

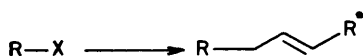
# $\pi$ -Allylnickel Halides as Selective Reagents in Organic Synthesis

By David C. Billington†

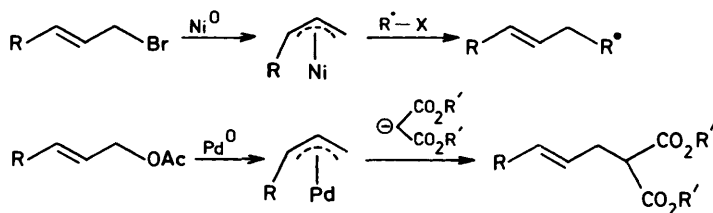
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## 1 Introduction

A central theme in organic synthesis is the formation of new carbon-carbon bonds in a selective manner. In this context, the introduction of an allylic unit into a carbon skeleton is an interesting and useful synthetic operation, which is formalized in Scheme 1. In recent years transition-metal  $\pi$ -allyl complexes have been recognized as efficient reagents for this type of reaction.<sup>1,2</sup> The advantage of these reagents lies primarily in their much higher selectivity, when compared with the more traditional allylmagnesium, lithium, and zinc species. Two classes of complexes have proved particularly useful, the  $\pi$ -allylnickel halides,<sup>1-4</sup> and the  $\pi$ -allyl complexes of palladium.<sup>2,5</sup> In synthetic terms these reagents are complementary to a degree, as  $\pi$ -allylnickel halides react with electron-poor centres, and may thus be classed as 'nucleophilic' reagents, whereas  $\pi$ -allyl palladium complexes react with electron-rich centres (normally stabilized anions) and may thus be considered to be 'electrophilic' reagents, Scheme 2. The complexes are, however, neither electrophilic or nucleophilic in the normal organic sense of the word.



Scheme 1



Scheme 2

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<sup>1</sup> M. F. Semmelhack, *Org. React.*, 1972, **19**, 115.

<sup>2</sup> L. S. Hegedus, *J. Organomet. Chem. Libr.*, 1976, **1**, 329.

<sup>3</sup> R. Baker, *Chem. Rev.*, 1973, **73**, 487.

<sup>4</sup> G. P. Chiusoli and G. Salerno, *Adv. Organomet. Chem.*, 1978, **17**, 195.

<sup>5</sup> B. M. Trost, *Acc. Chem. Res.*, 1980, **13**, 385.

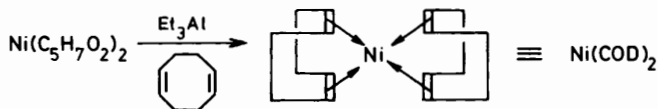


the dangers and precautions involved should be fully appreciated, and reference should be made to the technical bulletin, 'Nickel Carbonyl is Dangerous' available from the Matheson Company.

Allylic halides react readily with excess  $\text{Ni}(\text{CO})_4$  in benzene at 50–70 °C, giving the red dimeric  $\pi$ -allylnickel halide complexes.<sup>6</sup> The complexes may be isolated by removal of solvent and excess  $\text{Ni}(\text{CO})_4$  under reduced pressure, and purified by low-temperature recrystallization under an inert atmosphere. The complexes may also be sublimed, but large losses resulting from thermal decomposition normally preclude this method of isolation/purification. In the solid state the complexes are only moderately air sensitive, and storage for years under an inert atmosphere is possible.

Excellent experimental details are available for this method of preparation.<sup>1,6</sup>

**B. Preparation from  $\text{Ni}(\text{COD})_2$ .**—Reduction of nickel bis(acetylacetonate) in the presence of cyclo-octa-1,5-diene yields the yellow crystalline complex  $\text{Ni}(\text{COD})_2$ , Scheme 4.<sup>1,12</sup> The reduction is normally performed using aluminiumalkyls as reducing agents.  $\text{Ni}(\text{COD})_2$  is an air-sensitive solid which becomes highly air-sensitive in solution/suspension in organic solvents, and requires careful inert-atmosphere techniques for its preparation and use.<sup>1,2</sup> Allylic halides react with  $\text{Ni}(\text{COD})_2$  at 0 °C or below in non-polar (*i.e.* non-coordinating) solvents to give almost quantitative yields of the dimeric  $\pi$ -allylnickel halide complexes.<sup>1,7</sup> The by-product of this reaction, cyclo-octa-1,5-diene does not normally cause any problems, even when further reactions are performed *in situ*. The use of  $\text{Ni}(\text{COD})_2$  avoids the thermal decomposition observed when  $\text{Ni}(\text{CO})_4$  is used at 50–70 °C, and a number of thermally-sensitive complexes may only be successfully prepared using this reagent.<sup>13</sup> The preparation and use of  $\text{Ni}(\text{COD})_2$  have been well described in the literature.<sup>1,7,12,13</sup>



Scheme 4

**C. Structure and Properties.**—In the solid state, and in solution in non-coordinating solvents, the complexes exist as halogen-bridged dimers, as indicated in Scheme 3. <sup>1</sup>H N.m.r. spectroscopy confirms the presence of planar delocalized  $\pi$ -allyl ligands,<sup>1</sup> and X-ray crystallographic analysis<sup>14</sup> has allowed the assignment of the

<sup>12</sup> B. Bogdanovic, M. Kroner, and G. Wilkie, *Ann.*, 1966, **699**, 1

<sup>13</sup> L. S. Hegedus and S. Varaprath, *Organometallics*, 1982, **1**, 259.

<sup>14</sup> C. H. Dietrich and R. Uttech, *Z. Kristallogr.*, 1965, **122**, 60.

structure shown (Figure 1) for  $\pi$ -(2-carbethoxyallyl)nickel bromide. The plane of the allyl ligand is tilted at *ca.*  $110^\circ$  to the plane containing the halogen and metal atoms. A discussion of the bonding in the complexes is not germane to the present treatment, and the interested reader is directed to *refs.* 1 and 15—17.

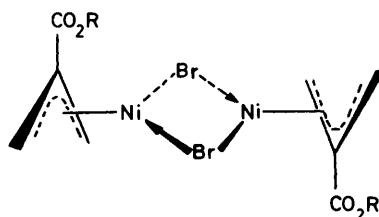
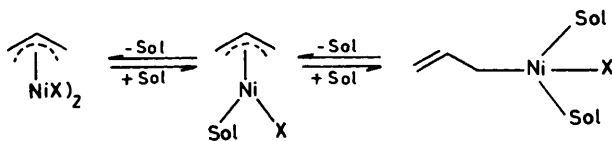


Figure 1

In polar co-ordinating solvents such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide, or hexamethylphosphoramide, or in the presence of good electron-donor ligands such as triphenylphosphine, the  $^1\text{H}$  n.m.r. spectra of the complexes change to the characteristic spectra of rapidly equilibrating  $\sigma$ -allyl species.<sup>18</sup> This change indicates the splitting of the bis  $\pi$ -allylnickel halide dimers into a highly reactive monomeric species, stabilized by solvent (or ligand) co-ordination, Scheme 5. Although the dimeric complexes are only moderately air-sensitive in the solid state, and may be stored in the absence of air for years, in solution the monomeric species are highly air-sensitive, and atmospheric oxygen must be rigorously excluded. The red complexes form deep-red solutions, and this colour is almost instantly discharged on the admission of air into the reaction system. Solutions of the complexes are also thermally unstable, normally decomposing above  $60^\circ\text{C}$ .



Scheme 5

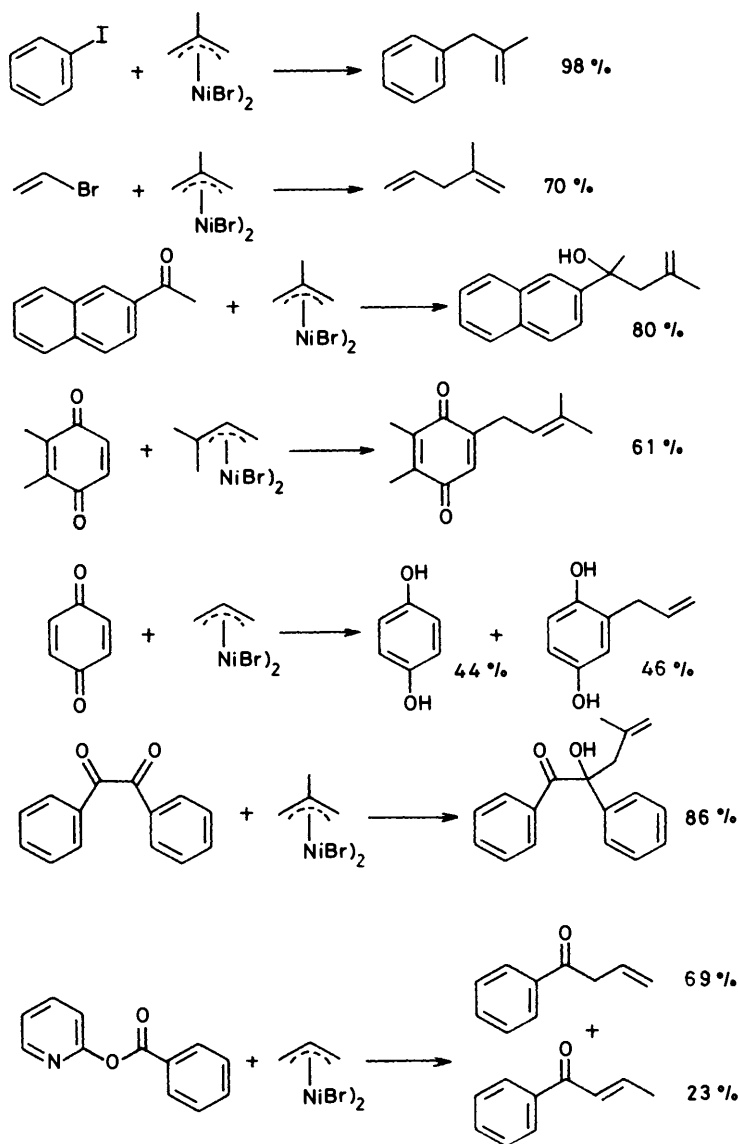
In practice, reactions with the complexes are normally carried out according to the following protocol. The complex is generated by treatment of an allylic halide with  $\text{Ni}(\text{CO})_4$  at  $50$ — $70^\circ\text{C}$  in benzene, or with  $\text{Ni}(\text{COD})_2$  at *ca.*  $0^\circ\text{C}$  in a similar non-polar solvent. The solvent and excess  $\text{Ni}(\text{CO})_4$  (or COD) are then removed by

<sup>15</sup> 'Metal Complexes in Organic Chemistry', by R. P. Houghton, Cambridge University Press, 1979.

<sup>16</sup> 'Advanced Inorganic Chemistry', 3rd Edn., by F. A. Cotton and G. Wilkinson, Interscience, 1972.

<sup>17</sup> S. F. A. Kettle and R. Mason, *J. Organomet. Chem.*, 1966, **5**, 573.

<sup>18</sup> D. Walter and G. Wilkie, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 897.



**Scheme 6** Reactions which proceed at or below 25 °C

application of vacuum, and this leaves the complex as a red solid or gum. The complex may then be isolated and purified by low-temperature crystallization, (for

simple complexes which are being prepared in bulk) or alternatively a polar co-ordinating solvent is added followed by the substrate. The reaction of the monomeric allyl species with the substrate is then allowed to proceed until the characteristic red colour of the complex is discharged, and the reaction products are then isolated. Reactions are usually conducted between 20 and 60 °C.

Excellent practical details for these straightforward reactions are available in the literature, and in the bibliography of this review, asterisks mark those references with particularly useful experimental sections.

### 3 Reactivity

**A. Chemoselectivity.**—As previously mentioned, the main advantage of the  $\pi$ -allylnickel halide complexes stems from their high selectivity compared to the traditional allylmetal derivatives.

In solution in polar co-ordinating solvents the complexes react at or below room temperature with 1° (primary) and 2° (secondary) alkyl, aryl, vinyl and allyl bromides and iodides, giving allylated products.<sup>19</sup> Phenyl ketones react to give homoallylic alcohols,<sup>20</sup> whereas quinones give allyl-substituted quinones, and/or hydroquinones.<sup>21</sup> 1,2-Diketones react with the complexes to give  $\alpha$ -keto-homoallylic alcohols (even in the presence of excess complex, reaction only occurs at one carbonyl group),<sup>20</sup> and 2-pyridyl carboxylates give  $\beta,\gamma$  unsaturated ketones as major products,<sup>22</sup> accompanied by the corresponding  $\alpha,\beta$ -unsaturated ketones. These reactions are summarized in Scheme 6.

At somewhat higher temperatures (40–53 °C) the complexes have been shown to react with aldehydes, cyclic, and some acyclic ketones, giving homoallylic alcohols,<sup>20</sup> allylic chlorides giving dienes,<sup>23</sup> and in one report with certain epoxides.<sup>20</sup>  $\alpha,\beta$ -Unsaturated ketones and simple ketones react under forcing conditions (55 °C and above) which cause thermal decomposition of the complexes, giving only the products of 1,2-addition (even in the presence of CuI).<sup>20</sup> These reactions are summarized in Scheme 7. In all of the above reactions *both* allyl ligands are used for carbon-carbon bond formation, so 1 mol of substrate reacts with  $\frac{1}{2}$  mol of complex.

The complexes do not react with acid chlorides, esters, ethers, nitriles, acetylenic protons, olefins, alcohols, aryl, vinyl, or alkyl chlorides, allylic ethers, or acetals. Allylic acetates are not always compatible with the reagents [ $\text{Ni}(\text{COD})_2$  is reported to cleave allylic acetates<sup>24</sup> and  $\text{Ni}(\text{CO})_4$  couples allylic acetates<sup>10</sup> giving 1,5-dienes]. There is also some evidence that easily reduced or oxidized groups, *e.g.* hydroquinones, are unstable to the nickel reagents.

The above reactivity pattern allows both the preparations of complexes with functional groups present in the reagent, and the reaction of the complexes with

<sup>19</sup> E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.*, 1967, **89**, 2755.

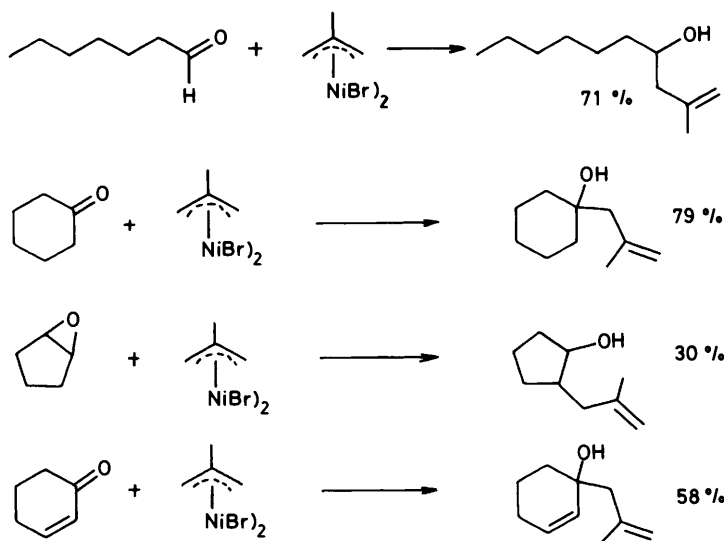
<sup>20</sup> L. S. Hegedus, S. D. Wagner, E. L. Waterman, and K. Siirala-Hansen, *J. Org. Chem.*, 1975, **40**, 593.

<sup>21</sup> L. S. Hegedus, B. R. Evans, D. E. Korte, E. L. Waterman, and K. Sjoberg, *J. Am. Chem. Soc.*, 1976, **98**, 3901.

<sup>22</sup> M. Onaka, T. Goto, and T. Mukiyama, *Chem. Lett.*, 1979, 1483.

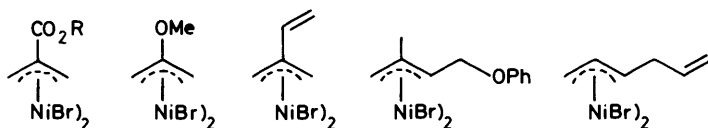
<sup>23</sup> K. Sato, S. Inoue, and K. Watanabe, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2411.

<sup>24</sup> T. Yamamoto, J. Ishizu, and A. Yamamoto, *J. Am. Chem. Soc.*, 1981, **103**, 6863.



Scheme 7

substrates containing more than one functional group, one or more of which is either less susceptible than the desired reactive centre or completely inert to the nickel reagents. Thus complexes may be prepared bearing functional groups such as ester, acetal, olefin *etc.* and some examples of this type of complex are given in Scheme 8. These complexes are all prepared from the corresponding allylic halides, and serve to introduce useful functionality into the reaction products. Examples of simple selective reactions with substrates containing more than one functional group are given in Scheme 9. It can be seen that hydroxyl functions are tolerated in the reaction,<sup>19,25</sup> iodides react faster than chlorides in the same molecule,<sup>19</sup> and in the case given, an allylic acetate is not affected.<sup>26</sup>



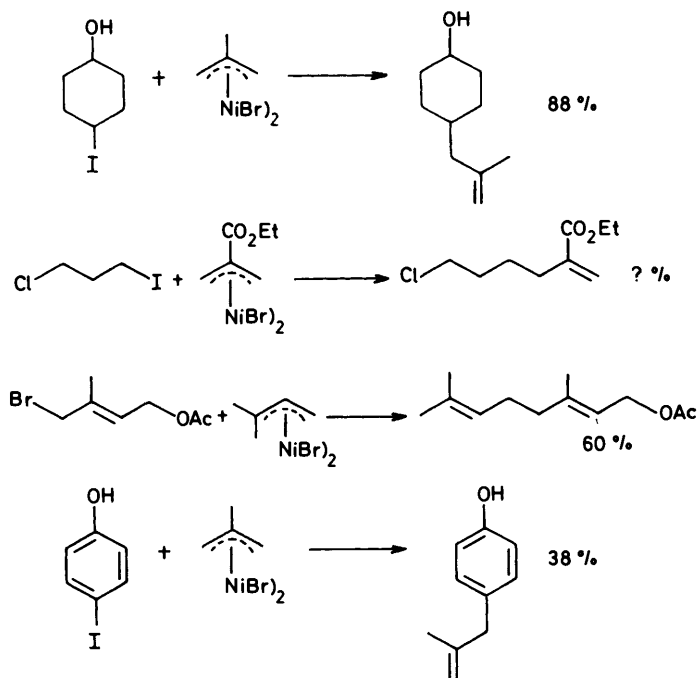
Scheme 8

The reactivity profile of the  $\pi$ -allylnickel halides thus contrasts markedly with the reactivity displayed by the more conventional allylmetal reagents, and some specific examples of this are identified below.

Allyl-lithium, magnesium, and zinc reagents react rapidly with simple ketones,

<sup>\*25</sup> K. Sato, S. Inoue, and R. Yamaguchi, *J. Org. Chem.*, 1972, 37, 1889.

<sup>\*26</sup> K. Sato, S. Inoue, S. Ota, and Y. Fujita, *J. Org. Chem.*, 1972, 37, 462.



Scheme 9

$\alpha,\beta$ -unsaturated ketones and, in the presence of copper salts, 1,4-addition may be observed. The nickel reagents react only sluggishly with simple ketones and  $\alpha,\beta$ -unsaturated ketones, and do not react in a 1,4-fashion.  $\pi$ -Allylnickel halides will tolerate a range of functional groups in the complex and the substrate, including esters, alcohols, and alkynes, whereas these groups interfere with some or all of the more conventional allylmetal reagents. The  $\pi$ -allylnickel halides can also differentiate successfully between closely related groups, such as 1° (primary) iodide and 1° chloride, and in some cases will react selectively with a single ketone in a dione substrate (*e.g.* 1,2-diketones, see above, and steroidal diones, see Schemes 29 and 34).

The ability to perform such selective reactions has led to the use of  $\pi$ -allylnickel halide complexes in the synthesis of complex natural-products, and these syntheses are presented, grouped by the nature of the electrophilic substrate, under the heading synthetic applications.

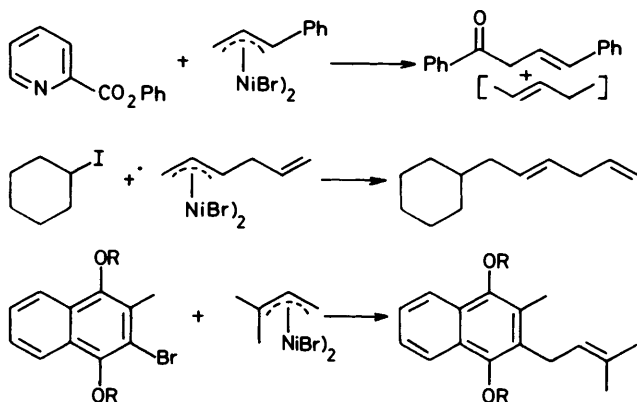
**B. Regioselectivity.**—Substituted  $\pi$ -allylnickel halide complexes which could give products by reaction at either a 1° or 2°/3° terminus almost invariably<sup>13,22,27,28</sup>

<sup>27</sup> K. Sato, S. Inoue, and K. Saito, *J. Chem. Soc., Chem. Commun.*, 1972, 953.

<sup>28</sup> K. Sato, S. Inoue, Y. Takagi, and S. Morii, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3351.



react only at the 1° position, and some examples are given in Scheme 10. There are, however, isolated reports<sup>20</sup> of regioisomeric products arising, for example, in the reaction of  $\pi$ -1,1-dimethylallyl nickel bromide with benzil, reaction at the primary terminus being the more favoured.



Scheme 10

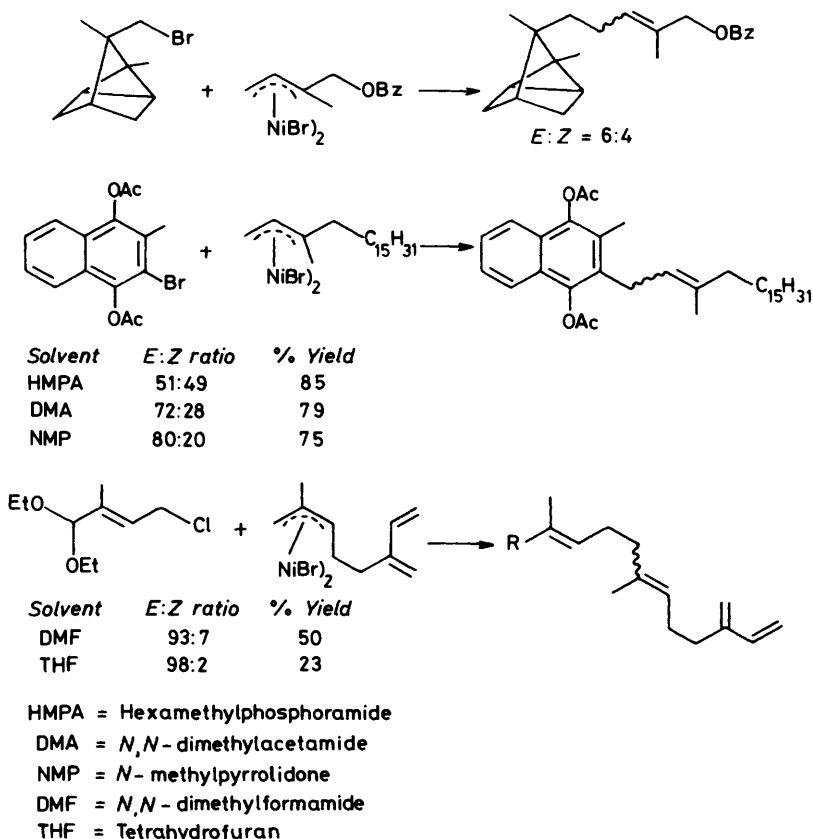
**C. Stereoselectivity.**—In the formation of a carbon–carbon bond between a  $\pi$ -allylnickel halide complex and a substrate, a carbon–carbon double bond is also generated, and if the substituents on this bond are not identical it may be either *E* or *Z*. The products obtained in this type of reaction are normally mixtures of *E* and *Z* isomers, either in a close to 1:1 ratio or with the *E* isomer in excess. In certain favourable cases it has proved possible to influence the course of the reaction by varying the reaction solvent, and *E*:*Z* ratios of up to 98:2 have been obtained.<sup>23</sup> Some representative examples of these reactions are given in Scheme 11. In general the use of solvents of low co-ordinating power, e.g. *N*-methylpyrrolidone or tetrahydrofuran, seems to give high *E*:*Z* ratios, but low overall yields, whilst solvents of high co-ordinating power, e.g. hexamethylphosphoramide, give lower *E*:*Z* ratios but higher overall yields,<sup>23,29</sup> see Scheme 11.

With regard to the stereochemistry of the substrate, partial epimerization is observed when, for example, *trans*-4-iodocyclohexanol is treated with  $\pi$ -2-methylallyl nickel bromide,<sup>1</sup> and substrates which are optically active at the electrophilic centre give racemic products.

#### 4 Synthetic Applications

The following reactions do not represent all the reported reactions of  $\pi$ -allylnickel halides with electrophilic substrates. In particular, many simple examples are not given, rather natural-product syntheses have been selected as they demonstrate both the selectivity and value of the reagents.

<sup>29</sup> K. Sato, S. Inoue, and K. Saito, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2289.



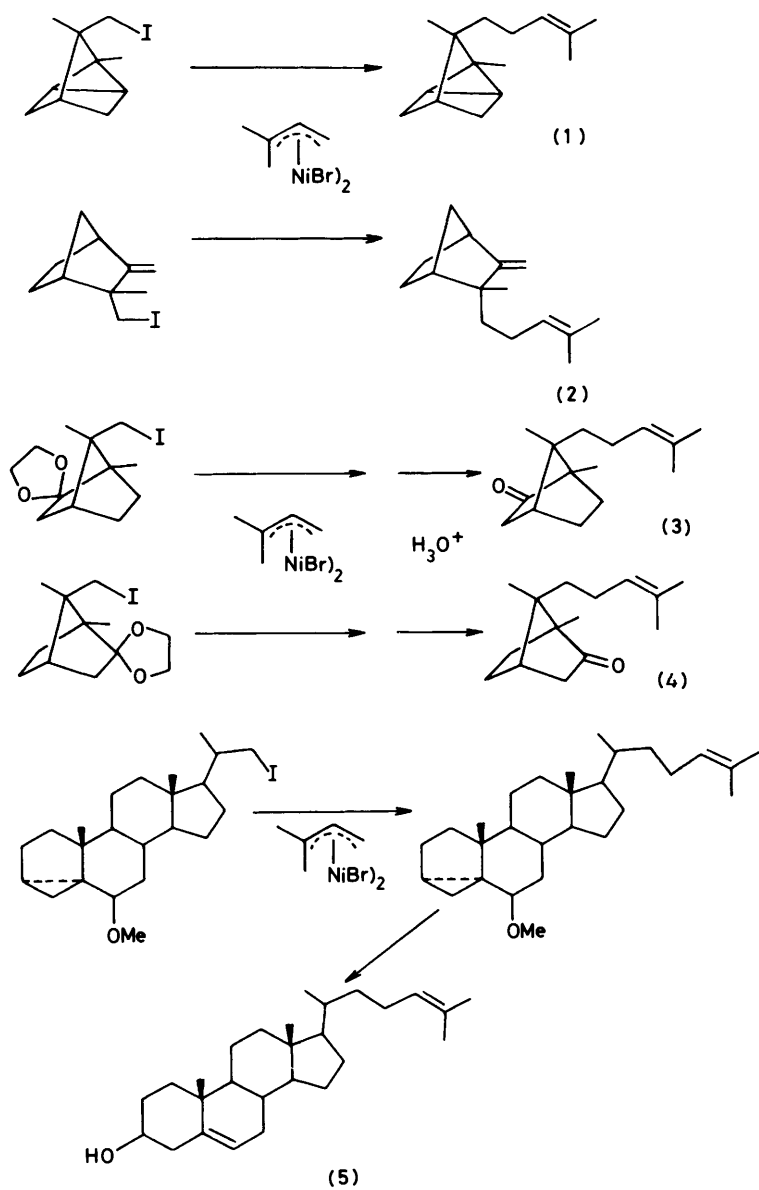
Scheme 11

**A. Reactions with Alkyl and Aryl Halides.**—The 1,1-dimethylallyl complex has been used to introduce a five-carbon unit into natural-product skeletons. Examples of syntheses with this complex include the preparation of  $\alpha$ -santalene (1) and *epi*- $\beta$ -santalene (2),<sup>19</sup> campherone (3) and *epi*-campherone (4) (in optically active forms by using single enantiomers of the alkyl iodides),<sup>30</sup> and desmosterol,<sup>31</sup> (5) Scheme 12. It is noteworthy that a more traditional approach to  $\alpha$ -santalene *via* the Grignard reagent gave only low yields, compared to excellent yields achieved using the nickel complex.<sup>32</sup>

<sup>30</sup> G. L. Hodgson, D. F. MacSweeney, R. W. Mills, and T. Money, *J. Chem. Soc., Chem. Commun.*, 1973, 235.

<sup>31</sup> S. K. Dasgupta, D. R. Crump, and M. Gut, *J. Org. Chem.*, 1974, **39**, 1658.

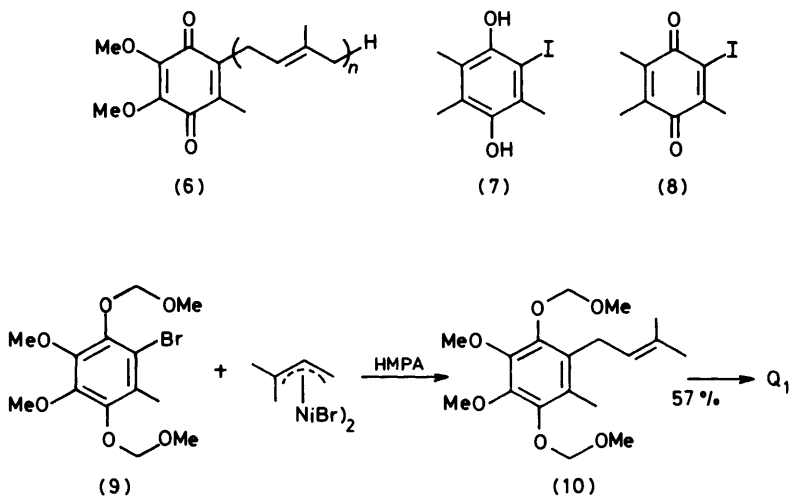
<sup>32</sup> E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Am. Chem. Soc.*, 1956, **79**, 5773.



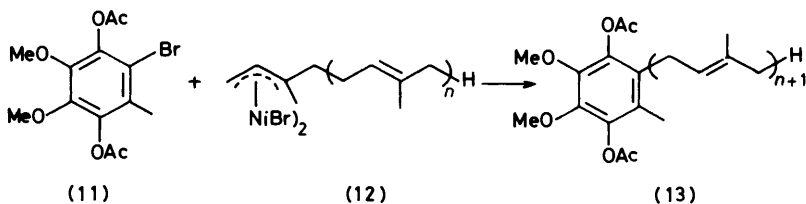
Scheme 12

The preparation of  $\pi$ -methallylnickel bromide and its reaction with bromobenzene in *N,N*-dimethylformamide, giving methallylbenzene in 67–72% yield, has been described in an *Organic Syntheses* preparation.<sup>6</sup>

The series of compounds known as coenzyme  $Q_n$ s (6) where  $n = 1-10$  [ubiquinones (6)] play an important role in electron transport and oxidative phosphorylation processes. In an early study, Sato, *et al.*<sup>25</sup> investigated the synthesis of coenzyme  $Q_1$  via the  $\pi$ -1,1-dimethallylnickel bromide complex. In model studies both iodobenzene and iodophenol gave the expected products, but iodotrimethylhydroquinone (7) and iodotrimethylbenzoquinone (8) both failed to give allylated products. These results indicated that although a hydroxyl (phenol) function was tolerated in the substrate, easily oxidized or reduced groups required protection. The synthesis of coenzyme  $Q_1$  was then achieved by reaction of the protected aryl bromide (9) with the  $\pi$ -1,1-dimethallyl complex, giving the allylated



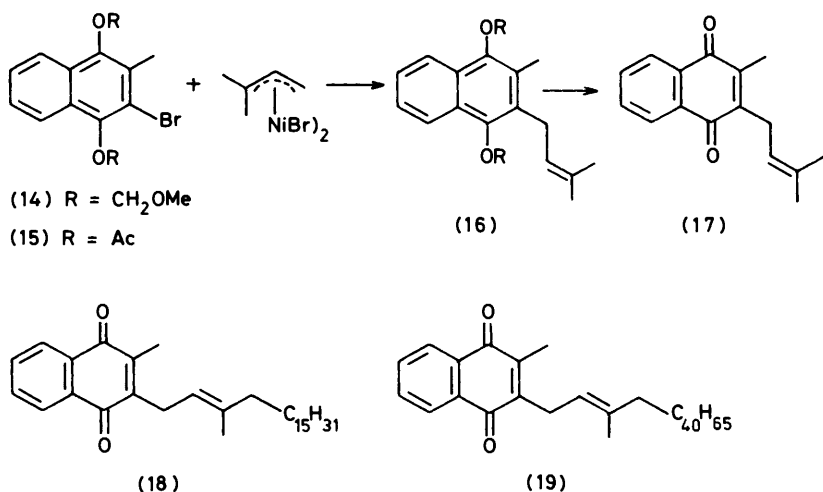
Scheme 13



Scheme 14

product (10) in 57% yield, followed by hydrolysis and oxidation, Scheme 13. A similar approach was used to prepare a series of coenzyme Qs from the bromoacetate (11) and substituted complexes (12).<sup>33</sup> Thus, reaction of (11) with  $\pi$ -geranyl nickel bromide (12;  $n = 1$ ) gave (13;  $n = 1$ ) in 88% yield, which was converted into coenzyme Q<sub>2</sub>, Scheme 14. Similarly, (11) reacted with  $\pi$ -phytyl,  $\pi$ -sodaneryl, and  $\pi$ -decaprenyl nickel bromide (12;  $n = 3, 8, 9$ ) to give (13;  $n = 3, n = 8$ , and  $n = 9$ ) in 45, 42, and 40% yields respectively. These (13)s were then converted into coenzymes Q<sub>4</sub>, Q<sub>9</sub>, and Q<sub>10</sub> by reduction and oxidation. The use of hexamethylphosphoramide as solvent for these reactions gave the highest chemical yields, but poor stereoselectivity for the newly formed C–C double bond (*ca.* 55:45 *E* to *Z* in each case). Less-polar solvents such as *N*-methylpyrrolidone gave somewhat lower overall yields generally, but higher stereoselectivity, with *E*:*Z* ratios of up to 70:30 being obtained.<sup>33</sup>

The above strategy has also been applied to the synthesis of vitamins K<sub>1</sub> and K<sub>2(5)}</sub> (17) by deprotection and oxidation, Scheme 15.<sup>29</sup> Thus, vitamins K<sub>1</sub> (18) and K<sub>2(4,5)}</sub> (19) were prepared from the requisite  $\pi$ -allyl nickel complexes and the acetate (15), with coupling proceeding in 52 and 70% yields, respectively. A solvent effect was again reported in these reactions, with less-polar solvents giving lower yields but higher stereoselectivity than highly polar solvents (the best *E*:*Z* ratio achieved was 80:20).<sup>29</sup>

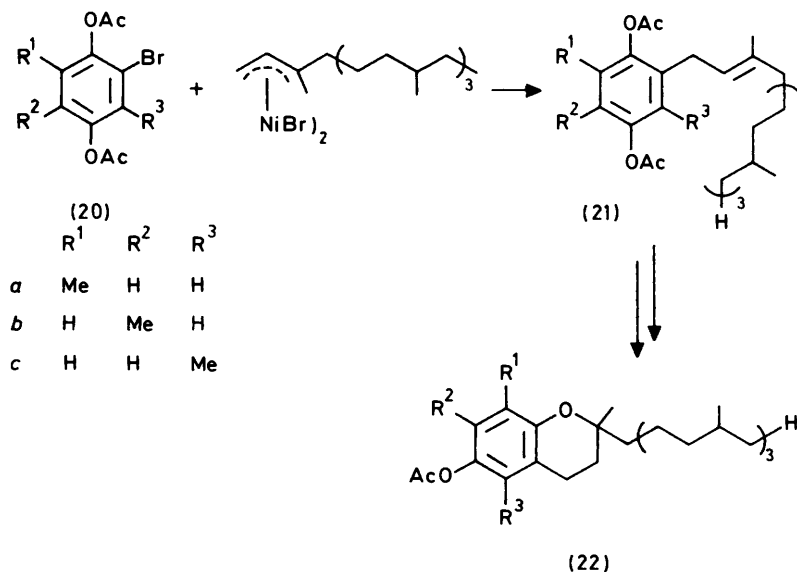


Scheme 15

The three isomeric monomethyltocols (22*a*–22*c*) have been prepared *via* the olefinic precursors (21*a*–21*c*). These olefins are conveniently obtained by reaction

<sup>33</sup> S. Inoue, R. Yamaguchi, K. Saito, and K. Sato, *Bull. Chem. Soc. Jpn.*, 1974, 47, 3098.

of the corresponding diacetoxybromotoluenes (20a—20c) with the  $\pi$ -phytylnickel bromide complex in hexamethylphosphoramide, giving the allylated products (21a—21c) in yields of between 52 and 93%, Scheme 16.<sup>34</sup>



**Scheme 16**

A series of isocoumarins and dihydroisocoumarins have been prepared by cyclization of the products obtained from the reaction of  $\pi$ -allylnickel halides with bromo-benzoic acids, present as either their sodium salts or methyl esters.<sup>35</sup> Some of these results are summarized in Scheme 17. Yields for the allylation reaction in these cases varied from 59 to 91%.<sup>35</sup>

**B. Reactions with Allylic Halides: Intermolecular Reactions.**—A very early report by Webb *et al.* established that allylic halides could be coupled to give 1,5-dienes by using  $\text{Ni}(\text{CO})_4$  as a reagent.<sup>36</sup> This approach to the synthesis of 1,5-dienes is very attractive for the synthesis of terpenoid compounds, by sequential addition of isoprenoid units. For example, the reaction, of  $\pi$ -1,1-dimethallylnickel bromide with the allylic halide shown in Scheme 18(a), gives the geranyl skeleton.<sup>26</sup>

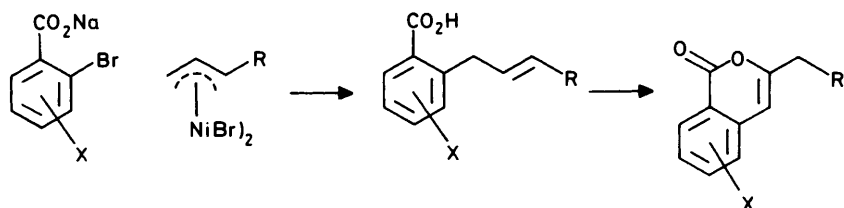
Unfortunately this approach is complicated by the fact that the  $\pi$ -allylnickel halide complex can undergo ligand exchange with the substrate allylic halide,<sup>37</sup>

<sup>34</sup> S. Inoue, K. Saito, K. Kato, S. Nozaki, and K. Sato, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2097.

<sup>35</sup> D. E. Korte, L. S. Hegedus, and R. K. Wirth, *J. Org. Chem.*, 1977, **42**, 1329.

<sup>36</sup> I. D. Webb and G. T. Borchardt, *J. Am. Chem. Soc.*, 1951, **73**, 2654.

<sup>37</sup> K. Sato, S. Inoue, and S. Morii, *Chem. Lett.*, 1975, 747.



X = R = H

X = H ; R = Me

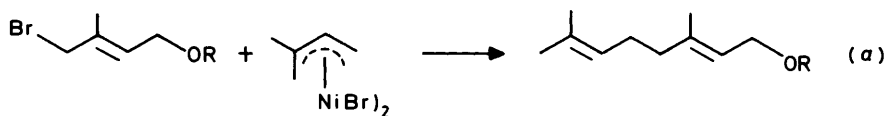
X = H ; R = (Me)<sub>2</sub>

X = 4 - Cl ; R = H

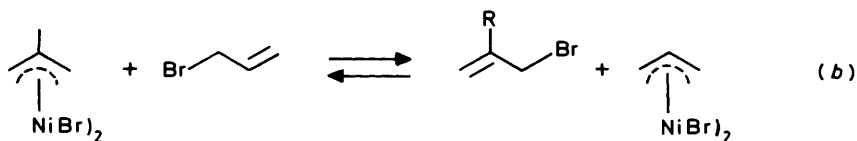
X = 4 - Cl ; R = Me

X = 5 - OMe ; R = H

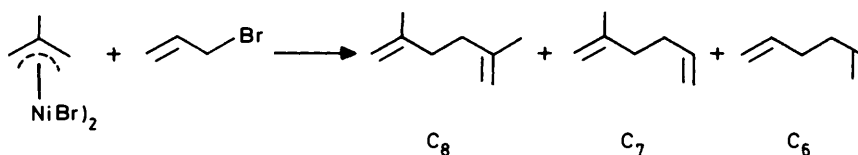
Scheme 17



but



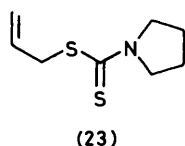
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Scheme 18

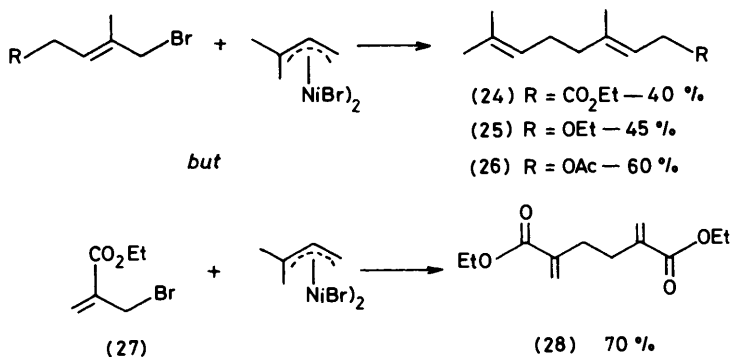
giving a new  $\pi$ -allylnickel complex, and the allylic halide corresponding to the original  $\pi$ -allylnickel complex. Thus, in solution a mixture of two allylic halides and two  $\pi$ -allylnickel halides will be present, the relative concentrations of each being dependent on the rate of ligand exchange of the complexes, and their rate of reaction with the allylic halides present to give 1,5-dienes. In simple cases, this

situation usually results in production of all possible 1,5-diene products in an approximately statistical distribution, and this is illustrated in Scheme 18(b).<sup>1</sup> Thus in the case illustrated all three coupling products are obtained, the desired crosscoupled product and the two unwanted symmetrical products, in the ratio 25:52:23; C<sub>6</sub>:C<sub>7</sub>:C<sub>8</sub>.<sup>18</sup> The ratio of these products is not significantly altered by changes in solvent, changes in ligand (iodine, chlorine, triphenylphosphine, or acetylacetonate in place of bromine in the complex), or changes in the leaving group of the allylic substrate (allyl chloride, bromide, iodide, *p*-toluenesulphonate and *N,N*-dimethylsulphamate all give the same product ratio). The only case in which a significant effect was observed was the reaction between the allyl pyrrolidine dithiocarbamate (23) and  $\pi$ -2-methallylnickel bromide which gave the crosscoupled product in 65% yield, accompanied by only 5% of the symmetrical coupling products.<sup>8</sup>



Despite the above apparent drawback, this method has found application in terpene synthesis due to the fact that certain substituted complexes only undergo slow ligand-exchange and thus give good yields of the desired crosscoupled products.

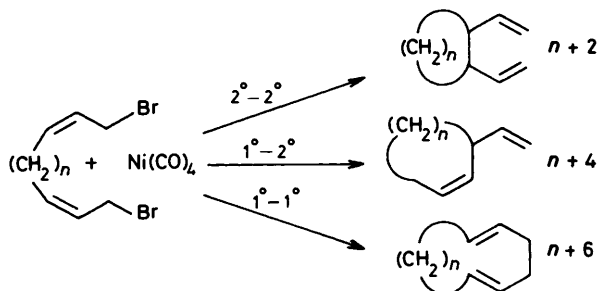
$\pi$ -1,1-Dimethallylnickel bromide reacts with the allylic bromo-ethers and esters shown to give geranyl derivatives [(24), (25), and (26)] in moderate yields,<sup>26</sup> with only small quantities of the symmetrical coupling products, Scheme 19. Some double bond isomerization (*E*  $\rightarrow$  *Z*) was observed in these reactions (between 5 and 30% of the *Z* compounds were isolated, starting from the *E* bromo-substrates). In contrast to these results, the reaction of (27) with the nickel reagent was reported to give (28) (the product of a symmetrical coupling) in 70% yield. Presumably in this



Scheme 19







Scheme 22

Table 1 Ring closures with  $\text{Ni}(\text{CO})_4$  in DMF; cf. Scheme 22

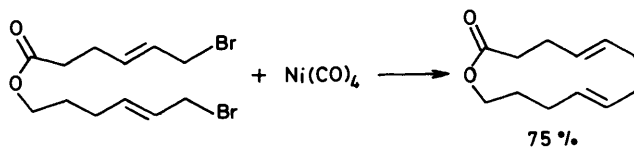
Value of $n$	Possible ring-size of product	Observed ring-size of product	% Yield
2	4/6/8	6	42
4	6/8/10	6	?
6	8/10/12	12	59
8	10/12/14	14	74
12	14/16/18	18	84

**B. Reactions with Allylic Halides; Intramolecular Reactions.**—Two allylic halide groups in the same molecule may, under suitable conditions (high dilution to discourage intermolecular reactions), undergo intramolecular coupling, leading to a cyclic product. As each allyl group may react at either of two positions, three possible cyclic products may be formed, with ring sizes of  $n+2$ ,  $n+4$ , or  $n+6$  in the example shown, Scheme 22.

In the simple example shown this corresponds to  $2^\circ-2^\circ$ ,  $1^\circ-2^\circ$ , and  $1^\circ-1^\circ$  reaction respectively. The degree to which each product is obtained for a given value of  $n$  depends on normal ring-closure effects, combined with the preference exhibited by  $\pi$ -allylnickel halide complexes to react at their  $1^\circ$  centres. The accepted normal rates of ring-closure reactions are  $3 < 4 < 5 > 6 > 7 > 8 < 9 < 10 < 11 < 12$  etc. up to 18. The results of the treatment of a series of bis-allylic bromides with  $\text{Ni}(\text{CO})_4$  in *N,N*-dimethylformamide are presented in Table 1.<sup>38</sup> From the results in Table 1 it can be seen that for  $n = 6, 8$ , and  $12$  the ring size which is obtained is dictated by the reaction of the two  $1^\circ$  centres, giving the largest ring in each case. For  $n = 2$  or  $4$ , however the preference for 6-membered ring formation overcomes this  $1^\circ-1^\circ$  effect and we see the 6-membered products from  $1^\circ-2^\circ$  and  $2^\circ-2^\circ$  closure only. The high yields for the larger ring sizes (12 and above) coupled with the observation that regardless of the geometry of the substrate double bonds, the products are over 95% *E,E* isomers, makes this approach attractive for large rings.

The stability of esters to the nickel reagents has allowed the extension of this

<sup>38</sup> E. J. Corey and E. K. W. Wat, *J. Am. Chem. Soc.*, 1967, **89**, 2757.

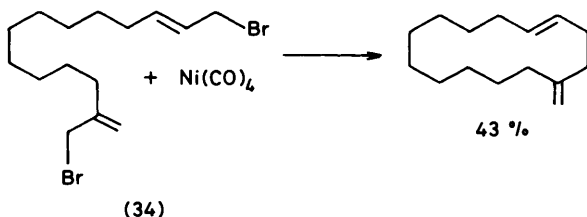


Scheme 23

general approach to the synthesis of macrocyclic lactones Scheme 23.<sup>39</sup> Again reaction only occurs at the 1° centres giving a 13-membered ring, rather than a 9- or 11-membered ring.

Somewhat different results are obtained when the newly formed double bonds are exocyclic rather than endocyclic.<sup>40</sup> Scheme 24 shows the results of studies in this area, and it is clear that the method is of no value for 12-membered rings with exocyclic double bonds.

	Value of <i>n</i>	Possible ring size	Observed ring size	% Yield
	6	8/10/12		Zero
	8	10/12/14	14	37 %
	10	12/14/16	16	81 %
	14	16/18/20	20	40 %



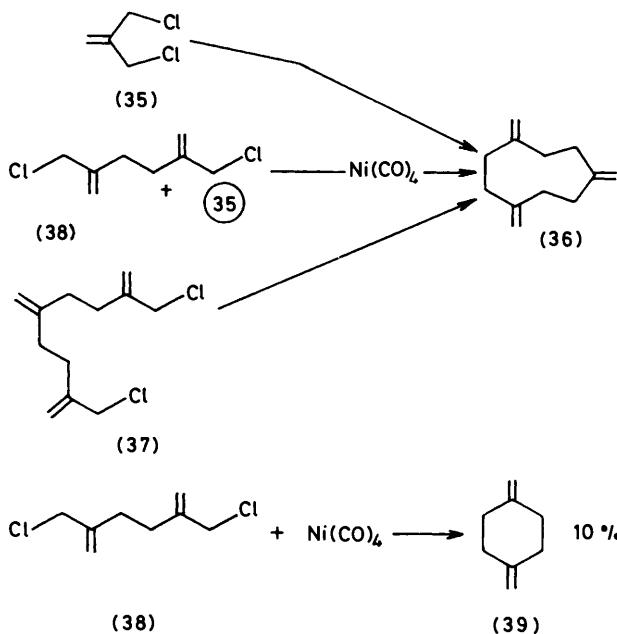
Scheme 24

An example with one endocyclic and one exocyclic double bond (34) gives a result between the two extremes, reacting only at the 1° centre of the 1°/2° allyl unit.

Related to these results is the interesting trimerization of (35) to give (36), Scheme 25.<sup>8</sup> In an elegant study, Corey *et al.* showed that (35), (37), and (38) + (35) all give (36) on treatment with Ni(CO)<sub>4</sub>.<sup>8</sup> This behaviour is very interesting as (38) preferentially undergoes intermolecular reaction with (35) followed by ring closure to the 9-membered ring, rather than intramolecular reaction to give the 6-

<sup>39</sup> E. J. Corey and H. A. Kirst, *J. Am. Chem. Soc.*, 1972, **94**, 667.

<sup>40</sup> E. J. Corey and P. Helquist, *Tetrahedron Lett.*, 1975, 4091.



Scheme 25

membered product. Indeed treatment of (38) with excess  $\text{Ni(CO)}_4$  yields only 10% of the intramolecular product and a series of polymers. Altering the nickel species to  $\text{Ni(CO)}_3\text{P(Ph)}_3$  raises the yield of the intramolecular cyclization of (38) to 60%. In the trimerization reaction, the same effect is observed as only minor amounts of (39) can be detected.

The above results have led to the application of these methods to natural-product synthesis.

Humulene (40) has been synthesized *via* its geometric isomer (41) obtained from  $\text{Ni(CO)}_4$  coupling of the bis-allylic bromide shown Scheme 26.<sup>41,42</sup> Three other products were reported in the coupling reaction, but not identified.

Two 14-membered carbocyclic natural products have been synthesized using this methodology, cembrene (42)<sup>43,44</sup> and casbene (43),<sup>45,46</sup> Scheme 27. In the cembrene synthesis a low yield of the cyclic coupled product was ascribed to

<sup>41</sup> E. J. Corey and E. Hamanaka, *J. Am. Chem. Soc.*, 1967, **89**, 2758.

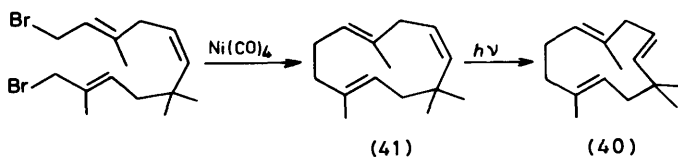
<sup>42</sup> E. J. Corey and E. Hamanaka, *J. Am. Chem. Soc.*, 1964, **86**, 1641.

<sup>43</sup> W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle, and C. Suter, *J. Am. Chem. Soc.*, 1974, **96**, 4724.

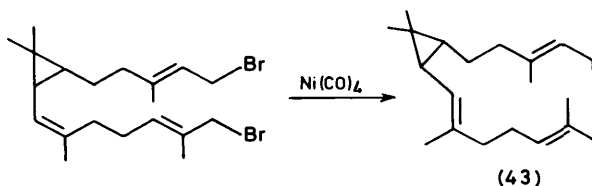
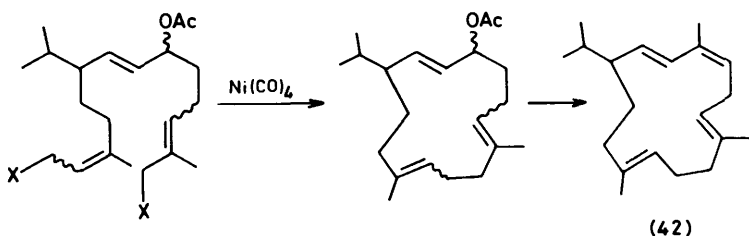
<sup>44</sup> W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle, and C. Suter, *J. Am. Chem. Soc.*, 1975, **97**, 4973.

<sup>45</sup> L. Crombie, G. Kneen, and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 1976, 66.

<sup>46</sup> L. Crombie, G. Kneen, G. Pattenden, and D. Whybrow, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1711.



Scheme 26



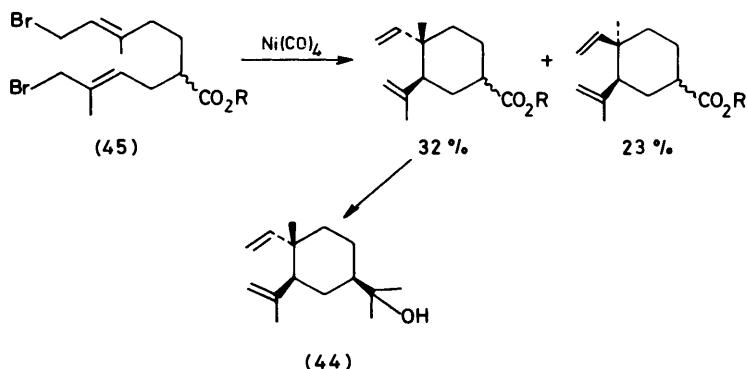
Scheme 27

interference of the allylic acetate function. In neither case was the coupling reaction as efficient as has been reported for simple bis-allylic substrates giving 14-membered rings.<sup>38</sup> Thus, in the synthesis of casbene, three isomeric products were obtained from the coupling reaction, in the ratio of 65:29:6, and a total yield of only 10%. Natural casbene was identified as the major component of this mixture.

The preference for 6-membered ring formation in the reaction of bis-allylic bromides with  $\text{Ni}(\text{CO})_4$  has been exploited in a synthesis of elemol (44),<sup>47</sup> Scheme 28. Treatment of the bis-allylic bromide (45) with  $\text{Ni}(\text{CO})_4$  in *N*-methylpyrrolidone gave the 6-membered ring products in 55% yield (a mixture of *cis* and *trans* divinylcyclohexanes formed by  $2^\circ-2^\circ$  coupling of the allyls) accompanied by 11% of the 10-membered ring product, formed by  $1^\circ-1^\circ$  coupling.

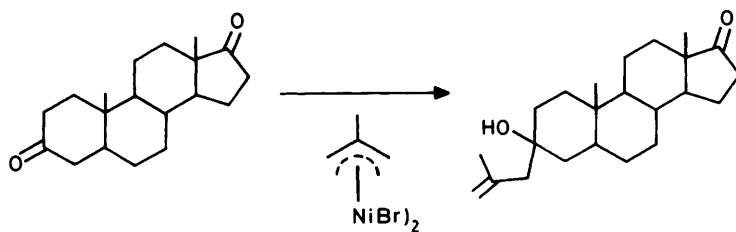
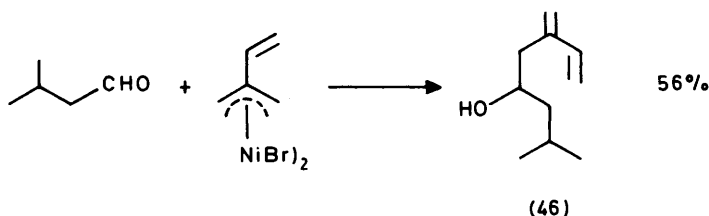
**C. Reactions with Carbonyl Groups.**—The reaction of a  $\pi$ -allylnickel halide with a carbonyl group produces a homoallylic alkoxide, which may either be stable, and lead to isolation of a homoallylic alcohol as product, or may undergo further reactions. The complexes react with 1,2-diketones, ketones, and aldehydes to give

<sup>47</sup> E. J. Corey and E. A. Broger, *Tetrahedron Lett.*, 1969, 1779.



**Scheme 28**

the expected homoallylic alcohols as products, and some examples are given in Schemes 6 and 7.<sup>20</sup> This reaction has not been widely used in synthesis, although tagetol (46) has been prepared in this way Scheme 29.<sup>13</sup> With 1,2-diketones, only one addition occurs, even in the presence of a large excess of nickel reagent, and  $\alpha,\beta$ -unsaturated ketones give only 1,2-addition products, even in the presence of added CuI (see Scheme 7).<sup>20</sup> The complexes also display a very interesting reactivity profile towards carbonyl groups. Thus, 1,2-diketones are the most reactive substrates, whilst cyclic ketones are less reactive, and both simple ketones and  $\alpha,\beta$ -

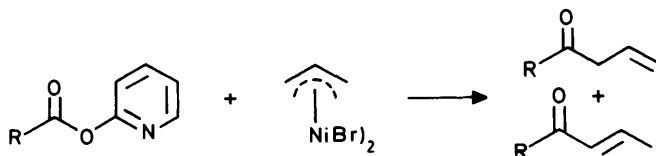


**Scheme 29**

unsaturated ketones are less reactive still. Aryl ketones are more reactive than their alkyl counterparts, and both esters and acid chlorides fail to react with the reagents.

The above reactivity pattern is in direct contrast to the allyl-lithium, zinc, and magnesium reagents, which normally attack both carbonyls in 1,2-disubstituted ketones, are highly reactive towards aliphatic and  $\alpha,\beta$ -unsaturated ketones, and may add in a 1,4 manner to the latter substrates under suitable conditions. Also in contrast to the other reagents, the nickel complexes are able to discriminate between similar ketones in a substrate, see Schemes 29 and 34.

2-Pyridyl carboxylates react with  $\pi$ -allylnickel halides, to give  $\beta,\gamma$  unsaturated ketones in good yields.<sup>22</sup> The presence of other functional groups in the substrate including esters, ketones, and even 1° alkyl bromides does not seem to affect the course of the reaction, indicating that 2-pyridyl carboxylates are very reactive electrophiles in this reaction. The products are mixtures of  $\beta,\gamma$  and  $\alpha,\beta$  unsaturated ketones in which the  $\beta,\gamma$ -isomers predominate. Some examples of these reactions are given in Scheme 30.<sup>22</sup>



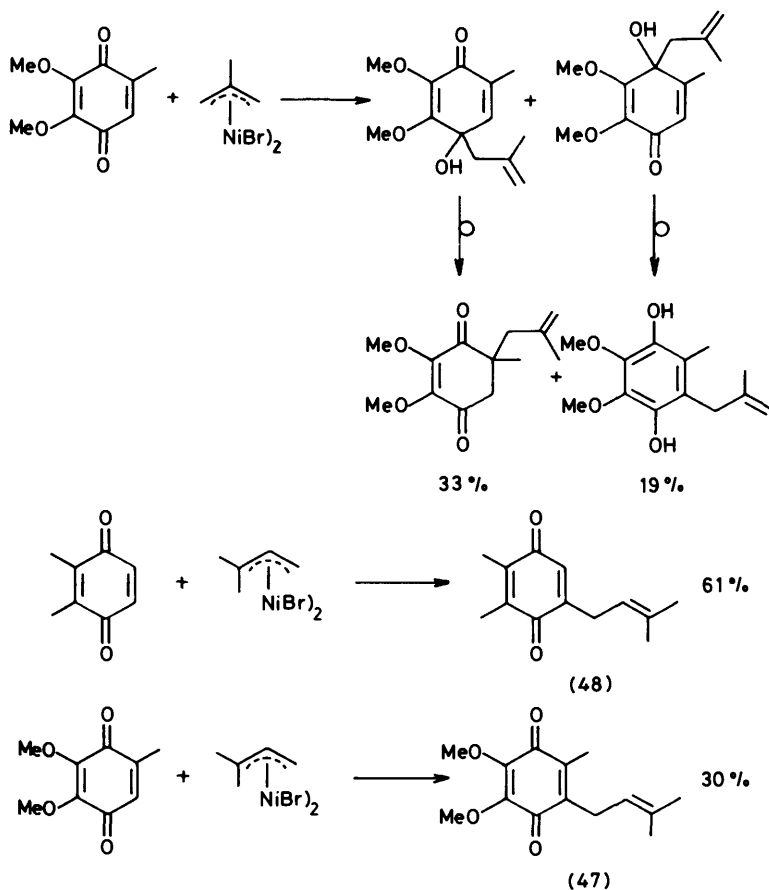
R	Yield %	Ratio $\beta,\gamma:\alpha,\beta$
Ph	92%	74 : 26
Ph(CH <sub>2</sub> ) <sub>3</sub>	72%	85 : 15
Br(CH <sub>2</sub> ) <sub>10</sub>	61%	88 : 12
MeCO(CH <sub>2</sub> ) <sub>4</sub>	57%	84 : 16
MeOCO(CH <sub>2</sub> ) <sub>3</sub>	71%	87 : 13

Scheme 30

$\pi$ -Allylnickel halides react with quinones to give substituted quinones or hydroquinones depending on the substrate and reaction conditions.<sup>21</sup> Electron-transfer processes have been implicated in these reactions,<sup>48</sup> and product analyses may be shown to correlate well with attachment of the allyl substituent to the site of the highest spin-density in the quinone radical anions. Recently the involvement of quinols has been demonstrated<sup>49</sup> and these quinols were shown to rearrange to the previously isolated substituted quinones/hydroquinones under the reaction conditions employed, Scheme 31. By suitable choice of conditions these

<sup>48</sup> L. S. Hegedus and E. L. Waterman, *J. Am. Chem. Soc.*, 1974, **96**, 6789.

<sup>49</sup> L. S. Hegedus and B. R. Evans, *J. Am. Chem. Soc.*, 1978, **100**, 3461.



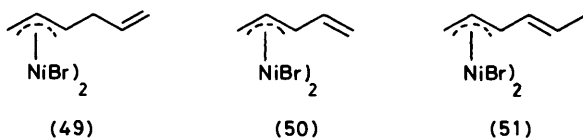
Scheme 31

observations have led to one-step syntheses of coenzyme  $Q_1$  (47) and plastoquinone-1 (48), Scheme 31.<sup>50</sup> A large body of experimental data is available in this area and the interested reader is directed to references 2, 21, 48, 49, and 50 for further examples.

**D. Reactions Involving Substituted Complexes.**—A number of substituted  $\pi$ -allylnickel complexes have been prepared and undergo reaction with substrates in the normal manner. Examples of substituted complexes which exhibit normal stability are given in Scheme 8, and examples of the use of substituted olefinic complexes,<sup>23,33</sup> and complexes containing protected hydroxyl functions<sup>28,37</sup>

<sup>50</sup> L. S. Hegedus, E. L. Waterman, and J. Catlin, *J. Am. Chem. Soc.*, 1972, **94**, 7155.

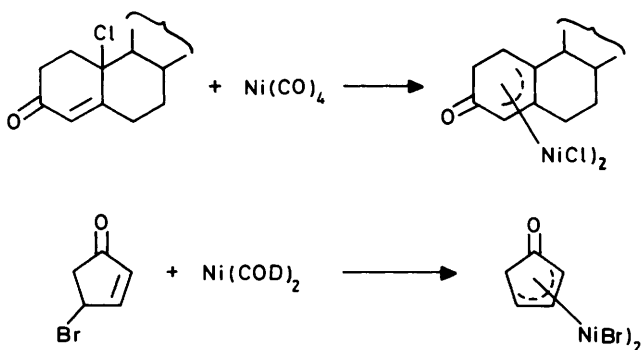




appear in Schemes 14 and 21 and Schemes 11 and 20 respectively.

In a study of substituted olefinic complexes,<sup>13</sup> the non-conjugated and cross-conjugated complexes (49) and (31) were found to be stable and reacted normally, whereas the conjugated complexes (50) and (51) were very unstable and could not be isolated. Complexes (50) and (51) could be generated and used *in situ*, but only the most reactive substrates (aryl iodides and vinyl or allyl bromides) reacted successfully due to ready thermal decomposition of the complexes. In agreement with the above results, the non-conjugated olefinic substituted complexes shown in Schemes 14 and 21 reacted normally.<sup>23,33</sup>

A single example of the formation of a  $\pi$ -allylnickel halide within an  $\alpha,\beta$ -unsaturated ketone has appeared in the literature,<sup>51</sup> although other examples are known,<sup>52</sup> Scheme 32.



Scheme 32

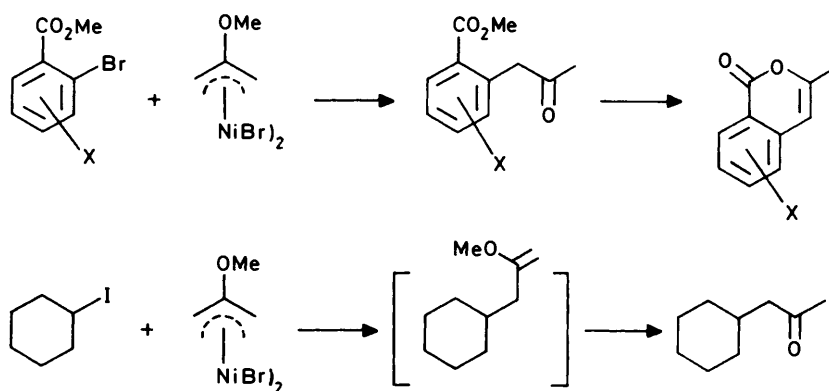
The  $\pi$ -(2-methoxy)allylnickel bromide complex has been shown to have potential as a reagent for the introduction of acetyl groups,<sup>53</sup> by ready hydrolysis of the initially formed enol ethers. This reaction has found application in the synthesis of isocoumarins,<sup>35</sup> and some examples are given in Scheme 33. The  $\pi$ -(2-methoxy)allyl complex exhibits normal stability characteristics, and will react with the usual range of substrates.<sup>53</sup>

Despite early reports of its instability,<sup>26</sup> the  $\pi$ -(2-carbethoxy)allylnickel bromide

<sup>51</sup> I. T. Harrison, E. Kimura, E. Bohme, and J. H. Fried, *Tetrahedron Lett.*, 1969, 1589.

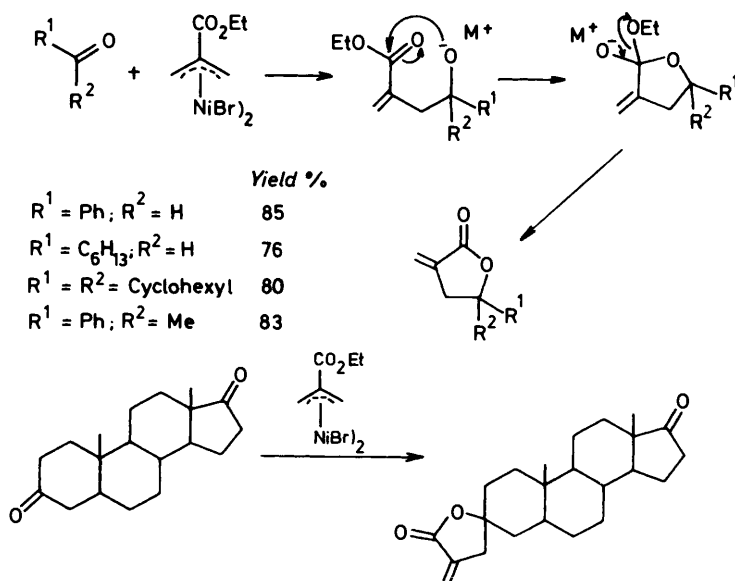
<sup>52</sup> R. Baker and D. C. Billington, unpublished results.

<sup>53</sup> L. S. Hegedus and R. K. Stiverson, *J. Am. Chem. Soc.*, 1974, **96**, 3250.



Scheme 33

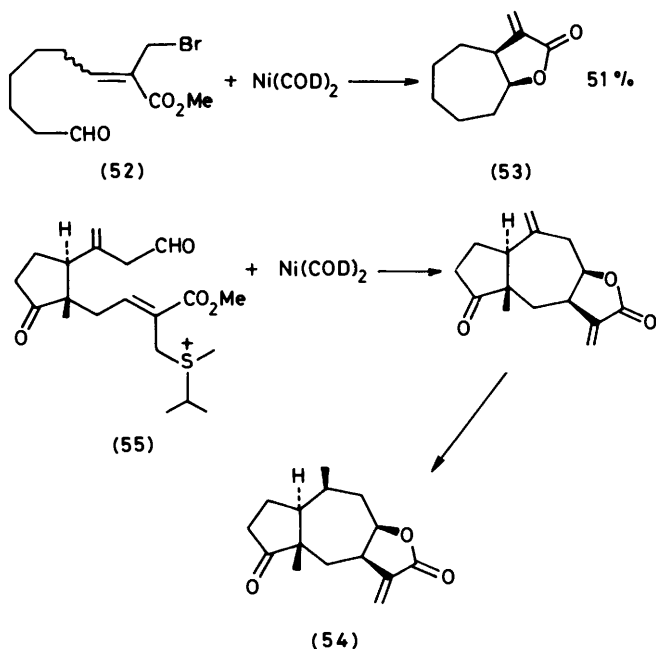
complex may be obtained from 2-carbethoxyallyl bromide and Ni(CO)<sub>4</sub>, and seems reasonably stable.<sup>20</sup> Reaction of this complex with aldehydes or ketones gives  $\alpha$ -methylene- $\gamma$ -butyrolactones, by addition of the initially formed nickel alkoxide to the ester carbonyl group, followed by elimination of EtO<sup>-</sup>, Scheme 34.<sup>20</sup> This complex has been shown to react with a range of aldehydes and ketones in this way,



Scheme 34

and in favourable cases discrimination between two ketones in the substrate is possible, as is the case for simple complexes, and examples are given in Scheme 34.

A logical extension of this reaction is intramolecular reaction between the complex and aldehyde, forming a cyclic system, followed by a second ring-closure giving an  $\alpha$ -methylene- $\gamma$ -butyrolactone fused to a second ring. This approach was proved valid by Semmelhack who cyclized the bromo-aldehyde (52), using  $\text{Ni}(\text{COD})_2$ , in good yield,<sup>54</sup> Scheme 35. Both *E* and *Z* allylic bromides gave only the *cis*-fused lactone (53) as product. This method was then extended to a total synthesis of the sesquiterpene confertin (54), by cyclization of the precursor (55).<sup>11</sup> Here the sulphonium salt acts as a leaving group in place of bromide for the formation of the  $\pi$ -allylnickel complex. Treatment of (55) with  $\text{Ni}(\text{COD})_2$  gave the desired *cis*-fused lactone, having the correct  $\beta$ -configuration for elaboration to natural confertin, in 28% yield (plus 14% of the *trans*-isomer). Cyclization of (55) using a  $\text{Zn}/\text{Cu}$  couple (*i.e.*  $\text{Zn}^0$ ), also gave a *cis*-fused lactone, in 30% yield, but this material had the  $\alpha$ -configuration, and thus could not be elaborated to confertin.

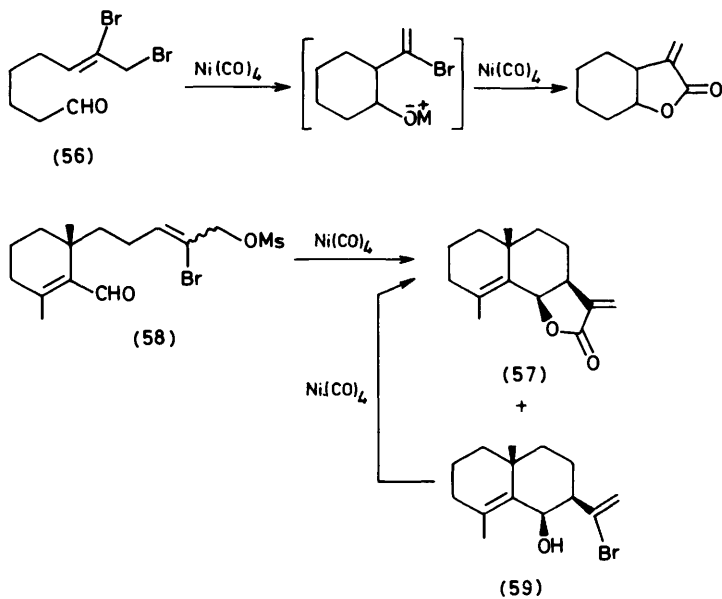


Scheme 35

In a related approach, 2-bromo-substituted complexes, derived from allylic bromides such as (56), were shown to undergo ring-closure followed by CO insertion in the presence of  $\text{Ni}(\text{CO})_4$ , giving  $\alpha$ -methylene- $\gamma$ -lactones.<sup>9</sup> This reaction has been used to prepare the sesquiterpene lactone frullanolide (57), by treatment of

<sup>54</sup> M. F. Semmelhack and E. C. S. Wu, *J. Am. Chem. Soc.*, 1976, **98**, 3384.

the bromo-aldehyde (58) with  $\text{Ni}(\text{CO})_4$ ,<sup>9</sup> Scheme 36. Treatment of either *E*-(58), or *Z*-(58) with  $\text{Ni}(\text{CO})_4$  gave a mixture of frullanolide (57), and the intermediate alcohol (59). Attempts to induce this reaction to go to completion failed, and the most efficient procedure is a two-step process, involving treatment of the mixture of (57) and (59) obtained in the coupling reaction with  $\text{Ni}(\text{CO})_4$  and triethylamine in benzene, which results in transformation of (59) into (57). This protocol gives frullanolide (57) in 40% yield from *E*-(58) and 31% yield from *Z*-(58).



**Scheme 36**