JOM 23338

Short Review

The [Ni(CO)$_4$]-promoted carbonylative cycloaddition of alkynes and allyl halides for the synthesis of 2-cyclopentenone derivatives *

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(Received October 2, 1992)

Abstract

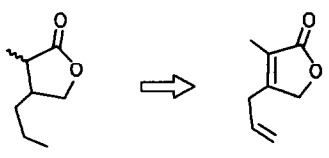
The [Ni(CO)$_4$]-mediated carbonylative cycloaddition of alkynes and allyl halides first reported by Chiusoli, has been reviewed, extended and optimized for application to cyclopentenone synthesis. An insight into the reaction mechanism is also given to explain the results obtained, in particular the regio- and stereo-chemistry of the process.

1. A fortunate encounter

Our first contact with Chiusoli's chemistry and more precisely with his [Ni(CO)$_4$]-mediated carbonylative cycloaddition of allyl halides and alkynes came quite by chance in the early eighties when, according to the name of our Department, we were fully involved in natural product chemistry. At that time, several structures of products isolated from *Ajuga* species with the properties of insect antifeedants were being elucidated [1]. Models were required to establish by NMR spectroscopy, the relative stereochemistry of the C-3 and C-4 substituents in an α-methyl-γ-butyrolactone ring in many of the mentioned products (Scheme 1). We envisaged that compound **2** might be a suitable precursor for the two different diastereomeric arrangements of **1**.

After several unsuccessful attempts to prepare **2** starting from allyl bromide and 2-butynol [2], we applied other butenolide syntheses to the reagents we had in hand. We found one reported by Chiusoli *et al.* using an alkynol and an allyl halide, where cyclization was accomplished in one step, the lactone carbonyl group being incorporated using [Ni(CO)$_4$] [3]. A requirement, difficult to assess at that time, would allow us to obtain the target compound: the regiochemistry of the reaction was to be as depicted in Scheme 2 (path a). Isomerization to the *cis* geometry enabling ring closure was predicted to be easy on thermodynamic grounds, specially, in the presence of Ni species.

After performing the reaction we were surprised to find that a mixture of two regioisomeric cyclopentenones **4** and **5** had been formed instead of the desired lactone. Certainly, cyclopentenones were already reported to arise from this reaction, sometimes as major products, but rarely reaching the 60% yield obtained for this particular alkyne. Considering these results, the practically simultaneous formation of four C–C bonds, and the high regiocontrol displayed for a disubstituted alkyne, we endeavoured to find all the factors influencing the outcome of this reaction for further synthetic applications. The mild reaction conditions and use of a common solvent were further advantages that outweighted the hazardous use of nickel carbonyl.



1 2

Scheme 1.

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* Dedicated to Professor G.P. Chiusoli, who rewarded us with his friendship, for his great contribution to the growth of organometallic chemistry.

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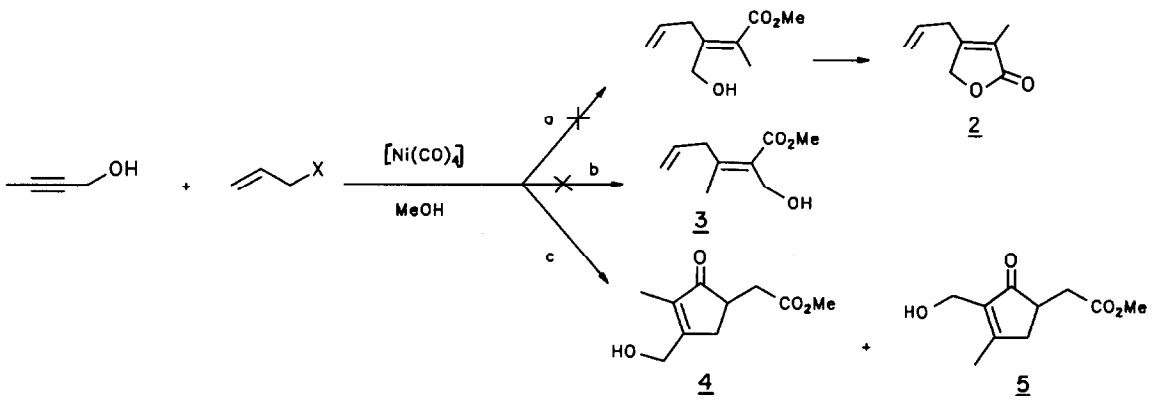


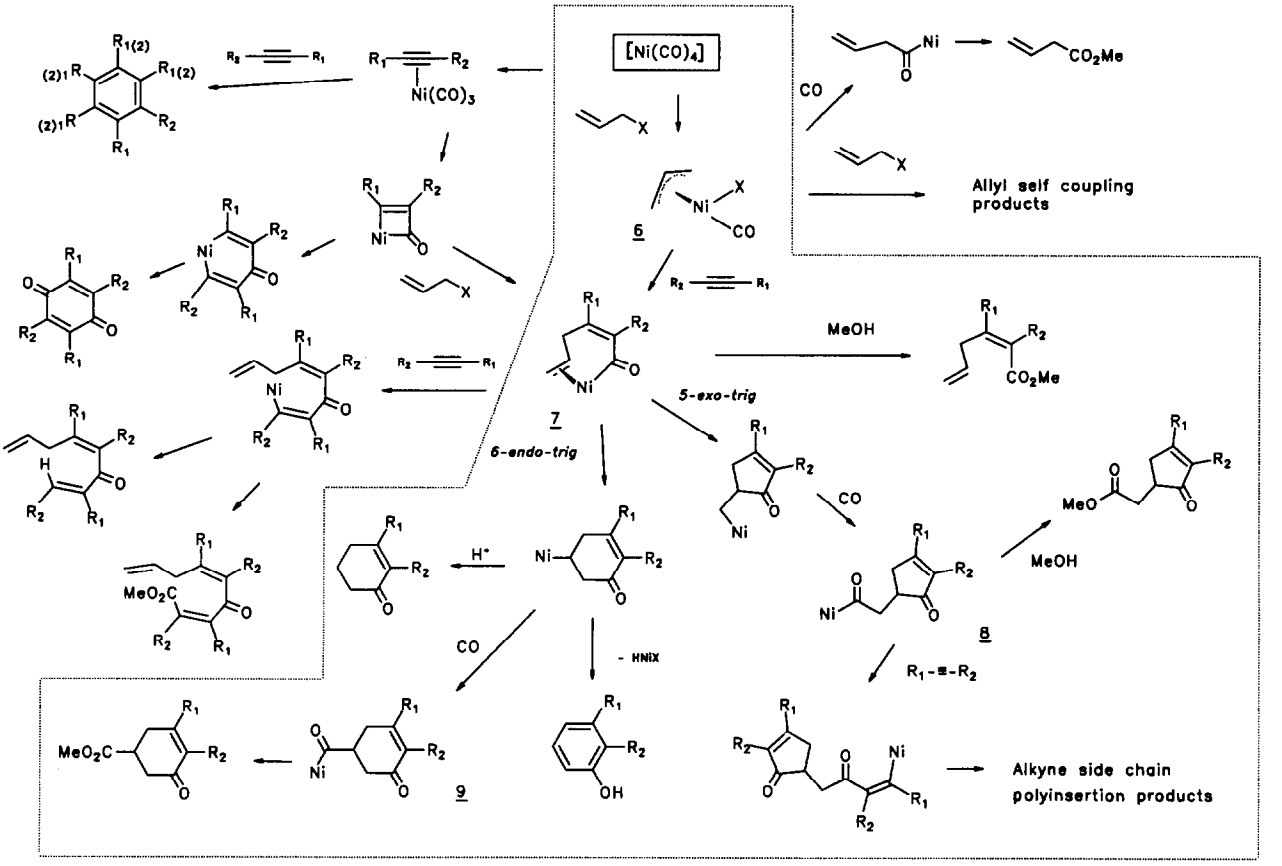
Scheme 2.

For the last eight years we have been studying different aspects of this process and the more outstanding results are summarized here.

2. The alkyne, more than a C_2 synthon

At the time we started our studies, the complexity of this reaction had been recognized from the variety of products that could be obtained from different reagents and the subtle variation of the reaction conditions. In fact, both allyl halides and alkynes react separately with $[Ni(CO)_4]$ (even methoxide does it to some extent). Therefore, many concurrent side reactions in the process contribute to product complexity. Scheme 3 depicts the different pathways that may be taken by the reaction.

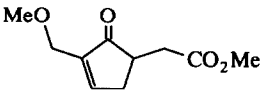
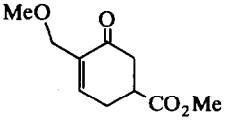
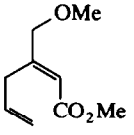
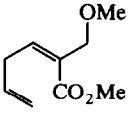
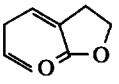
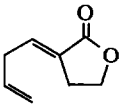
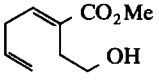
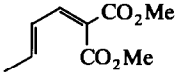
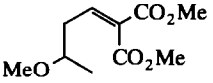
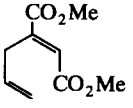
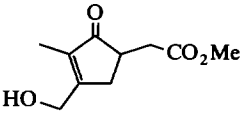
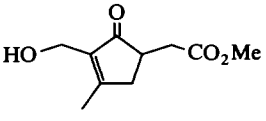
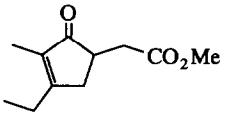
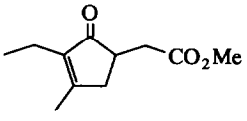
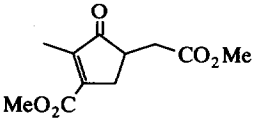
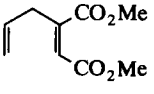
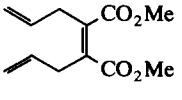
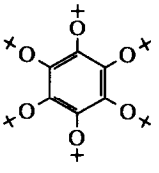
As a starting point we decided to analyze the effect of acetylene substitution. Methanol was soon found to



Scheme 3. Reaction pathways of $[Ni(CO)_4]$, acetylenes and allyl halides. Within dotted area the processes refer to the present work.

be the preferred solvent of choice. The more significant results are given in Table 1 [4]. Monosubstituted acetylenes gave mainly linear carbonylated adducts. However, from the general low yield of isolated products, the complex nature of the crude product (TLC and NMR spectroscopy) and the absence of the starting alkyne, it was deduced that polyinsertion of the acetylene could have been important [5]. Alkyne

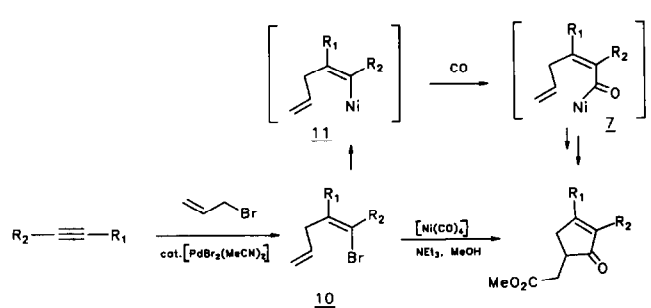
TABLE 1. Reaction of acetylenes, allyl chloride and $[Ni(CO)_4]$ in methanol

Entry	Alkyne	Products (isolated yield %)			
1	H-C≡C-CH_2OMe	 (9)	 (7)	 (7)	 (20)
2	H-C≡C-CH_2CH_2OH	 (11)	 (65)	 (8)	
3	H-C≡C-CO_2Me	 (19)	 (12)	 (11)	
4	Me-C≡C-CH_2OH	 (10)	 (46)		
5	Me-C≡C-Et	 (6)	 (6)		
6	Me-C≡C-CO_2Me	 (90)			
7	MeO_2C-C≡C-CO_2Me	 (42)	 (32)		
8	^{t}BuO-C≡C-O^{t}Bu	 (60)			

polyinsertion often prevents a good yield of specific adducts, in particular for monosubstituted alkynes, and is only absent when a suitable functional group such as hydroxyl is at an ideal position for an intramolecular termination (entry 2 of Table 1). We therefore developed an alternative method aimed at circumventing the simultaneous presence of alkyne and acyl-Ni intermediates, by performing the allyl addition to the triple bond separately from the subsequent reaction steps (see below).

A surprising feature is the high regioselectivity found in the insertion of the allyl and carbonyl into the triple bond. This regioselectivity was also found with disubstituted alkynes. For these, no alkyne polyinsertion was generally recorded and cyclopentenone adducts were the main products. In cases of low yield, most of the alkyne was recovered unchanged, suggesting a lower reactivity of the alkyne. A correlation between the ^{13}C NMR chemical shift of both acetylenic carbon atoms and the regioselectivity in alkyne–allyl insertion suggested that the carbonylation occurs at the more electrophilic end of the triple bond while the allyl moiety inserts at its negative counterpart, provided steric effects are not important. In almost all cases allyl insertion into the alkyne entailed concurrent carbonylation. However, two limiting cases showed exceptional results: while the very electron-rich di-t-butoxyacetylene readily underwent cyclotrimerization, the electron-poor dimethyl acetylenedicarboxylate was reluctant to carbonylate. Clearly, the electronic characteristics of the triple bond seem to be of the utmost importance in the present process.

As mentioned, the simultaneous presence of any free monosubstituted alkyne and acyl-Ni intermediates **8** or **9** was detrimental for formation of a discrete cyclopentenone due to further alkyne insertion. However, we succeeded in performing the allyl insertion separately by means of the catalytic presence of PdII leading to the intermediate bromodiene **10** and then we accomplished the remaining steps with a new $[Ni(CO)_4]$-based system [6] (Scheme 4). The regioselectivity was in the same sense and even more strict than that of the conventional reaction, allowing the corresponding cyclopentenones to be obtained in moderate-to-good yields (Table 2).



Scheme 4.

TABLE 2. Cyclopentenone synthesis by the two-step procedure.

R_1	R_2	Bromodiene yield (%)	Cyclopentenone yield (%)
Et	Et	93	80
Me	Me	67	95
H	Ph	87	43
H	$SiMe_3$	89	65
H	n-Pentyl	87	49
COOMe	H	88	27
H	$C(Me)_2OH$	98	70
H	CH_2OMe	72	92

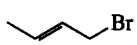
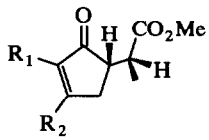
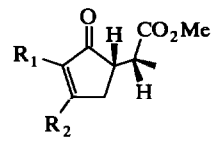
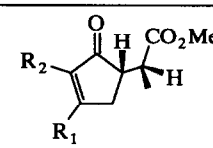
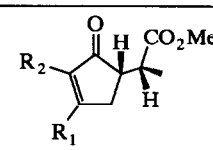
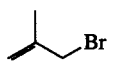
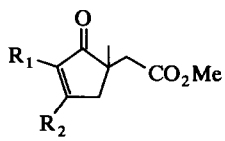
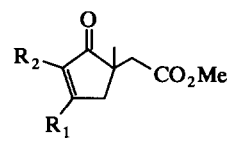
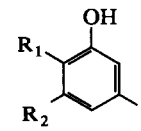
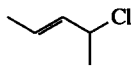
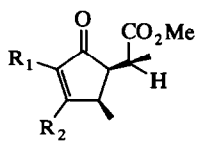
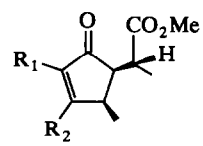
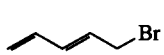
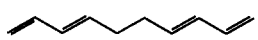
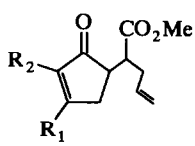
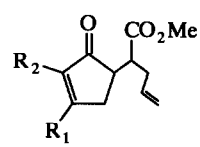
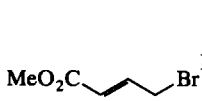
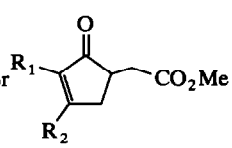
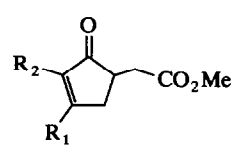
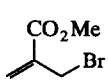
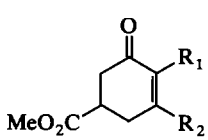
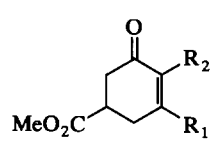
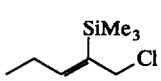
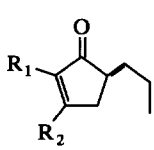
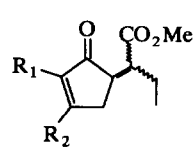
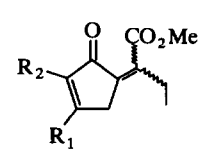
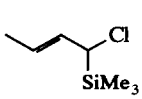
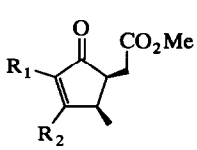
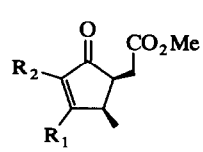
In this procedure, a vinylnickel intermediate **11** is suggested to be formed after an oxidative addition of the bromodiene, **10**. Subsequent CO insertion in **11** would lead to the acylnickel intermediate **7**, common to the original Chiusoli process depicted in Scheme 3. That the same type of products are obtained from reagents designed to enter the reaction sequence at the vinylnickel stage constitutes indirect evidence for the mechanism originally proposed by Chiusoli. Nonetheless, alkyne polyinsertion becomes less important with more crowded allyl halides, and is even susceptible to control by the use of additives (see below).

Two general consequences may be drawn. Most functional groups in the alkyne moiety are tolerated and, in addition, they may be used to improve yields in cycloadduct; and an efficient regiocontrol in the resulting adduct may be achieved by appropriate alkyne substitution.

3. The allyl moiety. The challenge for C-4 substitution leads to stereocontrol

We next come to the analysis of the effect of substitution of the allyl halide on the product distribution. The three different carbon atoms of the allyl halide must, *a priori*, introduce more complexity in the product mixture if strict regio- and stereo-control were lacking. Some simplification, however, was envisaged for those allyl halides with symmetric 1,3-disubstitution since, from the original work of Chiusoli and our own observations, a π-allyl intermediate was most probably involved, making the 1 and 3 positions equivalent. The tendency of 2-branched allyl halides to give cyclohexenone (or aromatic) adducts has also been reported. This was soon confirmed by us in the reactions of methallyl chloride or other centrally substituted allylic precursors (Table 3, entries 2 and 7).

TABLE 3. Reaction of 2-butyn-1-ol or 2-butynyl methyl ether, allyl halides and $[Ni(CO)_4]$ in methanol

Entry	Allyl derivative	Products (isolated yield %)			
1 [a]		 (45)	 (28)	 (15)	 (8)
2 [a]		 (46)	 (10)	 (23)	
3 [b]		 (38)	 (9)		
4 [b]		 (40)			
5 [b]		 (74)	 (18)		
6 [b]		 (34)	 (9)		
7 [b]		 (39)	 (9)		
8 [b]		 (12)	 (8)	 (11)	
9 [b]		 (17)	 (5)		

[a] $R_1 = CH_3$; $R_2 = CH_2OCH_3$. [b] $R_1 = CH_3$; $R_2 = CH_2OH$.

Alkyl monosubstitution at C-1 (or C-3) of the allyl halide led to cyclopentenone formation, with the original substituents on the side chain. Yields were not significantly affected by this type of substitution. They were, however, altered by functional variation [7]. Thus, while the five- or six-membered cyclic adducts were generally still obtained, in some cases the yields were low, or even zero when extended conjugation favoured allyl self-coupling. Occasionally, a change of solvent allowed moderate yields of cycloadducts to be obtained in such cases. Therefore, for functionalized allyl halides the factors observed for the alkyl-substituted analogues also control ring formation, and the presence of a functional group was only a minor perturbation favouring competitive side reactions. These observations showed that steric effects govern the regiochemistry of allyl insertion. However, an explanation based on electronic effects had to be sought for the results obtained for an allyl group centrally substituted by a bulky group such as Me_3Si (entry 8).

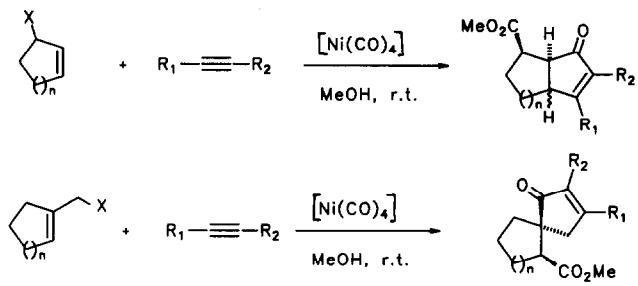
The steric influence on this reaction was revealed not only by the size of the ring in the product but also by the absence of substitution at C-4 in the adducts. We only accomplished this by using 1,3-disubstituted allyl halides. The results obtained with a trimethylsilyl derivative (entry 9) indicate that the less crowded side of the allyl group is again exclusively chosen to insert the alkyne (the adducts protodesilylate spontaneously).

All the products resulting from C-4 substitution had a single *cis* diastereomeric arrangement relative to C-5. This observation is important mechanistically, as it will be seen later.

In summary, the allyl moiety is always inserted into the alkyne by its less substituted end (the equivalence of C-1 and C-3 substitution in the allyl halide supports the intermediacy of a π-allyl system) and ring closure is achieved with high diastereomeric control. Functional substitution generally has only an indirect effect by stimulating competitive side reactions.

4. Extension to cyclic allylic systems. Further potential applications

As a logical extension of this reaction to the synthesis of bicyclic skeletons we studied the performance of 3-halo- and 1-halomethylcycloalkenes. We hoped that a fused or spiro bicyclic system might successfully arise intermolecularly as indicated in Scheme 5. Against this was the reported instability of small-ring bis(π-allyl)nickel complexes [8]. However, the six-membered derivative has been applied successfully in a heterocoupling reaction [9]. Our hopes were confirmed since bicycloadducts were obtained almost exclusively [10] (Table 4). The rather low yields of [5 + 5]-cycloadducts



Scheme 5.

were thought to be caused by the instability of the starting allyl halide towards elimination under the reaction conditions. In some cases, where low yields were probably obtained due to extensive alkyne polyinsertion, an improvement was obtained by the addition of specific amounts of KOAc.

1-Halomethylcycloalkenes generally gave the corresponding spiro bicycloadducts (Table 5). Nevertheless, for the six-membered cyclic series, the formation of products with ring fusion was important or even exclusive. Again, the presence of acetate ion was able to change the reaction to give preferentially the spiro adduct with a general improvement of yields *.

We again verified a strict stereocontrol in these processes: for all bicyclic compounds in the [5-5], [5-6] and [5-7] series the stereochemistry in the ring fusion was *cis* while that for the [5-8] adducts was *trans*. Similarly, for the spiro adducts a single diastereomeric arrangement was produced between the spiro centre and its adjacent chiral carbon, with the keto group in the newly formed ring and the methoxycarbonyl generated on the preexisting ring on the same side, confirming *syn* addition of the acylnickel intermediate to the coordinated olefin in the ring-closure step.

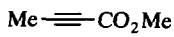
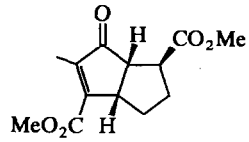
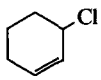
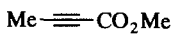
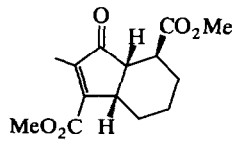
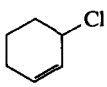
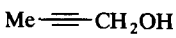
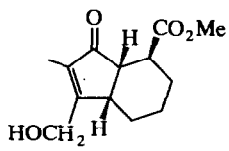
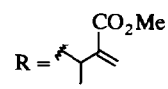
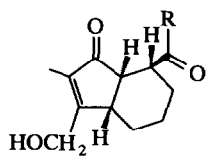
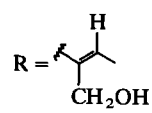
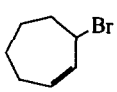
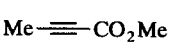
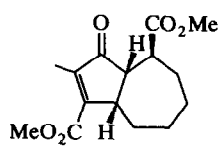
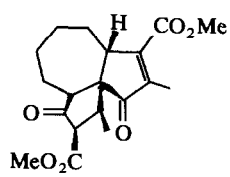
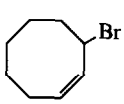
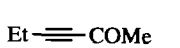
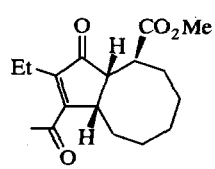
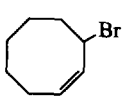
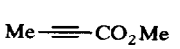
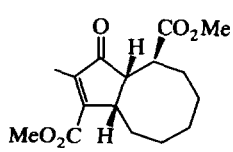
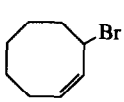
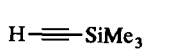
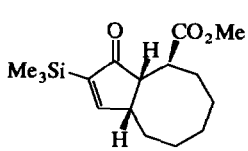
5. Synthetic applications

As a consequence of these results we wanted to look at practical applications to exploit this methodology. The efficient synthesis of mono-, di- and tri-cyclopentane derivatives obtained by the use of this reaction was explored.

The monocyclic antibiotic Methylenomycin B (**13**) was readily prepared in only four synthetic steps from allyl bromide and 2-butynol as indicated in Scheme 6

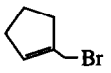
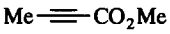
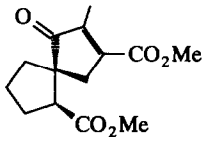
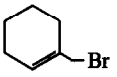
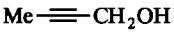
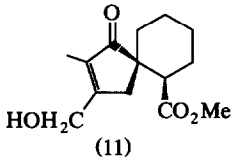
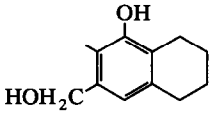
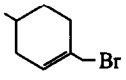
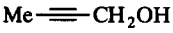
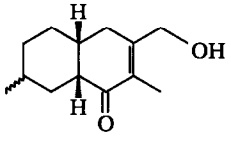
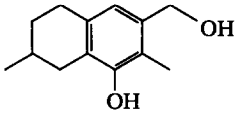
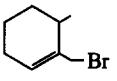
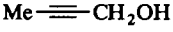
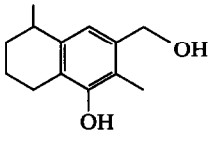
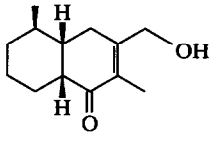
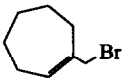
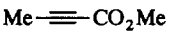
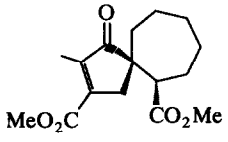
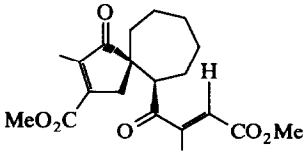
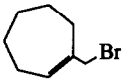
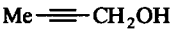
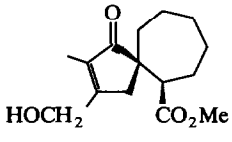
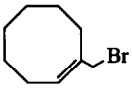
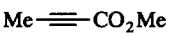
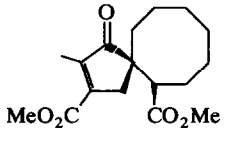
* Although not fully understood, the effects displayed by this ion seem to indicate that it is playing a ligand-like role within the coordination sphere of the metal. It can compete with the alkyne, blocking its site of activation prior to insertion, and it can also change the preferred conformation of the original ring in the ring-closure step, favouring the formation of the spiro compound.

TABLE 4. Reaction of acetylenes, 3-halocycloalkenes and $[Ni(CO)_4]$ in methanol

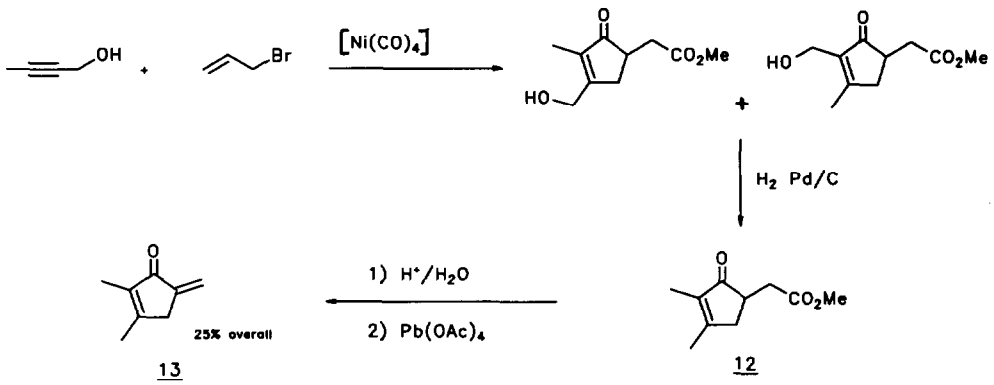
		 (40)	
		 (72)	
		 (0)	 (60)
		 (31) [a]	 (25) [a]
		 (70)	 (29)
		 (70)	
		 (81)	
		 (57)	

[a] In the presence of KOAc.

TABLE 5. Reaction of acetylenes, 1-halomethylcycloalkenes and [$Ni(CO)_4$] in methanol

		 (45)	
		 (11) (53) [a]	 (37) (10) [a]
		 (27) [a]	 (38) [a]
		 (29) [a]	 (20) [a]
		 (42) (72) [a]	 (25) (0) [a]
		 (48) (75) [a]	
		 (47) (63) [a]	

[a] In the presence of KOAc.



Scheme 6.

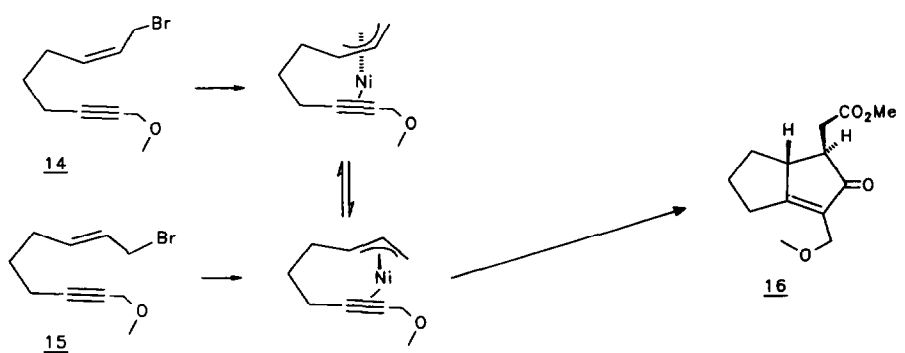
[11]. The sequence might have been shortened by using but-2-yne as starting alkyne, but the yield in cycloadduct was low and the use of the alternative alkynol was preferred. Particular attention needed to be paid to the oxidative decarboxylation step that required mild reaction conditions to avoid isomerization of the resulting exocyclic double bond and subsequent polymerization. While Wilkinsons's catalyst at reasonable temperatures, failed to give the final olefin from the acyl chloride of **12**, lead tetraacetate under flash-thermolysis conditions gave the required compound, although in modest yield. The overall yield was quite acceptable and the small number of steps outstanding when compared to other syntheses.

The present method also gave two different new routes to diquinane structures. One, leading to bicyclo[3.3.0]oct-3-en-2-one systems with a complete stereocontrol at C-8 by intermolecular reaction of alkynes with 3-halocyclopentenes has already been mentioned. Yields are 30–40%. Alternatively, intramolecular reaction of three methylene-spaced enynes **14** or **15** (Scheme 7) led to a bicyclo[3.3.0]oct-1-en-3-one derivative **16** with a complete relative stereocontrol at C-4 and C-5 [12]. We found that the stereoselectivity obtained in this reaction was not dependent on the geometry of the double bond of the starting allylic system, since the same diastereomer was obtained from both *Z* and *E* olefin isomers. This is further evidence of the intermediacy of a π-allyl nickel complex that may isomerize through the corresponding σ-allyl prior to cyclization. Similar results have been described by Oppolzer *et al.* for closely related processes [13].

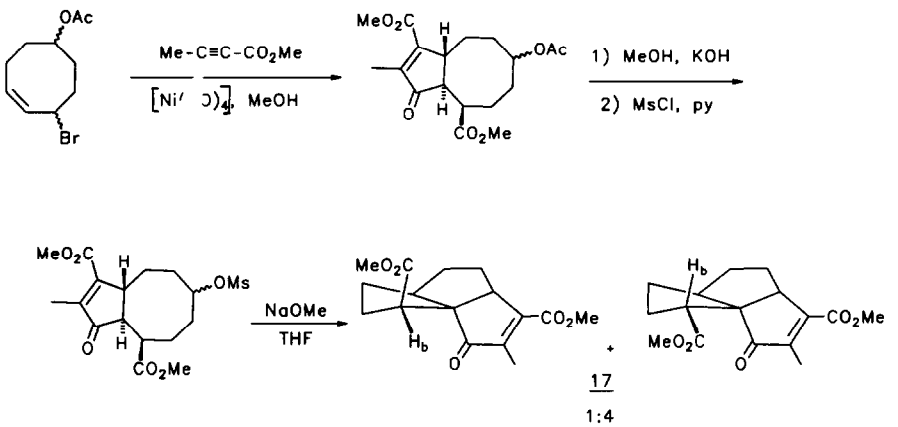
Finally, to illustrate the synthetic applications of Chiusoli's cycloaddition, we obtained a basic angulary fused triquinane skeleton **17** by a short reaction sequence (29% overall yield), starting from a cyclic allyl halide with a leaving group at the correct site [14] (Scheme 8). We took advantage of the high yields usually obtained starting with cyclooctenyl halides and the fact that the leaving group has to be placed symmetrically on the opposite side of the allyl unit.

6. New contributions to the mechanism

The mechanism originally proposed by Chiusoli (see Scheme 3) has proved, in the main, satisfactory to explain experimental results. Some of our results have shed light on the details of several aspects of the mechanism which we will briefly describe.



Scheme 7.



Scheme 8.

First of all, we shall examine the general carbonylation following allyl insertion at the triple bond (quasi concerted reaction). From the general absence of products arising independently from either carbonylation or allyl insertion on the alkyne we concluded that these processes are interrelated and that each immediately follows the other. We might expect an opposite regioselectivity in this addition, considering the nucleophilic behaviour generally displayed by either π- or σ-allylnickel reagents [15]. We have interpreted this change by assuming that the reaction takes place when the three components are simultaneously coordinated to the metal. Thus, the π-acidity of the carbonyl ligand may be conveyed onto the opposite end of the π-allyl ligand through the metal bridge, conferring on it a certain degree of electrophilicity (Fig. 1). Although we have been unable to find precedents for these effects it may be considered the converse of the well known nucleophilic *trans* labilization of π-allyl ligands brought about by basic phosphines [16]. Additional support for this is the isolation of π-allyl carbonyl nickel complexes stabilized by a phosphine ligand that gives the same type of cyclopentenone adducts with alkynes [17]. Complexes without a phosphine ligand are too unstable to be isolated, but have been spectroscopically characterized and they show considerable proton deshielding of the allyl system in their ^{1}H NMR spectrum and, in particular, of one of the methylene groups [18].

The preference for distal olefin insertion by the acyl–nickel bond (ring closure) rather than methanol attack (cleavage by the solvent) is quite surprising, especially for those intermediates generated from disubstituted alkynes. A similar trend for the acylnickel intermediate **8** towards the free alkyne, may explain the formation of products from acetylene polyinsertion so consistently obtained in some cases. Both facts point to a strong tendency for acyl–metal bonds to insert into π-ligands. Additional steric protection from methanolysis for the remaining metal-olefin coordination in the first acyl–metal intermediate by the alkyne substituents may be the reason for the difference in behaviour between mono- and di-substituted alkynes. In any case, intramolecular alkene coordination seems to stop acryloylnickel intermediate **7** attacking any alkyne since no linear products arising from further alkyne insertion into the acyl–nickel bond in **7** prior to cyclization (Scheme 3) have ever been isolated, and only intramolecular insertion of the coordinated double bond (either in *exo* or *endo* modes) or methanolysis to give linear allylacrylic esters were observed.

Another question posed by the acylnickel intermediate is the general preference for five-membered ring formation *vis-à-vis* that of six when the central position of the allyl group is unsubstituted. This is quite general in transition-metal mediated cyclizations [19]. Considering intermediate **7** (Scheme 9), a transition to **18** might be expected, allowing a perfectly planar four-centre transition state [20], unless steric crowding between R and the carbonyl force the alternative route to **19** to be taken. For this route, steric hindrance would be minimised since the four centres are in a quasi-tetrahedral arrangement. Following an analogy with the corresponding Main Group organometallic processes, and using Baldwin's cyclization rules [21], these routes

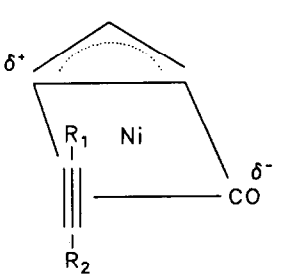
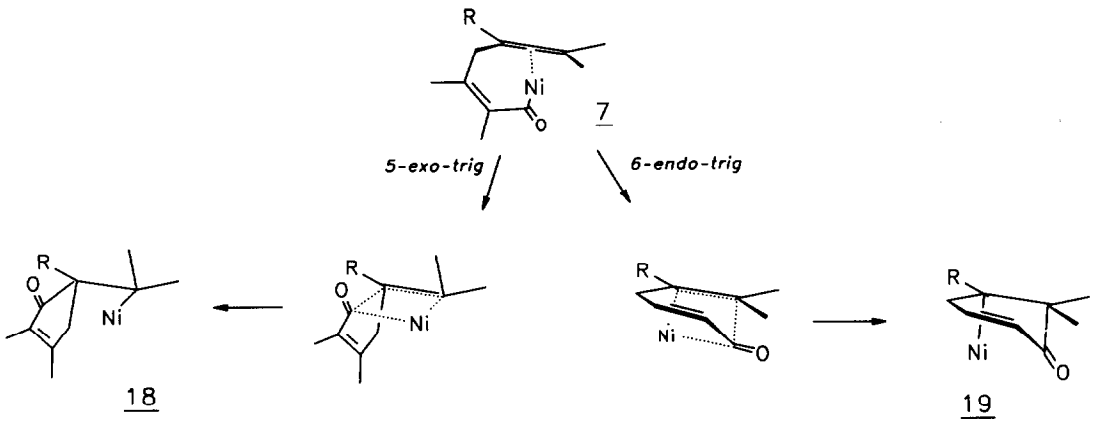


Fig. 1.



Scheme 9.

may be named as 5-*Exo*-Trig and 6-*Endo*-Trig ring closures. The relative stereochemistry for the ketone and the metal atom is that found in the final products after an additional carbonyl has replaced the metal in the intermediate.

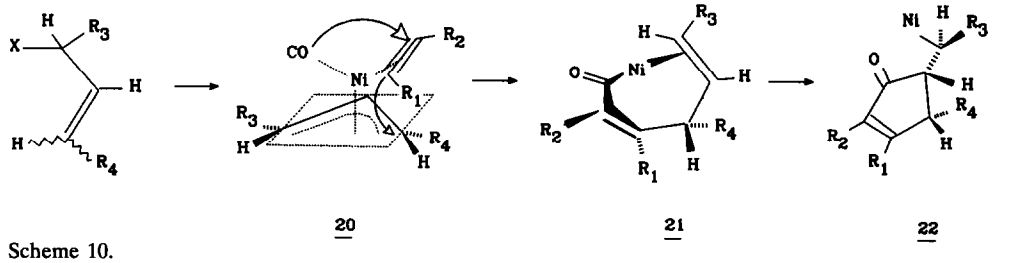
Substantial information was also gained from the relative stereochemistry of the substituents at C-4 and C-5 of the cyclopentenone rings obtained from 1,3-disubstituted allylic halides.

For open chain allyl halides the relative stereochemistry for these substituents was found to be *cis*. This stereochemistry is defined in the ring closure step related to that generated by the allylnickel insertion into the alkyne: once the intermediacy of a π-allyl alkyne carbonyl nickel intermediate **20** is accepted, it is reasonable to expect that allyl substituents R_3 and R_4 (Scheme 10) will adopt a *syn* geometry since it is preferred for most substituted π-allyl complexes. Alkyne attack would then take place, bisecting the angle R_4–C–H on the less hindered side of the allyl ligand (opposed to the apical carbon) while the resulting acylnickel intermediate **21** would add *syn* to the coordinated double bond giving **22**. As discussed above, all experimental facts seem to indicate that due to steric protection or intrinsic stability **21** undergoes this addition (or, alternatively, attack by methanol), since de- and re-coordination of the distal double bond at this stage would give mixtures of distereomers.

For cyclic allyl halides the conformational requirements are critical. Thus, although the relative stereochemistry for the adducts from allylic systems of 5, 6 and 7 members was analogous to that found from the open chain analogues, the corresponding *syn–syn* arrangement for the π-allyl complex would be too strained and only the *anti–anti* conformer **23** (Scheme 11) seems to be allowed. In this case, alkyne insertion (giving **24**) and *syn* addition closing the ring to give **25** should take place from the same side *. For the eight-membered ring, strain considerations suggest that both the *anti–anti* (**26**) and the *syn–anti* (**27**) geometries should be allowed. However, due to the transannular proton interactions in the *anti–anti* coordination mode, the *syn–anti* counterpart would be favoured. Thus, insertion of alkyne should take place at the less hindered *syn* centre and the resulting acryloylnickel chain would insert from the same side of the double bond, giving the *trans* fused adduct.

Concerning the cycloaddition of 1-halomethylcycloalkenes, the presence of products of ring fusion together with the corresponding spirocyclic compounds only for the cyclohexane members of the series may

* Exemplified for the six-membered cyclic system, the same reasoning would apply to five- and seven-membered allyl compounds.

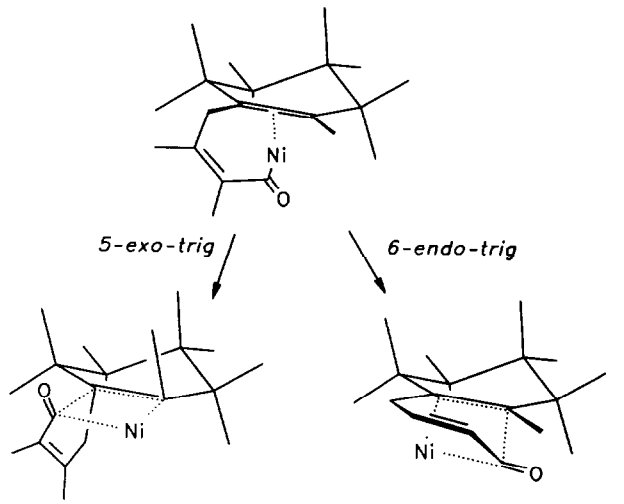


Scheme 10.

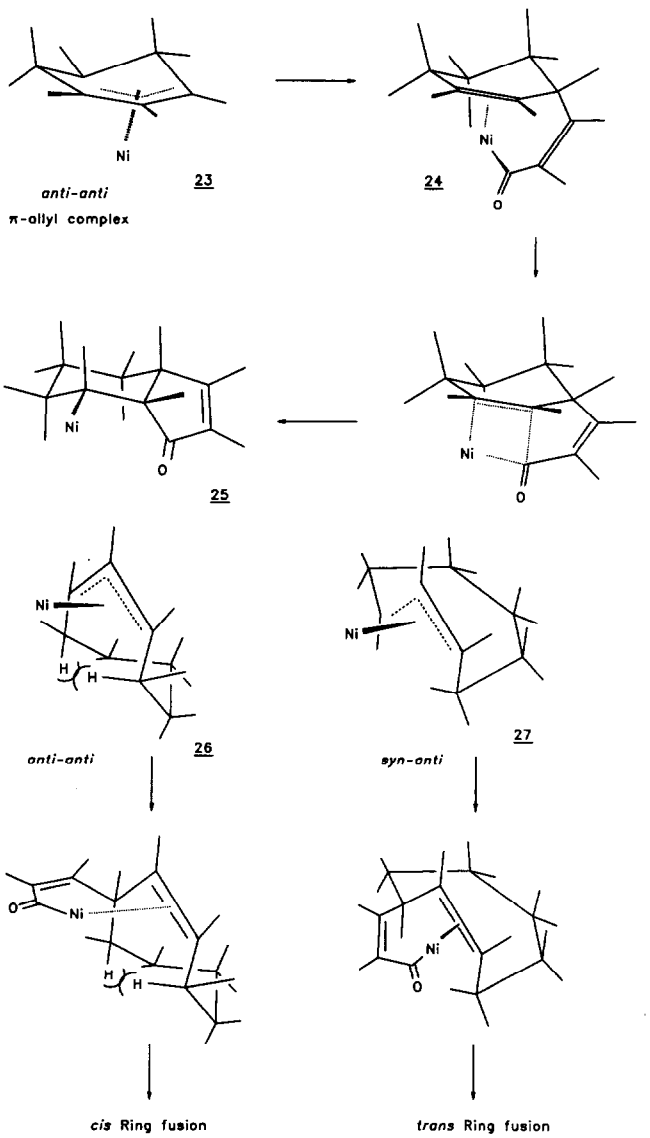
also be rationalized on basis of steric interactions in the acylnickel intermediates for both ring closure modes. Due to 1–3 diaxial interactions, the acryloylnickel chain would arrange preferentially in an equatorial disposition that would finally result in a six-membered ring closure (Scheme 12).

7. Outlook

The carbonylative cycloaddition of acetylenes and allylic halides mediated by $[Ni(CO)_4]$ represents a straightforward method for the synthesis of 2-cyclopentenone derivatives. The reaction proceeds under very mild conditions, with good functional tolerance, a high degree of regiocontrol and usually, strict stereocontrol. Its application to the synthesis of target cyclic products should shorten considerably other syntheses as the Pauson–Khand reaction has proved to do. However, the efficiency of the reaction depends on different and subtle factors and optimization for each case has to be sought.



Scheme 12.



Scheme 11.

Clearly, we have extended the Chiusoli reaction and contributed to a deeper understanding of the many factors influencing it. However, a higher degree of knowledge is still required to exploit this reaction to its full potential.

Acknowledgments

The fundamental contribution of the head of the Department of Bio-organic Chemistry, Professor F. Camps, and our coworkers Drs. Ll. Pagès, J. Torras, Mr. A. Jaumà and F. Boix is gratefully acknowledged. We also thank DGICYT for financial support (Project PB87-0201-C-03-03) and C.S.I.C. and S.E.D.E.Q. for fellowships (to A. Ll.).

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