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Reactions of Electrophilic Carbenes with α-Amino Acid Derivatives

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Contents

1. INTRODUCTION

Derivatives of naturally occurring α-amino acids are one of the most intensively exploited sources of asymmetry in organic synthesis.[1] Apart from their extensive use as ligands in transition metal-based enantioselective catalysts,[2] commercially available derivatives of α-amino acids have frequently been the starting material of choice for the asymmetric synthesis of more complex chiral molecules. In particular, for the preparation of unnatural α-amino acids, which are important intermediates for the synthesis of peptide analogues with increased metabolic stability and modified biological activity, readily available α-amino acids may be very convenient starting materials.[3,4]

In many conversions of natural amino acids into more elaborate molecules, carbanionic C-C bond forming reactions have played a crucial role.[3,4] In contrast to that, radicals or carbenes have only occasionally been used for the chemical transformation of α-amino acids. However, these reactive species offer the exquisite advantage that they can be generated under essentially neutral conditions, whereby the risk of racemization is minimized.

Electrophilic carbenes may react with α-amino acid derivatives in several different ways.[5] The final outcome of the reaction will depend on the precise nature of the carbene (singlet, triplet, metal-coordinated or

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uncoordinated) as well as on the type of α-amino acid derivative employed. Moreover, the reaction may be carried out intermolecularly or in an intramolecular fashion. As shown below, all these parameters may be important and have to be considered carefully in order to avoid surprises.

The present review will focus on insertion reactions of electrophilic "free" or metal-coordinated carbenes into C-H and N-H bonds of α-amino acid derivatives,[6] as well as on ammonium ylide formation, followed by Stevens rearrangement (Figure 1).

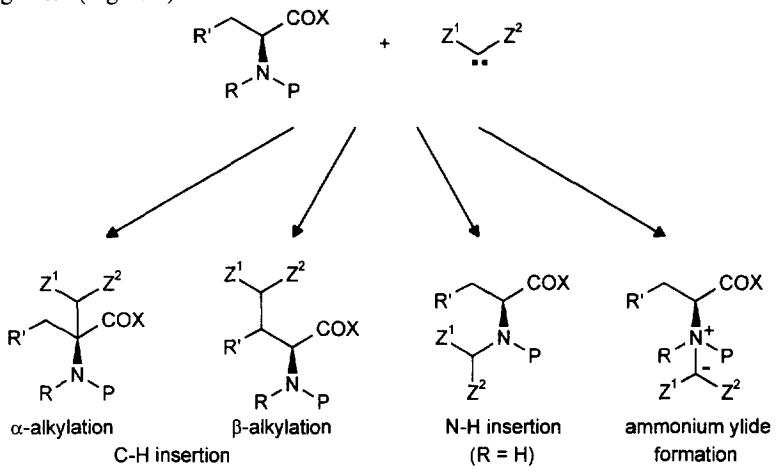


Fig. 1. X = OR, NR_2; R, R' = alkyl, H; Z = H, electron-withdrawing group; P = protective group

2. C-H INSERTION REACTIONS

2.1. α-Alkylation

The insertion of electrophilic carbenes into C-H bonds is inhibited by electron-withdrawing substituents[7] and facilitated by electron-donors[8, 9] at the carbon atom to be alkylated by the carbene. Due to the simultaneous and opposite effects of deactivation by the carbonyl group and activation by the nitrogen atom, it would be highly speculative to estimate the reactivity of the α-C-H bond of α-amino acids towards electrophilic carbenes. Since enantiomerically pure α,α-dialkyl α-amino acids are challenging synthetic targets,[4] a thorough investigation of carbene- and radical-mediated alkylations would certainly be desirable.[10]

Only one example for a successful α-alkylation of an α-amino acid derivative by an electrophilic carbene has been reported. Doyle, Taunton and Pho[11] described the high-yielding rhodium(II)-catalyzed conversion of the glycine derivative **1** (Figure 2) into the β-lactam **2**.

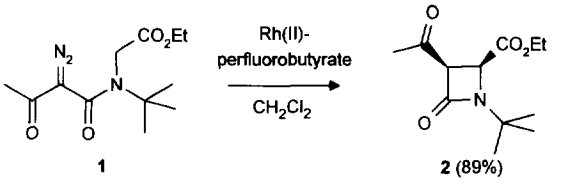


Figure 2

However, small structural changes within this type of substrate rapidly lead to different reaction

pathways. Rhodium-catalyzed degradation of the diazomalonamide **3**[12] (Figure 3), structurally closely related to the diazoacetamide **1**, yielded the morpholinones **4** and **5** (*via* an intermediate carbonyl ylide). Neither β-lactams nor products resulting from a C-H insertion into the (electron-rich) C-H bonds of the methoxyphenyl group were observed. In view of the reaction products resulting from the diazoamides **1** and **3**, the outcome of the diazodecomposition of the phenylalanine derivative **6**[13] was very surprising. As main product the nitroindole **7** was isolated, resulting from C-H insertion into an aromatic C-H bond.

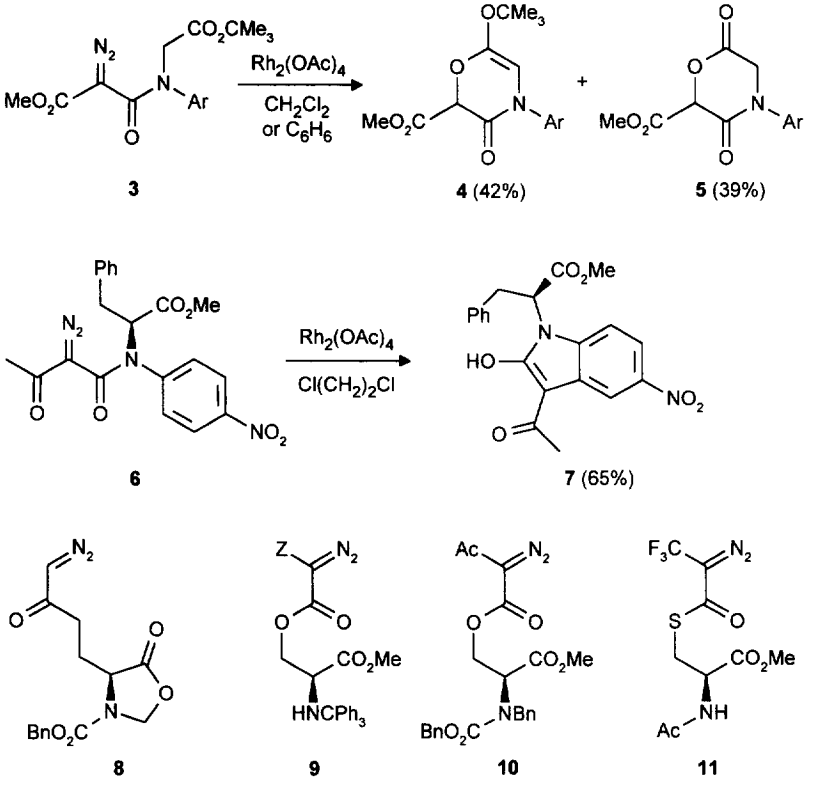


Fig. 3. Amino acid-derived carbene precursors, which fail to give α-alkylation by intramolecular C-H insertion.

Ar = 4-methoxyphenyl; Z = Ac, H

These reactions indicate that subtle electronic and steric effects may dramatically influence the course of such transformations. The mechanism sketched in Figure 4[14] suggests that not only the substituents Z, R and R' but also the precise nature of the catalyst M may determine whether electrophilic aromatic alkylation, hydride-abstraction (leading to carbene C-H insertion) or carbonyl ylide formation occurs. Therefore, additional experiments with other catalysts would certainly improve our understanding of the reasons for this mechanistic variability (cf. Figure 2 and Figure 3).

Other examples for α-amino acid-derived carbene precursors, which failed to give any products of intramolecular C-H insertion reaction upon carbene generation, are the diazocarbonyl compounds **8**,[15] **9**,[16] **10**[16] and **11**[17] (Figure 3).

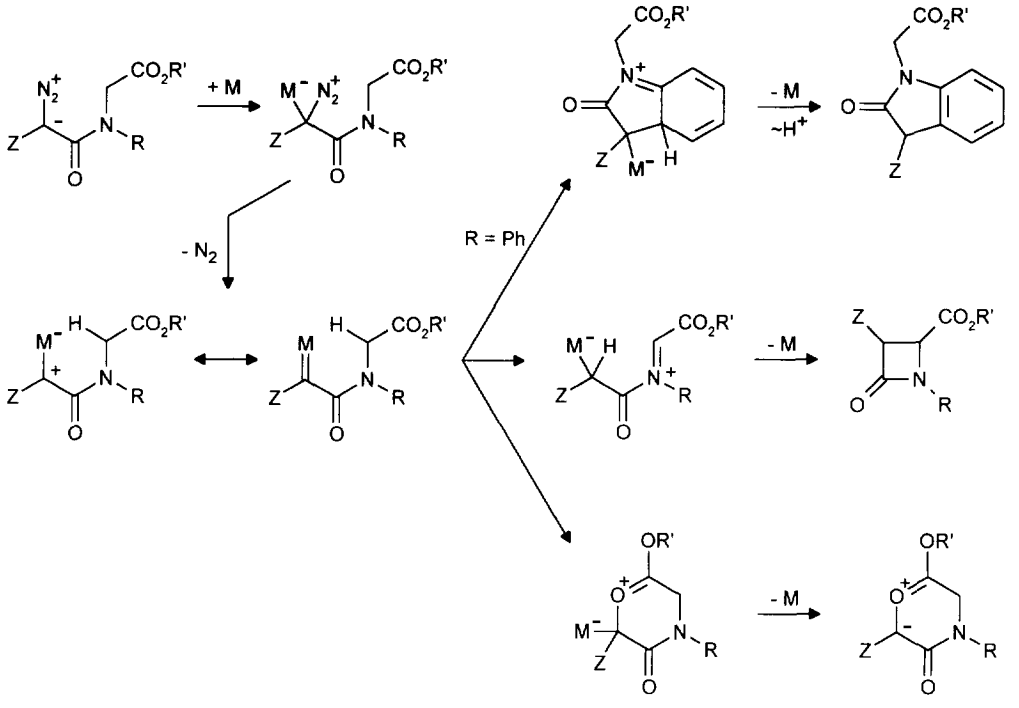


Fig. 4. A possible mechanism for intramolecular carbene C-H insertion and carbonyl ylide formation
Z = H, electron-withdrawing group; M = catalytically active transition metal complex

From the results available by now it has to be concluded, that α-amino acids are not easily alkylated *via* carbene C-H insertion at the α-position.

The generation of electrophilic carbenes in the presence of *N,N*-dialkylamino acid derivatives might yield α-alkylated products.[18] This type of transformation proceeds *via* ammonium ylide formation followed by proton migration and Stevens rearrangement, and will be discussed in Section 4.

2.2. C-H Insertion at Other Positions

Most of the naturally occurring α-amino acids possess a methylene group at the β-position. This β-methylene group is less strongly influenced by the electronic and steric effects of the α-amino and α-carboxy functionalities than the α-C-H bond and may therefore be more easily accessible to carbene C-H insertion reactions. However, only little work has been done for finding the appropriate reaction conditions/protecting groups for clean β-alkylation of α-amino acids by carbene C-H insertion. The only example reported so far is sketched in Figure 5.[13, 19] Rhodium(II) acetate-catalyzed decomposition of the phenylalanine derivatives **12a/b** gave, albeit in low yield, the products of carbene C-H insertion into the benzylic methylene group (**13a/b**) (Figure 5). The additional products **14a/b**, **15a/b** and **16a/b** resulted from reactions of the rhodium carbenoid with the diarylmethyl protective group. Hydride abstraction, cyclopropanation and C-H insertion yielded the imines **14a/b**, the cycloheptatrienes **15a/b** and the β-lactams **16a/b**, respectively.

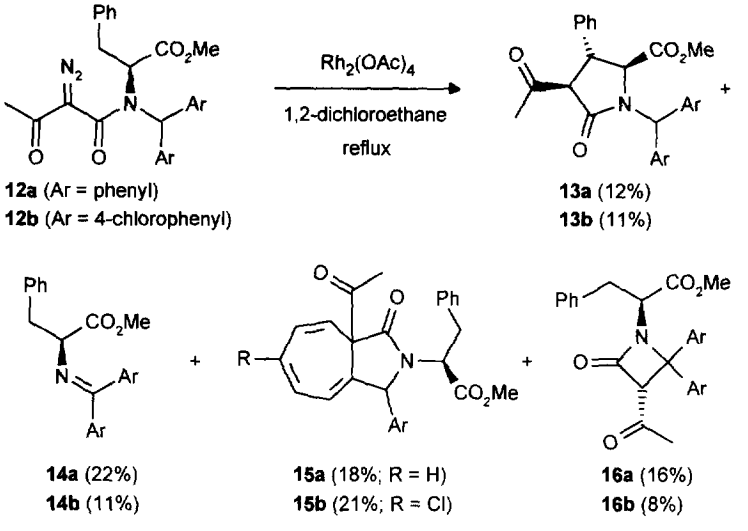


Figure 5

Several examples for carbene-mediated alkylations at different sites than at the β-position of α-amino acid derivatives have been reported (Figure 6).

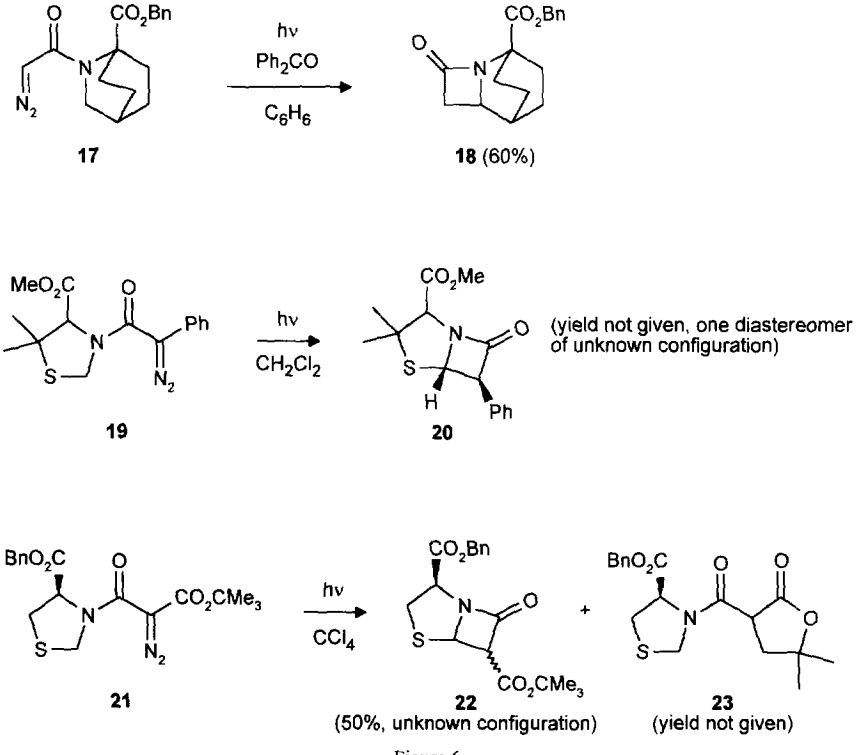


Figure 6

Figure 6 continued

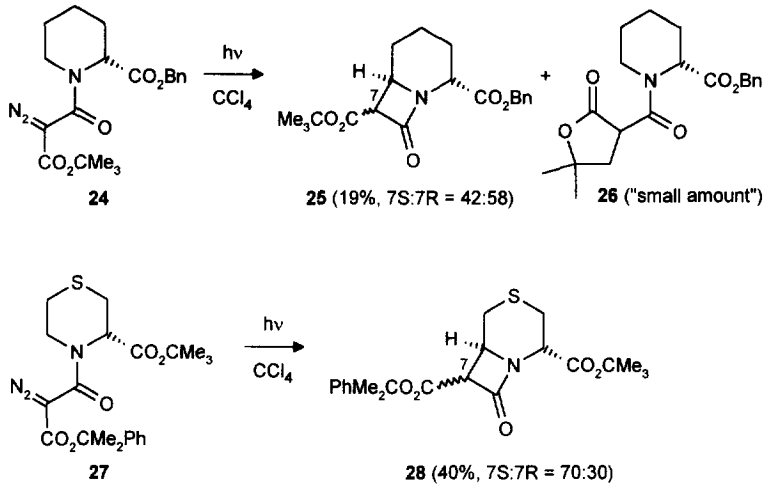


Fig. 6. Intramolecular carbene C-H insertion into α-amino acid derivatives of photolytically generated carbenes

Photolysis of the diazoacetamide **17**[20] yielded the β-lactam **18** through C-H insertion into the nitrogen-bound methylene group. This regioselectivity is typical for aminocarbonyl carbenes, which have a very pronounced tendency to yield β-lactams upon intramolecular carbene C-H insertion.[11, 21-24] Similarly, the carbenes generated from diazoacetamides **19**[25] (racemic) and **21**[26] reacted intramolecularly with the nitrogen- and sulfur-bound methylene group to yield the bicyclic β-lactams **20** and **22**, respectively. No insertion into the α-C-H bond of the amino acid fragment occurred. This observation is in accordance with the above mentioned tendency of electrophilic carbenes to react with electron-rich C-H bonds (i.e. the C-H bond which would most easily yield a carbocation and hydride upon heterolytic cleavage). Following this trend, the diazoacetamides **24**[27] and **27**[28] also yielded upon photolysis the corresponding β-lactams **25** and **28** by intramolecular carbene C-H insertion into the least acidic (and most easily oxidizable[19, 29]) C-H bond.

The reactions sketched in Figure 6, most of them reported prior to the discovery of the catalytic activity of rhodium(II) carboxylates,[30] will probably proceed more cleanly if rhodium(II) catalysis is used for carbene generation. Coordination of carbenes to rhodium(II) substantially lowers their reactivity and increases their chemoselectivity, thus reducing the extent of side reactions.[5]

3. N-H INSERTION

The insertion of electrophilic carbenes into the N-H bonds of suitably protected α-amino acid esters or amides is a powerful method for N-alkylating this important class of compounds. When more than one NH group is present in the same molecule, selective alkylation at one of the two nitrogen atoms can be achieved.[31, 32] In particular, the carbene methodology is one of the most efficient for N-alkylating β-lactams, both inter- and intramolecularly.[33]

Using electrophilic, metal-coordinated carbenoids also other α-amino acid-derived amides, as well as carbamates and hemiaminals have been chemoselectively N-alkylated under very mild conditions. There are

numerous examples for the construction of nitrogen containing heterocycles by intramolecular, carbene-mediated N-alkylation of carbamates (Figure 7).[5c-f] Aspartic and glutamic acid can for instance easily be transformed into carbene precursors such as **29**,[15, 34] **31**,[35] **33**[36, 37] and **35**.[38] Since these compounds can all be successfully cyclized to the corresponding pyrrolidinones or piperidinones, this synthetic sequence represents an attractive route to enantiomerically pure, conformationally restricted α-amino acid derivatives.

Particularly interesting is the ability of sulfoxonium ylides **33** to serve as precursors to rhodium(II)-coordinated acyl methylenes, displaying a similar reactivity as the corresponding carbenoids derived from diazomethyl ketones.[36, 37] Preparation of the latter often requires the use of diazomethane, so that sulfoxonium ylides may be an alternative to consider.

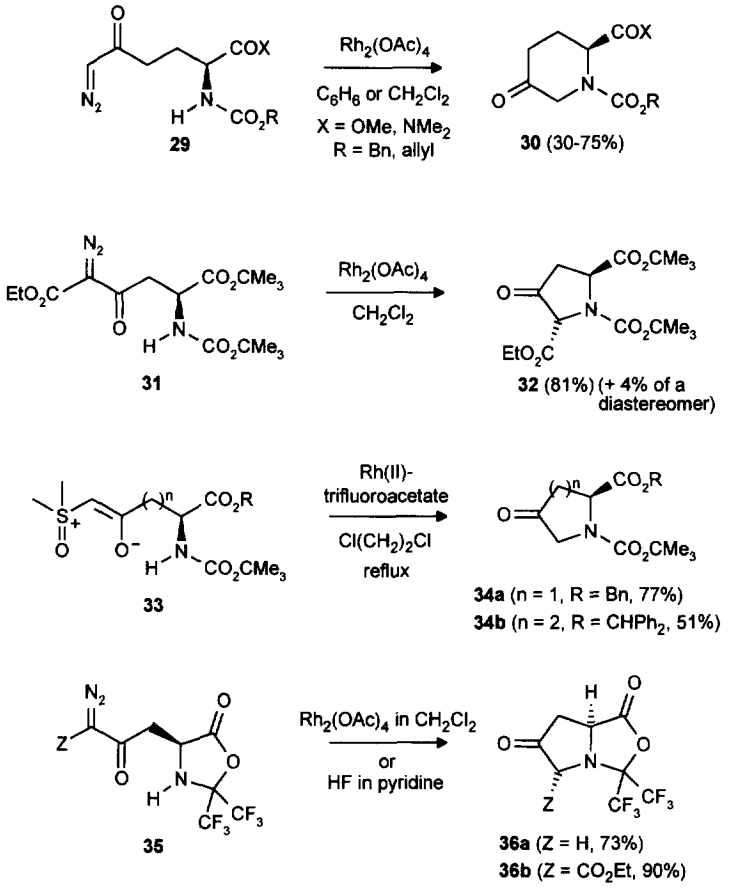


Fig. 7. N-H Insertion reactions of rhodium(II) carbenoids with α-amino acid derivatives

Extensive racemization could not be detected in any of the transformations shown in Figure 7. For this reason the carbene methodology may often be superior to the base-induced N-alkylation of amides or carbamates with alkyl halides.

4. AMMONIUM YLIDE FORMATION/STEVENS REARRANGEMENT

If carbenes are generated in the presence of unacylated amines, ammonium ylides are usually

formed.[5a, 5c-f] The most commonly observed further conversions of these ylides are elimination reactions or Stevens rearrangement,[39] occasionally preceded by proton migration.[18]

A schematic representation of possible pathways for the Stevens rearrangement of α-amino acid-derived ammonium ylides is given in Figure 8.

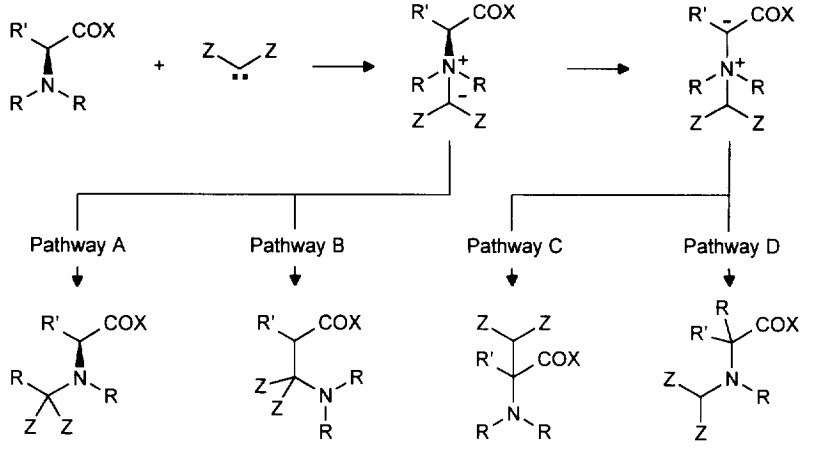


Fig. 8. Reaction pathways for the Stevens rearrangement of α-amino acid-derived ammonium ylides.
X = OR, NR_2; R = alkyl; Z = H, electron-withdrawing group

In most of the cases reported so far only one main product was isolated despite the numerous potential reaction pathways. Therefore, this reaction can certainly be rated as synthetically useful.

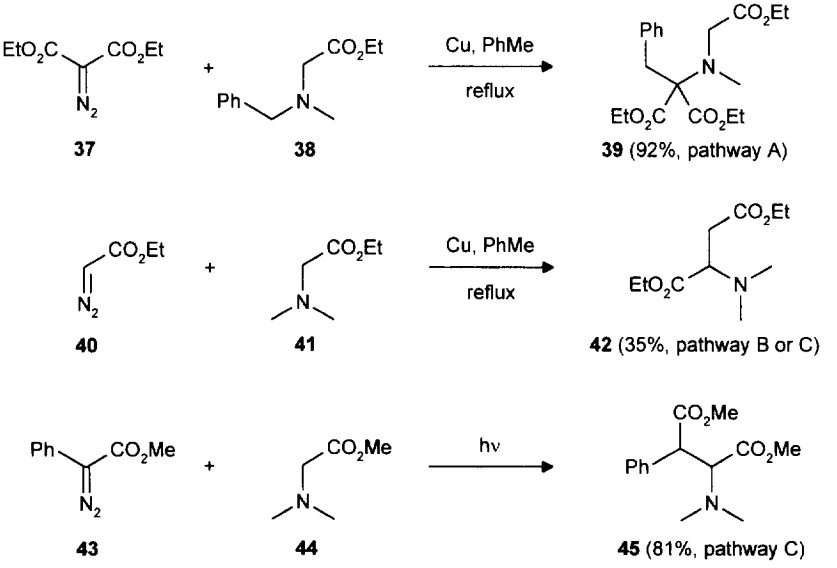


Figure 9

Figure 9 continued

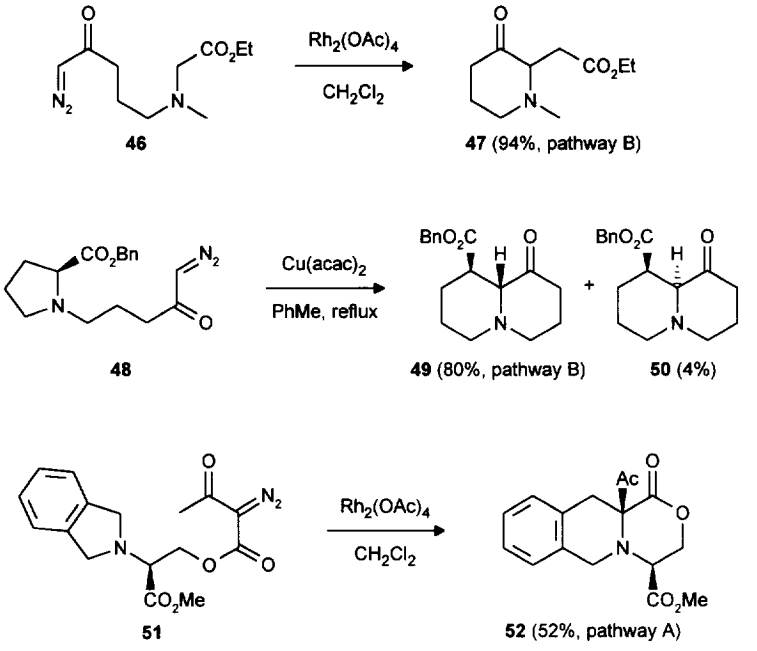


Fig. 9. Ammonium ylide formation from α-amino acid derivatives and electrophilic carbenes followed by Stevens rearrangement

Not surprisingly, this type of reaction is also strongly dependent on substituent effects. Carbene generation from the diazocarbonyl compounds **37**,[41] **40**[41] and **43**[18] (Figure 9) in the presence of *N,N*-dialkyl glycine esters yielded, despite the similarity of the starting materials, products resulting from three different reaction pathways. Most of the results shown in Figure 9 could have been anticipated by assuming that in the initially formed ammonium ylides the carbon atom bearing the best radical stabilizing group will migrate.[40] From these examples follows that in this particular case of Stevens rearrangement, the migratory ability decreases in the order benzyl > CH_2CO_2R > alkyl.

The intramolecular variant of this reaction gives access to heterocycles that are otherwise difficult to prepare. Catalytic degradation of the glycine derivative **46**[42] led to the piperidinone **47** in excellent yield. More complex, polycyclic heterocycles resulted from diazodecomposition of the proline and serine derivatives **48**[43] and **51**.[44]

The examples in Figure 9 indicate, that the predominant pathways for this reaction sequence are pathways A and B. This means that no proton migration within the primarily formed ammonium ylides (with concurrent racemization) is to be expected with sufficiently electrophilic carbenes.

As demonstrated by the two last examples in Figure 9, products resulting from pathways A and B can indeed be obtained in a highly enantio- and diastereoselective fashion. For this reason the reaction of electrophilic carbenes with *N,N*-dialkyl α-amino acid derivatives might become an important preparative method for the asymmetric synthesis of complex heterocycles.

5. MISCELLANEOUS

The reactions described so far in this review involve those functionalities present in all natural α-amino acids. In this last chapter additional conversions will be discussed, which are only relevant for specific types of α-amino acids.

5.1. Cyclopropanation

When electrophilic carbenes are generated in the presence of olefinic α-amino acid derivatives, clean cyclopropanation of the C-C double bond can be achieved.[45-47] Standard protection of the amino group (e.g. as benzyl or *tert*-butyl carbamate) is sufficient to prevent N-alkylation.

Some representative examples, which demonstrate the chemoselectivity of electrophilic carbenes towards olefinic α-amino acid derivatives, are given in Figure 10.

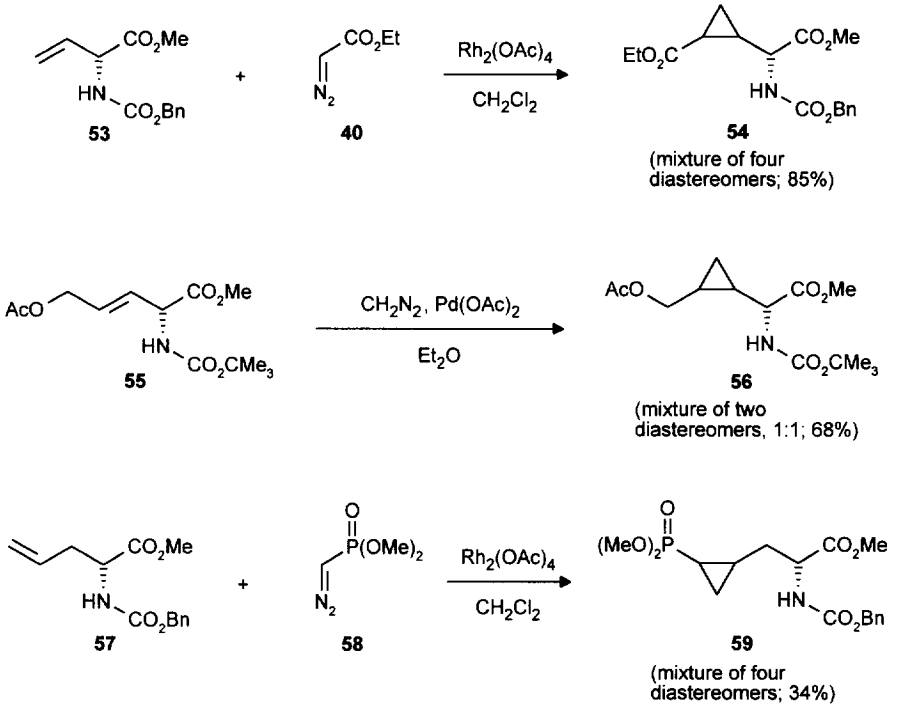


Fig. 10. Examples for the cyclopropanation of α-amino acid derivatives

Treatment of the carbamate protected, unnatural α-amino acid esters **53**,[45] **55**[46] and **57**[47] with transition-metal coordinated carbenes led to cyclopropanation of the C-C double bond. No extensive N-H insertion was observed. However, the diastereoselectivity for all these examples was very low, rendering this approach to conformationally restricted α-amino acid derivatives of rather limited use.

5.2. Sulfur-Containing α-Amino Acids

The reaction of electrophilic carbenes with thioles or thioethers usually leads to C-S bond formation.[5] This process is very fast and can therefore compete efficiently with other potential reaction pathways. Several research groups have thoroughly investigated and exploited this effect for the modification of penicillin derivatives.[48-51] Due to the low price of penicillates, these compounds are attractive starting materials for the preparation of other penicillin analogues as potential β-lactam antibacterials. In the key step of carbene-based transformations of penicillates a sulfonium ylide is generated. This intermediate undergoes thiazolidine ring fission *via* β-elimination, as exemplified in Figure 11.[48]

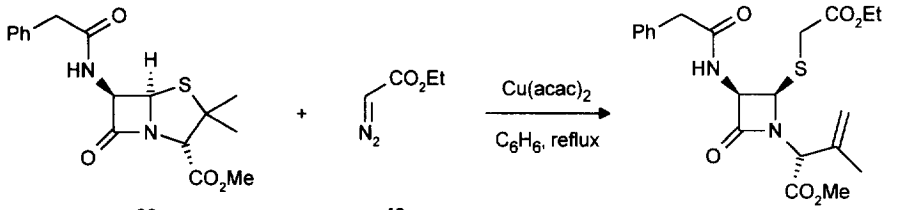


Figure 11

This approach has been used for the multistep conversion of easily accessible 6-aminopenicillic acid into 2-carboxylcephem.[49] A further example for the use of carbenes for the chemical transformation of β-lactams is sketched in Figure 12.[50]

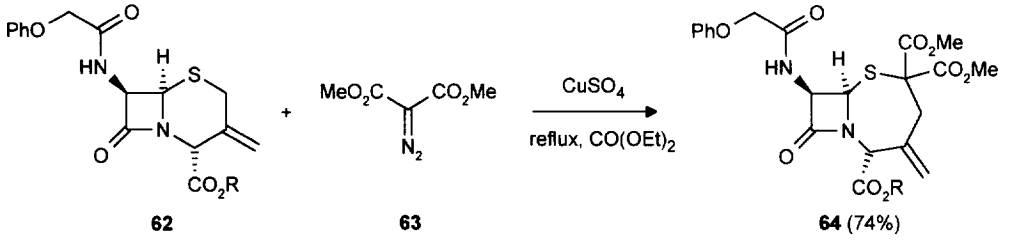


Figure 12

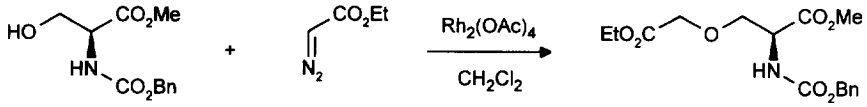
Refluxing the cephame **62** with dimethyl diazomalonate (**63**) and cupric sulfate in diethyl carbonate yielded the homocephame **64** in good yield without epimerization. This example demonstrates that electrophilic carbenes can react faster with thioethers than with C-C double bonds. The mechanism of this reaction consists presumably of initial sulfonium ylide formation, followed by a sulfonium ylide-thioether rearrangement. In this case both a concerted [2,3]-sigmatropic rearrangement or a Stevens-type [1,2]-rearrangement may occur, but additional experiments[50] indicated, that in this specific example [2,3]-sigmatropic rearrangement is most likely to operate.

5.3. O-H Insertion

The etherification of alcohols with rhodium carbenoids is an excellent alternative to the classical Williamson reaction.[30b, 52] The mild reaction conditions render this process highly suitable for the etherification of enantiomerically pure, sensitive molecules.[53] However, this reaction has not yet extensively been applied to

the O-alkylation of hydroxy group containing α-amino acids.

We found[16] that *N*-(benzyloxycarbonyl)serine methyl ester (**65**), which is difficult to O-alkylate with alkyl halides,[54] undergoes smooth etherification with ethyl diazoacetate (**40**) in the presence of catalytic amounts of rhodium(II) acetate.



65 **40** **66** (63%)

This reaction is closely related to the etherification of N-protected 2-aminoalcohols with rhodium carbenoids.[55] The experiments described by now suggest that standard carbamate N-protection is sufficient for permitting chemoselective O-alkylation of aminoalcohols with the aid of rhodium carbenoids.

6. SUMMARY AND OUTLOOK

The chemistry of enantiomerically pure α-amino acids remains a classical research area for the synthetic chemist. Transformations of α-amino acids with the aid of carbanions have exhaustively been investigated, unveiling very powerful and general synthetic approaches to unnatural α-amino acid derivatives.

However, only little attention has been directed to the radical and carbene chemistry of α-amino acids. With the discovery of rhodium(II) carbenoids, a new method for the alkylation of organic molecules under neutral, very mild reaction conditions has emerged. In this article, the insertion reactions of electrophilic carbenes with derivatives of α-amino acids have been reviewed, with the goal of systematizing the general mechanistic principles. From the research detailed, it is clear that these reactions offer interesting synthetic possibilities. However, it will have become apparent to the reader that the determining factors for regio- and stereoselectivity of this reaction are not yet fully understood. A more systematic investigation of the reactions discussed is needed to permit their successful application to target-directed, multistep syntheses. Hopefully, future research in this area will reveal synthetic sequences which permit regio- and stereoselective C-alkylations of not only derivatives of α-amino acids, but also of other, easily accessible natural products.

ACKNOWLEDGEMENTS

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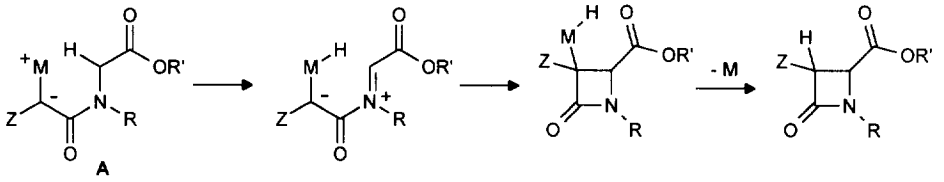
14. Pirrung, H. C.; Morehead, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 8991-9000. The authors propose that in rhodium carbenoids resulting from rhodium(II) carboxylates and diazocarbonyl compounds the negative charge is mainly localized on the rhodium complex (as indicated in Figure 4). In principle a mechanism consisting in initial hydride abstraction by the metal, C-C bond formation and reductive elimination of the catalyst could also be considered:



This mechanism, however, is unlikely to be correct for M = $Rh_2(O_2CR)_4$. The canonical form **A** will only contribute to a negligible extent to the structure of the intermediate formed from diazocarbonyl compounds and rhodium carboxylates (cf. Figure 4). **A** would be relevant only for *electron-rich* catalysts M, which on the other hand would not be able to react with the weakly nucleophilic diazo compounds. Moreover, if **A** contributes significantly to the structure of the intermediate, then this species should behave chemically as a (stabilized) ylide and not as a carbene. Ylides normally do not give carbene-type reactions, unless subjected to photolysis or pyrolysis.
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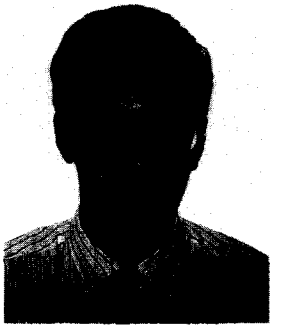
Biographical Sketch



Florencio Zaragoza

Florencio Zaragoza Dörwald was born 1964 in Hamburg and studied chemistry at the Georg-August University of Göttingen from 1982 to 1987. He then moved to Strasbourg (France), where he worked as "Kekulé-fellow" under the supervision of Michel Franck-Neumann on the use of alkynyl vinyl carbenes in natural product synthesis, obtaining his Ph.D. in 1990. After an one-year stay at the University of Basel (Switzerland) and an additional postdoctoral year at the University of North Texas (Denton, Texas) he moved to Dresden. Supported by a Liebig-fellowship he initiated research at the Technical University of Dresden on reactions of rhodium carbenoids with amino acid derivatives. In 1995 he was appointed by Novo Nordisk (Måløv, Denmark) where he is presently working on the development of organic syntheses on solid supports.