Efficient coupling reactions of allylamines with soft nucleophiles using nickel-based catalysts

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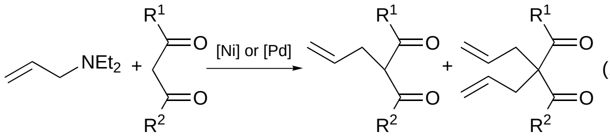
Substitution reactions of *N*,*N*-diethylallylamine 1 with soft nucleophiles such as active methylene compounds 2a–c and piperidine 5 proceed much more rapidly in the presence of Ni(dppb)$_2$ [dppb = 1,4-bis(diphenylphosphino)butane] as catalyst than with comparable palladium systems.

Recently we reported the effectiveness of preformed Ni^0-bisphosphine catalysts for the rearrangement of dialkyl allylmalonate derivatives,[1a] a recently discovered case of nucleophilic allylic substitution which proceeds *via* C–C bond cleavage.[1b] In this special reaction, nickel catalysts proved to be more active than comparable palladium systems, suggesting the superior ability of the former to activate allylic substrates having a poor leaving group. Here we report that such nickel-based systems are much more efficient than palladium catalysts for coupling of allylamines[2] with so-called 'soft' nucleophiles.[3]

The comparative study was performed using the simple *N*,*N*-diethylallylamine **1** and active methylene compounds **2a**–**c** as shown in eqn. (1). The results are summarized in Table 1. In all cases, the reaction was totally selective for allylation products, although a mixture of monoallylation (**3a–c**) and diallylation (**4a–c**) products was obtained. Using 2 mol% of Ni(dppb)$_2$ generated from Ni(COD)$_2$ and 2 mol equiv. of the diphosphine gave allylation products of dimethyl malonate **2a** in virtually quantitative yield with an initial activity of 50 h^{-1} (turnover frequency, TOF) at 80 °C in THF (entry 1). Additional base such as BSA [BSA = *N*,*O*-bis(trimethylsilyl)acetamide] did not affect the reaction (entry 2). On the other hand, a significant increase in the catalytic activity arose upon adding tetrabutylammonium perchlorate as a promoter (5 equiv. with respect to Ni) (entry 3), in direct line with our previous observations on nickel-catalysed coupling reactions of allylic alcohol derivatives.[4] Changing the solvent to DMF further increased the catalytic activity, so that the completion time decreased to 20 min at 80 °C (entry 4), allowing the reaction to be performed at 50 °C (entry 5). At this temperature, the best catalytic activity was observed by combining the solvent effect of DMF and the promoting effect of [NBu$_4$][ClO$_4$] (entry 6). Surprisingly, in light of palladium literature,[2b–h] the *in situ* formation of the allyl ammonium salt *via* addition of acetic acid proved somewhat detrimental (entry 7). The use of palladium catalysts led to poorer results. As a matter of fact, no reaction at all occurred using the *in situ* combination Pd(OAc)$_2$–PPh$_3$ (1 : 5) in THF with BSA as a base (entry 8). Modest activity was obtained with this catalytic system in DMF, which was slightly improved upon adding acetic acid (entries 9 and 10). The *in situ* combination Pd(OAc)$_2$–dppb (1 : 3) showed the best performance of the palladium catalysts tested (entry 11), but the latter is still at least ten times less active than the best nickel-based



(1)

1 **2** **3** **4**

a R^1 = R^2 = OMe
b R^1 = Me, R^2 = OMe
c R^1 = R^2 = Me

Table 1 Catalysed coupling reactions of *N*,*N*-diethylallylamine **1** with methylene active compounds **2a**–**c**

Entry	2	Catalytic system[a]	Solvent	Additive (equiv.)	T/°C	Conv. (%)	t/h[b]	3 : 4	TOF[c]/h^{-1}
1	**2a**	Ni^0/dppb	THF	—	80	100	12	87 : 13	35
2	**2a**	Ni^0/dppb	THF	BSA (75)	80	100	12	88 : 12	10
3	**2a**	Ni^0/dppb	THF	[NBu$_4$][ClO$_4$] (5)	80	100	2	90 : 10	200
4	**2a**	Ni^0/dppb	DMF	—	80	100	0.3	87 : 13	≫ 170
5	**2a**	Ni^0/dppb	DMF	—	50	95	3.5	87 : 13	85
6	**2a**	Ni^0/dppb	DMF	[NBu$_4$][ClO$_4$] (5)	50	95	2.8	88 : 12	100
7	**2a**	Ni^0/dppb	DMF	AcOH (10)	80	100	3	88 : 12	40
8	**2a**	Pd^{II}/PPh$_3$	THF	BSA (75)	80	0	15	—	0
9	**2a**	Pd^{II}/PPh$_3$	DMF	—	80	54	17	90 : 10	6
10	**2a**	Pd^{II}/PPh$_3$	DMF	AcOH (10)	80	64	15	94 : 6	8
11	**2a**	Pd^{II}/dppb	DMF	—	80	100	5	90 : 10	45
12	**2b**	Ni^0/dppb	DMF	—	80	100	< 0.1	73 : 27	≫ 600
13	**2b**	Ni^0/dppb	DMF	—	50	100	0.5	72 : 28	350
14	**2b**	Pd^{II}/PPh$_3$	DMF	—	80	93	9	77 : 23	25
15	**2b**	Pd^{II}/dppb	DMF	—	80	100	1	75 : 25	215
16	**2b**	Pd^0/dppb	DMF	—	80	95	1.5	81 : 19	110
17	**2b**	Pd^0/dppb	THF	—	80	80	15	76 : 24	5
18	**2c**	Ni^0/dppb	DMF	—	80	10	0.25[d]	97 : 3	20
19	**2c**	Pd^{II}/dppb	DMF	—	80	100	1	78 : 22	150

[a] [Metal]/[**1**]/[**2**] = 1 : 50 : 75; Ni^0/dppb: prepared from Ni(COD)$_2$ and 2 equiv. of the phosphine ligand; Pd^{II}/PPh$_3$: prepared *in situ* from Pd(OAc)$_2$ and 5 equiv. of PPh$_3$; Pd^{II}/dppb: prepared *in situ* from Pd(OAc)$_2$ and 3 equiv. of dppb. [b] Optimized time for conversion of **1** into **3** and **4** as indicated by quantitative GLC; No side products were observed. [c] Initial catalytic activity (< 10% conversion). [d] 10% yield after 15 min as after 16 h.

Table 2 Catalysed exchange reactions of *N*,*N*-diethylallylamine **1** with piperidine **5**[a]

Entry	Catalytic system	Solvent	Additive (equiv.)	Conv. (%)[b]	*t*/min	TOF/h^{-1}
1	Ni^0/dppb	DMF	—	100	360	35
2	Ni^0/dppb	DMF	$[NBu_4][ClO_4]$ (5)	100	150	60
3	Ni^0/dppb	DMF	AcOH (5)	100	40	400
4	Ni^0/dppb	THF	AcOH (5)	45	1020	4
5	Ni^0/dppb	DMF	AcOH (50)	100	5	$\gg$ 600
6	Pd^{II}/dppb	DMF	AcOH (50)	92	120	60

[a] [Metal]/[**1**]/[**5**] = 1:50:500; *T* = 50 °C. [b] Conversion of **1** into *N*-allylpiperidine **6** as indicated by quantitative GLC.

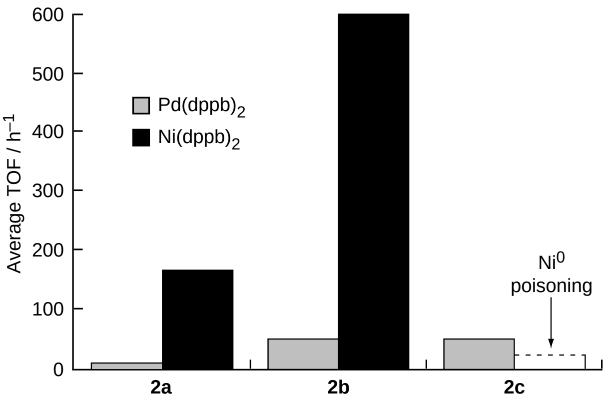
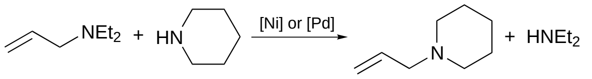


Fig. 1 Average turnover frequencies of nickel and palladium catalysts for the coupling of **1** with **2a–c** (see Table 1 for reaction conditions)

system for this reaction. A similar trend, with even more marked differences between nickel and palladium catalysts, was observed for the alkylation of **1** with methyl acetoacetate **2b**. The simple system using Ni(dppb)$_2$ as the catalyst and DMF as the solvent allowed the reaction carried out with 2 mol% to Ni to be completed within 5 min at 80 °C and with an average activity of 100 h^{-1} at 50 °C (entries 12 and 13).† The *in situ* combination Pd(OAc)$_2$–dppb proved once again to be the most effective palladium catalyst (entries 14–17), but its performance at 80 °C was still lower than that of the above nickel system at 50 °C. However, nickel catalysts proved inefficient for the coupling of **1** with acetylacetone **2c** (entry 18), because of a rapid catalyst poisoning evidenced by the gradual shift in the colour of the solution from orange–yellow [typical colour of Ni(dppb)$_2$] to pale green [Ni^{II} species, possibly Ni(acac)$_2$]. Although it must be pointed out that **2c** is the most acidic compound among active methylene compounds **2a–c**, there is no definitive evidence that this catalyst decay occurs *via* an oxidative protolysis of nickel intermediates.‡ Anyway, the catalyst poisoning was still observed in the presence of an excess of **1** ([Ni]:[**1**]:[**2c**] = 1:75:50). No comparable phenomenon was observed with palladium catalysts, such as the *in situ* combination Pd(OAc)$_2$–dppb, which afforded alkylation products **3c**/**4c** with performance similar to that observed for the coupling of **1** with **2b** (entry 19). Fig. 1 summarises the overall performance of best Ni–dppb and Pd–dppb systems.

The results of the exchange reaction between **1** and piperidine **5** to give *N*-allylpiperidine **6** (eqn. 2) bring further evidence of



1 **5** **6** (2)

the general ability of nickel catalysts to promote nucleophilic substitution of allylamines (Table 2). We found that the aforementioned trends for the nickel-catalysed coupling of **1** with active methylene compounds **2a**, **b** proved also to be true for this exchange reaction. A notable exception arose from the beneficial effect of added acetic acid as expected from the literature.[2b–h] Namely, the formation of **6** was best conducted by using Ni(dppb)$_2$ as the catalyst, DMF as the solvent and by adding 1 equiv., of AcOH with respect to **1** (Table 2, entry 5). The most efficient palladium catalyst found [*in situ* combination Pd(OAc)$_2$–dppb, 1:3] took at least 20 times longer for the exchange reaction to go to completion than the latter nickel-based system under the same conditions (entry 6).

In conclusion we have demonstrated that Ni(dppb)$_2$ easily generated from Ni(COD)$_2$ and 2 equiv. of the bisphosphine is generally a much more active catalyst than comparable palladium systems for substitution of allylamines with 'soft' nucleophiles. Two explanations can be proposed for this trend: (i) the higher ability of nickel catalysts to activate allylic substrates having a poor leaving group, *i.e.* here the C–N bond, and/or (ii) the lower propensity of Ni to be coordinated by amines, thus resulting in larger amounts of active Ni–phosphine species. The limitation of these nickel-based systems lies in the sensitivity of nickel intermediates towards acetylacetone.

Footnotes

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† In a typical experiment (Table 1, entry 13), to Ni(COD)$_2$ (36 mg, 0.13 mmol) in a 50 ml glass reactor equipped with a Teflon cap was added a degassed solution of dppb (111 mg, 0.26 mmol) in DMF (12.5 ml) under nitrogen. After 15 min of magnetic stirring, **1** (0.74 g, 6.5 mmol), **2b** (1.13 g, 9.75 mmol) and heptane (1.00 g, 10 mmol, GLC internal standard) were added. The solution was stirred at 50 °C and the reaction was monitored by quantitative GLC analysis of aliquot samples. Coupling reactions involving a co-reagent and exchange reactions of **1** with piperidine were carried out in a similar manner. *In situ* palladium catalysts were prepared by mixing Pd(OAc)$_2$ with a degassed solution (THF or DMF) of the phosphine ligand. The resulting yellow solution was stirred for 15 min at room temperature before use.

‡ Such a degradation of nickel intermediates could be rationalised as follows:

$$Ni^0(dppb) + 2\ acacH \rightarrow Ni(acac)_2 + H_2 + dppb$$

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