

New technologies in catalysis using base metals*

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Abstract: Formation of C–C, C–N, and C–H bonds using three heterogeneous catalysts in the form of nickel-in-charcoal (Ni/C), nickel-on-graphite (Ni/C_g), and copper-in-charcoal (Cu/C) are described.

Keywords: heterogeneous catalysis; nickel-in-charcoal; nickel-on-graphite; copper-in-charcoal; asymmetric hydrosilylation, cross-couplings.

INTRODUCTION

Part of the rich history of organometallic chemistry includes that period in time when alchemists were hard at work, looking for pathways to unlimited wealth by attempting to convert essentially worthless metals into gold. These metals of common occurrence are oftentimes referred to as “base” metals (Fig. 1) [1]. Chief among them are both Ni and Cu, and as late transition metals, they are both ideally suited for catalyzing highly valued cross-coupling reactions to arrive at C–C, C–H, and C-heteroatom bonds. When used as catalysts, the economics of these already inexpensive metals become all the more attractive relative to precious metals. Indeed, it could be argued that costs associated with their recovery from homogeneous reactions due to environmental concerns are likely to far outweigh their initial purchase price. One approach to minimizing catalyst exposure to the environment is to impregnate a metal within a solid support that retains its organometallic contents while allowing for catalysis. Recovery of the catalyst and its potential re-use without sacrificing activity would be additional advantages. In this contribution, we describe reagents of both Ni and Cu that have been mounted on various allotropic forms of carbon and that effect heterogeneous catalysis.

Representative:

<u>Base Metals</u>	<u>Precious Metals</u>
Pb, Al, Zn, Co	Pd, Pt, Rh, Ir
Ni, Cu	

Fig. 1

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NICKEL-IN-CHARCOAL

Since introducing this species in 1999 [2] as a viable alternative to solution-based Pd(0)-mediated couplings in many of the standard “name” reactions [3], one theme that was noted concerns the times associated with these heterogeneous reactions: They can be long. The explanation for this general observation goes beyond the obvious; that is, the notion of hetero- vs. homogeneity is not the full explanation. In fact, it might even be considered only a modest component responsible for the decrease in reaction rate. As discussed previously [4], with insight provided by surface analyses of nickel-in-charcoal (Ni/C), the chemistry is taking place *within* the charcoal matrix, where ligated Ni(0) atoms await arrival, in solution, of the coupling partners (Fig. 2). Thus, to produce the cross-coupled products, both educts must find their way into the charcoal particle and encounter available Ni(0), a far more demanding requirement than is interaction with an active metal center on the outside, or surface, of a support. Hence, the expression nickel-*in*-charcoal may be a more accurate descriptor of the catalyst and the phenomenon taking place.

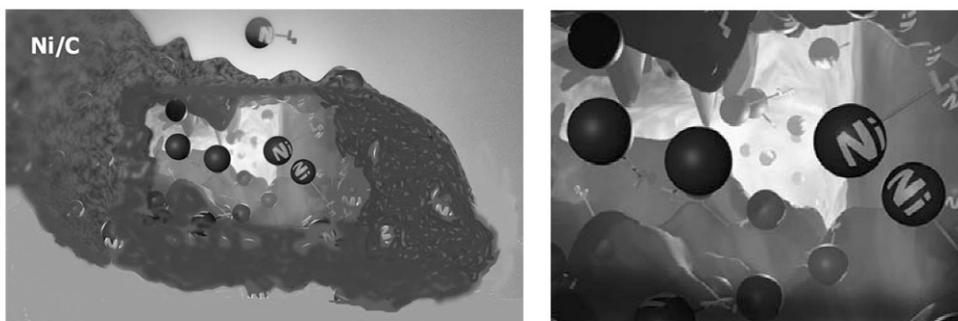
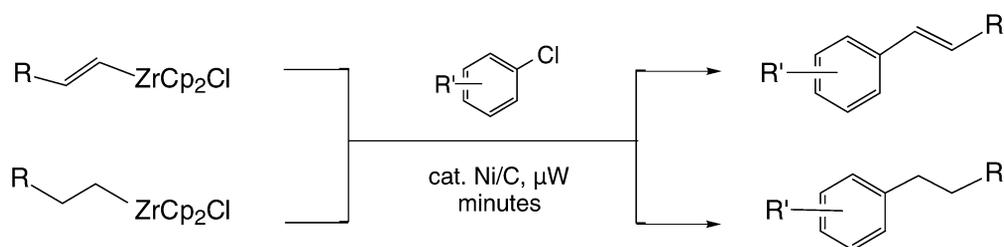
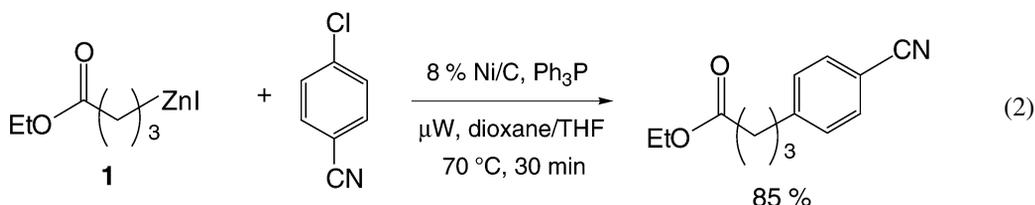
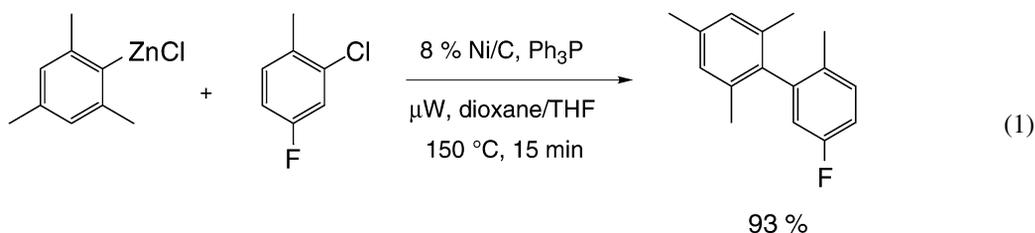


Fig. 2

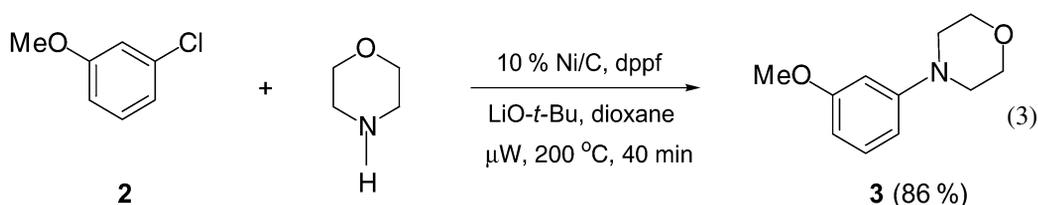
To enhance the rates of these heterogeneous reactions, we examined the impact of microwave irradiation [5], and have already documented the potential for this technology with organozirconium species to rapidly couple these otherwise sensitive intermediates with a variety of aryl halides (e.g., Scheme 1) [6]. Although Pd- and Ni-catalyzed couplings of vinyl zirconocenes, prepared via traditional hydrozirconations of terminal acetylenes, were originally described by Negishi [7], use of the derived organozinc complexes (RZnX) have come to be better known as “Negishi couplings” [8]. While these proceed readily under the influence of Ni/C in a traditional sense (i.e., simply heating at reflux in THF) [2], they can take up to 24 h to reach completion. Several aryl zinc halides have been found to react with aryl chlorides in the presence of Ni/C smoothly in an Emyry’s Optimizer (from Personal Chemistry, now Biotage), leading to substituted and functionalized biaryls (e.g., eq. 1). In most cases, reaction times are reduced to 15 min when the internal temperature is set to 150 °C. Functionalized zinc reagents, such as **1**, also participate in microwave-accelerated cross-couplings, placing an sp³ center on the aryl ring (e.g., eq. 2). In this case, however, a reaction temperature of 70 °C could not be exceeded due to decomposition of **1**. Nonetheless, the coupling was complete within 30 min.



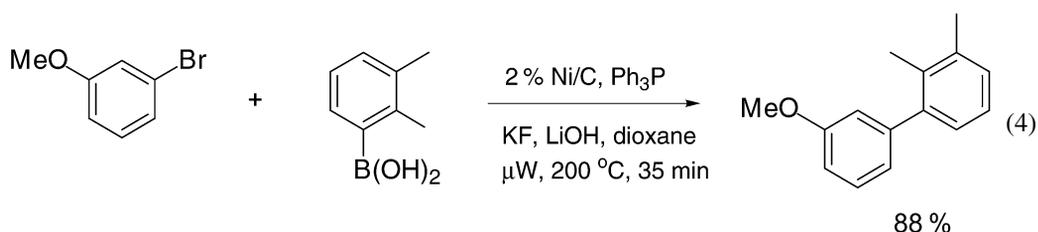
Scheme 1



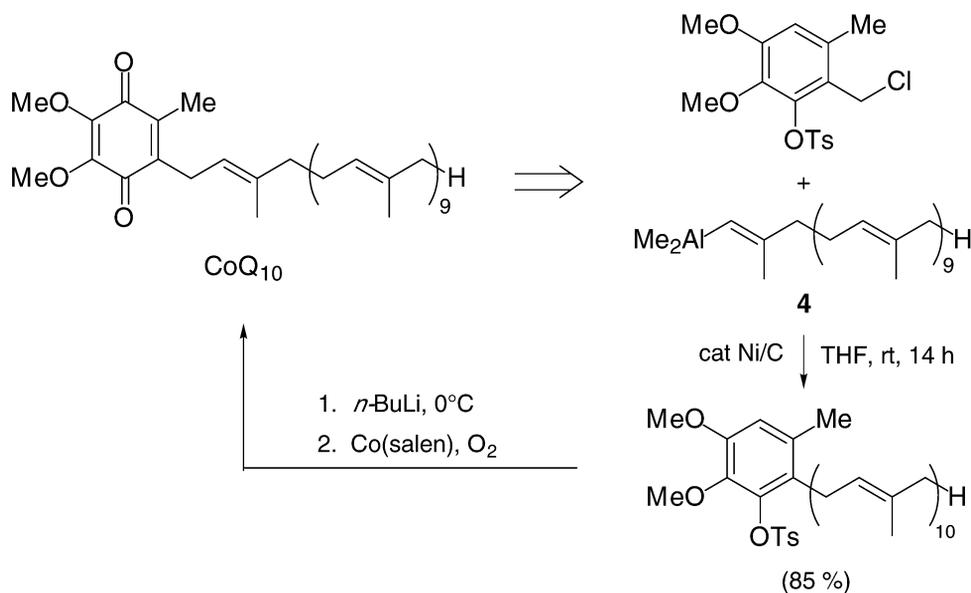
Aminations of aryl chlorides are also mediated by Ni/C, typically done in refluxing dioxane or toluene over the course of 1–2 days [9]. Recent studies have shown, however, that primary, secondary, and even aniline-like amines can be used to replace iodo-, bromo-, and chloro-aromatics in minutes under microwave irradiation at 200 °C. As anticipated, electron-rich chlorides require the longest reaction times, although a chloroanisole (**2**) is nonetheless cleanly converted to morpholino derivative **3** in good isolated yield (eq. 3). Activated cases of chlorides, bromides, and iodides tend to reach full conversion in only 10 min under similar conditions.



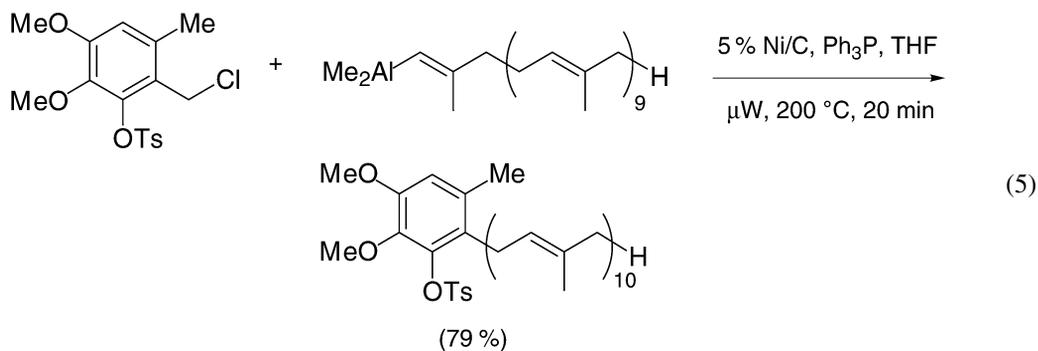
Biaryl formations routinely rely on Suzuki couplings, the vast majority of which are Pd(0)-catalyzed using privileged ligands under homogeneous conditions [10]. While also catalyzed by Ni/C without recourse to phosphines other than Ph₃P, usually 18–24 h are needed in hot dioxane to realize the intended targets [11]. Recently, we have found that activated aryl chlorides can be coupled with substituted boronic acids in ca. 35 min using microwave irradiation. Electron-rich aromatics, however, did not react reproducibly as their chlorides, and hence, the corresponding bromide was employed with good success (eq. 4). In these cases, KF (3 equiv) was found to be an important additive, perhaps forming a more reactive boronate intermediate.



As part of our program aimed at devising an especially short and efficient synthesis of the essential vitamin-like substance coenzyme Q₁₀ [12], Ni/C-mediated C–C bond formations between benzylic chlorides and vinyl alanes have been investigated (Scheme 2). The key attachment of the 49 carbon nonaprenoidal-containing side chain, in the form of vinyl alane **4** (prepared by a Negishi carboaluminumation of the corresponding terminal alkyne precursor), requires ca. 14 h to reach completion (85 % yield) [13]. Although to date the identical reaction run under microwave irradiation conditions has only been attempted once, the desired fully fashioned skeleton was realized in a mere 20 min (eq. 5). Final conversion to CoQ₁₀ is known, requiring only detosylation (*n*-BuLi, 0 °C) and a Co(salen) oxidation of the free phenol.



Scheme 2



NICKEL-ON-GRAPHITE

With an appreciation for some of the subtleties associated with charcoal as a solid support (e.g., importance of metal gegenion for impregnation, pore size and its relationship to percentage of metal being embedded, etc.) [4], it was also acknowledged that graphite offers a completely new frontier for related catalysis with nickel. With ca. 3.3 angstroms between the graphite sheets, intercalation of nickel atoms can be accomplished, presenting a completely different platform for interactions with coupling partners (Fig. 3) [14]. Presumably, catalysis can only take place upon exposure of Ni at the ends of its surrounding graphite walls.

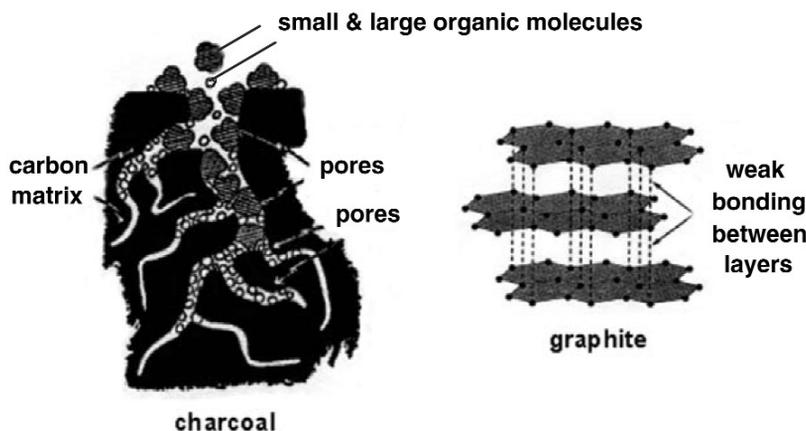
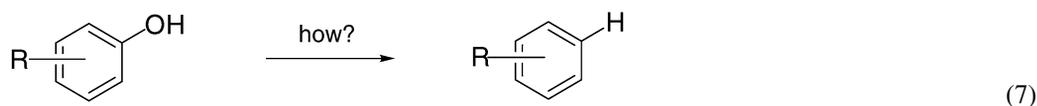
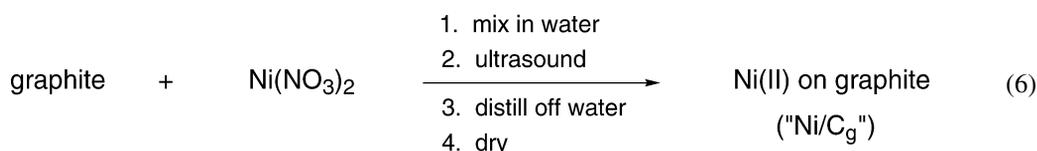


Fig. 3

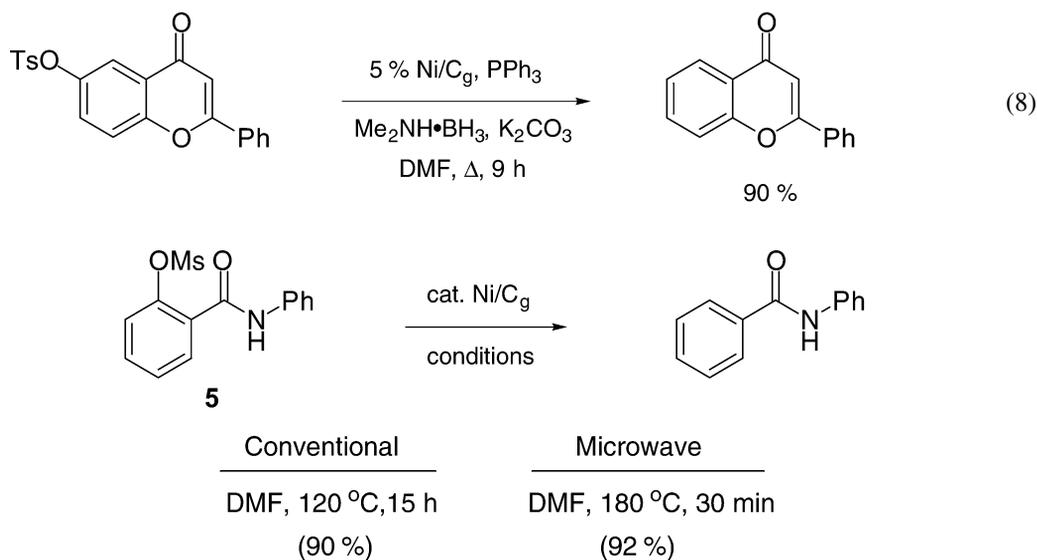
To prepare nickel-on-graphite (Ni/C_g), an only slightly modified approach as used with Ni/C could be applied (eq. 6) [15]. We opted to study phenolic reductions (eq. 7), as there are few alternatives in the literature for such a transformation [16], and yet, removal of an aryl C–O bond can be a critical component in complex molecule synthesis (e.g., vancomycin) [17]. Because $\text{Ni}(0)$ is the species to be undergoing insertion, the option for employing a tosylate or mesylate, rather than triflates as electrophiles toward $\text{Pd}(0)$, represented another potential bonus to the chemistry [18]. The chemoselectivity to be expected from group 10 metals also encouraged development of this reagent.



derivatives: triflate? tosylate? mesylate?

In fact, Ni/C_g readily inserts into both aryl tosylates and mesylates, with reactions being conducted in dry DMF at 120 °C. Triphenylphosphine (5 equiv vs. Ni/C_g) functions admirably as ligand, and with the reducing agent $[\text{Me}_2\text{N}\cdot\text{BH}_3]^- \text{K}^+$ (formed in situ from inexpensive $\text{Me}_2\text{NH}\cdot\text{BH}_3 + \text{K}_2\text{CO}_3$), many functional groups are tolerated in these reductions (e.g., eq. 8). As with Ni/C as catalyst, the heterogeneous nature of these reactions leads to reaction times in the 6–24 h range. Although yields are

generally high as well, the potential for the rate enhancement using microwaves was an obvious extension. Thus, under otherwise identical conditions, mesylate **5** was efficiently reduced in 30 min at 180 °C, while conventional heating required 15 h to reach the same end (Scheme 3).

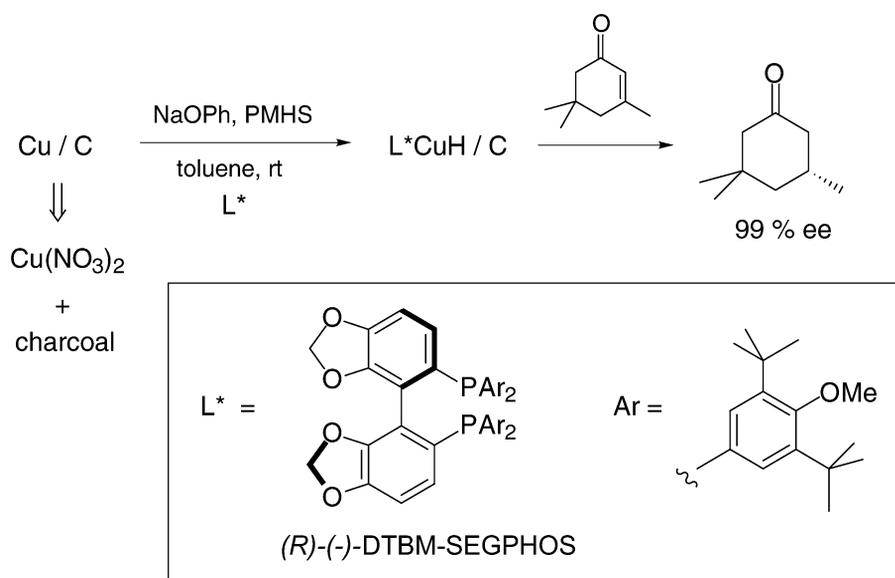


Scheme 3

COPPER-IN-CHARCOAL

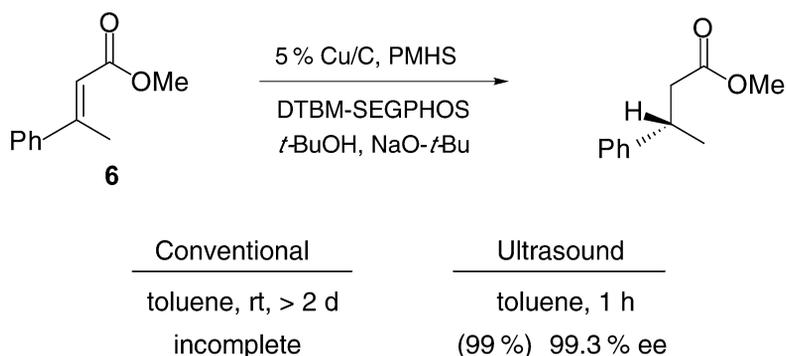
As alluded to in the introduction, copper is among the group of base metals that is virtually cost-free when utilized in a catalytic mode. It also has, perhaps, the most extensive service of all metals to organic synthesis in modern times [19]. Curiously, notwithstanding the time-honored history of organocopper chemistry, we were hard-pressed to cite any synthetic work that focuses on copper directly mounted on a solid support, in particular as a catalyst for any type of bond constructions. Thus, we set out to investigate copper-in-charcoal (Cu/C), logically looking to impregnate this metal within the pores of charcoal employing the same “tricks” used to prepare both Ni/C and Ni/C_g [i.e., using nitrate as counterion in Cu(NO₃)₂, along with ultrasonication; cf. eq. 6]. Fortunately, this “standard” procedure, augmented by azeotropic drying with toluene, led to the desired Cu/C. It was at this point, given the myriad uses of organocopper reagents, the question arose as to where to start.

With considerable recent success in CuH-catalyzed asymmetric hydrosilylations, we began by attempting to create a heterogeneous alternative to the solution-based, in situ derived [(*R*)-(-)-DTBM-SEGPHOS]CuH, a thermally stable yet kinetically extremely reactive species, recently introduced as “CuH in a bottle” [20]. Remarkably, by using an appropriate additive in the form of NaOPh, presumably to generate L*CuOPh/C, which is then readily converted in the presence of polymethylhydrosiloxane (PMHS) to L*CuH/C, reduction of even a highly hindered substrate such as isophorone [21] could be achieved in very high yield and ee (Scheme 4).



Scheme 4

Extension to β,β -disubstituted enoates, substrates that are far less reactive as Michael acceptors relative to enones [21,22], was somewhat problematic. For example, in the case of β -methyl-substituted cinnamate **6**, hydrosilylation was incomplete after 2 days at room temperature. Speculating that enhanced mixing might help to increase the extent of conversion, the mixture was subjected to ultrasonication. At a substrate-to-ligand ratio of still 1000:1, the asymmetric reduction took place in 1 h and afforded outstanding results (Scheme 5).



Scheme 5

SUMMARY

Three heterogeneous catalysts: Ni/C, Ni/C_g, and Cu/C, have been developed for use in synthesis. Both Ni/C and Ni/C_g behave as expected for a group 10 metal, mediating several important cross-coupling reactions. To enhance rates of these processes, the rare use of microwave technology applied to heterogeneous catalysis has led to product formation in minutes. Likewise, Cu/C can serve as precursor to in situ derived CuH/C, which in the presence of a nonracemic biaryl bis-phosphine ligand (DTBM-SEGPHOS) [23], effects asymmetric hydrosilylations on β,β -disubstituted enones and enoates. Many addi-

tional applications of these reagents, especially in the Cu(I) and Cu(II) manifolds, are envisioned and will be reported in due course.

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