On the Nature of the 'Heterogeneous' Catalyst:
Nickel-on-Charcoal

Bruce H. Lipshutz,*,[†,‡] Stefan Tasler,[†] Will Chrisman,[†] Bernd Spliethoff,[§] and Bernd Tesche*,[§]

*Department of Chemistry & Biochemistry, University of California,
Santa Barbara, California 93106-9510 and Max-Planck-Institut für Kohlenforschung,
Elektronenmikroskopie, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr, Germany*

lipshutz@chem.ucsb.edu

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Results from aromatic aminations and Kumada couplings, together with spectroscopic analyses (TEM, EDX, ICP-AES, React-IR), reveal that catalysis using nickel-on-charcoal (Ni/C) is most likely of a homogeneous rather than heterogeneous nature. In the course of a reaction with Ni/C, nickel bleed from the support was calculated to be as high as 78%. However, the existence of an equilibrium for this homogeneous species between nickel located inside vs outside the pore system of charcoal strongly favors the former, thus leaving only traces of metal detectable in solution. This accounts for virtually complete recovery of nickel on the charcoal following filtration of a reaction mixture and allows for recycling of the catalyst. TEM and EDX data were used to explain different reactivity profiles of Ni/C, which depended upon the method of reduction used to convert Ni(II)/C to Ni(0) as well as the level of nickel loading on the support.

Introduction

Following early work by Kharash et al. in the 1940s on nickel-catalyzed C—C bond forming reactions,[1] it was not before the 1970s that the organometallic chemistry of this metal began to accrue significant numbers of applications to organic synthesis,[2] as well as an appreciable level of study on mechanistic aspects of organonickel-based transformations.[3] Use of nickel catalysis in a heterogeneous context, unlike supported palladium which is well-known to effect several types of transformations of organic substrates,[4–8] was mainly used for hydrogenation of unsaturated systems.[9,10] Some recent

† University of California, Santa Barbara.
‡ Phone: +805-893-2521. Fax: +805-893-8265.
§ Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr.
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TABLE 1. Comparison of 1st and 2nd Generation Formation of Ni/C

	1st generation[a]	2nd generation[b]
impregnation	aqueous $Ni(NO_3)_2 \cdot 6H_2O$ distillation of H_2O (180 °C) addition of undistilled THF distillation of THF (100 °C)	aqueous $Ni(NO_3)_2 \cdot 6H_2O$ ultrasound, 30 min distillation of H_2O (175 °C, then 210 °C, 15 min)
washing	three times with H_2O twice with undistilled THF	twice with H_2O
drying	100 °C, vacuum, 12 h	predrying at room temperature, vacuum, 2 h 100 °C, vacuum, 18 h

[a] cf. ref 15. [b] cf. ref 27.

exceptions outside of our work[11] include hydrodehalogenation reactions of aryl chlorides using 'nickel-on-charcoal' (Ni/C)[12,13] and Kumada couplings with nickel mounted on a Merrifield resin.[14] The potential for Ni/C to catalyze a variety of cross-coupling reactions involving inexpensive aryl chlorides has recently been expanded to include Negishi-,[15] Suzuki-,[16] and Kumada-type couplings,[17] aromatic aminations,[18] and hydrodehalogenations.[19] Whereas the pathway for heterogeneous hydrogenation reactions using transition metal catalysts is an example of true surface chemistry involving chemisorption of the hydrogen on a metal surface,[20] the mode of action for transformations of aryl halides is not obvious. For Pd/C-based Suzuki couplings of aryl chlorides, a heterogeneous mechanism involving 'synergistic anchimeric and electronic effects' was suggested to account for the high catalytic activity; i.e., interactions of the substrate with Pd atoms which are in proximity to each other.[8] Can such a scheme also explain the activities found with Ni/C, as postulated previously for hydrodehalogenations of aryl chlorides,[13] or is a different hypothesis needed in this case? Is this chemistry truly heterogeneous; i.e., catalyzed only by nickel atoms attached to the support (denoted as 'Ni$_C$')? If so, then in addition to such an association with the charcoal, how can nickel accommodate both an oxidative addition and simultaneous coordination of (phosphine) ligands, all within the coordination sphere of the metal? Does Ni/C, rather, serve as a (reversible?) reservoir for nickel-in-solution (Ni$_{sol}$), as previously postulated for certain Pd/C-mediated conversions, involving a 'release/capture mechanism', determined by a 'three-phase test'[21,22] employing polymer-bound substrates[23] and by atomic absorption or emission spectroscopy as a quantitative indicator of the transition metal present in solution after filtration of the reaction suspension.[24–26] In this contribution, we offer physical evidence, for the first time, on the impact of varying methods of reduction of Ni(II)/C on the texture of the resulting catalyst, which is correlated with catalytic activity in organic transformations. Also addressed is the issue of catalyst bleed from the support, and results are presented on catalyst activity under differing reaction conditions.

Results and Discussion

Preparation, Texture, and Activity of Ni/C. In our original preparation of Ni/C,[15] an aqueous solution of Ni-$(NO_3)_2 \cdot 6H_2O$ was used to supply nickel(II) for impregnating activated charcoal by distillation of both the water and subsequently added undistilled THF. The 'crude' Ni(II)/C was then washed several times with H_2O and THF and dried in vacuo at 100 °C for 12 h (Table 1). In time, further study revealed that exposure to THF was not crucial for catalyst activity. Far more important for the new protocol is better control of temperature and time of impregnation and drying, which is essential for gaining

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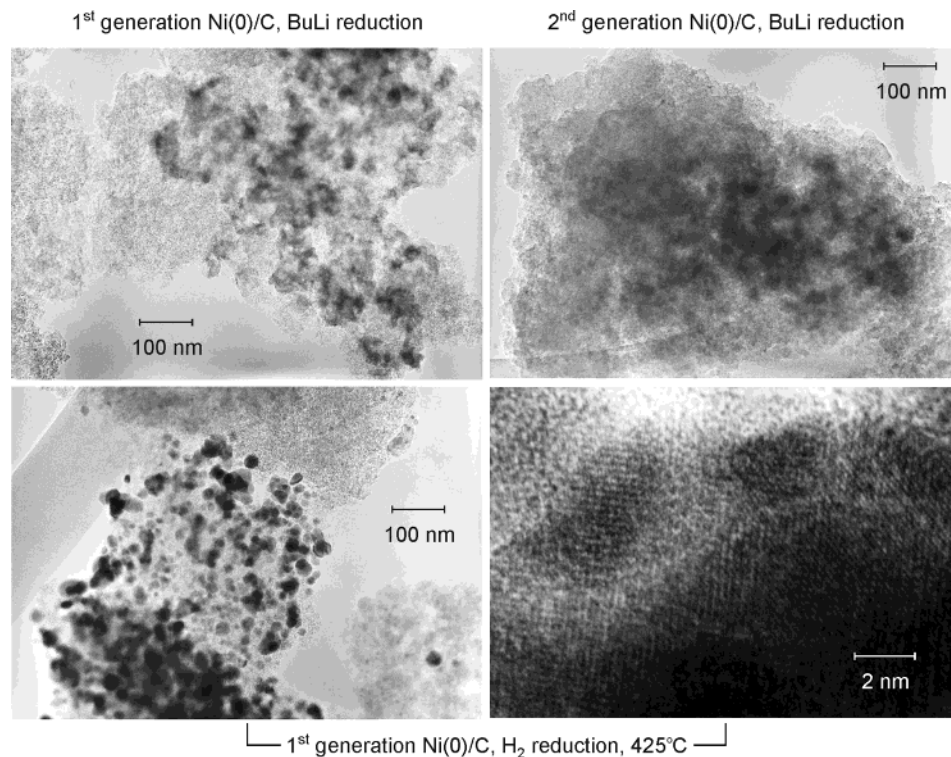
1st generation Ni(0)/C, BuLi reduction

2nd generation Ni(0)/C, BuLi reduction

100 nm

100 nm

100 nm

2 nm

1st generation Ni(0)/C, H₂ reduction, 425°C

FIGURE 1. TEM analyses of Ni(0)/C formed by reduction of 1st and 2nd generation Ni(II)/C with either BuLi (top row), or H$_2$ at 425 °C (1 atm) with lattice fringes resolved (bottom right).

a reproducible activity profile.[27] Additionally, pretreatment of the catalyst prior to distillation with ultrasound was anticipated to help achieve a more homogeneous distribution of Ni(NO$_3$)$_2$ within the matrix of the activated charcoal, simultaneously easing both the evolution of gas[28] out of the pore structure and the pore filling process.

Ni/C prepared by this "second generation" protocol displayed essentially the same catalytic activity in several cross-couplings (Negishi-, Suzuki-, Kumada-couplings, aromatic aminations, and hydrodehalogenations) as seen with catalyst prepared via our earlier method. These observations raised the question as to whether impregnation using ultrasound altered in a significant fashion the distribution pattern of nickel atoms on the charcoal support, aside from the obvious advantage of leading to complete and reproducible loading of Ni(NO$_3$)$_2$ in a simpler and faster procedure.[27] Transmission electron microscopy (TEM), in combination with energy dispersive X-ray analysis (EDX), were chosen to investigate structural features of the supported nickel catalysts. TEM micrographs (Figure 1) compare samples of Ni(0)/C prepared using our "first generation" and "second generation" processes. Reduction of impregnated Ni(II)/C of both generation catalysts by *n*-BuLi in THF in the presence of PPh$_3$ (room temperature, 10 min; top row) is contrasted with reduction by heat treatment (425 °C, 4.5 h) in an atmosphere of hydrogen (atmospheric pressure) *after* which PPh$_3$ was added in THF (bottom left).

In general, TEM micrographs display a 2D image taken of the sample mounted on a copper grid. The brighter grayish structures represent charcoal with only traces of nickel, while higher nickel concentrations lead to higher contrast and, therefore, to darker regions of the sample in the picture. EDX data for a sample of activated charcoal as purchased and unexposed to nickel nitrate showed a permanent phosphorus background caused by residual phosphates, an outgrowth of the procedure followed for preparing activated charcoal.[29] Thus, not all of the signal due to phosphorus found in the reduced Ni(0)/C samples can be attributed to added phosphine. Independent of the method of impregnation, neither Ni(II)/C nor Ni(0)/C formed via BuLi reduction display visible nickel particles, indications that, if present to any degree, their size is below 1 nm. The nickel atoms associate in conglomerates, most likely with inorganic material from the charcoal and/or the original nickel salt and what remained of it after impregnation and drying, which is known to cause decomposition of the nitrate and hydrate sphere, although those processes took place at temperatures above 110 °C and at atmospheric pressure.[10,27,28,30,31] The distribution of conglomerates on and within the pore structure of charcoal was found to be more homogeneous for second generation Ni(II)/C (not shown) and the corresponding Ni(0)/C formed via BuLi-reduction, as manifested by smoother transitions to regions with darker contrast, as expected from pretreatment with ultrasound. After BuLi reduction in THF, the general distribution of nickel particles was not changed, suggesting that nickel is not prone to migration under these conditions, an important observation for subsequent experiments (vide infra). Added PPh$_3$ is attracted

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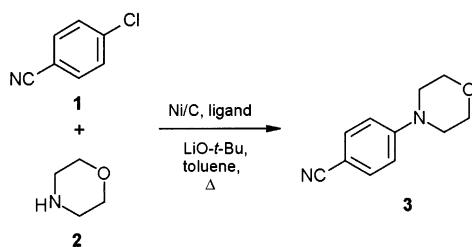
SCHEME 1.   Aromatic Amination

TABLE 2.   Results of Aromatic Aminations Using Ni(0)/C Formed under Different Reducing Conditions

entry	reducing agent for Ni(II)/C	phosphine ligand	time [h]	conv [%][a]	3 [%][a]
1	BuLi	dppf[b]	1	99	83
2	H_2	dppf	1	67	51
3	BuLi	PPh_3[c]	1.5	96	75
4	H_2	PPh_3	1.5	55	42

[a] By quantitative GC. [b] 0.5 equiv relative to nickel, cf. ref 18. [c] 4.0 equiv relative to nickel, cf. ref 33.

to the newly generated Ni(0) and can be detected in high concentrations in regions near the conglomerates (with a ratio of 1:2−1:3 Ni:P).

The tendency of nickel to migrate within the charcoal matrix, however, changes with increasing temperatures, as noted in the literature,[28,32] and is further documented by TEM analyses on Ni(0)/C prepared by heating Ni(II)/C to 425 °C in a hydrogen atmosphere (1 atm) over time. Under these conditions nickel atoms sinter together[10,28,32] to form almost spherical, monocrystalline particles with sizes up to 50 nm (average particles being in the range of 5 to 10 nm), clearly indicated by dark, sharp-edged regions in the TEM data (Figure 1, bottom left). For these crystallites, the lattice fringes are visible at sufficient amplification as parallel lines (Figure 1, bottom right). These nickel clusters are stabilized by subsequent addition of PPh_3 in THF, forming a phosphine shell around the particles (with a ratio of ca. 2.5:1 Ni:P).

While differences in metal distribution observed between the first and second generation catalyst did not influence catalyst activity after BuLi reduction,[27] thermally treated catalyst showed significant differences in activity. For example, with aromatic aminations of *p*-chlorobenzonitrile (**1**) with morpholine (**2**) (Scheme 1, Table 2), and Kumada couplings of *m*-chlorotoluene (**4**) with phenyl and butyl Grignard **5** (Scheme 2, Table 3), the conversion of aryl chloride after an identical time frame reached only a level of 47% (Table 3, entry 4 vs 3) to 67% (Table 2, entry 2 vs 1) compared to results obtained with Ni(0)/C formed via a BuLi- or Grignard-based reduction, respectively.[18,33] Decreased reactivity of the Ni(0)/C, formed upon initial heating of Ni(II)/C in an hydrogen atmosphere, may be due to chemisorbed H_2 still present at the beginning of the reaction,[6,28] thus blocking active sites for oxidative addition of the aryl chloride. Such a chemisorbed Ni−H-species should, however, cause

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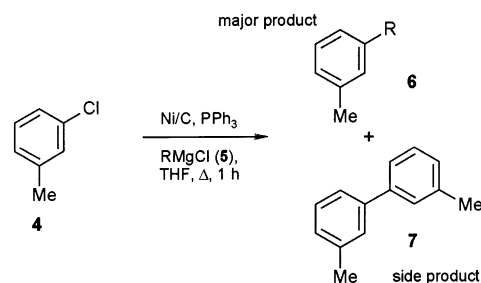
SCHEME 2.   Kumada Coupling

TABLE 3.   Results of Kumada Couplings Using Ni(0)/C Formed via Different Reducing Agents

entry	reducing agent for Ni(II)/C	R in 5	conv. [%][a]	6 [%][a]	7 [%][a]
1	PhMgCl[b]	Ph	100	81	2.5
2	H_2	Ph	54	50	0.5
3	BuMgCl[b]	Bu	66	40	2.7
4	H_2	Bu	47	25	0.2

[a] By quantitative GC; all reactions run with 2 equiv of PPh_3 relative to nickel, reaction time 1 h. [b] cf. ref 33.

hydrodehalogenation as a side reaction,[13,26] which was not observed during these reactions to any significant degree.

A TEM picture prepared for a Ni/C sample obtained from filtration of an incomplete Kumada coupling reaction mixture revealed the nickel distribution to be essentially the same as that observed prior to the reaction. An unambiguous analysis, however, was hampered by the presence of relatively large amounts of magnesium salts (from the Grignard reagent).

The structural data clearly reveal the important role played by the impregnation procedure in determining the final catalyst texture, but not necessarily catalyst activity, as long as significant heating to elevated temperatures is avoided. Our new method for generating Ni(II)/C,[27] therefore, includes a well-defined temperature and time regimen that reproducibly leads to active catalyst.

Heterogeneous vs Homogeneous Catalysis. For a truly heterogeneously catalyzed process based on Ni(0)/C and involving 'anchimeric effects', thermally treated material should lead to a more effective catalyst, since TEM data show nickel particles compared to conglomerates in BuLi-reduced samples. Therefore, reaction rates should be higher using catalyst prepared under the former set of conditions, mitigating the effect of having fewer metal atoms catalytically available in larger particles. However, this is not the case according to the results shown in Tables 2 and 3. Thus, either different mechanisms prevail for differently reduced Ni(0)/C with catalysts which rely on anchimeric effects being slower, or such a mechanism may be invalid for the catalysis presented herein. The catalytic cycle may be maintained only by nickel in solution (Ni_{sol}), resulting from bleeding from the support, and nickel conglomerates are a better source of atomic nickel than are nickel particles formed via heat treatment of Ni(II)/C in the presence of hydrogen. Even if the larger particles were released during the reaction, their redox potential should be higher than that of atomic nickel,[34] resulting in lower activity toward oxidative addition. Furthermore, coordination sites within the particles would be blocked by other nickel atoms,

TABLE 4. Percentage of Nickel Bleed from Ni/C Based on Reaction Type

reaction type	procedure	cold filtration Ni_{sol} [%][a]	hot filtration Ni_{sol} [%][a]
Suzuki	[b]	0.44[b]	1.0
Kumada	[c]	2.7[c]	2.6−6.8
	[d]	–	1.0−1.4
amination	[e]	2.9[e]	0.5
	[d]	–	1.2
	[f]	–	0.5
Negishi (RZnX)	[g]	3.0[g]	–
hydrodehalogenation	[h]	3.0[h]	–

[a] Determined by ICP-AES. [b] cf. ref 16. [c] cf. ref 17. [d] cf. ref 33. [e] cf. ref 18. [f] Ni(II)/C was reduced with hydrogen (1 atm) at 425 °C for 4.5 h. [g] cf. ref 15. [h] cf. ref 19.

raising the same mechanistic questions as with Ni_C. Moreover, ligand scrambling, as oftentimes seen in Kumada couplings, is not likely to apply directly to Ni_C or nickel particles since simultaneous coordination of phosphine and aryl chloride (via oxidative addition) at the reaction site is required.[35]

To assess the level of participation by Ni_{sol} in Ni/C-mediated conversions, filtrates of reaction mixtures were analyzed for nickel content by atomic absorption or emission spectroscopy. As noted by others, certain reaction parameters can lead to higher concentrations of metal in solution. Interactions between the metal and an aryl halide,[23,25] as well as reaction temperature at the time of filtration,[24] seem to play significant roles. Desorption of palladium from Pd/C was also postulated to be initiated or promoted to varying degrees by the level of added PPh_3,[5] or by different bases in Heck reactions.[25,26] For Ni/C, the Ni_{sol} content was usually determined by ICP-AES (inductively coupled plasma atomic emission spectroscopy)[36] after filtration of a cooled reaction mixture, and was found to be in the range of 0.4 to 3.0% of the original nickel used as Ni/C (Table 4). When filtrations were performed directly on hot reaction mixtures, the amounts of Ni_{sol} remained essentially within the same range. No apparent trend was noted, as the amounts of Ni_{sol} after hot filtration were higher for Suzuki[16] and Kumada couplings (of **4** with **5**, Scheme 2), but lower for aromatic aminations (of **1** with **2**, Scheme 1) than for cold filtered samples. These results are in contrast to a reported increase of metal in solution by a factor of 15 for Pd/support-mediated carbonylation reactions when switching from a cold to hot filtration of a reaction mixture.[24]

Several other parameters were analyzed for their effect on nickel bleeding from Ni/C. When the catalyst precursor Ni(II)/C was stirred in dioxane at room temperature, a metal leach of below 0.1% was observed. Heating this mixture at reflux, however, or reduction at room temperature with BuLi in the presence of four equiv of PPh_3

increased this amount to ca. 0.3%. Addition of base and/or salts such as K_3PO_4 and LiBr (as used for Suzuki couplings)[16] had no influence on the detectable Ni_{sol} concentration, whereas interaction of the aryl chloride with Ni(0)/C at reflux increased bleed to 0.9%. The amount of Ni_{sol}, however, proved to be independent of ligand concentration (2, 4, and 6 equiv of PPh_3 were used), in contrast to initial speculation regarding allylic substitutions catalyzed by Pd/C[5] which, however, did not survive scrutiny by different 'three-phase tests'.[22] Interesting work by Arai et al. dealing with metal leaching and re-deposition with different Pd/support catalysts in Heck reactions concluded that palladium accumulates in solution over time (for Pd(0)/C, a maximum of ca. 55% Pd_{sol} was detected after 1 h). Ultimately, however, it is re-deposited almost entirely back onto the support, especially upon consumption of the aryl iodide.[26] Such a time-dependent profile was not observed for the chemistry of Ni/C. Thus, at any stage of a reaction, the amount of detectable Ni_{sol} remained essentially constant and extremely low, in contrast to that found occasionally for Pd/C.[24−26] Interestingly, use of tetramethyldisiloxane in tandem with Ni/C led to detectable Ni_{sol} levels as high as 80%,[19] whereas triphenylsilane released only 7% nickel (albeit under modified reaction conditions).

From these observations new questions arose, in particular as to whether (1) the detected amount of Ni_{sol} is enough to account for the yields in nickel-catalyzed reactions reported in the literature;[11] (2) filtration/ICP analyses are capable of accurately revealing the level of Ni_{sol}; (3) there is an equilibrium between Ni_C and Ni_{sol}, or bleeding of the catalyst occurs solely just at the beginning of the reaction; (4) the chemistry is performed mainly by Ni_C or by Ni_{sol}. The latter question has been previously addressed by filtration of the catalyst during an ongoing reaction, and then reexposing the Ni/C-free filtrate to the reaction conditions to see if the extent of conversion increased.[6,15,37] Generally, such tests may be misleading, since during the filtration process substrates and/or reagents could be re-deposited on the charcoal to varying extents. Thus, failure of a filtered reaction mixture to achieve additional product formation does not guarantee that only low levels of transition metal are present in solution during a reaction with Ni/C.

Control reactions were carried out using 5% of the original 0.05 equiv of Ni/C in solution (relative to aryl chloride, i.e. 0.0025 equiv of $NiCl_2(PPh_3)_2$), assumed to reflect the extent of Ni_{sol} as determined by ICP, but which was *not* enough to complete Kumada couplings of chlorotoluene **4** (Table 6, entry 2) or aminations of chlorobenzonitrile **1** (Table 5, entries 2, 5) using reaction times that normally lead to 100% conversion (cf. Table 5, entries 1, 4 and Table 6, entry 1). The observed turnover number (TON) in the presence of only 0.0025 equiv of Ni was ca. 100, and so reactions with 0.009 equiv of Ni_{sol} (to aryl chloride) were expected to go almost to completion, which was found to be the case (Table 5, entries 3, 6, and Table 6, entry 3). Given these TONs, catalysis by Ni_{sol} cannot account for the 100% conversion normally observed using 0.05 equiv of Ni/C, so these reactions appear to be due to a combination of heterogeneous and homogeneous

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(36) *Inductively Coupled Plasma Mass Spectrometry*; Montaser, A., Ed.; Wiley-VCH: New York, 1998.

(37) For further applications of this method, see work cited in ref 25.

TABLE 5. Amination Reactions of 1 with 2 in the Presence of Varying Amounts of Ni$_{sol}$

entry	equiv of Ni[a]	source of Ni	BuLi reduction[b]	conv [%][c]	3 [%][c]	TON[d]
1	0.05	Ni/C	no	100	86	20
2	0.0025	NiCl$_2$(PPh$_3$)$_2$	no	23	20	92
3	0.009	NiCl$_2$(PPh$_3$)$_2$	no	98	92	109
4	0.05	Ni/C	yes	100	85	20
5	0.0025	NiCl$_2$(PPh$_3$)$_2$	yes	18	13	72
6	0.009	NiCl$_2$(PPh$_3$)$_2$	yes	100	91	111

[a] Relative to aryl chloride. [b] For procedures with and without prior BuLi reduction of Ni(II), see ref 18 and ref 33, respectively. [c] By quantitative GC; reactions run with 0.5 equiv of dppf relative to nickel, 2 h. [d] Numbers based on conversion.

TABLE 6. Kumada Couplings of 4 and 5 in the Presence of Varying Amounts of Ni$_{sol}$

entry	equiv of Ni[a]	source of Ni[b]	conv [%][c]	6 [%][c]	7 [%][c]	TON[d]
1	0.05	Ni/C	100	81	2.5	20
2	0.0025	NiCl$_2$(PPh$_3$)$_2$	29	16	2.0	116
3	0.009	NiCl$_2$(PPh$_3$)$_2$[e]	85	67	1.6	94

[a] Relative to aryl chloride. [b] Without prior BuLi reduction of Ni(II) and without added LiBr; run in the presence of 2 equiv of PPh$_3$ relative to nickel, 1 h; see ref 33. [c] By quantitative GC. [d] Numbers based on conversion. [e] Ni(0) had to be stabilized by an additional 2 equiv of PPh$_3$.

TABLE 7. Readsorption of Ni$_{sol}$ onto Charcoal

entry	NiCl$_2$(PPh$_3$)$_2$ [mmol]	adsorbance	Ni/C-loading [mmol/g]	aryl chloride	Ni$_{sol}$ [%][a]
1	0.038[b]	dry C[c]	—	none	1.0
2	0.038[b]	Ni/C[c]	0.333	none	0.7
3	0.038[b]	Ni/C[c]	0.594	none	1.3
4	0.038[d]	dry C[c]	—	present	1.0
5	0.019[d]	Ni/C[e]	0.594	present	5.0/2.5[f]

[a] Determined by ICP-AES after hot filtration. [b] Ni(II) was reduced with BuLi. [c] Same amount of charcoal in the mixture. [d] No prior reduction of Ni(II) with BuLi. [e] 0.019 mmol Ni/C added; thus, only ca. half the amount of charcoal in this mixture. [f] First percentage refers only to the amount of NiCl$_2$(PPh$_3$)$_2$ used, second to the total amount [NiCl$_2$(PPh$_3$)$_2$ + Ni/C].

catalysis. Alternatively, the amounts of Ni$_{sol}$ as measured by ICP after filtration may not reflect the actual levels of Ni$_{sol}$ present during the reaction.

If the latter were true, the supporting charcoal must retain Ni$_{sol}$ during filtration of a hot reaction mixture. To determine the adsorption[38] capacities of the support during this process, standard aromatic aminations were run with and without substrate using 0.05 equiv of NiCl$_2$-(PPh$_3$)$_2$ plus an amount of dried charcoal (Table 7, entry 1 vs 4) corresponding to that normally included when using 0.05 equiv of Ni/C. The nickel content in solution was determined by ICP after hot filtration. Similar experiments were then performed with additional Ni/C of varying loadings instead of the dried charcoal (entries 2, 3) so as to evaluate the extent to which existing metal sites on the support attract Ni$_{sol}$. Quite unexpectedly, these readsorption tests in the absence of aryl chloride (entries 1−3) showed (by ICP) uptakes as high as 99% of the original amount of Ni$_{sol}$ independent of preexisting nickel loadings on the support. For the two examples involving an aryl chloride and an amine (entries 4, 5),

the overall amount of nickel was kept constant so that the conversions of starting material became comparable. Both aminations were complete within 1 h, and after hot filtration, the amount of Ni$_{sol}$ in the presence of dry charcoal was again only 1% of that originally used (entry 4). When the reaction was run using less NiCl$_2$(PPh$_3$)$_2$ (0.025 equiv) and 0.025 equiv of Ni/C, 5% of the 0.025 equiv of NiCl$_2$(PPh$_3$)$_2$ used were found in the filtrate (or 2.5% of the total nickel present; entry 5). This increase of recovered Ni$_{sol}$ (from 1.0 to 2.5%; cf. entries 4 and 5) can be explained in that the amount of (dried) charcoal involved in this latter experiment (entry 5) was about half that involved in the reaction using only dried charcoal (entry 4).

Since the amounts of Ni$_{sol}$ detected after readsorption are comparable to levels obtained for the reactions listed in Table 4, ICP data becomes unreliable as a true indicator of nickel bleed from the support. Rather, these observations lead to the likelihood that the actual amount of available nickel in solution is far greater than was originally expected, potentially even surpassing the 0.009 equiv of Ni$_{sol}$ relative to aryl chloride (i.e., 18% bleeding from the original 0.05 equiv of Ni/C; i.e., 0.009 equiv of Ni$_{sol}$/0.05 equiv of Ni/C), which is more than enough homogeneous catalyst to effect these aminations (Table 5, entries 3, 6) and Kumada couplings (Table 6, entry 3). Clearly, the filtration process occurs too quickly to wash out all the Ni$_{sol}$ trapped within the charcoal matrix. The nature of the interactions of Ni$_{sol}$ with the pore structure of the charcoal remains unknown. There might be an equilibrium established for Ni$_{sol}$ with only 1% nickel outside and 99% inside the pores, with either (1) the Ni$_{sol}$ trapped mainly within a 'labyrinth'; hence, a sort of 'mechanical occlusion',[28] or (2) there might be interactions with the support, including weak Van der Waals attractions, stronger Coulombic interactions, ion exchange, interactions with nickel nuclei on the support, or even formation of complexes which are akin to those formed with graphite as a π-ligand.[32,39] Whatever the interaction(s), the net result would be Ni$_C$ as a 'storage device' from which Ni$_{sol}$ could be released during a reaction. It could not be excluded at this point that such a readsorption of nickel does not result in Ni$_C$ which is performing heterogeneous surface chemistry. Aryl halides apparently act as a 'shuttle' via oxidatively adding to Ni(0),[23,25] thereby transforming the metal into a species which is more prone to exit the pores of the support (vide supra). Silanes are somehow more effective than aryl halides at releasing nickel from the pores, most likely also initiated by an oxidative addition event.[40]

Reactions with Polymer-Bound Ligands: The 'Three-Phase Test'. Further evidence for potential participation of Ni$_{sol}$ in coupling reactions catalyzed by Ni/C was garnered from a set of experiments based on a 'three-phase test',[21−23] in our case using polymer-bound PPh$_3$ as ligand.[41] Given that solid-supported PPh$_3$ should only interact with Ni$_{sol}$ outside the matrix (and not with Ni$_C$),[21a] other preconditions had to be established so that

(38) 'Adsorption' is used here in a broad sense, including the trapping of substrates within the martix.

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TABLE 8. Preliminary Experiments for the 'Three-Phase Test' with Polymer-Bound PPh$_3$

entry	reaction type	Ni source	ligand	conv [%]^a	yield [%]^a	7 [%]^a
1	amination^b	Ni/C	PPh$_3$	100	78	–
2	amination^b	Ni/C	–	27	2	–
3	amination^b	NiCl$_2$	polymer	100	52	–
4	amination^c	Ni/C	PPh$_3$	67	50	–
5	amination^c	Ni/C	–	22	3	–
6	amination^c	NiCl$_2$	polymer	100	74	–
7	Kumada^d	Ni/C	PPh$_3$	86	77	5.6
8	Kumada^d	Ni/C	–	100	60	25
9	Kumada^{d,e}	NiCl$_2$	polymer	70	47	6.8
10	Kumada^{d,e}	Ni/C	polymer	42	24	2.4

^{a} By quantitative GC. ^{b} Ni(II) was reduced with BuLi; total reaction time 2 h. ^{c} No prior Ni(II) reduction with BuLi; total reaction time 2 h. ^{d} LiBr added according to ref 17, reaction time 1 h. ^{e} Same result after 2 h.

the derived data would be meaningful. First, with 0.05 equiv of Ni$_{sol}$, supplied in the form of anhydrous NiCl$_2$ (instead of Ni/C), a coupling reaction would need to be complete within the usual time frame in order to show that the polymer-bound ligand is capable of mediating the reaction as long as enough Ni$_{sol}$ is present. Second, a reaction in the absence of phosphine had to show no significant product formation, otherwise any positive result with the supported ligand could also, at least partly, result from coupling under ligandless conditions. As can be seen from Table 8, aromatic aminations (both variations; Scheme 1) did qualify for such a 'three-phase test'; the ligandless reaction gave at most only 3% product (entries 2, 5), while the polymer/NiCl$_2$-catalyzed transformation went to completion (entries 3, 6). However, Kumada coupling of aryl chloride **4** and PhMgCl (**5**) was not a good reaction for this test, as the ligandless version led to 60% product along with 25% homocoupling of the aryl chloride (entry 8) while the polymer/NiCl$_2$-based reaction stopped at 70% conversion (entry 9). Therefore, amination of *p*-chlorobenzonitrile (**1**) using morpholine (**2**), either with or without prior reduction of the Ni(II)/C precursor by BuLi, was used to test different ligand combinations to gain insight into the nature of the effective nickel catalyst.

Our strategy (Scheme 3) is discussed on the basis of the data obtained from aminations following BuLi reduction of Ni(II). Data from the second set of experiments (displayed in Table 9), i.e., aminations without prior reduction of Ni(II) with BuLi, eventually led to the same conclusions. Initial reactions were run using four equiv of polymer-bound PPh$_3$, which can only complex with Ni$_{sol}$ derived from bleeding of Ni/C. The data after two and 4 h clearly show that Ni$_{sol}$ loses all activity shortly after 2 h, giving a maximum of 62% conversion (entries 1, 2). The remaining 38% of starting material which cannot otherwise be consumed (since Ni$_C$ cannot interact with polymer-bound PPh$_3$), might generally react further with Ni$_C$ upon subsequent addition of PPh$_3$ (in solution) to the reaction mixture after this 2 h period, if Ni$_C$ was a catalytically active component. The result obtained from such an experiment (i.e., after an initial 2 h period followed by another 2 h reaction period where PPh$_3$ had been added in solution), however, was similar to that observed with polymer-bound phosphine alone after 4 h (compare entry 3 with entry 2). Thus, either PPh$_3$ can

SCHEME 3. Strategy for 'Three-Phase Tests' to Distinguish Ni$_{sol}$ from Ni$_C$ ('entries' refer to Table 9)
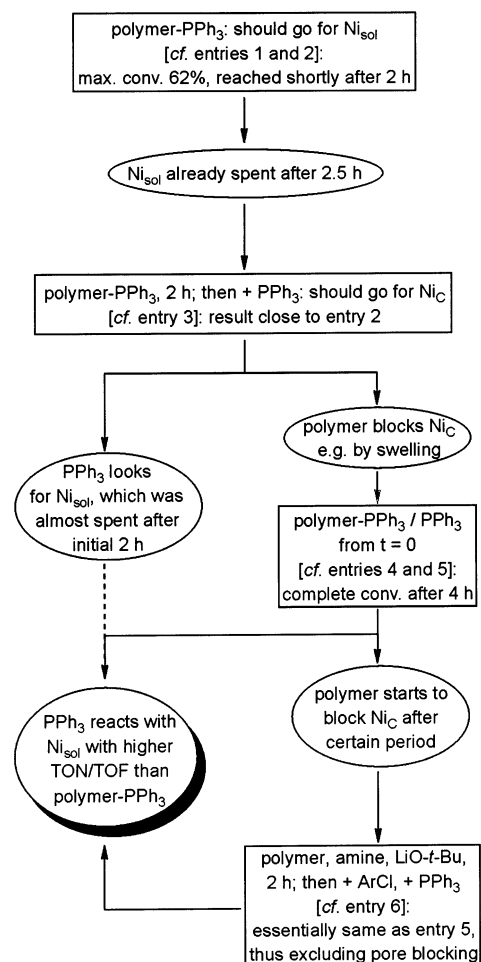
TABLE 9. 'Three-Phase Test' According to Scheme 3

entry	time [h]^a	conv [%]^b	3 [%]^b	conv [%]^c	3 [%]^c
1	2	54	35	49	30
2	4	62	46	56	37
3	2	71	55	52	33
4	2	87	70	63	47
5	4	100	86	71	60
6	4	95	84	84	72
7	2	71	56	–	–
8	4	76	60	64	49

^{a} Final reaction time at reflux, in addition to any pretreatment; cf. Scheme 3. ^{b} Ni(II) was reduced with BuLi; by quantitative GC. ^{c} No prior Ni(II) reduction with BuLi; by quantitative GC.

catalyze the reaction only with Ni$_{sol}$, the activity of which has already been lost during the initial couplings with polymer-bound PPh$_3$, or the polymer blocks the pores, e.g. by swelling, and prevents PPh$_3$ from reaching the still active Ni$_C$. To check the latter explanation, another sample was run with a preformed mixture of PPh$_3$ and polymer-PPh$_3$, which now resulted in complete conversion after the same 4 h period (entries 4, 5). Thus, this system seems to be more active than that with just polymer-based ligand. This could be due to either competition of ligand types for the same Ni$_{sol}$, with PPh$_3$ in solution giving rise to higher TONs and turnover frequencies (TOFs) compared to supported PPh$_3$, or there is a

combination of reactions with both Ni_{sol} and Ni_C early in the scheme, and it takes time for the polymer to block the pores of Ni/C effectively. The latter was excluded by experiment in which reduced Ni/C, morpholine (2), the base, and polymer-bound PPh_3, essentially all ingredients other than the aryl chloride, were heated in toluene at reflux for 2 h. This amount of time should have been long enough to cause significant pore blocking, assuming this phenomenon is actually taking place (cf. entry 3). After this time, chlorobenzonitrile 1 and PPh_3 were added and the mixture heated for an additional 4 h. If pore blocking had occurred, the result should be similar to that obtained with the polymer-bound PPh_3-based reaction (entry 2). Should this hypothesis be invalid, the result should resemble that realized from the reaction with premixed PPh_3 and polymer-bound PPh_3 (entry 5). Clearly, from this comparison (entry 6 vs entries 2, 5), pore blocking is not a factor in these aminations. A control experiment with only added aryl chloride (no additional PPh_3) after the first 2 h of heating, gave increased conversions (compare entries 7, 8 with 1, 2) that were still clearly below the 95% level already noted (entry 6). Thus, pretreatment for 2 h is not essential for activation of the catalytic system. The conclusion drawn from these data is that the catalysis is done by Ni_{sol} as a homogeneous catalyst, while Ni/C seems to function merely as a heterogeneous reservoir for this species. Furthermore, the TONs and TOF using PPh_3 seem to be higher than those with polymer-bound PPh_3, not surprising for a reaction between a macroscopic substrate and a polymer-ligated catalyst.[7]

Even though a related set of experiments for Kumada couplings was inconclusive (vide supra, Table 8), a similar assumption was reached since the analogous reaction with Ni/C in the presence of polymer-bound PPh_3 stopped after 42% conversion (Table 8, entry 10), whereas the ligandless variant did go to completion (Table 8, entry 8). If Ni_C was an active participant in the ligandless reaction, this species should have been equally effective in the polymer−PPh_3 mediated reaction, since the latter ligand is not likely to interact with Ni_C. Therefore, it is most likely that heterogeneous nickel (Ni_C) plays only a minor role, if any, as the catalytically active species. Furthermore, from the TONs for Ni_{sol} in the presence of polymer-bound PPh_3 (indicative of a 2 h lifetime for aminations and even less for Kumada couplings; cf. Table 8, entry 10), together with the fact that Ni_{sol} as detected by ICP-AES does not accumulate over time (vide supra), it can be concluded that the nickel bleeding from Ni/C is most likely not continuous,[25] but rather a one-time event during the first minutes of the reaction.[33,42]

Since the vast majority of active Ni_{sol} seems to be located within the channels of the charcoal as suggested from readsorption tests (vide supra), the question arises as to whether the chemistry is taking place there as well. Alternatively, the small amount of Ni_{sol} outside the pores could be catalyzing the reaction, which is continuously undergoing exchange with 'fresh' Ni_{sol} by diffusion in and out of the pores. An experiment designed to examine the kinetics of these aromatic aminations gave highly un-
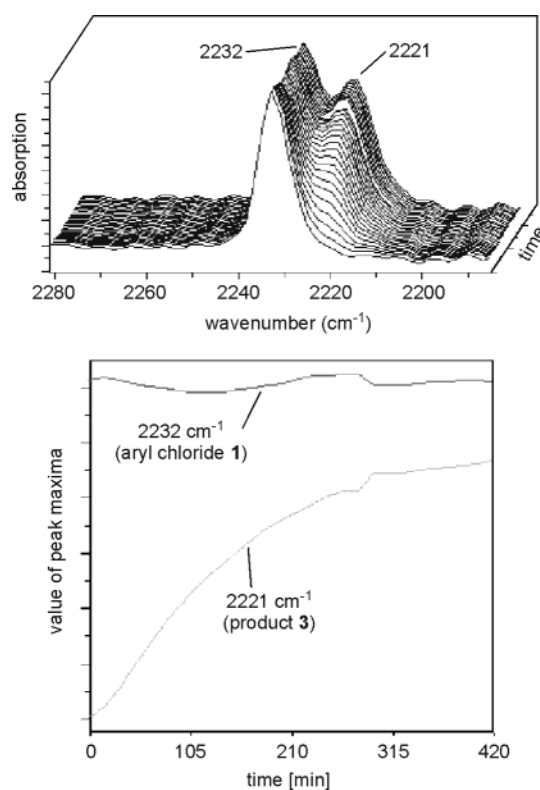

FIGURE 2. React-IR analysis: amination of chlorobenzonitrile 1 with morpholine (2).

usual adsorption profiles for educt and product. Progress in the amination of 1 with 2 was followed by React-IR at 110 °C, monitoring peaks for the nitrile groups in chloroarene 1 and in product 3 (Figure 2). A kinetic analysis of the data was precluded due to major overlap of IR signals. Moreover, the reaction course was altered most likely by contact of the catalytic system with the probe, which caused the extent of conversion to stop at ca. 22%. From the plot of the IR maxima, 2232 cm^{-1} for 1 and 2221 cm^{-1} for 3, however, it is curious that the concentration of the starting material in solution outside the support remained relatively constant while the product peak simultaneously increased. Thus, it is possible that a considerable amount of starting material is present within the matrix, undetectable by the probe, yet where it is converted to product.[43] For reasons that are not obvious, the product must possess some structural or electronic features resulting in its quick diffusion out of the pores. Another explanation is that the transformation occurs outside the pores, and the support again serves as a storage device, in this case for 1, helping to maintain a constant concentration of 1 outside the pores while not retaining product 3 to any significant degree.

Higher Loadings of Ni/C. The effectiveness of our newly established procedure for preparing Ni/C (i.e., including pretreatment with ultrasound)[27] was tested with regard to achieving higher loadings of nickel on charcoal. Our standard level is ca. 0.59 mmol Ni per gram catalyst, or about 3.5% Ni/catalyst by weight. For com-

(42) For a study concerning Pd/C-mediated Heck reactions during which Pd_{sol} concentrations reached a maximum after ca. 1 h reaction time, see ref 26; in the case of Ni/C, however, a trace level of bleed seems to occur in minutes.

(43) Macropores have average diameters of up to 500 nm (and even higher) and contribute up to 35% of the pore volume. Even mesopores (5−20 nm) should offer enough space for Ni_{sol} chemistry (up to 15% of total pore volume).[28,30,32]

TABLE 10. Amination and Kumada Couplings with Higher Loaded Ni/C

entry	reaction type	Ni/C-loading [%]	time [h]	conv [%][a]	yield [%][a]	7 [%][a]	Ni$_{sol}$ [%][b]
1	amination[c]	3.5	1.5	100	87	—	—
2	amination[c]	10	3	37	12	—	—
3	amination[c]	15	3	45	—[d]	—	—
4	amination[c]	10	4	44	17	—	—
5	amination[c]	15	4	51	—[d]	—	—
6	amination[e]	3.5	2	100	86	—	1.2
7	amination[e]	10	2	66	55	—	0.7
8	amination[e]	15	2	47	39	—	—
9	amination[e]	10	3	100	83	—	—
10	amination[e]	15	3	58	50	—	0.6
11	amination[e]	15	4	70	60	—	—
12	amination[e]	15	8	69	58	—	—
13	Kumada[f]	3.5	1.5	100	83	7.2	2.6
14	Kumada[f]	10	1.5	84	64	1.9	1.5
15	Kumada[f]	15	1.5	56	40	0.4	—
16	Kumada[f]	10	2.5	100	81	2.4	—
17	Kumada[f]	15	2.5	68	51	0.7	0.9
18	Kumada[f]	15	4.5	90	68	0.8	—

[a] By quantitative GC. [b] Determined by ICP-AES after hot filtration; percentage given relative to the amount of nickel added as Ni/C. [c] Ni(II)/C was reduced with BuLi; 0.5 equiv of dppf relative to nickel used. [d] Observed addition product of morpholine to the nitrile group. [e] No prior Ni(II)/C reduction with BuLi; 0.5 equiv of dppf relative to nickel used. [f] 4 equiv of PPh$_3$ relative to nickel + LiBr added according to ref 17.

parison purposes, catalysts with 10% and 15% Ni/catalyst were prepared, notwithstanding the already observed drop in catalyst activity which can accompany such high loadings.[32] The protocol developed proved to be quite efficient, as complete mounting of the Ni(NO$_3$)$_2$·6H$_2$O occurred such that no nickel salt was recovered in the filtrate after washing of the impregnated Ni(II)/C with H$_2$O (cf. Table 1). Activities of both the 10% and 15% catalysts were next determined in Kumada couplings of **4** with PhMgCl (**5**) (cf. Scheme 2) and aromatic aminations of **1** with **2** (cf. Scheme 1), using 0.05 equiv of nickel relative to aryl chloride. For aminations, two different protocols were used; one included a prior reduction of the Ni(II)/C with two equiv of BuLi (Table 10, entries 1–5), the other called for no formal reduction (entries 6–12).[33] In all three transformations (a Kumada coupling and two different aminations), catalyst activity decreased significantly with increasing nickel loading, as expected from literature precedent.[32] In the case of Kumada couplings, the extent of conversion using 10% loading decreased to 84% relative to reactions with 3.5% Ni/C (entry 13 vs 14). The conversion dropped further to 68% when using a 15%-catalyst loading (entry 14 vs 15 and 16 vs 17). Reactions with the 15% catalyst loading did not go to completion even after 4.5 h (entry 18), indicating that the active nickel was spent. This suggests that less metal is chemically available with increased loading of Ni/C, supported by ICP data which revealed less detectable Ni$_{sol}$[44] with increasing nickel loading on the support (entries 13, 14 and 17).

Another interesting aspect of these reactions is the formation of homocoupled product 3,3′-bistoluene. The higher the loading of the catalyst, the cleaner the conversion to the product **6** due to significantly less side-

(44) Recall that the amount of Ni$_{sol}$ detectable by ICP-AES apparently represents only a minor portion of available Ni$_{sol}$, most of which is 'stored' within the support.

product formation (cf. Table 10, entries 13–15), although this outcome is not readily understood.[33]

For aminations employing BuLi-reduced Ni(II)/C, the 10%-loaded catalyst resulted in at most 44% conversion and only 17% product **3** (Table 10, entries 2, 4). The 15% catalyst gave slightly higher conversions but did not yield any visible cross-coupled product **3** at all (entries 3, 5). Instead, significant amounts of a side product were detected by GCMS, the mass spectrum of which suggested that morpholine (**2**) had added to the nitrile group giving rise to an amidine-like structure. Efforts to isolate this product failed, but the same compound was observed by GCMS when chlorobenzonitrile (**1**) was treated directly with lithiated morpholine in toluene at ambient or elevated temperatures in the absence of any nickel catalyst. LiO-*t*-Bu (the base used during these aromatic aminations), in the presence of morpholine and nitrile **1**, was not sufficiently reactive by itself to significantly deprotonate morpholine to cause formation of the adduct. Only after addition of BuLi to this reaction mixture did the targeted addition product become detectable. Thus, in reactions catalyzed by 15%-loaded Ni/C, the BuLi added for purposes of reducing Ni(II)/C may not react completely and is ultimately 'quenched' in an acid/base sense by morpholine which goes on to attack the nitrile group. Residual BuLi might exist where higher loadings of nickel are involved since bigger particles may be formed during impregnation and/or pore blocking may occur,[28,32] thus excluding a certain amount of nickel from reduction. This assumption was supported by TEM and EDX data of a catalyst with 15% nickel loading, which showed a high nickel distribution throughout the charcoal, indicative of saturation of the support, with local formation of conglomerates of nickel (including nanocrystalline Ni particles; Figure 3). For the latter species, lattice fringes are again visible (Figure 3, right micrograph), but they clearly differ structurally from the particles obtained after hydrogen reduction at 425 °C (cf. Figure 1, bottom right). Apparently, at high concentrations nickel is forming colloids to some extent with a tendency to sinter. Interestingly, the Ni:P ratio was found to be extremely low (around a ratio of 20:1 to 100:1 Ni:P for regions of high nickel concentration and 1:1 to 10:1 Ni:P for average nickel distributions) compared to that from the 3.5%-loaded samples (1:2–1:3, Figure 1), despite the fact that all Ni(0)/C samples were prepared with the same amount of PPh$_3$ (4 equiv relative to nickel). This also strongly implicates pore blocking, which prevents organic material of any type from reaching nickel particles. Further support for a limited reduction of Ni(II) by BuLi is obtained from EDX data, which documents considerably greater quantities of oxygen in the conglomerates compared to the other samples, most likely due to nonreduced nickel.

Consequently, aminations with higher loaded catalysts were best performed avoiding prior BuLi reduction of Ni(II)/C.[33] The conversion dropped to 66% in going from the 3.5%- to the 10%-loaded catalyst (Table 10, entry 6 vs 7), and to 47–58% when the loading increased further from 10% to 15% Ni/C (entries 7 vs 8 and 9 vs 10), results consistent with decreasing concentrations of Ni$_{sol}$[44] detectable by ICP-AES (entries 6, 7, and 10). Intuitively, *greater* levels of Ni$_{sol}$ should be found with increased nickel loading on the support if all nickel mounted is
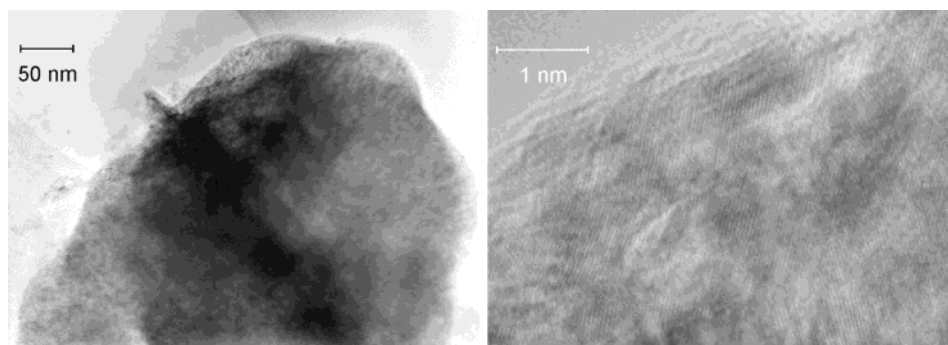
FIGURE 3. TEM analysis of Ni(0)/C with 15% nickel loading after BuLi reduction of Ni(II)/C.

TABLE 11. Amination Reactions of 1 with 2 Catalyzed by Varying Amounts of Ni/C

entry	equiv of Ni[a]	time [h]	conv [%][b,c]	3 [%][c]
1	0.05	2	100	87
2	0.025	2	90	78
3	0.025	4	100	88
4	0.0125	2	48	40
5	0.0125	4	66	57
6	0.005	2	39	33
7	0.005	4	39	31

[a] Relative to aryl chloride. [b] Without prior BuLi reduction of Ni(II)/C, 0.5 equiv of dppf relative to nickel used. [c] By quantitative GC.

TABLE 12. Results of Aminations and Kumada Couplings Catalyzed by Ni/C Stored in Air

entry	reaction type	storage [months][a]	reaction time [h]	conv [%][b]	yield [%][b]	7 [%][b]
1	amination[c]	6	1	33 (99)	23 (83)	—
2	amination[d]	5	2	56 (100)	42 (87)	—
3	amination[d]	9	5	80	73	—
4	Kumada[e]	6	1.5	76 (100)	52 (83)	10 (7.2)

[a] Catalyst was kept on the bench for the time indicated. [b] By quantitative GC; numbers in parentheses correspond to reactions using Ni/C stored under argon. [c] Ni(II)/C was reduced with BuLi, 0.5 equiv of dppf relative to nickel used. [d] No prior Ni(II)/C reduction with BuLi, 0.5 equiv of dppf relative to nickel used. [e] 4 equiv of PPh_3 relative to nickel + LiBr added according to ref 17.

available for a reaction. The opposite trend, revealed by ICP analysis, again indicates a certain percentage of nickel is excluded from participation due to pore blocking and/or the formation of bigger nickel particles.

While aminations with the 10%-loaded Ni/C can be run to completion over extended reaction times (Table 10, entry 9), the corresponding reaction involving a 15% loaded catalyst ended at ca. 70% conversion (entries 10−12). With TONs of ca. 100 for these transformations catalyzed by Ni_{sol} (cf. Table 5), and given that (1) the active nickel species obtained via reduction of $NiCl_2$-$(PPh_3)_2$ in solution and from Ni_{sol} resulting from Ni/C bleed show comparable activities, and (2) there is no Ni_C participation in the actual catalytic cycle, this leads to a net Ni_{sol} amount of 0.007 equiv available to react with the aryl chloride, corresponding to a 14% bleed of nickel from the originally used 0.05 equiv of Ni/C (i.e., 0.007 equiv of Ni_{sol}/0.05 equiv of Ni/C).

The same calculation could be applied to aminations without BuLi reduction of the Ni(II)-precursor using the standard catalyst with 3.5% nickel loading. To determine TONs for this catalyst, the amount of Ni/C used was decreased stepwise and the extent of conversion analyzed after 2 and 4 h (Table 11). A reduction from 0.05 equiv of nickel to aryl chloride (entry 1) to 0.005 (entries 6, 7) was needed to stop catalyst turnover prior to complete consumption of the aryl chloride. Recalling a TON of ca. 100 for Ni_{sol} chemistry, and having established the same preconditions as used previously, 0.0039 equiv of Ni_{sol} were needed to reach 39% conversion, corresponding to available Ni_{sol} from Ni/C of at least 78% (i.e., 0.0039 equiv of Ni_{sol}/0.005 equiv of Ni/C). As already shown by ICP-AES analyses of several reaction mixtures after filtration, only miniscule amounts of bled metal are actually found outside the charcoal network (vide supra), thus dramatically minimizing nickel content in the final products

compared to reactions run under homogeneous conditions. The calculated amounts of nickel "bleeding", 14% vs 78%, again suggest that with higher loaded catalysts, less nickel is actually available as Ni_{sol} due to more extensive pore blocking. Furthermore, the calculated level of 78% "bleeding" of Ni/C is in excellent agreement with the ca. 80% level of nickel found by ICP-AES for hydrodehalogenations with tetramethyldisiloxane,[19] where apparently the silane is shifting the equilibrium for Ni_{sol} to be strongly favored outside the matrix.

Storage of Ni/C Catalysts. Judging from the data in Table 12, which reflect both aromatic aminations and Kumada couplings with Ni/C which had been exposed to air for up to nine months, it appears to be essential that Ni(II)/C is stored in an inert atmosphere. Kumada couplings of chlorortoluene 4 and PhMgCl (5) using unprotected catalyst led to a significant loss of activity, along with formation of greater amounts of homocoupling side products.

Conclusions

Nickel-on-charcoal is a versatile 'heterogeneous' catalyst which mediates several useful organic transformations. Its removal by simple filtration usually leads to a reaction mixture containing only traces of transition metal, an important feature especially when potentially applied to syntheses of pharmaceutically valuable compounds. Thus, the 'green' nature of such catalysts should also not go unnoticed. The revised protocol for preparation of Ni/C offers cost advantages compared to our initial procedure; it is faster, simpler, and affords reproducible catalyst activities. As was shown by TEM analyses, exposure to ultrasound as part of the protocol leads to an enhanced distribution of nickel atoms within the

support structure, although there is no significant impact of this feature on catalytic activity for the reactions tested. Nonetheless, such treatment encourages complete impregnation of nickel nitrate on the charcoal, even up to levels as high as 15% nickel by weight. With increased loadings, however, catalyst activities as measured by aminations and Kumada couplings of aryl chlorides are *decreased*. Reductions of the Ni(II)/C to active Ni(0)/C using hydrogen at 425 °C, as opposed to use of BuLi at ambient temperatures, lead to formation of large monocrystalline nickel particles which, likewise, translates into reduced catalyst activity.

ICP-AES in combination with experimental results from cross-coupling reactions with different types and quantities of nickel catalysts clearly implicate participation of a homogeneous nickel species in the catalytic cycle, requiring that nickel bleeds from the solid support under the reaction conditions. The amount of nickel in solution detected by ICP-AES could be slightly increased by (1) heating the reaction mixture; (2) reducing Ni(II)/C with *n*-BuLi; and (3) by addition of the aryl chloride, although these levels proved to be independent of ligand (PPh$_3$) concentration, or reaction time. Readsorption of 99% of a standard amount of nickel in solution, as used for aromatic aminations, by dry charcoal or Ni/C led to the hypothesis that ICP-detected levels of soluble nickel are misleading; in fact, they reflect only a minor amount of the catalytically available Ni$_{sol}$ which appears to be 'stored' within the charcoal network. By means of a 'three-phase test', strong indications were obtained that the catalytic cycle is supported only by nickel in solution, i.e., little-to-no coupling occurs with nickel on the surface on the support. Comparison of TONs of different reactions under differing conditions led to an estimated availability of nickel from Ni/C (up to 78%) far in excess of that indicated by ICP data. *The available nickel, therefore, must be located almost entirely within the charcoal matrix, since only small percentages can be found at any time (by ICP) outside the support.* Thus, an equilibrium between Ni$_{sol}$ both inside and outside the pores is established early during the course of a reaction. This feature allows for effective recycling of the catalyst,[19] since almost no nickel is lost during filtration after completion of the reaction, and the catalyst displays identical activities in subsequent experiments.

Comparing TEM pictures, the activity profile of differently reduced (BuLi vs H$_2$ at 425 °C) or differently loaded Ni/C catalysts can be nicely correlated with their tendency to release nickel into solution. For Ni(0)/C (from BuLi reduction of Ni(II)/C) prepared using either our first or second generation process, the extent of bleed is seemingly identical despite varying nickel distributions, perhaps due to similar structural features of the nickel conglomerates. Had true surface chemistry with Ni$_C$ been involved, a change in nickel distribution would be expected to bring about a corresponding change in reactivity profile. With larger nickel particles on charcoal, formed with either H$_2$/heat-treated catalysts or with 15%-loaded Ni/C, these are less prone to leach nickel into solution. Correspondingly, their activities drop significantly. In addition, catalysts with higher loadings of nickel suffer from pore blocking, which contributes to reduced metal exposure in solution, and thus for reduced participation in the catalytic cycle.

The data, considered in its entirety, strongly support homogeneous catalysis by nickel (Ni$_{sol}$) as the decisive mechanism for transformations based on Ni/C. The outstanding adsorption properties of the support, however, allow for recovery of almost all of the nickel participating in such homogeneous catalysis by simple filtration of reaction mixtures. Therefore, in the final analysis, Ni/C offers all the advantages of a heterogeneous catalyst, while temporarily supplying the metal in an active, mainly internal yet homogeneous state. One noteworthy implication is that reaction times for these homogeneous nickel-catalyzed cross-couplings under microwave conditions may be reduced substantially.[45] Preliminary tests along these lines already suggest that such is indeed the case. Furthermore, the possibility of using charcoal simply as a scavenger for homogeneous nickel catalysis is currently under investigation. Details of this study, along with additional methods based on Ni/C catalyzed couplings, will be reported in due course.

Experimental Section

General. All transfers of catalyst and all reactions were conducted under an argon atmosphere, if not stated otherwise. Morpholine (**2**) and *m*-chlorotoluene (**4**) were distilled prior to use, and PPh$_3$ was recrystallized from hexanes. PhMgCl and BuMgCl (1.8 M in THF) and *n*-BuLi (2.1 M in hexanes) were titrated before use. All reactions were analyzed by quantitative GC using 1,3,5-trimethoxybenzene and *p*-fluorotoluene as standards for aromatic aminations and Kumada couplings, respectively. GC response factors were determined using commercially available compounds [3-phenyltoluene (**6**, R = Ph), 3,3′-bistoluene (**7**)] or isolated material [*N*-(*p*-cyanophenyl)morpholine (**3**), 3-butyltoluene (**6**, R = Bu)]. Unequivocal identification of products **6** (R = Ph) and **7** was accomplished by GC co-injection, GCMS analyses, and TLC comparison with authentic materials. All spectroscopic data obtained after product isolation were in accord with literature values.[2g,33,46] GC analyses were performed using an HP-5 capillary column (0.25 μm × 30 m; cross-linked 5% PH ME siloxane) and a time program with 5 min at 40 °C followed by 10 °C/min ramp to 280 °C, and 20 min holding at this temp. ICP-AES analyses were done on a Thermo Jarrell Ash IRIS plasma spectrometer. Transmission electron micrographs were taken using a Hitachi HF 2000, at an accelerating voltage 200 kV, with a cold field emission electron source and a point resolution of 0.23 nm. This instrument was equipped with an EDX detector, allowing for a beam diameter down to 1.2 nm. ReactIR analyses were performed on an ASI ReactIR 1000 using a Sicomp probe.

Preparation of Ni(II)/C. Activated charcoal (5.00 g) was impregnated with Ni(NO$_3$)$_2$·6H$_2$O (727 mg, 2.50 mmol) in H$_2$O (75 mL) according to ref 15 (1st generation) or ref 27 (2nd generation).

General Procedure for Ni/C-Catalyzed Aromatic Aminations of *p*-Chlorobenzonitrile (1) with Morpholine (2) [prior reduction of Ni(II) with *n*-BuLi]. These reactions were performed according to a literature protocol,[18] using 0.750 mmol **1** (103 mg), 2.0 equiv of **2** (132 μL, 130.7 mg, 1.50 mmol), and toluene (1.4 mL, total). Generally, 0.05 equiv of Ni/C (63.1 mg, 0.038 mmol, loading: 0.594 mmol/g), 0.025 equiv of dppf (10.4 mg, 0.019 mmol) or 0.2 equiv of PPh$_3$[33] (39.3 mg, 0.150

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mmol), and LiO-*t*-Bu (72.1 mg, 0.900 mmol) were added. The premixing period of catalyst and ligand in toluene was shortened from 90 to 25 min and the time for reduction after addition of BuLi (35.7 μL, 0.075 mmol, 2.1 M) was lowered from 30 to 15 min. After each reaction (see Tables), the mixture was cooled to room temperature and with stirring, 3 mL of CH_2Cl_2 was added. The suspension was filtered through a Büchner funnel, and the cake was washed with CH_2Cl_2, petroleum ether (10 mL each), and diethyl ether (25 mL). The filtrate was refiltered, the solvent volume was reduced to ca. 1 mL, after which it was filtered through a pipet filled with glass wool, Celite, and silica gel. The GC standard was added to the resulting clear solution, and the extent of conversion and percent product formed were determined by GC. Variations in reaction conditions and results for different reactions can be found in Tables 2, 5, 8, and 12.

General Procedure for Aromatic Aminations of *p*-Chlorobenzonitrile (1) with Morpholine (2) [*without prior reduction of Ni(II) with BuLi*]. These reactions were performed according to a literature protocol,[33] using 0.750 mmol of **1** (103 mg), 2.0 equiv of **2** (132 μL, 130.7 mg, 1.50 mmol), 0.05 equiv of Ni/C (63.1 mg, 0.038 mmol, loading: 0.594 mmol/g), 0.025 equiv of dppf (10.4 mg, 0.019 mmol) or 0.2 equiv of PPh$_3$ (39.3 mg, 0.150 mmol), and LiO-*t*-Bu (72.1 mg, 0.900 mmol) in toluene (1.4 mL). Workup and analysis of the product mixture obtained were identical to the procedure above. Variations of reaction conditions and results for different reactions can be found in Tables 2, 5, 8, 11, and 12.

Kumada Couplings of *m*-Chlorotoluene (4) and Grignard Reagents 5 [*prior reduction of Ni(II) with BuLi*]. Following a literature procedure,[17] aryl chloride **4** (118 μL, 127 mg, 1.00 mmol) was treated with Grignard **5** (835 μL, 1.50 mmol, 1.8 M) at −78 °C after BuLi reduction (47.6 μL, 0.100 mmol, 2.1 M) of 0.05 equiv of Ni(II)/C catalyst precursor (84.2 mg, 0.050 mmol, loading: 0.594 mmol/g) in the presence of 0.2 equiv of PPh$_3$ (52.5 mg, 0.200 mmol) and 1.0 equiv of LiBr (86.9 mg, 1.00 mmol) in THF (1.5 mL), and finally heated at reflux. After a selected reaction time (see Tables), the mixture was cooled to room temperature and upon stirring, 3 mL of aq NH$_4$Cl solution were carefully added. The suspension was filtered through a Büchner funnel, and the cake was washed with H$_2$O, diethyl ether, petroleum ether, CH$_2$Cl$_2$ (each 10 mL), and again diethyl ether (25 mL). The biphasic filtrate was shaken, the aqueous phase was removed with a pipet, and the organic layer was concentrated under reduced pressure. The GC standard was added to the resulting clear solution, and the extent of conversion and yield of product analyzed by GC. Variations of reaction conditions and results for different reactions can be found in Tables 8, 10, and 12.

Kumada Couplings of *m*-Chlorotoluene (4) and Grignard Reagents 5 [*without prior reduction of Ni(II) with BuLi*]. Following a literature procedure,[33] aryl chloride **4** (118 μL, 127 mg, 1.00 mmol) was treated with Grignard **5** (835 μL, 1.50 mmol, 1.8 M) at room temperature in the presence of 0.05 equiv of Ni(II)/C catalyst precursor (84.2 mg, 0.050 mmol, loading: 0.594 mmol/g) and only 0.1 equiv of PPh$_3$ (26.3 mg, 0.100 mmol) in THF (1.5 mL), and then heated to reflux. No LiBr was used in this case. After a selected reaction time (see tables), workup and analysis were preformed as described above. Variations in reaction conditions and results for different reactions can be found in Tables 3 and 6.

Reduction of Ni(II)/C by Heat in an Atmosphere of Hydrogen. Standard amounts of Ni(II)/C (63.1 mg, 0.038 mmol for aminations, and 84.2 mg, 0.050 mmol for Kumada couplings; loading: 0.594 mmol/g) were placed in a Schlenk tube which was evacuated and purged with H$_2$, the process being repeated three times. Under a balloon filled with H$_2$ attached to the top of the tube, the vial was heated to 425 °C in a sand bath for 4.5 h. Upon cooling the vial to room temperature, the hydrogen atmosphere was replaced by evacuation and purging with argon. A standard amount of solvent was added (1.4 mL toluene for aminations; 1.5 mL THF for

Kumada couplings), followed by the ligand (as given in the Tables), reagents, and the substrates. All reactions were performed at temperatures used previously.[17,18] Workup and product analysis were as described above. Conditions and results can be found in Tables 2 and 3.

Preparation of TEM Samples. Sample A: Ni(II)/C (84.2 mg, 0.050 mmol, loading: 0.594 mmol/g) was stirred with 4 equiv of PPh$_3$ (52.5 mg, 0.200 mmol) in THF (1.5 mL) at room temperature for 20 min and for another 5 min after addition of 2 equiv of *n*-BuLi (47.6 μL, 2.1 M). **Sample B:** Ni(II)/C (84.2 mg, 0.050 mmol, loading: 0.594 mmol/g) was reduced under hydrogen at 425 °C for 4.5 h as described above. THF (1.5 mL) and 4 equiv of PPh$_3$ (52.5 mg, 0.200 mmol) were then added. **Sample C:** This sample represented a standard Kumada coupling of **4** with PhMgCl (**5**) for a 1 h period with prior BuLi reduction of Ni/C as described above. **General workup:** All samples were filtered through a frit under an inert atmosphere and dried without further washing. **Preparation for measurement:** The samples were mounted on a Lacey carbon grid in the dry state under argon and transported to the spectrometer with a vacuum-transfer holder.

Sample Preparation for ICP-AES. Reaction mixtures were either filtered after cooling to room temperature or directly while hot. Use of a heated filter funnel for filtration of a hot mixture did not result in significant differences compared to filtration of a hot mixture through a cold funnel. Depending on the temperature chosen for the mixture, the filter cake was washed twice with cold or boiling solvent. The filtrate was refiltered, and washing was performed with cold solvent and H$_2$O. The solvents were removed, 10 mL of 20% HNO$_3$ and 5 mL concentrated HCl were added, and the mixture was heated at reflux for 5.5 h to digest as much material into the aqueous phase as possible. Upon being cooled and diluted with H$_2$O (20 mL), the mixture was extracted with hexanes (10 mL) and CH$_2$Cl$_2$ (2 × 7 mL), and the combined organic layers re-extracted with H$_2$O. The solvent was removed from the combined aqueous phases and the ICP-AES sample was prepared by adding 2% HCl in a way that the final (estimated) nickel concentration was adjusted to between 1 and 35 ppm. If the solution was not completely clear at that point, a short filtration through glass wool in a pipet was required. Results of the following measurements are listed in Tables 4, 7, and 10.

Readsorption Tests. Without substrates: NiCl$_2$(PPh$_3$)$_2$ (0.038 mmol, 24.5 mg) and 0.5 equiv (relative to nickel) of dppf (10.4 mg, 0.019 mmol) were stirred in toluene (1.4 mL) at room temperature for 25 min, after which the Ni(II) was reduced with 2 equiv of *n*-BuLi (35.7 μL, 0.075 mmol, 2.1 M) over an additional 15 min. Then, either 56 mg dried activated charcoal (Aldrich; drying in vacuo, 100 °C, 12 h) or ca. 62 mg Ni/C with different nickel loadings (cf. Table 7) were added, and the suspension was stirred at reflux for 1 h. **With substrates:** The first reaction was run as a typical amination of chlorobenzonitrile **1** with morpholine (**2**) with prior Ni(II) reduction by BuLi. In this case, however, NiCl$_2$(PPh$_3$)$_2$ (0.038 mmol, 24.5 mg) was used instead of Ni/C, along with 56 mg of dried activated charcoal added together with the reaction partners. The second reaction was performed with 0.019 mmol of both NiCl$_2$(PPh$_3$)$_2$ (12.5 mg) and Ni(II)/C (31.6 mg, loading: 0.594 mmol/g), such that the total amount of nickel theoretically available for reaction was kept constant compared to the former reaction. All samples were worked up as described for the preparation of ICP-AES samples (hot filtration) and spectroscopically analyzed.

Three-Phase Tests. Table 9, entries 1, 2: Reactions were run according to the standard protocol for amination of chlorobenzonitrile **1** with morpholine (**2**), each with and without BuLi reduction of Ni(II)/C. The ligand dppf was replaced by 4 equiv (relative to nickel) of polymer-bound PPh$_3$ (100−200 mesh, 1.20 mmol/g). Table 9, entry 3: This reaction was performed as with that in entry 1, and after 2 h, an additional 4 equiv of PPh$_3$ (not polymer-bound) was added and

the mixture heated at reflux for an additional 2 h. Table 9, entries 4, 5: As for that in entry 1, but with both 4 equiv of PPh₃ and 4 equiv of polymer-bound PPh₃ added at the beginning. To ensure that the outcome would not be impacted by the increase (to 8 equiv) in phosphine ligand, the same reaction was performed with half the amount of each ligand, which afforded identical yields (not shown in Table 9). Table 9, entry 6: Reactions were run as with that in entry 1, but no chlorobenzonitrile **1** was initially added. After 2 h at reflux, the reaction mixture was cooled to room temperature and the standard amount of **1** added, together with an additional 4 equiv of PPh₃ (not polymer-bound). The mixture was then heated for an additional 4 h at reflux. Table 9, entries 7 and 8: Run as in entry 6, but after the first 2 h of heating, only aryl chloride **1** was added (no additional PPh₃).

Aminations Monitored by ReactIR. A standard reaction between chlorobenzonitrile **1** and morpholine (**2**) (with BuLi reduction of Ni(II)/C) was run on a larger scale (2.00 mmol aryl chloride **1**), in 4 mL of toluene in a special Schlenck tube allowing for connection to the ReactIR probe. To avoid vigorous boiling around the detection window, the reaction was heated in an oil bath adjusted to 110 °C (rather than 130 °C as usually used). The reaction was monitored for 7 h.

Aminations with Higher Loaded Ni/C. These reactions were performed according to the standard procedures, using 0.038 mmol (aminations) or 0.050 mmol (Kumada couplings) nickel added in the form of differently loaded Ni/C catalysts. Catalysts used had the following nickel loadings: 0.594 mmol nickel/g catalyst (3.5 wt %), 1.704 mmol/g (10%), and 2.556 mmol/g (15%). Results are listed in Table 10.