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Bis(aminophosphine)-Nickel Complexes as Efficient Catalysts for Alkylation of Allylic Acetates with Stabilized Nucleophiles

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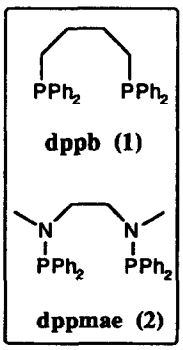
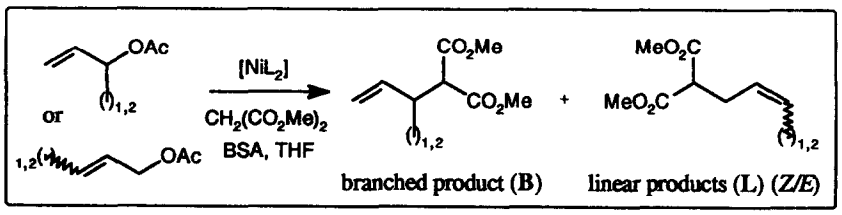
Abstract : The alkylation of a variety of allylic acetates with dimethyl malonate catalysed by nickel-diphosphine complexes is reported. It is shown that in most cases bis(aninophosphine) type ligands lead to much more efficient catalysts than dppb and other usual diphosphines. The use of chiral ligands during the alkylation of 3-acetoxycyclohexene affords dimethyl cyclohex-2-enylmalonate in up to 40% ee.

Despite the outstanding ability of nickel catalysts to promote carbon-carbon bond forming processes,[1] quite little attention has been devoted to nucleophilic substitution reactions of allylic compounds. As a matter of fact, nickel-catalysed allylic alkylations have mainly involved non stabilized nucleophiles such as Grignard reagents and other organometallic compounds,[2] and only very few studies have explored the area of stabilized nucleophiles.[3] This is essentially due to the fact that nickel catalysts suffer from low activity compared to palladium catalysts, which have thus retained almost all attention in this field.[4] Nevertheless, we recently reported that the use of a preformed zerovalent nickel complex, in combination with a polar solvent, enables the reaction of allylic alcohol derivatives with stabilized nucleophiles to proceed under mild conditions with high turnover frequencies.[5] Here we describe that, for the alkylation reaction of a variety of allylic acetates, bis(aminophosphine)-nickel complexes lead to significantly better results than Ni(dppb)$_2$, so far recognized as one of the most efficient nickel catalysts for this type of reaction.[3c,d,e,5]

First, the substitution reactions of various allylic acetates by a combination of dimethyl malonate with BSA (*N,O*-bis(trimethylsilyl)acetamide)[6] were investigated in the presence of 2 mol% of a nickel catalyst prepared *in situ* by mixing Ni(COD)$_2$ and 2 equiv. of diphosphine ligand[7] (schemes 1 and 2). The results are summarized in Table 1.

Schemes 1 and 2

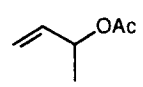
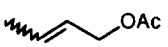
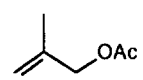
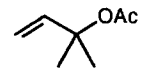
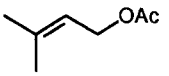
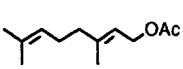




When the reaction was carried out with 1-methylallyl acetate at room temperature in THF in the presence of Ni(dppb)$_2$, the expected branched and linear alkylation products were obtained in an overall quantitative yield in 8 min. (entry 1). The use of Ni(dppmae)$_2$ as the catalyst considerably increased the reaction rate, since the reaction time was halved (entry 2). The superiority of the Ni(dppmae)$_2$ catalyst system was also observed during the alkylation of 3-methylallyl acetate (entries 3, 4), and of 2-

methylallyl acetate, both for the synthesis of the product of mono- or diallylation, upon the amounts of reagents (entries 5-8). This trend was even more marked for 1,1-dimethylallyl acetate since the reaction was totally inefficient with Ni(dppb)$_2$ even at 80 °C,[8] whilst it could be carried out under smooth conditions in the presence of Ni(dppmae)$_2$ (entries 9, 10).

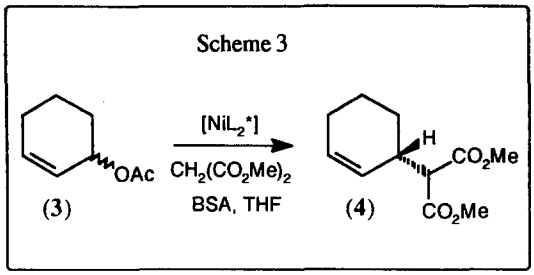
Table 1. Nickel-catalysed Alkylation of Allylic Acetates with Dimethyl Malonate[a]

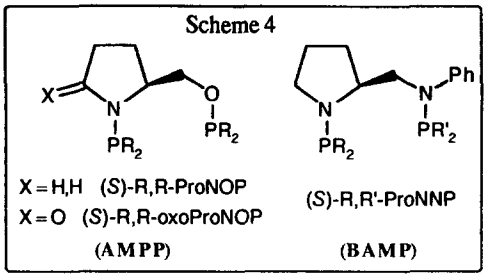
entry	substrate	ligand	temp. (°C)	conv (%)	(time)[b] (min)	TOF°[c] (h^{-1})	selectivity (%) B / L[d]	(Z/E)[e]	diallyl[f]
1		1	20	100	(8)	375	65/35	(78/22)	0
2		2	20	100	(3.5)	900	70/30	(78/22)	0
3		1	50	100	(75)	125	61/37	(78/22)	2
4	(Z/E: 95/5)	2	20	100	(45)	207	66/34	(82/18)	0
5		1	50	100	(10)	1500	98.5	-	1.5
6		2	20	100	(19)	158	98.7	-	1.3
7[g]		1	50	100	(135)	600	0	-	100[g]
8[g]		2	20	100	(120)	400	0	-	100[g]
9		1	80	0[h]	(60)	0[h]	-	-	0
10		2	20	100	(120)	25	69/31	-	0
11		1	80	96	(20h)	8	49/51	-	0
12		2	80	84	(15h)	14	56/43	-	1
13		1	80	94	(70h)	3	13/87	(14/86)	0
14		2	80	44	(68h)	4	13/87	(11/89)	0

[a] [Ni] / [L_2] / [allyl] / [malonate] / [BSA] = 1 / 2 / 50 / 75 / 75 (unless otherwise stated); Ni(COD)$_2$ = 35 mg (0.13 mmol), THF = 12.5 ml; for a typical procedure see reference 5. [b] Optimized reaction time for the specified conversion of the default reagent to alkylation products, as determined by quantitative GLC analysis. [c] Initial turnover frequency of Ni for the production of alkylation products. [d] GLC selectivities into the linear and branched alkylation products related to the dimethyl malonate moiety. [e] *Z/E* ratio of the linear alkylation product. [f] Selectivity into diallylation products. [g] [Ni] / [L_2] / [allyl] / [malonate] / [BSA] = 1 / 2 / 75 / 25 / 75. [h] See Note 8.

However, the use of Ni(dppmae)$_2$ did not improve the results for the reactions of 3,3-disubstituted allylic derivatives such as 3,3-dimethylallyl acetate (entries 11,12) and geranyl acetate (entries 13,14), which required very long reaction times to go to completion. For all these reactions (entries 1-14), insignificant variations of the regioselectivity and stereoselectivity were observed between the two catalytic systems.

In a second time, the possibility to extend the scope of these nickel catalyst systems to asymmetric synthesis was evaluated by using chiral ligands. The results summarized in Table 2 for the conversion of 3-acetoxycyclohexene (3) into dimethyl cyclohex-2-enylmalonate (4) (scheme 3) are the first examples of a nickel-catalysed asymmetric alkylation with a *stabilized* nucleophile.[9]





Concerning the catalytic activity of the reactions, bis(aminophosphine) ligands (BAMP) proved once more to be the most efficient ones among those investigated. Namely, all nickel catalyst systems based on usual phosphine ligands required 50 °C for reasonable rates, whilst in the presence of dppmae (2) , PNNP or R,R-ProNNP ligands[10] (scheme 4) the reactions could be carried out at 0-20 °C (entries 16, 25-29). The results obtained by varying the R substituent in R,R-ProNOP, R,R-oxoProNOP (AMPP),[11] and R,R-ProNNP ligands (Scheme 4, R = Ph: phenyl; Cy: cyclohexyl) (entries 21-28) show that the introduction of the electron-donating cyclohexyl substituents is beneficial in AMPP ligands, whereas for BAMP ligands, best performances are observed with electron-withdrawing phenyl groups. This indicates that the activity of the nickel catalyst is probably controlled by the electron density at the phosphorus moieties.

Table 2. Asymmetric Alkylation of 3-Acetoxycyclohexene with Dimethyl Malonate[a]

entry	ligand	temp. (°C)	conv[b] (%)	time[c] (h)	TOF[cd] (h^{-1})	ee (%)[e] (config)
15	dppb (1)	50	100	0.75	231	-
16	dppmae (2)	20	100	0.85	353	-
17	(*R,R*)-DIOP	50	100	25	3.6	5 (*R*)
18	(*S,S*)-BPPM	50	100	7	17	15 (*S*)
19	(*R*)-BINAP	50	97	21	17	11 (*R*)
20	(*R,S*)-BPPFA	50	100	2	50	12 (*S*)
21	(*S*)-Ph,Ph-ProNOP	50	83	188	0.6	29 (*R*)
22	(*S*)-Cy,Cy-ProNOP	50	100	2	110	14 (*R*)
23	(*S*)-Ph,Ph-oxoProNOP	50	100	14	10	40 (*R*)
24	(*S*)-Cy,Cy-oxoProNOP	50	100	4.5	45	5 (*R*)
25	(*S*)-Ph,Ph-ProNNP	50	100	<0.1	>1500	17 (*S*)
26	(*S*)-Ph,Ph-ProNNP	0	100	7	17	31 (*S*)
27	(*S*)-Cy,Cy-ProNNP	0	100	65	1	21 (*R*)
28	(*S*)-Cy,Ph-ProNNP	0	100	35	7.5	15 (*R*)
29	(*S,S*)-PNNP	0	100	11	11	8 (*S*)

[a] [Ni] / [L_2] / [3-acetoxycyclohexene] / [dimethyl malonate] / [BSA] = 1 / 2 / 50 / 75 / 75; $Ni(COD)_2$ = 35 mg (0.13 mmol), THF = 12.5 ml. [b] Conversion of 3-acetoxycyclohexene to dimethyl cyclohex-2-enylmalonate, as determined by quantitative GLC analysis. [c] Optimized reaction time for the specified conversion. [d] Initial turnover frequency of Ni (0-20% conv). [e] Determined from ^1H NMR spectra of the isolated product in the presence of $Eu(hfc)_3$; absolute configuration determined by polarimetry (*c* 2.6, $CHCl_3$) on the basis of (+)/R, ref 12c,d.

Concerning the enantioselectivity of the alkylation, the ee's are generally quite low and the best result is obtained in the presence of Ph,Ph-oxoProNOP[11b] (40% ee, entry 23). However, as evidenced by the lower ee's produced with outstanding ligands (entries 17-20), a high asymmetric induction is rather difficult to achieve, even in the presence of palladium catalysts.[4] Indeed, very few efficient chelates have been reported for the palladium-catalysed reaction of **3** with dimethyl malonate,[12] and the results presented here should be considered as encouraging. Another interesting feature arises from the reversal of product configuration by replacing a phenyl group by a cyclohexyl group in R,R-ProNNP ligands (entries 25-28). In agreement with our previous conclusions related to rhodium-based asymmetric hydrogenations, the enantioselectivity seems to be mainly controlled by the pyrrolidinic aminophosphine residue.[10,11]

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