New Aspects of Old Reactions. Cations and Radicals in Heterocyclic Synthesis

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Introduction

The electrophilic N-acyliminium intermediate forms carbon-carbon bonds with nucleophilic carbon irreversibly yielding amidoalkylation products [1]. Of the various structural modifications in the electrophile the substitution of a carboxyl group for a hydrogen is highly useful since it may lead to α-amino carboxyl derivatives. In such a process the reactive intermediate obviously will be destabilized by the presence of the electron-withdrawing carboxyl substituent requiring the use of activated carbon nucleophiles or intramolecular addition to achieve satisfactory coupling. Given the rapidly expanding interest in the reactions of electrophilic oxonium intermediates [2] the analogous methoxycarbonyl oxonium ion may also be used advantageously for the synthesis of novel oxacycles.

Upon lowering the oxidation state of the reactive carbon a radical intermediate will be formed. In the latter structure the presence of both an electron-donating and an electron-withdrawing substituent is said to have a synergistic effect on radical stability the so-called capto-dative effect [3]. In this lecture a discussion is given of the various possibilities for intra- and intermolecular carbon-carbon bond formation between the reactive intermediates described above and suitable nucleophiles viz. radicophiles (Figure 1).

A simple and straightforward application of the iminium electrophile is found in the synthesis of amino acids [4] (Figure 2). Particularly the use of activated carbon nucleophiles such as silanes [5a], silylenol ethers [5b] and stannanes in combination with an enzymatic resolution process [6] allows the synthesis of (S)-amino acids in an efficient manner. The efficacy of the electrophile can be further increased by changing the ester group into an amide or even a methoxyamide.

In the latter case the choice of the nucleophile may have a profound influence on the type of product formed (Figure 3).

While with alkyl silanes the expected addition

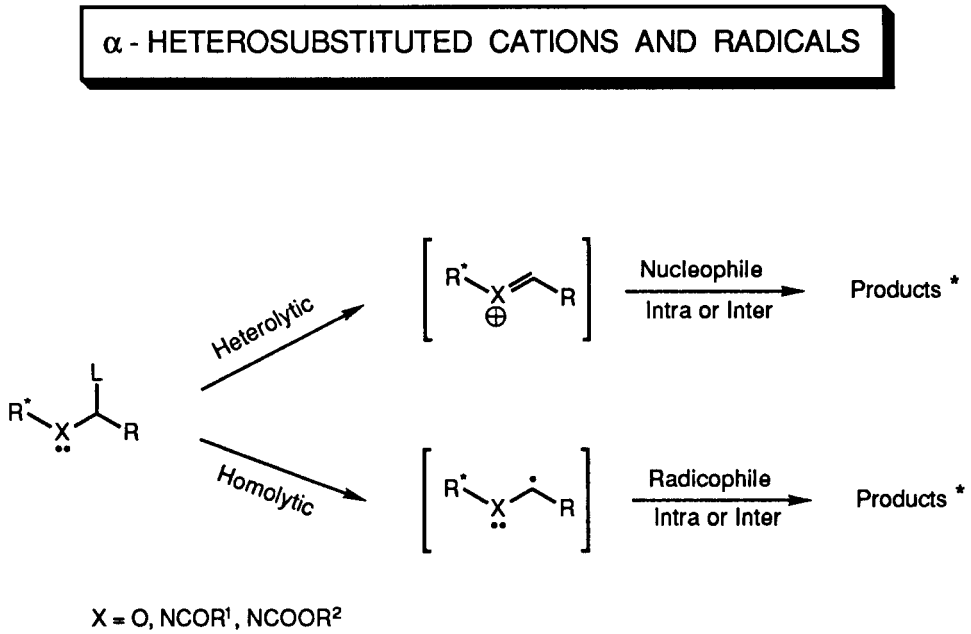


Figure 1

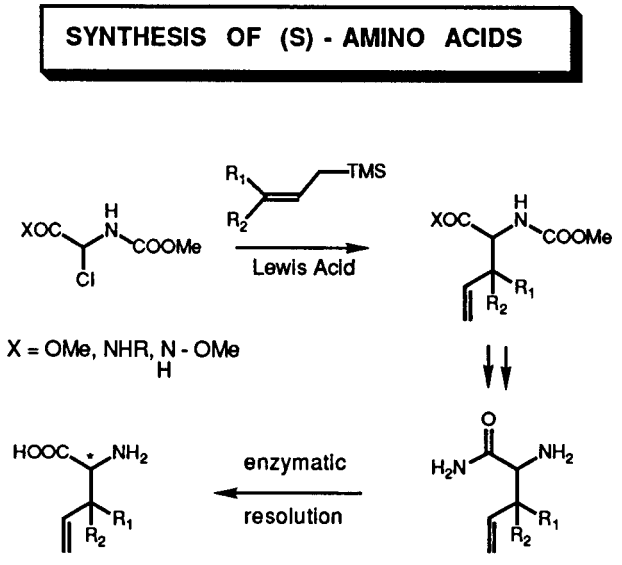


Figure 2

products are obtained the use of silyl enol ethers leads to substituted pyrrolidones. The initially formed carbonyl addition product now cyclizes to a hydroxy lactam due to the enhanced nitrogen nucleophilicity of the methoxyamide. Then subsequently a new acyliminium intermediate may form which either undergoes prototropic double bond isomerization or repeated addition of the less sterically hindered nucleophile ultimately yielding a disubstituted pyrrolidine. An interesting application of the glycine cation methodology is found in the synthesis of a natural norvaline amino acid (HON) [5b] which requires the use of a substituted silylenol ether (Figure 4).

The above mentioned intermolecular addition reaction can be also adapted to an intramolecular variant yielding cyclic amino acids. Now the use of simple carbon π-nucleophiles suffices to induce bond formation [7]. Due to the well-known preference for the ionic 6-endo process the synthesis of pipecolic acids operates best (Figure 5).

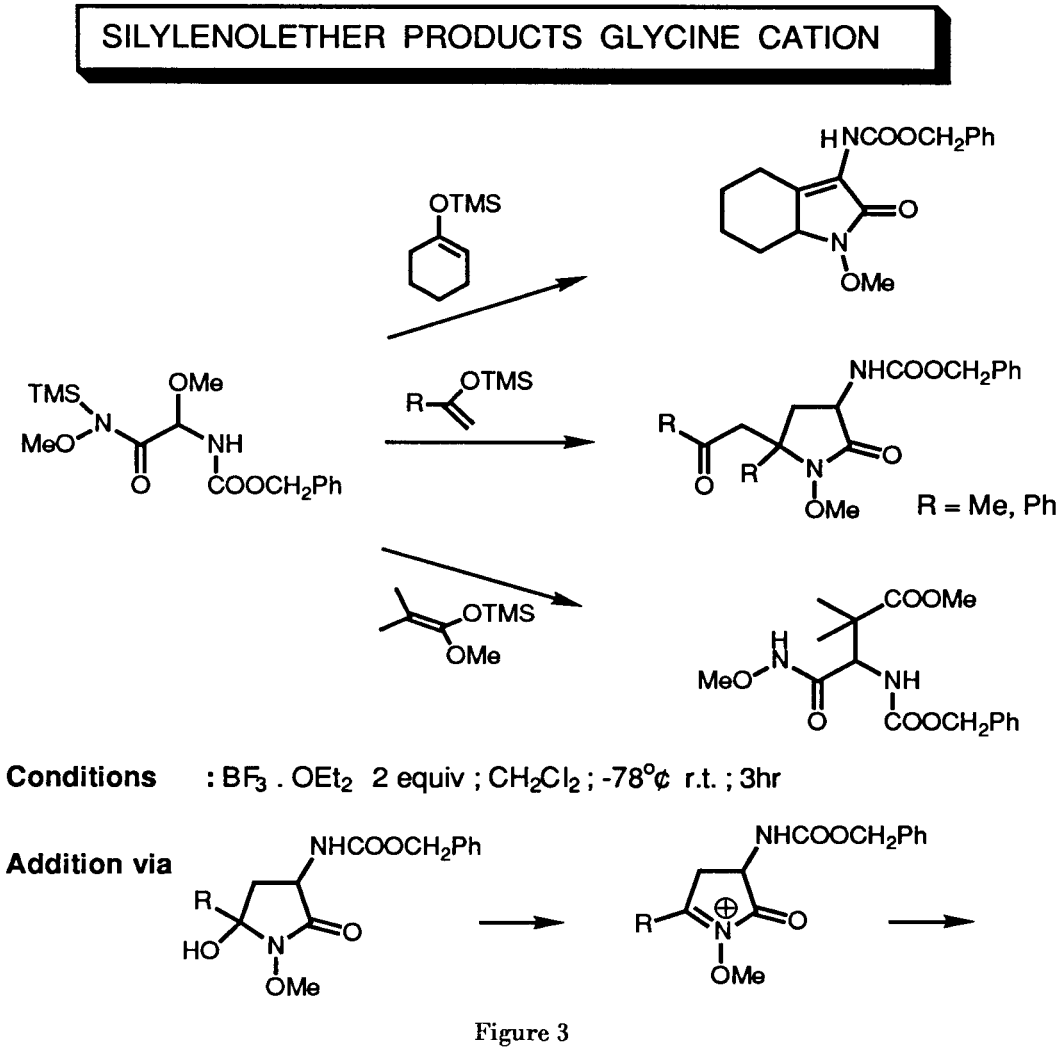


Figure 3

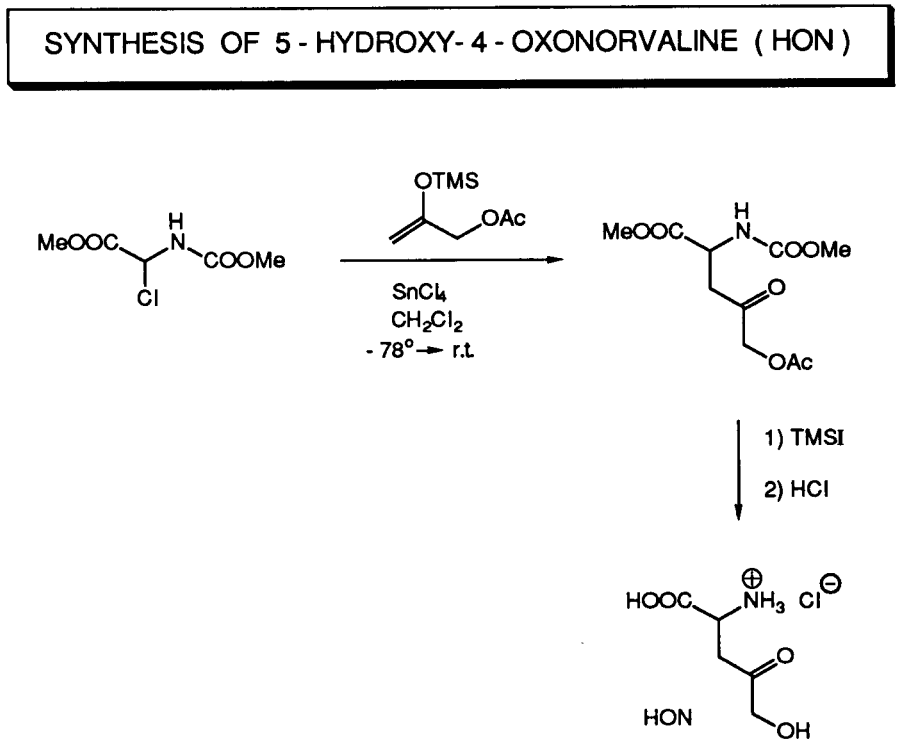


Figure 4

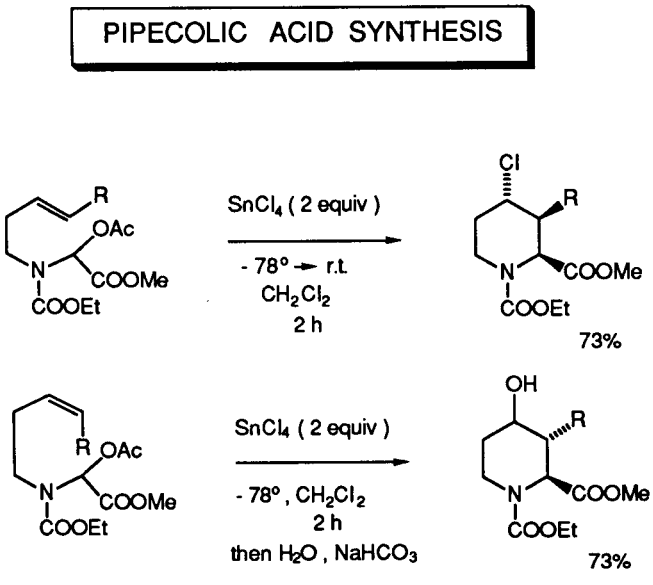


Figure 5

Depending on the stereochemistry of the olefin syn or anti addition products are obtained in which the incoming nucleophile such as a chloride enters in an equatorial manner while in the transition state the ester group as a result of 1,3 allyl strain is axially oriented. A complicating factor is the possibility of an aza-Cope type rearrangement which together with the possibility of a ring inversion and the stabilization of the incipient C-4 carbenium intermediate sometimes leads to unpredicted results (Figure 6).

The aforementioned Cope rearrangement while obscured in the azacyclic series by steric interactions between nitrogen substituent and α-ester moiety also plays a dominant role in the oxacyclic series. Thus the ring closure of a simple oxonium intermediate affords a mixture of axially and equatorially chlorinated pyran carboxylic esters [8] (Figure 7).

The seemingly anomalous *cis* addition to the double bond is straightforwardly explained by considering the results of (*E*)- and (*Z*)-olefins (Figure 8). While the (*E*)-olefin almost exclusively yields the 3,4-*cis*-pyrancarboxylic ester the corresponding (*Z*)-olefin affords the 3,4-*trans*-isomer. A rationale for this behaviour invokes the oxa-Cope rearrangement of the intermediate oxonium ion in which the ester group is pseudo-equatorially oriented. After a chair-chair interconversion the ester group now occupies the axial position and exerts a neighbouring stabilizing effect upon the electron deficient positions at C-2 and/or C-4. A second factor is connected with the 1,3 diaxial destabilization energy, which will countereffect any electronic stabilization. We therefore decided to investigate the C-6 mono- and disubstituted ester

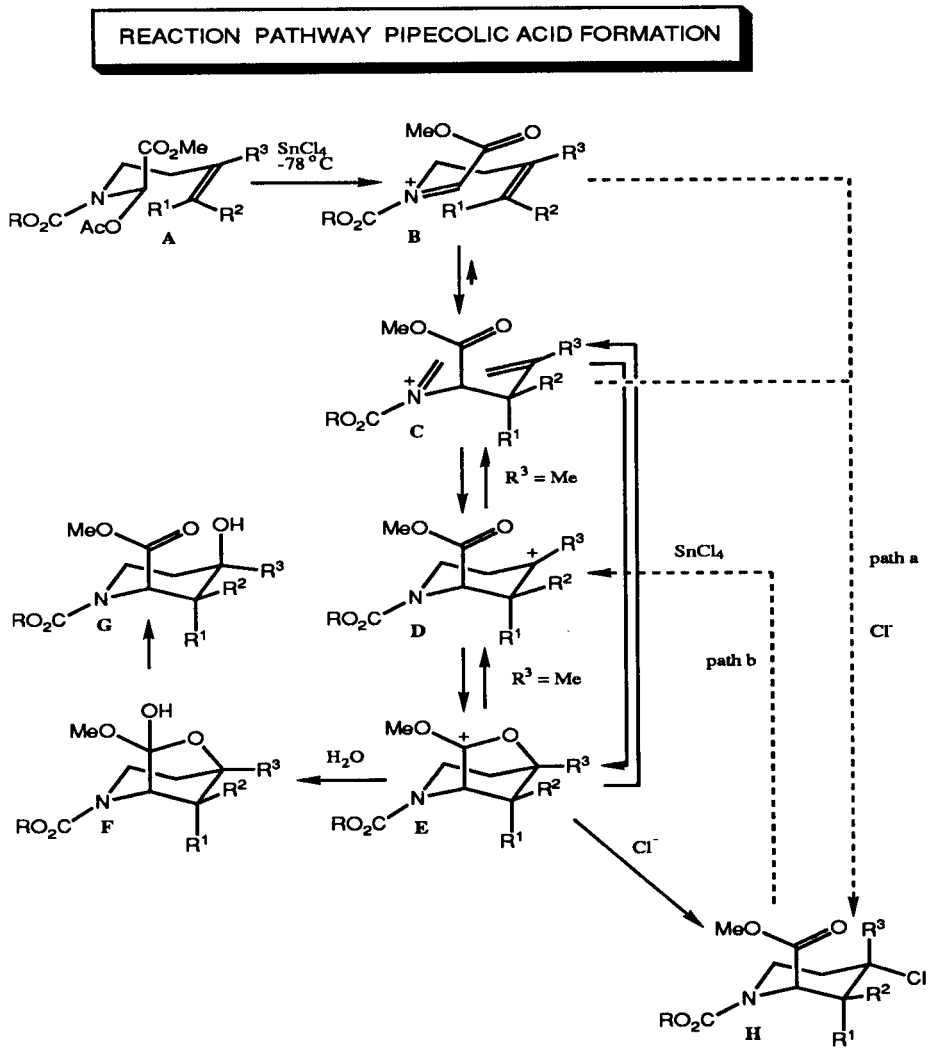


Figure 6

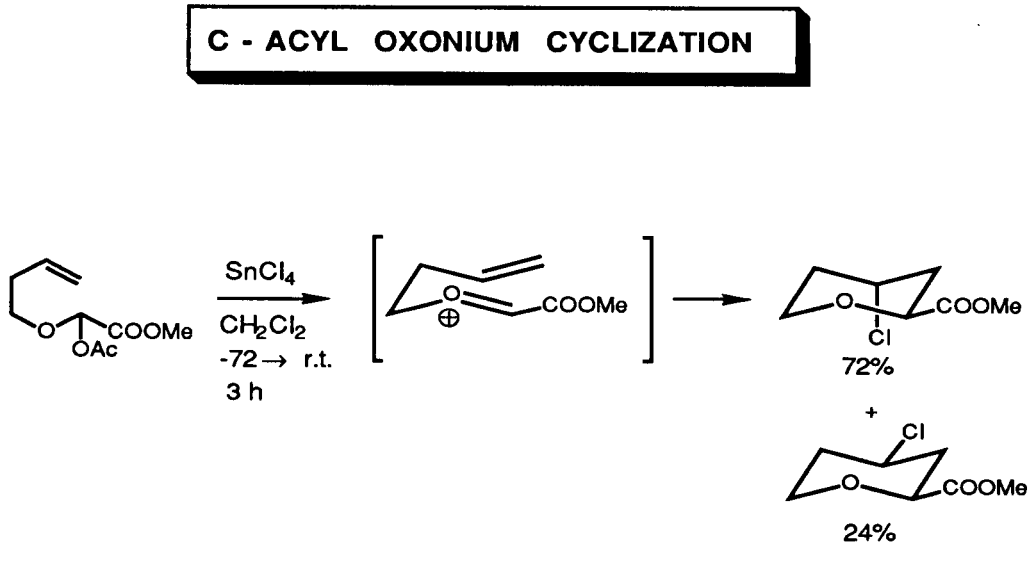


Figure 7

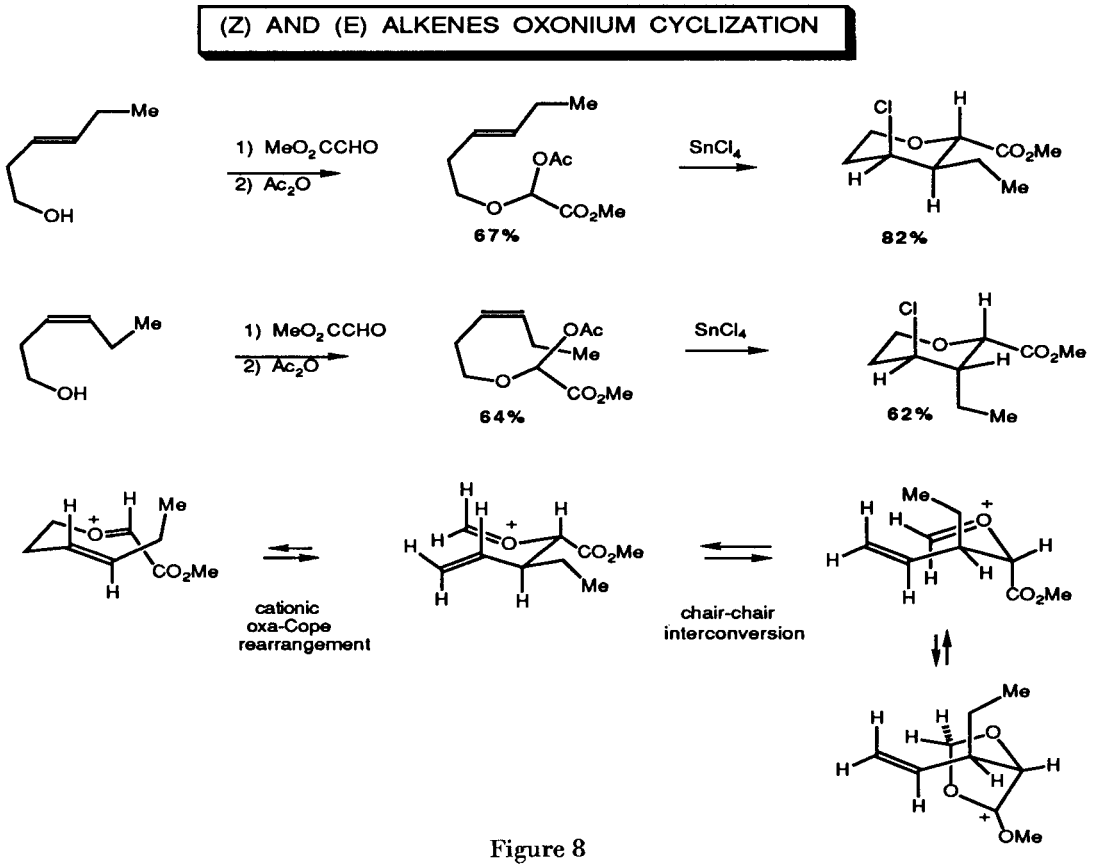


Figure 8

derivates. Most significantly the mono-ester readily underwent cyclization to virtually produce a single stereoisomer (Figure 9) in which both ester moieties occupy the equatorial position while the chlorine atom is axially oriented. Thus apparently even the 1,3 diaxially unfavorable interaction of two ester groups does not prevent the electronic stabilization of the C-4 electron deficient position. One other aspect of this system is the degenerate nature of the oxa- Cope rearrangement process. Further study of this interesting phenomenon through disubstituted systems failed to yield more data. The diester system only led to fragmentation of the precursor while the dimethyl derivative afforded the normal cyclization product with chloro- and ester substituents both equatorial. The unfavorable axial Me ↔ COOMe 1,3 interaction may effectively prevent the alternate conformation to occur.

A novel element to be introduced in this process is the chirality at the C-6 position. Here not only the study of the chirality transfer to C-2 and C-4 would be of obvious interest but also the resulting pyran derivatives - in principle convertible to a KDO type structure - could be challenging synthetic targets (Figure 10). The starting alcohol was obtained according to the procedure of Roush [9] and although the addition of methyl glyoxylate suffered from the increased steric hindrance the desired acetate could be obtained as a 1:1 mixture of diastereomers upon chromatography. After considerable experimentation success was achieved upon quenching of the reaction mixture with formaldehyde methyl acetal. Gratifyingly a single diastereomer was obtained in which the chlorine atom is axially positioned. Further study is necessary to optimize the yield and evaluate the overall degree of stereocontrol. Also in the field of hydrazine synthesis considerable progress has been achieved by using the cationic cyclization technique. As reported earlier [10] cyclic hydrazines are obtainable in high yield by formic acid cyclization of the acetylene precursors (Figure 11).

While initially serious difficulties were met in removing the nitrogen protecting groups the choice of the allyloxycarbonyl proved benificial especially when combined with an adaptation of the method of removal (Figure 12). Thus while the conventional palladium dealkylation [11] produced mixtures of various substitution products the change of acetic acid for the corresponding anhydride provided a quantitative yield of the acetylated product. Although no systematic

α' MONO - AND DISUBSTITUTED OXONIUM ION

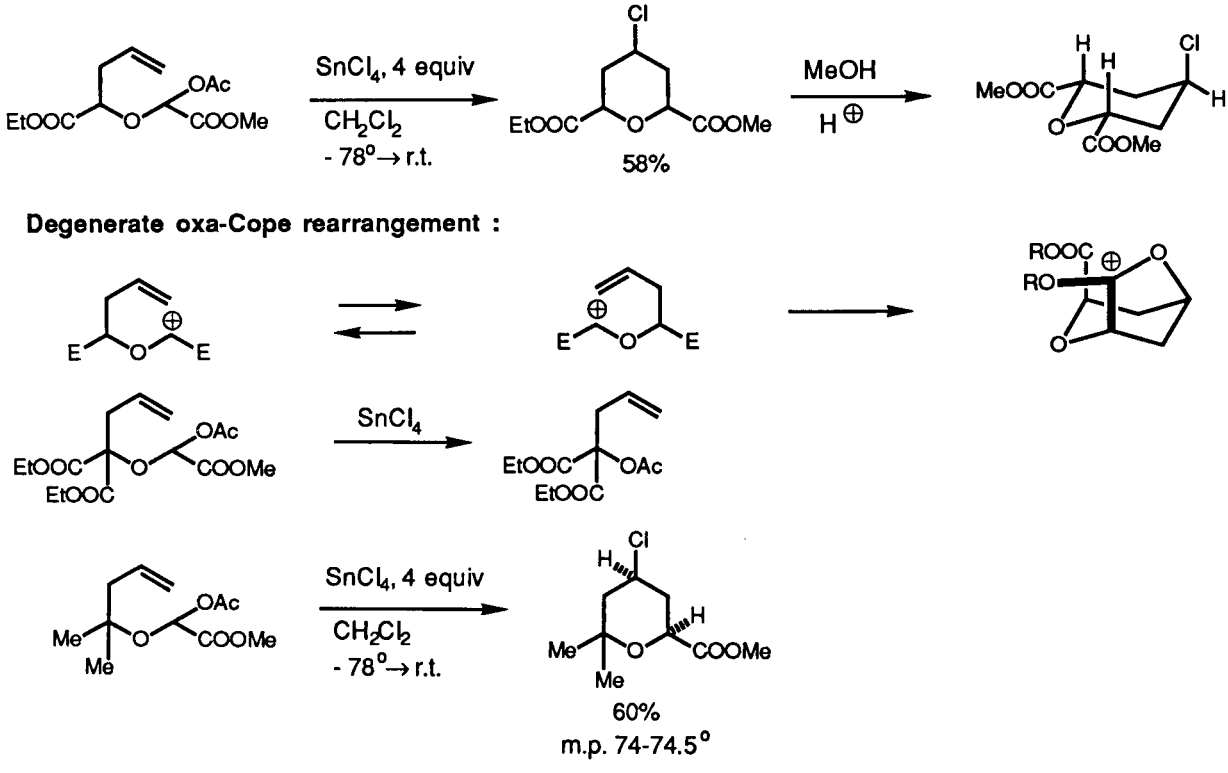


Figure 9

KDO MODEL STUDIES

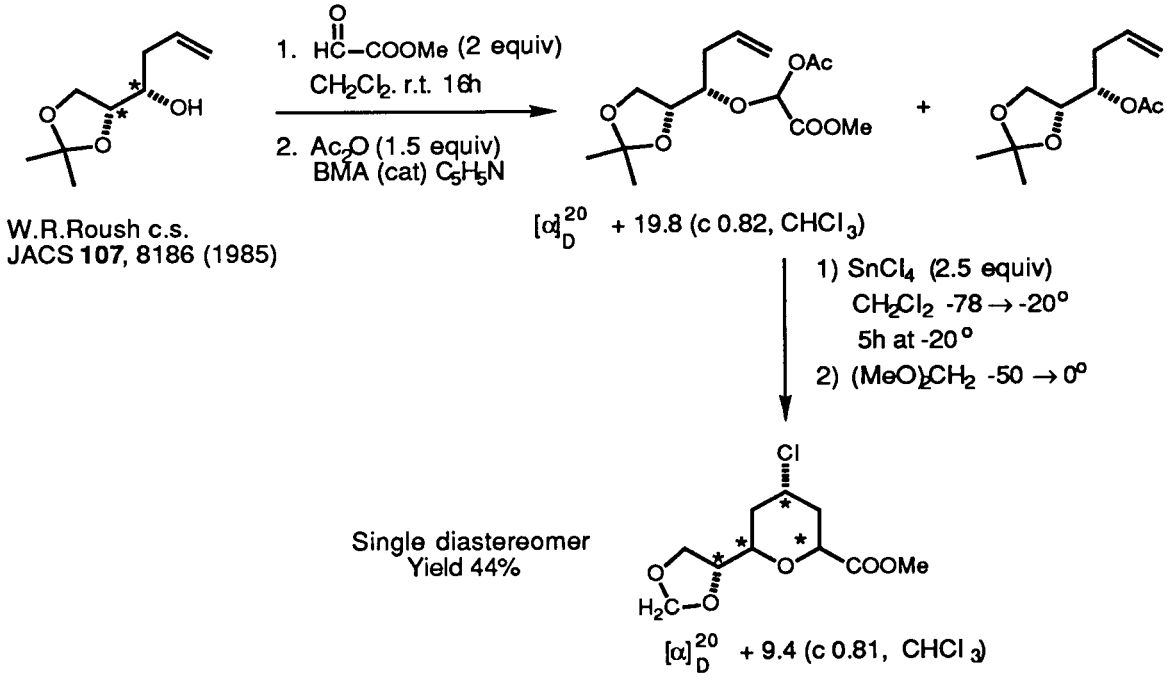


Figure 10

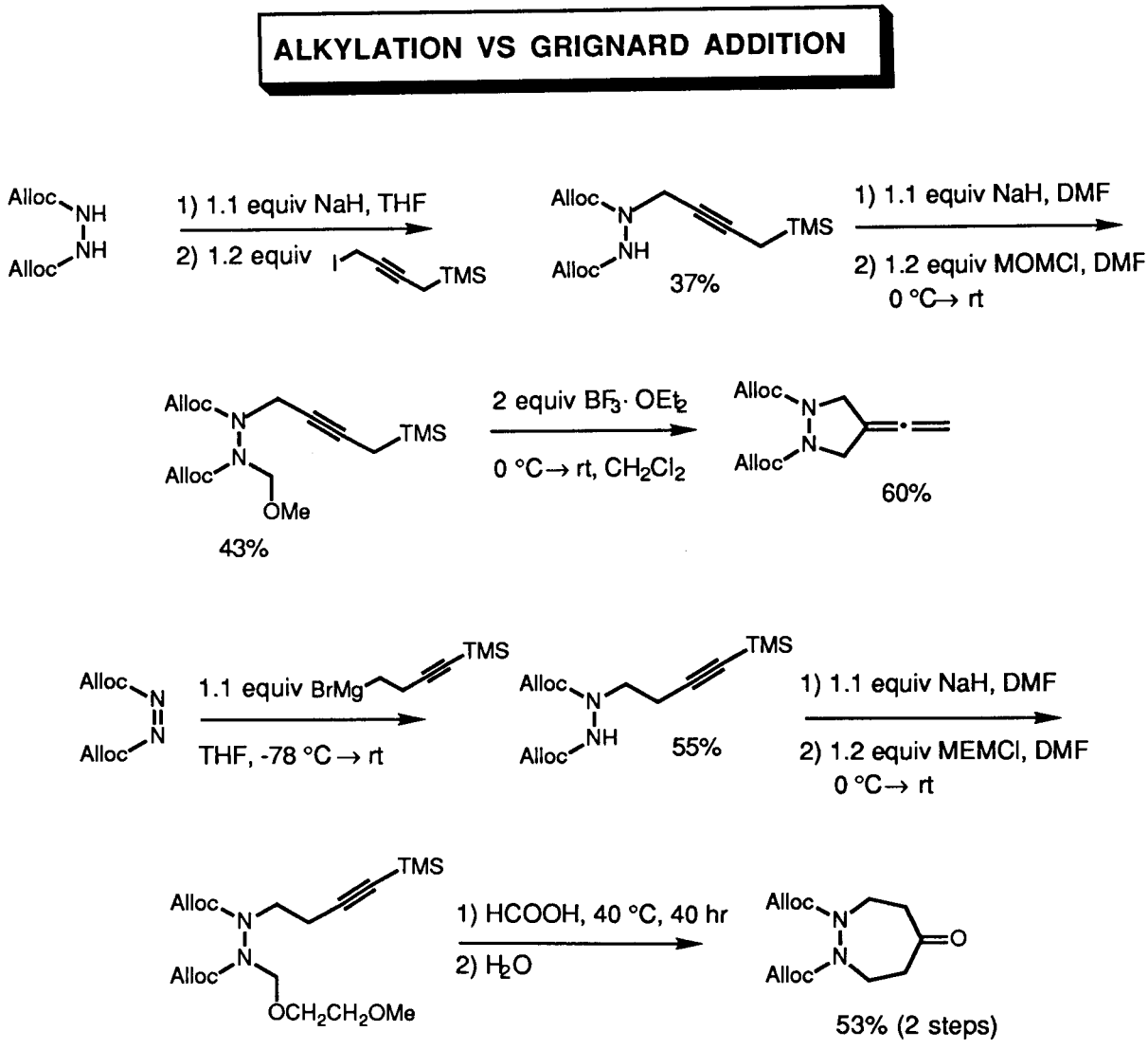


Figure 11

study of the mechanism of this interesting transamidation was performed the reaction seemed to involve the tin-carbamate salt and not the free amine. Furthermore the palladium dealkylation occurred instantaneously (Figure 13) and the process is general for different types of activated carbonyl groups. Depending on the bulkiness of the anhydride one of the two nitrogen atoms is substituted while direct quench with strong acid immediately produced the crystalline hydrazine salt in quantitative yield. The stability of the corresponding free hydrazine proved however to be rather low in coupling reactions with activated dihalides and only small amounts of the desired bicyclic nitrogen ring systems were obtained. A non-trivial ramification of the above discussed deprotection method is the possibility of forming peptide bonds in a one-pot operation (Figure 14).

Although the results of this study will be published separately it proved indeed possible to couple activated amino acids with allyloxycarbonyl protected nitrogen compounds in high yields under essentially neutral conditions.

In a projected synthesis of 5-chloropiperazic acid [12] the method outlined in figure 11 was applied to ethyl carbazate.

While the first steps proceeded in good yields, the ringclosure gave a different product rather than the expected six-membered ring (figure 15). Due to the

PALLADIUM CATALYZED DEPROTECTION

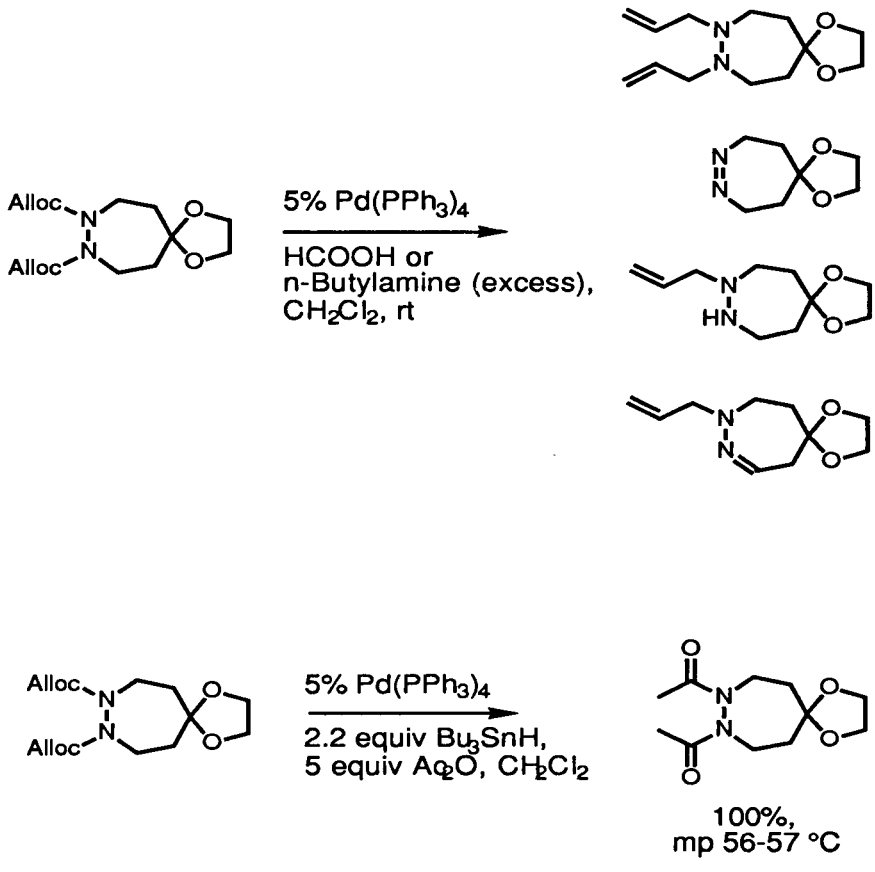


Figure 12

ISOLATION OF THE DEPROTECTED HYDRAZINES

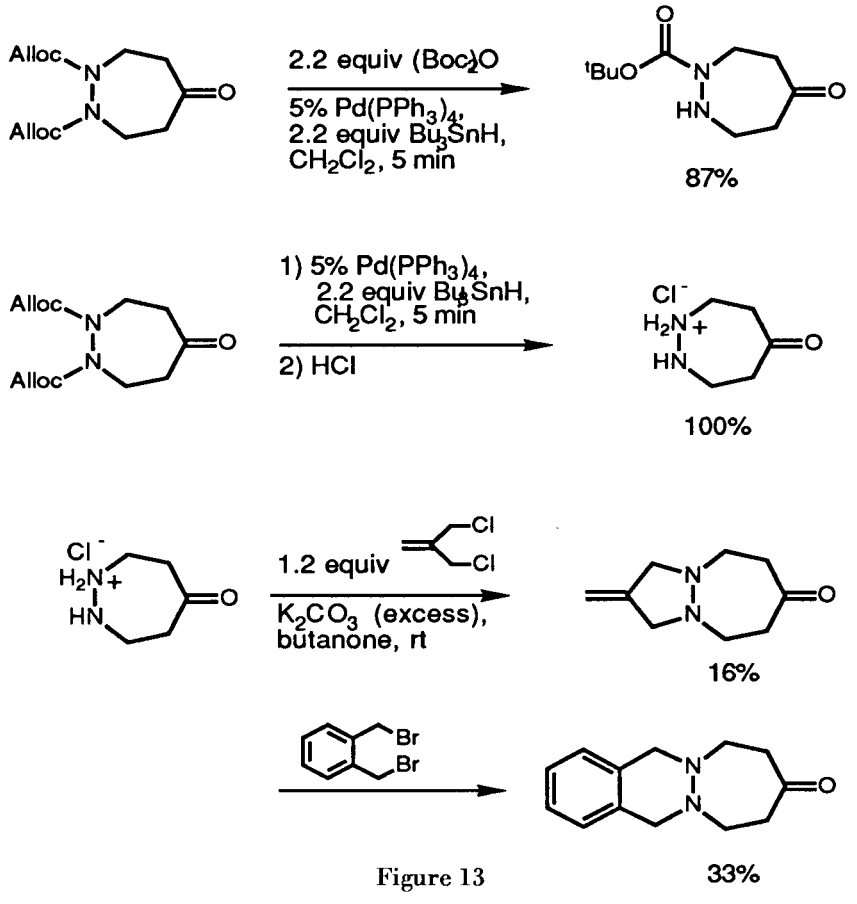


Figure 13

FORMATION OF PEPTIDE BONDS

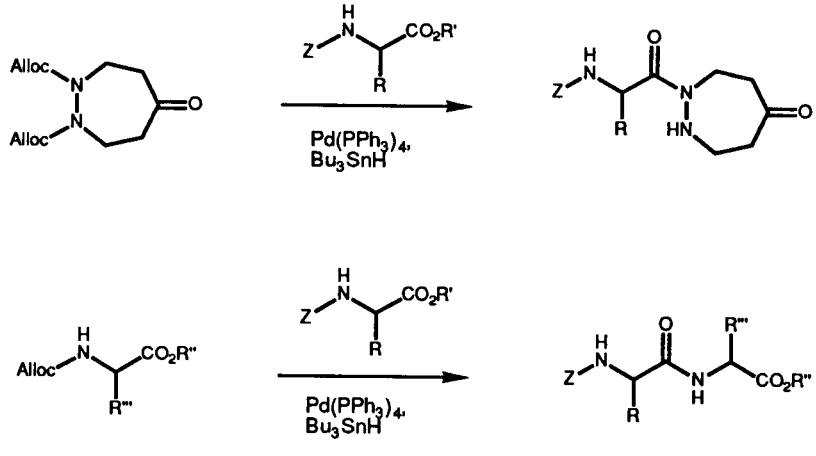


Figure 14

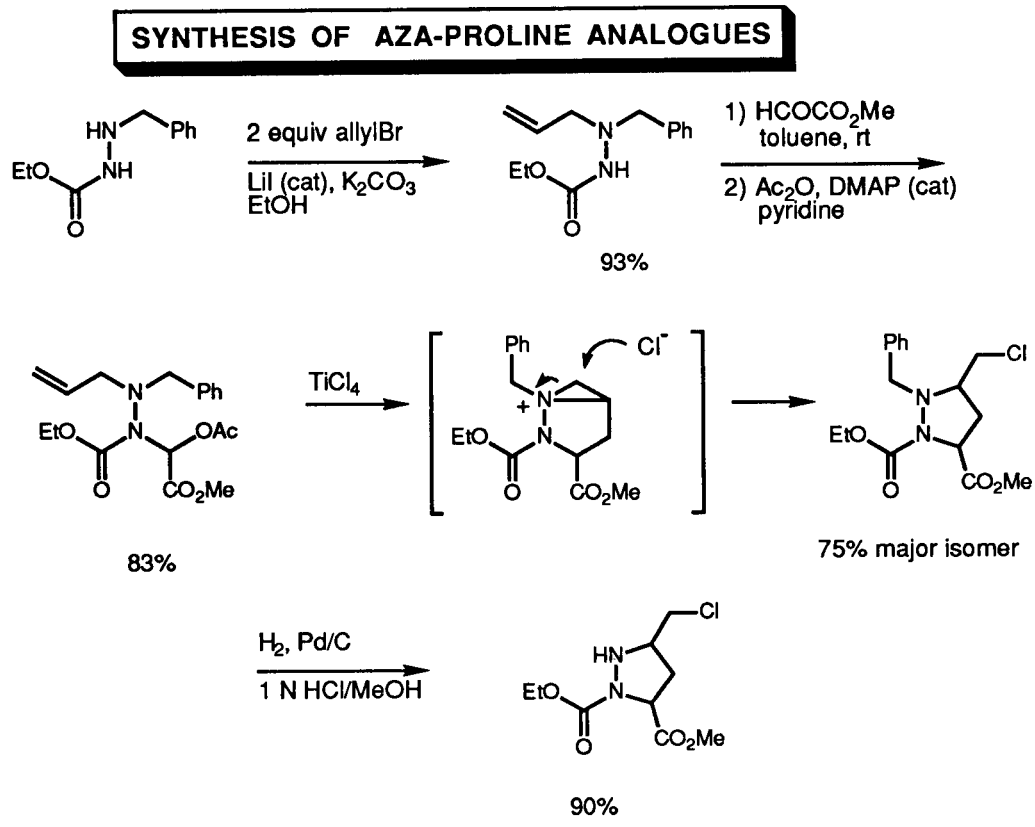


Figure 15

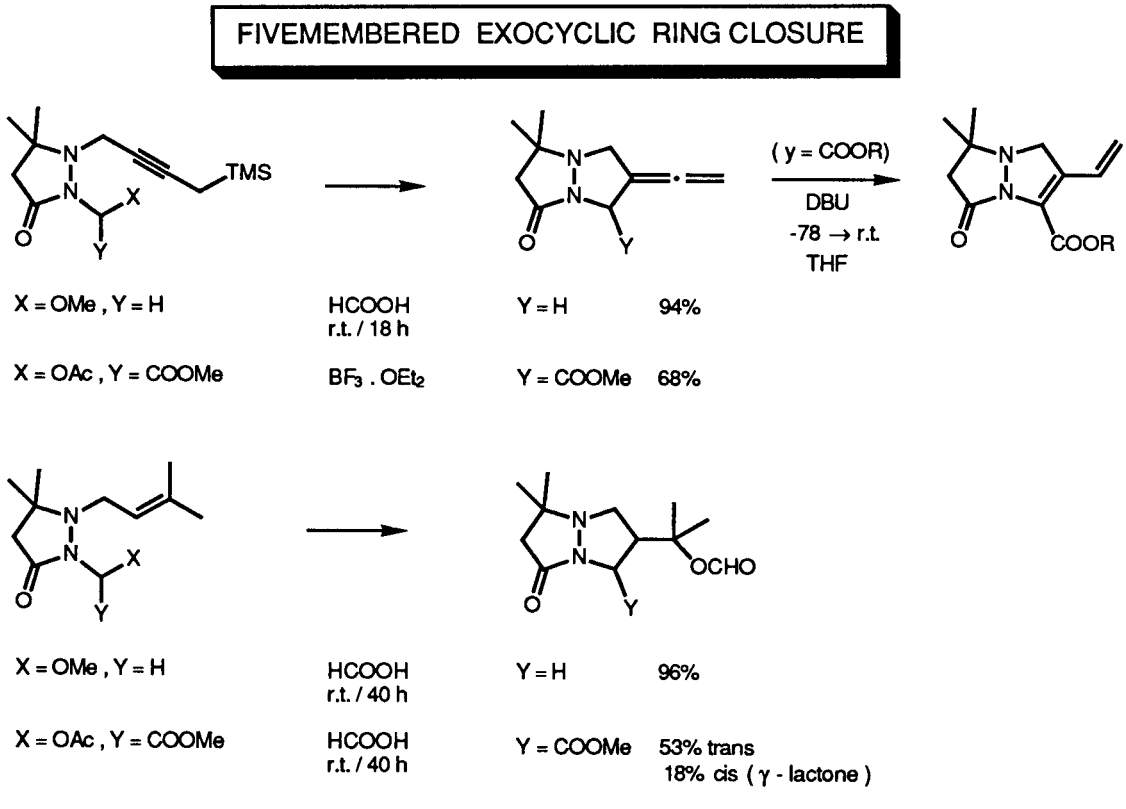


Figure 16

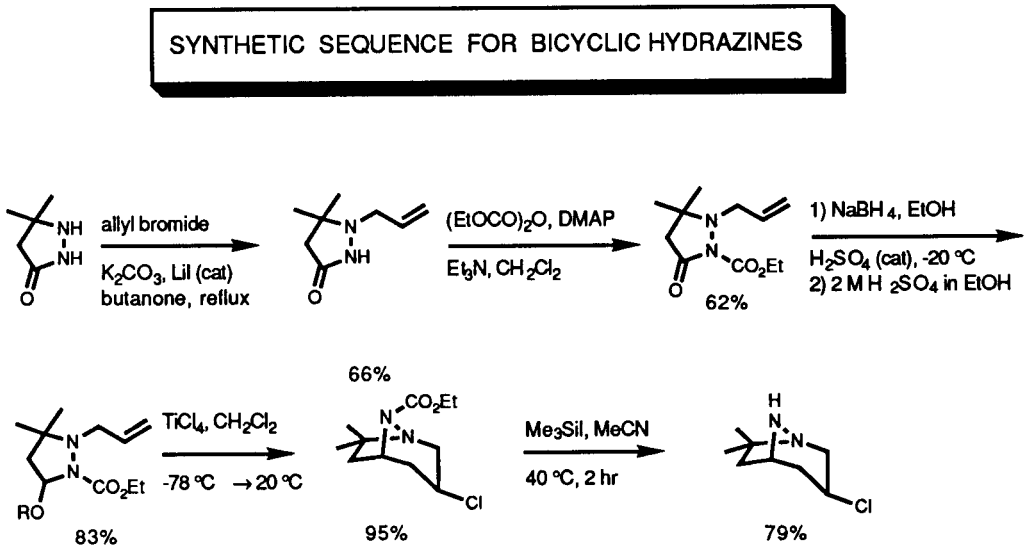


Figure 17

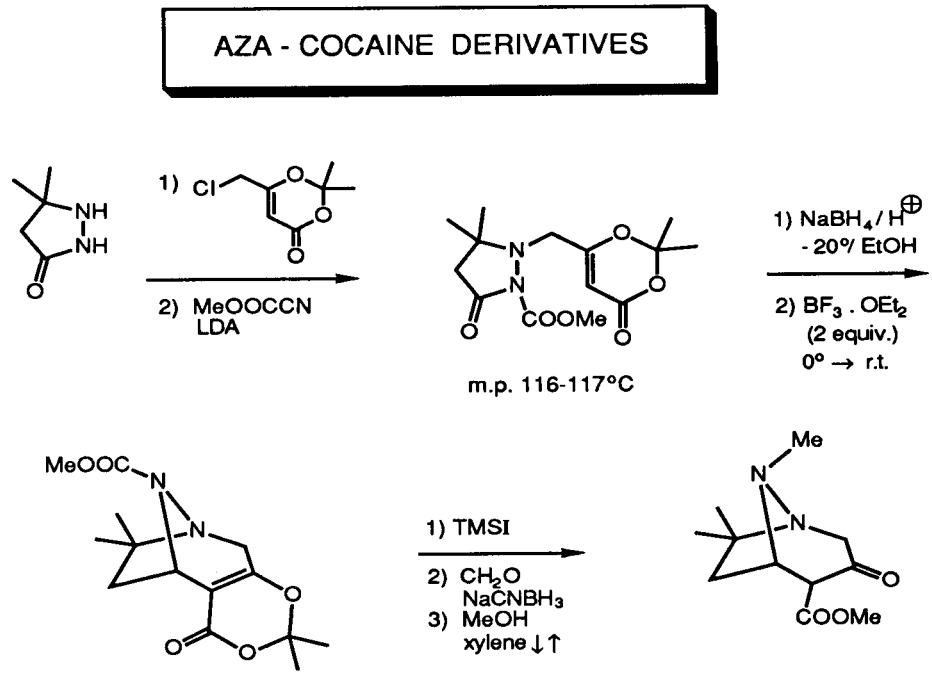


Figure 18

participation of the basic nitrogen atom the cation is rearranged via the intermediate aziridinium to an aza-proline derivative. The major isomer most likely possesses the *trans* stereochemistry.

Formation of bicyclic hydrazino esters, derivatives of which were recently reported to possess high anti-bacterial activity [13] is also easily accomodated (Figure 16). Provided that activated nucleophiles are the reaction components good yields of five-membered rings are obtained of which the allene is isomerized to the unsaturated dienic ester upon DBU treatment. A final variation on this theme is the use of the endocyclic hydrazonium intermediate for the synthesis of bicyclic [m, n, 1] hydrazines (Figure 17).

Remarkable steps in the sequence are the selective reduction of the pyrazolon and the high-yield

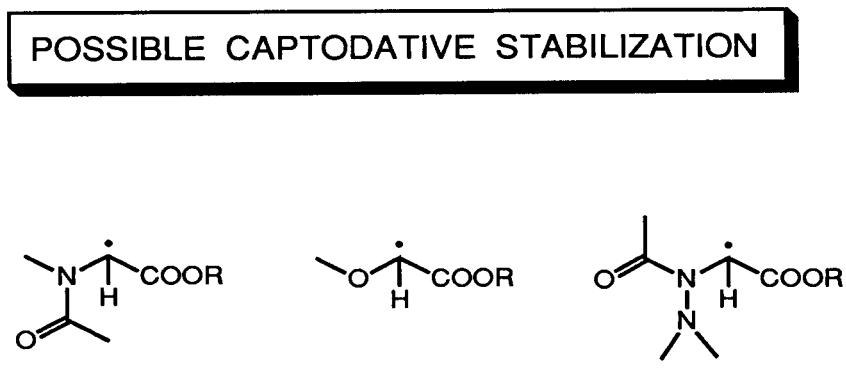


Figure 19

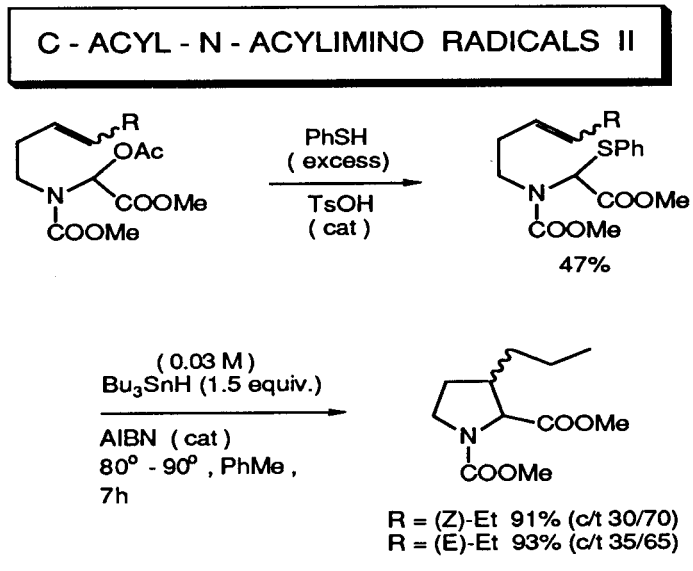


Figure 20

cyclization of the unactivated alkene [14]. An application of the endocyclic technique is the synthesis of some aza-cocaine derivatives (Figure 18). By using the dioxenine derivative as a masked equivalent of the 1,3-dioxo-derivative the cyclization upon the cyclic enolether proceeded in high yield to the bicyclic dioxenine. After removal of the carbamate protecting group and reductive methylation the β-keto ester was formed upon methanolysis of the acylketene.

The previously discussed cyclizations virtually all proceeded by way of a cationic α-ester substituted intermediate the stability of which will be supposedly lowered as compared to most N-acyliminium intermediates. This situation, however, may be reversed upon generating the α-N-acylamino or α-oxa radical as the reactive species. The so-called captodative effect in fact is predicted to stabilize radicals possessing electron donating and accepting substituents (Figure 19). In practical terms the regiocontrol upon addition of the radical to the alkene may promote the formation of five-membered rings as a result of the preferred 5-exo-addition. Thus depending on the choice of the reaction conditions it will be possible to selectively construct either type of ring system from a single starting material. An example of this dual reaction pathway is the ring closure of the previously described acetate (Figure 20) which upon conversion to a thiophenyl derivative and Bu3SnH reduction afforded a high yield of the propyl substituted proline as an approximately 2:1 mixture of *trans* and *cis* isomers [15].

Since the conformational constraints for the radical intermediate will be less secure as compared to the cation mixtures of stereoisomers are obtained the composition of which will hardly be dependent of the geometry of the reacting olefine. That, however, some 1,3-allyl strain is present follows from the analogous reaction in the oxa-series (Figure 21). Here the starting olefin geometry has a definite influence on the product

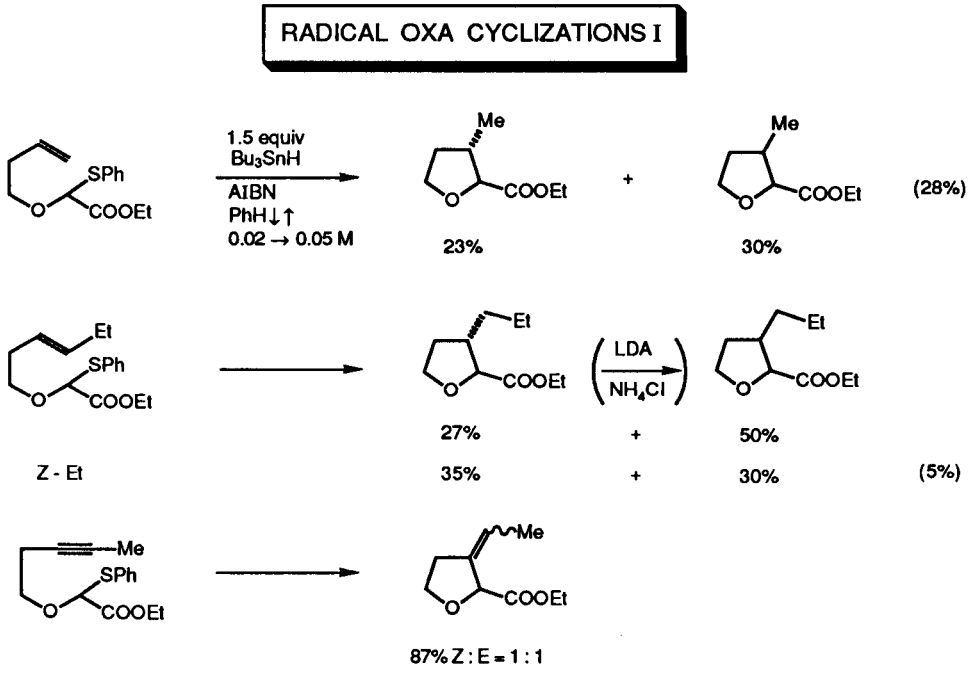


Figure 21

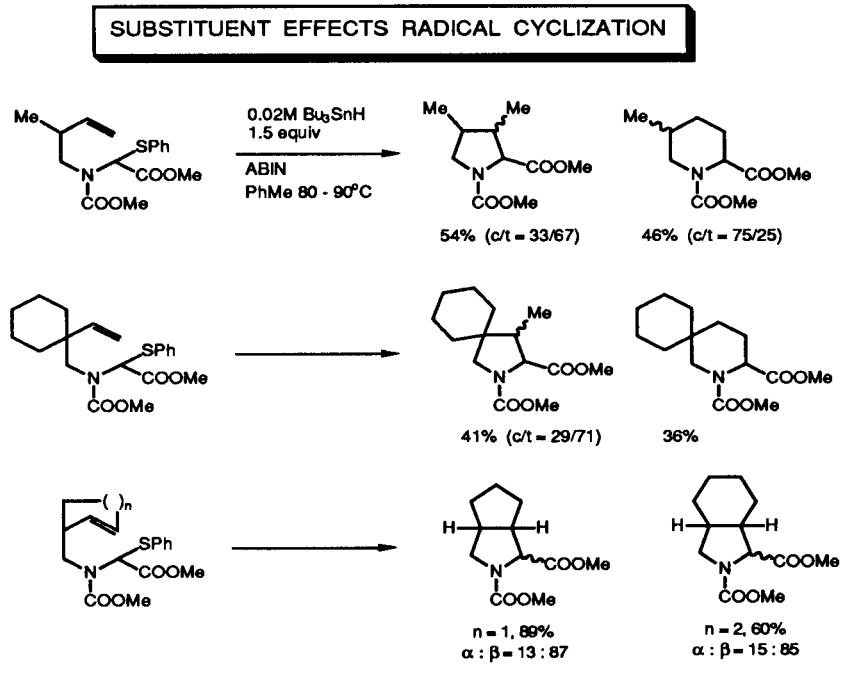


Figure 22

composition in which the *cis*-isomer has a relatively larger proportion. Both results agree with the preferred 5-exo addition mode in the radical cyclization process. Slight variations in the ratio of isomers between the N-acylimino- and oxa series are also manifest in the reaction of substituted precursors (Figure 22). Especially in the cyclohexenyl precursor the stereoselectivity for the carbamate precursor is much higher. The *trans*-isomer is predominating which

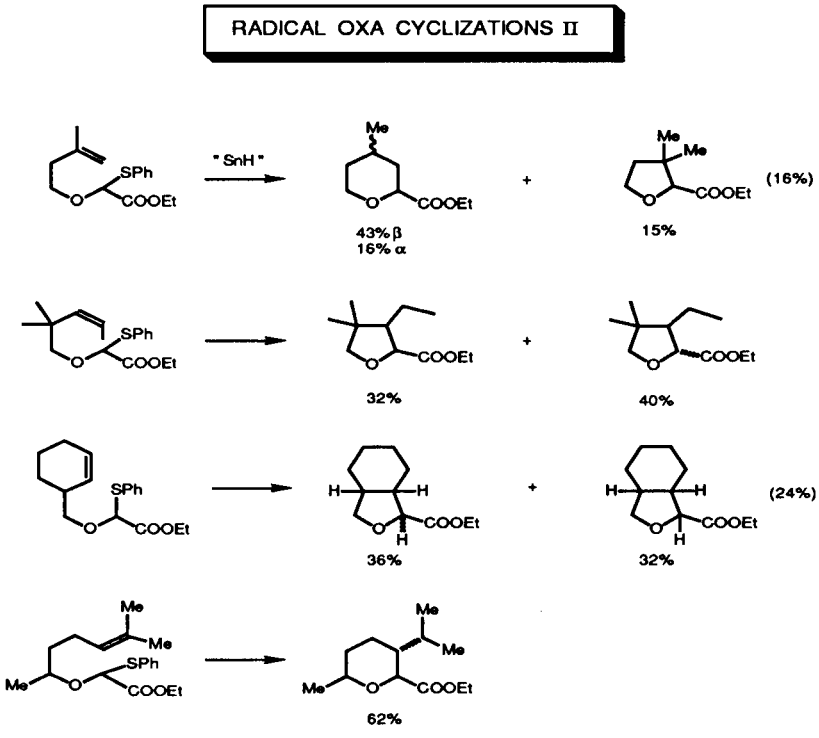


Figure 23

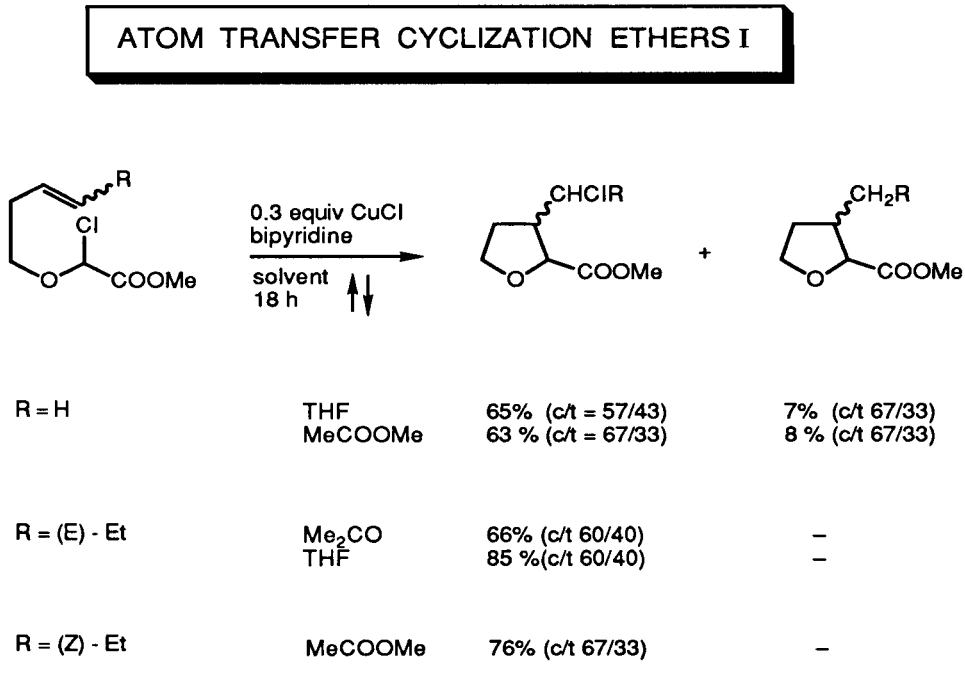


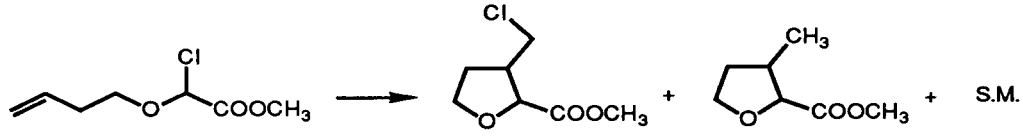
Figure 24

is indicative for the influence of the allyl strain. Furthermore the presence of a methyl or a gem-cyclohexenyl substituent tends to increase the amount of 6-endo product. For the corresponding oxacyclohexenyl case there is hardly any stereocontrol (Figure 23). Due to the slightly different substituent angle around the oxa-atom the preference for 5-exo cyclizations remains manifest except when tertiary radicals are formed.

All of these processes - albeit that hitherto unavailable ring systems can be formed - suffer from the reductive nature of the bond forming process in which

RADICAL TRANSFER CYCLIZATION INFLUENCE SOLVENT, CATALYST AND TEMPERATURE

Reaction :



Cat	Solvent	Time/Temp	*cis/trans* 57/43 %	%	%
0.1 equiv A	THF	18h /↓↑	53	15	16
0.3 equiv A	THF	18h /↓↑	65	7	–
0.3 equiv A	CH_2Cl_2	18h /↓↑	74	–	16
0.3 equiv A	CH_2Cl_2	48h /↓↑	100	–	0
0.3 equiv A	CH_2Cl_2	21h / r.t.	22	–	78
0.3 equiv A	$ClCH_2CH_2Cl$	18h /↓↑	95	–	<3
0.1 equiv B	benzene	48h /↓↑	95	–	<3

Catalyst A CuCl / Bipyridine (2,2)
Catalyst B $RuCl(PPh_3)_3$

Figure 25

INTERCEPTION OF INTERMEDIATE

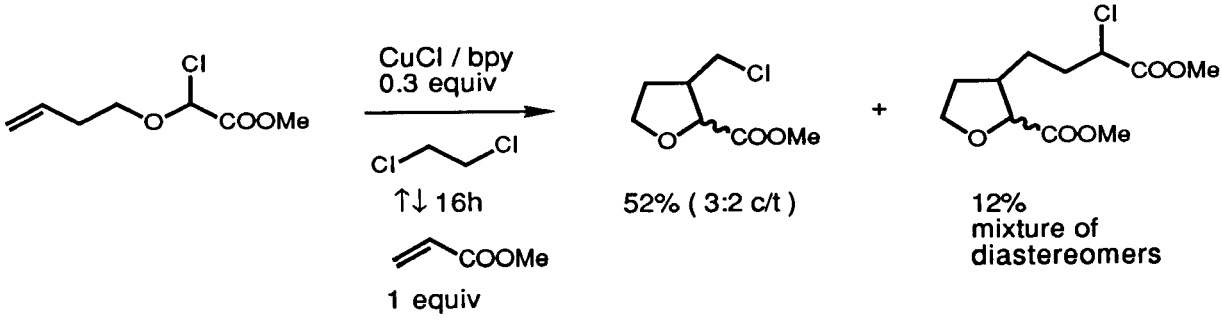


Figure 26

functionality is lost. A current trend in radical cyclizations therefore is to develop methods whereby the newly formed radical terminus is not simply reduced but may pick up a different group or atom to incorporate a starting point for further transformation. An important part of these reactions are the catalytic atom transfer cyclizations [16] creating new opportunities in radical chemistry. Although experiments with $Pd(PPh_3)$ as catalyst [17] were negative the use of the CuCl-bipyridine system [18] gave good results (Figure 24).

The unsubstituted olefin cyclized both in THF or methyl acetate to a mixture of furan caboxylic esters in which the *cis* isomer predominated. Only a small

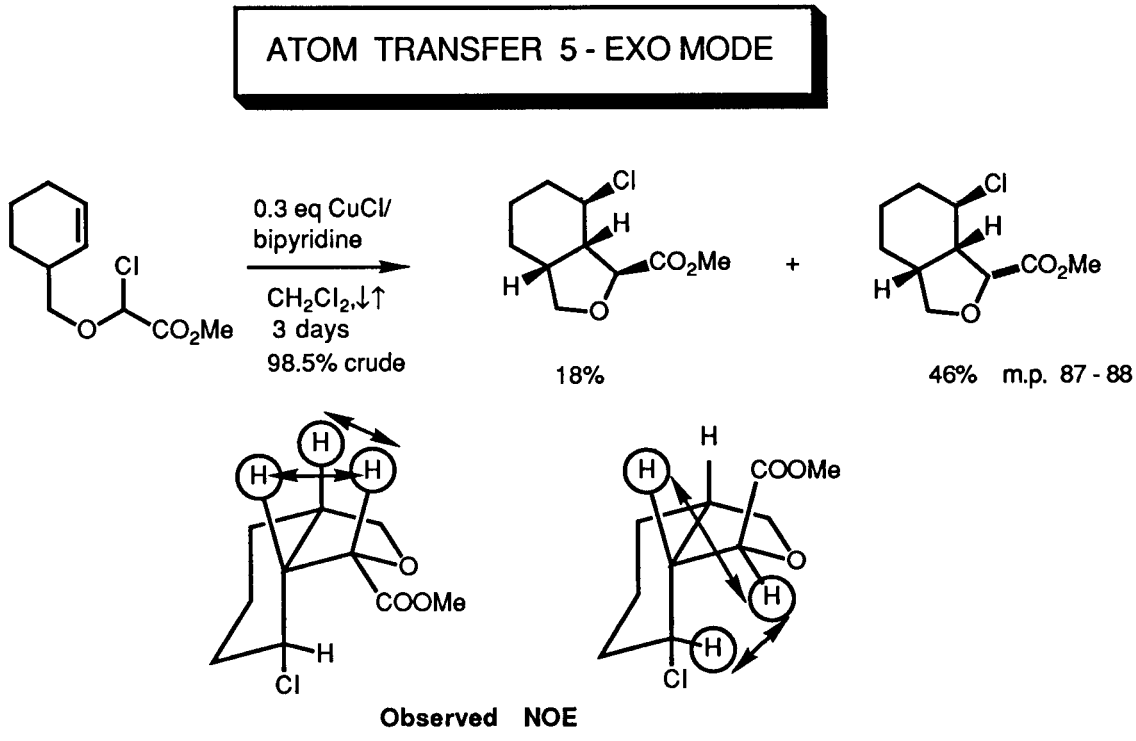


Figure 27

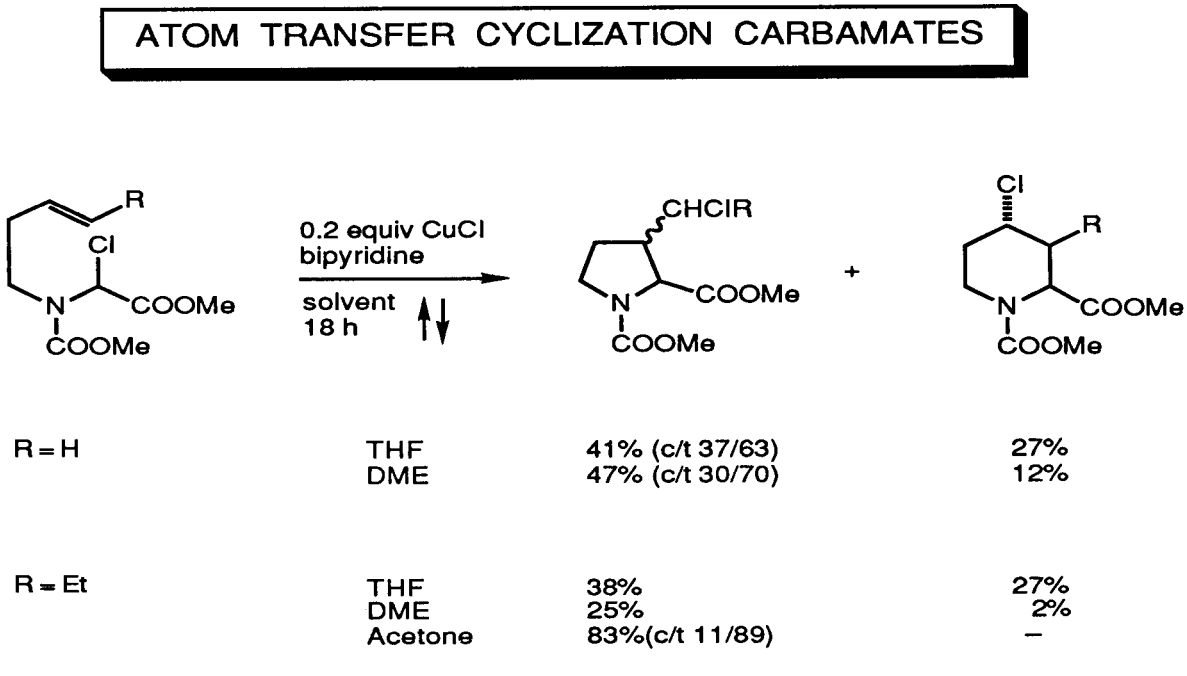
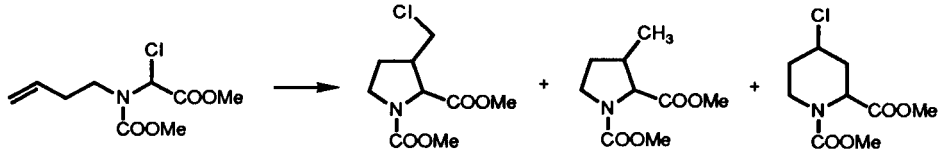


Figure 28

amount of reduction product was found presumably formed by hydrogen abstraction from the solvent. Similar data were obtained from (*E*)- or (*Z*)-olefin albeit that no reduction product could be detected. A systematic study of the reaction revealed that 1,2-dichloroethane (DCE) is an excellent solvent for the ring closure (Figure 25). With 0.3 equivalent of the catalyst system an almost quantitative conversion was

CONDITIONS RADICAL TRANSFER CYCLIZATION

Reaction :



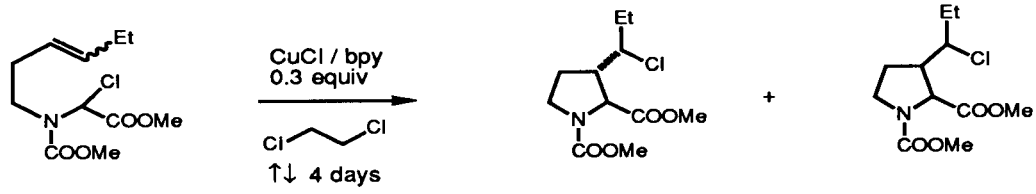
Entry	Cat	Solvent	Time/Temp	*cis/trans* 30/70 %	%	%
1	0.3 equiv A	THF	17h /↓↑	41	4	27
2	0.3 equiv A	DME	17h /↓↑	47	4	12*
3	0.3 equiv A	$ClCH_2CH_2Cl$	16h /↓↑	50	–	25
4	0.1 equiv B	benzene	16h /↓↑	49	–	25

Catalyst A CuCl / Bipyridine (2,2)
Catalyst B $RuCl_2(PPh_3)_3$

* isolated fraction

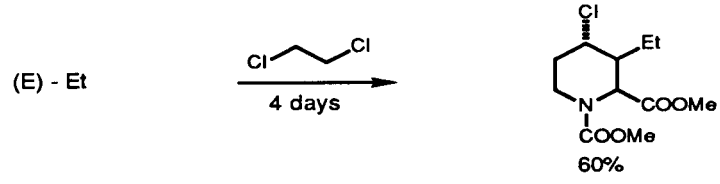
Figure 29

ATOM TRANSFER AND CATIONIC RING CLOSURE



(E) - Et	78%	85	15
(Z) - Et	86 %	64	36

1: 1 mixture of diastereomers one *cis* and one *trans* isomer obtained pure . mp. trans isomer 78-79°C



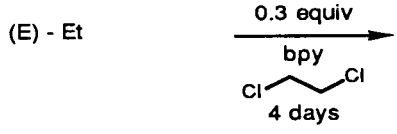


Figure 30

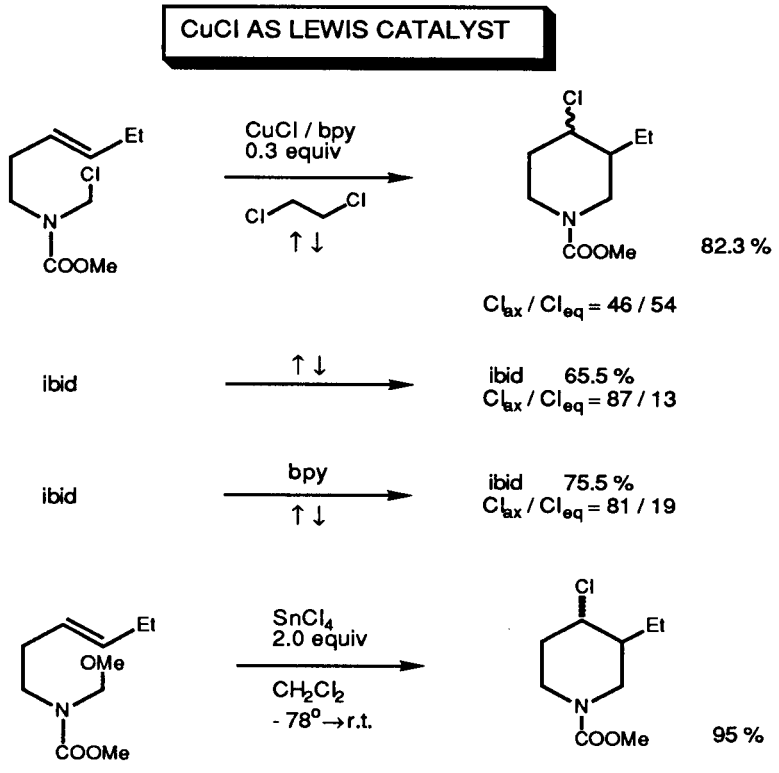


Figure 31

attained upon reflux overnight [19]. Lower temperature as well as smaller amounts of the catalyst resulted in diminished rates of reaction. Interestingly the cyclization also proceeded well in benzene with the catalyst $RuCl_2(PPh_3)_3$. While the mechanism of this metal catalyzed carbon-carbon bond formation has not been established with certainty its free-radical nature is commonly accepted and the results in Figure 26 also agree with such behaviour. Thus in presence of 1.0 equivalent of an acceptor the corresponding radical adduct is formed in 12% yield as a mixture of diastereomers. Higher adducts could not be identified. Such a result almost excludes other mechanistic pathways especially the one in which the metal forms an initial complex with the π-system followed by a nucleophilic displacement of the chloride. The atom transfer technique is also applicable to substituted and cyclic olefins (Figure 27). Remarkably while the corresponding reductive cyclizations produce equal amounts of both ester stereoisomers in the oxa-series (*cf* Figure 23) and show even a high preference for the β-COOMe in the cyclic carbamate (*cf* Figure 22) the atom transfer mode furnishes a higher proportion of the α–COOMe. The stereochemistry cleanly follows from a comparison of NOE effects in both stereoisomers in which the ester and one of the tertiary hydrogens are *cis* or *trans* oriented. Since it may be expected that the role of the halo atom only comes into play after the initial linking of the two carbon atoms one might speculate about a decisive role of the metal-radical complex in the steps controlling the stereochemistry (*vide infra*). Of additional interest are the results in the carbamate series (Figure 28). As has been found in the radical cyclization - *cf* Figure 20 - the *trans* isomer predominates in the reaction mixture. Yields are, however, slightly diminished while in addition a significant amount of the pipecolic ester is formed. The latter process is almost independent of the solvent and also takes place when the reaction is carried out in benzene with $RuCl_2(PPh_3)_3$ as the catalyst (Figure 29).

Only with a substituted (*E*)-olefin a high yield of the presumed radical adduct is obtained. The latter result induced a series of experiments to establish the origin of the anomaly (Figure 30). Both (*E*)- and (*Z*)-olefin isomers were examined and found to react completely according to the atom transfer mechanism in DCE as a solvent giving rise to pyrrolidine type products. Omitting the metal-catalyst and merely heating of the starting material in DCE, however, gave the pipecolic ester which most likely is formed according to an ionic mechanism. A control experiment in the presence of 2,2-bipyridine gave a roughly similar result. These

findings strongly suggest the existence of two cyclization pathways in the carbamate series of which the cationic variant is operative due to the high stabilizing nature of the amino function. In case of an unsubstituted olefin both mechanisms are simultaneously occurring thereby accounting for the formation of two types of products. One final question remains to be answered. Recently, the importance of the capto-dative effect, that is the extra stabilization of the α-heteroradical by an electron-attracting substituent has been critically evaluated in both theoretical [20] and quantitative respects [21]. While we have no kinetic data on the reactions discussed herein the role of the α-ester function particularly stabilizing the corresponding radical seems strongly indicated. In order to find additional experimental support for this effect it seemed desirable to run some of the reactions in the system possessing no ester substituent. From the data in Figure 31 the exclusive cationic mode of addition can be hardly disputed. Even in presence of the transition metal only pipecolic acid was obtained which result paralleled earlier findings in the $SnCl_4$ mediated cyclization of the methoxycarbinolamide. The deviations in the stereochemical course of the reaction may origin from the role of CuCl as a Lewis catalyst. Such behaviour is even more pronounced in the cyclization of the cyclopentene substrate (Figure 32). The apparent 5-exo mode leading to the fused pyrrolidine is also established upon the use of the Lewis catalyst $SnCl_4$ while reactions in absence of catalyst only lead to decomposition. The efficacy of CuCl in promoting the ionic transfer of the halogen atom is also remarkable.

As a conclusion it may be stated that in order to use the atom transfer technique advantageously in amidoalkylation the presence of an added electron-withdrawing substituent at the reacting carbon is mandatory.

As indicated before cycloalkenyl precursors also may be used in this type of reaction. Some additional examples are presented in Figure 33.

The earlier discussed stereochemical preferences for the *cis* isomer in the oxa-series and for the *trans* isomer in the aza-series are also found in the bicyclic compounds. The relative position of the chloro atom possessing mainly the exo stereochemistry again emphasizes the free radical nature of the atom transfer process although the observed stereochemical differences in the oxa- and aza-series are as yet difficulty to rationalize. Further studies with substituted alkenes and different ester groups have to be awaited before a coherent explanation can be given. Although α'-alkyl substituents are tolerable in this reaction the synthetic potential will be further increased if different functional groups can be used. In this connection the α' carboxylic moiety is of interest since it can be easily converted into a carbonyl function by lead tetraacetate oxidation [22]. The α,α' diester substrate indeed provided a good yield of the furan derivative as a 63:37 mixture of *cis* and *trans* isomers (Figure 34).

A second obvious transformation is the internal substitution of the chlorine by the carboxylate anion. In the latter respect the outcome on the pyrrolidine esters is somewhat surprising. Clean isomerization of the *cis* into the *trans* isomer was observed upon reflux in KOH/MeOH the chloro substituent being unaffected (Figure 35). Concomitant hydrolysis of the ester produced a good yield of the haloalkyl proline. On the contrary in the furan series the *cis* isomer underwent

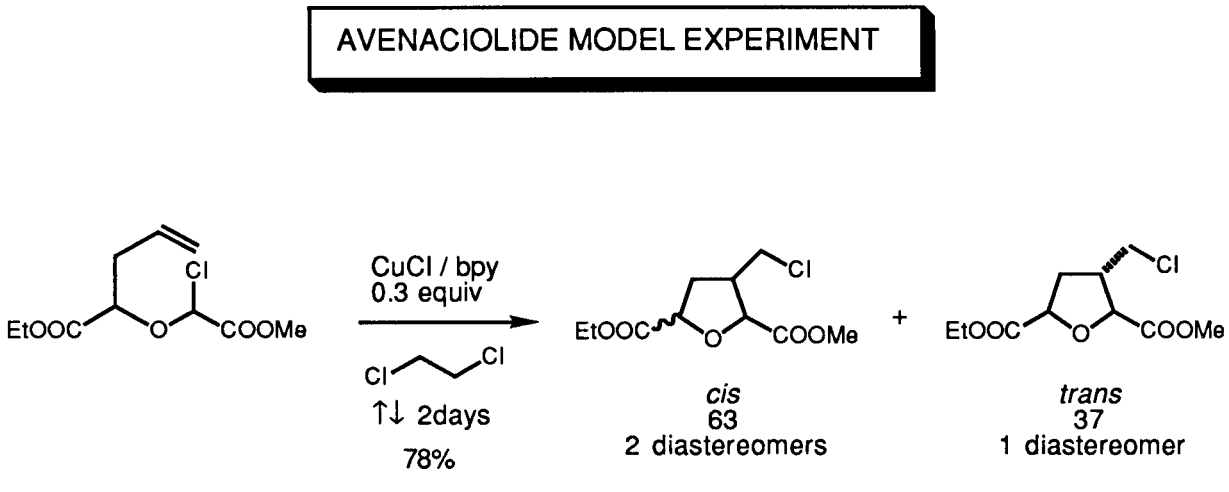


Figure 34

CATIONIC CYCLIZATION IN ABSENCE OF CAPTODATIVE EFFECT

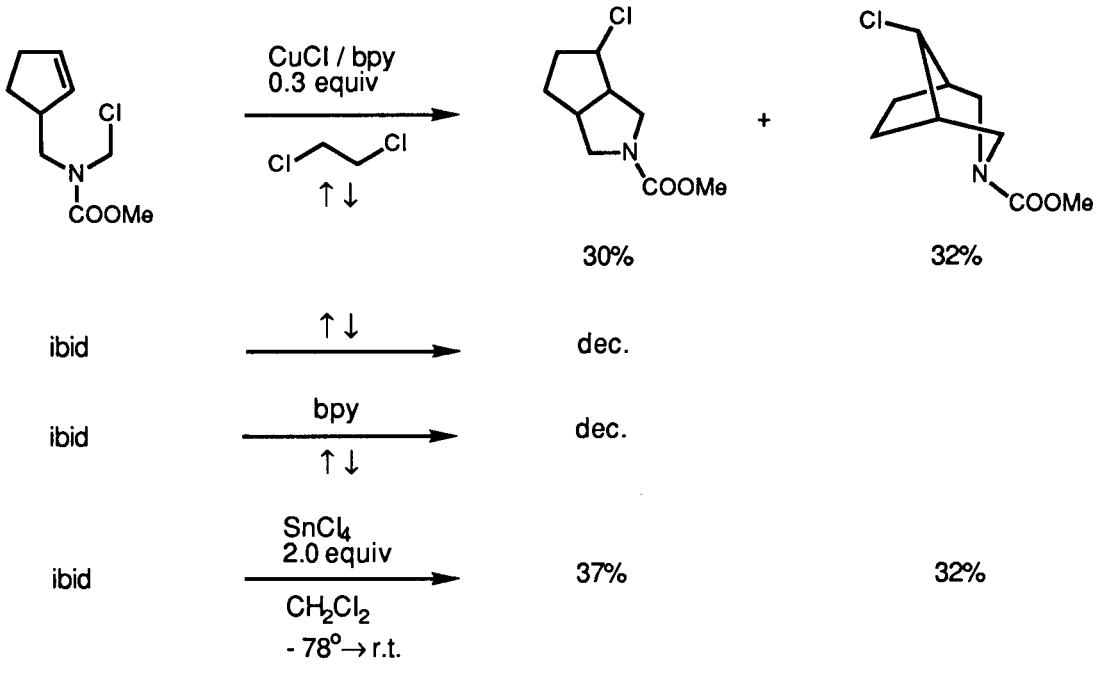
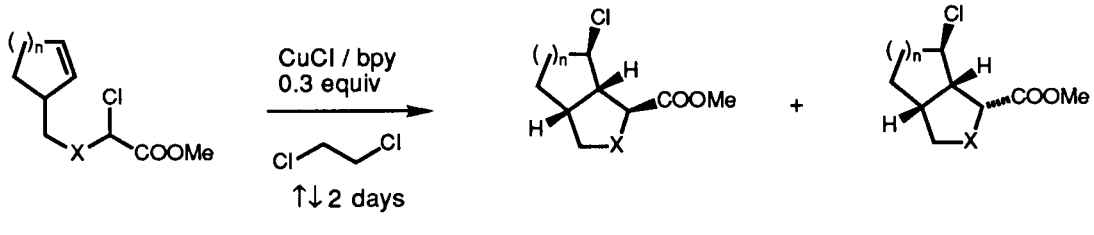


Figure 32

ATOM TRANSFER SYNTHESIS OF BICYCLICS



n = 1	X = O	95%	18	82
n = 1	X = NCOOMe	75%	66*	34
n = 2	X = O	63%	34	66
n = 2	X = NCOOMe	53%	68*	32

* other Cl isomer also formed

Figure 33

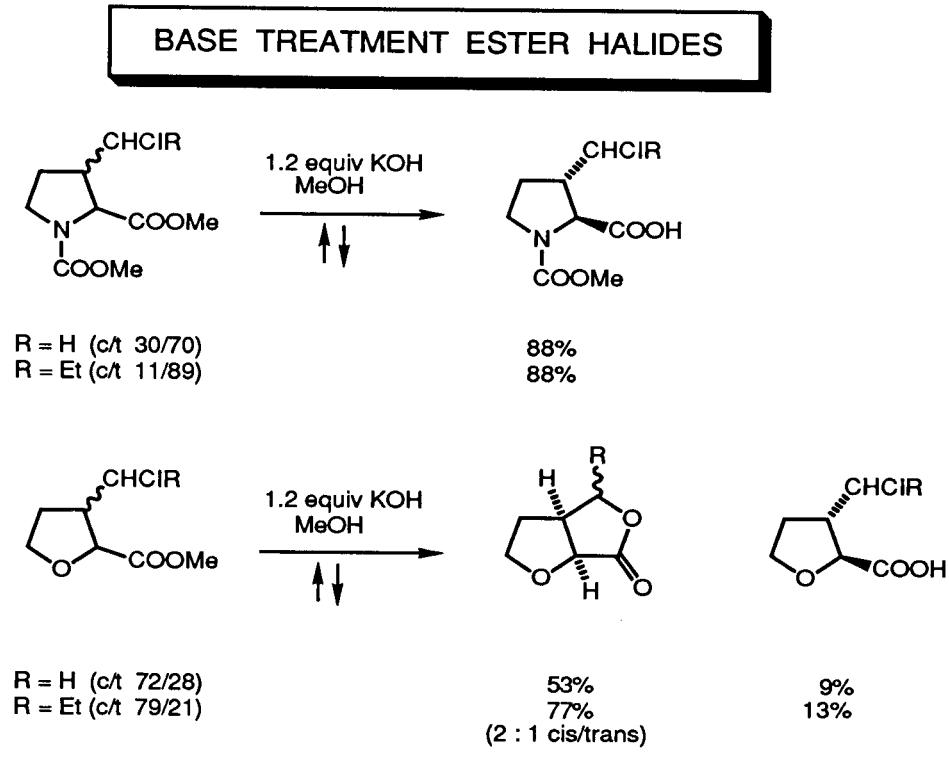
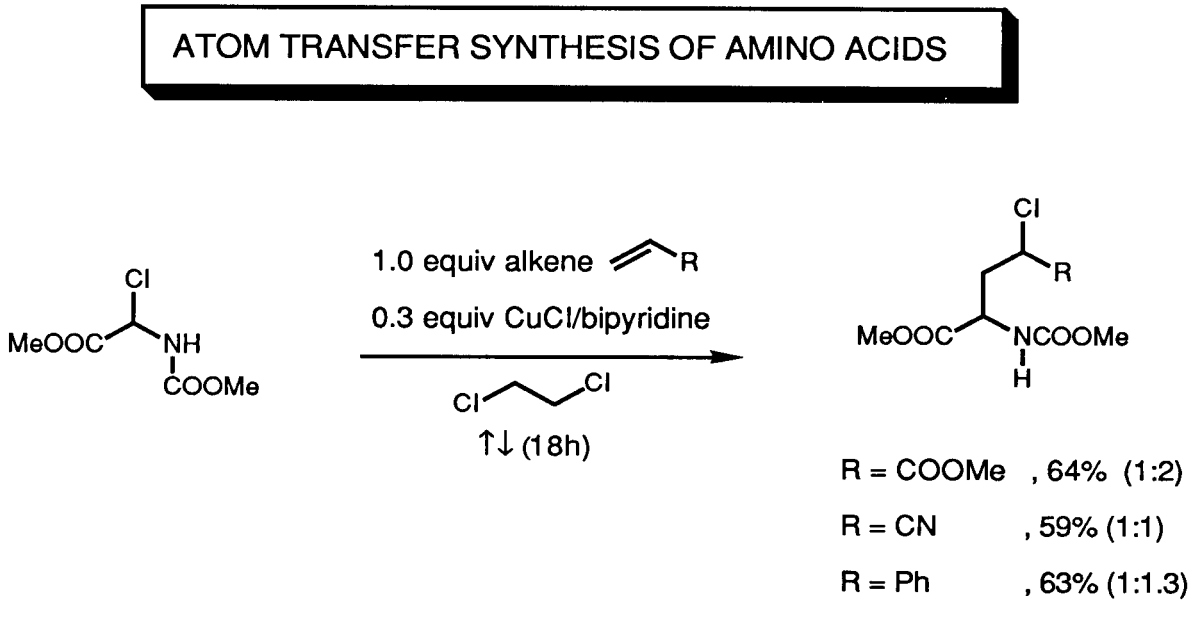


Figure 35



Slightly lower yields with 5% $RuCl_2(PPh_3)_3$

Figure 36

lactone formation while in the *trans* isomer only the ester was hydrolyzed. Consequently in both series the separation of the atom transfer stereoisomers was greatly facilitated.

Since the work described started with an intermolecular cationic coupling of a glycine derived precursor I shall end this lecture with a description of the work starting with the same precursor in the intermolecular atom transfer series. As is shown in Figure 36 the reaction occurs smoothly with different types of alkenes giving rise to the formation of novel amino acid derivatives thus adding in a complementary way new possibilities for the synthesis of this interesting compound class. The work presented here has been performed by a number of excellent and devoted co-workers to whom I wish to express my warmest thanks. Their names are listed in the appropriate references.

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