One-Pot Synthesis of Stilbenes from Alcohols through a Wittig-Type Olefination Reaction Promoted by Nickel Nanoparticles

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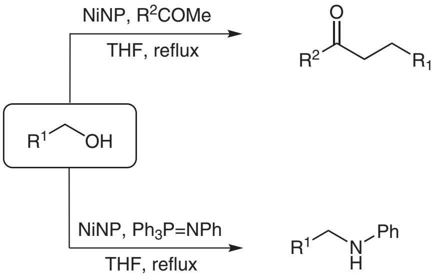
Dedicated to Professor Santiago Olivella on occasion of his 65th birthday

Abstract: A series of stilbenes has been synthesised in one pot from benzyl alcohols and benzylidenetriphenylphosphorane through a Wittig-type olefination reaction in the presence of nickel nanoparticles.

Key words: alcohols, Wittig, olefination, stilbenes, nickel nanoparticles

The Wittig reaction[1] is one of the fundamental and most reliable methods in synthetic organic chemistry. In a classic Wittig reaction, a phosphorus ylide reacts with a carbonyl compound to give the corresponding alkene and phosphane oxide.[2] In general, alcohols are cheaper and commercially more abundant than the corresponding aldehydes. Thus, the oxidation of primary alcohols to aldehydes and subsequent Wittig reaction is a common practice in organic synthesis. In some cases, however, aldehydes may be difficult to handle because of their volatility, toxicity, or high reactivity. A variety of procedures for the in situ oxidation–Wittig olefination of primary alcohols have been developed to overcome this problem with Swern,[3] MnO_2,[4] Dess–Martin,[5] $BaMnO_4$,[6] IBX,[7] TPAP,[8] PCC,[9] SO_3·py,[10] and BAIB[bis(acetoxy)iodobenzene]–TEMPO[11] as oxidising systems. Most of these procedures involve stabilised ylides and, though all are carried out in one pot, some of them are sequential. Therefore, the course of the alcohol oxidation needs monitoring before the ylide addition. Williams et al. reported, for the first time, the so-called indirect 'Wittig' olefination from alcohols for the formation of carbon–carbon single bonds.[12] This methodology coupled a Wittig-type olefination with a crossover transfer hydrogenation under iridium or ruthenium catalysis. Stabilised ylides and phosphonates were combined with benzyl alcohols leading, mainly, to products with a new carbon–carbon single bond, together with variable amounts of the corresponding aromatic aldehydes and alkenes.

On the other hand, and due to our ongoing interest on active metals,[13] we studied a mild methodology for the fast synthesis of nickel(0) nanoparticles, from different nickel(II) chloride containing systems in THF, using lithium powder and a catalytic amount of an arene as reducing agent.[14] These nanoparticles were applied to different functional-group transformations,[15] and more recently, to the hydrogen-transfer reduction of carbonyl compounds[16] and reductive amination of aldehydes.[17] Additionally, we recently reported for the first time that nickel, in the form of nanoparticles (NiNP), was a potential alternative to the use of noble-metal-based catalysts for the α-alkylation of ketones and indirect aza-Wittig reaction with alcohols.[18] These reactions involved the hydrogen transfer from the alcohol to the intermediate α,β-unsaturated ketone or imine, respectively, proceeding in short reaction times and in the absence of any added ligand, hydrogen acceptor or base, under mild conditions (Scheme 1).



Scheme 1 α-Alkylation of ketones and indirect aza-Wittig reaction with primary alcohols promoted by nickel nanoparticles

In view of the above precedents, we were intrigued about the behaviour of the nickel nanoparticles in Wittig-type reactions using alcohols as phosphorus ylide partners. As a result of our studies, we wish to report herein what, to the best of our knowledge, is the first metal-promoted selective Wittig olefination reaction with alcohols in which there is no standard redox step.

The nickel nanoparticles (NiNP) were generated from anhydrous nickel(II) chloride, lithium powder, and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl, 5 mol%) in THF at room temperature.[14] A preliminary study was carried out using benzyl alcohol and benzylidenetriphenylphosphorane (generated from commercially available benzyltriphenylphosphonium chloride and *n*-BuLi) as model substrates in order to optimise the amount of catalyst and compare with other nickel catalysts (Table 1). A blank experiment in the absence of any nickel catalyst led to the unmodified starting materials (entry 1). We were

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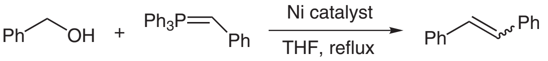
delighted to observe that our NiNP, in a 1:1 NiNP/substrate ratio, afforded stilbene in 77% isolated yield as a ca. 1:1 *cis*/*trans* mixture after six hours at reflux (entry 2). Attempts to decrease the NiNP/substrate ratio were, however, unsuccessful (entry 3). It is noteworthy that under the same conditions as in entry 2, the commercially available Raney nickel (entry 4), Ni-Al alloy (entry 5), and Ni/SiO_2–Al_2O_3 (entry 6) did not work at all.

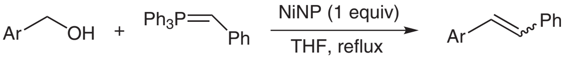
Table 1 Wittig-Type Olefination of Benzyl Alcohol and Benzylidenetriphenylphosphorane in the Presence of Different Nickel Catalysts



Entry	Ni catalyst/substrate (mmol)	Time (h)	Yield (%)[a]
1	none	24	0
2	NiNP 1:1	6	77[b]
3	NiNP 1:10	24	0
4	Raney Ni 1:1	24	0
5	Ni–Al alloy 1:1	24	0
6	Ni/SiO_2–Al_2O_3 1:1	24	0

[a] GLC yield, unless otherwise stated.

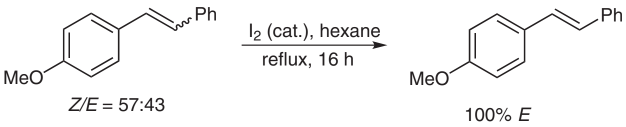
[b] Isolated yield after column chromatography as a ca. 1:1 *cis/trans* mixture.



Scheme 2 *Reagents and conditions*: alcohol (1 mmol), phosphorus ylide (1 mmol), NiNP (1 mmol), THF (4 mL).

The optimised reaction conditions (Scheme 2) were extended to a variety of benzyl alcohols (Table 2).[19] Both the reaction time and yield were shown to be very dependent on the electronic character and position of the substituent. For instance, 4-methylbenzyl alcohol and 3-methylbenzyl alcohol provided the corresponding stilbenes in high yields after eight hours (entries 2 and 3). In contrast, 2-methylbenzyl alcohol (entry 4) did not react under the standard conditions. Interestingly, the expected stilbene could be formed when the phosphorus ylide was in situ generated from benzyltriphenylphosphonium chloride and metal lithium in a one-pot reaction.[20] The electron-deficient trifluoromethyl-substituted benzyl alcohols displayed lower reactivity, furnishing the corresponding olefins in moderate yields after longer heating (entries 5 and 6). Moderate-to-good yields of methoxy-substituted stilbenes were achieved (entries 7–9), the reaction being faster when the substituent was located at the *para*- and *meta*-positions. Other benzyl alcohols such as furan-2-ylmethanol or some polymethoxylated benzyl alcohols furnished the expected alkenes in good isolated yields (entries 10–12). The latter results are promising in relation with the synthesis of resveratrol analogues.[21]

With regard to the stereochemistry, it is well known that semistabilised ylides, such as benzyl ylides, usually yield mixtures of *Z*- and *E*-isomers.[22] In particular, the reactions with benzylidenetriphenylphosphorane and aromatic aldehydes are practically nonselective. A slight increase in favour of the *Z*-stereoisomer (ca. 60:40) was described in the presence of a lithium salt,[22] whereas a catalytic amount of 18-crown-6 was reported to improve notably the *Z* stereoselectivity.[23] In our study, *Z*/*E* mixtures of stilbenes were also obtained with low stereoselectivity, with the *E*-isomer being normally the major one (up to ca. 1:4, entry 5). In some cases, the purification step by column chromatography allowed the separation of both stereoisomers (entries 1–4, 6, and 12). Moreover, the isomerisation of *Z*- to *E*-stereoisomers can be easily accomplished under iodine catalysis.[24] Thus, when a 57:43 *Z*/*E* mixture of 1-(4-methoxyphenyl)-2-phenylethene was treated with a catalytic amount of iodine in hexane at reflux, a quantitative conversion into the corresponding *E*-stereoisomer was achieved (Scheme 3).

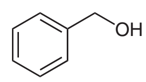
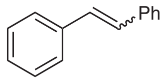
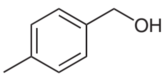
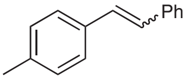
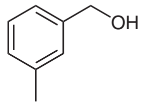
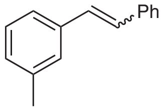
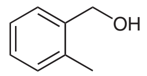
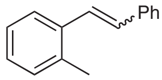
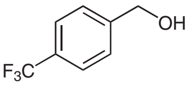
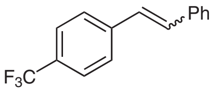
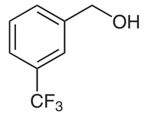
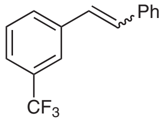
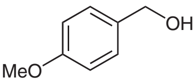
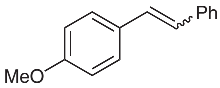
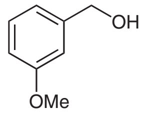
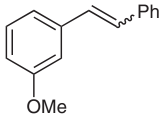
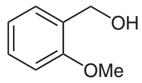
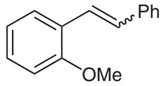
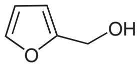
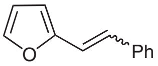
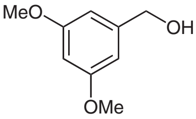
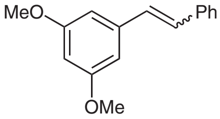
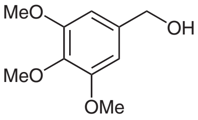
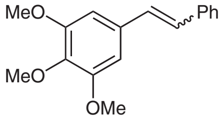


Scheme 3 Iodine-catalysed *Z*/*E* isomerisation of 1-(4-methoxyphenyl)-2-phenylethene

We must point out that the success of this olefination methodology resides in the fact that hydrogen transfer from the alcohol to the corresponding stilbene is not an effective process. In fact, we have never detected the reduced stilbene. This unexpected behaviour might be attributed to a loss of the catalyst activity during the reaction or to a preferential hydrogen transfer to some other species present in the reaction medium. Experiments to test the possible hydrogen transfer from benzyl alcohol to either the phosphorus ylide of triphenylphosphane oxide failed. In addition, we found out that the hydrogen transfer from benzyl alcohol to added stilbene was substantially depleted in the presence of the phosphorus ylide, triphenylphosphane oxide, or triphenylphosphane.[25] Moreover, an increase in the size of the NiNP from 2.5 ± 1.5 nm to 8–20 nm (before and after a standard reaction, respectively) was observed by transmission electron microscopy. Therefore, we can conclude that catalyst deactivation very likely, accounts for this particular performance.

In summary, we have demonstrated that nickel, in the form of nanoparticles, can promote the Wittig-type reaction of benzyl alcohols and benzylidenetriphenylphosphorane in THF under reflux. The corresponding stilbenes are obtained in modest-to-high isolated yields, depending on the electronic character of the substituent and position in the aromatic ring. The *Z*/*E* mixtures can be separated, in some cases, by column chromatography or quantitatively transformed into the *E*-stereoisomers by iodine-catalysed isomerisation. To the best of our knowledge, this is the first metal-mediated chemoselective Wittig-type olefina-

Table 2 Wittig-Type Olefination of Benzyl Alcohols and Benzylidenetriphenylphosphorane Promoted by Nickel Nanoparticles

Entry	Alcohol	Time (h)	Product[a]	*Z*/*E*[b]	Yield (%)[c]
1		6		51:49	77 (*Z* = 36, *E* = 41)
2		8		36:64	81 (*Z* = 31, *E* = 50)
3		8		42:58	86 (*Z* = 41, *E* = 45)
4		4[d]		44:56	28 (*Z* = 18, *E* = 10)
5		30		21:79	41
6		24		25:75	51 (*Z* = 13, *E* = 38)
7		4		57:43	67
8		4		53:47	62
9		20		36:64	83
10		6		51:49	70
11		15		24:76	67
12		24		47:53	70 (*Z* = 30, *E* = 40)

[a] All isolated products were ≥95% pure (GLC and/or ^{1}H NMR).

[b] *Z*/*E* ratio determined from the reaction crude by GLC and/or ^{1}H NMR.

[c] Isolated yield after column chromatography, in parenthesis the isolated yield for each stereoisomer.

[d] Benzylidenetriphenylphosphorane was in situ generated from benzyltriphenylphosphonium chloride and metal Li.

tion reaction with alcohols, in which there is no standard redox step.[26] Moreover, the reaction proceeds in the absence of any additive as a hydrogen acceptor. Further research to widen the scope of this methodology to other alcohols and phosphorus ylides is under way.

Acknowledgment

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(19) **General Procedure for the Wittig-Type Olefination with Alcohols Promoted by Nickel Nanoparticles**
n-BuLi (1.6 M, 625 μL, 1.0 mmol) was added dropwise to a suspension of commercially available benzyltriphenylphosphonium chloride (583 mg, 1.5 mmol) in THF (2 mL) at 0 °C. While the corresponding ylide was being formed (ca. 20 min), nickel(II) chloride (130 mg, 1 mmol) was added over a suspension of lithium (14 mg, 2 mmol) and DTBB (13 mg, 0.05 mmol) in THF (2 mL) at r.t. under argon. The reaction mixture, which was initially dark blue, changed to black indicating that nickel(0) had been formed. After 10 min, the requisite benzyl alcohol (1 mmol) and the initially prepared ylide suspension were added to the NiNP suspension. The reaction mixture was warmed up to reflux and monitored by GLC-MS. The resulting mixture was diluted with EtOAc (10 mL), filtered through a pad containing Celite, and the filtrate was dried over $MgSO_4$. The residue obtained after removal of the solvent (0.02 bar) was purified by column chromatography (silica gel, hexane, or hexane–EtOAc) to give the pure stilbene. The diastereomeric ratio was determined on the basis of the GC and ^{1}H NMR analyses.
Stilbene was characterized by comparison of its physical and spectroscopic properties with those of a commercially available sample (Aldrich). 1-(4-Methylphenyl)-2-phenylethene,[27] 1-(3-methylphenyl)-2-phenylethene,[28] 1-(2-methylphenyl)-2-phenylethene,[27] 1-(4-trifluoromethylphenyl)-2-phenylethene,[29] 1-(3-trifluoromethylphenyl)-2-phenylethene,[30] 1-(4-methoxyphenyl)-2-phenylethene,[31] 1-(3-methoxyphenyl)-2-phenylethene,[31] 1-(2-methoxyphenyl)-2-phenylethene,[32] 1-(2-furyl)-2-phenylethene,[33] 1-(1,3-dimethoxyphenyl)-2-phenylethene,[31] and 1-(1,2,3-trimethoxyphenyl)-2-phenylethene[34] were characterised by comparison of their physical and spectroscopic data with those described in the literature.

(20) Following the general procedure but using double the amount of lithium metal (28 mg, 4 mmol) and adding successively the phosphonium salt and the alcohol to the NiNP suspension.

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(26) This assertion is made on the basis that in every redox process a species is oxidised at the same time that the oxidant agent is reduced. In the present case, we assume that dehydrogenation of the alcohol occurs leading to the intermediate aldehyde (the 'oxidation' product). However, other species resulting from a reduction step are not detected.

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