Synthetic Methods

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Heterogeneous Catalysis with Nickel-on-Graphite (Ni/C_g): Reduction of Aryl Tosylates and Mesylates[**]

Bruce H. Lipshutz,[*] Bryan A. Frieman, Tom Butler, and Vladimir Kogan

Graphite, one of four allotropic forms of carbon, occurs in well-ordered sheets and in a relatively pure state.[1] With approximately 3.3 Å between two-dimensional layers of carbon atoms, nickel atoms can be readily impregnated,[2] akin to alkali-metal atoms that form well-known graphite intercalation compounds.[3] In the appropriate oxidation state, valuable yet inexpensive metal-catalyzed cross-couplings could be anticipated. Herein, we describe a new preparation of this active species, nickel-on-graphite (Ni/C_g), as well as the first study of its manipulation and use as a catalyst for synthetic purposes. For this initial investigation, we chose the challenging and valuable transformation involving reduction of an aromatic tosylate or mesylate,[4] for which there is no generally recognized technology to our knowledge.[5]

Ni/C_g (3–5% by weight) is conveniently prepared by mixing nickel nitrate and graphite in water (Scheme 1).

$$\text{graphite} + \text{Ni(NO}_3)_2 \xrightarrow[\substack{\text{3. distill off H}_2\text{O} \\ \text{4. dry}}]{\substack{\text{1. mix in H}_2\text{O} \\ \text{2. ultrasound}}} \text{Ni}^{\text{II}} \text{ on graphite (Ni/C}_g)$$

Scheme 1. Preparation of Ni/C_g.

Maximum distribution is obtained by ultrasonication at ambient temperatures over the course of an hour. Distillation of the water at atmospheric pressure drives off oxides of nitrogen to lead to Ni^{II}/C_g (presumably in the form of NiO/C_g). Drying this material under vacuum affords the catalyst, which can be generated in multigram quantities and is best stored in a dry, inert environment.

Reduction of a phenolic OH moiety in the presence of a multitude of functionality, in general, is a nontrivial operation.[4] Most often, as highlighted by Larock,[6] one relies on a chemoselective insertion of Pd^0 into a derived triflate in the

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[*] Prof. B. H. Lipshutz, B. A. Frieman, T. Butler, Dr. V. Kogan
Department of Chemistry and Biochemistry
University of California
Santa Barbara, CA 93106 (USA)
Fax: (+1) 805-893-8265
E-mail: lipshutz@chem.ucsb.edu

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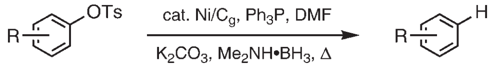
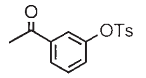
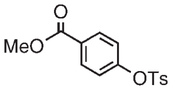
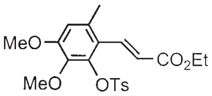
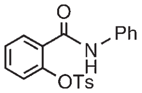
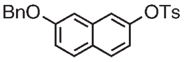
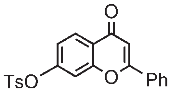
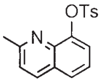
presence of a mild source of hydride (e.g., Bu_3SnH, formate, etc.).[7] No recommendations are offered for the corresponding, far more common, and economically attractive tosylate or mesylate,[5c] let alone under heterogeneous conditions.

The combination of Ni/C_g and preformed dimethylamide borane (1.1 equiv; used in its kaliated form and prepared from $Me_2NH{\cdot}BH_3$[8] + K_2CO_3) in hot dimethylformamide (DMF; 120 °C) is very effective for the reduction of aryl tosylates. Switching to Cs_2CO_3 results in a much faster generation of the amide, although the rates and efficiencies of the subsequent reductions of sulfonates are unaffected. Reactants bearing ketone, ester, enoate, and amide functionalities are untouched (Table 1, entries 1–4, respectively).

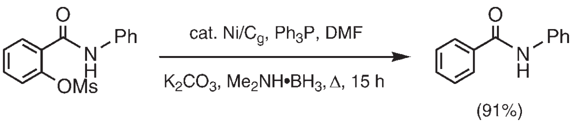
Table 1: Reduction of aryl tosylates catalyzed by Ni/C_g.



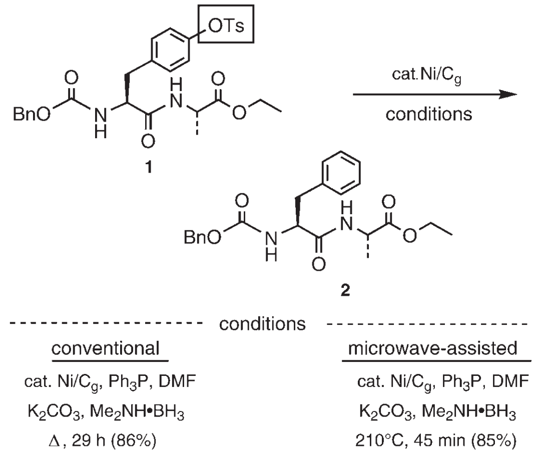
Entry	Substrate	*t* [h]	Yield [%][a]
1		9	quant[b]
2		6	quant[b]
3		14	88
4		14	91
5	 **9**	6	92
6		9	92
7		6	93

[a] Yield of the isolated products as purified by chromatography. [b] Quantitative yield indicated by quantitative GC. Ts = *p*-toluenesulfonate.

Also worthy of note is that benzyl protecting groups on aromatic alcohols (e.g., entry 5) remain intact, and conjugate reduction does not take place under these conditions. Reactions performed at approximately 0.33 M tended to require 6–15 h, with longer times likely reflecting both steric and electronic factors in the substrates. Mesylates behave akin to tosylates (Scheme 2). The reduction of nonracemic tyrosine derivative **1** to the corresponding phenylalanine-containing dipeptide **2** occurs smoothly using conventional heating without loss of stereochemical integrity (Scheme 3; "conventional").

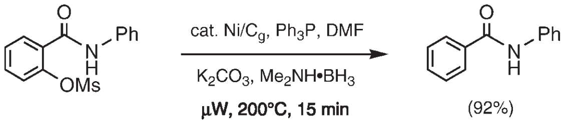


Scheme 2. Ni/C_g-catalyzed reduction of an aryl mesylate (Ms).



Scheme 3. Conversion of a tyrosine-containing dipeptide into the corresponding phenylalanine derivative under conditions of conventional and microwave heating.

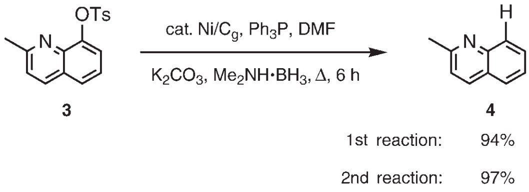
One approach to increasing the pace at which these heterogeneous reductions take place is to apply microwave irradiation.[9,10] While uncommonly employed for heterogeneous catalysis,[11] it has been found that Ni/C_g is indeed amenable to such cross-couplings. Reactions that otherwise take several hours with conventional heating (cf. Table 1) can be effected in minutes (Schemes 3 ("microwave-assisted") and 4).



Scheme 4. Rapid reduction of an aryl mesylate assisted by microwave irradiation.

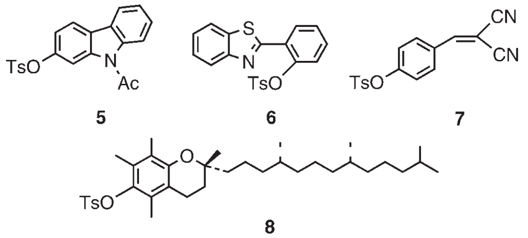
Although $Ni(NO_3)_2$ and graphite are both of low cost, opportunities nonetheless exist for catalyst recycling. Following conversion of tosylate **3** into the reduced aromatic compound **4**, reuse of the filtered and collected Ni/C_g in a second and otherwise identical reduction afforded similar results (Scheme 5).

Not all of the tosylates examined were successfully reduced by Ni/C_g. Those reactions attempted that failed, notwithstanding considerable effort under modified condi-



Scheme 5. Recycling of Ni/C_g.

tions (e.g., higher amounts of catalyst, more electron-rich ligands, microwave heating, rigorously dried solvent, etc.), are illustrated in Scheme 6. For carbazole **5**, *N*-deprotection was observed, whether the nitrogen atom was masked as the acetyl derivative or otherwise (e.g., pivaloyl, etc.). Both the benzthiazole **6** and dicyanostyrene **7** cases led to net hydrolysis of the tosylate (with or without the presence of drying agents, molecular sieves, etc.), and the vitamin E derivative **8** appears to be too hindered and/or deactivated to react even at elevated temperatures (up to 210 °C under microwave irradiation).



Scheme 6. Substrates that were not susceptible to reduction.

To gauge the level of bleed of nickel from graphite under conventional heating conditions, inductively coupled plasma (ICP) analyses[12] were conducted on a sample reaction mixture. Thus, following the conversion of tosylate **9** (cf. Table 1, entry 5) into the corresponding reduced aromatic compound,[13] hot filtration of the crude mixture was followed by solvent removal and digestion in refluxing aqua regia. The data indicated that 4.99 % of the 5 % Ni/C_g (or 0.155 mg nickel for the amount of catalyst used) in the reaction mixture could be determined to be in solution. Thus, only 0.0025 equivalents of nickel relative to substrate were detected, an amount insufficient to effect the observed chemistry.

Transmission electron microscopy (TEM) was used to examine the physical nature of Ni-on-graphite.[14] There appears to be no visible sign of extensive clustering of nickel atoms, presumably due to the use of ultrasonication during the preparation of the catalyst. From Figure 1 a, scaled at 100 nm, two graphite sheets can be distinguished that indicate independent nickel clusters. A cross section of the catalyst at 200 nm (Figure 1 b), taken from a different perspective, shows that nickel is indeed impregnated within the sheets. In conjunction with our ICP-atomic emission spectrometric (AES) data indicating that only approximately 0.25 % nickel relative to substrate is in solution, these data suggest that reactions of Ni/C_g primarily take place on the surface of the graphite layers. Thus, as is the case with nickel-in-charcoal (Ni/C),[15] the hydrocarbon appears to support, retain, and maintain the metal in a catalytically active state.

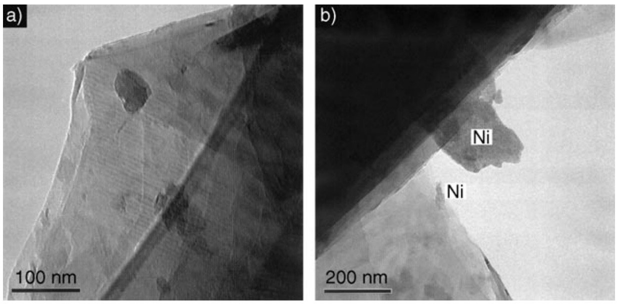


Figure 1. TEM images of Ni/C_g. a) Nickel clusters on graphite sheets; b) cross section showing exposed nickel atoms on the support.

In summary, a readily available, very inexpensive catalyst in the form of nickel-on-graphite has been prepared and shown to afford chemoselective reductions of aryl tosylates and mesylates. This heterogeneous material is amenable to use under either conventional heating conditions, or microwave irradiation which greatly enhances reaction rates. Catalyst reisolation and recycling can be effected without loss of activity. New additional chemistry associated with Ni/C_g will be reported in due course.

Experimental Section

Preparation of Ni^{II}/C_g: Graphite powder (3.75 g, 1–2 μm) was added to a 100-mL round-bottomed flask containing a stirring bar. A solution of $Ni(NO_3)_2 \cdot 6H_2O$ (727 mg, 2.30 mmol; Aldrich, 24,407-4, Ni content determined by ICP analysis: 92 %;) in deionized H_2O (35 mL) was added to the graphite, and deionized H_2O (40 mL) was added to wash down the sides of the flask. The flask was purged under argon and stirred vigorously for 1 min. The flask was submerged in an ultrasonic bath under a positive argon flow for 60 min. The flask was attached to an argon-purged distillation setup and placed in a sand bath preheated at 175–180 °C with a stirring plate. As the distillation ended, the flask temperature rises automatically, but should be kept below 210 °C for an additional 15 min. Upon cooling to room temperature, the black solid was washed with H_2O (2×50 mL) under argon into an in vacuo predried 150-mL course-fritted funnel. The H_2O used to wash the Ni/C was removed with a rotatory evaporator and analyzed for remaining nickel. The fritted funnel was inverted under vacuum and allowed to stand for 3 h until the Ni/C_g fell from the frit into a collection flask. Any Ni/C_g that remained on the fritted funnel was scraped off with a spatula and collected. The collection flask was then dried in vacuo at 100 °C for 18 h. Using these specific amounts, all of the nickel, which corresponded to 0.552 mmol $Ni^{II}\,g^{-1}$ catalyst or 3.2 % Ni/catalyst by weight, was mounted on the support.

Representative procedure for Ni/C_g-catalyzed reductions of aryl tosylates: Ni/C_g (96 mg, 0.05 mmol), PPh_3 (70 mg, 0.27 mmol), K_2CO_3 (150 mg, 1.10 mmol), and borane–dimethylamine complex (68 mg, 1.10 mmol) were added to an argon-purged, flame-dried long-necked 10-mL round-bottomed flask in a glove box. Dry DMF (2 mL) was added to the reaction mixture and allowed to stir at room temperature for 2 h. The tosylate (1.00 mmol) was added to the reaction mixture and washed down the sides of the flask with additional DMF (1 mL). The flask was then equipped with a reflux condenser and placed into a preheated oil bath at 120 °C. The reaction was followed by TLC until complete disappearance of the starting material was observed. The flask was then allowed to cool to room temperature and filtered to remove Ni/C_g. The flask was washed with methanol (3×10 mL) and CuCl (27 mg, 0.27 mmol) was added to sequester PPh_3.[16] The solvent was evaporated under reduced pressure, and the reduced material was afforded by column chromatography on silica gel of the residue.

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[11] For example, see R. K. Arvela, N. E. Leadbeater, *Org. Lett.* **2005**, *7*, 2101; for a review, see: B. Desai, C. O. Kappe in *Top. Curr. Chem.* (Ed.: A. Kirschning), Springer, **2004**, pp. 177–207.

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[13] Although all examples in Table 1 were run with 1 mmol of reactant, the scale was increased to 5 mmol for the case of tosylate **9**; under otherwise identical conditions (albeit for 12 vs. 6 h), the reaction led to a 90% yield of isolated product of the reduced material.

[14] Data was acquired using a JEOL 2011 STEM operated at 200 keV; the EDX detector is an EDAX Genesis.

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