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Wittig-Type Olefination of Alcohols Promoted by Nickel Nanoparticles: Synthesis of Polymethoxylated and Polyhydroxylated Stilbenes

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Nickel nanoparticles were found to promote the Wittig-type olefination of primary alcohols with phosphorus ylides. The latter can be prepared from the corresponding phosphonium salts with *n*BuLi or in situ generated with lithium metal. The methodology is especially efficient for the synthesis of stilbenes and is applied in the absence of any additive as a hydrogen acceptor. A new approach to the synthesis of polymethoxylated and polyhydroxylated stilbenes, including resveratrol, DMU-212 and analogues, is presented.

Introduction

The Wittig reaction[1] was discovered in 1953 as a new and reliable method to form carbon–carbon double bonds. In a typical Wittig reaction, carbonyl compounds are treated with phosphorus ylides to give the corresponding alkenes and phosphane oxide.[2] 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, as 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, a variety of oxidising systems have been implemented for the in situ oxidation–Wittig olefination of primary alcohols, namely, 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] These procedures are primarily applied to stabilised 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.[12] In this methodology, stabilised ylides and phosphonates were combined with benzyl alcohols in a domino Wittig-type olefination–transfer hydrogenation reaction, either under 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. Very recently, Park et al. reported the one-pot synthesis of α,β-unsaturated esters from primary alcohols and stabilised Wittig reagents catalysed by Ru/AlO(OH). The reaction proceeded in the presence of oxygen as the terminal oxidant and did not require any additive.[13]

On the other hand, in recent years, both natural and synthetic polymethoxylated and polyhydroxylated stilbenes have attracted the attention of an important part of the scientific community as a result of their outstanding biological activity.[14] Therefore, these molecules are considered as preferential targets from a synthetic point of view.[15] Among them, resveratrol [(*E*)-3,4′,5-trihydroxystilbene] is a naturally occurring phytoalexin present in vine bark, leaves and grapes, as well as in many other plants.[16] A plethora of remarkable biological properties have been attributed to this special molecule, such as antioxidant,[16,17] radioprotective,[16] phytooestrogen,[16] antibacterial[16] and antifungal.[16] Its therapeutic potential includes the chemoprevention of cancer,[16,18] inflammation,[16] aging,[16,19] obesity,[16,20] cardiovascular diseases[16] and neurodegeneration.[16,21] Interestingly, some methoxylated analogues of resveratrol exhibit a pharmacological profile comparable or even superior to that of resveratrol because of their higher lipophilicity.[22] Such is the case of DMU-212 [(*E*)-3,4,4′,5-tetramethoxystilbene], which has recently disclosed a strong anticancer activity with higher chemoprotective activity than that of resveratrol.[23]

As part of our continuous interest in the preparation and application of active metals,[24] we reported the fast synthesis of nickel(0) nanoparticles (NiNPs), from different nickel(II) chloride-containing systems in THF, by using

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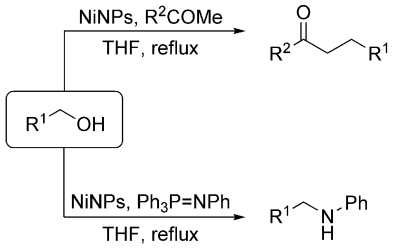
lithium powder and a catalytic amount of an arene, as reducing agent, under mild conditions.[25] These nanoparticles found application in different functional group transformations,[26] as well as in the hydrogen transfer reduction of carbonyl compounds[27] and reductive amination of aldehydes.[28] We also discovered that nickel, in the form of nanoparticles, can activate alcohols for the α-alkylation of ketones and indirect aza-Wittig reactions, with this being a potential alternative to noble-metal-based methodologies.[29] These reactions involved hydrogen transfer from the alcohol to the intermediate α,β-unsaturated ketone or imine, respectively. Moreover, in contrast with the use of noble-metal catalysts, the reactions proceeded in the absence of any added ligand, hydrogen acceptor or base, under mild conditions (Scheme 1).



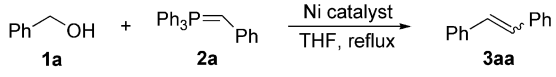
Scheme 1. α-Alkylation of ketones and indirect aza-Wittig reaction with primary alcohols promoted by nickel nanoparticles.

In relation with the aforementioned antecedents, we recently studied the behaviour of the nickel nanoparticles in Wittig-type reactions by using alcohols as phosphorus ylide partners.[30] In particular, we discovered that NiNPs, readily prepared from $NiCl_2$, lithium metal and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl) in THF, can promote the one-pot Wittig-type olefination of benzylidenetriphenylphosphorane with different benzyl alcohols.[30a] Furthermore, this reaction was used as the key step in a novel synthesis of resveratrol, DMU-212 and analogues.[30b] To the best of our knowledge, this is the first metal-promoted selective Wittig olefination reaction with alcohols (instead of aldehydes) in which there is no standard redox step.[31] We wish to report herein a more detailed and complete study on this reaction, additionally including: (a) the alternative in situ generation of the phosphorus ylides, (b) the substrate scope, which is extended to non-benzylic substrates and (c) the synthesis of a wide range of polymethoxylated stilbenes.

Results and Discussion

As in previous studies, the NiNPs were readily generated from anhydrous nickel(II) chloride, lithium powder and a catalytic amount of DTBB (5 mol-%) in THF at room temperature.[25] First, we optimised the amount of catalyst by treating benzyl alcohol and benzylidenetriphenylphosphorane (previously generated from commercially available benzyltriphenylphosphonium chloride and *n*BuLi) in THF at reflux (Table 1). The reaction did not occur in the absence of any nickel catalyst, leading to the unmodified starting materials (Table 1, Entry 1). A 1:1 NiNPs/substrate ratio, however, afforded stilbene in 77% isolated yield as a ca. 1:1 *cis*/*trans* mixture in 6 h (Table 1, Entry 2). Unfortunately, no reaction was observed for a lower NiNPs/substrate ratio (Table 1, Entry 3). The reactivity of the NiNPs in the model reaction was compared with that of commercially available nickel catalysts. To our delight, Raney nickel (Table 1, Entry 4), Ni–Al alloy (Table 1, Entry 5) and Ni/SiO_2–Al_2O_3 (Table 1, Entry 6) were shown to be inactive under the same conditions as those in Entry 2 (Table 1). Interestingly, we found that the phosphorus ylide could be alternatively obtained in situ from the corresponding phosphonium salt and an excess amount (2 equiv.) of the lithium metal used for the generation of the NiNPs. This method simplifies the experimental procedure, although stilbene was obtained in a lower yield (Table 1, Entry 7).

Table 1. Wittig-type olefination of benzyl alcohol and benzylidenetriphenylphosphorane in the presence of different nickel catalysts.

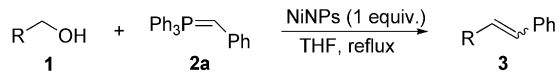


Entry	Catalyst	Catalyst/substrate	*t* [h]	Yield [%][a]
1	none	–	24	0
2	NiNPs	1:1	6	77[b]
3	NiNPs	1:10	24	0
4	Raney Ni	1:1	24	0
5	Ni–Al alloy	1:1	24	0
6	Ni/SiO_2–Al_2O_3	1:1	24	0
7	NiNPs	1:1	12	56[b,c]

[a] GLC yield, unless otherwise stated. [b] Isolated yield after column chromatography as a ca. 1:1 *cis*/*trans* mixture. [c] Compound **2a** was generated in situ from benzyltriphenylphosphonium chloride and lithium metal.

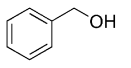
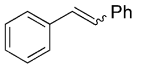
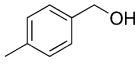
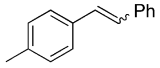
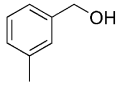
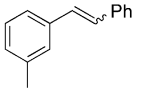
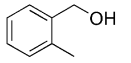
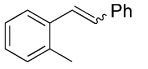
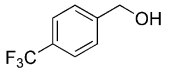
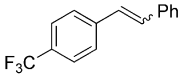
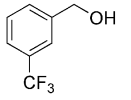
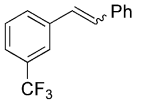
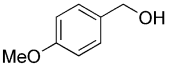
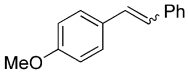
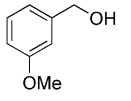
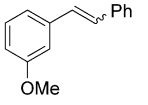
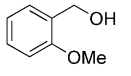
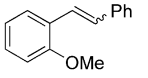
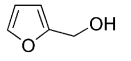
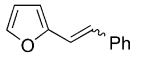
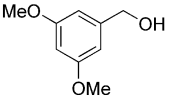
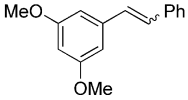
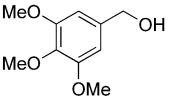
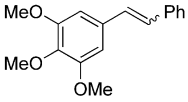
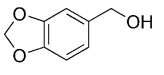
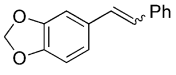
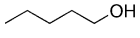
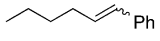
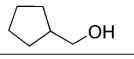
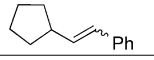
The optimised reaction conditions (Scheme 2), with both the phosphorus ylide previously generated with *n*BuLi (method A) or in situ generated with lithium (method B), were extended to a variety of benzyl alcohols (Table 2). The reaction time, yield and diastereoselectivity were shown to be dependent on the electronic character and position of the substituents, as well as on the preparation method of the ylide. For instance, 4-methylbenzyl alcohol (**1b**) and 3-methylbenzyl alcohol (**1c**) provided the corresponding stilbenes **3ba** and **3ca** in high yields after 8 h with method A (Table 2, Entries 2 and 3). In these cases, however, the yields were rather low with method B. Surprisingly, 2-methylbenzyl alcohol (**1d**) did not react under the conditions of method A but the expected stilbene could be obtained in modest yield by method B (Table 2, Entry 4). Lower reactivity was displayed by the electron-deficient trifluoromethyl-substituted benzyl alcohols **1e** and **1f** (Table 2, Entries 5 and 6). The corresponding olefins were obtained in moderate yields after longer heating, independently of the method used. In contrast, moderate-to-good yields of stilbenes were achieved for methoxy-substituted benzyl

alcohols (Table 2, Entries 7–9). The reaction was faster when the methoxy group was located at the *para* and *meta* positions, albeit the highest yield was reached for 2-methoxybenzyl alcohol (**1i**) by method A (Table 2, Entry 9). It is noteworthy that method B improved the yield of stilbene **3ga** (Table 2, Entry 7) but lowered that of **3ia** (Table 2, Entry 9). Method A was the method of choice for the olefination of furan-2-ylmethanol (**1j**) and piperonyl alcohol (**1m**), whereas polymethoxylated benzyl alcohols **1k** and **1l** furnished the expected alkenes in good isolated yields, irrespective of the method used (Table 2, Entries 10–12). The substrate scope seemed to be more limited in the case of alkyl alcohols. Nonetheless, *n*-hexanol (**1n**) and cyclopentylmethanol (**1o**) gave the corresponding alkenes **3na** and



Scheme 2. Alcohol (1 mmol), phosphorus ylide (1 mmol), NiNPs (1 mmol), THF (4 mL).

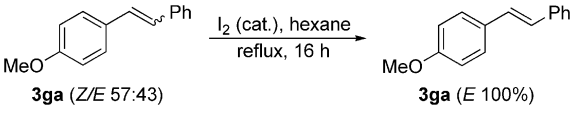
Table 2. Wittig-type olefination of primary alcohols with benzylidenetriphenylphosphorane promoted by nickel nanoparticles.

Entry	Alcohol		*t* [h][a]	Product		*Z*/*E*[a,b]	Yield [%][a,c]
1		**1a**	6 {12}		**3aa**	51:49 {54:46}	77 (*Z* 36, *E* 41) {56}
2		**1b**	8 {6}		**3ba**	36:64 {46:54}	81 (*Z* 31, *E* 50) {52}
3		**1c**	8 {4}		**3ca**	42:58 {53:47}	86 (*Z* 41, *E* 45) {47}
4		**1d**	{4}		**3da**	{44:56}	{28} (*Z* 18, *E* 10)
5		**1e**	30 {12}		**3ea**	21:79 {32:68}	41 {54}
6		**1f**	24		**3fa**	25:75	51 (*Z* 13, *E* 38)
7		**1g**	4 {4}		**3ga**	57:43 {54:46}	67 {76}
8		**1h**	4 {12}		**3ha**	53:47 {52:48}	62 {59}
9		**1i**	20 {24}		**3ia**	36:64 {37:63}	83 {43}
10		**1j**	6 {12}		**3ja**	51:49 {35:65}	70 {31}
11		**1k**	15 {10}		**3ka**	24:76 {47:53}	67 {65}
12		**1l**	24 {48}		**3la**	47:53 {44:56}	70 (*Z* 30, *E* 40) {64}
13		**1m**	10		**3ma**	50:50	74
14		**1n**	24 {5}		**3na**	65:35 {32:68}	40 {58}
15		**1o**	8 {12}		**3oa**	26:74 {32:68}	70 {48}

[a] Values in curly brackets obtained by in situ generation of the phosphorus ylide with lithium metal (method B). [b] *Z*/*E* ratio determined from the crude product by GLC and/or ^{1}H NMR spectroscopy. [c] Isolated yield after column chromatography; the isolated yield for each stereoisomer is given in parentheses.

3oa in moderate-to-good yields (Table 2, Entries 14 and 15, respectively). Curiously, method B was proven to be faster and higher yielding for **3na**, whereas method A was more effective for **3oa**.

In general, the process displayed low diastereoselectivity, mainly in favour of the *E* diastereoisomer. It is well known that benzyl ylides are semistabilised ylides leading to *Z*/*E* mixtures.[32] In particular, the reactions with benzylidenetriphenylphosphorane and aromatic aldehydes are practically nonselective. It was reported that the presence of a lithium salt slightly increased the diastereoselectivity in favour of the *Z* stereoisomer (ca. 60:40),[32] whereas a catalytic amount of 18-crown-6 notably improved the *Z* stereoselectivity.[33] In our study, a maximum ca. 1:4 *Z*/*E* ratio of diastereomeric stilbenes was obtained for alcohol **1e** (Table 2, Entry 5). The lithium chloride present in the reaction medium (from the reduction of $NiCl_2$ with Li) seems not to exert any positive effect concerning the stereoselectivity. Nevertheless, the purification step by column chromatography allowed the separation of both stereoisomers for some stilbenes (Table 2, Entries 1–4, 6 and 12). Fortunately, *Z* to *E* isomerisation was easily accomplished under iodine catalysis.[22b] For instance, a 57:43 *Z*/*E* mixture of 1-(4-methoxyphenyl)-2-phenylethene (**3ga**) was quantitatively converted into the corresponding *E* stereoisomer by treatment with a catalytic amount of iodine in hexane at reflux (Scheme 3).



3ga (*Z*/*E* 57:43) **3ga** (*E* 100%)

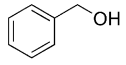
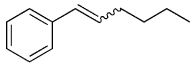
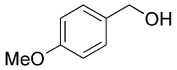
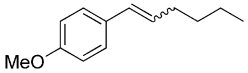
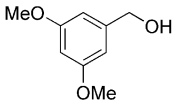
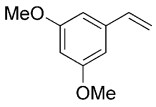
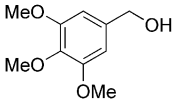
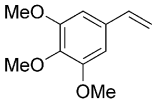
Scheme 3. Iodine-catalysed *Z*/*E* isomerisation of 1-(4-methoxyphenyl)-2-phenylethene.

The Wittig-type olefination reaction was extended to the reaction of various benzyl alcohols with the nonstabilised ylides **2b** and **2c**, derived from commercially available (*n*-pentyl)-triphenylphosphonium and methyltriphenylphosphonium bromides, respectively (Table 3). The NiNPs exhibited a lower activity in promoting these reactions, with the corresponding alkenes being obtained in modest-to-moderate isolated yields, independently on the method of synthesis of the ylide.

As a result of the abundance of polymethoxylated stilbenes in nature,[14] we decided to synthesise a variety of this type of compounds by applying the above-mentioned methodology (Table 4). In all cases, the phosphorus ylide was previously prepared with *n*BuLi (method A). Monomethoxylated ylide **2d** was coupled with the three regioisomeric methoxybenzyl alcohols **1g**–**i**, with the corresponding dimethoxylated stilbenes being obtained in moderate-to-good yields (Table 4, Entries 1–3). The highest yield was achieved for the olefination reaction of piperonyl alcohol (**1m**) and ylide **2d** (Table 4, Entry 4). Other polymethoxylated stilbenes were also prepared in good-to-high yields from the corresponding polymethoxylated benzyl alcohols and ylide partners (Table 4, Entries 5–7). The reaction of *meta*-substituted monomethoxy- and dimethoxybenzyl alcohols **1h** and **1k** with **2d** and **2e** led to **3hd** and the symmetrically substituted polymethoxylated stilbene **3ke** with the highest diastereoselectivities (*Z*/*E* ca. 1:7; Table 4, Entries 2 and 6, respectively). Chromatographic separation of the *Z* and *E* isomers was possible in most cases (Table 4, Entries 1, 2 and 4–6).

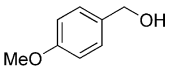
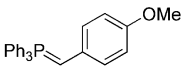
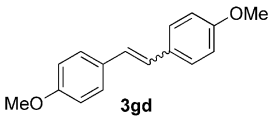
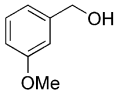
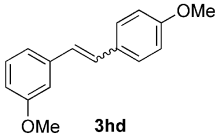
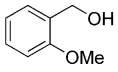
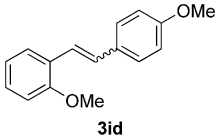
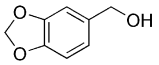
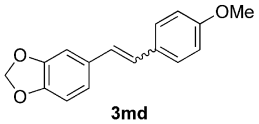
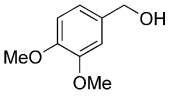
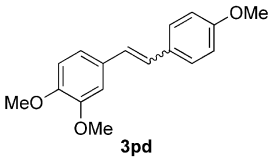
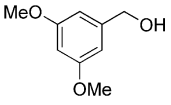
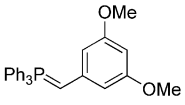
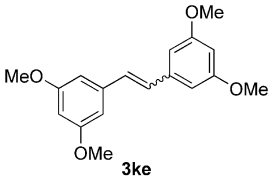
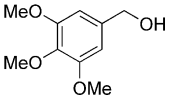
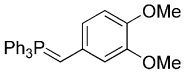
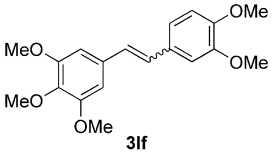
It is worthwhile mentioning that the success of this olefination methodology resides in the fact that, in contrast with the work of Williams,[12] hydrogen transfer from the alcohol to the corresponding stilbene is not effective. In

Table 3. Wittig-type olefination of benzyl alcohols with nonstabilised phosphorus ylides promoted by nickel nanoparticles.

Entry	Alcohol	Ylide	*t* [h][a]	Product	*Z*/*E*[b]	Yield [%][a,c]
1	 **1a**	$Ph_3P{=}CH(CH_2)_3Me$ **2b**	3	 **3ab**	46:54	54
2	 **1g**	$Ph_3P{=}CH(CH_2)_3Me$ **2b**	12	 **3gb**	65:35	40
3	 **1k**	$Ph_3P{=}CH_2$ **2c**	8 {48}	 **3kc**	–	40 {23}
4	 **1l**	$Ph_3P{=}CH_2$ **2c**	48	 **3lc**	–	30

[a] Values in curly brackets obtained by in situ generation of the phosphorus ylide with lithium metal (method B). [b] *Z*/*E* ratio determined from the crude product by GLC and/or ^1H NMR spectroscopy. [c] Isolated yield after column chromatography.

Table 4. Synthesis of polymethoxylated stilbenes by Wittig-type olefination of benzyl alcohols and phosphorus ylides promoted by nickel nanoparticles.[a]

Entry	Alcohol	Ylide	*t* [h]	Product	*Z*/*E*[b]	Yield [%][c]
1	 **1g**	 **2d**	24	 **3gd**	55:45	57 (*Z* 40, *E* 17)
2	 **1h**	**2d**	10	 **3hd**	13:87	71 (*Z* 4, *E* 67)
3	 **1i**	**2d**	15	 **3id**	61:39	50
4	 **1m**	**2d**	24	 **3md**	54:46	>99 (*Z* 74, *E* 26)
5	 **1p**	**2d**	8	 **3pd**	55:45	75 (*Z* 43, *E* 32)
6	 **1k**	 **2e**	24	 **3ke**	11:89	73 (*Z* 24, *E* 49)
7	 **1l**	 **2f**	24	 **3lf**	23:77	93

[a] Alcohol (1 mmol), Ph_3P=CHAr (1 mmol), NPsNi (1 mmol), THF (4 mL), 76 °C. [b] *Z*/*E* ratio determined from the crude product by GLC and/or ^{1}H NMR spectroscopy. [c] Isolated yield after column chromatography; the isolated yield for each stereoisomer is given in parentheses.

fact, we never detected the corresponding dihydrostilbenes. In principle, this behaviour was unexpected and might be attributed either to the preferential hydrogen transfer to some other species present in the reaction medium or to a loss of the catalyst activity during the reaction. The first argument was ruled out, as different experiments to test the possible hydrogen transfer from benzyl alcohol to either the phosphorus ylide or triphenylphosphane oxide failed. We found, however, that the hydrogen transfer reduction of stilbene with benzyl alcohol was substantially depleted in the presence of the phosphorus ylide, triphenylphosphane oxide or triphenylphosphane. It is well known that phosphorus compounds can bind strongly to metal centres, therefore blocking the access of the substrate to the active site.[34] Transmission electron microscopy images, obtained before and after a standard olefination reaction, revealed an increase in the size of the NiNPs from 2.5 ± 1.5 nm to 8–20 nm (Figure 1). From these results, it can be inferred that

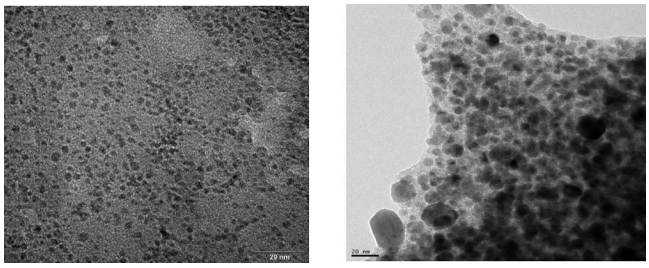


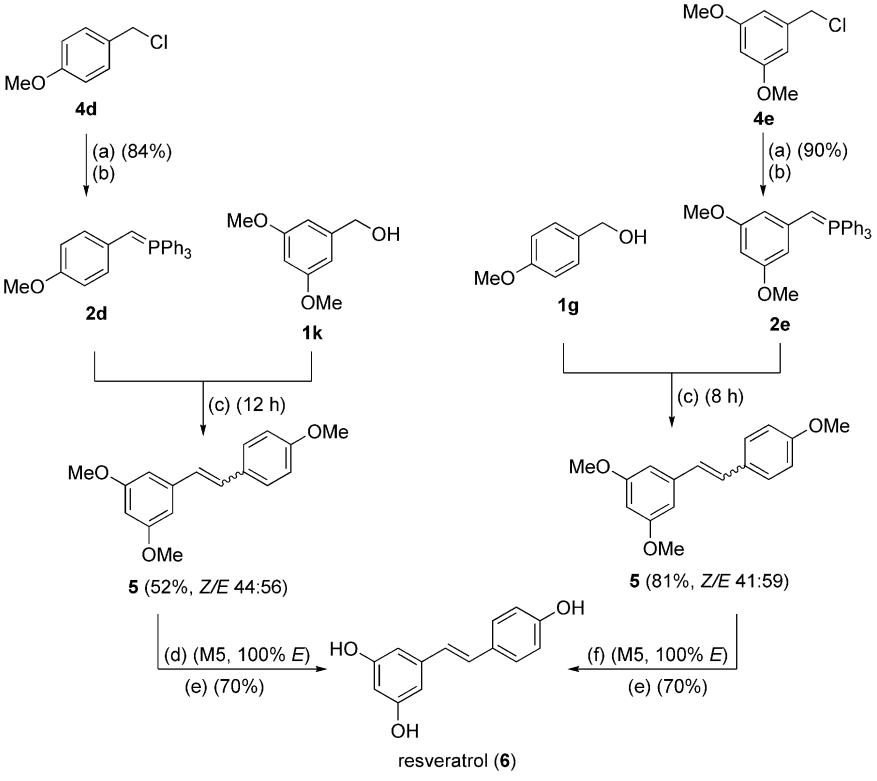
Figure 1. TEM micrograph of the NiNPs before (left) and after (right) a Wittig-type olefination.

catalyst deactivation by poisoning with phosphorus compounds, together with some nanoparticle agglomeration, are very likely the main reasons that account for this particular performance.

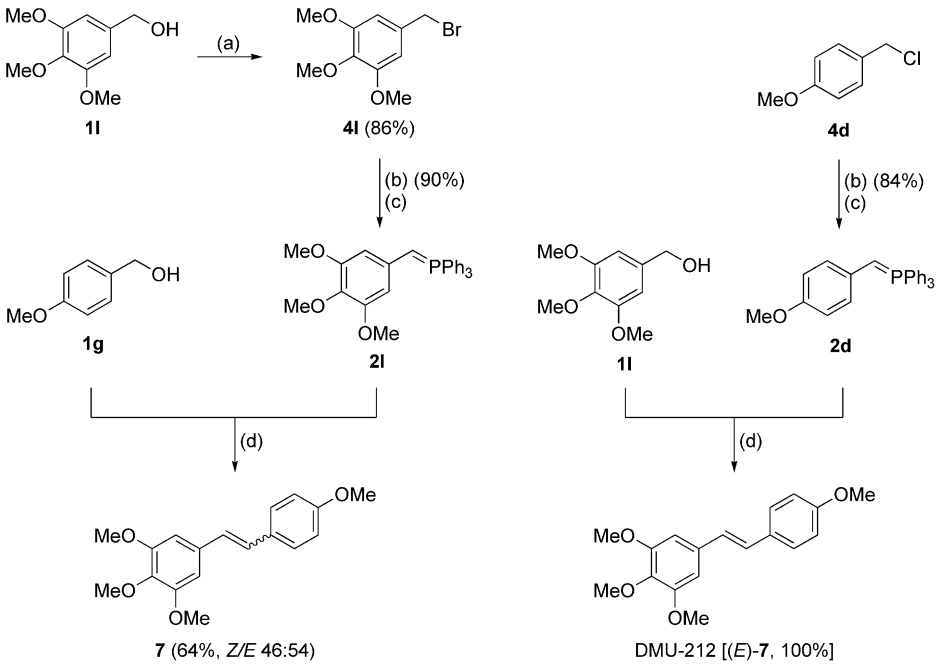
As a result of the successful synthesis of polymethoxylated stilbenes by the NiNPs-promoted Wittig-type olefination of alcohols, we turned our attention to the synthesis of some stilbenes of prominent biological activity, such as resveratrol, DMU-212 and analogues. With regard to the synthesis of resveratrol, we attempted two different approaches starting from the commercially available benzyl halides **4d** and **4e** (Scheme 4). In the first approach, **4d** was transformed into the corresponding phosphonium salt in good yield, followed by deprotonation with *n*BuLi. Wittig-type olefination of the resulting benzyl phosphorus ylide **2d** with 3,5-dimethoxybenzyl alcohol (**1k**) furnished methylated resveratrol (**5**) in moderate yield as a 44:56 *Z*/*E* mixture of diastereoisomers. Iodine-catalysed isomerisation of (*Z*)-**5** into (*E*)-**5** (M5) and subsequent demethylation with BBr_3 afforded resveratrol (**6**) in 31% overall yield.

In a second approach, the Wittig partners **1k** and **2d** were changed into **1g** and **2e**, respectively (Scheme 4). Following the above-described steps, a higher yield was obtained for the phosphonium salt derived from **4e** in comparison with that of **4d**. The Wittig-type olefination of ylide **2e** and benzyl alcohol **1g** was shown to be faster and higher yielding than that in the first approach. The *Z* to *E* isomerisation of **5** was catalysed in this case by diphenyl disulfide in the presence of AIBN,[35] with a notable reduction in the reaction time (48 vs. 8 h). Final treatment with BBr_3 led to resveratrol in 51% overall yield. This yield is comparable to that obtained with the decarbonylative Heck reaction from resorcylic acid, which, to the best of our knowledge, is the most effective synthesis reported so far.[36]

On the basis of a similar strategy, we undertook the synthesis of DMU-212 [*E*-(**7**)] (Scheme 5). In the first synthetic variant, phosphorus ylide **2l** was prepared in high yield by bromination of benzyl alcohol **1l**, followed by phosphonium salt formation and deprotonation. The olefination of **2l** with benzyl alcohol **1g** led to **7** in 64% yield as a 46:54 *Z*/*E* diastereomeric mixture. A 50% overall yield of (*Z*/*E*)-**7** was achieved after three synthetic steps prior to isomerisation. In the search for a more effective variant, we discovered that the Wittig-type olefination reaction proceeded quantitatively by changing **2l** and **1g** into **2d** and **1l**, respectively. To our delight, in this case DMU-212 (**7**) was obtained as a single diastereoisomer in 84% overall yield after two synthetic steps from commercially available **4d**. In principle, the high diastereoselectivity obtained in the synthesis of **7** was unexpected. We observed, however, that this type of compounds can undergo partial isomerisation during their handling (e.g., in $CDCl_3$). In addition, resveratrol and methoxylated analogues have been reported to be photosensitive.[37] Therefore, there may be some parameters that are difficult to control or that go unnoticed that could condition the final diastereoselectivity of the reaction.

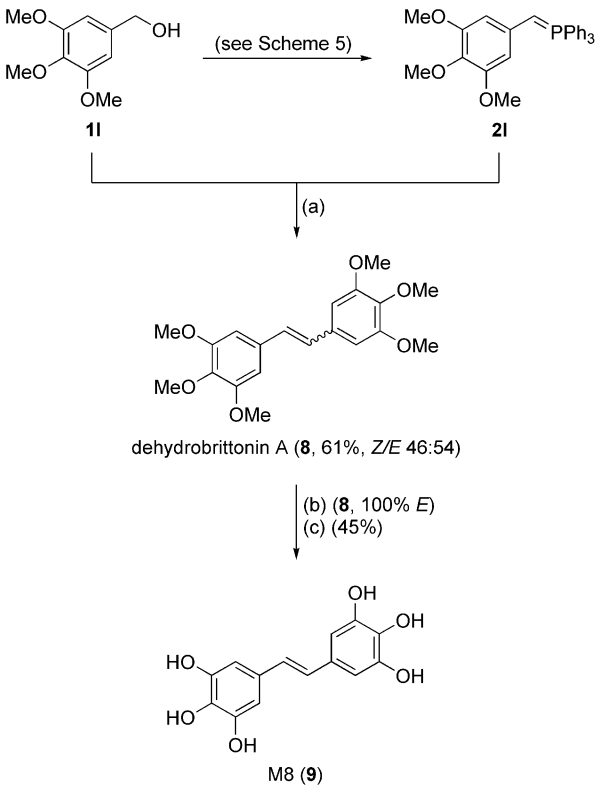


Scheme 4. (a) PPh_3, PhMe, reflux, 6 h; (b) *n*BuLi, THF, 0 °C, 20 min; (c) NiNPs, THF, reflux; (d) cat. I_2, hexane, reflux, 48 h; (e) BBr_3, CH_2Cl_2, 0 °C to r.t., 5 h; (f) $(PhS)_2$, AIBN, THF, reflux, 8 h.



Scheme 5. (a) PBr_3, CH_2Cl_2, 0 °C to r.t., overnight; (b) PPh_3, PhMe, reflux, 6 h; (c) *n*BuLi, THF, 0 °C, 20 min; (d) NiNPs, THF, reflux, 12 h.

Finally, we dealt with the synthesis of the highly polymethoxylated and polyhydroxylated stilbenoids dehydrobrittonin A (**8**)[38] and M8 (**9**). In particular, M8 (**9**) was recently found to exhibit many remarkable biological effects, including, highly selective cyclooxygenase-2 inhibition,[39] much higher antioxidant activity than resveratrol in different leukemic cell lines,[40] apoptosis induction at concentrations significantly lower than resveratrol in HL-60 human promyelocytic leukemia cells[41] and apoptosis induction and cell cycle arrest in prostate cancer [also observed for DMU-212 (**7**)][42] and HT29 human colon cancer cells [also observed for M5, (*E*)-**5**].[43]



Scheme 6. (a) NiNPs, THF, reflux, 24 h; (b) $(PhS)_2$, AIBN, THF, reflux, 8 h; (c) BBr_3, CH_2Cl_2, –30 °C to r.t., 5 h.

Dehydrobrittonin A (**8**, 3,3′,4,4′,5,5′-hexamethoxystilbene) is a symmetrically substituted stilbene, the synthesis of which was accomplished from 3,4,5-trimethoxybenzyl alcohol (**1l**) as the only starting material (Scheme 6). This alcohol had a double role, acting as both the precursor of ylide **2l** and its partner in the NiNPs-promoted Wittig-type olefination. The latter reaction was slower in comparison with those involving homologue substrates with a lower number of methoxy groups. Notwithstanding, the expected stilbene **8** was obtained in moderate yield as a mixture of diastereoisomers. Quantitative radical isomerisation of (*Z*)-**8** into (*E*)-**8** followed by demethylation[39] afforded the resveratrol analogue M8 [**9**, (*E*)-3,3′,4,4′,5,5′-hexahydroxystilbene].

Conclusions

We have demonstrated for the first time that nickel, in the form of nanoparticles, can promote the Wittig-type reaction of primary alcohols and phosphorus ylides. The latter could be previously prepared from the corresponding phosphonium salts by deprotonation with *n*BuLi or generated in situ with lithium metal. The NiNPs were shown to be catalytically superior to other forms of nickel in this re-

action. The reaction works especially well for benzyl alcohols and semistabilised benzyl ylides, whereas the substrate scope is more limited in the case of alkyl alcohols or nonstabilised ylides. 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. In general, the process exhibits low diastereoselectivity, though the *Z*/*E* mixtures could be separated, in some cases, by column chromatography or quantitatively transformed into the *E* stereoisomers by iodine-catalysed or radical isomerisation. 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. Moreover, the reaction proceeds in the absence of any additive as a hydrogen acceptor. A series of polymethoxylated stilbenes as well as resveratrol, DMU-212 and analogues, such as M5, dehydrobrittonin A or M8, were synthesised by using this novel Wittig-type olefination as the key step.

Experimental Section

General Procedure for the NiNPs-Promoted Wittig-Type Olefination of Primary Alcohols and Phosphorus Ylides

Method A: *n*BuLi (1.6 M in hexanes, 625 μL, 1.0 mmol) was added dropwise to a suspension of the corresponding phosphonium halide (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 room temperature under an atmosphere of argon. The reaction mixture, which was initially dark blue, changed to black, indicating that nickel(0) was formed. After 10 min, the corresponding benzyl alcohol (1 mmol) and the initially prepared ylide suspension were added to the NiNPs suspension. The reaction mixture was warmed to reflux and monitored by GLC–MS. The resulting mixture was diluted with EtOAc (10 mL), filtered through a pad of Celite and the filtrate was dried with anhydrous $MgSO_4$. The residue obtained after removal of the solvent (15 Torr) was purified by column chromatography (silica gel, hexane or hexane/EtOAc) to give the pure product.

Method B: Following method A but the phosphorus ylide was generated in situ (ca. 20 min) by addition of the phosphonium halide to a NiNPs suspension, prepared as aforementioned by using an excess amount of lithium powder (28 mg, 4 mmol). Then, the corresponding alcohol was added to the resulting mixture. The diastereomeric ratio was determined on the basis of the GC and ^{1}H NMR spectroscopic analyses.

Supporting Information (see also the footnote on the first page of this article): General experimental details, methods and compound characterisation data.

Acknowledgments

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