

Silver(I) salts as useful reagents in pyrazole synthesis

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Dedicated to Professor Luisa Garanti

Abstract

This account provides a survey on the synthesis of a huge variety of pyrazole-containing molecules by 1,3-dipolar cycloadditions promoted by silver(I) salts. The data on this subject are listed in a systematic way according to the type of the cycloaddition involved, with an emphasis to improvements with respect to reactions performed in the presence of the usual organic basic agents.

Keywords: Silver carbonate, silver acetate, 4,5-dihydropyrazoles, nitrilimine cycloaddition, diazoketone cycloadditions

Contents

1. Introduction
2. Intermolecular cycloadditions
3. Intramolecular cycloadditions
 - 3.1 Formation of pyrazoles annulated to a five- or six- membered ring
 - 3.2 Formation of pyrazoles annulated to a medium-sized ring
 - 3.3 Formation of pyrazoles annulated to a large-sized ring
4. Stereoselective cycloadditions
 - 4.1 Intermolecular stereoselective cycloadditions
 - 4.2 Intramolecular stereoselective cycloadditions

1. Introduction

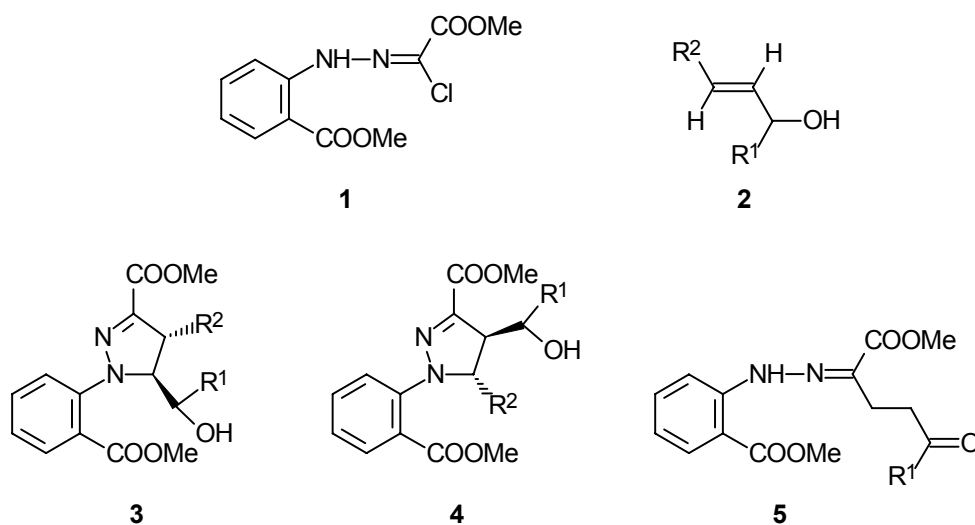
Due to its wide occurrence in the field of heterocyclic chemistry,¹ the pyrazole ring constitutes a relevant synthetic target in both academia and industry. In fact, such a heterocyclic moiety represents the core structure of a number of drugs,² including the widely prescribed Celebrex and Viagra.³ Among the various synthetic routes which are amenable for the preparation of substituted pyrazoles,⁴ the cycloadditive method occupies a prominent place due to its versatility in the construction of complex heterocycles.⁵ To this respect, 1,3-dipolar species which have been traditionally exploited in pyrazole synthesis are diazocompounds⁶ and nitrilimines.⁷ These latter are well-known labile intermediates⁸ which are generated *in situ* in the presence of the dipolarophile as beautifully described from early works by Huisgen.⁹ The classical way followed in order to generate the nitrilimine implies the base-promoted dehydrohalogenation of the corresponding hydrazonoyl halides. This step is usually carried out in homogeneous conditions by using an organic base fully soluble in the reaction medium, which involves deprotonation of the NH group and subsequent loss of the halide ion.⁷ The aim of the present account is to describe the synthesis of pyrazole-containing molecules by means of an 1,3-dipolar cycloaddition as the key step, in which the generation of the reactive species is promoted by a non-conventional basic agent, namely silver(I) salts, in heterogeneous conditions.

2. Intermolecular cycloadditions

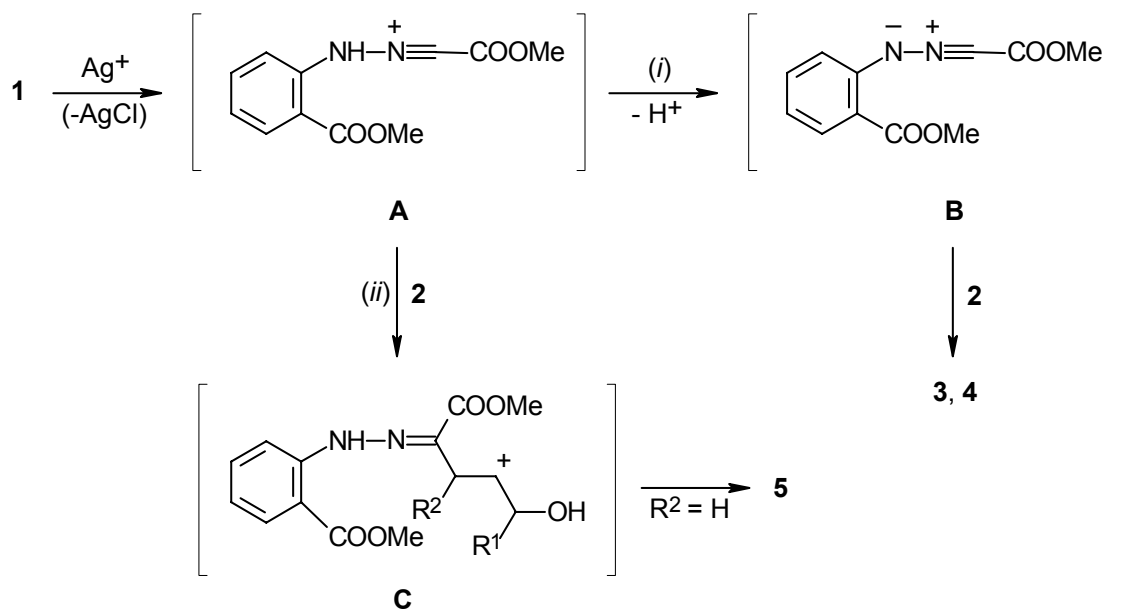
An early report describing the behaviour of silver(I) carbonate as an efficient enhancer of hydrazonoyl halides reactivity was concerned to the synthesis of cyclopropa[*c*]cinnolines by way of an 1,7-electrocyclisation of *N*-(2-vinylphenyl)-substituted nitrilimines.¹⁰

The application of such reagent to the intermolecular nitrilimine cycloaddition were first exploited onto allylic alcohols as dipolarophiles (Scheme 1).¹¹ The expected pyrazolinic cycloadducts **3** and **4** were obtained with low combined yields (10-28%) with respect to the similar reaction between allyl alcohol and diphenylnitrilimine (80%).¹² These results may appear, *prima facie*, disappointing. However, the formation of open-chain products **5** gave some useful mechanistic insights about the reaction occurring between **1** and **2** in the presence of silver(I) carbonate.

As a rationalisation, it was proposed the mechanistic picture illustrated in the Scheme 2. Due to the well-known ability of the silver ion to facilitate the heterolysis of the carbon-halogen bond,¹³ it was envisaged the initial formation of the nitrilium ion **A**. This intermediate can then evolve following alternative pathways: (i) proton elimination to generate the nitrilimine intermediate **B**, (ii) electrophilic attack to the π bond of the alkenol **2** to form the new carbocation **C**. The pinacol-type rearrangement of the latter¹⁴ gave the carbonyl derivatives **5**, whose formation have no precedent in the base-promoted reactions of hydrazonoyl halides with alkenols.¹⁵



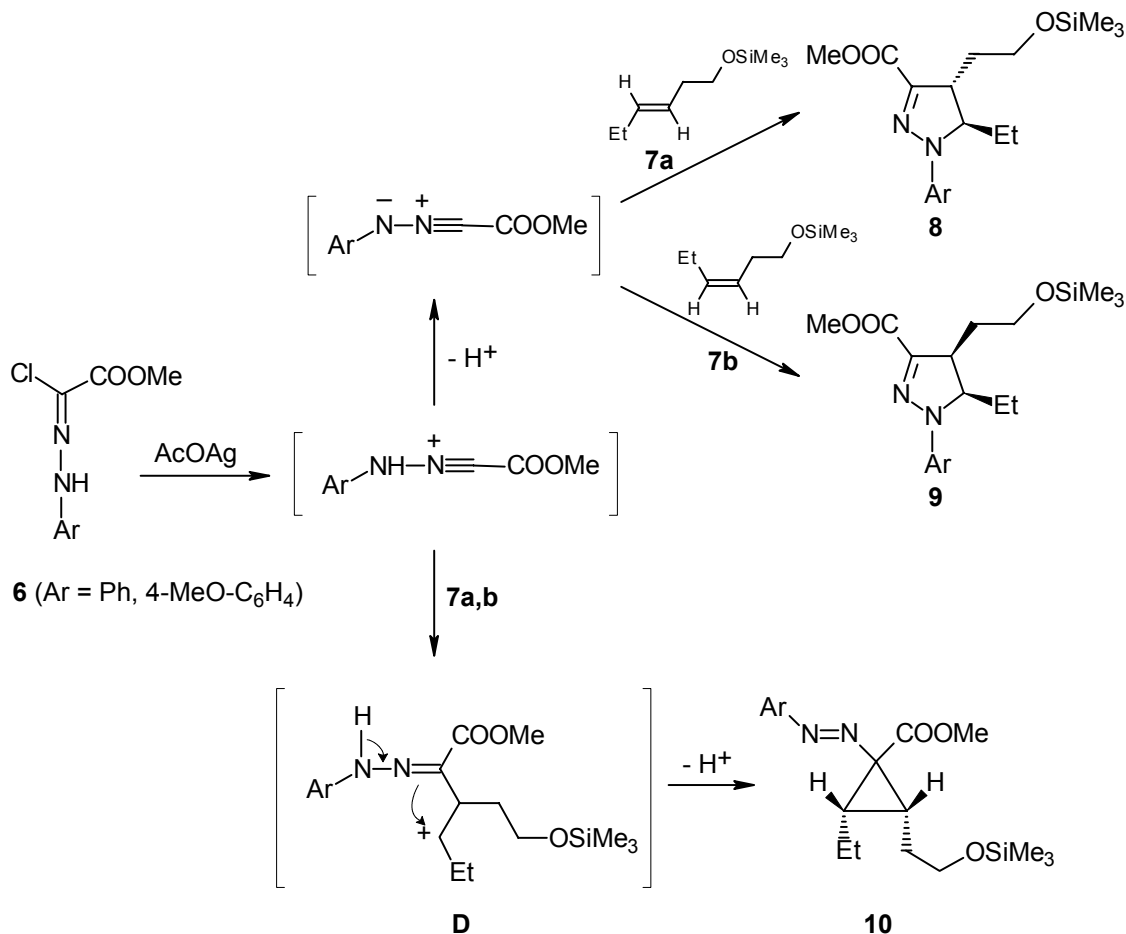
Scheme 1



Scheme 2

Open-chain products similar to **5** were also found in the silver(I) carbonate-promoted reaction between hydrazoneyl chlorides and homoallylic or homopropargylic alcohols,¹⁶ thus further supporting the above mechanistic picture. As a common drawback, however, it should be pointed out that cycloaddition yields were low and a number of side-products were always formed. Furthermore, the cycloadditions were not regioselective when R^1 and R^2 were other than hydrogens. This unappealing behaviour was avoided using trimethylsilyl homoallylethers **7a** and

7b as dipolarophiles in the presence of silver(I) acetate (Scheme 3).¹⁷ The major cycloadducts **8** and **9** were highly preferred, being the regioisomeric ratio between 90:10 and 92:8. Further removal of the trimethylsilyl group from the latter cycloadducts with TBAF gave unprotected 4-(1-hydroxy)ethyl-4,5-dihydropyrazoles with good overall yield (59-65%). Cyclopropane derivatives **10** are unusual products whose formation can be ascribed to the multi-step ionic mechanism depicted in the Scheme 3. Electrophilic attack from the nitrilium-like ion to the C=C double bond of **7** gave the new carbocation **D**. Proton loss from the latter intermediate and subsequent ring closure gave cyclopropane derivatives **10**.



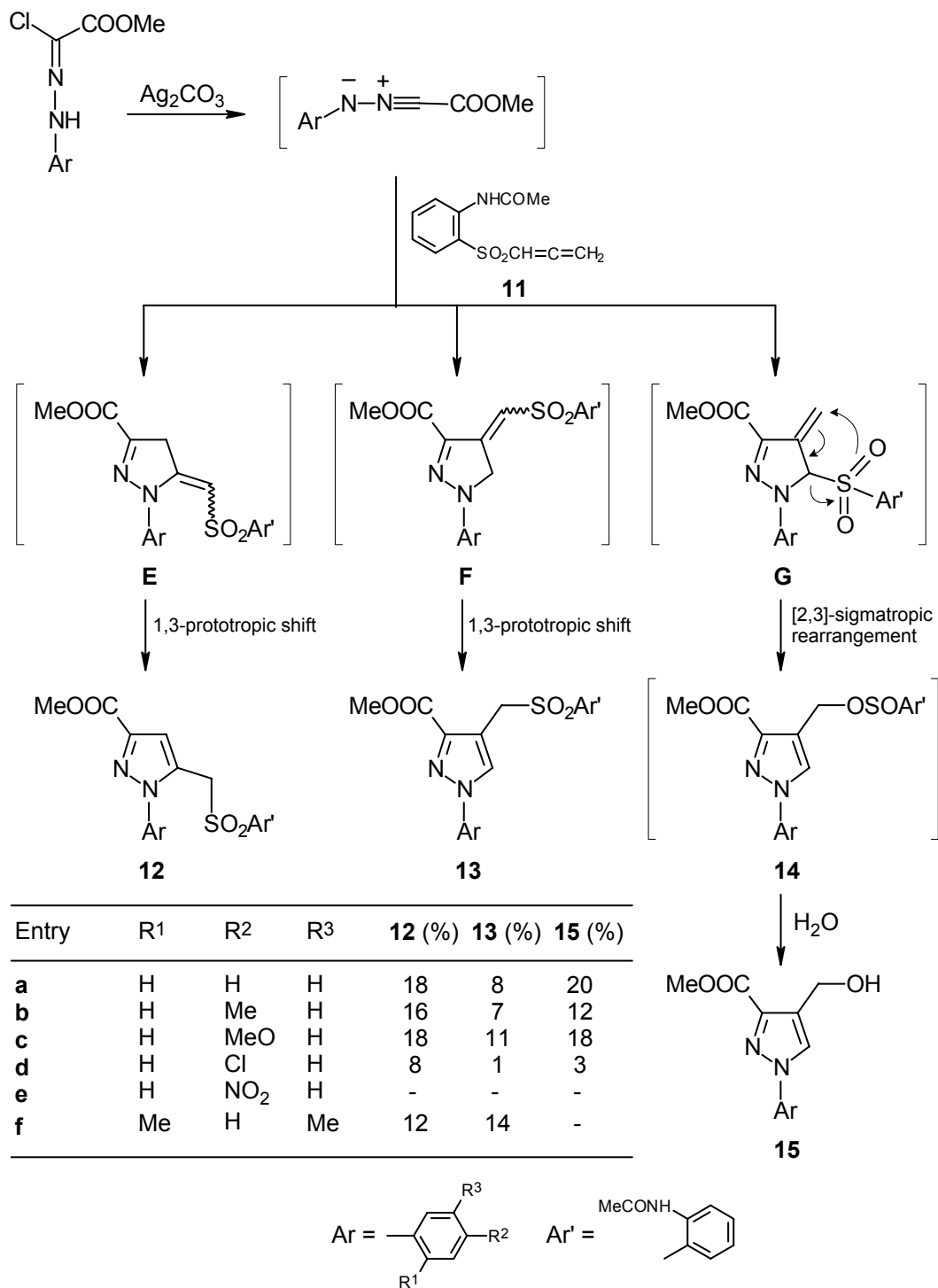
Scheme 3

The use of silver(I) carbonate as an unconventional basic agent has been exploited in the cycloaddition between nitrilimines and (arylsulfonyl)allene **11** (Scheme 4).¹⁸ The choice of silver(I) carbonate in the place of more common organic bases, like triethylamine^{19,20} comes from the following considerations: (i) the allene → acetylene isomerisation is suppressed in the current reaction conditions; (ii) room temperature and heterogeneous reaction medium allow a smooth generation of the nitrilimine, so minimising the degradative processes of the 1,3-dipole. From a mechanistic standpoint, it is likely that the final pyrazoles **12** and **13** would originate

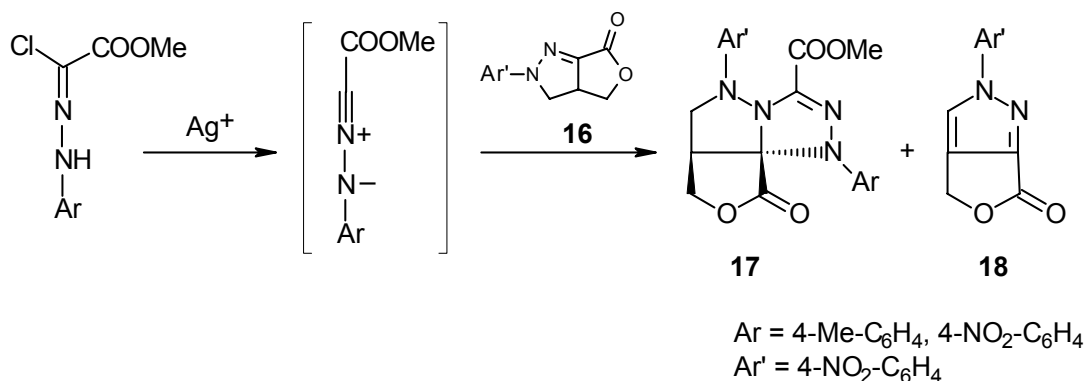
from the first-formed cycloadducts **E** and **F**, respectively, *via* 1,3-prototropic shift.^{19,21} The formation of the sulfinic ester intermediates **14** can be rationalised by invoking a [2,3]sigmatropic rearrangement of cycloadduct **G** *via* a sulfur-to-oxygen bond migration.²² It needs to be added that, due to the HOMO-nitrilimine control of the cycloaddition, electron-rich nitrilimines (entries **a-c,f**) gave better results, while the cycloaddition pathway appeared impervious with electron-poor nitrilimines (entries **d,e**). The computational aspects of this reaction have been investigated by means of DFT reactivity indices.²³

Nitrilimine cycloadditions to partially saturated heterocycles as (hetero)dipolarophiles are attractive reactions since it is possible to synthesise complex tri-, tetra- and pentacyclic heterocycles which are not easy to obtain by other routes.

The C=N bond of the furo[3,4-*c*]pyrazoline **16** is able to react with hydrazoneyl chlorides in the presence of both silver(I) carbonate or silver(I) acetate giving the tricyclic compounds **17** with 2-32% yield (Scheme 5).²⁴ The better results were obtained with silver(I) acetate, since some amount of the oxidation product **18** was always formed in the presence of silver(I) carbonate. This behaviour is not surprising in the light of the known oxidising ability of silver(I) carbonate.²⁵ Notwithstanding these low cycloaddition yields, it has to be underlined that by performing the above reactions in the presence of triethylamine no noticeable reaction occurred onto the C=N bond of **16**.

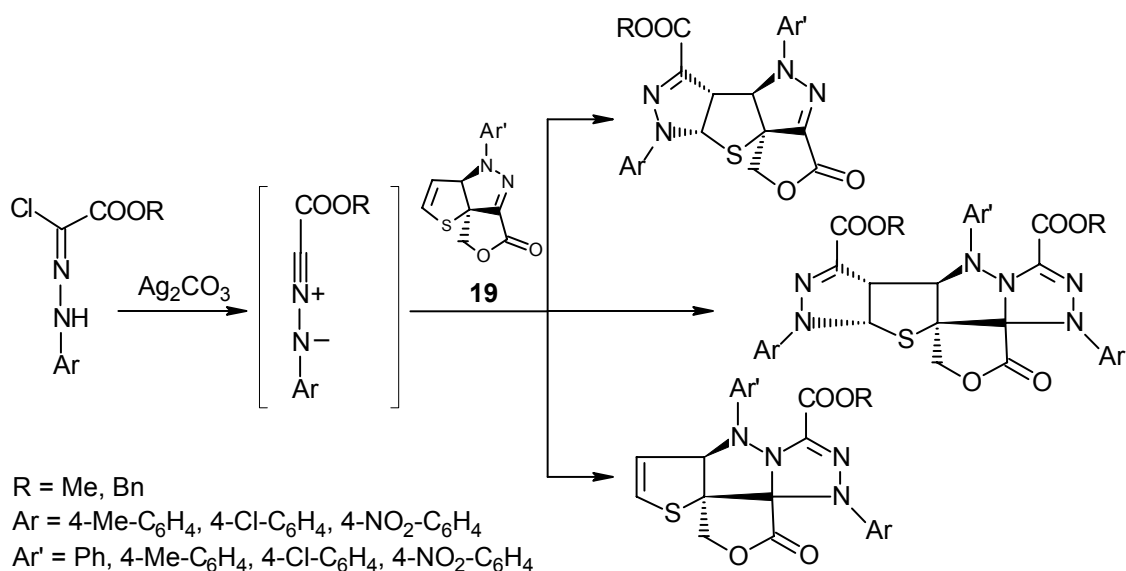


Scheme 4



Scheme 5

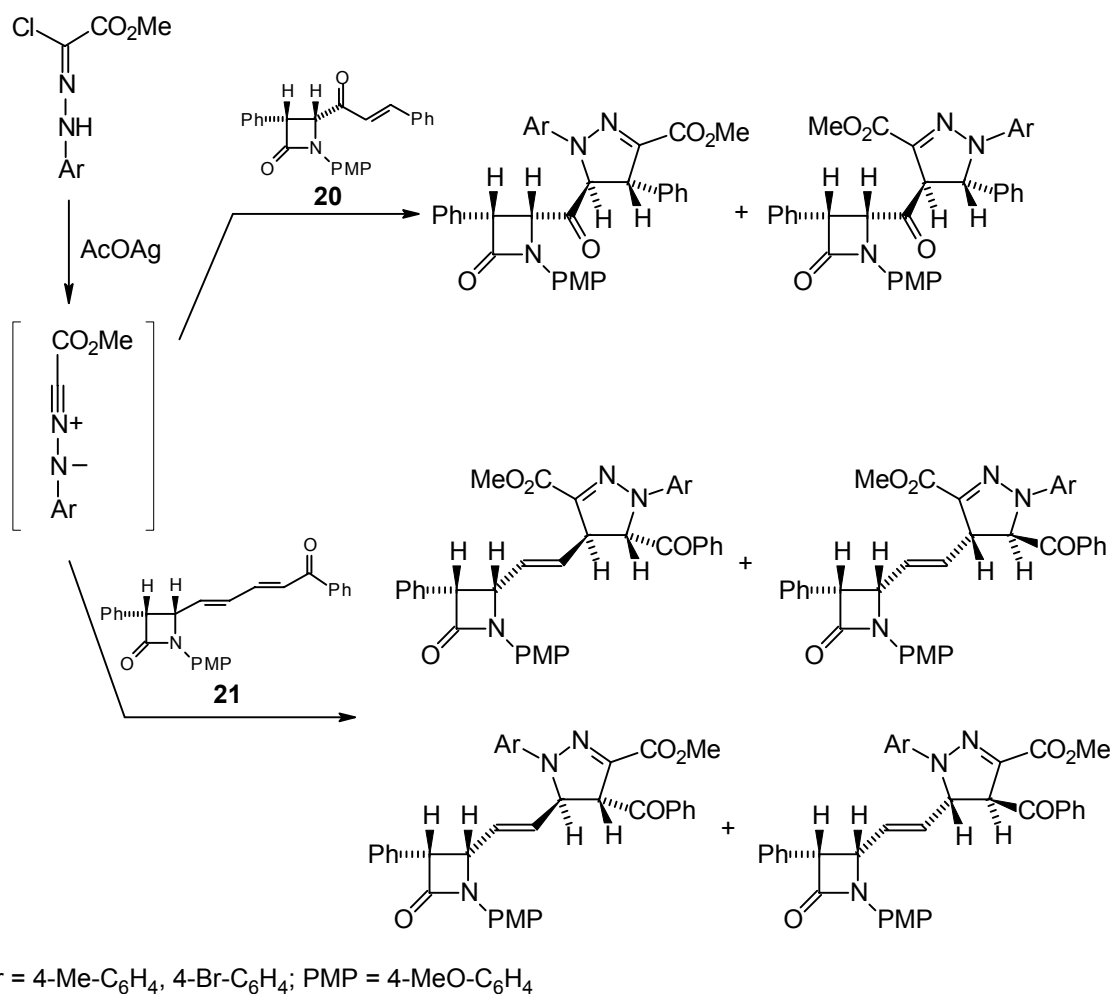
Complex heterocycles have been obtained from partially saturated furo[3,4-*c*]thieno [2,3-*d*]pyrazoles **19** (Scheme 6).²⁶ The competitive formation of products due to the nitrilimine attack at different dipolarophilic sites has been observed, and the experimental evidence was discussed by taking into account electronic features of the reactive species as well as their steric encumbrance.



Scheme 6

Since the known antibiotic activity of 2-azetidinone-based heterocycles²⁷ and the anti-inflammatory features of some pyrazolines,²⁸ some compounds which brings together these heterocyclic fragments have been synthesised. The key step was an efficient nitrilimine cycloaddition to racemic 2-azetidinones **20** and **21** promoted by silver(I) acetate. Although not regioselective (regioisomeric ratio between 80:20 and 83:17), the cycloaddition to compound **20**

was fully stereoselective,²⁹ while from the conjugated 2-azetidinone **21** was obtained a complex mixture of regio- and stereoisomers.³⁰



Scheme 7

3. Intramolecular cycloadditions

The most prominent features of intramolecular 1,3-dipolar cycloadditions³¹ are related to the linkage between the reacting groups, which allows the simultaneous formation of two annulated (or fused) rings. Furthermore, the entropic advantage due to intramolecularity³² works to improve the reactivity of the dipolarophilic fragment.

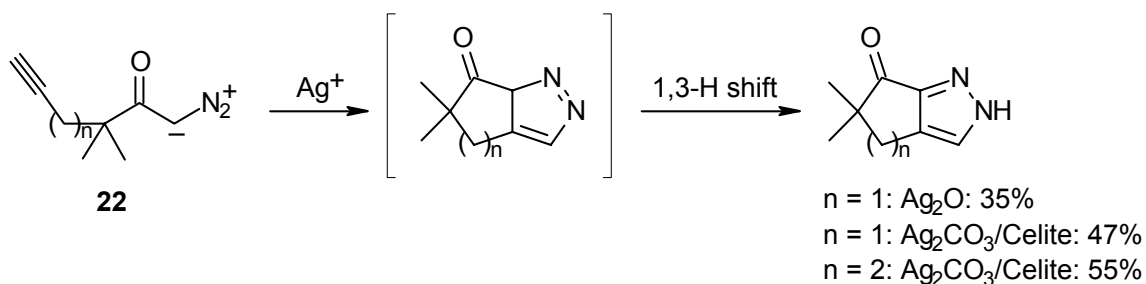
As far as intramolecular nitrilimine cycloadditions are concerned, the effect of the basic species used to generate these intermediates plays a key role in the whole process. The presence of triethylamine or very strong bases (e.g. sodium hydride) often cause the fast and irreversible generation of the nitrilimine which can force intermolecular processes leading to resinous

materials. The effectiveness of silver(I) salts in a heterogeneous medium is the consequence of the very slow generation of the nitrilimine intermediate, which mimics high-dilution conditions favouring intramolecular over intermolecular pathways.

The following sections will be illustrated according to the length of the tether joining the reactive groups, *i.e.* to the size of the ring to which the pyrazole nucleus is annulated.

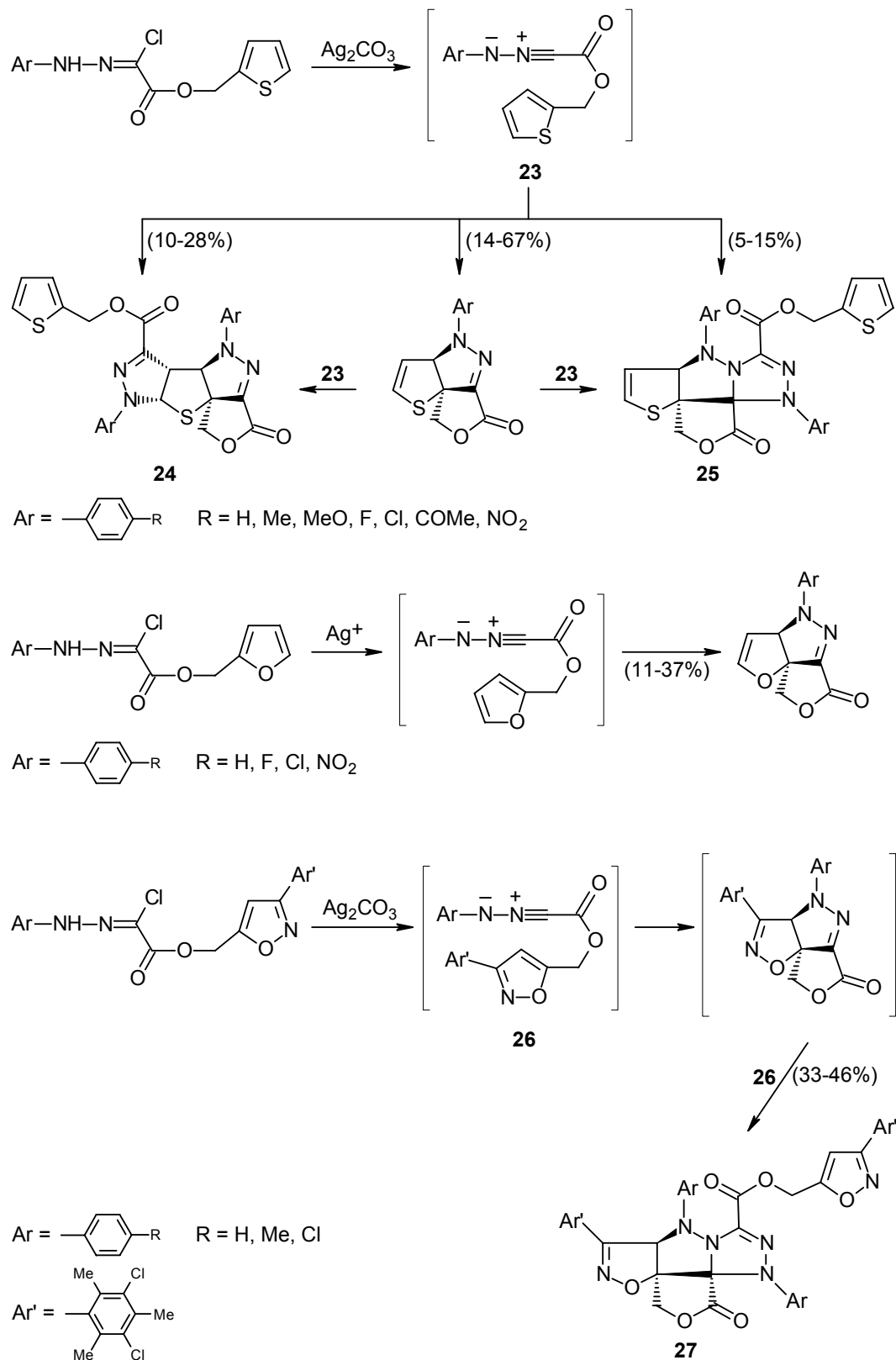
3.1 Formation of pyrazoles annulated to a five- or six- membered ring

Acetylenic α -diazoketones **22** bearing gem-dimethyl substituents in the α' -position were capable to undergo intramolecular cycloaddition in the presence of silver(I) carbonate or silver(I) oxide giving the corresponding bicyclic pyrazoles (Scheme 8).³³ This behaviour was somewhat surprising since no trace of the expected Wolff rearrangement product was observed. However, bicyclic pyrazole derivatives were isolated with 35 to 55% yields depending on the silver(I) salt only in the presence of the mentioned gem-dimethyl substitution, which finds a rationale in terms of steric effects on conformational energies in the transition state.



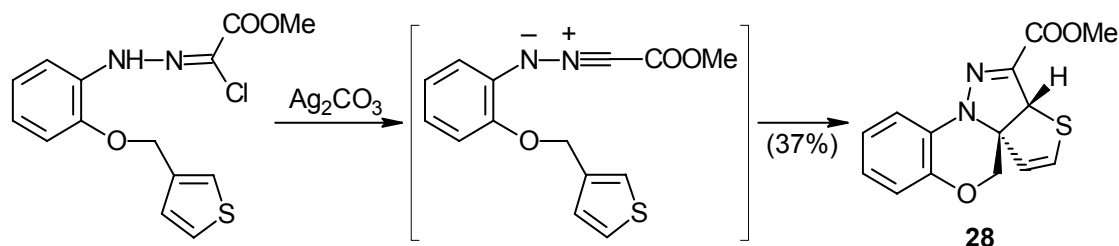
Scheme 8

Despite their propensity for substitution rather than addition reactions, various five-membered heteroaromatics can behave as dipolarophiles in intramolecular cycloadditions of 1,3-dipoles.³⁴ Plausibly, the high energy barrier due to the loss of aromaticity is overcome by favourable entropic contributions working in intramolecular reactions.³² Intramolecular nitrilimine cycloaddition onto a thiophene,³⁵ furan,³⁶ and isoxazole³⁷ ring (Scheme 9) were described as a synthetic route to a number of tricyclic pyrazoline derivatives. All these cycloadditions work well only in the presence of silver(I) salts, while the use of triethylamine as the base did not produce any appreciable reaction. In the case of the thiophene and isoxazole dipolarophiles the formation of diadducts **24**, **25** and **27** can be ascribed to a sequential intramolecular cycloaddition pathway.



Scheme 9

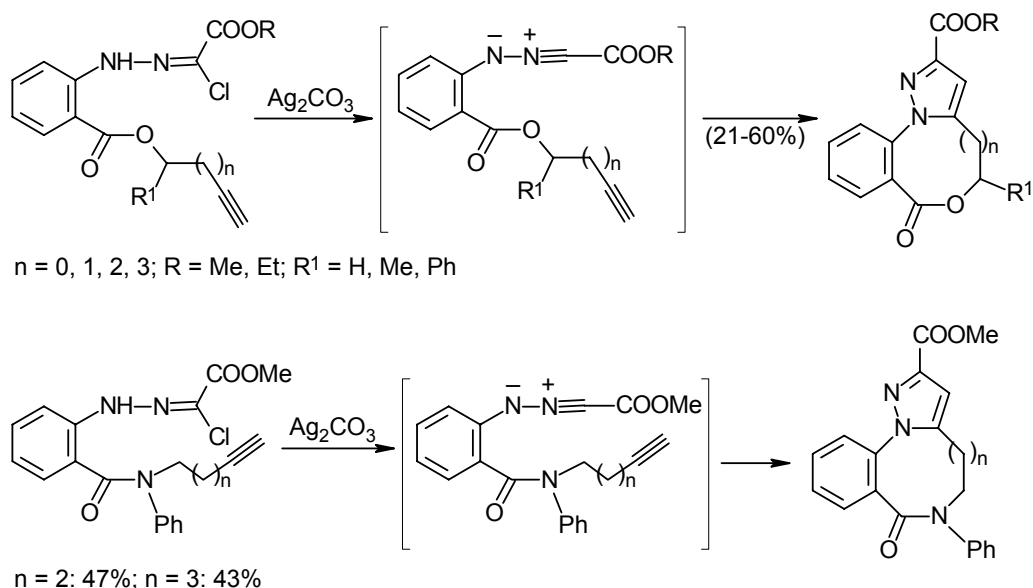
The examples described above involve intramolecular reactions in which the dipolarophile is linked to the *C* terminus of the 1,3-dipole. Only one recent report deals with the behaviour of *N*-substituted nitrilimines in which the thiophene ring acts as the dipolarophile (Scheme 10).³⁸ The formation of the cycloadduct **28** have been rationalised on the basis of the corresponding transition state optimised at the B3LYP/cc-pVDZ level.



Scheme 10

3.2 Formation of pyrazoles annulated to a medium-sized ring

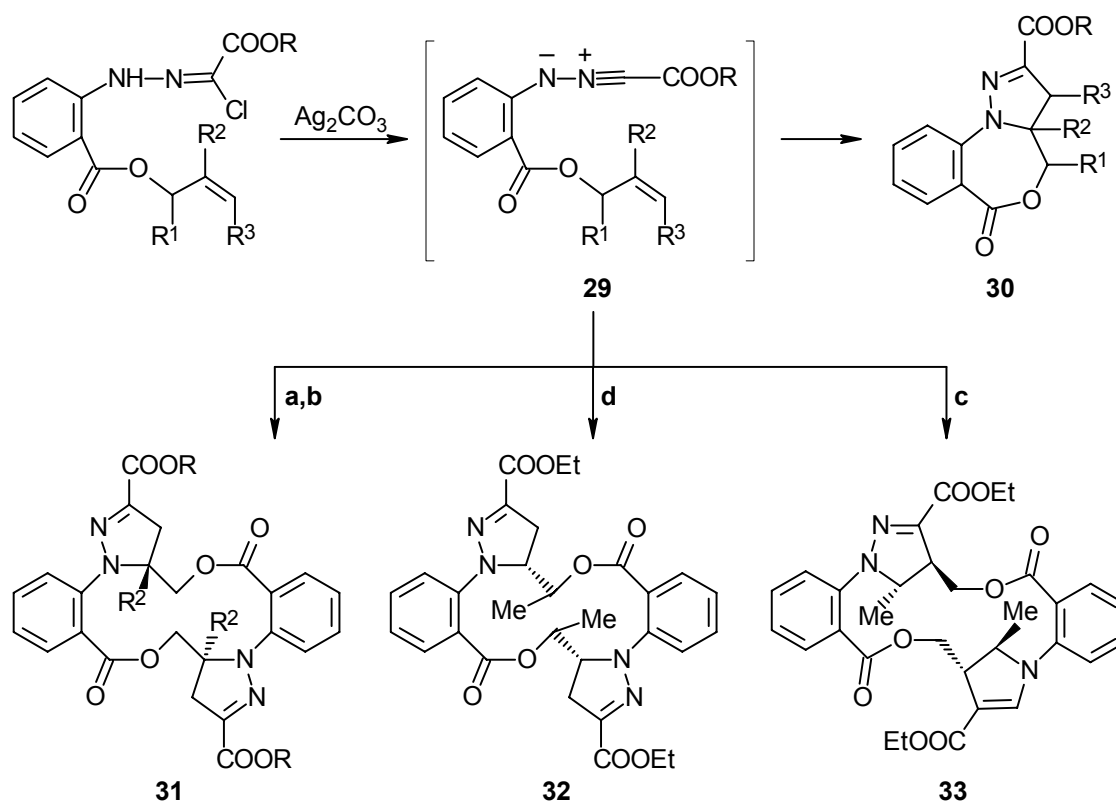
Pyrazoles annulated with a seven-,³⁹ eight-,³⁹ nine-^{40,41} and ten-^{40,41} membered ring have been synthesised by nitrilimine cycloaddition onto a terminal $C\equiv C$ bond in the presence of silver(I) carbonate (Scheme 11). Partially unsaturated analogues of the latter cycloadducts have been obtained under the same reaction conditions from the corresponding hydrazonoyl chlorides bearing an ethylenic dipolarophile.^{42,43} For the sake of comparison, some of the starting hydrazonoyl chlorides were found very slow to react with triethylamine or similar bases even in more severe conditions.⁴⁴



Scheme 11

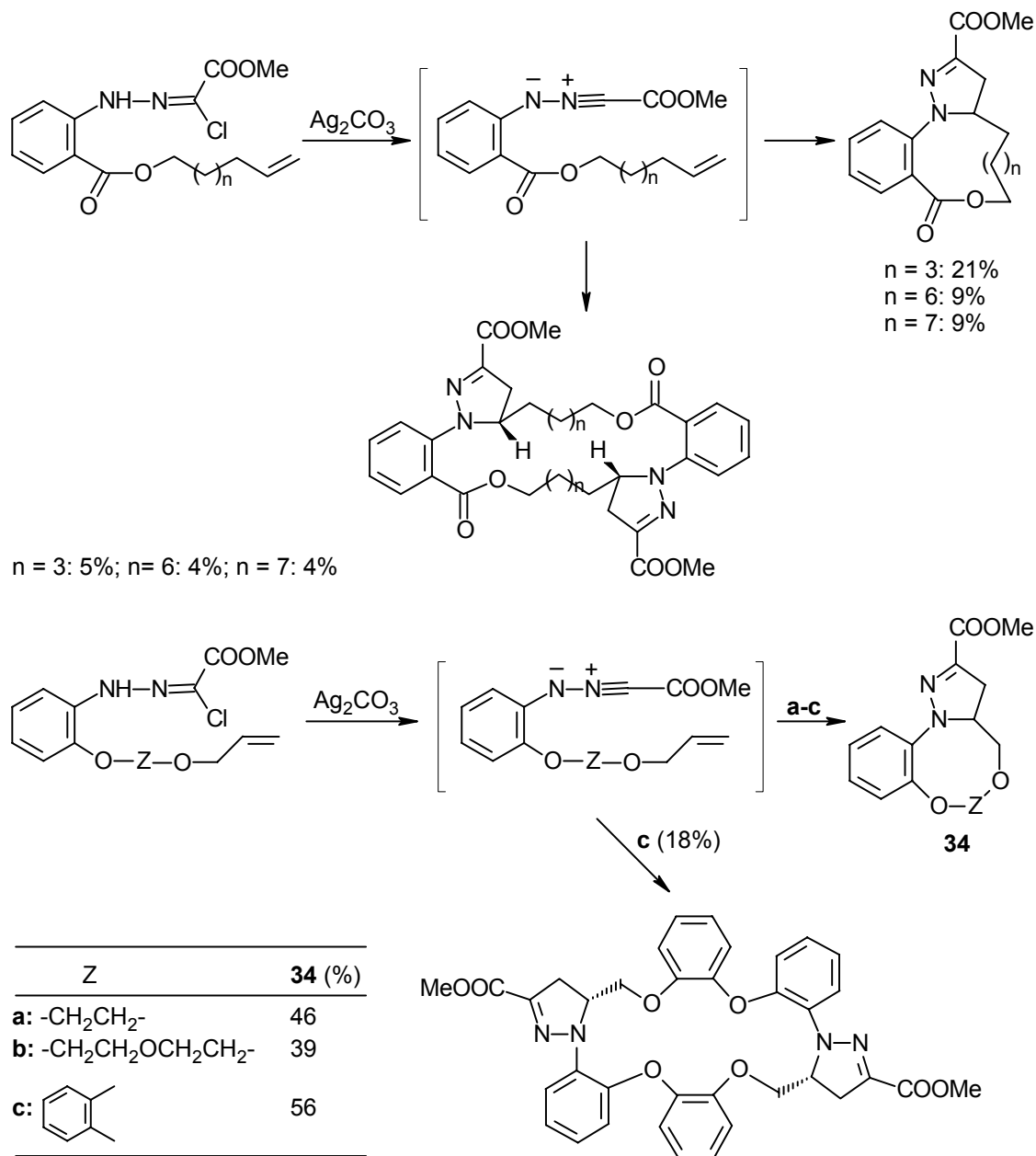
3.3 Formation of pyrazoles annulated to a large-sized ring

A number of strategies have been devoted to the synthesis of macrocyclic systems, including that based upon a multiple 1,3-dipolar cycloaddition sequence. This latter approach has been pioneered by Garanti and co-workers in a 1975 paper which describes the formation of macrocyclic compounds using intermolecular followed by intramolecular cycloadditions of nitrile oxides bearing an alkenyl dipolarophile.⁴⁵ The synthesis of a variety of (1,5)pyrazolophanes^{42,43,46} can be accomplished by treating a suitably functionalised hydrazonoyl chloride with silver(I) carbonate (Schemes 12 and 13). Of course, the intermolecular plus intramolecular cycloaddition sequence is competitive with the direct intramolecular cycloaddition, and the predominance of one pathway over the other is dependent on the length and the rotational freedom of the tether joining the reactive groups.



Entry	R1	R2	R3	30 (%)	31 (%)	32 (%)	33 (%)
a	H	H	H	18	14	-	-
b	H	Me	H	14	16	-	-
c	H	H	Me	-	-	12	-
d	Me	H	H	28	-	-	8

Scheme 12

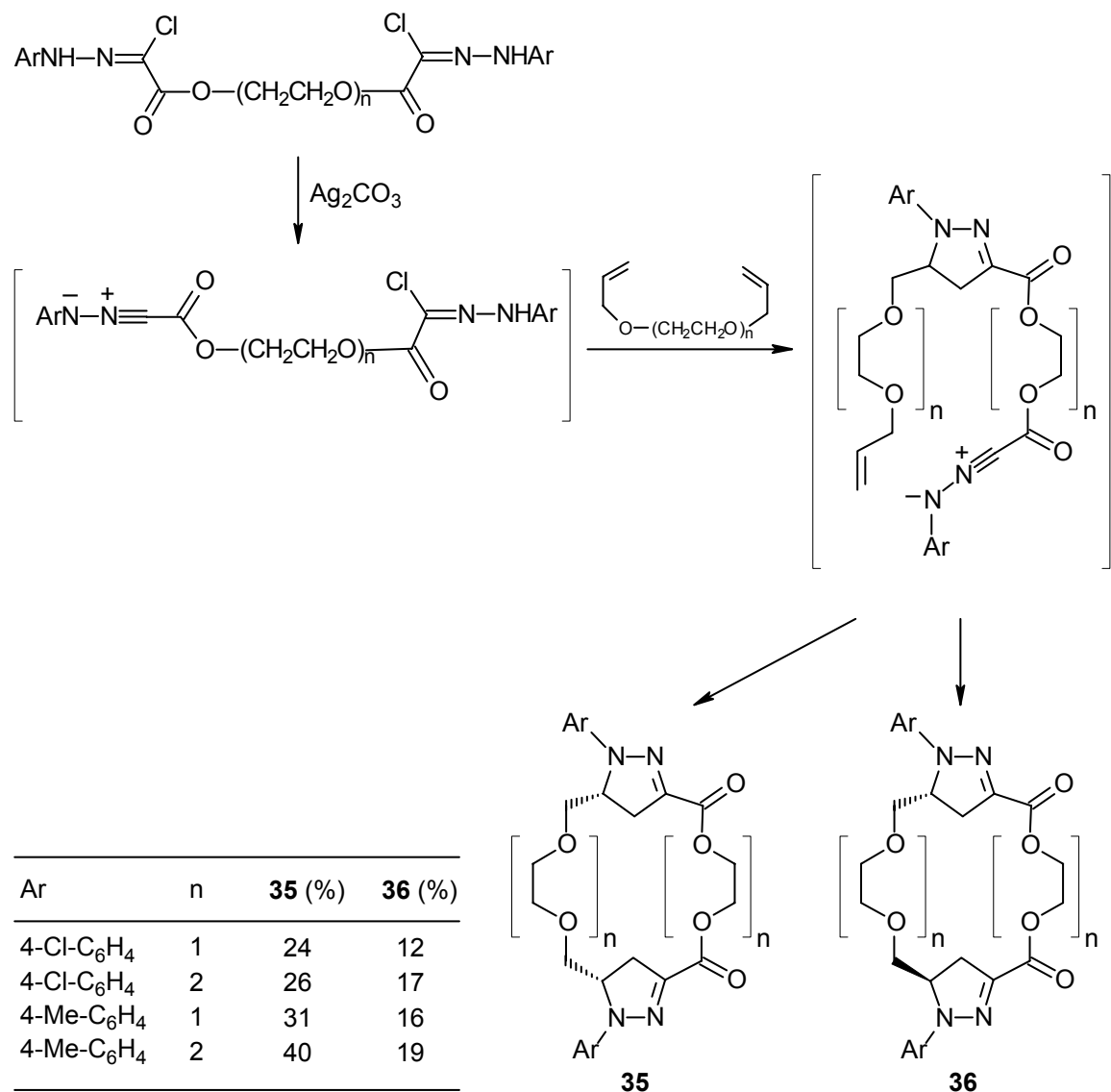


Scheme 13

Here again, the presence of a common base like triethylamine did not produce any appreciable result since large amounts of tarry material were usually formed. The intermolecular-intramolecular cycloadditive protocol promoted by silver(I) carbonate was also applied to *C*-substituted nitrilimines as precursors of bis-(3,5)pyrazolophanes.⁴⁷

Following the multiple cycloadditive macrocyclisation between bis-nitrile oxides and bifunctional dipolarophiles introduced by Kim and co-workers,⁴⁸ it was reported a version of the same methodology based upon the double cycloaddition between bis-hydrazoneyl chlorides and

bis-dipolarophiles in the presence of silver carbonate as the basic agent (Scheme 14).⁴⁹ Macrocylic products **35** and **36** were obtained with good combined yields (36-59%).



Scheme 14

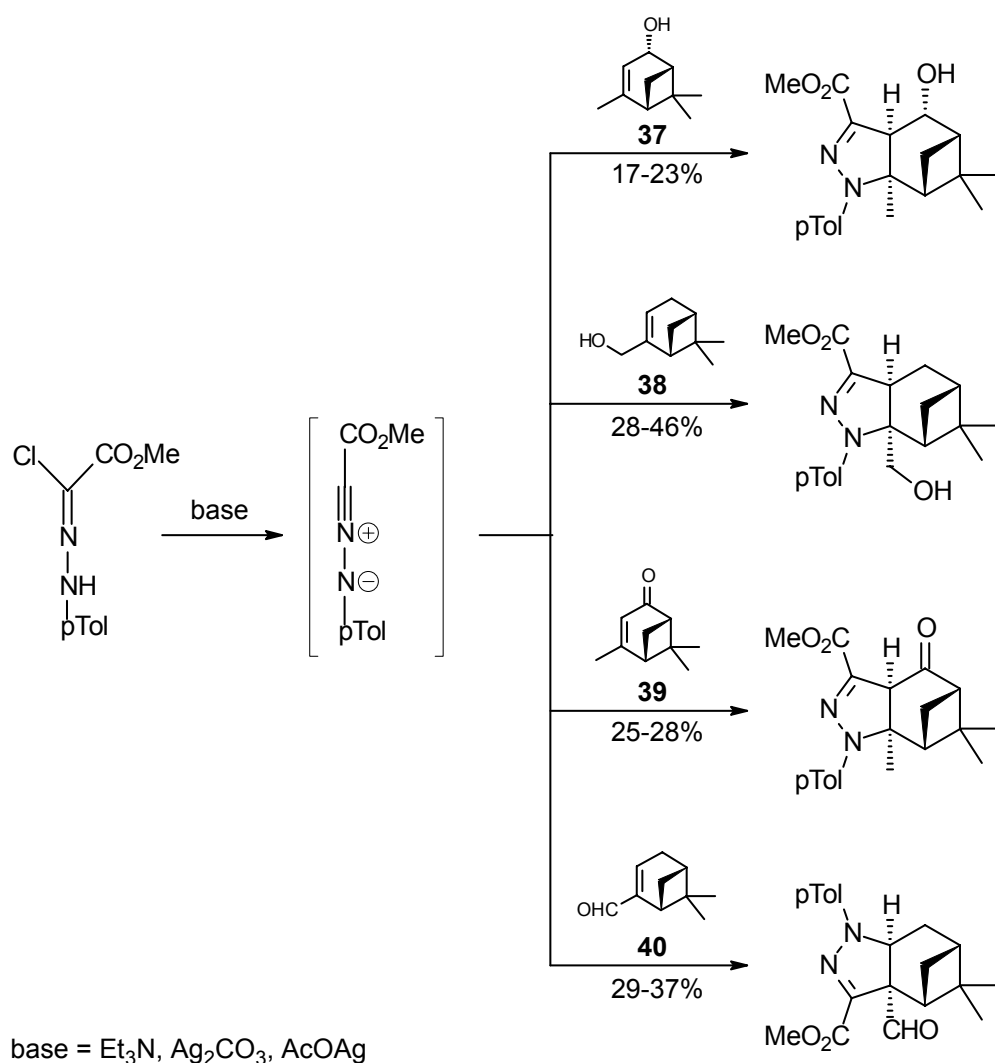
4. Stereoselective cycloadditions

Due to the utility of enantiopure pyrazolines in organic synthesis and some interesting applications of related products, stereoselective cycloadditions of nitrilimines have become useful in the last few years, and the subject have been recently reviewed.⁵⁰ Much of the examples discussed above actually involves stereoselective cycloadditions, although onto racemic

substrates. The aim of this paragraph is to present the behaviour of silver(I) salts-promoted nitrilimine cycloadditions towards stereoselectivity in the synthesis of enantiopure heterocycles. For this reason the discussion will be restricted to cover cycloadditions in which the product(s) is optically active.

4.1 Intermolecular stereoselective cycloadditions

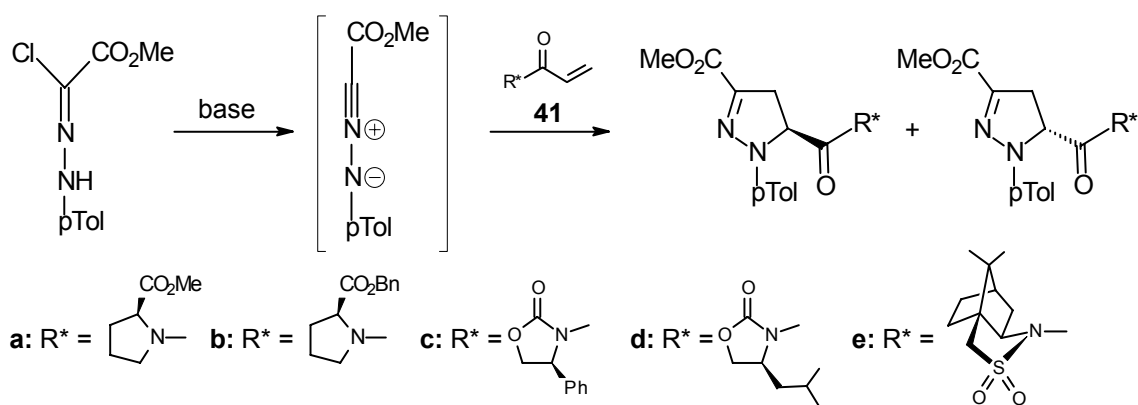
A variety of naturally-occurring pinane derivatives, namely (*S*)-*cis*-verbenol **37**, (1*R*)-(-)-myrtenol **38**, (1*S*)-(-)-verbenone **39** and (1*R*)-(-)-myrtenal **40** have been submitted to nitrilimine cycloaddition in the presence of both triethylamine and silver(I) salts (Scheme 15).⁵¹ Due to the severe steric hindrance exerted by the two methyl groups placed onto the cyclobutyl ring of the dipolarophiles, these processes resulted fully stereoselective irrespective to the basic agent.



Scheme 15

In contrast to the above examples, nitrilimine cycloadditions to limonene derivatives (1*S*)-(-)-perillyl alcohol and (*S*)-(-)-perillaldehyde resulted as site- and regioselective but not stereoselective processes.⁵¹

The behaviour of nitrilimines towards a series of enantiopure acrylamides **41** was investigated in the presence of several basic agents, namely triethylamine, (-)-sparteine and silver(I) acetate⁵² (Scheme 16). The diastereoisomeric ratio ranges between 58:42 and 83:17 depending upon the chiral auxiliary connected to the α,β -unsaturated dipolarophile. The best results, obtained with acrylamides **41c** and **41e**, possibly reflect the lower conformational flexibility of the latter two substrates compared to **41a**, **41b** and **41d**. The base and the presence of salts as LiCl and (AcO)₂Mg, which were investigated as potential complexing agents, exerted little or no influence on cycloaddition diastereoselectivity.



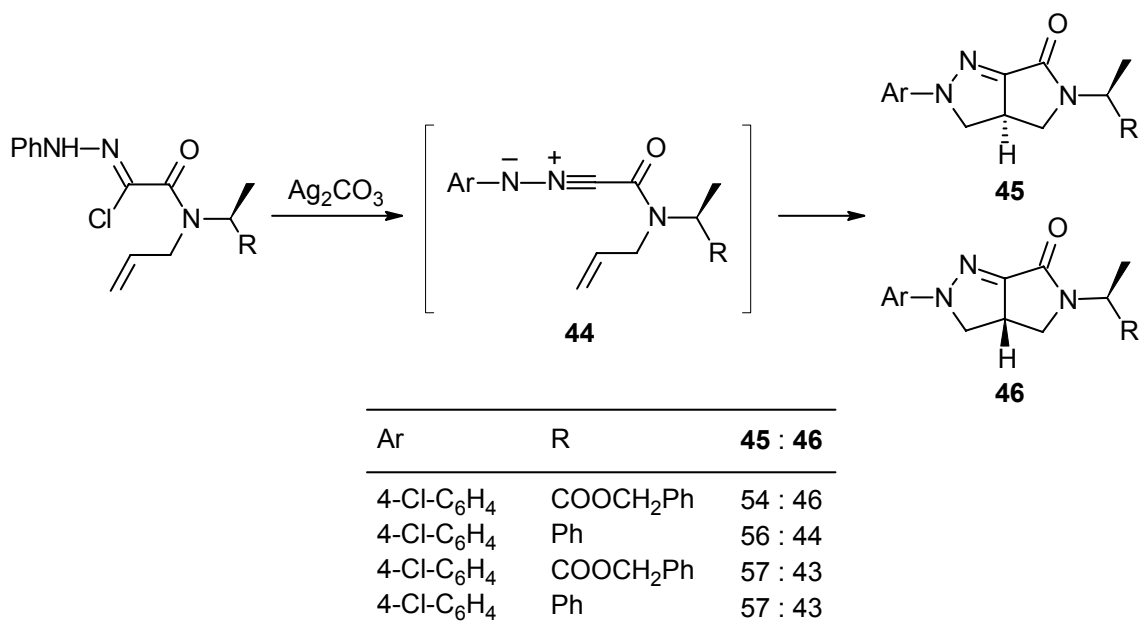
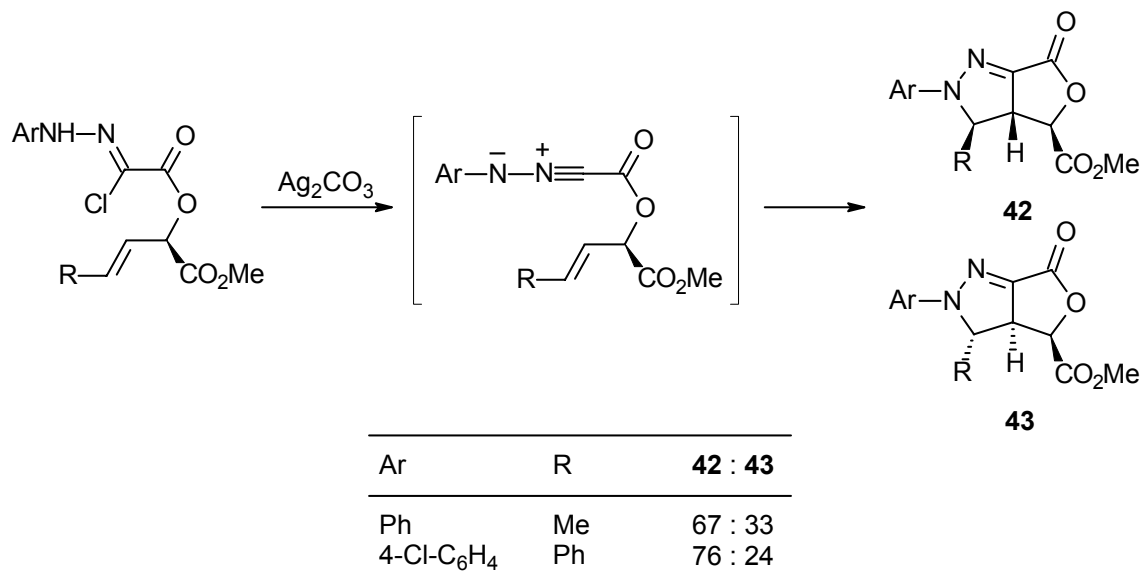
Scheme 16

4.2 Intramolecular stereoselective cycloadditions

Due to their versatility, intramolecular nitrilimine cycloadditions constitute a powerful approach to a wide range of heterocyclic systems.⁵³ Furthermore, the products arising from these processes are generally complex polycyclic, annulated, and fused ring heterocycles that are difficult to prepare by any other method. From these preliminary remarks, it can be argued that a way which allows the synthesis of the mentioned products in the enantiopure form should be highly desirable.

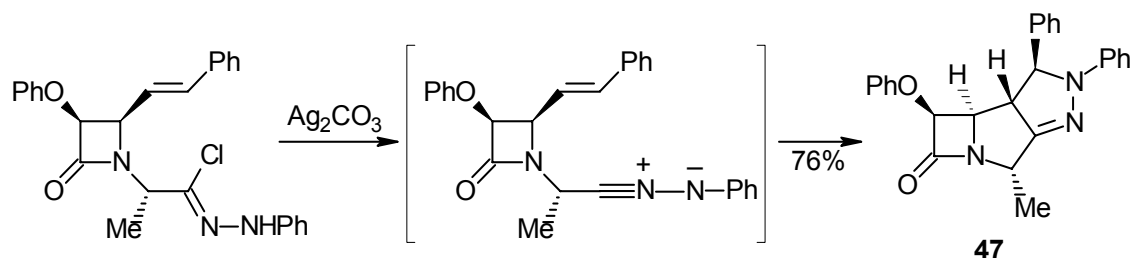
As far as the synthesis of pyrazoles annulated to a five-membered ring is concerned, it may be recalled that the construction of the furo[3,4-*c*]pyrazole skeleton belongs to the first success of the intramolecular nitrilimine cycloaddition methodology.⁵⁴ The first case of asymmetric induction in such reactions promoted by silver(I) carbonate was reported in 1999,⁵⁵ giving rise to a mixture of enantiopure cycloadducts **42** and **43** (Scheme 17). Since the intramolecular cycloaddition of nitrilimines **44** occurred with a lower degree of diastereoselectivity,⁵⁶ it is

apparent that better results are obtained if the pre-existing stereocentre is placed in the α -position to the ethylenic dipolarophile or the 1,3-dipole (closer to the reaction site).

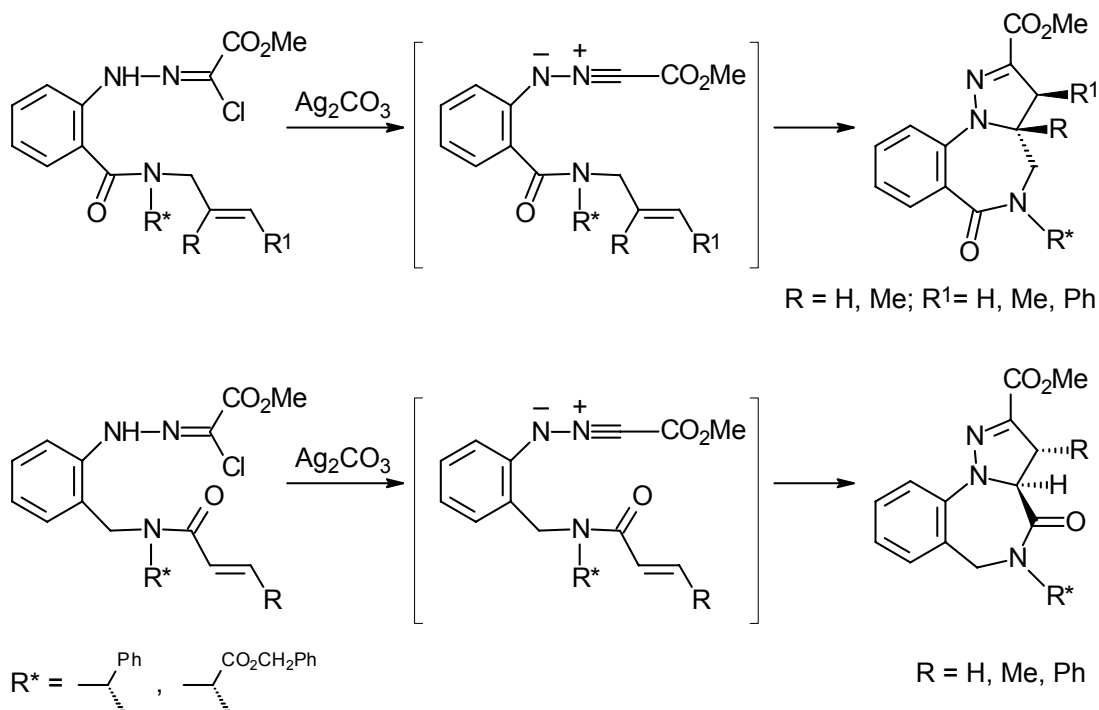


Scheme 17

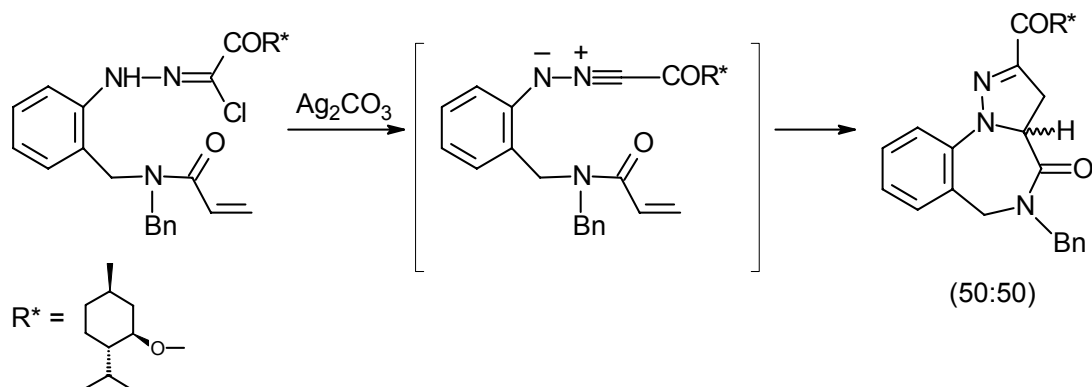
A further example of pyrazoline annulated to a five-membered ring is given by the tricyclic β -lactam **47**, which was obtained with full stereoselectivity.⁵⁷

**Scheme 18**

Annulated [1,4]benzodiazepines represent valuable synthetic targets due to their well-known pharmacological activity as hypnotics and sedatives.⁵⁸ Their stereoselective synthesis by silver(I) carbonate-promoted nitrilimine cycloaddition have been achieved with selectivities ranging from low (54:46) to good (80:20) in favour of the depicted enantiopure diastereoisomer (Scheme 19).⁵⁹⁻⁶¹ Anyway, this stereochemical outcome is worth noting because the distance between the pre-existing and the newly-formed stereocentres is rather large.

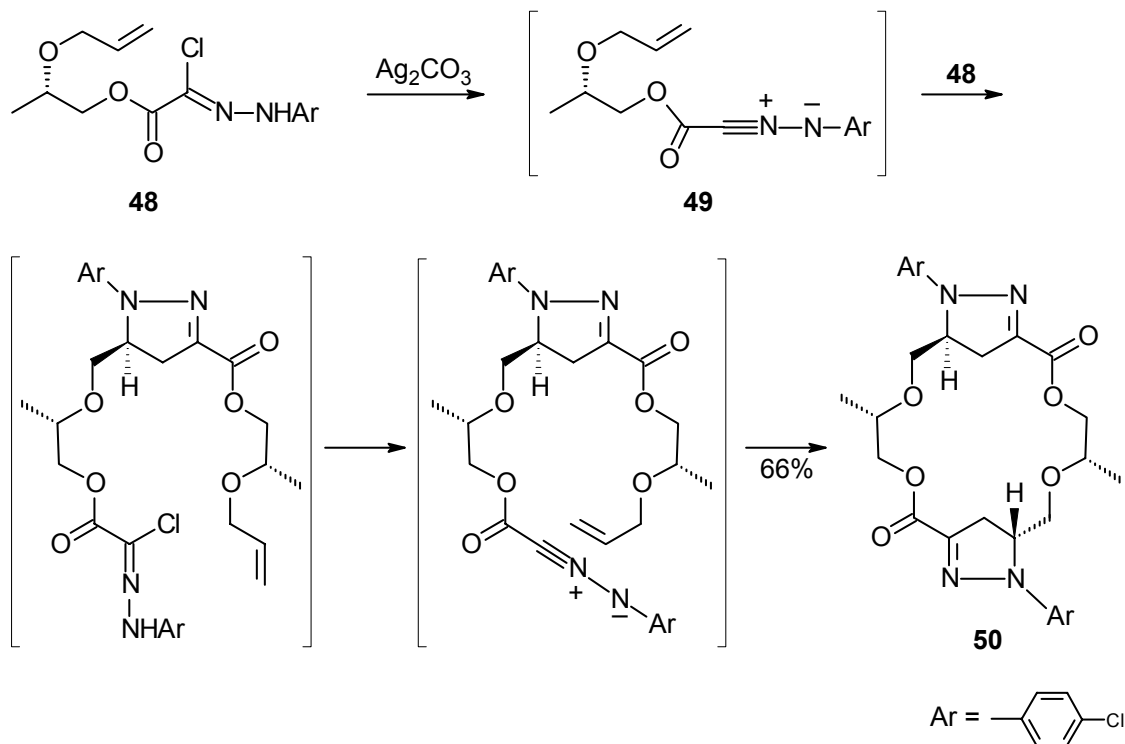
**Scheme 19**

The replacement of the 2-(*S*)-phenylethyl or the benzyl 2-(*S*)-propionate chiral auxiliaries with the (1*R*,2*S*,5*R*)-(-)-menthyl one caused a drop of the cycloaddition stereoselectivity since no diastereoisomeric excesses were produced (Scheme 20).⁶²



Scheme 20

The sequential inter- intramolecular cycloadditions of nitrilimine **49** (Schemes 21) gave the enantiopure pyrazolophane **50**.⁶³ This macrocyclic compound have been obtained as a single diastereoisomer, possibly due to the asymmetric induction of the pre-existing stereocentre reinforced by some kind of coordination between the silver ion and the etheral oxygens of the reactants.



Scheme 30

Acknowledgements

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