

## Nickel-catalysed Substitution Reactions of Allylic Compounds with Soft Nucleophiles: an Efficient Alternative to Palladium Catalysis

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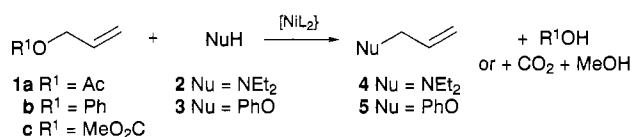
Substitution reactions of allyl alcohol derivatives **1a–c** with diethylamine, phenol and dimethyl malonate are efficiently carried out in the presence of Ni(dppb)<sub>2</sub> (dppb = 1,2-diphenylphosphinobutane) as catalyst and ammonium salts or bases as promoters or co-reagents.

Transition metal catalysed substitution reactions of allylic alcohol derivatives with nucleophilic reagents is an important carbon–carbon bond forming process. Most of the work in this field has been devoted to palladium complexes for the design of chemo-, regio-, stereo- and enantio-selective catalyst systems.<sup>1</sup> Nickel catalysts have also, to a lesser extent, attracted attention and have almost essentially been used with hard nucleophiles such as organometallic reagents.<sup>2</sup> Soft nucleophiles require much more drastic reaction conditions and afford quite poor results compared to palladium catalysts.<sup>3</sup> Here we describe some nickel catalyst systems that enable the reaction of allylic alcohol derivatives with soft nucleophiles to proceed under mild conditions with high turnover frequencies.

The substitution reactions were first examined using allyl acetate **1a** or allyl phenyl ether **1b** and 2–3 equiv. of diethylamine **2** in the presence of 0.5 mol% of a nickel catalyst (Scheme 1). The results are summarised in Table 1. When the reaction was carried out with **1a** at 80 °C in THF in the presence of Ni(dppe)<sub>2</sub> (dppe = 1,2-diphenylphosphinoethane) or Ni(dppp)<sub>2</sub> (dppp = 1,2-diphenylphosphinopropane) (prepared *in situ* by mixing Ni(COD)<sub>2</sub> and 2 equiv. of phosphine ligand), the expected product **4** was obtained in a quantitative yield after 4.5 and 2.75 h respectively (entries 1 and 2). The use of Ni(dppb)<sub>2</sub> resulted in a large increase in the catalytic activity<sup>3d</sup> and the same reaction proceeded under much milder conditions,

*i.e.* 50 °C within 2 h (entry 3). The catalytic activity of Ni(dppb)<sub>2</sub> was also greatly affected by the solvent nature. Namely, under comparable conditions, the time to complete the reaction was slightly increased by using toluene as the solvent (entry 4). Conversely, more interesting results were observed in the presence of DMF and acetonitrile (entries 5 and 6), despite the partial solubility of Ni(dppb)<sub>2</sub> in acetonitrile. Owing to the apparent relation between the catalytic activity and polarity of the solvent and to the fact that all the Ni(dppb)<sub>2</sub>-catalysed reactions exhibited increasing rates as far as the reaction proceeded,† the effect of added ammonium salts was investigated. The introduction of diethylammonium acetate (the salt normally produced by neutralisation of the acetic acid formed by excess diethylamine) in the early stages of the reaction between allyl acetate **1a** and diethylamine **2** allowed the reaction time to be reduced (entry 7). Somewhat better results were obtained by using diethylammonium phenoxide (entry 8) or tetrabutylammonium hexafluorophosphate (entry 9).‡ In the latter case, the optimised time to perform the reaction was reduced from 90 to 14 min by using a minute amount of [NBu<sub>4</sub>][PF<sub>6</sub>] (2.5 mol% with respect to the allylic substrate) (compare entries 3 and 9). A further example (reaction of allyl phenyl ether **1b** with diethylamine **2** shows a similar salt effect and the expected product **4** was obtained selectively in toluene at 50 °C within 2 min (entries 10 and 11).

The catalytic activity of Ni(dppb)<sub>2</sub> was further investigated by using other combinations of allylic substrates **1a–c** and the nucleophiles **3** and **6** (Table 1). Substitution of methyl allyl carbonate **1c** with phenol **3** in toluene also afforded a quantitative yield of **5** but the reaction was quite slow even at 80 °C (entry 12). In this case, the use of a polar solvent such as acetonitrile almost totally inhibited the process; this may be

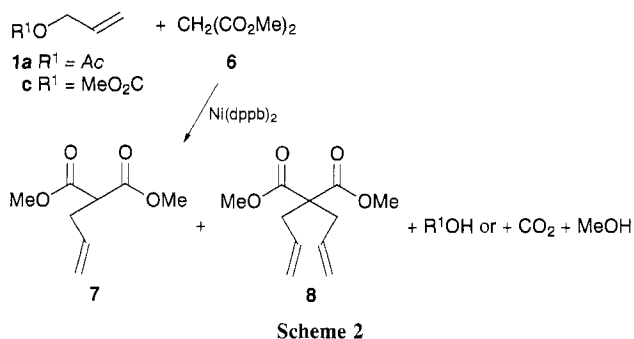


Scheme 1

Table 1 Nickel-catalysed substitution reactions of allyl compounds with soft nucleophiles

Entry	Catalyst <sup>a</sup>	Reagents			Solvent	Additive (equiv. Ni)	T/°C	Product <sup>b</sup>	t/ min
		Allyl <b>1</b>	NuH	Allyl : NuH : Ni					
1	Ni(dppe) <sub>2</sub>	<b>a</b>	<b>2</b>	200 : 600 : 1	THF	—	80	<b>4</b>	270
2	Ni(dppp) <sub>2</sub>	<b>a</b>	<b>2</b>	200 : 600 : 1	THF	—	80	<b>4</b>	165
3	Ni(dppb) <sub>2</sub>	<b>a</b>	<b>2</b>	200 : 600 : 1	THF	—	50	<b>4</b>	90
4	Ni(dppb) <sub>2</sub>	<b>a</b>	<b>2</b>	200 : 600 : 1	PhMe	—	50	<b>4</b>	110
5	Ni(dppb) <sub>2</sub>	<b>a</b>	<b>2</b>	200 : 600 : 1	DMF	—	50	<b>4</b>	6
6	Ni(dppb) <sub>2</sub> <sup>d</sup>	<b>a</b>	<b>2</b>	200 : 600 : 1	MeCN	—	50	<b>4</b>	< 2
7	Ni(dppb) <sub>2</sub>	<b>a</b>	<b>2</b>	200 : 600 : 1	THF	[NH <sub>2</sub> Et <sub>2</sub> ][AcO] (100)	50	<b>4</b>	36
8	Ni(dppb) <sub>2</sub>	<b>a</b>	<b>2</b>	200 : 600 : 1	THF	[NH <sub>2</sub> Et <sub>2</sub> ][PhO] (100)	50	<b>4</b>	9
9	Ni(dppb) <sub>2</sub>	<b>a</b>	<b>2</b>	200 : 600 : 1	THF	[NBu <sub>4</sub> ][PF <sub>6</sub> ] (5)	50	<b>4</b>	14
10	Ni(dppb) <sub>2</sub>	<b>b</b>	<b>2</b>	200 : 400 : 1	PhMe	—	50	<b>4</b>	11
11	Ni(dppb) <sub>2</sub>	<b>b</b>	<b>2</b>	200 : 400 : 1	PhMe	[NH <sub>2</sub> Et <sub>2</sub> ][PhO] (100)	50	<b>4</b>	< 2
12	Ni(dppb) <sub>2</sub>	<b>c</b>	<b>3</b>	300 : 200 : 1	PhMe <sup>e</sup>	—	80	<b>5</b>	210
13	Ni(dppb) <sub>2</sub>	<b>c</b>	<b>3</b>	300 : 200 : 1	PhMe <sup>e</sup>	NEt <sub>3</sub> (200)	80	<b>5</b>	60
14	Ni(dppb) <sub>2</sub>	<b>c</b>	<b>6</b>	250 : 100 : 1	THF	—	80	<b>8</b> <sup>f</sup>	150
15	Ni(dppb) <sub>2</sub>	<b>a</b>	<b>6</b>	200 : 300 : 1	THF	BSA <sup>g</sup> (300)	25	<b>7</b> / <b>8</b> <sup>h</sup>	< 1
16	Ni(dppb) <sub>2</sub>	<b>a</b>	<b>6</b>	250 : 100 : 1	THF	BSA <sup>g</sup> (250)	25	<b>8</b>	50
17	Ni(dppb) <sub>2</sub>	<b>b</b>	<b>6</b>	250 : 100 : 1	THF	BSA <sup>g</sup> (250)	25	<b>8</b>	< 2

<sup>a</sup> Prepared *in situ* from Ni(COD)<sub>2</sub> and 2 equiv. of the corresponding phosphine ligand. <sup>b</sup> No side products were observed. <sup>c</sup> Optimized time for total conversion of the reagents to the desired product as indicated by GLC. <sup>d</sup> Catalyst was partially soluble. <sup>e</sup> Reaction carried out in 5 ml of solvent. <sup>f</sup> A mixture of **7** and **8** was obtained after 30 min. reaction in 20 and 75% GLC yields, respectively. <sup>g</sup> *N,O*-bis(trimethylsilyl)acetamide. <sup>h</sup> Compounds **7** and **8** were obtained in 92 and 8% GLC yields, respectively.



Scheme 2

explained by the higher acidity of phenol in acetonitrile than in toluene which contributes to the destruction of the active  $\text{Ni}^0$  species, as is evident by the rapid discoloration of the reaction medium. Actually, catalytic results were improved by introducing an equimolar amount of triethylamine with respect to phenol (entry 13).

The reaction of allylic substrates **1a-c** with dimethyl malonate **6** afforded the mono- and/or di-allylated products (**7** and **8**, respectively), (Scheme 2). The reaction proceeded rather slowly with methyl allyl carbonate **1c** (entry 14), but the combination of allyl acetate **1a** or phenoxide **1b** with BSA [*N,O*,-bis(trimethylsilyl)acetamide]<sup>4</sup> considerably increased the reaction rates, and turnover frequencies higher than  $12\,000 \text{ mol (7/8).mol(Ni)}^{-1}.\text{h}^{-1}$  were observed at room temperature (entries 15–17). Thus, the synthesis of **7** was carried out in 92% yield from allyl acetate **1a**, whereas the selective formation of the diallyl compound **8** was best performed from allyl phenoxide **1b**.

The originality of this efficient nickel-based catalyst system compared to previous ones reported arises from (i) the use of a preformed zerovalent nickel complex, and (ii) the judicious choice of the polarity of the reaction medium.

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## Footnotes

† Exponential plots for the conversion to **4** vs. reaction time were observed for all  $\text{Ni(dppb)}_2$ -catalysed runs, whereas those conducted in the presence of dppe and dppp exhibited classical sigma profiles.

‡ In a typical experiment, to  $\text{Ni(COD)}_2$  (36 mg, 0.13 mmol) was added a solution of dppe (111 mg, 0.26 mmol) and  $[\text{NBu}_4][\text{PF}_6]$  (252 mg, 0.65 mmol) in THF (12.5 ml) under nitrogen. After stirring for 15 min, allyl acetate **1a** (2.60 g, 26 mmol), diethylamine **2** (5.70 g, 78 mmol) and heptane (1.00 g, 10 mmol) as an internal standard were added. The solution was stirred at 50 °C and the reaction was monitored by GC analysis of aliquot samples. After the reaction was complete, compound **4** was isolated from the reaction mixture by distillation and fully characterised by NMR and MS techniques.

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