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# Nickel Nanoparticles in Hydrogen Transfer Reactions

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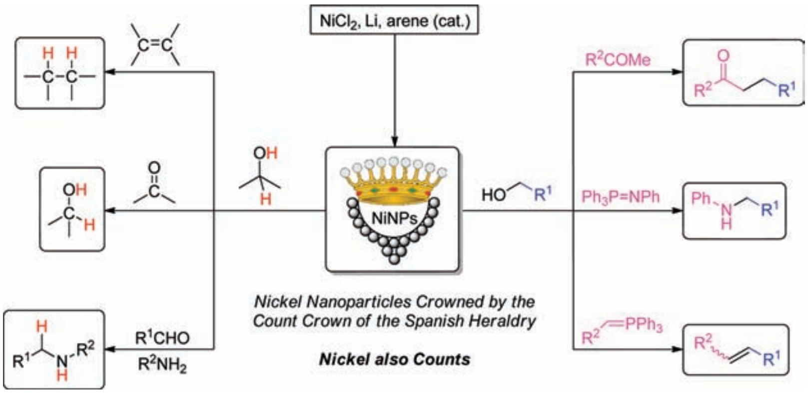
## CONSPECTUS



The transfer hydrogenation of organic compounds is a much safer and more environmentally benign process than reduction reactions involving molecular hydrogen, metal hydrides, or dissolving metals. In transfer hydrogenation, 2-propanol is often preferred as the source of hydrogen because it is cheap, easy to remove, and environmentally friendly. This class of transformation has been mostly pursued through the use of expensive noble metals, such as Ru, Pd, and so forth; research involving cheaper catalytically active metals has been relatively neglected.

On the other hand, alcohols have recently emerged as desirable alkylating agents, a useful alternative to organic halides, in reactions of hydrogen autotransfer, also known as the "borrowing of hydrogen" methodology. For instance, the α-alkylation of ketones with alcohols is an atom-efficient process that produces water as the only byproduct in the presence of a noble metal catalyst. Hydrogen autotransfer is also successful in the synthesis of amines through a reductive aza-Wittig reaction, which involves an iminophosphorane and primary alcohol under iridium catalysis. The in situ oxidation–Wittig olefination of primary alcohols with stabilized phosphorus ylides is a commonly practiced method in organic synthesis that precludes the necessity of handling aldehydes. These reactions are normally performed in one pot but sequentially; thus the course of the alcohol oxidation needs monitoring before the ylide addition.

In this Account, we describe the development of our discovery that nickel(0), in the form of nanoparticles, can replace the more expensive noble metals in both transfer hydrogenation and hydrogen autotransfer reactions. These nanoparticles were found to catalyze the transfer hydrogenation of olefins and carbonyl compounds, as well as the reductive amination of aldehydes, with 2-propanol as the hydrogen donor. All reactions proceeded in the absence of base, and the catalyst could be easily and successfully reutilized in the case of the carbonyl compounds. The catalyst was fully characterized, and the reaction mechanism, kinetics, and heterogeneous nature of the process were established through a variety of experiments. Moreover, the nickel nanoparticles enabled the activation of primary alcohols for the α-alkylation of ketones and reductive aza-Wittig reaction, with the latter leading to secondary amines. For the first time, these two reactions were achieved with a catalyst that was not one of the noble metals.

We also observed that nickel nanoparticles can activate alcohols in the presence of phosphorus ylides. In this case, although the autotransfer of hydrogen failed, the reaction could be used as a key tool to construct carbon–carbon double bonds. In this respect, we describe the one-pot synthesis of stilbenes from alcohols through a Wittig-type olefination reaction promoted by nickel nanoparticles. We report a wide range of polymethoxylated and polyhydroxylated stilbenes, including the naturally occurring polyphenol resveratrol. The utility of the nickel nanoparticles was exceptional in all of the aforementioned reactions when compared with other forms of nickel, including Raney nickel.

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## 1. Introduction

Transition metal catalysis is dominated by the elements of the three triads, where ruthenium, rhodium, iridium and, above all, palladium, generally stand out from the others because of their incomparable catalytic activity and efficiency. These noble metals have darkened the role of the first triad metals in catalysis until the recent revival of iron.[1] Indeed, methodologies based on the "modest" transition metals that can promote the organic transformations typically reserved to the noble metals are challenging and praiseworthy. This assertion gains points when we compare the relative prices of some transition metals referred to their corresponding anhydrous chlorides (Figure 1). Thus, iridium and rhodium are extraordinarily expensive; palladium and ruthenium are somewhat cheaper, whereas nickel and iron are 100-fold and more than 1000-fold cheaper than ruthenium, respectively.

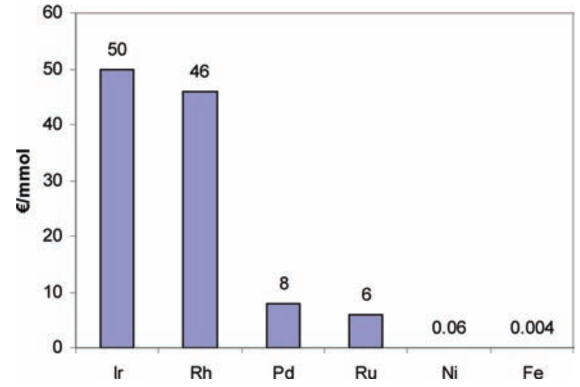
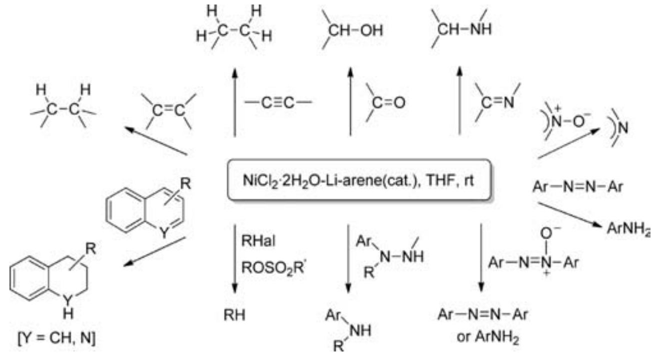


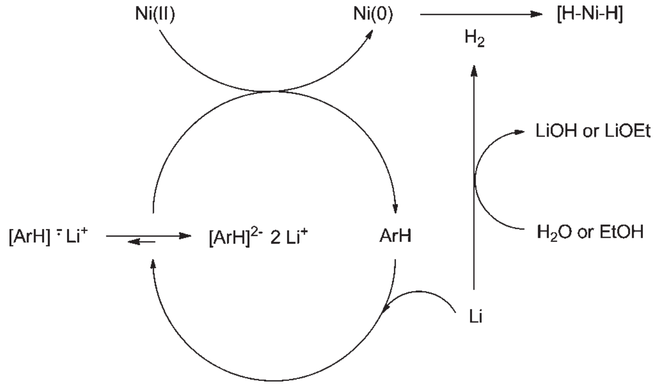
**FIGURE 1.** Relative prices for some transition metals (Sigma-Aldrich).

In 1996, due to our incipient interest in active metals,[2] we discovered the $NiCl_2 \cdot 2H_2O$–Li–arene(cat.) combination as a useful and versatile mixture able to reduce a broad range of functionalities bearing carbon–carbon multiple bonds, as well as carbon–heteroatom and heteroatom–heteroatom single and multiple bonds (Scheme 1).[3] Two different and independent processes were postulated to take part in the reduction pathway:[3b] (a) the reduction of nickel(II) to nickel(0) by the action of the radical anion or the dianion derived from the activation of metal lithium by the arene (which acts as an electron carrier) and (b) the generation of molecular hydrogen by reaction of the excess of lithium and the crystallization water present in the nickel salt (Scheme 2). The combination of this molecular hydrogen with the highly reactive nickel(0) would lead to a sort of nickel hydride species, which was considered the real reducing agent. Interestingly, the analogous deuterated combination, $NiCl_2 \cdot 2D_2O$–Li–arene(cat.), allowed the easy incorporation of deuterium in the reaction products. In addition, a polymer-supported arene could be used as electron-transfer agent, instead of the free arene, this methodology facilitating the recovery and reuse of the arene component. Alternatively, almost the same type of functionalities mentioned above could be reduced by catalytic hydrogenation utilizing active nickel, generated from anhydrous nickel(II) chloride, and external molecular hydrogen at atmospheric pressure [$NiCl_2$–Li–arene(cat.)–$H_2$ or $NiCl_2$–Li–(polymer-supported arene)(cat.)–$H_2$].[4]

**SCHEME 1.** Reduction of Organic Functionalities with the $NiCl_2 \cdot 2H_2O$–Li–Arene(cat.) System

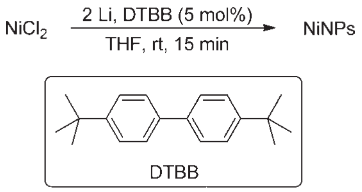


**SCHEME 2.** Proposed Reduction Pathway with the $NiCl_2 \cdot 2H_2O$–Li–Arene(cat.) and $NiCl_2$–Li-Arene(cat.)–EtOH Systems



Some years later, we demonstrated that the highly reactive nickel, obtained by reduction of anhydrous nickel(II) chloride with lithium powder and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl) in THF at room temperature, was in the form of nanoparticles (2.5 ± 1.5 nm).[5] Similar systems to $NiCl_2$–Li–DTBB(cat.), utilized in reduction reactions, such as $NiCl_2$–Li–copolymer(cat.)–$H_2$, $NiCl_2 \cdot 2H_2O$–Li–DTBB(cat.), $NiCl_2$–Li–DTBB(cat.)–EtOH, or $NiCl_2$–Li–copolymer(cat.)–EtOH, were also disclosed to generate nanosized metallic nickel in the absence of any antiagglomeration additive or nucleation catalyst at room temperature.[6] The introduction in the reducing system of an alcohol as a source of molecular

**SCHEME 3.** Synthesis of the Nickel Nanoparticles



hydrogen, by reaction with Li (Scheme 2), was a very convenient method for the highly selective semihydrogenation of alkynes and dienes[7] and conjugate reduction of $\alpha,\beta$-unsaturated carbonyl compounds[8] under mild reaction conditions. We observed, however, that a hydrogen-transfer process might be operating, at least in part, in the reactions involving an alcohol. From this finding, we envisaged the possibility of applying the nickel nanoparticles (NiNPs) in hydrogen-transfer reactions.

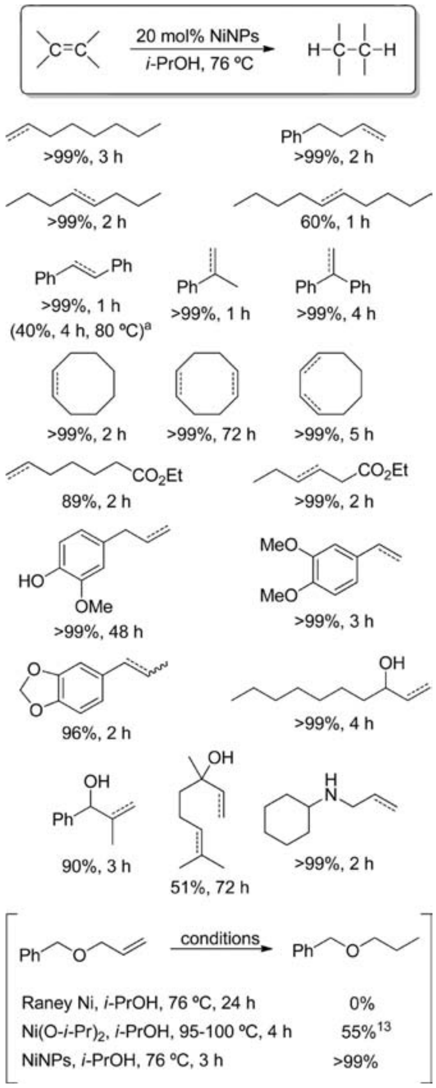
It is noteworthy and somehow surprising that the combination of inexpensive transition metals with green and safe sources of hydrogen has been practically unexplored until recently. In this sense, the potential of nickel has been undervalued in favor of the more "exotic" and attractive catalytic systems containing noble metals. We want to present herein the scope and versatility of an easily prepared and simple catalytic system based on unsupported nickel nanoparticles, as an alternative to noble-metal catalysts in hydrogen transfer reactions. All the reactions discussed in this Account were effected with NiNPs prepared from anhydrous nickel(II) chloride, metal lithium, and a catalytic amount of DTBB (5 mol %) as an electron carrier (Scheme 3). On one hand, we will deal with the transfer hydrogenation of olefins and carbonyl compounds and reductive amination of aldehydes, using 2-propanol as a hydrogen donor. On the other hand, the activation of alcohols for the $\alpha$-alkylation of ketones and reductive aza-Wittig reaction (through hydrogen autotransfer), as well as for the Wittig reaction, will be described.

## 2. Discussion

### 2.1. Reduction Reactions by Hydrogen Transfer.

**2.1.1. Introduction.** The catalytic transfer hydrogenation of organic compounds[9] is an advantageous methodology with respect to other reduction methods for several reasons: (a) the hydrogen source is easy to handle (no gas containment or pressure vessels are necessary), (b) possible hazards are minimized, (c) the mild reaction conditions used can afford enhanced selectivity, and (d) catalytic asymmetric transfer hydrogenation can be applied in the presence of chiral ligands. Within the different types of hydrogen donors, 2-propanol is probably the most popular one since it is cheap, nontoxic, and volatile, possesses good solvent properties, and is transformed into acetone, which is environmentally friendly and easy to remove from the reaction medium.

**SCHEME 4.** Transfer Hydrogenation of Alkenes

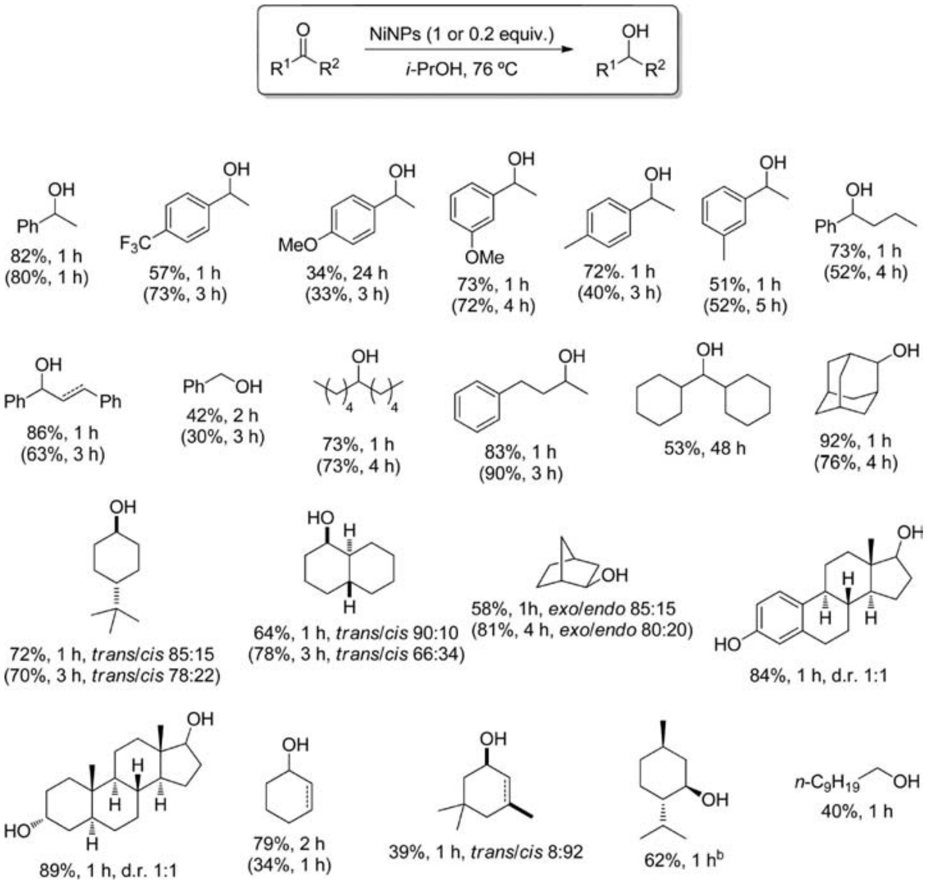


| | |
|---|---|
| Raney Ni, *i*-PrOH, 76 °C, 24 h | 0% |
| Ni(O-*i*-Pr)$_2$, *i*-PrOH, 95-100 °C, 4 h | 55%[13] |
| NiNPs, *i*-PrOH, 76 °C, 3 h | >99% |

[a] Reported data with Raney nickel.[12]

**2.1.2. Hydrogen-Transfer Reduction of Alkenes.** The transfer hydrogenation of olefins has been little studied in comparison with that of carbonyl compounds, using alcohols, formic acid, or hydroaromatic compounds, mainly in the presence of noble-metal catalysts.[10] The transfer hydrogenation of styrenes has been recently reported using hydrazine as the hydrogen source and a catalyst consisting of clay-entrapped nickel nanoparticles.[11] To the best of our knowledge, however, only two reports describe the application of nickel and 2-propanol to the transfer

**SCHEME 5.** Transfer Hydrogenation of Carbonyl Compounds[a]



[a] Data in parentheses refer to the use of 20 mol % NiNPs. The dashed bond indicates the original position of the carbon−carbon double bond.
[b] Diastereomeric ratio: (−)-menthol/neoisomenthol/neomenthol 77:9:14.

hydrogenation of olefins. In the first one, Raney nickel (10−50 wt % of total substrate) was used under reflux, showing high conversions for cinnamates and cyclic olefins and low conversions for acyclic olefins.[12] In the second report, activated metallic nickel, prepared by thermal decomposition of *in situ* generated nickel diisopropoxide in boiling 2-propanol, was more effective in the reduction of nonfunctionalized and nonactivated olefins (10−30 mol % Ni, 95−100 °C).[13]

We demonstrated that NiNPs can effectively catalyze the heterogeneous transfer hydrogenation of olefins using 2-propanol as the hydrogen donor.[14] Raney nickel behaved similarly to the NiNPs in the reduction of 1-octene but longer reaction time was needed in order to achieve the same conversion at 76 °C, while the activity of the former drastically dropped at room temperature. Other commercially available nickel catalysts, such as Ni−Al, Ni/$SiO_2$−$Al_2O_3$, or NiO, were totally inactive under the above-mentioned conditions. A variety of nonfunctionalized and functionalized olefins were successfully reduced under the optimized reaction conditions (20 mol % NiNPs, *i*-PrOH, 76 °C) (Scheme 4). The process was shown to be highly chemoselective for substrates that are prone to undergo isomerization (allylic alcohols) or hydrogenolysis (allyl benzyl ether or allylcyclohexylamine), where a clear superiority of the NiNPs was manifested with respect to other nickel catalysts. Moreover, the monoterpene (±)-linalool, which contains both a mono- and a trisubstituted carbon−carbon double bond, was transformed into tetrahydrolinalool in moderate isolated yield after prolonged heating. Unfortunately, an important decrease in the conversion of the olefins was observed in the second cycle when reutilization of the catalyst was attempted, due to progressive deactivation.

**2.1.3. Hydrogen-Transfer Reduction of Carbonyl Compounds.** The transfer hydrogenation of carbonyl compounds has been mostly accomplished using 2-propanol as hydrogen donor, under homogeneous conditions in the presence of noble-metal complexes (such as those of Ru, Rh, or Ir).[15] In this field, ruthenium complexes have been by far the most studied catalysts, especially for the asymmetric transfer hydrogenation of aromatic ketones[16] and from the

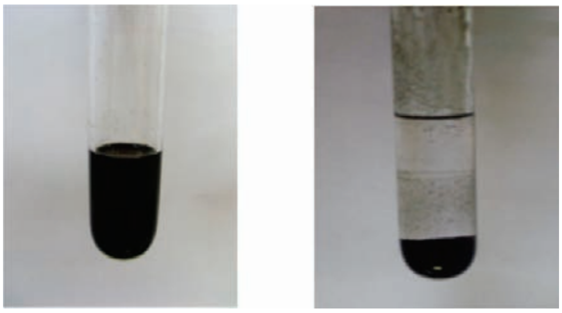
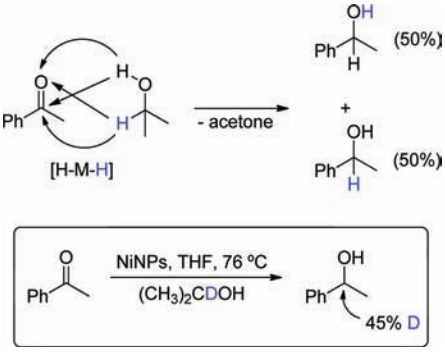


**FIGURE 2.** Reutilization of the NiNPs.

mechanistic point of view.[17] Nickel has been used either under homogeneous[18] or heterogeneous conditions,[13,19] mainly for aromatic substrates. In all these cases, the addition of an external base was mandatory for the reaction to take place. More recently, an excess of Raney nickel in refluxing 2-propanol, containing a trace of HCl, reduced a series of aliphatic aldehydes and ketones to the corresponding primary and secondary alcohols, respectively.[20]

We reported on the application of NiNPs to the transfer hydrogenation with 2-propanol of an array of carbonyl compounds in the absence of any added base at 76 °C. Both a stoichiometric[21a] and a substoichiometric (20 mol % Ni) version[21b] were studied and compared. Modest-to-good yields of the corresponding alcohols were obtained in relatively short reaction times (Scheme 5). The reduction of substituted acetophenones was shown to be very dependent on the electronic character and position of the substituent, whereas, in general, better yields were attained for aliphatic ketones. The reducing system was shown to be diastereoselective for most of the cyclic ketones studied, with the stereoselectivity achieved with 20 mol % NiNPs being somewhat lower than that achieved with stoichiometric NiNPs. The NiNPs exhibited a superior performance in comparison with other forms of nickel under the same reaction conditions. Moreover, the NiNPs could be easily separated by decantation with an extra amount of 2-propanol and reutilized up to five times, maintaining a high activity in a very simple reaction medium composed of the NiNPs, 2-propanol and the substrate, with no base (Figure 2). According to some deuteration experiments, the reaction seemed to proceed through a dihydride-type mechanism, in which the two hydrogens of the donor are transferred to the metal, thus losing their original identity and becoming equivalent (Scheme 6). After our work, several reports emerged describing the application of supported NiNPs, prepared by different methods, to the transfer hydrogenation with 2-propanol of aromatic ketones.[22]

**SCHEME 6.** The Dihydride-Type Mechanism

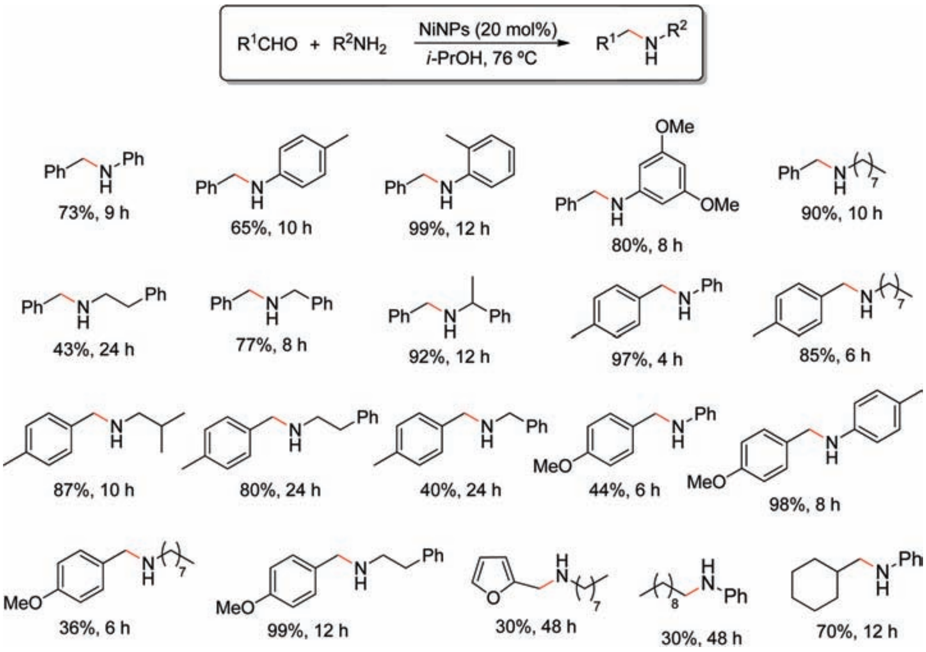


### 2.1.4. Hydrogen-Transfer Reductive Amination of Aldehydes.

The reductive amination of aldehydes and ketones, an important transformation in biological systems, is a direct and convenient route to amines.[23] The reductive amination with metal hydrides[24] or by catalytic hydrogenation[25] are widespread methods, whereas transfer hydrogenation is more restricted to the reduction of preformed imines.[26] It is worthy of note that, in contrast with other transition metals, nickel has been scarcely used in reductive aminations or in the transfer hydrogenation of imines. Reductive aminations involving nickel were performed with hydrazine and borohydride exchange resin−nickel acetate[27a] or with stoichiometric nickel boride in methanol.[27b] On the other hand, the transfer hydrogenation of preformed imines was carried out with 2-propanol and excess aluminum isopropoxide in the presence of Raney nickel (the reaction failed in the absence of aluminum isopropoxide)[28a] or with sodium isopropoxide catalyzed by a nickel(0)/*N*-heterocyclic carbene complex.[28b]

To the best of our knowledge, however, nickel-mediated reductive-amination reactions by transfer hydrogenation had not been reported previously. We proved that NiNPs can catalyze the reductive amination of aldehydes by transfer hydrogenation, using 2-propanol as the hydrogen source in the absence of any added base (Scheme 7).[29] The process was especially effective in the reductive amination of aromatic aldehydes, most of the corresponding secondary amines being obtained in good-to-excellent yields. The application to aliphatic aldehydes was, however, more limited. Although any attempt to reuse the NiNPs failed, this methodology can be considered advantageous because (a) the preparation step of the imine is avoided, aldehydes and amines being directly used as starting materials, (b) the source of hydrogen is 2-propanol, a cheap and environmentally friendly solvent, and (c) the NiNPs were shown to be superior to other nickel catalysts in this reaction.

**SCHEME 7.** Reductive Amination of Aldehydes



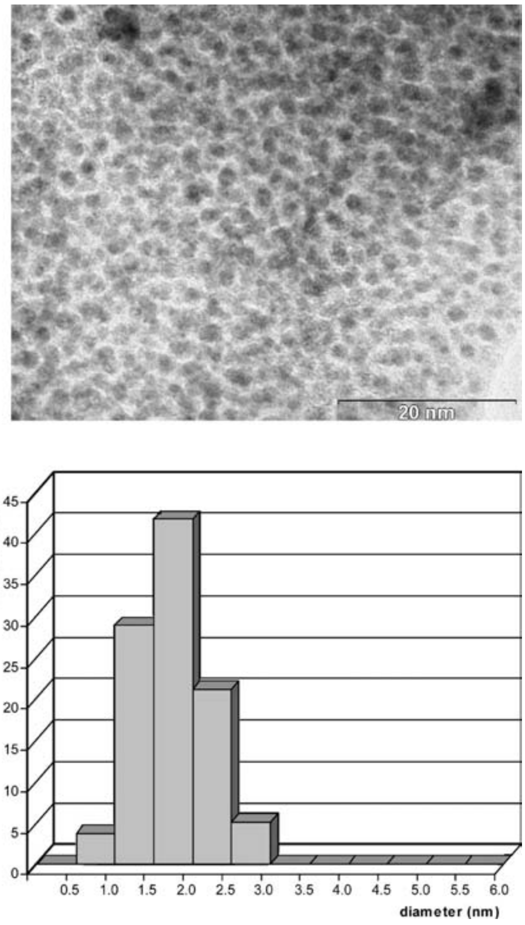
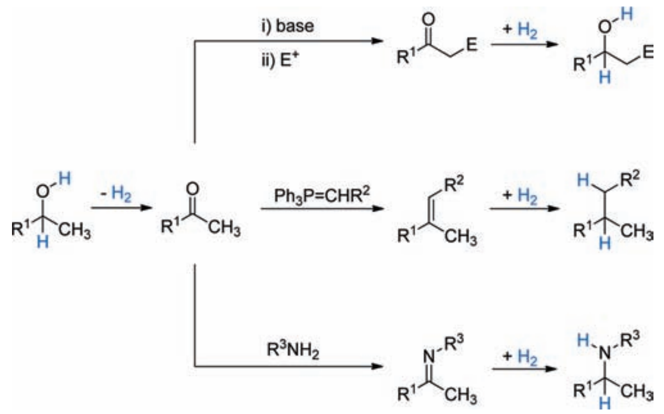


**FIGURE 3.** TEM micrograph and size distribution of the NiNPs.

**2.1.5. Characterization and Nature of the Catalyst.** The NiNPs utilized in the transfer hydrogenations with 2-propanol were characterized by TEM, EDX, XPS, XRD, EPR, and BET area.[30] Spherical, monodisperse, and highly uniform nanoparticles were obtained with a narrow size distribution (0.75−2.88 nm, ca. 1.75 ± 1.00 nm) (Figure 3). Notably, the morphology and size distribution were very similar irrespective of the reaction time (1, 4, 8, and 24 h). Therefore, the presence of 2-propanol at 76 °C was shown to exert a beneficial effect in the generation of the NiNPs as regards their size, uniformity, and stabilization. The only XPS peak at 852.2 eV, corresponding to the Ni $2p_{3/2}$ level, was characteristic of Ni(0), with the broad and low intensity peaks in the XRD diffractogram corresponding to face-centered cubic nickel. These data were in agreement with the observation of diffuse intensity rings in the selected area electron diffraction pattern (SAED), thus suggesting a very small size for the crystalline domains or an amorphous character. The surface area of a NiNP sample was determined to be 33.04 $m^2/g$.

Catalytic and kinetic studies in the transfer hydrogenation of acetophenone revealed that the reaction rate was dependent upon the amount of acetophenone with a negative slope, not proportional to the amount of 2-propanol, and independent of the LiCl concentration.[30] The fastest conversion was reached at 76 °C (88.5% in 8 min). Based on TPO experiments, Raman spectroscopy, TG, and XPS analysis, the

**SCHEME 8.** Examples of Alcohol Activation by Borrowing of Hydrogen or Hydrogen Autotransfer



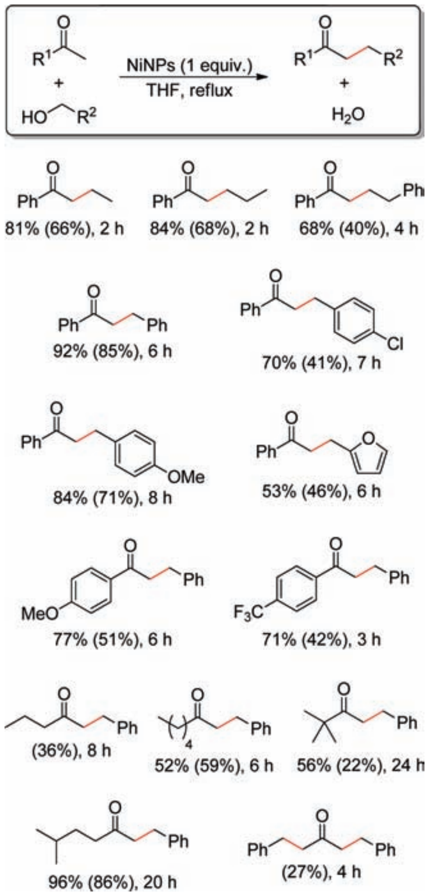
deactivation of the catalyst with reiterative reuse was ascribed to surface oxidation, while the formation of coke was ruled out. Moreover, the NiNPs were demonstrated to be the true catalyst in this reaction, the heterogeneous nature of the process being unequivocally established on the basis of TEM, kinetic, poisoning, and filtration experiments.

### 2.2. Carbon–Carbon and Carbon–Nitrogen Bond Formation by Alcohol Activation.

**2.2.1. Introduction.** In general, alcohols exhibit a limited reactivity unless they are properly activated. Alcohols can be activated by reaction with a base, to form a nucleophilic alkoxide, or by transformation into good leaving groups. An alternative to the activation of alcohols is their temporary oxidation to the corresponding carbonyl compounds. Carbonyl compounds are more reactive than alcohols, which behave as electrophiles in nucleophilic addition reactions or as nucleophiles through their enolates. The oxidation of an alcohol to a carbonyl compound is especially interesting when, catalytically, a hydrogen transfer occurs from the alcohol to a derivative of the carbonyl compound *in situ* generated (Scheme 8). This type of process has been defined as "hydrogen autotransfer" or "borrowing of hydrogen" and is useful to form carbon–carbon and carbon–nitrogen bonds.[31]

**2.2.2. α-Alkylation of Ketones.** The α-alkylation of ketone enolates with alkyl halides is probably the most frequently used method for the synthesis of ketones.[32] In recent years, alcohols have emerged as potential alternative alkylating agents of ketones by proper activation with a transition-metal catalyst. This strategy can improve both the atom efficiency and the regioselectivity of the process producing only water as a side product. Until recently, this research was carried out only with catalysts containing some group 8 noble metals, such as ruthenium, iridium, and palladium. The presence of a sacrificial hydrogen acceptor (such as 1-dodecene or 1-decene) was, however, mandatory in many cases in order to avoid the over-reduction of the alkylated ketone.

**SCHEME 9.** α-Alkylation of Ketones with Primary Alcohols[a]

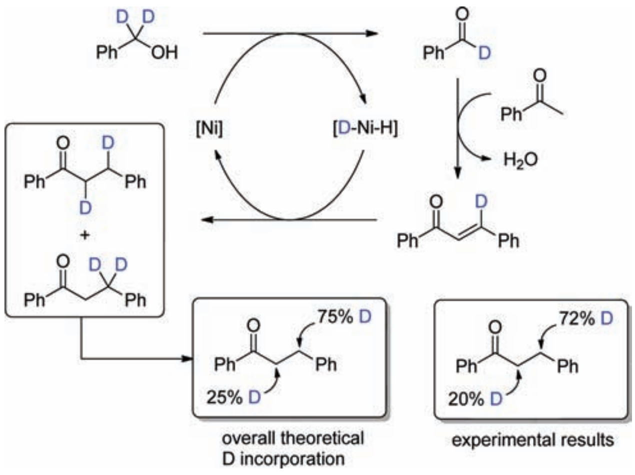


[a] GLC yield, isolated yield in parentheses.

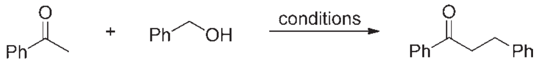
We discovered that NiNPs were a potential alternative to the aforementioned noble-metal catalysts in this reaction.[33] A variety of acetophenones were successfully alkylated with aliphatic and benzylic alcohols to give the corresponding products in moderate-to-high yields (Scheme 9). We must highlight that ethanol and *n*-propanol were used for the first time as alkylating agents in this reaction. The alkylation of alkyl methyl ketones was, in general, less efficient and could only be applied to benzylic alcohols. Deuterium labeling experiments brought some evidence about a dihydride-type reaction mechanism operating in these reactions, as depicted in Scheme 10. Furthermore, the NiNPs were shown to be superior to other common nickel catalysts and potentially alternative to noble-metal containing catalysts (Scheme 11). In addition, all reactions proceeded in the absence of any hydrogen acceptor, ligand, or added base.

**2.2.3. Reductive Aza-Wittig Reactions.** The aza-Wittig reaction is another important tool in organic synthesis

**SCHEME 10.** The Dihydride-Type Reaction Mechanism

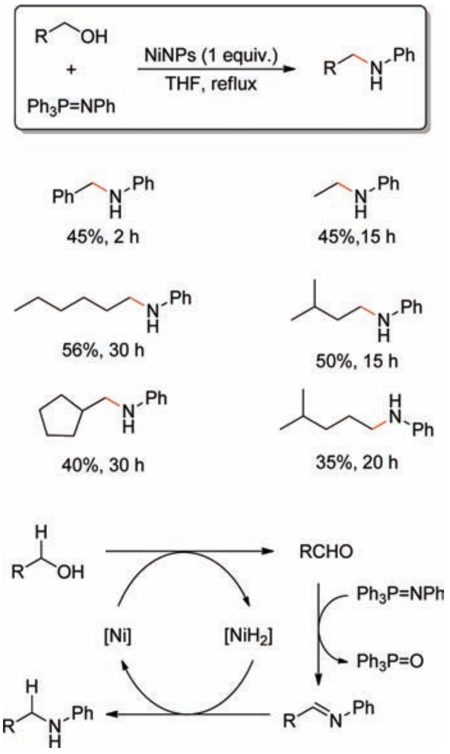


**SCHEME 11.** $\alpha$-Alkylation of Acetophenone with Different Catalytic Systems



| | | |
|---|---|---|
| $RuCl_2(PPh_3)_3$, KOH, 1-dodecene, dioxane | 80 °C, 20 h | 82% |
| $[Ir(COD)Cl]_2$-$PPh_3$, KOH, solvent-free | 100 °C, 4 h | 86% |
| Pd/C, KOH, 1-decene, dioxane | 100 °C, 20 h | 66% |
| Pd/AlO(OH), $K_3PO_4$, toluene | 80 °C, 8 h | 92% |
| $RuCl_2(DMSO)_4$, KOH, dioxane | 80 °C, 24 h | 72% |
| Pd/viologen, $Ba(OH)_2{\cdot}H_2O$, 7 equiv $H_2O$ | 100 °C, 24 h | 82% |
| NiNPs, THF | 76 °C, 6 h | 85% |

**SCHEME 12.** Reductive Aza-Wittig Reaction

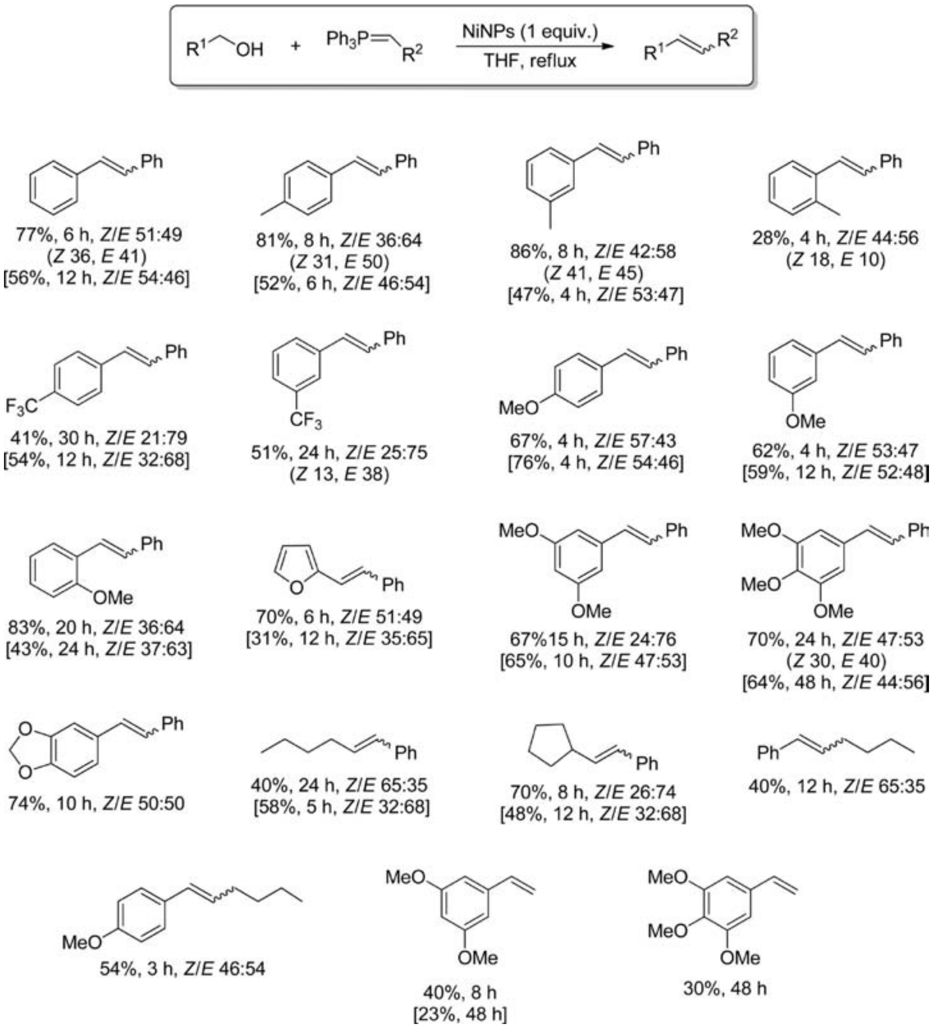


directed toward the construction of acyclic and cyclic compounds that has experienced a tremendous development in recent years.[34] In this reaction, phosphazenes (iminophosphoranes) react with carbonyl compounds, in an analogous manner to phosphorus ylides in the Wittig reaction, to give carbon−nitrogen double bonds. At the time we were carrying out the research, the conversion of alcohols into *N*-alkyl anilines through a reductive aza-Wittig reaction was only described under iridium catalysis by Williams et al.[35] In this research, several benzylic alcohols reacted with *N*-(triphenylphosphoranylidene)aniline in the presence of 2 mol % $[IrCl(COD)]_2$, 5 mol % 1,1′-bis(diphenylphosphino)ferrocene, and $K_2CO_3$ at 110 °C for 24 h. To our delight, the NiNPs were also active in the reductive aza-Wittig reaction of a series of primary alcohols with commercially available *N*-(triphenylphosphoranylidene)aniline (Scheme 12). The expected N-alkylated anilines were obtained (under similar reaction conditions as those described for the $\alpha$-alkylation of ketones with alcohols) in moderate yields but with a wider substrate scope, milder conditions, and simpler reaction system than under iridium catalysis. A reaction pathway, akin to that proposed for the alkylation of ketones, was invoked for the reductive aza-Wittig reaction.

**2.2.4. Wittig-Type Reactions.** In a typical Wittig reaction, carbonyl compounds are reacted with phosphorus ylides to give the corresponding alkenes and phosphane oxide.[36] Sometimes, however, the carbonyl compound is not readily available and has to be prepared by oxidation of the precursor alcohol. In fact, the oxidation of primary alcohols to aldehydes and subsequent Wittig reaction is a common practice in organic synthesis. This strategy is advantageous since it avoids the handling of aldehydes, especially when they are volatile, toxic, or highly reactive. In addition, alcohols are, in general, cheaper, more commercially available, less toxic, and more stable than the corresponding aldehydes. In this sense, about 10 oxidizing systems have been implemented for the *in situ* oxidation−Wittig olefination of primary alcohols.[37] These procedures are primarily applied to stabilized ylides, and though in all cases the reactions are performed in one pot, some of them are sequential. Therefore, the course of the alcohol oxidation needs monitoring before the ylide addition.

The activation of alcohols for the formation of carbon−carbon single bonds through an indirect Wittig olefination was pioneered by Williams et al.[31b,c] In this methodology, stabilized ylides or phosphonates were combined with benzyl alcohols in a domino Wittig-type olefination−transfer

**SCHEME 13.** Wittig-Type Olefination[a]

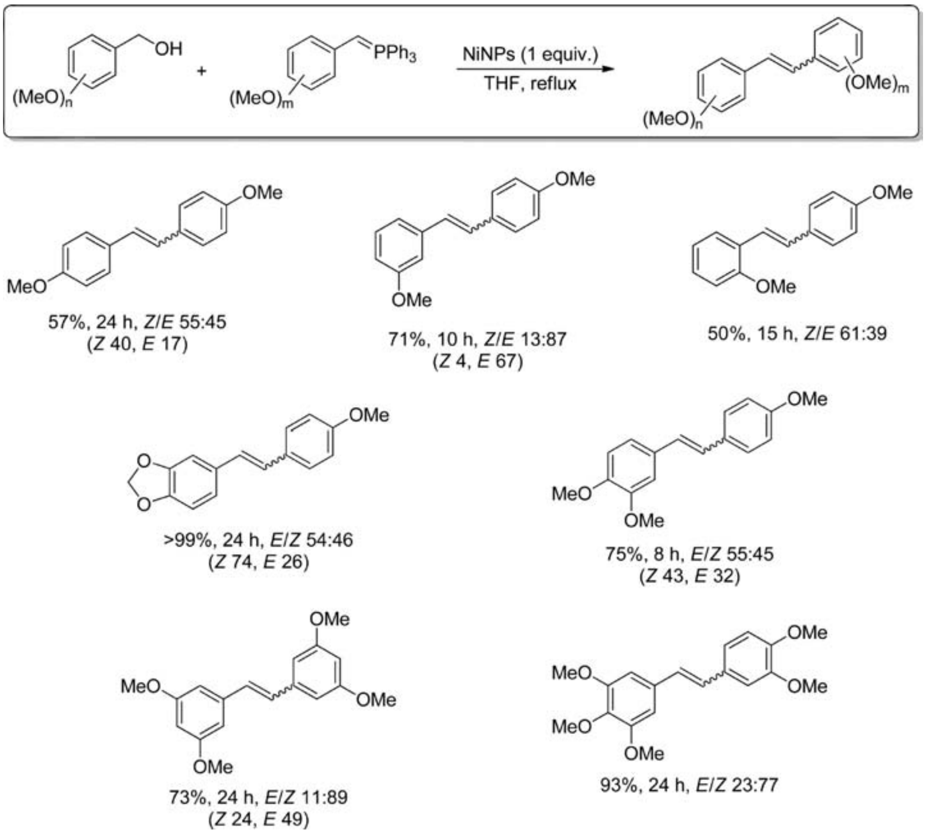


[a] Values in brackets correspond to the in situ generation of the phosphorus ylide with lithium metal, in parentheses the isolated yield for each stereoisomer.

hydrogenation, under either iridium or ruthenium homogeneous catalysis. As a result, products with a new carbon−carbon single bond, together with variable minor amounts of the corresponding aromatic aldehydes and alkenes, were obtained. More recently, Park et al. have reported the one-pot synthesis of $\alpha,\beta$-unsaturated esters from primary alcohols and stabilized Wittig reagents catalyzed by Ru/AlO(OH) in the presence of oxygen as the terminal oxidant without any additive.[38]

We found out that the NiNPs could promote the Wittig-type reaction of primary alcohols and phosphorus ylides giving rise to the corresponding olefins.[39] The ylides could be previously prepared from the corresponding phosphonium salts by deprotonation with *n*-BuLi or, more interestingly, generated *in situ* with the same lithium metal used for the generation of the NiNPs. The reaction worked especially well for benzyl alcohols and semistabilized benzyl ylides, whereas the substrate scope was more limited in the case of alkyl alcohols or nonstabilized ylides (Scheme 13). In the former case, a wide range of stilbenes were obtained in modest-to-high isolated yields, depending on the electronic character of the substituent and position in the aromatic ring. As expected for semistabilized phosphorus ylides, the process exhibited, generally, low diastereoselectivity, albeit the *Z*/*E* mixtures could be separated, in some cases (by column chromatography), or quantitatively transformed into the *E* stereoisomers by iodine-catalyzed or radical isomerization. Furthermore, the reaction proceeded in the absence of any additive as a hydrogen acceptor, and the NiNPs were shown to be catalytically superior to other forms of nickel in this reaction. It is worthwhile mentioning that the success of this olefination methodology resides in the fact that the hydrogen transfer from the alcohol

**SCHEME 14.** Synthesis of Polymethoxylated Stilbenes[a]



[a] In parentheses, the isolated yield for each stereoisomer

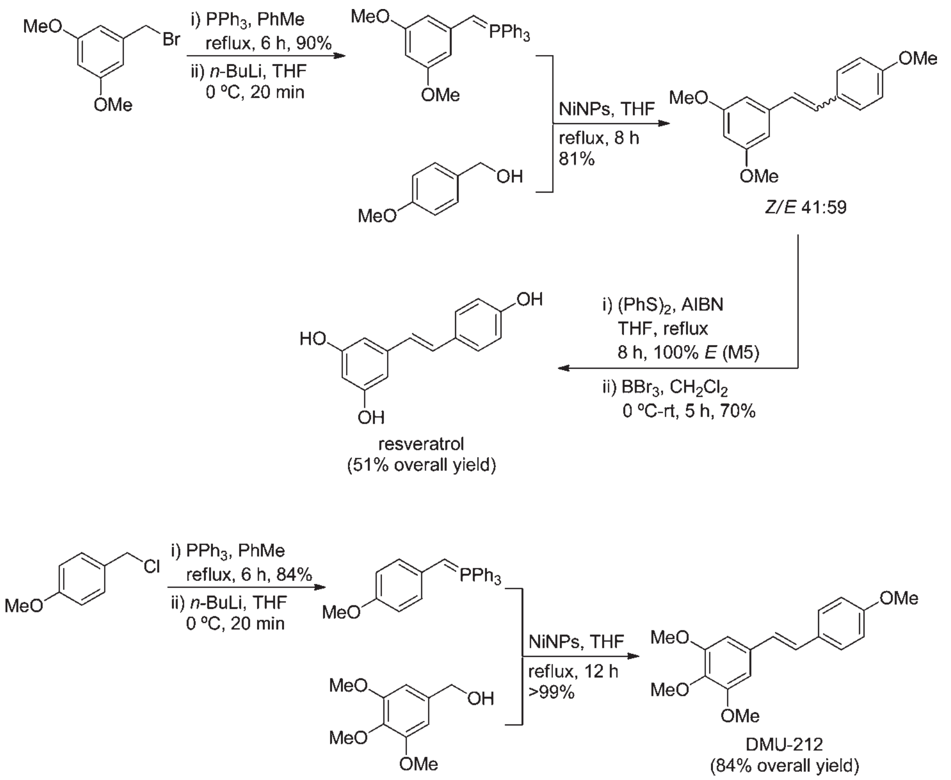
to the corresponding alkene was not effective. From different experiments and observations, it could be inferred that catalyst deactivation by poisoning with phosphorus compounds, together with some nanoparticle agglomeration were, very likely, the main reasons that accounted for this particular performance. To the best of our knowledge, this is the first metal-mediated chemoselective Wittig-type olefination reaction with alcohols, in which there is no standard redox step (i.e., the alcohol is oxidized but no reduced species are detected).

Due to the abundance of polymethoxylated stilbenes in nature, a variety of this type of compound was synthesized by applying the above-mentioned methodology (Scheme 14). The highest yield was achieved for the olefination reaction of piperonyl alcohol, with the maximum stereoselectivity reached being *Z*/*E* 1:7. Then, we turned our attention to the synthesis of some stilbenes of prominent biological activity such as resveratrol,[40] M5, and DMU-212, which were synthesized using this novel Wittig-type olefination as the key step.[39b,41] Thus, the precursor of resveratrol was obtained in 81% yield by NiNP-promoted olefination of the appropriate benzyl ylide and alcohol partners (Scheme 15). Subsequent *Z* to *E* isomerization, followed by demethylation, furnished resveratrol in 51% overall yield (Scheme 15). Following a similar strategy, DMU-212 was obtained in two steps and 84% overall yield after a quantitative and stereoselective olefination reaction.

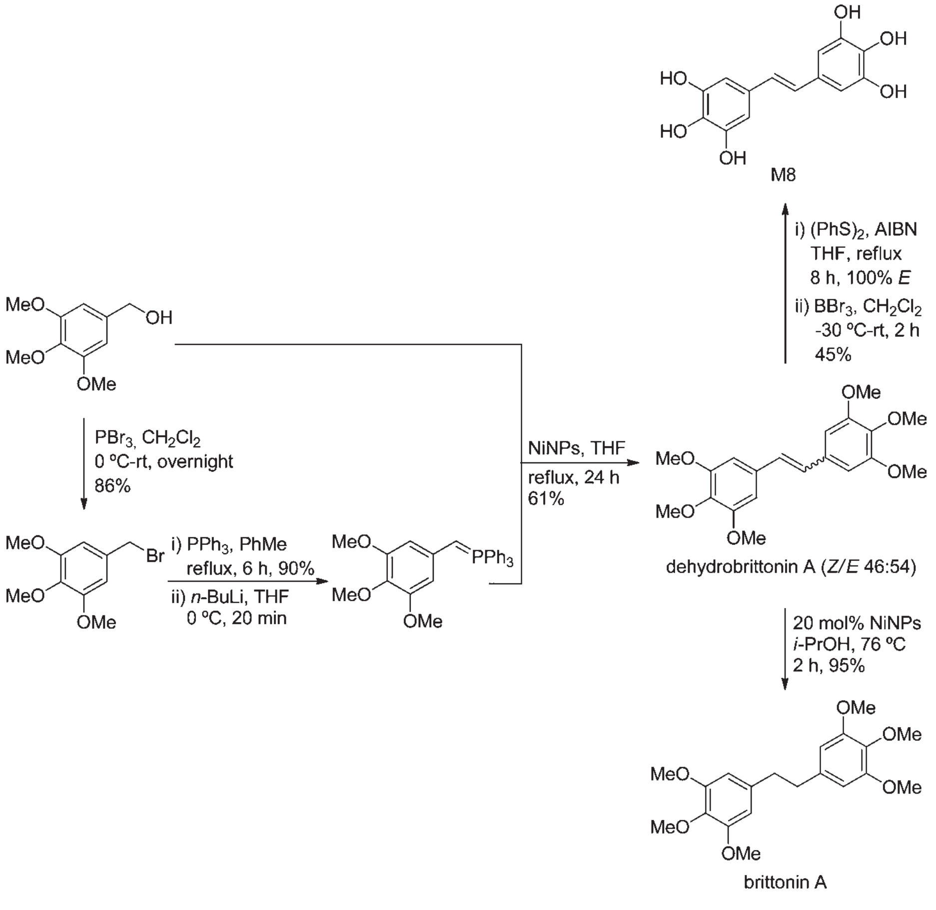
Finally, we dealt with the synthesis of the highly polymethoxylated and polyhydroxylated stilbenoids dehydrobrittonin A and M8, respectively.[39b,41] Compound M8 has been recently found to exhibit remarkable manifold biological effects[42] including (a) much higher antioxidant activity than resveratrol in different leukemic cell lines, (c) apoptosis induction at concentrations significantly lower than resveratrol in HL-60 human promyelocytic leukemia cells, and (d) apoptosis induction and cell cycle arrest in prostate cancer and HT29 human colon cancer cells. Dehydrobrittonin A is a symmetrically substituted highly polymethoxylated stilbene, which could be used as a precursor of brittonin A, a natural dihydrostilbene isolated from *Frullania brittoniae* subsp. *truncatifolia* (*F. muscicola*).[43]

3,4,5-Trimethoxybenzyl alcohol was used as the only starting material in these syntheses, which served both as the precursor of the corresponding ylide and as its partner in

**SCHEME 15.** Synthesis of Resveratrol, M5, and DMU-212



**SCHEME 16.** Synthesis of Dehydrobrittonin A, M8, and Brittonin A



the Wittig-type olefination (Scheme 16). This reaction was shown to be slower, in comparison with the homologues with less methoxy substituents, leading to dehydrobrittonin A in moderate yield as a mixture of diastereoisomers. Quantitative radical *Z* to *E* isomerization followed by demethylation afforded the resveratrol analogue M8, whereas near quantitative NiNP-catalyzed transfer hydrogenation of dehydrobrittonin A furnished brittonin A.[14]

## 3. Conclusion

We have summarized the application of easily prepared NiNPs to some organic transformations, which are typically implemented by noble-metal-based catalysts. A simple catalytic system composed of NiNPs and 2-propanol exhibited a high performance in the transfer hydrogenation of olefins, carbonyl compounds, and reductive amination of aldehydes. To the best of our knowledge, this represents the first transition-metal-catalyzed transfer hydrogenation in 2-propanol performed in the absence of any base or acid. We also discovered that the NiNPs could activate primary alcohols for the $\alpha$-alkylation of ketones and reductive aza-Wittig reaction, a field hitherto restricted to noble-metal catalysts. The particular reactivity of the NiNPs was further exploited in the one-pot oxidation−olefination of alcohols in the presence of phosphorus ylides. A wide range of olefins, stilbenes, polymethoxylated stilbenes, resveratrol, and analogues was synthesized using this novel Wittig-type olefination as the key step. It is remarkable that all reactions involving the activation of alcohols took place in the absence of any additive, such as base, ligand, or hydrogen acceptor. Moreover, in all the reactions practiced, the unsupported NiNPs exhibited reactivity much superior to other nickel catalysts, including Raney nickel. The results presented herein open an array of possibilities for further research in reactions where the more expensive, and sometimes sophisticated, noble-metal catalysts might be replaced by the cheaper and easy-to-prepare NiNPs.

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FOOTNOTES

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### REFERENCES

1 *Iron Catalysis in Organic Chemistry. Reactions and Applications*; Plietker, B., Ed.; Wiley-VCH: Weinheim, Germany, 2008.

2 (a) For the first applications of finally divided metals (including nickel) in Organic Chemistry, see: Sabatier, P. *La Catalyse en Chimie Organique*; Librairie Polytechnique Ch. Béranger: Paris, 1913. (b) Rieke, R. D. Use of Activated Metals in Organic and Organometallic Synthesis. *Top. Curr. Chem.* **1975**, *59*, 1–31. (c) Fürstner, A. *Active Metals*; Wiley-VCH: Weinheim, Germany, 1996. (d) *Nanoparticles and Catalysis*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2008.

3 (a) Alonso, F.; Radivoy, G.; Yus, M. Active-Nickel Based Reduction of Organic Compounds. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 2563–2576. (b) Alonso, F.; Yus, M. The $NiCl_2$-Li-Arene(cat.) Combination: A Versatile Reducing Mixture. *Chem. Soc. Rev.* **2004**, *33*, 284–293. (c) Alonso, F.; Yus, M. New Synthetic Methodologies Based on Active Transition Metals. *Pure Appl. Chem.* **2008**, *80*, 1005–1012.

4 (a) Alonso, F.; Yus, M. Catalytic Hydrogenation of Organic Compounds using the $NiCl_2$-Li-Naphthalene(cat.) Combination. *Adv. Synth. Catal.* **2001**, *343*, 188–191. (b) Alonso, F.; Candela, P.; Gómez, C.; Yus, M. The $NiCl_2$-Li-Arene(cat.) Combination as Reducing System, Part 9. Catalytic Hydrogenation of Organic Compounds Using the $NiCl_2$-Li-(Naphthalene or Polymer-Supported Naphthalene)(cat.) Combination. *Adv. Synth. Catal.* **2003**, *345*, 275–279.

5 Alonso, F.; Calvino, J. J.; Osante, I.; Yus, M. A New Straightforward and Mild Preparation of Nickel(0) Nanoparticles. *Chem. Lett.* **2005**, *34*, 1262–1263.

6 Alonso, F.; Calvino, J. J.; Osante, I.; Yus, M. Preparation of Nickel(0) Nanoparticles by Arene-Catalyzed Reduction of Different Nickel Chloride-Containing Systems. *J. Exp. Nanosci.* **2006**, *1*, 419–433.

7 (a) Alonso, F.; Osante, I.; Yus, M. Highly Stereoselective Semihydrogenation of Alkynes Promoted by Nickel(0) Nanoparticles. *Adv. Synth. Catal.* **2006**, *348*, 305–308. (b) Alonso, F.; Osante, I.; Yus, M. Highly Selective Hydrogenation of Multiple Carbon-Carbon Bonds Promoted by Nickel(0) Nanoparticles. *Tetrahedron* **2007**, *63*, 93–102.

8 Alonso, F.; Osante, I.; Yus, M. Conjugate Reduction of $\alpha,\beta$-Unsaturated Carbonyl Compounds Promoted by Nickel Nanoparticles. *Synlett* **2006**, 3017–3020.

9 (a) Johnstone, R. A. W.; Wilby, A. H. Heterogeneous Catalytic Transfer Hydrogenation and Its Relation to Other Methods for Reduction of Organic Compounds. *Chem. Rev.* **1985**, *85*, 129–170. (b) Kellogg, R. M. Reduction of C═X to CHXH by Hydride Delivery from Carbon. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, Chapter 1.3.

10 (a) Kitamura, M.; Noyori, R. Hydrogenation and Transfer Hydrogenation. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 31—32. (b) Brunel, J. M. Scope, Limitations and Mechanistic Aspects in the Selective Homogeneous Palladium-Catalyzed Reduction of Alkenes Under Transfer Hydrogen Conditions. *Tetrahedron* **2007**, *63*, 3899–3906.

11 Dhakshinamoorthy, A.; Pitchumani, K. Clay Entrapped Nickel Nanoparticles as Efficient and Recyclable Catalysts for Hydrogenation of Olefins. *Tetrahedron Lett.* **2008**, *49*, 1818–1823.

12 Andrews, M. J.; Pillai, C. N. Hydrogen Transfer Reactions: Part VII—Hydrogen Transfer Reactions Catalysed by Raney Nickel. *Indian J. Chem.* **1978**, *16B*, 465–468.

13 Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. A New Route to an Active Form of Nickel. Transfer Hydrogenation of Alkenes and Carbonyl Compounds with 2-Propanol. *J. Org. Chem.* **1985**, *50*, 3082–3086.

14 Alonso, F.; Riente, P.; Yus, M. Transfer Hydrogenation of Olefins Catalysed by Nickel Nanoparticles. *Tetrahedron* **2009**, *65*, 10637–10643.

15 Klomp, D.; Hanefeld, U.; Peters, J. A. Transfer Hydrogenation Including the Meerwein-Ponndorf-Verley Reduction. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007; Vol. 1, Chapter 20.

16 (a) Ikariya, T.; Blacker, A. J. Asymmetric Transfer Hydrogenation of Ketones with Bifunctional Transition Metal-Based Molecular Catalysts. *Acc. Chem. Res.* **2007**, *40*, 1300–1308. (b) Wang, C.; Wu, X.; Xiao, J. Broader, Greener, and More Efficient: Recent Advances in Asymmetric Transfer Hydrogenation. *Chem.—Asian J.* **2008**, *3*, 1750–1770.

17 (a) Clapham, S. E.; Hadzovic, A.; Morris, R. H. Mechanisms of the $H_2$-Hydrogenation and Transfer Hydrogenation of Polar Bonds Catalyzed by Ruthenium Hydride Complexes. *Coord. Chem. Rev.* **2004**, *248*, 2201–2237. (b) Samec, J. S. M; Bäckwall, J.-E.; Andersson, P. G.; Brandt, P. Mechanistic Aspects of Transition Metal-Catalyzed Transfer Reactions. *Chem. Soc. Rev.* **2006**, *35*, 237–248.

18 (a) Le Page, M. D.; James, B. R. Nickel Bromide as a Hydrogen Transfer Catalyst. *Chem. Commun.* **2000**, 1647–1648. (b) Phukan, P.; Sudalai, A. Chemoselective Transfer Hydrogenation of Carbonyl Compounds Catalyzed by Macrocyclic Nickel(II) Complex. *Synth. Commun.* **2000**, *30*, 2401–2405.

19 (a) Upadhya, T. T.; Katdare, S. P.; Sabde, D. P.; Ramaswamy, V.; Sudalai, A. Chemoselective Transfer Hydrogenation of Nitroarenes, Aldehydes, and Ketones with 2-Propanol Catalysed by Ni-Stabilized Zirconia. *Chem. Commun.* **1997**, 1119–1120. (b) Mohapatra, S. K.; Sonavane, S. U.; Jayaram, R. V.; Selvam, P. Regio- and Chemoselective Catalytic Transfer Hydrogenation of Aromatic Nitro and Carbonyl as Well as Reductive Cleavage of Azo Compounds over Novel Mesoporous NiMCM-41 Molecular Sieves. *Org. Lett.* **2002**, *4*, 4297–4300.

20 (a) Mebane, R. C.; Mansfield, A. J. Transfer Hydrogenation of Aldehydes with 2-Propanol and Raney Nickel. *Synth. Commun.* **2005**, *35*, 3083–3086. (b) Mebane, R. C.; Holte, K. L.; Gross, B. H. Transfer Hydrogenation of Ketones with 2-Propanol and Raney Nickel. *Synth. Commun.* **2007**, *37*, 2787–2791.

21 (a) Alonso, F.; Riente, P.; Yus, M. Hydrogen Transfer Reduction of Carbonyl Compounds Promoted by Nickel(0) Nanoparticles. *Tetrahedron* **2008**, *64*, 1847–1852. (b) Alonso, F.; Riente, P.; Yus, M. Hydrogen Transfer Reduction of Carbonyl Compounds Catalysed by Nickel Nanoparticles. *Tetrahedron Lett.* **2008**, *49*, 1939–1942.

22 (a) Polshettiwar, V.; Baruwati, B.; Varma, R. S. Nanoparticle-Supported and Magnetically Recoverable Nickel Catalyst: A Robust and Economic Hydrogenation and Transfer Hydrogenation Protocol. *Green Chem.* **2009**, *11*, 127–131. (b) Park, J. C.; Lee, H. J.; Bang, J. U.; Park, K. H.; Song, H. Chemical Transformation and Morphology Change of Nickel-Silica Hybrid Nanostructures via Nickel Phylosilicates. *Chem. Commun.* **2009**, 7345–7347.

23 (a) Tarasevich, V. A.; Kozlov, N. G. Reductive Amination of Oxygen-Containing Organic Compounds. *Russ. Chem. Rev.* **1999**, *68*, 55–72. (b) Gomez, S.; Peters, J. A.; Maschmeyer, T. The Reductive Amination of Aldehydes and Ketones and the Hydrogenation of Nitriles: Mechanistic Aspects and Selectivity Control. *Adv. Synth. Catal.* **2002**, *344*, 1037–1057.

24 (a) Baxter, E. W.; Reitz, A. B. Reductive Aminations of Carbonyl Compounds with Borohydride and Borane Reducing Agents. *Org. React.* **2002**, *59*, 1–714. (b) Abdel Magid, A. F.; Mehrman, S. J. A Review on the Use of Sodium Triacetoxyborohydride in the Reductive Amination of Ketones and Aldehydes. *Org. Process Res. Devel.* **2006**, *10*, 971–1031.

25 (a) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Boerner, A. Homogeneous Rhodium(I)-Catalyzed Reductive Aminations. *Org. Prep. Proced. Int.* **2004**, *36*, 99–120. (b) Tararov, V. I.; Boerner, A. Approaching Highly Enantioselective Reductive Amination. *Synlett* **2005**, 203–211.

26 Roszkowski, P.; Czarnocki, Z. Selected Recent Developments in the Enantioselective Reduction of Imines by Asymmetric Transfer Hydrogenation. *Mini-Rev. Org. Chem.* **2007**, *4*, 190–200.

27 (a) Nah, J. H.; Kim, S. Y.; Yoon, N. M. Reductive Amination of Ketones and Aldehydes with Hydrazine Using Borohydride Exchange Resin (BER)-Nickel Acetate in Methanol. *Bull. Korean Chem. Soc.* **1998**, *19*, 269–270. (b) Saxena, I.; Borah, R.; Sarma, J. C. Reductive Amination of Aromatic Aldehydes and Ketones with Nickel Boride. *J. Chem. Soc., Perkin Trans. 1* **2000**, 503–504.

28 (a) Botta, M.; De Angelis, F.; Gambacorta, A.; Labbiento, L.; Nicoletti, R. Reduction of Schiff Bases with Isopropyl Alcohol and Aluminum Isopropoxide in the Presence of Raney Nickel. *J. Org. Chem.* **1985**, *50*, 1916–1919. (b) Khul, S.; Schneider, R.; Fort, Y. Transfer Hydrogenation of Imines Catalyzed by a Nickel(0)/NHC Complex. *Organometallics* **2003**, *22*, 4184–4186.

29 Alonso, F.; Riente, P.; Yus, M. Hydrogen-Transfer Reductive Amination of Aldehydes Catalysed by Nickel Nanoparticles. *Synlett* **2008**, 1289–1292.

30 Alonso, F.; Riente, P.; Sirvent, J. A.; Yus, M. Nickel Nanoparticles in Hydrogen-Transfer Reductions: Characterization and Nature of the Catalyst. *Appl. Catal., A* **2010**, *378*, 42–51.

31 (a) Guillena, G.; Ramón, D. J.; Yus., M. Alcohols as Electrophiles in C—C Bond-Forming Reactions: The Hydrogen Autotransfer Process. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358–2364. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. Borrowing Hydrogen in the Activation of Alcohols. *Adv. Synth. Catal.* **2007**, *349*, 1555–1575. (c) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. Transition Metal Catalysed Reactions of Alcohols Using Borrowing Hydrogen Methodology. *Dalton Trans.* **2009**, 753–762. (d) Guillena, G.; Ramón, D. J.; Yus, M. Hydrogen Autotransfer in the *N*-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles. *Chem. Rev.* **2010**, *110*, 1611–1641. (e) Alonso, F.; Foubelo, F.; González, J. C.; Martínez, R.; Ramón, D. J.; Riente, P.; Yus, M. Efficiency in Chemistry: From Hydrogen Autotransfer to Multicomponent Catalysis. *Mol. Divers.* **2010**, *14*, 411–424.

32 *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000.

33 (a) Alonso, F.; Riente, P.; Yus, M. The $\alpha$-Alkylation of Methyl Ketones with Primary Alcohols Promoted by Nickel Nanoparticles Under Mild and Ligandless Conditions. *Synlett* **2007**, 1877–1880. (b) Alonso, F.; Riente, P.; Yus, M. Alcohols for the $\alpha$-Alkylation of Methyl Ketones and Indirect Aza-Wittig Reaction Promoted by Nickel Nanoparticles. *Eur. J. Org. Chem.* **2008**, 4908–4914.

34 Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. The Aza-Wittig Reaction: An Efficient Tool for the Construction of Carbon—Nitrogen Double Bonds. *Tetrahedron* **2007**, *63*, 523–575.

35 Cami-Kobeci, G.; Williams, J. M. J. Conversion of Alcohols into *N*-Alkyl Anilines via an Indirect Aza-Wittig Reaction. *Chem. Commun.* **2004**, 1072–1073.

36 Edmonds, M.; Abell, A. The Wittig Reaction. In *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2009; Chapter 1.

37 See, for instance: Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. Tandem Oxidation Processes Using Manganese Dioxide: Discovery, Applications, and Current Studies. *Acc. Chem. Res.* **2005**, *38*, 851–869.

38 Lee, E. Y.; Kim, Y.; Lee, J. S.; Park, J. Ruthenium-Catalyzed, One-Pot Alcohol Oxidation-Wittig Reaction Producing $\alpha,\beta$-Unsaturated Esters. *Eur. J. Org. Chem.* **2009**, 2943–2946.

39 (a) Alonso, F.; Riente, P.; Yus, M. One-Pot Synthesis of Stilbenes from Alcohols through a Wittig-Type Olefination Reaction Promoted by Nickel Nanoparticles. *Synlett* **2009**, 1579–1582. (b) Alonso, F.; Riente, P.; Yus, M. Wittig-Type Olefination of Alcohols Promoted by Nickel Nanoparticles: Synthesis of Polymethoxylated and Polyhydroxylated Stilbenes. *Eur. J. Org. Chem.* **2009**, 6034–6042.

40 *Resveratrol in Health and Disease*; Aggarwall, B. B., Shishodia, S., Eds.; Taylor & Francis: Boca Raton, FL, 2006.

41 Alonso, F.; Riente, P.; Yus, M. Synthesis of Resveratrol, DMU-212, and Analogues Through a Novel Wittig-type Olefination Promoted by Nickel Nanoparticles. *Tetrahedron Lett.* **2009**, *50*, 3070–3073.

42 Saiko, P.; Pemberger, M.; Horvath, Z.; Savinc, I.; Grusch, M.; Handler, N.; Erker, T.; Jaeger, W.; Fritzer-Szekeres, M.; Szekeres, T. Novel Resveratrol Analogs that Cause Cell Cycle Arrest in HT29 Human Colon Cancer Cells: Inhibition of Ribonucleotide Reductase Activity. *Oncol. Rep.* **2008**, *19*, 1621–1626 and references cited therein.

43 Asakawa, Y.; Tanikawa, K.; Aratani, T. New Substituted Bibenzyls of Frullania Brittoniae Subsp. Truncatifolia. *Phytochemistry* **1976**, *15*, 1057–1059.