representative Procedure for Ni/C-Catalyzed Negishi Coupling with Ultrasonication

(4-butylphenyl)phenylmethanone: Ni^{II}/C (135 mg, 0.08 mmol, 0.59 mmol g)$^{-1}$ and PPh_3 (78 mg, 0.30 mmol) were added to a flame-dried Biotage process vial (2–5 mL) under argon at room temperature. Dry dioxane (1 mL) was added by syringe, and the slurry was stirred for 20 min. *n*-Butyllithium (62 μL, 2.5 M in hexanes, 0.16 mmol) was then added dropwise with swirling. After 5 min, 4-chlorobenzophenone (216 mg, 1.0 mmol) in THF and *n*-butylzinc chloride (1.50 mmol, in dry THF) were added by cannula. The resulting heterogeneous mixture was then subjected to ultrasonication for 18 h. The crude reaction mixture was filtered through celite, and the filter cake was further rinsed with ethyl acetate. The filtrate was collected, the solvent was removed with a rotary evaporator, and the residue was purified by flash chromatography on silica gel with hexanes/EtOAc (9:1) to yield the pure product (226 mg, 95%) as an oil.

4′-Methoxybiphenyl-2-carboxylic acid ethyl ester (Table 1, entry 1): The representative procedure was used with 2-chlorobenzoic acid ethyl ester (184 mg, 1.0 mmol) and 4-methoxyphenylzinc chloride (1.50 mmol, in dry THF). The pure product (240 mg, 94%) was obtained as an oil after flash chromatography on silica gel with hexanes/EtOAc (9:1). IR: $\tilde{\nu}$= 2979, 1714, 1610, 1517, 1282, 1047, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.89 (d, J=7.6 Hz, 1H), 7.51 (t, J=7.6 Hz, 1H), 7.40–7.35 (m, 2H), 7.25 (d, J=6.4 Hz, 2H), 6.93 (d, J=6.8 Hz, 2H), 4.12 (q, J=6.8 Hz, 2H), 3.85 (s, 3H), 1.06 ppm (t, J=8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 169.3, 159.2, 142.1, 134.0, 131.5, 131.3, 130.9, 129.8, 127.7, 127.0, 113.7, 61.2, 55.5, 14.1 ppm; MS (EI): *m/z* (%): 257 (17), 256 (100), 212 (11), 211 (69), 168 (16), 140 (10), 139 (17); HRMS: calcd for $C_{16}H_{16}O_3$: 256.1099; found: 256.1095.

3,5,4′-Trimethoxybiphenyl (Table 1, entry 2): The representative procedure was used with PPh_3 (104 mg, 0.4 mmol), 5-chloro-1,3-dimethoxybenzene (172 mg, 1 mmol), and 4-methoxyphenylzinc chloride (3.0 mmol, in dry THF). Temperature: 200 °C, time: 1800 s. The pure product (183 mg, 75%) was obtained as an oil after flash chromatography on silica gel with hexanes/EtOAc (9:1). IR: $\tilde{\nu}$= 3053, 2935, 2839, 1598, 1515, 1504, 1253, 1041, 1029, 825, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.25 (d, J=8 Hz, 2H), 6.98 (d, J=8 Hz, 2H), 6.70 (d, J=2.4 Hz, 2H), 6.44 (t, J= 2.4 Hz, 1H), 3.85 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 161.2, 159.5, 143.3, 133.9, 128.4, 114.3, 105.3, 98.9, 55.6, 55.6 ppm; MS (EI): *m/z* (%): 245 (15), 244 (100), 229 (10); HRMS (EI): calcd for $C_{15}H_{16}O_3$: 244.1099; found: 244.1105.

5′-Fluoro-2,4,6,2′-tetramethylbiphenyl (Table 1, entry 3): The representative procedure was used with 2-chloro-4-fluorotoluene (144 mg, 1.0 mmol) and 2,4,6-trimethylphenylzinc chloride (1.50 mmol, in dry THF). The pure product (205 mg, 90%) was obtained as an oil after flash chromatography on silica gel with hexanes/EtOAc (9:1). IR: $\tilde{\nu}$= 2920, 1612, 1587, 1479, 1167, 877 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.22 (t, J=2.4 Hz, 1H), 6.97–6.94 (m, 3H), 6.75 (dd, J=7.2, 2.8 Hz, 1H), 2.34 (s, 3H), 1.93 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 161.5 (d, J= 242.8 Hz), 142.5, 137.4, 137.0, 135.7, 131.8, 131.3, 128.3, 116.0 (d, J= 20.5 Hz), 113.80 (d, J=20.5 Hz), 21.26, 20.93, 18.84 ppm; MS (EI): *m/z* (%): 229 (15), 228 (92), 214 (16), 213 (100), 198 (25), 197 (20), 196 (14), 183 (21); HRMS: calcd for $C_{16}H_{17}F$: 228.1314; found: 228.1313.

4′-Fluorobiphenyl-4-carbaldehyde (Table 1, entry 4): The representative procedure was used with 4-chlorobenzaldehyde (140 mg, 1.0 mmol) and 4-fluorophenylzinc chloride (1.50 mmol, in dry THF). The pure product (160 mg, 80%) was obtained as an oil after flash chromatography on silica gel with hexanes/EtOAc (9:1). IR: $\tilde{\nu}$= 3026, 3043, 2850, 2754, 1703, 1604, 1566, 1519, 1494, 1228, 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 10.06 (s, 1H), 7.95 (d, J=8 Hz, 2H), 7.10 (d, J=8 Hz, 2H), 7.63–7.59 (m, 2H), 7.18 ppm (t, J=8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 190.0, 163.3 (d, J=247.3 Hz), 146.3, 136.1, 135.4, 130.5, 129.3 (d, J=7.6 Hz), 127.7, 116.2 ppm (d, J=21.3 Hz); MS (EI): *m/z* (%): 201 (13), 200 (100), 199 (93), 172 (10), 171 (36), 170 (46), 85 (10); HRMS (EI): calcd for $C_{13}H_9F$: 200.0637; found: 200.0632.

4′-Methylbiphenyl-4-carbonitrile (Table 1, entry 5): The representative procedure was used with 4-chlorobenzonitrile (137 mg, 1.0 mmol) and 4-methylphenylzinc chloride (1.50 mmol, in dry THF). The pure product (183 mg, 95%) was obtained as an oil after flash chromatography on silica gel with hexanes/EtOAc (9:1). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with spectral data already reported.[29]

2′,4′,6′-Trimethylbiphenyl-4-carbonitrile (Table 1, entry 6): The representative procedure was used with 4-chlorobenzonitrile (137 mg, 1.0 mmol) and 2,4,6-trimethylphenylzinc chloride (1.50 mmol, in dry THF). The pure product (209 mg, 95%) was obtained as an oil after flash chromatography on silica gel with hexanes/EtOAc (9:1). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with spectral data already reported.[30]

4-(4-Cyanophenyl)butyric acid ethyl ester (Table 1, entry 8): The representative procedure was used with 4-chlorobenzonitrile (137 mg, 1.0 mmol) and ethoxycarbonylpropylzinc iodide (1.50 mmol, in dry THF). Temperature: 70 °C. The pure product (184 mg, 85%) was obtained in an oil after flash chromatography on silica gel with hexanes/EtOAc (7:3). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with spectral data already reported.[30]

2: The representative procedure was used with Ni/C (38.5 mg, 0.022 mmol, 0.59 mmol g^{-1}), Ph_3P (18.5 mg, 0.09 mmol), toluene-4-sulfonic acid 2-formyl-5,6-dimethoxy-3-methylphenyl ester (100 mg, 0.29 mmol), and 4-methylphenylzinc chloride (1.50 mmol, in dry THF). The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (8:2) to yield **2** (74 mg, 96%) as a solid. IR: $\tilde{\nu}$= 2927.4, 2765.7, 1681.8, 1330.8, 1112.8, 768.9 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 9.64 (s, 1H), 7.23 (d, J=8 Hz, 2H), 7.18 (d, J=8 Hz, 2H), 6.78 (s, 1H), 3.96 (s, 3H), 3.50 (s, 3H), 2.64 (s, 3H), 2.42 ppm (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 193.6, 156.2, 144.5, 142.1, 138.2, 137.7, 131.4, 130.6, 128.9, 126.6, 114.6, 60.9, 56.1, 22.3, 21.6 ppm; MS (EI): *m/z* (%): 271 (18), 270 (100), 169 (29), 255 (38), 254 (16), 240 (13), 127 (14), 115 (10); HRMS: calcd for $C_{17}H_{18}O_3$: 270.1256; found: 270.1256.

Representative Procedure for Ni/C-Catalyzed Suzuki Coupling

3-(3-Trifluoromethylphenyl)pyridine (Table 3, entry 1): Ni^{II}/C (32 mg, 0.02 mmol, 0.59 mmol g^{-1}) and Ph_3P (32.40 mg, 0.12 mmol) were added to a flame-dried Biotage process vial (2–5 mL) under a blanket of argon at room temperature. Dry dioxane (1.0 mL) was added by syringe, and the mixture was allowed to stir for 1 h. *n*-Butyllithium (0.020 μL, 2.55 M in hexanes, 0.05 mmol) was then added dropwise. The mixture was allowed to stir for 5 min while the nickel was reduced. In a second flame-dried, argon-flushed container, potassium fluoride (174 mg, 3.0 mmol), lithium hydroxide (75 mg, 3.0 mmol), and 3-trifluoromethylphenylboronic acid (344 mg, 2.0 mmol) were weighed out under a blanket of argon. The cap of the process vial was removed and the solids in the second container were quickly added to the vial. The cap was replaced and the vial was flushed with argon. 2-Chloropyridine (114 mg, 1.0 mmol, 96.0 μL) was

then added to the vial by syringe. The sides of the vial were rinsed free of solids with dioxane (1.5 mL), and the resulting heterogeneous mixture was heated in an Emrys Optimizer with the following settings: temperature: 200 °C, time: 1800 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After cooling to room temperature, the crude reaction mixture was filtered through celite, and the filter cake was further rinsed with ethyl acetate. The filtrate was collected, the solvent was removed with a rotary evaporator, and the crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (4:1) to yield a pale yellow oil (208 mg, 90 %). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with spectral data already reported.[31]

2′-Methoxybiphenyl-4-carbonitrile (Table 3, entry 2): The representative procedure was used with 4-chlorobenzonitrile (136 mg, 1.0 mmol) and 2-methoxyphenylboronic acid (230 mg, 1.5 mmol), and the reaction mixture was heated for 1800 s at 200 °C. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (6:1) to yield a white solid (175 mg, 84 %). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with spectral data already reported.[32]

3′-Acetylbiphenyl-4-carbonitrile (Table 3, entry 3): The representative procedure was used with 4-chlorobenzonitrile (136 mg, 1.0 mmol) and 3-acetylphenylboronic acid (246 mg, 1.5 mmol), and the reaction mixture was heated for 1800 s at 180 °C. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (5:1) to yield an off-white solid (224 mg, 86 %). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with spectral data already reported.[33]

4′-Cyanobiphenyl-4-carboxylic acid isopropyl ester (Table 3, entry 4): The representative procedure was used with 4-chlorobenzonitrile (136 mg, 1.0 mmol) and 4-isopropoxycarbonylphenylboronic acid (213 mg, 1.5 mmol), and the reaction mixture was heated for 2100 s at 200 °C. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (10:1) to yield a white solid (215 mg, 81 %). R_f = 0.33 (hexanes/ethyl acetate = 10:1); IR (thin film): $\tilde{\nu}$ = 2989, 2225, 1700, 1607, 1282, 1099, 840, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.13 (m, 2H), 7.67–7.73 (m, 4H), 7.62–7.64 (m, 2H), 5.30 (sept, J = 6 Hz, 1H), 1.40 ppm (d, J = 6.4, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 144.5, 143.2, 132.7, 131.0, 130.3, 128.0, 127.2, 118.8, 111.7, 68.7, 22.0 ppm; MS (EI): *m/z* (%): 265 (58), 223 (77), 206 (100), 177 (26), 151 (27), 127 (5), 59 (29); HRMS (EI): *m/z* calcd for $C_{17}H_{15}NO_2$: 265.1109; found: 265.1103.

4′-Trifluoromethylbiphenyl-4-carboxylic acid isopropyl ester (Table 3, entry 5): The representative procedure was used with 4-isopropoxycarbonylphenylboronic acid (312 mg, 1.5 mmol) and 4-chlorotrifluoromethylbenzene (181 mg, 1.0 mmol, 134.0 μL), and the reaction mixture was heated for 1500 s at 200 °C. The crude product was then purified by flash chromatography on silica gel with hexanes/EtOAc (10:1) to yield a clear oil (246 mg, 80 %). R_f = 0.30 (hexanes/ethyl acetate = 10:1); IR (thin film): $\tilde{\nu}$ = 2996, 1708, 1335, 1283, 1167, 1120, 1073, 832, 773, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.16 (m, 2H), 7.73 (br s, 4H), 7.66–7.69 (m, 2H), 5.261 (sept, J = 6 Hz, 1H), 1.41 ppm (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 143.9, 143.7, 130.6, 130.3, 130.1 (q, J = 114.4), 127.7, 127.2, 125.9 (d, J = 16), 124.2 (q, J = 1082.0), 68.7, 22.0 ppm; MS (EI): *m/z* (%): 308 (45), 289 (7), 266 (75), 249 (100), 221 (7), 201 (31), 152 (35), 59 (26); HRMS (EI): *m/z* calcd for $C_{17}H_{15}O_2F_3$: 308.1036; found: 308.1024.

1-(4′-Trifluoromethylbiphenyl-4-yl)ethanone (Table 3, entry 6): The representative procedure was used with 4-trifluoromethylphenylboronic acid (380 mg, 2.0 mmol) and 4-chloroacetophenone (154 mg, 1.0 mmol, 130.0 μL), and the reaction mixture was heated for 2400 s at 180 °C. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (8:1) to yield a clear oil (211 mg, 80 %). R_f = 0.50 (hexanes/ethyl acetate = 8:1); IR (thin film): $\tilde{\nu}$ = 1685, 1605, 1395, 1328, 1158, 1131, 1071, 823, 592 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.4, 2H), 7.73 (bs, 4H), 7.69 (d, J = 8.4, 2H), 2.65 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 144.3, 143.5, 136.7, 130.3 (q, J = 130.8), 129.2, 127.8, 127.6, 126.1 (d, J = 16.4), 124.3 (q, J = 1082.4), 26.9 ppm; MS (EI): *m/z* (%): 264 (68), 249 (100), 221 (6), 201 (24), 152 (22), 124 (2), 75 (5); HRMS (EI): *m/z* calcd for $C_{15}H_{11}OF_3$: 264.0756; found: 264.0762.

3′-Trifluoromethylbiphenyl-4-carbonitrile (Table 3, entry 7): The representative procedure was used with 4-chlorobenzonitrile (136 mg, 1 mmol) and *m*-trifluoromethylphenylboronic acid (285 mg, 1.5 mmol), and the reaction mixture was heated for 1800 s at 180 °C. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (20:1) to yield a white solid (224 mg, 91 %). R_f = 0.2 (hexanes/ethyl acetate = 20:1); IR (thin film): $\tilde{\nu}$ = 3057, 2230, 1609, 1439, 1337, 1263, 1169, 1128, 1097, 1076, 1054, 845, 804, 739, 700, 561 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (br s, 1H), 7.76–7.80 (m, 3H), 7.68–7.72 (m, 3H), 7.61–7.65 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 140.0, 132.9, 131.6 (q, J = 130.4), 130.6, 129.8, 127.9, 125.4, 124.1, 123.9 (q, J = 1086.0), 118.7, 111.9 ppm; MS (EI): *m/z* (%): 247 (100), 228 (8), 208 (2), 177 (11), 151 (7), 145 (3), 99 (2), 75 (5); HRMS (EI): *m/z* calcd for $C_{14}H_8NF$: 247.0610; found: 247.0609.

3′-Methoxy-3-methylbiphenyl (Scheme 4): The representative procedure was used with 3-tolylboronic acid (274 mg, 2.0 mmol) and 3-bromoanisole (188 mg, 1.0 mmol, 128.0 μL), and the reaction mixture was heated for 2100 s at 180 °C. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (10:1) to yield a clear oil (178 mg, 89 %). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with spectral data already reported.[34]

3′-Methoxy-2,3-dimethylbiphenyl (Scheme 4): The representative procedure was used with 2,3-dimethylphenylboronic acid (304 mg, 2.0 mmol) and 3-bromoanisole (188 mg, 1.0 mmol, 128.0 μL), and the reaction mixture was heated for 2100 s at 180 °C. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (15:1–10:1) to yield a clear oil (180 mg, 84 %). R_f = 0.70 (hexanes/EtOAc = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.40 (m, 1H), 7.14–7.23 (m, 3H), 6.90–6.95 (m, 3H), 3.87 (s, 3H), 2.40 (s, 3H), 2.22 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 144.2, 142.3, 137.4, 134.2, 129.14, 129.08, 127.7, 125.4, 122.1, 115.2, 112.3, 55.4, 20.9, 17.2 ppm; MS (EI): *m/z* (%): 212 (100), 197 (27), 181 (46), 165 (18), 153 (13), 115 (6), 84 (18), 58 (16), 43 (60); HRMS (EI): *m/z* calcd for $C_{15}H_{16}O$: 212.1194; found: 212.1201.

Representative Procedure for Ni/C-Catalyzed Amination of Aryl Halides

4-Morpholinobenzonitrile (Table 4, entry 5): Ni^{II}/C (135 mg, 0.08 mmol, 0.59 mmol g^{-1}), dppf (22 mg, 0.04 mmol), and lithium *tert*-butoxide (164 mg, 2.0 mmol) were added to a flame-dried Biotage process vial (2–5 mL) under a blanket of argon at room temperature. Dry dioxane (1.5 mL) was added by syringe, and the slurry was stirred for 1 h. *n*-Butyllithium (62.0 μL, 2.55 M in hexanes, 0.16 mmol) was then added dropwise and, after 5 min, morpholine (140 μL, 1.60 mmol) and 4-chlorobenzonitrile (110 mg, 0.80 mmol) in dioxane (1 mL) were added by cannula. The resulting heterogeneous mixture was then heated in the Emrys Optimizer with the following settings: temperature: 200 °C, time: 600 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After cooling to room temperature, the crude reaction mixture was filtered through celite, and the filter cake was further rinsed with ethyl acetate. The filtrate was collected, the solvent was removed with a rotary evaporator, and the crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (7:3; R_f = 0.20) to yield a white solid (143 mg, 95 %). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with the spectral data already reported.[35]

n-Butyl-3-(trifluoromethyl)benzeneamine (Table 4, entry 1): The representative procedure was used with Ni^{II}/C (67.3 mg, 0.04 mmol, 0.59 mmol g^{-1}), dppf (11 mg, 0.02 mmol), and lithium *tert*-butoxide (82 mg, 1.0 mmol) in dry dioxane (2.5 mL). *n*-Butylamine (158 μL, 1.60 mmol) and 3-iodobenzotrifluoride (115 μL, 0.80 mmol) were then added dropwise, and the mixture placed in the microwave reactor at 180 °C for 600 s. The pure product (139 mg, 80 %) was obtained after flash chromatography on silica gel with hexanes/EtOAc (9:1; R_f = 0.68). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, J = 7.2 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.77 (s, 1H), 6.70 (d, J = 7.2 Hz, 1H), 3.78 (s, 1H), 3.11 (t, J = 7.2 Hz, 2H), 1.60 (tt, J = 7.3, 7.3 Hz, 2H), 1.42 (tt, J = 7.3, 7.3 Hz, 2H), 0.96 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 133.7 (q, J = 18.9 Hz), 129.8, 124.8 (q, J = 281 Hz), 115.8, 113.5 (q, J = 3.8 Hz), 108.8 (q, J = 3.8 Hz), 43.6, 31.6, 20.5, 14.1 ppm; MS (EI): *m/z*

(%): 217 (15), 174 (100); HRMS: *m/z* calcd for $C_{11}H_{14}F_3N$: 217.1078 $[M]^+$; found: 217.1078.

1-(3-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline (Table 4, entry 2): The representative procedure was used with Ni^{II}/C (67.3 mg, 0.04 mmol, 0.59 mmol g^{-1}), dppf (11 mg, 0.02 mmol), and lithium *tert*-butoxide (82 mg, 1.00 mmol) in dry dioxane (1 mL). 1,2,3,4-Tetrahydroquinoline (200 μL, 1.60 mmol) and 3-iodobenzotrifluoride (115 μL, 0.80 mmol) were added dropwise, and the mixture placed in the microwave reactor at 200 °C for 600 s. The pure product (195 mg, 88 %)was obtained after flash chromatography on silica gel with hexanes/EtOAc (9:1; R_f = 0.22). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 7.43–7.42 (m, 2H), 7.29 (dd, J = 7.1, 7.1 Hz, 1H), 7.11 (d, J = 7.2 Hz, 1H), 7.02 (dd, J = 7.1, 7.1 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.83 (dd, J = 7.3, 7.3 Hz, 1H), 3.68 (t, J = 6.4, Hz, 2H), 2.87 (t, J = 6.4 Hz, 2H), 2.07 ppm (dd, J = 6.4, 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 143.4, 131.9 (q, J = 31.9 Hz), 129.9, 129.7, 124.3 (q, J = 272 Hz), 126.7, 126.4, 119.8, 119.7, 119.3, 119.2, 116.9, 50.5, 27.8, 23.2 ppm; MS (EI): *m/z* (%): 277 (100), 261 (6), 248 (7), 180 (5), 91 (6); HRMS: *m/z* calcd for $C_{16}H_{14}F_3N$: 277.1071 $[M]^+$; found: 277.1078.

1-(Pyridin-2-yl)-1,2,3,4-tetrahydroquinoline (Table 4, entry 3): The representative procedure was used with Ni^{II}/C (67.3 mg, 0.04 mmol, 0.59 mmol g^{-1}), dppf (11 mg, 0.02 mmol), and lithium *tert*-butoxide (82 mg, 1.0 mmol) in dry dioxane (1 mL). 1,2,3,4-Tetrahydroquinoline (200 μL, 1.60 mmol) and 2-bromopyridine (76 μL, 0.80 mmol) were then added dropwise, and the mixture placed in the microwave reactor at 200 °C for 900 s. The pure product (152 mg, 91 %) was obtained after flash chromatography on silica gel with hexanes/EtOAc (9:1; R_f = 0.42). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with the spectral data already reported.[36]

1-(3-Fluorophenyl)pyrrolidine (Table 4, entry 4): The representative procedure was used with Ni^{II}/C (67.3 mg, 0.04 mmol, 0.59 mmol g^{-1}), dppf (11 mg, 0.02 mmol), and lithium *tert*-butoxide (82 mg, 1.0 mmol) in dry dioxane (1 mL). Pyrrolidine (134 μL, 1.60 mmol) and 1-bromo-3-fluorobenzene (89 μL, 0.80 mmol) were then added dropwise, and the mixture placed in the microwave reactor at 200 °C for 600 s. The pure product (121 mg, 92 %) was obtained after flash chromatography on silica gel with hexanes/EtOAc (9:1; R_f = 0.20). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with the spectral data already reported.[37]

4-(3,4-Dihydroquinolin-1-yl)benzonitrile (Table 4, entry 6): The representative procedure was used with 1,2,3,4-tetrahydroquinoline (200 μL, 1.60 mmol) and 4-chlorobenzonitrile (110 mg, 0.80 mmol) in dioxane (1 mL). The pure product (157 mg, 84 %) was obtained after flash chromatography on silica gel with hexanes/EtOAc (9:1; R_f = 0.25) followed by recrystallization (Et_2O). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with the spectral data already reported.[38]

2-(Indolin-1-yl)benzonitrile (Table 4, entry 7): The representative procedure was used with indoline (180 μL, 1.60 mmol) and 4-chlorobenzonitrile (110 mg, 0.80 mmol) in dioxane (1 mL). The pure product (163 mg, 92 %) was obtained after flash chromatography on silica gel with hexanes/EtOAc (9:1; R_f = 0.25). IR (nujol): $\tilde{\nu}$ = 2923, 2854, 2221, 1592, 1490, 1459, 1376 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, J = 7.8, 1.7 Hz, 1H), 7.57–7.48 (m, 2H), 7.23 (dd, J = 7.7, 0.9 Hz, 1H), 7.12–7.08 (m, 2H), 6.86 (m, 2H), 4.17 (t, J = 8.5 Hz, 2H), 3.21 ppm (t, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 146.6, 134.5, 133.6, 131.3, 126.8, 125.2, 123.0, 120.9, 120.5, 118.3, 110.3, 106.0, 54.3, 28.9 ppm; MS (EI): *m/z* (%): 221 (12), 220 (82), 219 (100), 218 (11), 91 (15); HRMS: *m/z* calcd for $C_{15}H_{12}N_2$: 220.1001 $[M]^+$; found: 220.1000.

4-(3-(Trifluoromethyl)phenyl)morpholine (Table 4, entry 8): The representative procedure was used with dioxane (2.5 mL), morpholine (140 μL, 1.60 mmol), and 3-chlorobenzotrifluoride (108 μL, 0.80 mmol), and the reaction mixture was heated for 900 s. The pure product (152 mg, 82 %) was obtained after flash chromatography on silica gel with hexanes/EtOAc (9:1; R_f = 0.20). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agreed with the spectral data already reported.[39]

4-(4-Piperonylpiperazin-1-yl)benzonitrile (Table 4, entry 9): The representative procedure was used with 1-piperonylpiperazine (352 mg, 1.60 mmol) and 4-chlorobenzonitrile (110 mg, 0.80 mmol) in dioxane (1 mL), and the reaction mixture was heated for 900 s. The pure product (228 mg, 89 %) was obtained after flash chromatography on silica gel with hexanes/EtOAc (4:1; R_f = 0.20). IR (nujol): $\tilde{\nu}$ = 2923, 2853, 2220, 1606, 1514, 1490, 1441, 1250, 1183, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 9.1 Hz, 2H), 6.90–6.75 (m, 5H), 5.95 (s, 2H), 3.46 (s, 2H), 3.32 (t, J = 5.2 Hz, 4H), 2.56 ppm (t, J = 5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 147.8, 146.8, 133.5, 131.7, 122.3, 120.2, 114.2, 109.5, 108.0, 101.0, 100.1, 62.7, 52.5, 47.2 ppm; MS (EI): *m/z* (%): 320 (38), 185 (43), 162 (42), 161 (15), 135 (17), 134 (100), 129 (12), 128 (14), 104 (10), 101 (17), 76 (32), 55 (52), 50 (24); HRMS: *m/z* calcd for $C_{19}H_{19}N_3O_2$: 321.1477 $[M]^+$; found: 321.1477.

N-4-Biphenyl-2,3-dihydroindole (Table 4, entry 10): The representative procedure was used with indoline (180 μL, 1.60 mmol) and 4-chlorobiphenyl (150 mg, 0.80 mmol) in dioxane (1 mL), and the reaction mixture was heated for 1200 s. The pure product (199 mg, 91 %) was obtained after flash chromatography on silica gel with hexanes/EtOAc (19:1; R_f = 0.25). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agree with the spectral data already reported.[40]

4-(3-Methoxyphenyl)morpholine (Table 4, entry 11): The representative procedure was used with dioxane (2.5 mL), morpholine (280 μL, 3.2 mmol), and 3-chloroanisole (98 μL, 0.80 mmol), and the reaction mixture was heated for 2400 s. The pure product (133 mg, 86 %) was obtained after flash chromatography on silica gel with hexanes/EtOAc (9:1; R_f = 0.20). The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and HRMS data agree with the spectral data already reported.[41]

3: The representative procedure was used with Ni^{II}/C (33.7 mg, 0.02 mmol, 0.59 mmol g^{-1}), dppf (22 mg, 0.04 mmol), and lithium *tert*-butoxide (21 mg, 0.25 mmol) in dry dioxane (1 mL). Morpholine (53 μL, 0.60 mmol) and 3-(4-bromo-3-fluorophenyl)-5-((tert-butyldiphenylsilyloxy)methyl)oxazolidin-2-one (105.7 mg, 0.20 mmol) in dioxane (0.5 mL) were added by cannula, and the mixture placed in the microwave reactor at 200 °C for 1800 s. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (3:1; R_f = 0.25) to yield **3** (93 mg, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, J = 7.4, 7.4 Hz, 5H), 7.48–7.33 (m, 6H), 7.15 (dd, J = 8.8, 2.8 Hz, 1H), 6.95 (t, J = 9.1 Hz, 1H), 3.81 (d, J = 3.8 Hz, 1H), 3.77 (d, J = 3.8 Hz, 1H), 4.68 (tt, J = 5.4, 5.4 Hz, 1H), 4.00–3.93 (m, 2H), 3.89 (t, J = 4.7 Hz, 4H), 3.08 (t, J = 4.7 Hz, 4H), 1.02 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 153.2 (d, J = 250 Hz), 135.8, 132.8 (d, J = 41.7 Hz), 130.2, 128.1, 128.0, 127.8, 119.0, 113.9, 107.4 (d, J = 26.6 Hz), 72.5, 67.2, 64.4, 51.3, 47.0, 26.9, 19.4 ppm; MS (EI): *m/z* (%): 534 (90), 479 (32), 348 (30), 313 (34), 254 (100), 225 (70), 199 (32), 183 (46), 163 (14), 135 (26), 124 (29), 114 (42), 70 (25); HRMS: *m/z* calcd for $C_{30}H_{35}FN_2O_4Si$: 534.2353 $[M]^+$; found: 534.2350.

9: Carboalumination: $[Cp_2ZrCl_2]$ (73 mg, 0.25 mmol) was added to a round-bottomed flask (10 mL) under argon. Me_3Al (0.75 mL, 2.0 M in hexanes, 1.5 mmol) was then added by syringe at 0 °C, and the solution stirred under reduced pressure until the hexanes were removed. 1-Triisopropylsiloxy-3-butyne (0.26 mL, 1.0 mmol) dissolved in $ClCH_2CH_2Cl$ (1.0 mL) was transferred by cannula to the reaction mixture. After 3 h at 0 °C, the carboalumination was complete and the solvent was removed in vacuo. Freshly distilled hexanes (2 mL) were added and then also removed in vacuo. More hexanes (5 mL) were then added to the flask so as to precipitate the zirconium salts. The vinyl alane in hexanes was then transferred to a second flask by cannula (with great care taken to avoid contamination by the zirconium salts). The golden-yellow solution of hexanes was concentrated under reduced pressure, and the residue was redissolved in THF (1 mL) in preparation for the coupling.

Nickel-on-charcoal catalyzed coupling in the microwave: Ni/C (67 mg, 0.04 mmol) and PPh_3 (21 mg, 0.08 mmol) were added to a flame-dried microwave vessel (5 mL) purged with argon. THF (1 mL) was then added, followed by *n*BuLi (30 μL, 2.7 M, 0.08 mmol). A solution of **7** (300 mg, 0.80 mmol) in THF (1 mL) was transferred by cannula to the Ni/C catalyst, followed by the solution of vinyl alane. The reaction mixture was subjected to microwave irridiation at 200 °C for 30 min, at which point GC analysis indicated complete consumption of the benzylic chloride. The reaction mixture was diluted with petroleum ether and quenched with aqueous HCl (0.10 M). The mixture was filtered to removed the Ni/C, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The

combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Silica-gel chromatography (EtOAc/hexanes = 10%) afforded the product as a colorless oil (370 mg, 82%). $R_f = 0.42$ (EtOAc/hexanes = 20%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.94$ (d, $J =$ 8.4 Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H), 6.65 (s, 1H), 5.06 (dt, $J = 6.6$, 0.8 Hz, 1H), 3.82 (s, 3H), 3.71 (t, $J = 7.5$ Hz, 2H), 3.47 (s, 3H), 3.32 (d, $J = 6.6$ Hz, 2H), 2.47 (s, 3H), 2.24 (s, 3H), 2.21 (t, $J = 7.5$ Hz, 2H), 1.71 (d, $J = 0.8$ Hz, 3H), 1.08 (m, 3H), 1.05 ppm (d, 18H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 12.2$, 18.2, 20.0, 21.9, 26.6, 29.9, 43.3, 56.2, 60.7, 62.9, 113.2, 123.8, 127.1, 128.4, 129.6, 133.0, 133.1, 139.0, 142.5, 142.6, 144.7, 151.1 ppm; MS (EI): m/z (%): 533 (95), 334 (24), 269 (53), 247 (100), 233 (12), 219 (25), 205 (26), 181 (28), 163 (20), 139 (13), 115 (16), 91 (33), 75 (22), 59 (31); HRMS (EI): m/z calcd for $C_{31}H_{48}O_6SSi$: 533.2393 $[M-C_3H_7]^+$; found: 533.2379.

12: Carboalumination: $[Cp_2ZrCl_2]$ (39 mg, 0.13 mmol) was added to a round-bottomed flask (25 mL) under argon. Me_3Al (0.40 mL, 2.0 M in hexanes, 0.80 mmol) was then added by syringe at 0 °C, and the solution stirred under reduced pressure until the hexanes were removed. Solanesol-derived alkyne **10** (351 mg, 0.537 mmol) was dissolved in CH_2Cl_2 (0.54 mL) and transferred by cannula to the reaction mixture. After 6 h at 0 °C, the carboalumination was complete and the solvent was removed in vacuo. Freshly distilled pentane (2 mL) was added and then also removed in vacuo. More pentane (5 mL) was added to the flask so as to precipitate the zirconium salts. The vinyl alane in pentane was then transferred to a second flask by cannula (with great care taken to avoid contamination by the zirconium salts). The golden-yellow solution of pentane was concentrated under reduced pressure, and the residue dissolved in THF (1 mL) in preparation for the coupling.

Nickel-in-charcoal-catalyzed cross-couplings in a microwave reactor: Ni/C (36 mg, 0.02 mmol) and PPh_3 (11 mg, 0.04 mmol) were added to a flame-dried microwave vessel (5 mL) purged with argon. THF (0.5 mL) was then added, followed by *n*BuLi (16 μL, 2.7 M, 0.04 mmol). A solution of **7** (219 mg, 0.59 mmol) in THF (1 mL) was transferred by cannula to the Ni/C catalyst, followed by the solution of vinyl alane. The reaction mixture was subjected to microwave irradiation at 200 °C for 30 min, then diluted with petroleum ether and quenched with aqueous HCl (0.10 M). The mixture was filtered to remove the Ni/C, and the aqueous layer was extracted with petroleum ether (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and then concentrated in vacuo. Silica-gel chromatography (EtOAc/hexanes = 10%) afforded the product as a colorless oil (424 mg, 80%). $R_f = 0.28$ (CH_2Cl_2/petroleum ether = 5%). Spectral data matched that previously reported.[42]

Preparation of Samples for ICP-AES of Negishi Couplings

(4-Butylphenyl)phenylmethanone under microwave irradiation: Ni^{II}/C (135 mg, 0.08 mmol, 0.59 mmol g^{-1}) and PPh_3 (78 mg, 0.30 mmol) were added to a flame-dried Biotage process vial (2–5 mL) under argon at room temperature. Dry dioxane (1 mL) was added by syringe, and the slurry was stirred for 20 min. *n*-Butyllithium (38 μL, 2.5 M in hexanes, 0.10 mmol) was then added dropwise. After 5 min, 4-chlorobenzophenone (216 mg, 1.0 mmol) was dissolved in THF (1 mL), and it and *n*-butylzinc chloride (1.5 mmol, in dry THF) prepared in situ were both added by cannula to the Ni/C. The resulting heterogeneous mixture was then heated in the Emrys Optimizer with the following settings: temperature: 150 °C, time: 900 s, fixed hold time: on, sample absorption: normal, pre-stirring: 10 s. After cooling to room temperature, the crude reaction mixture was filtered through celite, and the filter cake was further rinsed with ethyl acetate. The solvent was evaporated under reduced pressure, and the mixture was treated with HNO_3 (20%, 10 mL) and concentrated HCl (5 mL) and heated at reflux for 8 h. Upon cooling to room temperature, the residue was dissolved in aqueous HCl (2%, 5 mL) and filtered through a cotton plug to remove any solids. The ICP-AES sample was prepared by adding HCl (2%) such that the final (estimated) nickel concentration was between 1 and 35 ppm. The analytical sample prepared was determined to have 0.73 ppm of Ni, which amounts to 0.025 mg of Ni in solution. This amount of nickel corresponds to 0.57% of the 8% nickel used in the reaction, which corresponds to a substrate/nickel ratio of 2192:1 in the reaction solution.

(4-Butylphenyl)phenylmethanone with conventional heating: Ni^{II}/C (135 mg, 0.08 mmol, 0.59 mmol g^{-1}) and PPh_3 (78 mg, 0.30 mmol) were added to a flame-dried round-bottomed flask (10 mL) under argon at room temperature. Dry dioxane (1 mL) was added by syringe, and the slurry was stirred for 20 min. *n*-Butyllithium (38 μL, 2.5 M in hexanes, 0.10 mmol) was then added dropwise. $ZnCl_2$ and *n*BuLi were added to a second flame-dried round-bottomed flask (10 mL) purged under argon to prepare in situ the *n*-butylzinc chloride as described above, and the mixture was then added by cannula to the Ni/C. In a third flame-dried round-bottomed flask (10 mL) purged under argon, 4-chlorobenzophenone (216 mg, 1.0 mmol) dissolved in THF (1 mL) was added. The 4-chlorobenzophenone was added by cannula to the Ni/C; the flask was then equipped with a reflux condenser. The flask was placed in a preheated sand bath at 65 °C and the mixture refluxed overnight until the reaction was complete by TLC analysis. After cooling to room temperature, the crude reaction mixture was filtered through celite, and the filter cake was further rinsed with ethyl acetate. The solvent was evaporated under reduced pressure, and the mixture was treated with HNO_3 (20%, 10 mL) and concentrated HCl (5 mL) and heated at reflux for 8 h. Upon cooling to room temperature, the residue was dissolved in aqueous HCl (2%, 5 mL) and filtered through a cotton plug to remove any solids. The ICP-AES sample was prepared by adding HCl (2%) such that the final (estimated) nickel concentration was between 1 and 35 ppm. The analytical sample prepared was determined to have 0.90 ppm of Ni, which equates to 0.046 mg of Ni in solution. This amount of nickel corresponds to 1.06% of the 8% nickel used in the reaction, which corresponds to a substrate/nickel ratio of 1179:1 in the reaction solution.

Preparation of Samples for ICP-AES of Suzuki Couplings

3′-Trifluoromethylbiphenyl-4-carbonitrile under microwave irradiation: Ni^{II}/C (32 mg, 0.02 mmol, 0.59 mmol g^{-1}) and Ph_3P (27 mg, 0.10 mmol) were added to a flame-dried Biotage process vial (2–5 mL) under a blanket of argon at room temperature. Dry dioxane (1.0 mL) was added by syringe, and the mixture was allowed to stir for 1 h. *n*-Butyllithium (0.020 mL, 2.55 M in hexanes, 0.05 mmol) was then added dropwise. The mixture was allowed to stir for 5 min. In a second flame-dried, argon-flushed container, potassium fluoride (174 mg, 3.00 mmol), lithium hydroxide (75 mg, 3.00 mmol), 4-chlorobenzonitrile (136 mg, 1.00 mmol), and *m*-trifluoromethylphenylboronic acid (285 mg, 1.50 mmol) were weighed out under a blanket of argon. The cap of the process vial was removed and the solids in the second container were quickly added to the vial. The cap was replaced and the vial was flushed with argon. The sides of the vial were rinsed free of solids with dioxane (1.5 mL), and the resulting heterogeneous mixture was heated in an Emrys Optimizer with the following settings: temperature: 180 °C, time: 1800 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After cooling to room temperature, the crude reaction mixture was filtered through celite, and the filter cake was further rinsed with ethyl acetate. The solvent was evaporated under reduced pressure, and the mixture was treated with HNO_3 (20%, 10 mL) and concentrated HCl (5 mL) and heated at reflux for 8 h. Upon cooling to room temperature, the residue was dissolved in aqueous HCl (2%, 5 mL) and filtered through a cotton plug to remove any solids. The ICP-AES sample was prepared by adding HCl (2%) such that the final (estimated) nickel concentration was between 1 and 35 ppm. The analytical sample prepared was determined to have 0.03 ppm of Ni, which amounts to 0.001 mg of Ni in solution. This amount of nickel corresponds to 0.24% of the 2% nickel used in the reaction, which corresponds to a substrate/nickel ratio of 20833:1 in the reaction solution.

3′-Trifluoromethylbiphenyl-4-carbonitrile with conventional heating: Ni^{II}/C (32 mg, 0.02 mmol, 0.59 mmol g^{-1}) and Ph_3P (27 mg, 0.10 mmol) were added to a flame-dried round-bottomed flask (10 mL) under a blanket of argon at room temperature. Dry dioxane (1.0 mL) was added by syringe, and the mixture was allowed to stir for 1 h. *n*-Butyllithium (0.020 mL, 2.55 M in hexanes, 0.05 mmol) was then added dropwise. The mixture was allowed to stir for 5 min. In a second flame-dried, argon-flushed container, potassium fluoride (174 mg, 3.00 mmol), lithium hydroxide (75 mg, 3.00 mmol), 4-chlorobenzonitrile (136 mg, 1.00 mmol), and *m*-trifluoromethylphenylboronic acid (285 mg, 1.50 mmol) were

weighed out under a blanket of argon. The solids in the container were quickly added to the round-bottomed flask, which was equipped with a reflux condenser. The sides of the flask were rinsed free of solids with dioxane (1.5 mL), and the flask placed in a preheated oil bath at 110 °C overnight until the reaction was complete according to TLC. After cooling to room temperature, the crude reaction mixture was filtered through celite, and the filter cake was further rinsed with ethyl acetate. The solvent was evaporated under reduced pressure, and the mixture was treated with HNO_3 (20 %, 10 mL) and concentrated HCl (5 mL) and heated at reflux for 8 h. Upon cooling to room temperature, the residue was dissolved in aqueous HCl (2 %, 5 mL) and filtered through a cotton plug to remove any solids. The ICP-AES sample was prepared by adding HCl (2 %) such that the final (estimated) nickel concentration was between 1 and 35 ppm. The analytical sample prepared was determined to have 0.12 ppm of Ni, which amounts to 0.007 mg of Ni in solution. This amount of nickel corresponds to 0.94 % of the 2 % nickel used in the reaction, which corresponds to a substrate/nickel ratio of 5319:1 in the reaction solution.

Preparation of Samples for ICP-AES of Aminations

4-Morpholinobenzonitrile under microwave irradiation: According to the standard procedure for amination reactions outlined above, Ni^{II}/C (135 mg, 0.08 mmol, 0.59 mmol g^{-1}), dppf (22 mg, 0.04 mmol), and lithium *tert*-butoxide (164 mg, 2.0 mmol) were added to a flame-dried Biotage process vial (2–5 mL) under a blanket of argon at room temperature. Dry dioxane (1.5 mL) was added by syringe, and the slurry was stirred for 1 h. *n*-Butyllithium (0.062 mL, 2.55 M in hexanes, 0.16 mmol) was then added dropwise, and after 5 min, morpholine (140 μL, 1.60 mmol) and 4-chlorobenzonitrile (110 mg, 0.80 mmol) in dioxane (1 mL) were added by cannula. The resulting heterogeneous solution was then heated in the Emrys Optimizer with the following settings: temperature: 200 °C, time: 600 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After cooling to room temperature, the crude reaction mixture was then filtered through celite, and the filter cake was further rinsed with ethyl acetate. The solvent was evaporated under reduced pressure, and the mixture was treated with HNO_3 (20 %, 10 mL) and concentrated HCl (5 mL) and heated at reflux for 8 h. Upon cooling to room temperature, the residue was dissolved in aqueous HCl (2 %, 5 mL) and filtered through a cotton plug to remove any solids. The ICP-AES sample was prepared by adding HCl (2 %) such that the final (estimated) nickel concentration was between 1 and 35 ppm. The analytical sample prepared was determined to have 0.27 ppm of Ni, which amounts to 0.014 mg of Ni in solution. This corresponds to 0.35 % of the 10 % nickel used in the reaction, which equates to a substrate/nickel ratio of 2285:1 in the reaction mixture.

4-Morpholinobenzonitrile conventional heating: Ni^{II}/C (135 mg, 0.08 mmol, 0.59 mmol g^{-1}), dppf (22 mg, 0.04 mmol), and lithium *tert*-butoxide (164 mg, 2.0 mmol) were added to a flame-dried round-bottomed flask (10 mL) purged under argon. Dry dioxane (1.5 mL) was then added by syringe, and the slurry was stirred for 1 h. *n*-Butyllithium (0.062 mL, 2.55 m in hexanes, 0.16 mmol) was then added dropwise, and after 5 min, morpholine (140 μL, 1.60 mmol) and 4-chlorobenzonitrile (110 mg, 0.80 mmol) in dioxane (1 mL) were added by cannula. The round-bottomed flask was equipped with a reflux condenser and was heated in a preheated oil bath at 110 °C until the reaction was judged complete by TLC. After cooling to room temperature, the crude reaction mixture was filtered through celite, and the filter cake was further rinsed with ethyl acetate. The solvent was evaporated under reduced pressure, and the mixture was treated with HNO_3 (20 %, 10 mL) and concentrated HCl (5 mL) and heated at reflux for 8 h. After cooling to room temperature, the residue was dissolved in aqueous HCl (2 %, 5 mL) and filtered through a cotton plug to remove any solids. The ICP-AES sample was prepared by adding HCl (2 %) such that the final (estimated) nickel concentration was between 1 and 35 ppm. The analytical sample prepared was determined to contain 0.84 ppm of Ni, which amounts to 0.041 mg of Ni in solution. This amount of nickel corresponds to 1.0 % of the 10 % nickel used in the reaction, which corresponds to a substrate/nickel ratio of 800:1 in the reaction solution.

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