

Asymmetric Intramolecular Cyclopropanation. Synthesis of Conformationally Constrained Aminocyclopropane Carboxylic Acids

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Conformationally constrained amino acids are useful for the construction of peptidomimetics with certain beneficial features for medicinal applications. In this paper we discuss some of the features which make these non-natural amino acids desirable candidates, and present a facile approach to the title compounds. Metal-catalyzed asymmetric induction provides a straightforward entry into the title compounds. The successes and shortcomings of this approach are discussed, and plausible rationalizations for the observed stereochemical control are presented.

Specificity in biological processes is an intrinsic property of the interacting molecular species, whether they are small molecules or macromolecular assemblies. The three-dimensional surface properties of interacting peptides and proteins determine the selectivity and specificity of recognition processes. Understanding the factors involved in these processes will help us not only to rationalize the selectivities of natural peptides, but also, it is hoped, that from this information to develop new design paradigms for the discovery of novel drug lead candidates.

The structural theory of peptides has developed substantially over the past three decades.¹ At present, one can distinguish various structural motifs generally occurring in different regions of proteins.

Protein structure levels

Protein structures have been more thoroughly scrutinized and found to contain certain often-repeated patterns.² The primary amino acid sequence of proteins and peptides contains structural patterns which define the secondary structure of the protein. Further association of these structural motifs into common expressions in the form of, say, bundles of α -helices, generates the supersecondary structure of the protein, characterized by its domain structure. One speaks of structural and functional

domains. The former generally form a stable assembly of protein subregions not necessarily playing any functional role, whereas the latter, by definition, form a functional ensemble. Thus, enzyme catalytic sites are often found at the intersection of two subunits, one half of the binding site provided by one protein unit, the other half by a second unit.

The tertiary structure defines the actual three-dimensional structure (shape) of the protein, and the assembly of different subunits into a functional ensemble is described as the quaternary structure.

Turns in peptides and proteins

At the secondary structure level, one can distinguish several structural motifs which are generally found in the protein structures. The first motifs to be recognized were the α -helix and the β -sheet,³ and the regions joining these were not so long ago described simply as random loops. However, they are neither random nor loops.⁴ In the apparently random regions one can distinguish regions where the protein chain folds back on itself, i.e. forms a turn. Two major categories of turn are defined: β -turn

Table 1. Secondary structure levels.

Structural motif	Hydrogen bonding	Ring size
β -Sheet	Interstrand	None
α -Helix	$i+4$	13
β -Turn	$i+3$	10
γ -Turn	$i+2$	7

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(reverse turn, β -bend, inverse turn, U-turn) and γ -turn. The former is distinguished by a hydrogen bond between residue $i(\text{C}=\text{O})$ and $i+3(\text{N}-\text{H})$ (forming a ten-membered ring), and the latter similarly between $i(\text{C}=\text{O})$ and $i+2(\text{N}-\text{H})$ (seven-membered ring).⁵

The pronounced occurrence of β -turns on the protein surface makes them viable candidates for molecular recognition, as exemplified by antigenic recognition, cell-cell recognition and protein-DNA recognition.⁶ The importance of the structural patterns in the β -turn regions can hardly be overemphasised.⁷ A crystallographic study at high resolution has established for instance that the active site of an aspartic proteinase from *Rhizopus chinensis* contains two β -turns: both of the catalytic asparagines are involved in type I turns.⁸

Classification and structural features

In their primitive form, β -turns were defined by having an intramolecular hydrogen bond over four amino acid residues, and as not containing a helix.⁹ Three different types of β -turn are defined: two non-helical (I and II) and one close to the 3_{10} -helix (type III). The difference between types I and II lies in the second residue: it seems to be flipped over in one of them. Inverse conformations have also been recognized, and named types I', II' and III', respectively. A further requirement for a β -turn is that the distance between the α -carbons of residues i and $i+3$ is $\approx 4.8 \text{ \AA}$ in types I and II. The requisite dihedral angles ϕ and ψ are shown in Table 2.

Peptidomimetics

Peptides of even quite large size are routinely available relatively readily, thanks to the rapid developments in molecular biology and enzyme transformations. To offset this major advantage, peptides as drug candidates are typically associated with several adverse properties, including usually low stability towards thermal and pro-

teolytic denaturation. Owing to the very nature of peptides' dynamic conformation, they typically are prone to present a multitude of conformations leading to the possibility of non-specificity. As pharmaceutical candidates, peptides can furthermore be hampered by oral inactivity (owing to proteolysis and poor absorption), poor chances for the adjustment of lipophilicity and usually high potential for antigenicity.

Peptidomimetics have gained a central role in the development of new approaches to the discovery of lead compounds and drug development. This is mainly due to the fact that these compounds are typically less restricted by the limitations described above for peptides. In particular, the possibility of chemically altering the structures gives possibilities for fine tuning the conformations of the amide bonds and the side chain dihedral angles (cf. Table 2), increasing stability towards hydrolysis by increasing steric bulk around the amide group, and facilitating adjustment of the lipophilicity of the compound. In theory, given a suitable starting point one could design a drug candidate with high probability of success. Of course, this is still more fiction than fact, and this activity can easily lead to vastly more complex structures which are increasingly more elusive as synthetic targets.

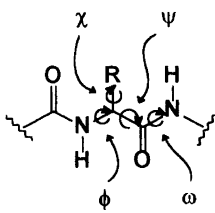
Figure 1 shows a typical structure of a β -turn in a peptide backbone representation, and the cyclopropano analogue designed from this structure.

Asymmetric intramolecular cyclopropanation

The synthesis of the cyclopropanoid β -turn mimetics requires a facile entry into to the component aminocyclopropanecarboxylic acids, for which we have earlier described a high-yielding racemic approach based on an intramolecular cyclopropanation of allyl diazomalonates (Scheme 1).¹⁰ Relying on the same general strategy called for an intramolecular catalytic asymmetric cyclopropanation.

Cyclopropanation of diazocarbonyl compounds was one of the earliest described metal-catalyzed asymmetric transformations.¹¹ Nearly three decades ago, through the pioneering work by the groups of Nozaki and Aratani (Fig. 2),¹² the foundations were laid for the eventual development of pyrethroid insecticide intermediates (permethrinic acid and chrysanthemate esters) as well as the so-called Sumitomo process¹¹ for the industrial manufacture of cilastatin, an enzyme inhibitor used in conjunction with broad-spectrum antibiotics.

Table 2. β -Turn dihedral angles.



$\omega_i = 0$ for $\text{C}_\alpha - \text{C}_i$ cis to $\text{N}_{i+1} - \text{C}_{i+1}$
 $\psi_i = 0$ for $\text{C}_\alpha - \text{N}_i$ trans to $\text{C}_i - \text{O}_i$
 $\phi_i = 0$ for $\text{C}_\alpha - \text{C}_i$ trans to $\text{N}_i - \text{H}_i$
 $\chi_i = 0$ for $\text{C}_\alpha - \text{N}_i$ cis to $\text{C}_\beta - \text{O}_\gamma$

Turn type	(ϕ_{i+1}, ψ_{i+1})	(ϕ_{i+2}, ψ_{i+2})
Type I	(-60, -30)	(-90, 0)
Type I'	(60, 30)	(90, 0)
Type II	(-60, 120)	(80, 0)
Type II'	(60, -120)	(-80, 0)
Type III	(-60, -30)	(-60, -30)
Type III'	(60, 30)	(60, 30)

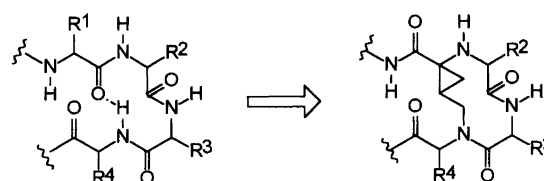
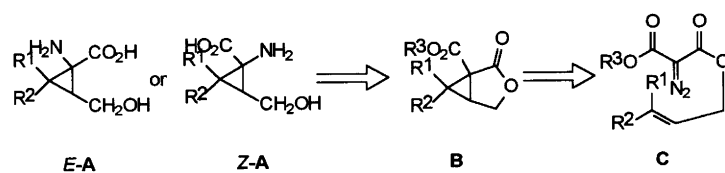


Fig. 1. Design of a β -turn mimetic cyclopropanoid.



Scheme 1.

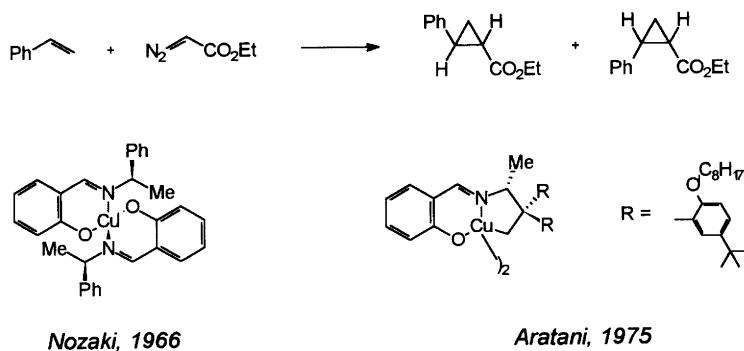


Fig. 2. Early examples of asymmetric Cu-catalyzed cyclopropanation.

More recent developments have centered on the development of semicorrin ligands¹³ and recently bisoxazolines by Masamune, Evans and Pfaltz (Fig. 3).^{13–15} It is noteworthy that although the enantioselectivities have reached quite acceptable levels (up to 98% ee in the reaction of styrene with diazoacetate), a major problem has remained within the control of diastereoselectivity.

Prompted by the feasibility of inducing chirality using the newer generation semicorrin or bisoxazoline ligands, we initially attempted the cyclopropanation reaction (Scheme 2).¹⁶ To our astonishment, the observed absolute sense of the major enantiomer turned out to be the opposite of that predicted by the Pfaltz model [Fig. 4(a)]. This observation, as well as the cases in the literature reporting markedly inferior enantioselectivities for intramolecular cyclopropanations versus intermolecular cyclopropanations,¹⁷ encouraged us to embark on a more thorough investigation on the factors controlling selectivity. On the basis of our results we tentatively constructed an alternative transition state model [Fig. 4(b)].

We soon established that the reactions of diazomalonates must indeed follow a somewhat different pathway from those of diazoacetates, although obvious similarities were discovered as well. In intermolecular cyclopropanation the stereoselectivity has been shown to depend on three separate, more or less independent factors. The structure of the catalytic complex, which eventually becomes a question of having different substituents

around the ligand framework, is one of the most obvious ones and can be modified according to the substrate molecule(s) to give best selectivity. Whenever possible, modification of the substrate structure, either the alkoxy moiety of the diazo ester and/or substituents at the olefinic carbons, can be used to improve selectivity with a given catalyst. We were quite happy also to find all these features present in the intramolecular version of this reaction, although a change in any one of these may have opposite effects in these two cases.

Our first results clearly indicated that a relatively open coordination sphere around the metal center is required for efficient induction of enantioselectivity. The best selectivity was achieved using a catalyst with benzyl groups attached to stereogenic carbons of the ligand (Scheme 2); a ligand which, in intermolecular reactions, was able to induce only moderate enantioselectivity compared with more bulky di-*tert*-butyl substituted ligands. This tendency has since then been observed by others as well.¹⁵ The buttressing effect of the *gem*-dimethyl group in the bisoxazoline reported by Evans^{14e} plays only a minor role thus suggesting that the effect in intermolecular reaction is mainly of steric rather than electronic origin.

Preliminary studies on olefin substitution show increased reactivity upon addition of electron-donating

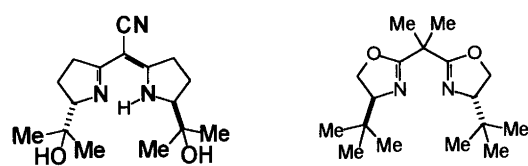
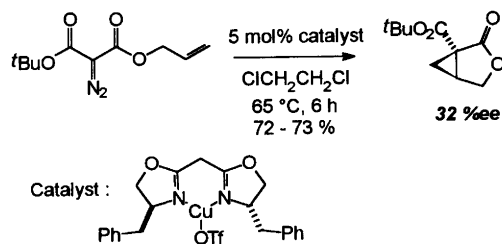


Fig. 3. Typical semicorrin and bisoxazoline used as chiral ligands in Cu-catalyzed cyclopropanation.



Scheme 2.

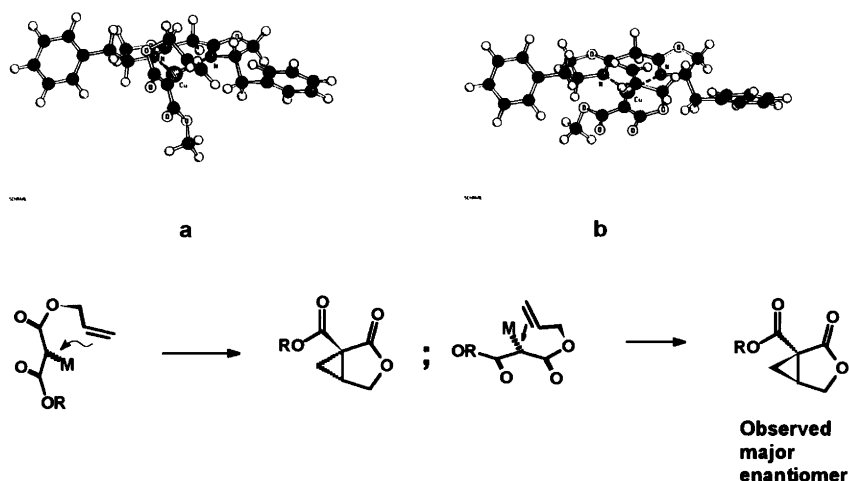


Fig. 4. Arrangement of the transition state according to the Pfaltz suggestion (a) and the alternative configuration (b).

groups and thereby increased electron density of the double bond. This observation is hardly surprising since the reaction is supposed to proceed via coordination and subsequent addition of the olefin to an electrophilic center, whether it be the copper ion or the carbene carbon. We have also observed that the allyl unit can only poorly accommodate *E*-geometry, as evidenced by dramatic decrease in enantioselectivity in the cyclization of a cinnamyl alcohol derived diazomalonate.

The most striking effect, however, was discovered when size of the non-allyl ester moiety in the substrate was increased. A substantial threefold increase in enantioselectivity was observed when the methyl group was replaced with a *tert*-butyl group and further almost doubled upon introduction of a bulky diethyl phosphonate group. A similar trend has been observed in intermolecular reactions and we are hoping to be able to bring these two reactions together mechanistically by using this common feature as a starting point.

Considering the mechanistic rationalizations for the metal-catalyzed cyclopropanation of diazocarbonyl compounds, the structure of the first formed intermediate derived from the diazo compound is critical. In particular, the existence of a conformational preference along the metal-carbon bond in the metalcarbenoid intermediate is a major question to be answered when a mechanistic rationalization is developed. Therefore it is worth having a look at the bonding process itself to gain an idea of the factors that may have effect on the preferential geometry.

In the metal carbene double bond the bonding process is described as donation of electron density from a filled carbon sp^2 hybrid orbital to an empty acceptor orbital of the metal and subsequent donation of electron density from a filled metal d orbital to an empty p orbital of the carbene carbon (Fig. 5).¹⁹ In its pure form this kind of back bonding process is indeed likely to give rise to a relatively rigid bond geometry, where orientation of the

substituents is determined by the orbital interaction described above.

This kind of bonding, however, is possible mainly for singlet-state carbenes, i.e., carbenes having both electrons on the same hybrid orbital. Electron-withdrawing substituents, π -electron acceptors in particular, at the carbene carbon are likely to induce a triplet ground state rather than a singlet.²⁰ The energy gap between the singlet and triplet states and thereby the 'effective spin state' is very much likely to be affected by the nature and number of π -acceptors attached to the carbene. This effective spin state determines the preferred way of forming a bond with the metal center.

Bonding in a carbene complex can well be compared to bonding in an olefin complex, since interaction from the metal's point of view occurs through the same orbitals in both cases. Back donation is not regarded to be very important for copper(I), which most probably is the oxidation state of the metal at this stage.²¹ Therefore it is quite safe to assume that the carbene carbon, and its effective spin state, plays a decisive role in setting up the electronic configuration at the metal which ultimately leads to a stabilizing interaction between the two entities. If the carbene has a pure triplet ground state the metal can also act as a diradical, and in the case of a singlet

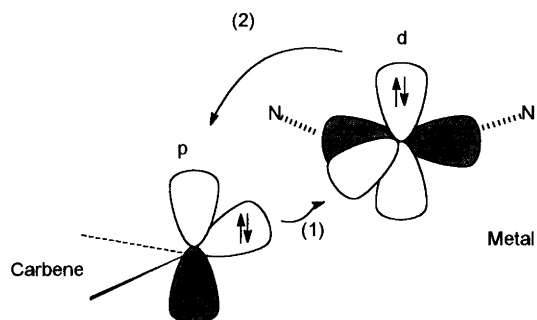


Fig. 5. Metal-carbene bond.

carbene the metal can easily accept the electron pair and subsequently donate enough electron density to neutralize the charge at the carbene carbon.

Bonding involving a considerable degree of back donation can occur only through a distinct geometrical conformation, where the metal d orbitals and carbene p orbitals are able to overlap. If, however, the carbene carbon prefers a triplet ground state both centers become more or less independent and rotation around the metal carbene bond is thus allowed. Indeed, preliminary calculations have shown that the rotational barrier along the metal carbene bond is considerably lowered upon addition of electron withdrawing substituents to the carbon atom.

In conclusion it seems likely that in carbene complexes where the carbene carbon carries strong π -acceptors the carbene bond is allowed and the coordination geometry is determined mainly by secondary interactions, such as steric repulsion between the carbene fragment and the ligand framework. When the electron density at the carbene carbon is increased the singlet state becomes more favorable, a higher rotational barrier is established and a perpendicular orientation between the ligand plane and carbene substituents becomes preferred. We are currently working on this hypothesis with the purpose of being able to develop a model, which would be capable of both explaining observations reported in the literature so far and, on the other hand, predicting the outcome of reactions not yet performed.

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