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Synthetic and Kinetic Aspects of Nickel-Catalysed Amination of Allylic Alcohol Derivatives

Hervé Bricout, Jean-François Carpentier, and André Mortreux*

Laboratoire de Catalyse Hétérogène et Homogène associé au CNRS,
Groupe de Chimie Organique Appliquée, Ecole Nationale Supérieure de Chimie de Lille
B.P. 108 - 59652 Villeneuve d'Ascq, France

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***Abstract** : The design of efficient nickel-based catalytic systems for coupling of diethylamine (1) with esters and ether derivatives of allyl alcohol (2a-c) and related allyl-substituted compounds (4a-e) is reported. Special attention is paid to solvent and salt effects on catalytic activities and kinetic profiles for the formation of allylamines. The results are discussed in terms of the influence of some reaction parameters (polarity, ion exchange processes, substrate) on the rate determining step of the catalytic cycle.*

INTRODUCTION

Transition-metal catalysed substitution of allylic alcohol derivatives with nucleophilic reagents provides a highly valuable tool in organic synthesis for the formation of carbon-carbon as well as carbon-heteroatom bonds. Considerable work in this field has been devoted to palladium complexes for the design of chemo-, regio-, stereo- and enantioselective catalysts.[1] In particular, palladium-catalysed allylation of diethylamine with allyl acetate[2a] and allyl phenyl ether[2b] is a well known process. However, to the best of our knowledge, the sole investigations with nickel in this area have been conducted by Yamamoto *et al.* through stoiechiometric reactions of (π-allyl)nickel-phosphine complexes with secondary amines.[3] The authors reported a non quantitative nucleophilic attack of morpholine and diethylamine onto these complexes, thus casting doubt on the possibility to perform the corresponding catalytic reactions. In fact, nickel-based catalysts have retained less attention in allylic substitution than palladium catalysts and have been used above all with non stabilised nucleophiles such as Grignard reagents and other organometallic compounds for C-C bond forming processes.[4] There are a few reports on coupling of allylic alcohol derivatives with so-called soft nucleophiles;[5] These reactions require somewhat severe conditions because of the relative low activity of nickel catalysts obtained from *in situ* combinations of Ni(II) complexes with a reducing agent.[5] Nevertheless, we recently reported that the use of the preformed zerovalent nickel complex Ni(dppb)$_2$ (dppb = 1,4-bis(diphenylphosphino)butane) enables the reaction of simple allylic alcohol derivatives with soft nucleophiles to proceed under mild conditions with high turnover frequencies.[6] For the alkylation of various allylic acetates, we showed that these performances could be improved by using bis(aminophosphine)-Ni(0) catalysts which most often proved to be significantly superior to Ni(dppb)$_2$, allowing reactions to be performed at room

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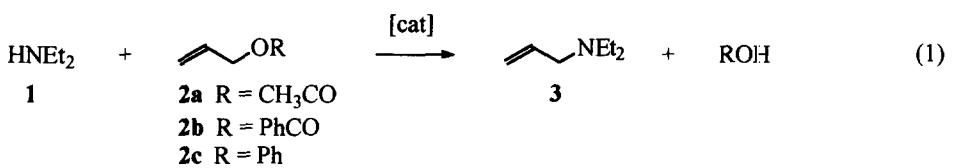
temperature.[7] Also, Ni(dppb)$_2$ catalyses allylic C-C bond cleavage in dimethyl 2-allylmalonate derivatives,[8a] a process recently discovered with palladium catalysts[8b] and which may open interesting synthetic applications. The aim of this paper is to give a full account of how reaction parameters affect selectivity and kinetics of nickel-phosphine-catalysed coupling reactions between diethylamine and simple or substituted allylic alcohol derivatives.

RESULTS AND DISCUSSION

Reactivity of simple allylic substrates

Allylation of diethylamine (**1**) was first investigated with simple derivatives of allyl alcohol (**2a-c**) (eqn 1). Preliminary experiments aimed at evaluating the ability of different diphosphines to promote reaction (1) demonstrated the superiority of dppb.[5d] As a matter of fact, reaction of **1** with allyl acetate (**2a**) in the presence of 0.5 mol% of Ni(dppb)$_2$ [9] at 50 °C yielded quantitatively *N,N*-diethylallylamine (**3**), whereas the catalytic systems produced from dppe (1,2-bis(diphenylphosphino)ethane) and dppp (1,3-bis(diphenylphosphino)propane) required 80 °C for completion of the reaction in reasonable times (Fig. 1). Similar trends were observed in the reaction of **1** with allyl benzoate (**2b**) or, even more markedly, with allyl phenyl ether (**2c**) (Fig. 2). Such differences in the performances of dppe, dppp and dppb have been outlined several times in organometallic chemistry and homogeneous catalysis,[10] and probably stem from changes in the conformation of the metallacycle.[10c,11]



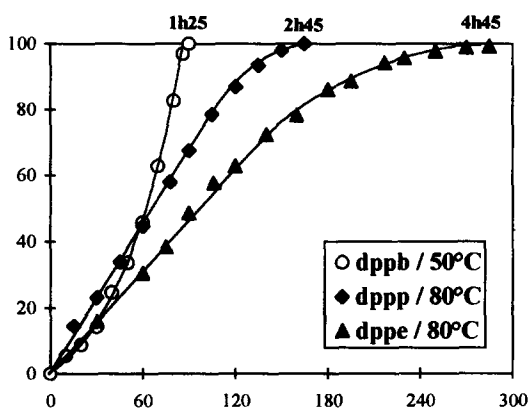


Fig. 1 : Allyl acetate conversion (mol %) vs time (min); Ni(L$_2$)$_2$ / **2a** / **1** : 1 / 200 / 600 ; THF

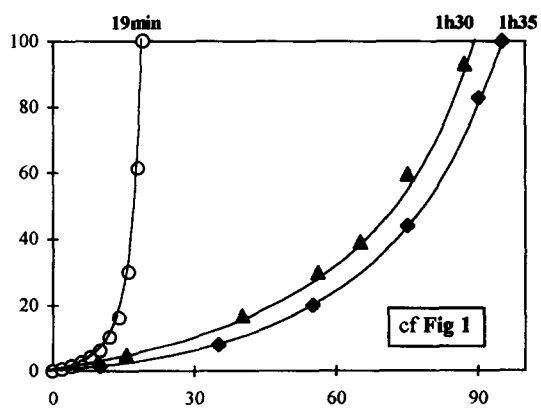


Fig. 2 : Allyl phenyl ether conversion (mol %) vs time (min); Ni(L$_2$)$_2$ / **2c** / **1** : 1 / 200 / 600 ; THF

The influence of the diphosphine/Ni ratio (n) was examined for the allylation of diethylamine by allyl acetate, chosen afterwards as a model reaction for the development of these catalytic systems (Fig. 3). Somewhat surprisingly, the higher the dppb/Ni ratio, the faster the allylation of diethylamine. The absence of inhibiting effect of the diphosphine, at least in the range $1 < \text{dppb/Ni} < 4$, can be rationalized on the basis of equation (2) in which the diphosphine competes with diethylamine to coordinate onto zerovalent nickel, leading respectively to active or inactive catalytic species.

$$Ni^{\circ}(dppb) + x\ NHEt_2 \rightleftharpoons Ni^{\circ}(NHEt_2)_x + dppb \qquad (2)$$

Also, as expected from the production of acetic acid in the course of the reaction, the presence of an excess of amine with respect to the stoiechiometric amount of allyl acetate is necessary to achieve completion (Fig. 4). In fact, whilst a maximum of ca. 60% of **2a** was converted into **3** in the presence of 1 equiv. of diethylamine, 2 equiv. of **1** led to a quantitative yield and the reaction was even better conducted with 3 equiv.

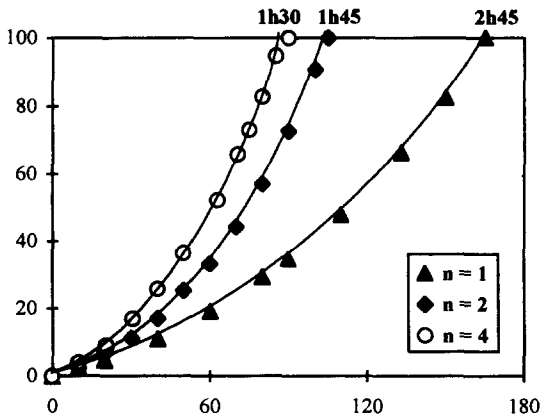


Fig. 3 : Allyl acetate conversion (mol %) vs time (min); $Ni(COD)_2$ / dppb / **2a** / **1** : 1 / **n** / 200 / 600 ; PhMe, 50 °C

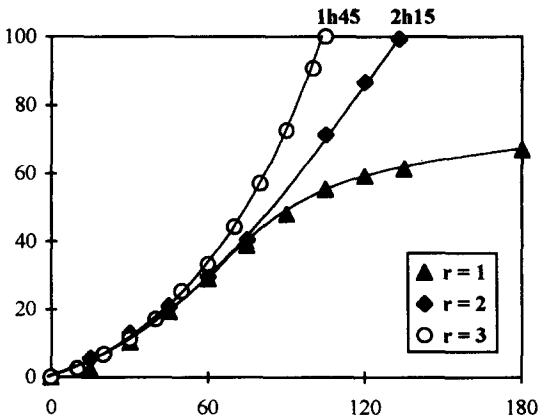


Fig. 4 : Allyl acetate conversion (mol %) vs time (min); $Ni(dppb)_2$ / **2a** / **1** : 1 / 200 / 200×**r** ; PhMe, 50 °C

At this stage, it is noteworthy that almost all of the conversion plots so far described are exponential, i.e. catalytic activity increased with reaction time. We assumed that the accumulation of *N,N*-diethylammonium acetate formed as by-product was responsible for this speed up. Indeed, the introduction of 100 equiv. (with respect to the catalyst) of this salt at the beginning of the reaction resulted in a significant increase of the reaction rate (Fig. 5). With 200 equiv., i.e. close to the solubility limit in toluene at 50 °C, the completion time was halved and a linear plot for conversion of **2a** vs time was observed, indicating that *N,N*-diethylammonium acetate further produced in a solid form did not affect the catalytic activity. The beneficial influence of the *N,N*-diethylammonium salt initially added to the system was also observed with other allylic substrates such as **2c** and in other apolar solvents such as THF (Fig. 6). In this solvent, the phenoxide salt proved to be more efficient than acetate. This fact prompted us to conduct a systematic study by varying the nature of the cation and the anion.

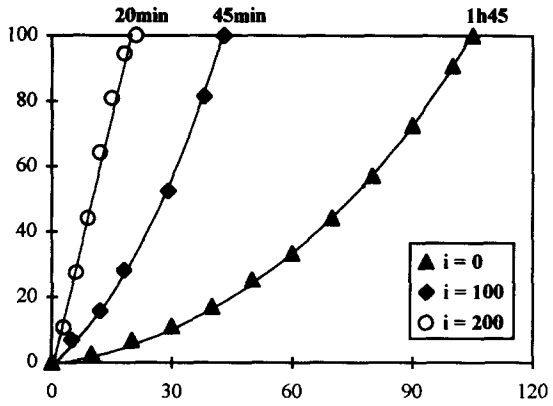


Fig. 5 : Allyl acetate conversion (mol %) vs time (min); Ni(dppb)$_2$ / **2a** / **1** / [**1**, AcOH] : 1 / 200 / 600 / **i** ; PhMe, 50 °C

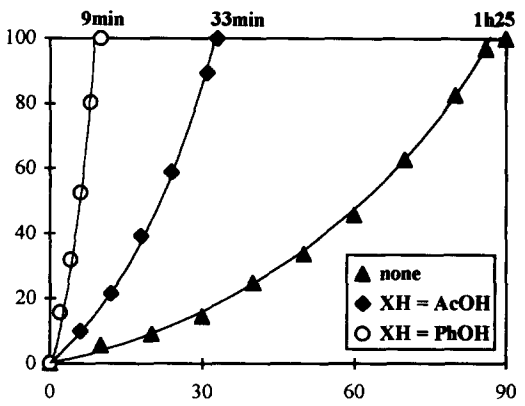


Fig. 6 : Allyl acetate conversion (mol %) vs time (min); Ni(dppb)$_2$ / **2a** / **1** / [**1**, **XH**] : 1 / 200 / 600 / 100 ; THF, 50 °C

Thus, various tetrabutylammonium salts and LiI were evaluated as promoters. The results are depicted in Figures 7 and 8 according to the beneficial or detrimental influence of the salt, respectively. All the salts that enhanced catalytic activity have a non or a poor-coordinating anion: NO_3^-, TsO^-, PF_6^-, BF_4^-, ClO_4^- (Fig. 7). Due to the low solubility of some of them in THF, small amounts were used to compare their relative influence. As a matter of fact, the completion time was significantly reduced from 85 min in the absence of [NBu_4][PF_6] to 5 min with 100 equiv. of this salt (with respect to Ni), but already to 14 min with 5 equiv. and to 33 min with only 1 equiv. On the contrary, other tetrabutylammonium salts and LiI led to a decrease in the reaction rate (Fig. 8). Noteworthy in this regard are [NBu_4][Br] and, even more surprisingly, [NBu_4][OAc] which almost inhibited the allylation reaction at 50 °C, in obvious contrast with the beneficial effect of [NH_2Et_2][OAc].

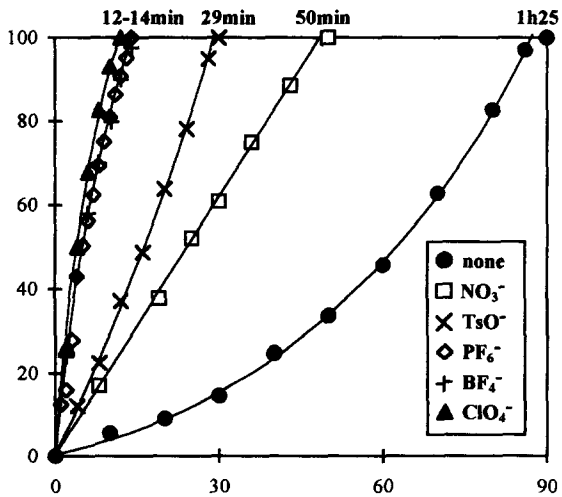


Fig. 7 : Allyl acetate conversion (mol %) vs time (min); Ni(dppb)$_2$ / **2a** / **1** / [NBu_4][**X**] : 1 / 200 / 600 / 5 ; THF, 50 °C

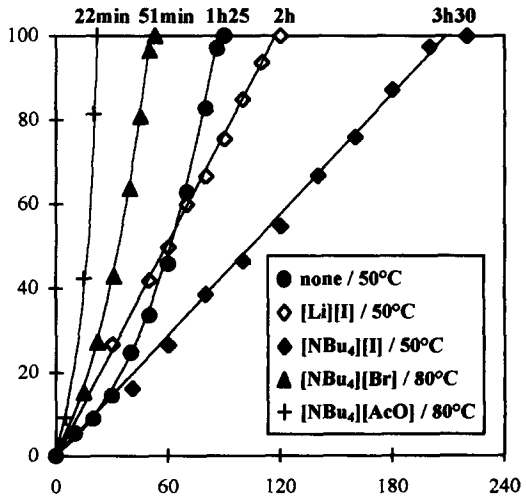


Fig. 8 : Allyl acetate conversion (mol %) vs time (min); Ni(dppb)$_2$ / **2a** / **1** / Salt : 1 / 200 / 600 / 5 ; THF

As expected from the above results, catalytic performances were also strikingly affected by the nature of the solvent (Fig. 9). Reactions conducted in toluene and THF yielded exponential plots with average turnover frequencies (TOF's) at 50 °C of ca. 2 min^{-1} (mol of **3** x mol of Ni^{-1} x min^{-1}), but highly polar solvents allowed to improve considerably these values.[12] Namely, a TOF up to 33 min^{-1} was obtained in DMF and more than 100 min^{-1} using acetonitrile, in which the allylation reaction was completed with a total selectivity for **3** within 2 min, despite a partial solubility of $Ni(dppb)_2$ in this solvent.

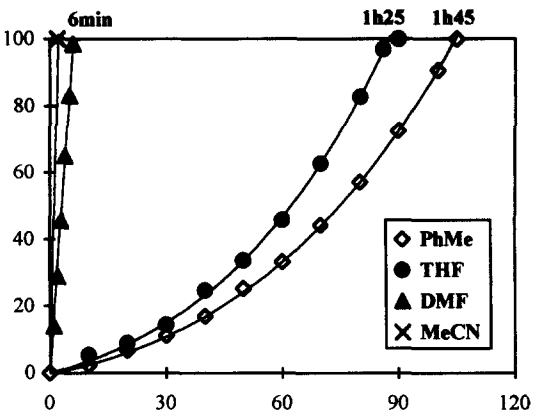
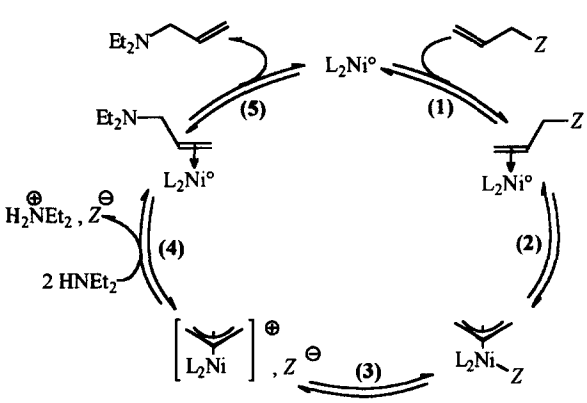


Fig. 9 : Allyl acetate conversion (mol %) vs time (min); $Ni(dppb)_2$ / **2a** / **1** : 1 / 200 / 600 ; 50 °C

Discussion of solvent and salt effects

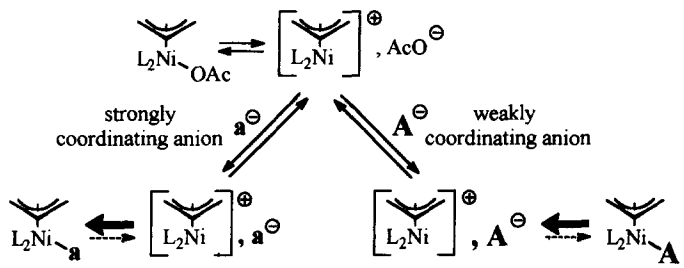
One of the most interesting features in this study arises from the variety of kinetic profiles observed upon reaction conditions (exponential, logarithmic, and linear plots), as well as the beneficial or detrimental influence of added promoters. Addressing this issue allows to discuss about elementary steps of the mechanistic scheme, and particularly of the rate determining step (r.d.s.). It is likely that nickel catalysis involves similar species and mechanistic pathways to those established for palladium.[5] The latter includes association of the allylic substrate onto zerovalent nickel species (1), subsequent oxidative addition (2), ionization of the formed π-allyl-nickel complex (3), nucleophilic attack of the amine (4), and final release of free or protonated allylamine (5) (scheme 1). Obviously, all these steps are equilibriums that can be affected or not by the polarity of the medium and/or the presence of a salt. As a matter of fact, none charged species are involved in the course of association (1) and dissociation (5) steps, which are hence not sensitive to the polarity of the medium.[13] On the contrary, the oxidative addition step (2) is usually described as an intramolecular S_N2, whose transition state exhibits separated opposite charges, and which is therefore stabilized in polar medium. The case of the C-N bond forming step (4) is somewhat more confuse. Namely, the transition state of such nucleophilic attack is destabilized in polar medium,[13] but the overall rate of step (4) also depends on the concentration of the cationic π-allyl-nickel complex (equilibrium 3); As the latter greatly increases with the polarity,[13] one can consider that the overall C-N bond forming step is favoured in polar medium.



Scheme 1

Many conversion plots described in this study are *exponential*. We have demonstrated that this speed up is due to the salt formed in the course of the allylation reaction. Since the accumulation of this salt in solvents such as THF and toluene results in an increasing polarity and, according to the previous statements, the r.d.s. of the catalytic process is either the oxidative addition (2) or the C-N bond forming (4) step. For most cases, we believe that the r.d.s. is the nucleophilic attack because of the limiting concentration of the cationic π-allyl-nickel species. This proposal is supported by the lower promoting effect of $[NH_2Et_2][AcO]$ compared to $[NH_2Et_2][PhO]$ (Fig. 6), most likely because of a mass limitation of acetate ions on equilibrium (3).[14] The superiority of $[NH_2Et_2][PhO]$ over the acetate salt appears even more clearly with nickel systems involving phosphines other than dppb. Actually, while the reaction of allylphenyl ether (**2c**) with diethylamine led to exponential plots with the three catalyst systems (Fig. 2), the corresponding reaction with allyl acetate catalysed by Ni-dppp and Ni-dppe exhibited non-exponential profiles, thus indicating the inefficiency of $[NH_2Et_2][AcO]$ to improve the catalytic activity (Fig. 1). However, this last reaction is significantly sped up by introducing either $[NH_2Et_2][PhO]$ (100 eq, THF, completion within 28 min, linear profile), $[NBu_4][ClO_4]$ (5 eq, THF, 16 min, best described as a linear plot up to 80% conversion, and then as a logarithmic plot) or using acetonitrile as solvent (28 min, logarithmic plot); Such a variety of kinetic profiles illustrates the complexity of the catalytic process and makes obviously problematic the determination of the r.d.s.

Nevertheless, it must be pointed out that the salts formed or added to the medium affect not only the polarity but also, and even more importantly, the reactivity of the π-allyl-nickel complex *via* an ion pair exchange process (scheme 2). In fact, the rate of step (4) also depends on the coordinating ability of the counter-anion which affects the electrophilicity of the cationic π-allyl-nickel complex. Taube and Gehrke have established by conductimetry and ^{13}C NMR spectroscopy that, in $[(\pi\text{-allyl})Ni(P(OPh)_3)_2]X$ complexes, the coordinating ability of X^- increases from $PF_6^- < BF_4^- < TsO^- <<$ halides.[15] This trend is in direct line with the beneficial or detrimental effect of promoters depicted in Figures 7 and 8.



Scheme 2

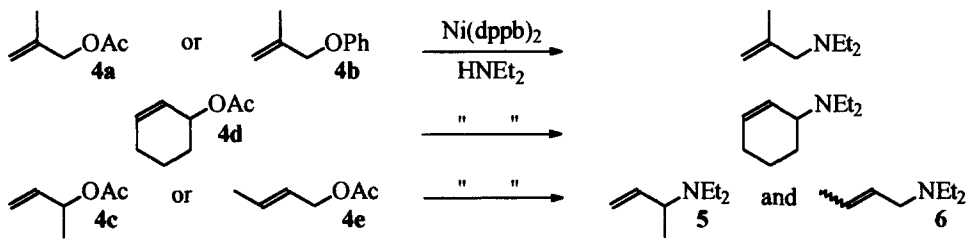
Namely, the presence of tetrabutylammonium salts having non-coordinating anions (ClO_4^-, BF_4^-, PF_6^-, and to a lesser extent TsO^- and NO_3^-) strongly favours the cationic π-allyl-nickel species. The improvment of average TOF's in these cases (Fig. 7) corroborates that the r.d.s. is most likely the nucleophilic attack of the amine. In this regard, the logarithmic plots obtained with ClO_4^-, BF_4^- and PF_6^- are explained in terms of progressive depletion of diethylamine in the reaction course and indicate that accumulation of acetate anions does not affect significantly the concentration of the cationic nickel complex. On the contrary, the exponential

conversion plot in the presence of $[NBu_4][TsO]$ suggests that the production of $[NH_2Et_2][OAc]$ increases the amount of the latter key intermediate by increasing the polarity of the medium.

The presence of a coordinating anion, by introducing e.g. tetrabutylammonium halides or LiI,[16] shifts equilibrium (3) towards covalent π-allyl-nickel species, which lead to a decrease of the average TOF's with respect to the reference system (Fig. 8). The exponential conversion plots observed with $[NBu_4][Br]$ and $[NBu_4][OAc]$ as promoters are in agreement with the increase of the concentration of the cationic key intermediate via polarity by accumulation of $[NH_2Et_2][OAc]$ in the reaction medium. The strong inhibiting effect of $[NBu_4][OAc]$ compared to $[NH_2Et_2][OAc]$ illustrates the influence of the cation. Another example in this regard arises from the superiority of LiI over $[NBu_4][I]$ (Fig. 8). For these two cases, the maximal inhibiting effect was observed with the less associated ions pair, in which the anion has the strongest nucleophilic character.

Reactivity of substituted allylic derivatives

We further investigated the reactivity of related substrates bearing alkyl substituents at their allylic moiety (scheme 3).



Scheme 3

Using $Ni(dppb)_2$ under the same conditions as those defined for allyl acetate was inefficient with this class of substrates. For instance, only 10% conversion was obtained in 90 min at 80 °C for the reaction of 2-methylallyl acetate (**4a**) with **3** (3 equiv. vs **4a**) in THF. After 16 h, the yield in the allylation product (*N,N*-diethyl 2-methylallylamine) reached a maximum of 13% because of a catalyst poisoning, evidenced by the gradual change in coloration from orange yellow ($Ni(dppb)_2$) to pale green. This poisoning was still existing in DMF but the initial catalytic activity was even so greatly enhanced (30 h^{-1} at 50 °C in DMF vs 15 h^{-1} at 80 °C in THF). Hence, the beneficial effect of polar solvents observed with allylic alcohol derivatives **2a-c** could be also extended to substituted compounds **4a-e**. In order to prevent the catalyst decay, we used an excess of diethylamine (10 equiv. vs **4a**). Under such conditions, **4a** was quantitatively converted into the corresponding allylamine within 1 h (TOF = 50 h^{-1}; Fig. 10). This observation suggests that catalyst deactivation occurs by protolysis of zerovalent nickel species (eqn. 3). The fact that this poisoning is not observed with allyl

derivatives **2a-c** probably stems from higher rates for the association and oxidative addition steps (scheme 1), leaving π-allyl-nickel species as the resting state (in agreement with the nucleophilic attack of amine as the r.d.s.), which is *a priori* insensitive to protolysis (Ni(II) species).

$$Ni°(dppb) + 2\ [H_2NEt_2\ ,\ AcO] \longrightarrow Ni^{II}(OAc)_2 + H_2\uparrow + dppb + 2\ HNEt_2 \qquad (3)$$

Figure 10 shows kinetic profiles for the reaction of various monosubstituted allylic derivatives with diethylamine performed under the above defined "optimal" conditions. In each case, a total conversion into the expected amino products was observed (selectivity issues are discussed afterwards). The conversion plots for 2-methylallyl acetate (**4a**), 2-methylallyl phenyl ether (**4b**) and 1-methylallyl acetate (**4c**) are exponential in the first stage of the reaction and then logarithmic; this exponential part almost disappeared with 2-cyclohexenyl acetate (**4d**), whereas crotyl acetate (**4e**) led to a pure logarithmic plot. The apparent first order rate with respect to the substrate, corresponding to the logarithmic part of the plots, indicates that the r.d.s. is most probably the association step (1). This is in agreement with the proposed protolysis of a zerovalent nickel species, [(substrate)NiL_2], responsible for the observed catalyst decay. Furthermore, it accounts for the differences in reactivity of the susbtrates: **2a** > **4c** > **4a** > **4d** ~ **4e** (Fig. 10), i.e. the higher the steric hindrance around the C=C allylic bond,[17] the harder the coordination onto the zerovalent nickel species, the longer the completion time. The significantly higher reactivity of 1-methylallyl acetate over crotyl acetate, albeit both substrates lead to the same π-allyl-nickel intermediate, is a meaningful example. It is also noteworthy that, using the same conditions, disubstituted allylic derivatives such as prenyl and 1,1-dimethylallyl acetates did not react at all with diethylamine.

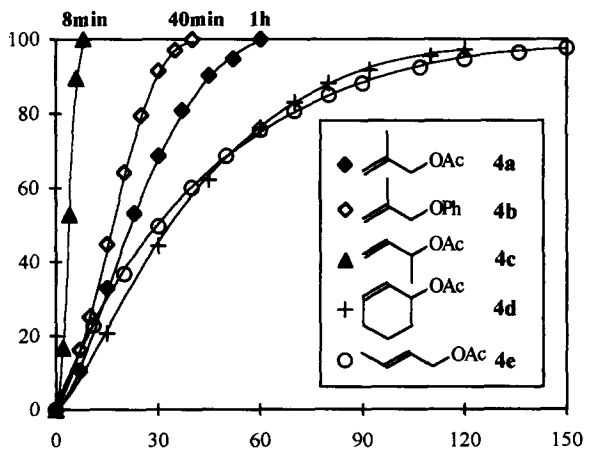
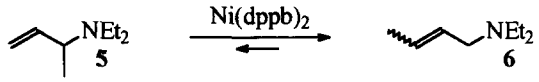


Fig. 10 : Allylic derivative conversion (mol %) vs time (min); $Ni(dppb)_2$ / Allylic derivative / **1** : 1 / 50 / 500 ; DMF, 50 °C

The chemoselectivity of these reactions for allylation products of diethylamine is total; In particular, no elimination product (buta-1,3-diene or cyclohexa-1,3-diene) was detected. Substrates **4a**, **4b** and **4d** yield symmetrical π-allyl-nickel complexes, and thus give only one substitution product through nucleophilic attack of diethylamine. However, 1-methylallyl acetate (**4c**) and crotyl acetate (**4e**) give rise to mixtures of branched (*N,N*-diethyl 1-methylallylamine, **5**) and linear (*N,N*-diethyl 3-methylallylamine, **6**) amines, the latter having two stereoisomers (*Z*, *E*). Interestingly, the regioisomers **5**/**6** ratio was found to change during the reaction course (Fig. 11 and 12).[18] With both substrates, the branched amine is the kinetic product, but the latter

gradually disappears to give the thermodynamically favoured linear product. The maximum amount of branched amine **5** reached ca. 60% from **4c**, but only 10% from **4e**. As the rate constant of isomerization is identical in both experiments, it is obvious that this difference arises from the allylation rate: whereas with **4c**, the branched amine **5** isomerizes much slower than it is produced, the latter isomerizes as fast as it is formed from **4e**.



(4)

The consecutive isomerization process of **5** into **6** is catalyzed by zerovalent nickel species (eqn 4). Catalytic experiments from **4c** and **4e** leading to *in situ* mixtures of **5/6** brought evidences: (i) no reaction at all was observed in the absence of preformed $Ni(dppb)_2$, and (ii) introduction of oxygen (air) in the reaction course immediately stopped allylation *and* isomerization processes. To the best of our knowledge, there is only one report on the isomerization of branched into linear amines, in the presence of palladium catalysts.[19] In order to compare catalytic activities of nickel and palladium-based systems, we conducted the allylation of diethylamine by **4c** with the usual combination $Pd(OAc)_2/PPh_3$ (Pd / P / **4c** / **1** : 1 / 5 / 50 / 500 ; DMF). As expected, the allylation proceeded rapidly at room temperature with this catalyst (100% conversion in 8 min, **5/6** = 38/62), but the isomerization was much slower than with the nickel catalyst: while the latter isomerized about 90% of branched amine **5** within 30 min at 50 °C (Fig. 11), the palladium system required more than 2 h at 80 °C.

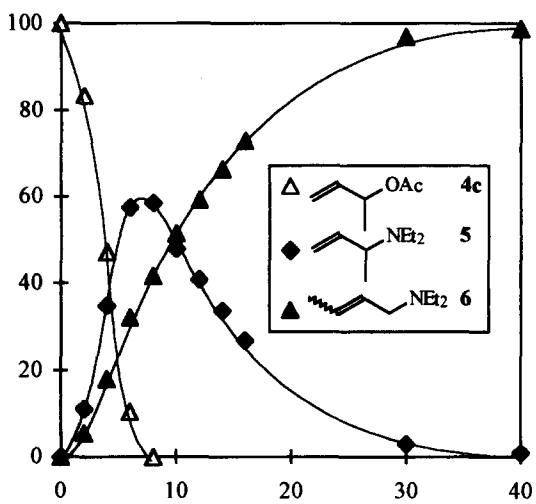


Fig. 11 : Product distribution (mol %) vs time (min); $Ni(dppb)_2$ / **4c** / **1** : 1 / 50 / 500 ; DMF, 50 °C

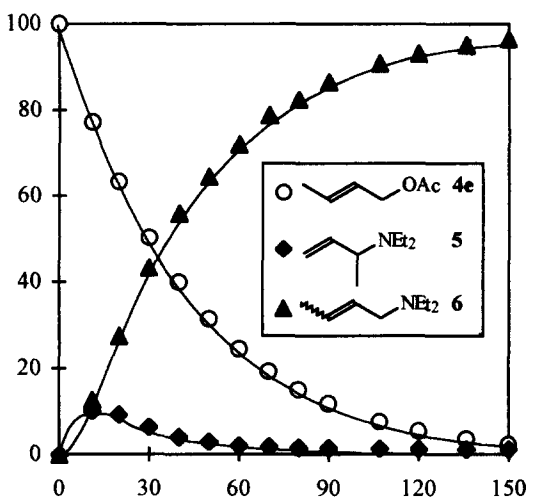


Fig. 12 : Product distribution (mol %) vs time (min); $Ni(dppb)_2$ / **4e** / **1** : 1 / 50 / 500 ; DMF, 50 °C

The ability of zerovalent nickel catalysts to activate the C-N bond in allylic derivatives opens further applications, such as the catalytic coupling of allylamines with stabilised carbanions. [20]

EXPERIMENTAL SECTION

General considerations. The following acetates 2-methylallyl (**4a**), 1-methylallyl (**4c**), 2-cyclohexenyl (**4d**) and crotyl (**4e**) were synthesized through reaction of the corresponding alcohols with acetic anhydride (1.1 eq) in pyridine (3 eq.) at room temperature for 16 h. Allyl benzoate (**2b**) was prepared similarly using benzoic anhydride. Bis(cycloocta-1,5-diene)nickel was purchased from Strem Chemicals. Other reagents were purchased from commercial suppliers in >99% purity and used as received. Toluene and THF were distilled from sodium benzophenone ketyl and degassed by freeze thaw cycles before use. Acetonitrile (Aldrich, 99%) and DMF (Aldrich, 99%) were just degassed before use.

General Procedure for Coupling of Allylic derivatives with Diethylamine. All the reactions were performed under nitrogen using standard Schlenk techniques. In a typical experiment, 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) and $[NBu_4][PF_6]$ (252 mg, 0.65 mmol) in THF (12.5 ml). After 15 min of magnetic stirring, allyl acetate (**2a**) (2.60 g, 26 mmol), diethylamine (**1**) (5.70 g, 78 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. After total completion, *N,N*-diethylallylamine (**3**) was isolated from the reaction mixture by distillation.

All the diethylamine allylation products described in this paper are known. Unambiguous identification was made by comparison of GLC retention times (CP-Sil 5 CB, 25 m × 0.12 mm) with authentic samples, GC-MS, and ^1H, ^{13}C NMR data of isolated products.

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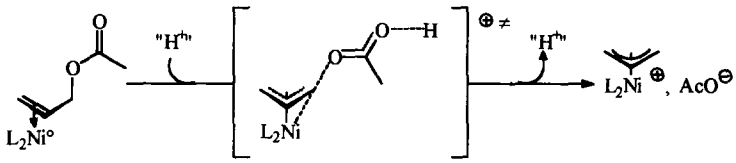
14. The hypothesis of the oxidative addition as the r.d.s. could not account for the experimental observations since the influence of a salt on this elementary step is rationalized by an acidic assistance, i.e. the acetate salt should lead to higher activities than the phenate did;



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16. The apparent zero order rate observed with $[NBu_4][I]$, LiI and $[NBu_4][NO_3]$ suggest that the oxidative addition is the r.d.s, although we have no explanation for such a peculiar behaviour of iodide and nitrate anions.
17. It is assumed that the presence of two susbtituents on the C=C allylic bound in **4d** vs only one in **4e** is counterbalanced by the *Z* stereochemistry in **4d** compared to (*E*)-**4e**.
18. Whichever the starting substrate (**4c** or **4e**), the *E/Z* ratio in **6** started from 85/15 in the first stage of the reaction to stabilize after a few minutes at 78/22, i.e. the thermodynamic ratio.
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