

Nickel-on-Charcoal-Catalyzed Aromatic Aminations and Kumada Couplings: Mechanistic and Synthetic Aspects

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Received April 29, 2002

Protocols for aromatic aminations and Kumada couplings catalyzed by 'heterogeneous' nickel-on-charcoal (Ni/C) have been revised, making them simpler and more time efficient. For both types of reactions, reduction of the catalyst precursor Ni(II)/C using *n*-BuLi prior to addition of a substrate can be avoided. Instead, in amination reactions, the amine in combination with lithium *tert*-butoxide was found to convert Ni(II)/C to active Ni(0). For Kumada couplings, direct reduction of Ni(II)/C by the Grignard reagent is easily achieved. Reactions run in the presence of triarylphosphine ligands of varying substitution patterns and with differing electronic properties provided insight into the mechanism of these nickel-catalyzed transformations. Ligandless Kumada couplings were facile with aryl Grignards, which may be a consequence of π -complexation of nickel by the aryl group in the reagent. Larger scale reactions of both types of couplings have been successfully performed, suggesting that Ni/C-based processes can be scaled-up as needed.

Introduction

Aromatic aminations and Kumada-type couplings represent powerful tools for the formation of C–N and C–C bonds, respectively. While Kumada developed a coupling strategy for aryl halides and Grignard reagents based on nickel catalysis,^{1–3} aromatic aminations are mainly performed using palladium catalysts.^{4–6} Generally, nickel(0) complexes display greater reactivity toward oxidative addition with aryl halides relative to palladium(0).^{7,8} Thus, transformations based on catalytic Ni(0) were readily performed on aryl chlorides,^{1,9–14} while

special ligands had to be developed to allow for the corresponding conversions via Pd(0) catalysis.^{8,15,16} An aromatic amination catalyzed by nickel was first reported in 1950,¹⁷ and the method was further extended by Cramer et al. in 1975.¹⁸ The real breakthrough for transition metal-catalyzed amination reactions, however, was achieved during the past decade by extensive work from the Buchwald and Hartwig groups.^{4–6,11,12}

The high reactivity of nickel toward inexpensive and readily available aryl chlorides, combined with the

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(d) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665. (e) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem.* **1995**, *107*, 1989; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844. (f) Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *Angew. Chem.* **1995**, *107*, 1992; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848. (g) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (h) Mathews, C. J.; Smith, P. J.; Welton, T. *J. Chem. Soc., Chem. Commun.* **2000**, 1249. (i) Andreu, M. G.; Zapf, A.; Beller, M. *J. Chem. Soc., Chem. Commun.* **2000**, 2475. (j) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719. (k) Carpentier, J. F.; Petit, F.; Mortreux, A.; Dufaud, V.; Basset, J.-M.; Thivolle-Cazat, J. *J. Mol. Catal.* **1993**, *81*, 1.

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advantages of heterogeneous catalysis, has led to development of a catalytic system based on nickel-on-charcoal ('Ni/C'). Applications of this reagent to several different C–C bond-forming reactions (including Kumada-type couplings), hydrodehalogenations, and aromatic aminations have already been reported.¹³ Although an extensive study has strongly implicated solution-based catalysis, Ni/C can be considered as a heterogeneous catalyst in that essentially complete recovery of the nickel in solution is ultimately achieved on the support after filtration.¹⁴ In the course of our investigations on the nature of the catalytically active species in Ni/C-mediated reactions, several interesting mechanistic and synthetic aspects of aromatic aminations¹⁹ and Kumada couplings²⁰ have been uncovered, which are the subject of this contribution.

Results and Discussion

Aromatic Amination Reactions. Aminations of aryl chlorides using Ni/C, as previously described,¹⁹ required a 90 min premixing period of Ni(II)/C and dppf in toluene prior to the addition of *n*-BuLi for reduction of this catalyst precursor to active Ni(0). From more recent studies on this catalyst, which revealed an equilibrium involving nickel in solution (Ni_{sol}) located both inside and outside the charcoal matrix which occurs during the first minutes of a reaction,¹⁴ such a long premixing is no longer justified. Furthermore, potential replacement of dppf by PPh₃ was targeted for economic reasons, in addition to exploring the possible use of reductants other than BuLi for Ni(II)/C.

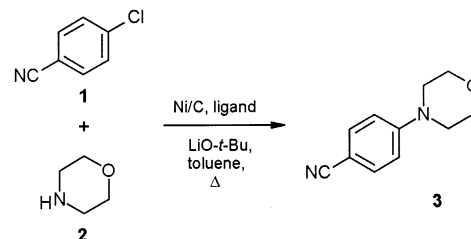
Reduction of Ni(II)/C by heat (425 °C) in a hydrogen atmosphere has already been shown to cause migration of nickel atoms and sintering, leading to bigger nickel particles with decreased activity.¹⁴ Since phosphines and phosphites reduce Pd(II),²¹ while phosphites²² and amines¹⁸ mediate reduction of Ni(II), amination of *p*-chlorobenzonitrile (**1**) with morpholine (**2**) was carried out in the presence of dppf without prior reduction of Ni(II)/C by BuLi. The mixture was simply heated at reflux after the substrate and all reagents had been added without any period of incubation. As seen from Table 1, the reaction proceeds somewhat more slowly but goes to completion with similar yields of product **3** (entry 1 vs entries 2–4). When 4 equiv of PPh₃ (instead of 0.5 equiv of dppf) were used relative to nickel, the reaction again was slower. However, the amination eventually went to completion either with (entry 1 vs entries 6, 7) or without (entries 3, 4 vs entries 8–10) prior reduction of Ni(II) by BuLi (albeit with differing amounts of the two ligands; vide infra), although yields varied slightly (compare entries 7, 10 vs entries 1, 4). Also examined was dppp, as it is electronically relatively similar to PPh₃ but offers bidentate complexation as with dppf. It has also been described

TABLE 1. Aromatic Aminations of **1** with **2** Catalyzed by Ni/C

entry	phosphine ligand	BuLi	time [h]	conv [%] ^a	3 [%] ^a
1	dppf ^b	yes	1	99	83 ^c
2	dppf ^b	no	1	78	65
3	dppf ^b	no	1.5	93	77
4	dppf ^b	no	2	100	86
5	PPh ₃ ^d	yes	1	72	47
6	PPh ₃ ^d	yes	1.5	96	75
7	PPh ₃ ^d	yes	2	100	78
8	PPh ₃ ^d	no	2	67	50
9	PPh ₃ ^d	no	3	83	63
10	PPh ₃ ^d	no	6	100	76
11	dppp ^e	yes	1	12	0.4
12	dppp ^e	no	2	11	—
13	— ^f	no	2	3	2

^a By quantitative GC. ^b 0.5 equiv relative to nickel. ^c Isolated yield: 85%. ^d 4.0 equiv relative to nickel. ^e 1.0 equiv relative to nickel. ^f No nickel source added.

SCHEME 1. Amination of Chlorobenzonitrile **1** with Morpholine (**2**)



as the ligand of choice in nickel-catalyzed Kumada couplings.^{1,23,24} The outcome of these experiments (entries 11, 12) was that no product was formed above the amount found in an uncatalyzed reaction (entry 13).²⁵ Clearly, bidentate complexation is not sufficient for high conversion, and complexes of nickel ligated by dppf or dppp can be assumed to be quite different. Comparing results from aminations with Ni(0)/C (from BuLi-reduced Ni(II)/C) with those obtained with Ni(II)/C directly raised the question as to whether the decreased reaction rate²⁶ with the latter catalyst was due to involvement of a different nickel species [e.g. Ni(0) vs Ni(I)]. Alternatively, rate differences could be a consequence of an induction period during which Ni(II)/C was being reduced and/or the equilibrium involving Ni_{sol} was being established. Figure 1 shows the plot of conversion versus time for aminations with and without prior BuLi reduction of Ni(II)/C, using either 0.5 equiv of dppf or 4 equiv of PPh₃ as ligand. With both phosphines, the conversion for reactions after BuLi treatment progressed linearly, indicating that the reaction is basically (pseudo) zero order in aryl chloride.²⁷ The BuLi-free variation, however, showed a delay of ca. 15 to 50 min with dppf and PPh₃, respectively, during which essentially no aryl chloride was consumed. After this

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(25) Similar findings were mentioned in refs 11 and 19, although PPh₃ was also unsuitable for these aromatic aminations.

(26) Comparison of rates is based on the assumption that similar amounts of nickel are involved in the catalysis, not regarding possible differences in lifetime of the catalytic species due to differing reaction conditions. Previous work has shown that most likely around 80% of Ni/C is actually available in solution for homogeneous catalysis within the charcoal matrix, not depending on ligand concentration.¹⁴

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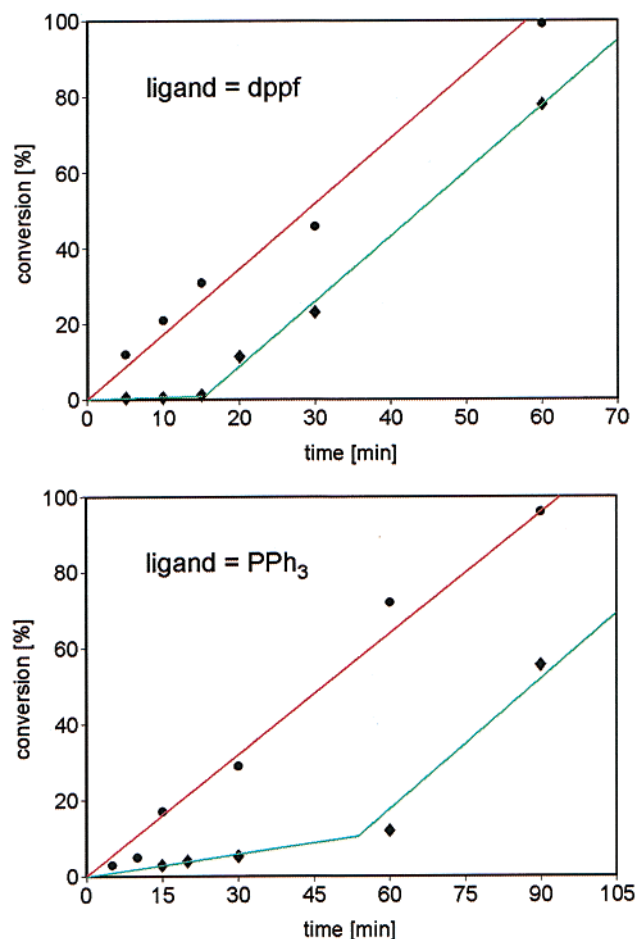


FIGURE 1. Extent of conversion of aryl chloride **1** in aminations with morpholine (**2**) in the presence of dppf (top) or PPh₃ (bottom) using preformed Ni(0)/C (●) or Ni(II)/C (◆).

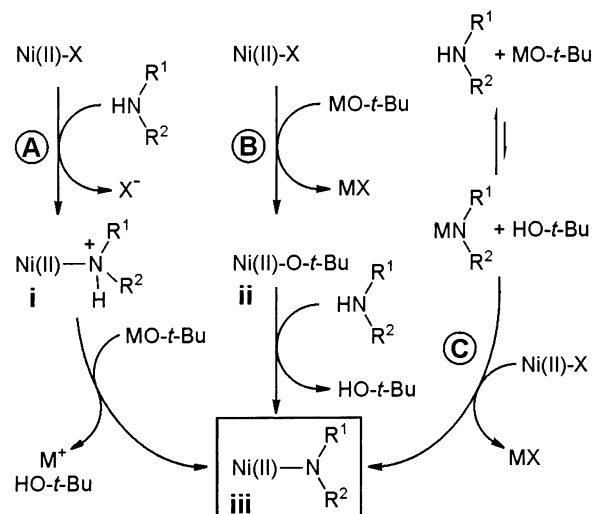
time, the amination of **1** proceeded at a nearly identical rate²⁶ as for that with Ni(0)/C arrived at via BuLi reduction of Ni(II)/C. Hence, similar catalytically active species seem to be involved as soon as a reduced nickel species is formed. Attempts to monitor and kinetically analyze the amination reaction using React-IR failed due to significant overlap of IR signals of educt and product.¹⁴ Given that Ni_{sol} was the only catalytically active species, linear product formation right from the start in reactions of Ni(0)/C indicates that the postulated¹⁴ equilibrium for Ni_{sol} had to be established during the first few minutes, otherwise a delay in conversion should have occurred.

As potential reducing agents in the *absence* of BuLi, phosphine ligands^{21,22} and the tertiary amine **3**²⁸ were excluded experimentally.²⁹ Another possibility was that morpholine serves as a reducing agent for Ni(II)/C. Its reduction potential was checked simply by monitoring the color of a reaction mixture with anhydrous NiCl₂ as a Ni(II) source. Reduction of a yellow suspension of NiCl₂ in toluene with BuLi at room temperature resulted in a quick color change to black, indicating significant generation of Ni(0). On the other hand, mixtures of NiCl₂,

(28) For a similar reduction of Pd(II) by tertiary amines, see: (a) McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J.; Stephenson, D. K. *J. Chem. Res. (S)* **1984**, 360. (b) Beckwith, A. L. J.; Eichinger, P. H.; Mooney, B. A.; Prager, R. H. *Aust. J. Chem.* **1983**, 36, 719.

(29) For experimental details, see Supporting Information.

SCHEME 2. Possible Mechanistic Pathways for the Formation of Nickel(II) Amide



ligand, and *either* morpholine or LiO-*t*-Bu did not result in such a color change, even upon heating in refluxing toluene (i.e., our standard reaction conditions for aminations), again excluding the phosphine as the reducing agent.²⁹ In both cases, the yellow color prevailed after 1 h. However, as soon as *both* morpholine and LiO-*t*-Bu were present, these yellow mixtures developed the dark purple color, usually observed for aromatic aminations catalyzed by NiCl₂ without prior reduction with BuLi, within 10 minutes. Therefore, the combination of base *and* amine affords a reducing agent for Ni(II). Aromatic amines can likewise be used for this purpose, as the same tests performed on aniline resulted in similar observations.²⁹

The question then arises as to which of three pathways (A–C, Scheme 2) is involved en route to the amide complex **iii**. These include (1) complexation of Ni(II) by the amine to form **i**, which then undergoes deprotonation (path A); (2) prior complexation with *tert*-butoxide to generate **ii** and subsequent deprotonation/complexation of the amine (path B); (3) an already deprotonated amide is directly complexed, with the latter species generated via an acid/base equilibrium between amine and *tert*-butoxide as the rate-limiting factor (path C). Insight was gained from a reaction in which lithium morpholide (from BuLi plus morpholine), was directly added to a NiCl₂/PPh₃ mixture in toluene. Here, the darkening process was slightly slower, with a brown-black color reached after 30 min. Consequently, pregeneration of uncomplexed amide (path C) appears not to play a major rate-limiting role (for differentiation between pathways A and B: vide infra). Whether Ni(0) is eventually generated from Ni-morpholide (**iii**) by single electron transfer (SET)²⁸ or by a direct two electron process was not further investigated.

Interestingly, the ligandless reaction with NiCl₂ (not reduced with BuLi) led to 56% consumption of aryl chloride **1** and 35% product formation (Table 2, entry 4), whereas a ligandless reaction using Ni/C with or without prior BuLi reduction of Ni(II) (entries 1, 2), or with NiCl₂ reduced with BuLi (entry 3), resulted only in yields comparable to the uncatalyzed reaction (Table 1, entry 13), even though there was partial consumption of aryl chloride (but not into product **3**). Apparently, BuLi

TABLE 2. Ligandless Amination Reactions of **1** with **2**

entry	source of Ni	BuLi	conv [%] ^a	3 [%] ^a
1	Ni/C	yes	27	2
2	Ni/C	no	22	3
3	NiCl ₂	yes	45	3
4	NiCl ₂	no	56	35

^a By quantitative GC, reaction time 2 h.

reduces Ni(II) so rapidly that the Ni(0) formed cannot be stabilized by weak 'ligands'; e.g., a substrate, perhaps leading to nickel colloids (black in color)^{12,30} that seem to be catalytically inactive under these amination conditions. Not so easily explained, however, is the difference between NiCl₂- and Ni/C-catalyzed couplings without prior BuLi reduction. Reduction of NiCl₂ by amine/LiO-*t*-Bu appears to be sufficiently mild and somewhat slower than that by BuLi such that at least a minor stabilizing effect can be exerted by a substrate, probably by oxidative addition,¹⁸ resulting in partial product formation. That Ni/C fails to catalyze formation of product **3** suggests that NiCl₂ may not mimic the Ni/C system. This may be due to differing nickel species involved in the catalysis (dependent on the nickel source, *not* the reduction method used). Alternatively, the lack of product formation could be attributed to additional steric and/or electronic effects exerted by the charcoal matrix on Ni(0), perhaps in the form of π -interactions of graphite-like substructures,³¹ thereby rendering this phosphine-free system unreactive in these aminations.

While in early investigations aromatic aminations were catalyzed by ligandless NiCl₂ with reduction of Ni(II) assumed to be effected by the amine,^{17,18} Buchwald et al. noted that such a process did not occur in their system.¹¹ Reduction of Ni(II), therefore, seems to be a function of reaction temperature. The original literature work was performed in sealed tubes under pressure and with temperatures above 150 °C being described as necessary,^{17,18} the amine serving simultaneously as nucleophile, base, and reductant. Apparently, addition of lithium or sodium *tert*-butoxide increases the reducing ability of the mixture, although temperatures above 100 °C are still essential (i.e. no reduction occurs at 100 °C,¹¹ but in overheated toluene reduction does take place; vide supra). Under conditions described herein, even aniline is capable of mediating the reduction, an observation questioned long ago by Cramer et al. for *N*-methylaniline.¹⁸

The experiments discussed above lead to the conclusion that aromatic aminations can be performed by combining all ingredients in the reaction flask at the same time; that premixing of certain reagents and prior reduction of Ni(II)/C with BuLi are *not* required, resulting in a faster and simplified procedure. That aromatic aminations of **1** with morpholine (**2**) can proceed with PPh₃ allowed for evaluation of electronic effects within this

(30) Formation of palladium colloids was postulated to generate reactive species in ligandless Heck reactions and homocoupling of chlorobenzene; see: (a) Reetz, M. T.; Westermann, E. *Angew. Chem.* **2000**, *112*, 170; *Angew. Chem., Int. Ed.* **2000**, *39*, 165. (b) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Sasson, Y. *J. Org. Chem.* **2000**, *65*, 3107.

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TABLE 3. Aromatic Aminations of **1** with **2** in the Presence of Different Phosphines

entry	ligand ^a	BuLi	time [h]	conv. [%] ^b	10 [%] ^b
1	dppf	yes	1	99	83
2	P(<i>p</i> -anis) ₃	yes	1	84	66
3	P(<i>p</i> -tol) ₃	yes	1	70	55
4	PPh ₃	yes	1	72	47
5	P(<i>p</i> -F-Ph) ₃	yes	1	60	42
6	dppf	no	2	100	86
7	P(<i>p</i> -anis) ₃	no	2	85	67
8	P(<i>p</i> -tol) ₃	no	2	69	58
9	PPh ₃	no	2	67	48
10	P(<i>p</i> -F-Ph) ₃	no	2	67	50

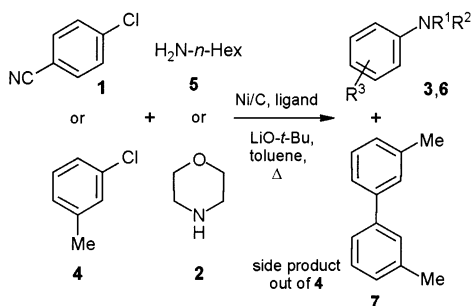
^a 0.5 equiv of dppf; otherwise 4 equiv of PR₃ were used (relative to nickel). ^b By quantitative GC.

ligand type, with tri(*p*-anisyl)-, tri(*p*-tolyl)-, and tri(*p*-fluorophenyl)phosphines chosen for this purpose. For both variants of these aminations [i.e., with and without BuLi reduction of Ni(II)/C], the same reactivity patterns were noted, with reaction rates decreasing in the order dppf > P(*p*-anis)₃ > P(*p*-tol)₃ > PPh₃ ≥ P(*p*-fluorophenyl)₃ (Table 3). For the monodentate phosphines, the major trend is such that greater electron density at phosphorus leads to faster reactions. Oxidative addition is generally rapid with Ni(0) (cf. Kumada couplings; vide infra).³² On the other hand, reductive elimination is usually considered rate-determining in palladium-catalyzed aminations⁵ and is accelerated by ligands with less electron density, a trend not observed in these Ni/C-mediated reactions. Reductive elimination should be further enhanced in the presence of highly nucleophilic morpholine,^{5,6} and the rate-determining step should thus be associated with the deprotonation/complexation of the amine.³³ In principle, two routes can be envisioned leading to nickelamido complex **iii** (pathways **A** and **B**, Scheme 2); either by complexation of *tert*-butoxide and subsequent deprotonation/complexation of the amine (**B**), or by complexation of the amine and deprotonation of this activated species by free *tert*-butoxide (**A**).⁵ Whereas the rate for pathway **B** should be enhanced by electron-rich ligands which increases the basicity of *tert*-butoxide in species **ii**, the rate for pathway **A** should decrease in this case since the N–H bond in ammonium ion **i** should be less activated toward deprotonation with weaker Lewis acidic nickel. Using electron-rich ligands, the Lewis acidity of the original nickel(II) fragment might be so low that complexation of *tert*-butoxide (pathway **B**) is highly favored over complexation of free amine (pathway **A**), which is indeed reflected in the order of reactivity for PR₃ (Table 3).

Whether the newly established reaction conditions for coupling *p*-chlorobenzonitrile (**1**) and morpholine (**2**) are applicable to other substrate combinations was next examined. Aromatic aminations of *p*-chlorobenzonitrile

(32) Kumada couplings displayed higher levels of conversion even with electron-rich aryl chlorides (i.e., deactivated for oxidative addition) in the same reaction times as aromatic aminations (albeit in different solvents, THF vs toluene). Hence, oxidative addition is not likely to be rate-limiting.

(33) That different mechanistic pathways are operating for reductive elimination with different ligands cannot be ruled out; e.g., triggering of reductive elimination by SET: (a) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 1634. (b) Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262. (c) Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421. See also ref 40.

SCHEME 3. Aromatic Aminations with a Variety of Substrates**TABLE 4. Aromatic Aminations of 1 with 5 Catalyzed by Ni/C**

entry	equiv of Ni ^a	equiv of ligand ^a	equiv of ligand ^a	BuLi	time [h]	conv. [%] ^b	6 [%] ^b	7 [%] ^b
1	0.05	dppf	0.025	yes	1	22	6	
2	0.05	dppf	0.025	yes	8	30	8	
3	0.05	dppf	0.1	yes	7	100	73	
4	0.05	dppf	0.1	no	7	100	74 ^c	
5	0.075	dppf	0.15	yes	5	100	73	
6	0.075	PPh ₃	0.3	yes	5	46	13	

^a Relative to aryl chloride. ^b By quantitative GC. ^c Isolated yield: 76%.

TABLE 5. Aromatic Aminations of 4 with 2 Catalyzed by Ni/C

entry	ligand	equiv of ligand ^a	BuLi	time [h]	conv [%] ^b	6 [%] ^b	7 [%] ^b
1	dppf	0.5	yes	5	66	54	1.8
2	dppf	0.5	yes	10	82	66	3.1
3	dppf	1	yes	10	100	88 ^c	1.1
4	dppf	1	no	10	77	65	1.0
5	dppf	1.5	no	17	100	85	2.5
6	PPh ₃	4	yes	10	36	5	–

^a Relative to nickel; 0.05 equiv of nickel used (relative to aryl chloride). ^b By quantitative GC. ^c Isolated yield: 84%.

TABLE 6. Aromatic Aminations of 4 with 5 Catalyzed by Ni/C

entry	ligand	equiv of ligand ^a	BuLi	time [h]	conv [%] ^b	6 [%] ^b	7 [%] ^b
1	dppf	0.5	yes	5	33	20	0.7
2	dppf	0.5	yes	16	84	35	1.1
3	dppf	1	yes	19	100	53	1.0
4	dppf	1	no	19	100	53 ^c	1.3
5	PPh ₃	4	yes	19	81	–	–

^a Relative to nickel; 0.05 equiv of nickel used (relative to aryl chloride). ^b By quantitative GC. ^c Isolated yield: 53%.

(1) and *m*-chlorotoluene (4) were therefore performed using either *n*-hexylamine (5) or morpholine (2) (Scheme 3) under both our original and newly developed conditions, and with either dppf or PPh₃ as ligand. Aminations with anilines were not tested in this study, but a successful outcome without prior BuLi reduction of Ni(II)/C is likely based on our results from NiCl₂ reductions performed with this aromatic amine (vide supra). Aminations with anilines in the presence of PPh₃ are not likely to proceed, however, according to our preliminary results.¹⁹

As can be seen from Tables 4–6, aminations without prior Ni(II)/C reduction by BuLi resulted in essentially

TABLE 7. Scale-up of Aromatic Aminations of 1 with 2

entry	equiv of dppf ^a	BuLi	time [h]	conv [%] ^b	3 [%] ^b
1	0.5	yes	1	100	85
2	0.5	no	6	80	65
3	1.5	no	3	99	88

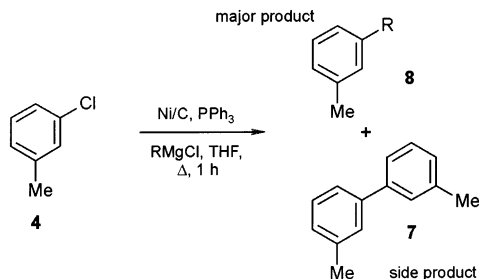
^a Relative to nickel; 0.05 equiv of nickel used (relative to aryl chloride). ^b By quantitative GC.

identical yields in comparable reaction times to those using BuLi as reducing agent (Tables 4, 6, entries 3, 4; Table 5, entries 3, 5). For the reaction of *m*-chlorotoluene (4) with morpholine (2), longer reaction times and additional dppf were necessary for complete conversion (Table 5, entries 4, 5). Generally, all three transformations were expectedly slower than that between 1 and 2 and required increased amounts of dppf (from 0.5 to at least 1.0 equiv) relative to nickel. This increase is most likely needed to further stabilize the active nickel species which might otherwise decompose during the extended reaction times, or due to decomposition of dppf. Replacement of dppf by PPh₃ (4 equiv) proved to be detrimental in all three cases (Tables 4, 5, entry 6; Table 6, entry 5); thus, this ligand cannot be considered of general utility in these reactions. The moderate yield (53%) for amination of chlorotoluene 4 with hexylamine 5 (Table 6, entries 3, 4) is in good agreement with results published by Buchwald, who stated that hexylamine leads to decent yields only with activated aryl chlorides due to competing β-elimination and hydrodehalogenation in slower reactions with nonactivated substrates.¹¹ This was verified by the amination reaction of activated aryl chloride 1 with this amine, resulting in a higher (74%) yield (Table 4, entries 3, 4). Using the electron-rich substrate chlorotoluene 4, small amounts of homocoupling to give 3,3'-bistoluene (7) were detectable (Tables 5, 6).

The feasibility of scaling up an amination was also studied, with and without prior reduction of Ni(II)/C with BuLi. Conducting the coupling of 1 on a 15.0 mmol scale, as opposed to using 0.75 mmol as the standard amount of aryl chloride, amination with morpholine (2) using Ni(II)/C reduced with BuLi was reproduced in exactly the same time and with identical results as with the smaller scale reaction (Table 7, entry 1). For the BuLi-free variant, however, the amount of dppf had to be increased from 0.5 to 1.5 equiv (relative to nickel; entries 2, 3) to obtain identical results in slightly increased reaction times compared to our standard reactions (cf. Table 7, entry 3 vs. Table 1, entry 4).

Kumada Couplings. On the basis of our study of aromatic aminations, premixing of ligands and Ni(II)/C for a given period of time is not essential for these reactions to take place. A similar simplification was anticipated for Kumada couplings²⁰ as well. Furthermore, reduction of Ni(II)/C was likely to be easily achieved by the Grignard reagent being used, in place of BuLi. For inexpensive Grignard reagents this alternative would be another improvement in the original procedure. A time savings was also expected by adding the Grignard at room temperature rather than at –78 °C, thus avoiding initial cooling followed by warming.

Initial studies were performed on *m*-chlorotoluene (4), which was treated in separate experiments with PhMgCl,

SCHEME 4. Kumada Couplings of Chlorotoluene 4 with Grignard Reagents**TABLE 8. Kumada Couplings of 4 with PhMgCl**

entry	addition of PhMgCl at	LiBr	time [h]	conv. [%] ^a	8 [%] ^a	7 [%] ^a
1	-78 °C ^b	yes	1.5	100	83	7.2
2	-78 °C ^b	yes	1	86	74	5.6
3	-78 °C	no	1	75	68	0.9
4	rt	yes	1	100	80	7.8
5	rt	no	1	79	70	1.2

^a By quantitative GC; reactions run with 4 equiv of PPh₃ (relative to nickel). ^b Procedure according to ref 20.

TABLE 9. Kumada Couplings of 4 with (*p*-Anisyl)MgCl

entry	addition of ArMgCl at	LiBr	conv. [%] ^a	8 [%] ^a	7 [%] ^a
1	-78 °C ^b	yes	75	66	7.1
2	-78 °C	no	68	62	1.6
3	rt	yes	75	63	11.2
4	rt	no	69	61 ^c	1.8

^a By quantitative GC; reactions run with 4 equiv of PPh₃ (relative to nickel), reaction time 1 h. ^b Procedure according to ref 20. ^c Isolated yield: 58%.

TABLE 10. Kumada Couplings of 4 with BuMgCl

entry	addition of BuMgCl at	LiBr	conv [%] ^a	8 [%] ^a	7 [%] ^a
1	-78 °C ^b	yes	74	49	6.4
2	-78 °C	no	66	43	2.1
3	rt	yes	85	60	7.7
4	rt	no	65	45	2.6

^a By quantitative GC; reactions run with 4 equiv of PPh₃ (relative to nickel), reaction time 1 h. ^b Procedure according to ref 20.

(*p*-anisyl)MgCl, and BuMgCl in refluxing THF (Scheme 4). The results are listed in Tables 8–10. Some general trends found from these experiments include: (1) The additive LiBr (1.0 equiv relative to aryl chloride), originally used to avoid homocoupling of **4**,²⁰ appears to actually encourage this side reaction. (2) Without added LiBr, reactions are generally slower but cleaner. (3) The new procedure involving Grignard addition to Ni(II)/C at room temperature produces slightly more homocoupling product. (4) Of the two procedures, the one more recently developed is faster in the presence of LiBr. Without LiBr, both protocols result in essentially identical conversions and product formations.

Using a ratio of Ni:PPh₃:**4** = 1:4:20, the reaction rate (based on consumption of **4**)²⁶ decreases in the order PhMgCl > (*p*-anisyl)MgCl ≥ BuMgCl. Reactions run with the latter Grignard (Table 10) seemed to be more 'destructive', resulting in ca. 10% (absolute percentage) greater losses of starting material which cannot be

attributed to either product **8** or homocoupled material **7** (compare with Tables 8, 9). If the transmetalation step were rate-determining, reactions with PhMgCl should have been slower than those with the electron-rich (*p*-anisyl)MgCl, assuming limited interactions of the latter reagent with magnesium salts in the pot, which might diminish the electron-donating abilities of the *p*-methoxy groups. Moreover, BuMgCl is more nucleophilic than PhMgCl and thus should have led to a faster transmetalation. However, it cannot be ruled out that the observed 'rates' are just a result of differing lifetimes of the active catalytic species in the presence of different Grignard reagents.

Further mechanistic insight was expected from experiments using phosphine ligands of varying electronic properties. Additionally, the optimal amount of phosphine relative to nickel had yet to be determined. An initial test reaction between chlorotoluene **4** and PhMgCl was chosen. With PPh₃ as ligand, 0–6 equiv were used in the new coupling protocol (no LiBr, Grignard addition at room temperature), with comparisons in yield and conversion being made after a 1 h reaction time (Figure 2). The reaction rate²⁶ increased continuously with decreasing amounts of ligand resulting in a maximum yield of 88% for product **8** when using 1 equiv PPh₃, while the amount of homocoupled product **7** increased (from 0.6% to 4.3%). Interestingly, the ligandless reaction resulted in complete conversion but led to substantial homocoupling (25%, along with 64% of product **8**). Thus, a compromise between extent of homocoupling and rate was made, choosing to use 2 equiv of ligand. Given the levels of homocoupled product found, the mechanistic pathway leading to **7** seems to be based on nickel complexes without participation of the specific ligand present. If true, different ligands should not significantly influence the amount of homocoupling observed. Indeed, using P(*p*-anisyl)₃ or P(*p*-tol)₃ in place of PPh₃, the yields for **7** were essentially identical (Figure 2, bottom). The only exceptions turned out to be reactions using P(*p*-fluorophenyl)₃ as ligand, which gave rise to lesser amounts of homocoupling product (below 1%), although a drastic decrease was also observed for the yields of product **8**. The drop in efficiency using this ligand was far greater than expected and was independent of the amount of ligand used. GCMS analysis of reaction mixtures revealed involvement of the ligand itself in a Kumada coupling with fluorine as the leaving group,¹ as well as in hydrodehalogenation and ligand scrambling.^{27,34} Therefore, the nickel catalyst was diverted from its intended role in Kumada couplings with aryl chloride **4**, preventing complete conversion under the given conditions.

The order of reaction rates²⁶ was quite unexpected as well: P(*p*-tol)₃ ≥ PPh₃ ≥ P(*p*-anisyl)₃ > P(*p*-fluorophenyl)₃. If oxidative addition were the rate-determining step, higher rates would have been expected with more electron-rich ligands. Either the rate-determining step is changing for P(*p*-anisyl)₃ or its strong electron-donating ability due to the *p*-methoxy groups is altered by complexation with

(34) (a) Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12. (b) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441. (c) Grushin, V. V. *Organometallics* **2000**, *19*, 1888. (d) Kwong, F. Y.; Lai, C. W.; Tian, Y.; Chan, K. S. *Tetrahedron Lett.* **2000**, *41*, 10285. (e) Kwong, F. Y.; Chan, K. S. *Organometallics* **2001**, *20*, 2570.

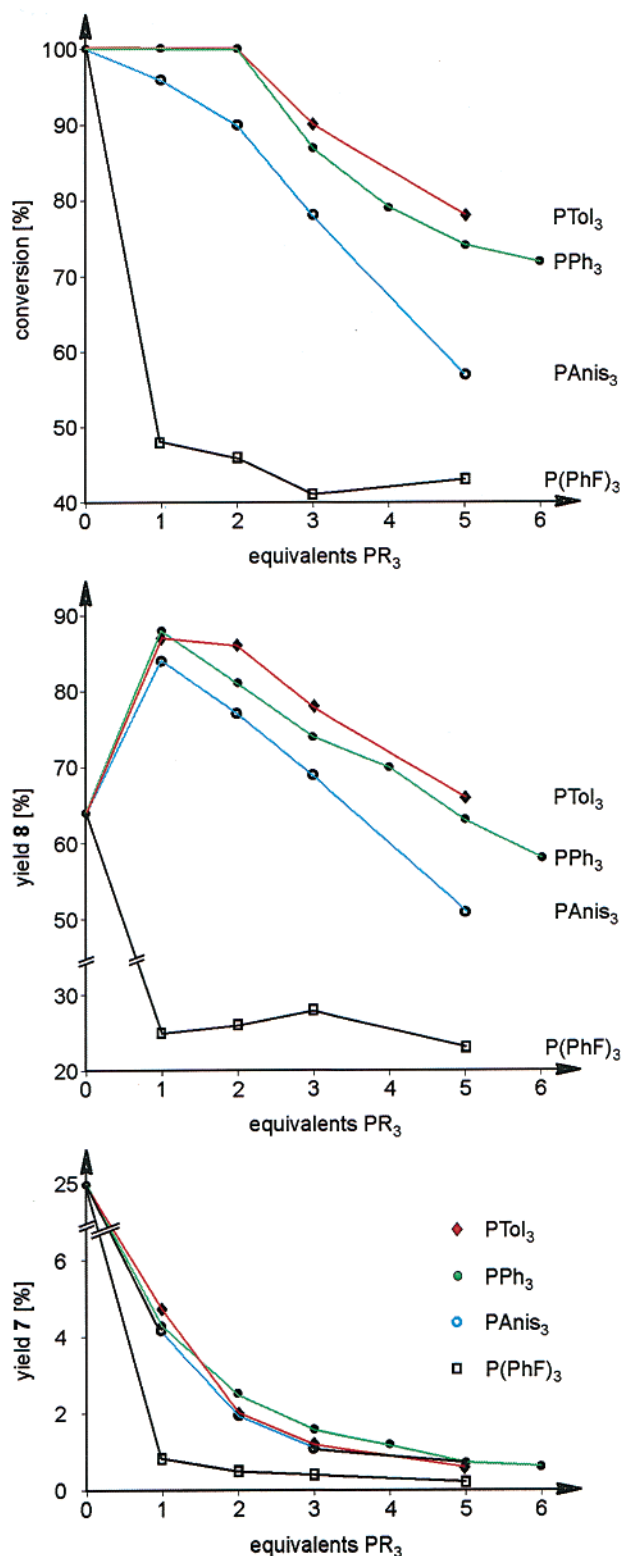


FIGURE 2. Dependence of Kumada couplings of **4** with PhMgCl on amount of phosphine ligand PR₃ (equiv relative to nickel; Grignard addition at room temperature, no LiBr, reaction time 1 h).²⁹

magnesium salts accruing in the reaction mixture. One approach to address this question was to use a strongly deactivated aryl chloride so as to slow the oxidative addition, ensuring that this step in the mechanistic picture becomes rate-determining. Therefore, *p*-chloro-

SCHEME 5. Kumada Coupling of Chloroanisole **9** with PhMgCl

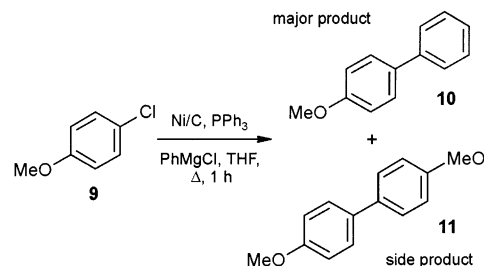


TABLE 11. Kumada Couplings of Chloroanisole **9** with PhMgCl

entry	PR ₃ R =	equiv of PR ₃ ^a	LiBr	time [h]	conv [%] ^b	10 [%] ^b	11 [%] ^b
1	Ph	2	yes	1.5	94	79	6.6
2	Ph	2	yes	2.5	100	84	8.3
3	Ph	2	no	1	69	60	1.6
4	Ph	2	no	3	99	87	3.5
5	Ph	2 ^c	no	2	97	85	3.3
6	Ph	-	no	1.5	100	73	17
7	Ph	1	no	1.5	87	78	3.0
8	Ph	2	no	1.5	84	74	2.0
9	Ph	3	no	1.5	76	64	1.1
10	Ph	5	no	1.5	64	56	0.6
11	<i>p</i> -tol	2	no	1.5	92	84	1.7
12	<i>p</i> -anisyl	2	no	1.5	82	73	2.4
13	<i>p</i> -F-Ph	2	no	1.5	30	23	0.4

^a Relative to nickel. ^b By quantitative GC; Grignard addition at room temperature. ^c Run with 0.075 equiv of nickel instead of 0.05 equiv relative to aryl chloride.

anisole (**9**) was selected for a Kumada coupling with PhMgCl (Scheme 5). In the event, the same order of reactivity for the four different ligands (Table 11, entries 8, 11–13) was found, also confirming our earlier observations that without LiBr the reaction is slower but cleaner (entries 1–4) and that decreasing amounts of phosphine result in faster reactions along with more homocoupling (entries 6–10). These findings do not allow for an interpretation regarding the rate-determining step of these reactions, nor can additional steps involved in the catalytic cycle be ruled out; e.g. electron transfer leading to reductive elimination.³³ In general, reductive elimination from Ni(II) species is supposed to be relatively slow compared to oxidative addition with Ni(0) to aryl halides, whereas this is variable for Ni(I)/Ni(III) systems.^{27,35,36}

For couplings with *p*-chloroanisole (**9**), the turnover numbers (TON) for Ni/C seemed lower than those for aryl chloride **4**. That is, with LiBr added (1.0 equiv relative to aryl chloride) an additional hour was required to achieve full conversion of the remaining 6% educt (Table 11, cf. entries 1 and 2). Without LiBr, either a 3 h reaction time (entry 4), or more catalyst (entry 5), was necessary for the reaction to reach completion.

In changing the Grignard reagent from aryl to an alkyl species in couplings with chlorotoluene **4**, the reactivity order using different ligands was essentially identical to that observed in previous couplings (Table 12). However, the behavior of the reaction varied dramatically as the amount of ligand was changed (Table 13). The reaction

(35) Amatore, C.; Jutand, A. *Organometallics* **1988**, *7*, 2203.

(36) (a) Amatore, C.; Jutand, A.; Mottier, L. *J. Electroanal. Chem.* **1991**, *306*, 125. (b) Jutand, A.; Mosleh, A. *J. Org. Chem.* **1997**, *62*, 261.

TABLE 12. Influence of Ligands on Kumada Couplings between **4** and BuMgCl

entry	PR ₃ R =	conv [%] ^a	8 [%] ^a	7 [%] ^a
1	<i>p</i> -tol	69	51	2.1
2	Ph	69	49	3.0
3	<i>p</i> -anisyl	61	42	1.7
4	<i>p</i> -F-Ph	52	35	0.7

^a By quantitative GC; Grignard addition at room temperature, 3 equiv of PR₃ (relative to nickel), no LiBr, reaction time 1 h.

TABLE 13. Dependence of Kumada Couplings of **4** with BuMgCl on Amount of PPh₃

entry	equiv of PPh ₃ ^a	conv [%] ^b	8 [%] ^b	7 [%] ^b
1	–	20	–	–
2	1	39	20	1.1
3	2	66	40	2.7
4	3	69	49	3.0
5	4	65	45	2.6
6	3 ^c	87	66	5.5
7	3 ^d	100	78	7.0

^a Relative to nickel. ^b By quantitative GC; Grignard addition at room temperature, no LiBr, reaction time 1 h. ^c Reaction time 2 h. ^d Reaction time 4 h; isolated yield: 75%.

rate increased with increasing amounts of PPh₃, reaching a maximum conversion at ca. 3 equiv (Table 13, entry 4), while the corresponding ligandless reaction afforded no cross-coupling or homocoupled product (entry 1). With this substrate combination, fewer side reactions involving the fluorophenyl group in the ligand were detectable by GCMS, thus leading to reasonable conversions of aryl chloride (Table 12, entry 4), to be expected given the electronic properties of this ligand. Interestingly, the TONs for Ni/C in these reactions with BuMgCl again appeared to be lower than those with PhMgCl, since extended reaction times were required to go from 69 to 100% conversion (Table 13, entries 4, 6, 7), indicating that the active nickel species had essentially lost its activity.

Homocoupling of aryl halides, triflates, or mesylates with catalytic amounts of nickel requires the presence of a reducing agent to regenerate the catalytically active species.^{35–38} In the case of Kumada couplings, this should be provided by the Grignard reagent itself. The discrepancy between couplings with PhMgCl and BuMgCl, however, cannot be accounted for by differences in reducing capabilities of these two reagents, since based on their electrochemical potentials,³⁹ BuMgCl should be a more powerful reducing agent than PhMgCl. Homocoupling of an aryl chloride seems to be catalyzed by nickel species nonligated by phosphine ligands (vide supra). Hence, PhMgCl might act as a π -basic ligand for nickel(II) following initial oxidative addition, forming a charge-transfer complex which leads to SET to the nickel center (Scheme 6). Such species are analogous to Ni(0) charge-transfer complexes involving aryl halides, in

which the interaction of d-orbitals on nickel with the π^* LUMO of the aryl moiety facilitates electron transfer from nickel to the arene.⁴⁰ In the case of Ni(II) reduction, interaction between d-orbitals (hybrids) and the π HOMO in **i** would be required to mediate reduction of Ni(II) to Ni(I), or a rearrangement from a π - to a σ -complex has to precede the actual reduction step leading to formation of Ni(I) complex **iii**. The newly created Ni(I) species **iii** can then undergo a second oxidative addition to **iv** followed by reductive elimination of the biaryl, and regeneration of a species within the catalytic cycle by one of several ways postulated in the literature, e.g. by reduction to Ni(0).^{27,35–38} Product formation from complex **i** also requires a π - σ -rearrangement followed by reductive elimination of cross-coupled product from **ii** and regeneration of Ni(0).^{41,42}

The involvement of charge transfer π -complexes would account for the complete loss of activity (product formation and homocoupling) in Kumada couplings with BuMgCl in the absence of ligands, since the butyl group cannot form such a complex.⁴² The small amounts of homocoupling found with more equivalents of ligand present in Kumada couplings with (aryl)MgCl or with BuMgCl in general can best be explained by standard SET from a σ -complex associated with a species stabilized by phosphines.

The effects observed upon addition of LiBr (1.0 equiv relative to aryl chloride) to Kumada couplings might be explained as follows. Stille et al. introduced additives such as LiCl, LiBr, or LiI for coupling reactions of vinyl triflates with organostannanes and explained their effects by anion exchange at the palladium center after oxidative addition, resulting in a complex more prone to participate further in the catalytic cycle.⁴³ With bromide or iodide counterions on palladium, the reaction rates increased but led to more rapid catalyst decomposition.⁴³ In our case, the oxidative addition directly leads to a Ni–Cl bond, whereupon addition of bromide leads to slightly faster reactions, as seen previously.^{27,43} In general, the addition of halide additives could accelerate either oxidative addition or reductive elimination by formation of nickelate complexes,^{15b,21e,27} thus leading to a higher overall rate of the reaction. Furthermore, halide exchange would result in Ni–Br species, which facilitate reduction at nickel,²⁷ resulting in higher amounts of homocoupling. In this vein, it should be recalled that the addition of halide only influences the amount of homocoupling in the presence of phosphines; for ligandless reactions, no significant difference was observed (100% conversion, 60% yield of product **8**, 25% homocoupling with added LiBr compared to 100/64/25% without LiBr).²⁹

Recent studies have shown that Kumada couplings can be carried out at ambient temperatures.^{3,24,44,45} Our attempts to couple chloride **4** with both PhMgCl and

(40) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319.

(41) For further examples of cross-coupling reactions of aryl halides with only aromatic Grignard reagents catalyzed by nonligated nickel, see: (a) Ikoma, Y.; Taya, F.; Ozaki, E.-i.; Higuchi, S.; Naoi, Y.; Fuji-i, K. *Synthesis* **1990**, 147. (b) Ikoma, Y.; Ando, K.; Naoi, Y.; Akiyama, T.; Sugimori, A. *Synth. Commun.* **1991**, *21*, 481.

(42) NiCl₂ was also used recently for cross-couplings of alkyl halides with alkyl Grignard reagents. Similar to our results, ligandless reactions did not provide the desired products, addition of 1,3-butadiene derivatives as ligands was required. Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.

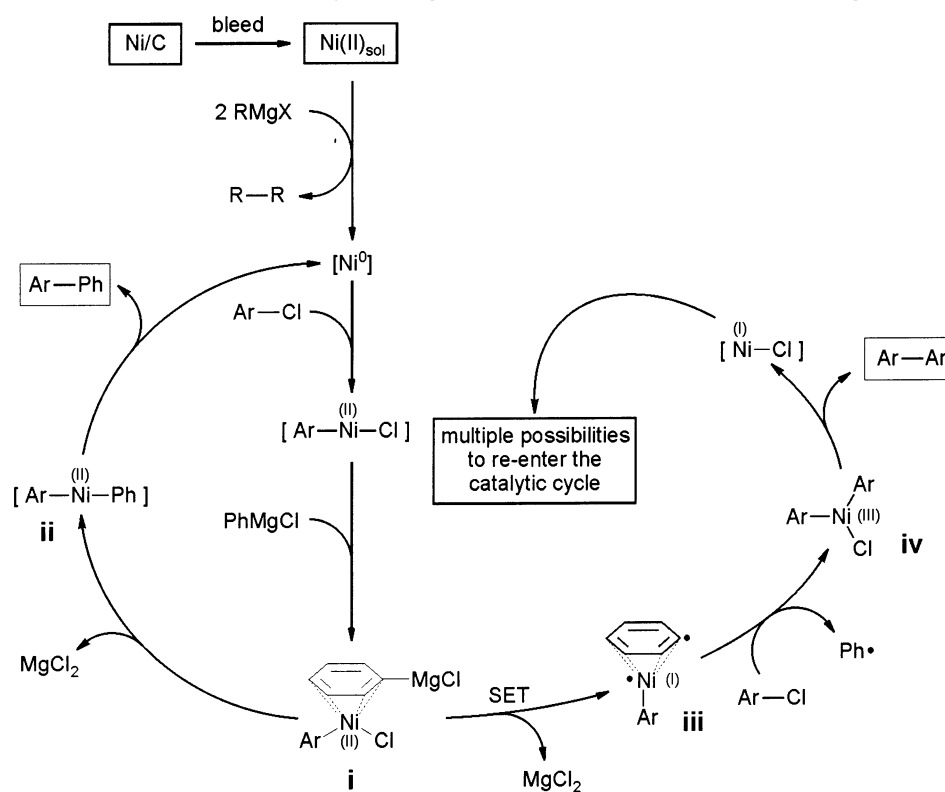
(43) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(37) (a) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176. (b) Amatore, C.; Jutand, A.; Perichon, J.; Rollin, Y. *Monatsh. Chem.* **2000**, *131*, 1293.

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SCHEME 6. Possible Mechanistic Pathway for Ligandless Cross- and Homocouplings of Aryl Chlorides



BuMgCl at room temperature were unsuccessful (28 and 12% yields, respectively). Substrates bearing electrophilic ester or nitrile substituents are also unfortunately not as yet amenable to Ni/C-catalyzed cross-couplings with Grignard reagents, unlike a novel palladium-catalyzed process using imidazolium ligands¹⁶ or couplings based on iron.⁴⁵

Finally, the simplified protocol described herein for Kumada couplings using Ni/C without prior reduction by BuLi was tested on a larger scale reaction (15.0 mmol of aryl chloride **4**) using PhMgCl. After 1 h in refluxing THF, the coupling was complete, with the yield of **8** (77%) comparable to that realized in the corresponding small scale reaction (81%).²⁹

Conclusions

Simpler procedures for utilizing Ni/C as a 'heterogeneous' catalyst in aromatic aminations and Kumada couplings have been developed. Since Ni/C is serving as a reservoir for active nickel in solution which is the species involved in the catalytic cycle,¹⁴ premixing periods of catalyst precursor Ni(II)/C with ligands prior to reduction of Ni(II) was shown to be unnecessary. Moreover, a separate reduction of Ni(II)/C with *n*-BuLi is no longer required. The conversion of Ni(II)/C to Ni(0) can be achieved either by the amine in combination with LiO-*t*-Bu (for aromatic aminations), or by the Grignard reagent involved in Kumada couplings. Under the new

amination conditions, reduction of Ni(II)/C requires an induction period of several minutes to allow for Ni(0) to be formed. Thereafter, reaction rates are similar to reactions mediated by preformed Ni(0)/C, suggesting that similar nickel species are involved. Experiments with phosphine ligands with different electronic properties led to the conclusion that deprotonation/complexation of the amine by preformed nickel(II) *tert*-butoxide is likely to be the rate-limiting step for aromatic aminations catalyzed by nickel complexes. The new protocol proved to be applicable to transformations involving either activated and nonactivated aryl chlorides with primary or secondary aliphatic amines. Aromatic amines were not tested in the course of this work, but it was shown that aniline is capable of reducing Ni(II) under these reaction conditions. A consistent trend for Kumada couplings based on electronic effects in the ligand was not found, potentially due to alternative catalytic cycles involving other species in addition to Ni(II)/Ni(0). With aromatic Grignard reagents, ligandless Kumada couplings led to complete consumption of the aryl chloride, yielding a 2:1 ratio of cross- and homocoupled products. This interesting reactivity might be explained by the formation of π-complexes with the aromatic residue in PhMgCl which can stabilize nickel as a ligand and simultaneously facilitate electron transfer to nickel, a necessary precondition for homocoupling of an aryl halide.

Scaled-up versions of these reactions (15.0 mmol of aryl chloride) succeeded for both reaction types using these new procedures. Combined with the advantages of a 'heterogeneous' catalyst (i.e., only traces of nickel can be found in the product after filtration of the reaction mixture), these protocols may be applicable to selected industrial processes.

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(45) Fürstner, A.; Leitner, A. *Angew. Chem.* **2002**, *114*, 632; *Angew. Chem., Int. Ed.* **2002**, *41*, 609.

Experimental Section

General. All reactions, and catalyst transfers, were conducted under an argon atmosphere. Morpholine (**2**), *m*-chlorotoluene (**4**), *n*-hexylamine (**5**), and *p*-chloroanisole (**9**) were distilled prior to use; PPh₃ was recrystallized from hexanes. PhMgCl and BuMgCl (both 1.8 M in THF) and *n*-BuLi (2.1 M in hexanes) were obtained from commercial sources and 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 [3,3'-bistoluene (**7**), 3-phenyltoluene (**8**, R = Ph), 4-phenylanisole (**10**), 4,4'-bisanisole (**11**)] or isolated materials [*N*-(*p*-cyanophenyl)morpholine (**3**), *N*-(*p*-cyanophenyl)-*n*-hexylamine, *N*-(*m*-tolyl)morpholine, *N*-(*m*-tolyl)-*n*-hexylamine (**6**; the three previous amines), 3-butyltoluene (**8**, R = Bu), 4-(3-tolyl)anisole (**8**, R = *p*-MeO-Ph)]. For chromatographic purposes, 200–425 mesh Fisher Brand silica gel was used. Unequivocal identification of products **7**, **8** (R = Ph), **10**, and **11** was accomplished by GC coinjection, GCMS analyses, and TLC comparison with authentic materials.

Preparation of Ni(II)/C. Activated charcoal (5.00 g) was impregnated with Ni(NO₃)₂·6H₂O (727 mg, 2.50 mmol) in H₂O (75 mL).⁴⁶

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,¹⁹ using 0.750 mmol of **1** (103 mg), 2.0 equiv of **2** (132 μL, 131 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 PPh₃ (39.3 mg, 0.150 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 was added CH₂Cl₂ (3 mL). The suspension was filtered through a Büchner funnel and the cake washed with CH₂Cl₂, petroleum ether (10 mL each), and diethyl ether (25 mL). The filtrate was refiltered, and 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 (ligand, amount of ligand, nickel source, reaction times) and results for different reactions can be found in Tables 1, 3 and Tables S1, S2 in the Supporting Information.

General Procedure for Aromatic Aminations of *p*-Chlorobenzonitrile (1**) with Morpholine (**2**) [without prior reduction of Ni(II) with BuLi].** To a mixture of Ni/C (63.1 mg, 0.038 mmol, loading: 0.594 mmol/g), dppf (10.4 mg, 0.019 mmol) or PPh₃ (39.3 mg, 0.150 mmol), LiO-*t*-Bu (72.1 mg, 0.900 mmol), and *p*-chlorobenzonitrile (**1**, 103 mg, 0.750 mmol) in a Schlenk tube were added toluene (1.4 mL) and morpholine (**2**, 132 μL, 131 mg, 1.50 mmol). The tube was placed in a preheated oil bath (130 °C) and kept at reflux for the time indicated in the Tables. Workup and analysis of the product mixtures obtained were identical to the procedure above. Variations of reaction conditions (ligand, amount of ligand, nickel source, reaction times) and results for different reactions can be found in Tables 1, 3 and Tables S1, S2 in the Supporting Information.

Scale-up of Amination Reactions. Using *p*-chlorobenzonitrile (**1**, 2.06 g, 15.0 mmol) and toluene (25 mL), all other reagents were added in identical ratios as stated in the general procedures. Variations in reaction conditions (amount of ligand, reaction times) and results can be found in Table 7.

Kumada Couplings of *m*-Chlorotoluene (4**) and Grignard Reagents [prior reduction of Ni(II)/C with BuLi].** Following a literature procedure,²⁰ aryl chloride **4** (118 μL, 127 mg, 1.00 mmol) was treated with a Grignard (PhMgCl or BuMgCl: 835 μL, 1.50 mmol, 1.8 M) at -78 °C after reduction of 0.05 equiv of Ni(II)/C catalyst precursor (84.2 mg, 0.050 mmol, loading: 0.594 mmol/g) by BuLi (47.6 μL, 0.100 mmol, 2.1 M) in the presence of 0.2 equiv of PPh₃ (52.5 mg, 0.200 mmol) and 1.0 equiv of LiBr (86.9 mg, 1.00 mmol) in THF (1.5 mL), and then heated at reflux. After a selected reaction time (see Tables), the mixture was cooled to room temperature and upon stirring, 3 mL of aq NH₄Cl solution were carefully added. The suspension was filtered through a Büchner funnel and the cake was washed with H₂O, diethyl ether, petroleum ether, CH₂Cl₂ (each 10 mL), and again with 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. A 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.

Kumada Couplings of *m*-Chlorotoluene (4**) and Grignard Reagents [without prior reduction of Ni(II) with BuLi].** To a mixture of Ni(II)/C (84.2 mg, 0.050 mmol, loading: 0.594 mmol/g) and PPh₃ (52.5 mg, 0.200 mmol) in THF (1.5 mL) were added *m*-chlorotoluene (**4**, 118 μL, 127 mg, 1.00 mmol) and RMgCl (1.50 mmol) at room temperature, and the suspension was placed in a preheated oil bath (75 °C) and kept at reflux. No LiBr was used in this case. After a selected reaction time (see Tables), workup and analyses were performed as described above. Variations in reaction conditions (especially amounts of ligand) and results for different reactions can be found in Tables 8–10, 12, 13, and Tables S3–S6 in the Supporting Information. The best compromise between reaction rate and amount of homocoupled side product was obtained with 2.0 equiv of PPh₃ (26.3 mg, 0.100 mmol) relative to nickel using ArMgCl, and 3.0 equiv of PPh₃ (39.3 mg, 0.150 mmol) when using BuMgCl.

Scale-up of Kumada Couplings. Using *m*-chlorotoluene (**4**, 1.77 mL, 1.90 g, 15.0 mmol) and THF (20 mL), all other reagents were added in identical ratios as stated in the general procedure without prior reduction of Ni(II)/C with *n*-BuLi, except for PPh₃ which was used only in a 2:1 ratio relative to nickel. Results can be found in Table S3, Supporting Information (100% conversion, 77% **8**, 5.4% **7**).

Acknowledgment. Financial support provided by the NIH (GM 40287) and the DAAD (fellowship to S. Tasler, Hochschulsonderprogramm III) is gratefully acknowledged. Thanks also go to Randy Vivian and Will Chrisman for inspiring discussions.

Supporting Information Available: Further experimental details of amination and Kumada reactions, isolation, and characterization of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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