

# 1

## Asymmetric Isocyanide-based MCRs

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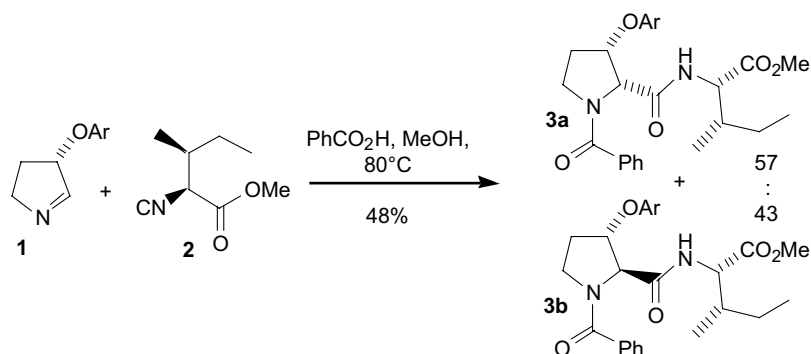
### 1.1 Introduction

Although the great utility of isonitrile-based multicomponent reactions in assembling complex pharmacologically important structures in a small number of steps and with the possibility of several diverse inputs is widely recognized [1, 2], the stereochemical issues still represent a challenge. Usually in Passerini and Ugi reactions (P-3CRs and U-4CRs) a new stereogenic center is generated, but most reactions reported so far suffer from low or absent stereoselectivity. It seems that MCRs are following the evolutionary trend experienced in the past by conventional organic syntheses. While in the 1960s and 1970s the main efforts were directed toward the discovery of new reactions, in the 1980s and 1990s the focus moved towards selectivity, in particular stereoselectivity, leading to highly efficient methodologies. For MCRs it is probable that the same thing will happen. Promising results are already appearing in the literature. We can foresee that in the next 20 years more and more researchers will dedicate their skills and ingenuity to devise methods to control the stereoselectivity in P-3CR and U-4CR, as well as in other less well-known isonitrile-based MCRs. We hope that this chapter may help to stimulate these efforts by describing the present state of the art.

### 1.2 Racemization Issues

Since asymmetric induction in P-3CRs or U-4CRs is achieved in most cases by using one or more chiral components in enantiomerically pure form, it is important to assess the possibility of racemization under the reaction conditions. While this does not seem to be a problem for carboxylic acid and amine components, there are some reports of racemization of chiral aldehydes or isocyanides.

For example, aldehydes having an  $\alpha$ -alkyl substituent have been reported to be stereochemically unstable during Ugi condensation [3]. On the contrary,  $\alpha$ -alkoxy substituted aldehydes do not racemize.



Scheme 1.1

While enantiomerically pure  $\alpha$ -substituted isocyanoacetates have been used in Passerini condensation without significant racemization [4–6], the same class of compounds is believed to be configurationally unstable under the conditions of U-4CRs [7]. However, one notable exception is the reaction shown in Scheme 1.1, where L-isoleucine-derived isocyanide **2** has been condensed without such problems with pyrroline **1** [8]. The bulkiness of this isocyanide or the use of a pre-formed cyclic imine, thus avoiding the presence of free amine in solution, may be the reasons for the absence of racemization.

Care should be taken during the preparation of chiral  $\alpha$ -isocyanoesters from the corresponding formamides: while the use of diphosgene or triphosgene under controlled temperatures (especially with *N*-methylmorpholine as the base) seems to afford products endowed with high optical purity [5, 6, 8, 9], the combination of other dehydrating agents and bases, such as phosphorus oxychloride and diisopropylamine, leads to various degrees of racemization [10].

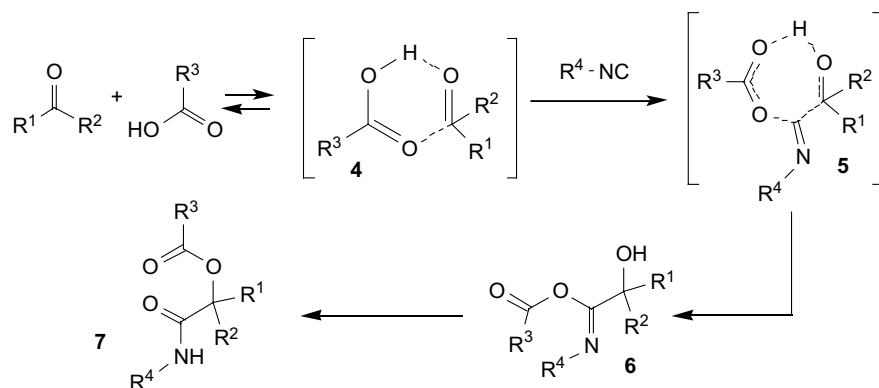
### 1.3

#### Asymmetric Passerini Reactions

##### 1.3.1

##### Classical Passerini Reactions

In the classical Passerini reaction [11], an isocyanide is condensed with a carbonyl compound and a carboxylic acid to afford  $\alpha$ -acyloxyamides **7** (Scheme 1.2). When the carbonyl compound is prochiral, a new stereogenic center is generated. It is generally accepted that the reaction proceeds through intermediate **6**, which rearranges to the product. The way this intermediate is formed is more debated. A possibility is a concerted non-ionic mechanism involving transition state **5**. Since the simultaneous union of three molecules is not a very likely process, another possibility is a stepwise mechanism, with the intermediacy of a loosely bonded adduct **4** between the carbonyl compound and the carboxylic acid [2]. Since all three

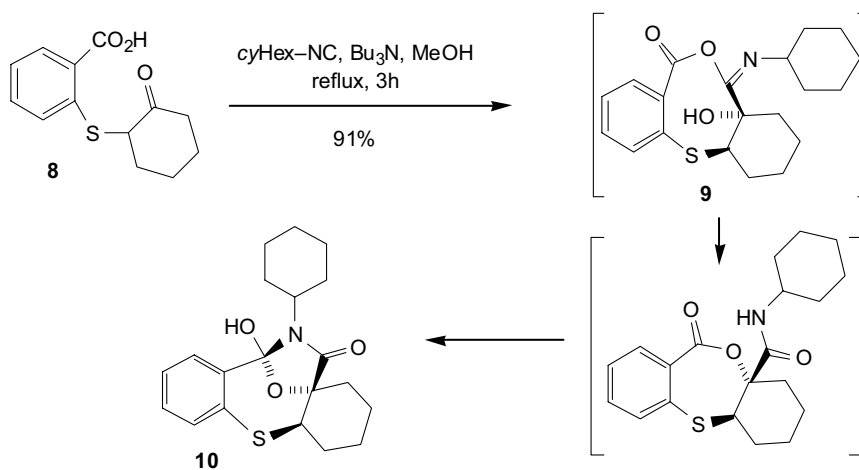


Scheme 1.2

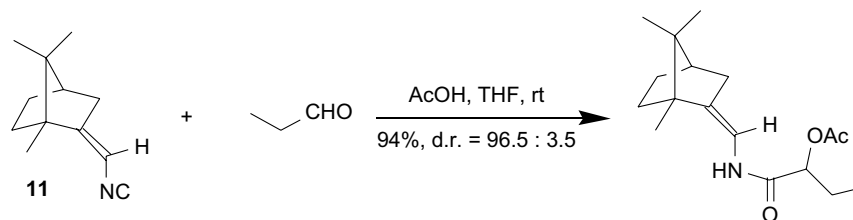
components are involved in rate-determining steps [12], in principle asymmetric induction may be achieved when at least one of them is chiral.

In nearly all the reported cases involving chiral carbonyl compounds, however, the diastereoselectivity is moderate, ranging from 1:1 to 4:1. This is somewhat surprising for the reactions of aldehydes with an  $\alpha$  stereogenic center, which often afford high stereoselectivity in other types of nucleophilic additions. The low steric requirement of the isocyanide group may account for this generally low stereoselectivity. A notable exception is the intramolecular reaction of chiral racemic keto-acid **8** to give **10** (Scheme 1.3) [13]. Only one of the two possible diastereoisomeric products is formed. The tricyclic nature of intermediate **9** makes the alternative diastereoisomer more sterically strained.

While chiral isocyanides such as  $\alpha$ -substituted isocyanacetates also usually react with low stereoselectivity, the specially designed, camphor-derived, isonitrile **11**



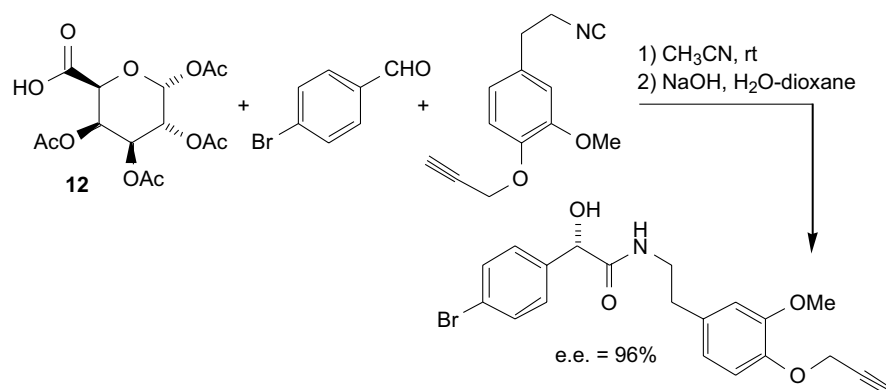
Scheme 1.3



Scheme 1.4

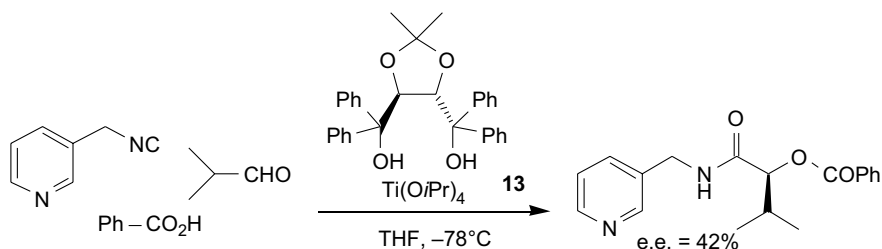
gives high asymmetric induction in the reaction with some aliphatic aldehydes [14] (Scheme 1.4). The chiral auxiliary may be removed after the condensation reaction to give a carboxylic acid or ester [15].

A recent screening of various chiral carboxylic acids has allowed the selection of galacturonic derivative **12** as a very efficient control in the stereochemical course of some Passerini reactions (Scheme 1.5). Although the *de* seems to be strongly dependent on the isocyanide employed, this result suggests the possibility of employing carboxylic acids as easily removable chiral auxiliaries in the asymmetric synthesis of biologically important mandelamides [16].



Scheme 1.5

Finally a fourth way to achieve asymmetric induction in the Passerini reaction is by way of a chiral catalyst, such as a Lewis acid. This approach is not trivial since in most cases the Lewis acid replaces the carboxylic acid as third component, leading to  $\alpha$ -hydroxyamides or to other kinds of products instead of the “classical” adducts **7** (*vide infra*). After a thorough screening of combinations of Lewis acids/chiral ligands, it was possible to select the couple **13** (Scheme 1.6), which affords clean reaction and a moderate *ee* with a model set of substrates [17]. Although improvements are needed in order to gain higher *ees* and to use efficiently substoichiometric quantities of the chiral inducer, this represents the first example of an asymmetric classical Passerini reaction between three achiral components.

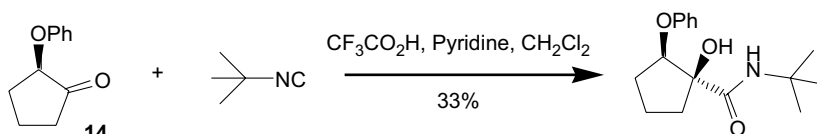


Scheme 1.6

## 1.3.2

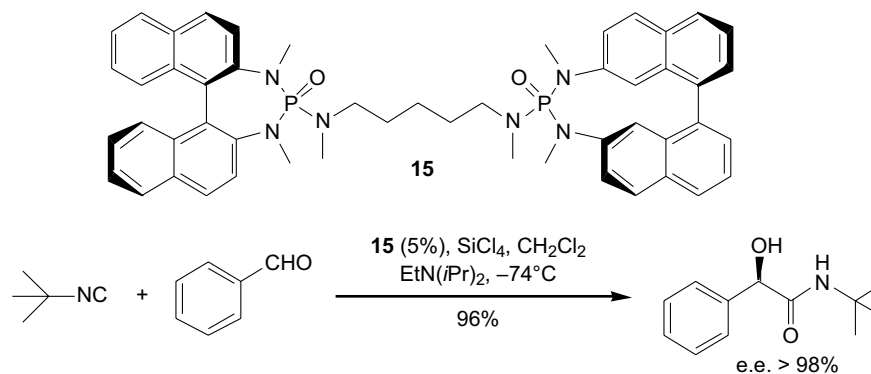
## Passerini-type Reactions

When a mineral or Lewis acid replaces the carboxylic component in the Passerini reaction, the final products are usually  $\alpha$ -hydroxyamides. Also in this case, when chiral carbonyl compounds or isocyanides are employed, the asymmetric induction is, with very few exceptions, scarce [18, 19]. For example, the pyridinium trifluoroacetate-mediated reaction of racemic cyclic ketone **14** with *t*-butyl isocyanide is reported to afford a single isomer [19] (Scheme 1.7). This example, together with those reported in Schemes 1.3 and 1.4, suggests that high induction may be obtained only by using rigid cyclic or polycyclic substrates.



Scheme 1.7

The Lewis acid-mediated Passerini reaction is particularly well suited for the exploitation of chiral mediators. However, after the pioneering unsuccessful attempts by Seebach et al. [6], this strategy has only recently been reinvestigated by Denmark and Fan [20]. They not only succeeded in obtaining excellent *ees*, but also solved the problem of efficient catalyst turnover, by taking advantage of the concept of “Lewis base activation of Lewis acids”. The weak Lewis acid  $\text{SiCl}_4$  can be activated by catalytic quantities of chiral phosphoramides such as **15** (Scheme 1.8). Best results are achieved at low temperature, by slow addition of the isocyanide, since its low concentration favors the catalyzed pathway versus the uncatalyzed one. The *ees* are excellent with aromatic or  $\alpha,\beta$ -unsaturated aldehydes. On the other hand with aliphatic aldehydes they range from 35% to 74%. Also replacing *tert*-butyl isocyanide with other isonitriles brings about a slight decrease of the *ees*.



Scheme 1.8

## 1.4

### Asymmetric Intermolecular Ugi Reactions

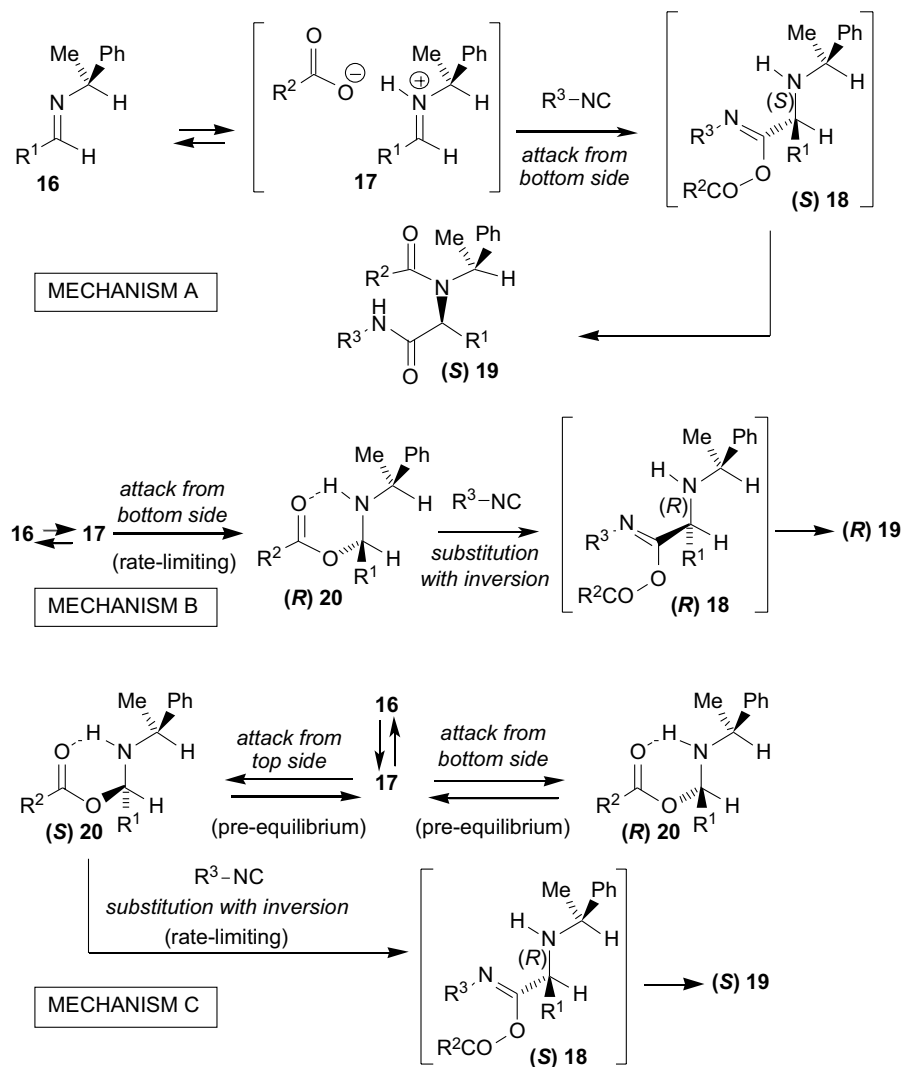
#### 1.4.1

##### General Remarks

The classical Ugi reaction [2] involves interaction of a carbonyl compound, an isocyanide, an amine and a carboxylic acid to obtain an  $\alpha$ -acylaminoamide. The first step is the condensation of the carbonyl compound with the amine to give an imine. Preformed imines can be employed as well, in some cases with certain advantages in terms of reaction time and yields. The reaction of such imines with isocyanides and carboxylic acids can be considered as an aza analogue of the Passerini reaction and therefore, at first sight, one might assume that the two mechanisms are similar. However some experimental evidence suggests that the mechanistic scenario for the U-4CR may be different and more complex than that shown in Scheme 1.2 for the P-3CR. First of all it is well known that a U-4CR is favored in a polar solvent (MeOH being the most common) while a P-3CR is faster in relatively unpolar media such as CH<sub>2</sub>Cl<sub>2</sub> and Et<sub>2</sub>O. Secondly, the chiral isocyanide **11** (Scheme 1.4), that leads to excellent *dr* in the P-3CR, affords no stereoselectivity at all in the related U-4CR [21]. Finally it has been demonstrated by a thorough study [21, 22] that in a model asymmetric Ugi reaction involving (*S*)- $\alpha$ -methylbenzylamine as chiral auxiliary, at least two competing mechanisms, leading to opposite stereoselectivity, are operating.

In Scheme 1.9 this model reaction will be used as an example to show three possible competing mechanisms (A, B and C) that may be working. The first is similar to the one proposed in Scheme 1.2 for a P-3CR. Assuming that the imine has an (*E*) configuration and that the preferred conformation of the chiral auxiliary is the one shown (on the basis of allylic strain arguments) [23], the isocyanide should attack from the less encumbered bottom face, leading to (*S*)-**19** as the final product.

In mechanisms B and C, on the contrary, the iminium ion is first attacked by the carboxylate, which forms the hydrogen-bonded intermediate **20**. Then substitu-



Scheme 1.9

tion by the isocyanide proceeds with inversion of configuration [21]. The difference between B and C is the rate-limiting step. In B, addition of the carboxylate is rate-limiting and the stereochemical course is kinetically controlled to give intermediate (*R*)-20 and hence (*R*)-19 as major diastereoisomers [21].

Mechanism B may explain why in many cases chiral isocyanides (e.g. 11) give no asymmetric induction at all [21]. Indeed, the isocyanide is not involved in the transition state. In mechanism C the substitution by the isocyanide is rate-limiting and reversible formation of 20 originates a pre-equilibrium. Although (*R*)-20 should be kinetically favored, (*S*)-20 may be more stable because of the destabilizing interac-

tion between Ph and R<sup>1</sup> in the (*R*) isomer [21]. After substitution and rearrangement, (*S*)-**20** again affords (*S*)-**19** as the major adduct, as for mechanism A.

The competition between mechanisms B and C has been invoked in order to explain the surprising inversion of diastereoselectivity achieved by a simple variation of the overall reactant concentration: at low concentration (*S*)-**19** prevails, while at high concentration (*R*)-**19** is formed in greater amounts [22, 23]. An increase in concentration of the isocyanide is indeed expected to favor mechanism B over C, because it accelerates the isonitrile attack, making it non-rate-limiting. The concentration of the other components has the same effect for all mechanisms.

Also the reaction temperature has been shown to have a remarkable effect on the extent of diastereoselectivity. Low temperatures seem to favor the formation of (*S*) diastereoisomers. This may be explained supposing that mechanisms A and C are more entropically disfavored than mechanism B. Therefore the entropy component in  $\Delta G^\ddagger$  is higher and the decrease of rate on lowering the temperature is less pronounced.

In conclusion, the hypothesis that the Ugi reaction proceeds, at least in polar solvents, through the competing mechanisms B and C seems reasonable, and may explain some unexpected experimental results. The intervention of mechanism A, especially in non-polar solvent, may not, however, be definitely ruled out.

In any case, we must stress that these are at present only working hypotheses, not supported by unambiguous proofs. A better comprehension of the mechanism of U-4CRs, based on more solid grounds, is highly desirable for the development of efficient asymmetric modifications.

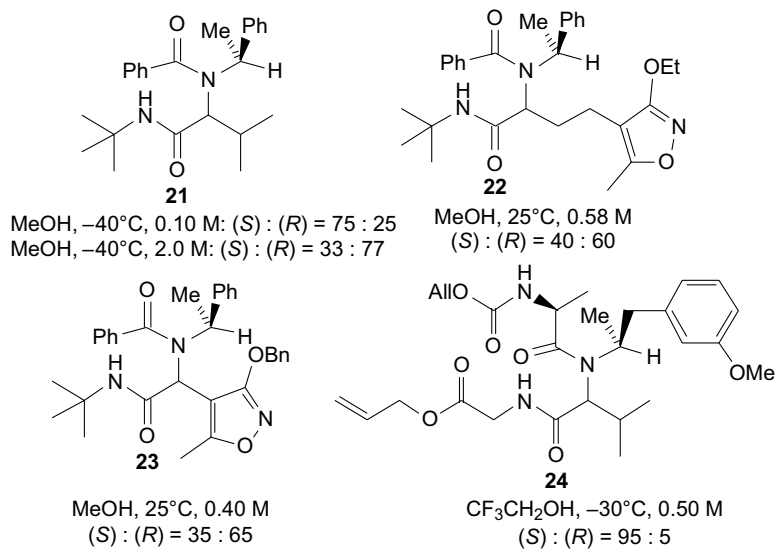
As in the case of P-3CRs, any of the four components can in principle, if chiral, control the generation of the new stereogenic center (with the exception of the isonitrile if mechanism B is operating). To date most efforts have been carried out with chiral amines, partly because removal of the chiral auxiliary is in this case easier and leads to synthetically useful secondary amides (instead of the tertiary amides usually obtained by the classical U-4CR).

#### 1.4.2

##### Chiral Amines

###### 1.4.2.1 $\alpha$ -Methylbenzylamines

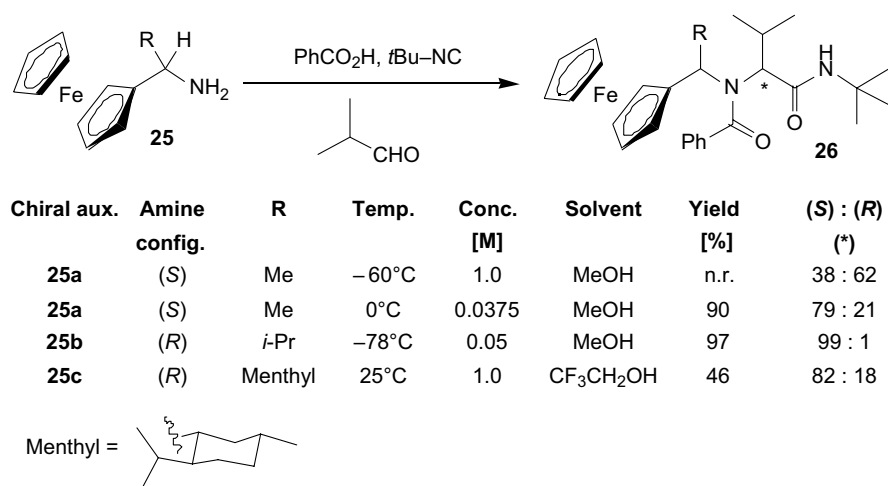
$\alpha$ -Methyl benzylamines have been used several times in order to control the new stereogenic center in U-4CR [3, 21–28]. The chiral auxiliary can be easily removed by hydrogenolysis. Scheme 1.10 shows selected literature examples regarding the synthesis of compounds **21** [3, 22], **22** [24], **23** [25] and **24** [26]. As already mentioned, either the (*R*) or (*S*) (at the new stereocenter) adducts are formed preferentially, depending on the reaction conditions, especially the concentration of reactants, the solvent and the temperature, but also on the structure of reactants. The asymmetric induction is usually only moderate, with the notable exception of **24**. In this case, the stereoselectivity strongly depends on the temperature. At 0 °C the *dr* was only 75:25! Although in the case of **24** the carboxylic acid is also chiral, its influence on the stereoselectivity is expected to be scarce.



Scheme 1.10

## 1.4.2.2 Ferrocenylamines

At the beginning of the 1970s Ugi et al. [29] reported the use of (+)- $\alpha$ -ferrocenylethylamine **25a** in the condensation with *iso*-butyraldehyde, benzoic acid and *tert*-butylisocyanide (Scheme 1.11). The Ugi adduct **26** could be obtained with different diastereomeric excesses, varying solvent, concentration and temperature in analogy [29] with the above described  $\alpha$ -methylbenzylamine. Following this first study, different  $\alpha$ -ferrocenylalkylamines have been employed [30, 31] and improvements in



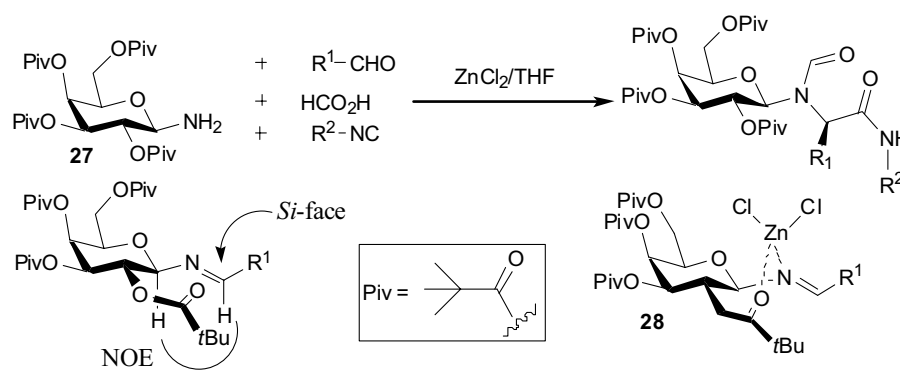
Scheme 1.11

diastereomeric excesses have been realized by substituting the methyl group with bulkier substituents, as in **25b** and **25c**. In particular, for  $R = iPr$ , diastereomeric excesses up to 99% could be obtained working at  $-78\text{ }^{\circ}\text{C}$  [31]. It is interesting to note that an overall reversal of stereoselectivity was obtained on passing from **25a** ( $R = \text{Me}$ ) to **25b** and **25c**. Under the conditions used for entry 3 (low concentration and temperature), one would indeed have expected a preponderance of the (*R*) diastereoisomer, starting from the (*R*) chiral auxiliary. It is possible that in this case the isopropyl group plays the role of a “large” group.

Despite some interesting results, these chiral auxiliaries have not been investigated further, probably because of their structural complexity and chemical instability. In addition to these problems, the Ugi products are not always isolated in high yields and the removal of the chiral auxiliary requires an acid treatment not always compatible with the other parts of the molecule.

#### 1.4.2.3 Glycosylamines

In 1987 Kunz [32] reported the use of 2,3,4,6-tetra-*O*-pivaloyl- $\beta$ -D-galactopyranosylamine **27** as chiral auxiliary in the preparation of  $\alpha$ -aminoacid derivatives *via* the Strecker reaction with aldehydes and trimethylsilyl cyanide. One year later he reported [33, 34] the use of the same chiral auxiliary in the Ugi reaction, where trimethylsilyl cyanide was replaced by an isocyanide and a carboxylic acid (Scheme 1.12).



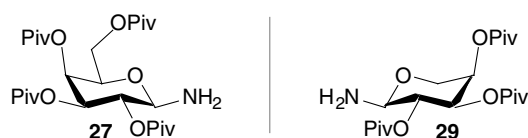
Scheme 1.12

Diastereomeric excesses were usually higher than 90% working between  $-25\text{ }^{\circ}\text{C}$  and  $-78\text{ }^{\circ}\text{C}$  in the presence of a Lewis acid such as zinc chloride; reaction times ranged from 24 h to 72 h and yields were generally high. Interestingly no reaction occurred in the absence of the Lewis acid. The observed stereoselectivity was attributed to the preferential geometry of the imine generated by reaction of **27** with an aldehyde [34]. NMR analysis showed a strong NOE between the anomeric and the aldiminic hydrogen, explainable *via* the conformation reported in Scheme 1.12,

where the *Re*-face of the imine is shielded by the 2-*O*-acyl substituent; therefore the attack by the isocyanide can take place only from the *Si*-face and an (*R*)-configured amino acid is generated. The presence of a Lewis acid like zinc chloride reinforces this geometry, presumably by its coordination to the iminic nitrogen and the carboxyl oxygen, as shown in formula **28**. Moreover, probably, the Lewis acid favors direct attack of the isonitrile (mechanism A of Scheme 1.9).

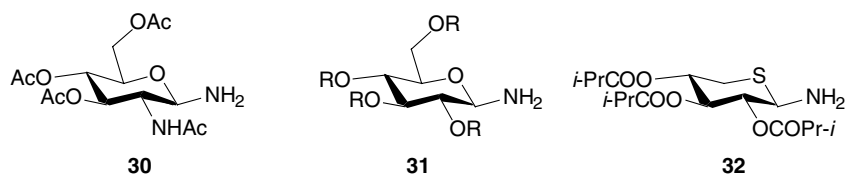
The substantial independence of the stereoselectivity from the structure of the aldehyde makes this methodology extremely convenient to prepare D-amino acid derivatives [35]. It has also been used for solid-phase syntheses [36]. However, some drawbacks can be envisaged, including the harsh conditions required for the removal of the chiral auxiliary (the acyl group of the Ugi product does not survive such conditions) and the difficulty in preparing L-amino acids following the same methodology, since L-galactose is not easily obtainable.

Therefore further modifications of this methodology have been mainly directed to overcome the above drawbacks. In order to obtain L-amino acids, Kunz [37] reported the use of 2,3,4-tri-*O*-pivaloyl- $\alpha$ -D-arabinopyranosylamine **29**, which can be considered with good approximation the enantiomer of **27**, but it is more easily synthesized (Scheme 1.13).



Scheme 1.13

In order to have a milder cleavage of the chiral auxiliary, various other glycosylamines have been introduced, such as 2-acetamido-3,4,6-tri-*O*-acetyl-1-amino-2-deoxy- $\beta$ -D-glucopyranose **30** [38], 2,3,4,6-tetra-*O*-alkyl- $\beta$ -D-glucopyranosylamines **31** [39] and 1-amino-5-desoxy-5-thio-2,3,4-tri-*O*-isobutanoyl- $\beta$ -D-xylopyranose **32** [40] (Scheme 1.14).



Scheme 1.14

There are some interesting features related to these aminosugars; compound **30** possesses very high stereochemical inductivity, but cleavage conditions are still too

harsh. Interestingly the authors report that no stereoselectivity is observed when the Ugi reaction is performed without the Lewis acid; this is in contrast with what was reported earlier by Kunz, that no reaction occurred without the Lewis acid. The loss of stereoselectivity may be due to the intervention of alternative mechanisms B and C.

Cleavage conditions for aminosugars **31** are sufficiently mild; however, yields are usually not higher than 50% and stereoselectivities are lower and depend on the size of the R groups; interestingly in this case no influence of the temperature on the stereoselectivity is observed.

Compound **32** may be removed, after the Ugi reaction, under particularly mild conditions, thanks to sulfur activation by soft electrophiles, such as mercury salts. The yields obtained in zinc-mediated Ugi reactions are excellent and the diastereomeric ratios are in line with those obtained with **27**. Cleavage of the chiral auxiliary can be performed, after methylamine-promoted deacylation of the sugar hydroxy groups, by a diluted solution of CF<sub>3</sub>CO<sub>2</sub>H in the presence of Hg(OAc)<sub>2</sub>. Under these conditions the acyl group on nitrogen is retained. However, the enantiomer of **32** is not easily accessible.

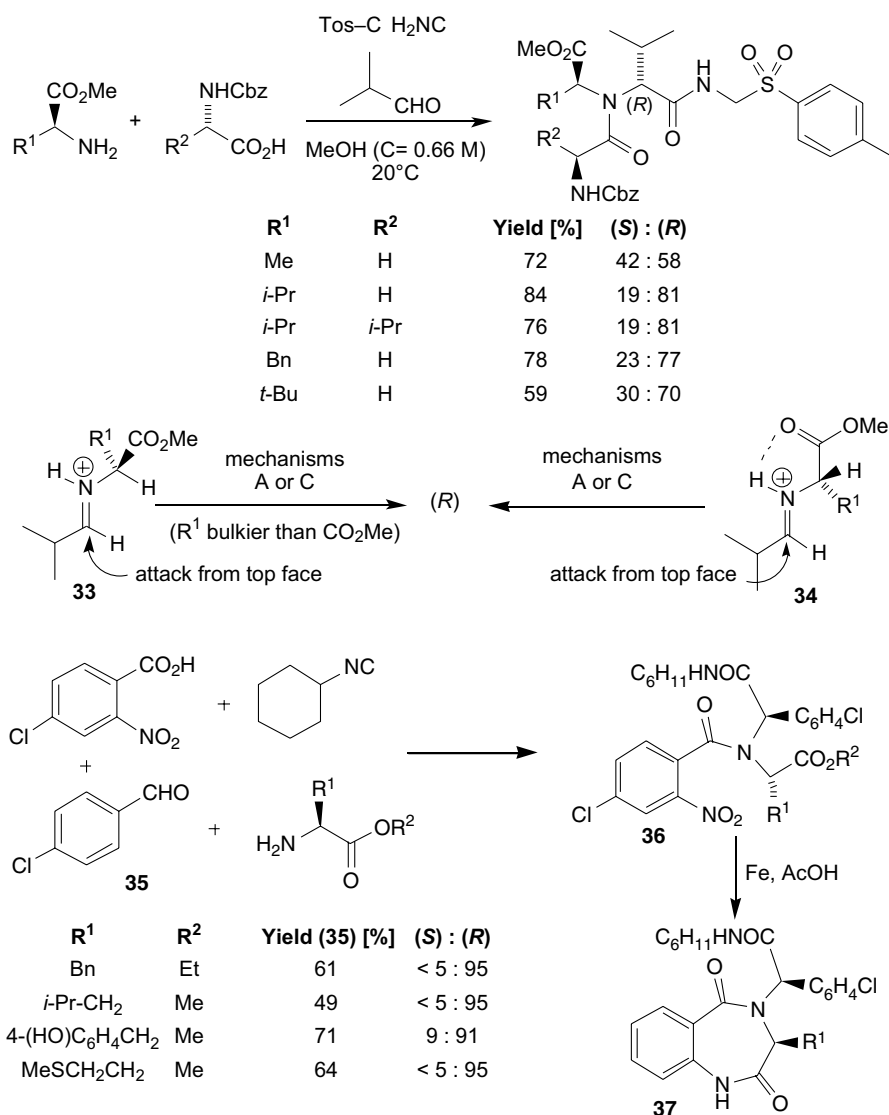
#### 1.4.2.4 Esters of $\alpha$ -amino Acids

Esters of  $\alpha$ -aminoacids can be conveniently used as amine components in the Ugi reaction. In principle they could be used in the Ugi reaction as chiral auxiliaries since they are readily available in both enantiomeric forms and there is a number of literature procedures for their removal at the end of the synthesis. Moreover in several synthetic applications in the field of peptidomimetics their structure may also be retained.

However, they have not yet found many applications in asymmetric Ugi reactions [41–43], and this is probably due to the fact that diastereomeric excesses are often only moderate and strongly influenced by the structure of the side chain of the  $\alpha$ -amino acid. A thorough study was carried out by Yamada et al. [42], who observed that the configuration of the newly generated stereocenter of the major diastereoisomer is always opposite to that of the amino ester. Representative examples are shown in Scheme 1.15. Although Yamada often also used chiral protected aminoacids as the carboxylic component, they were proved to have a negligible influence on the stereoselectivity.

The preferential formation of (*R*) adducts may be explained by the arguments already outlined for  $\alpha$ -methylbenzylamine. In this case, R<sup>1</sup> should play the role of “large” group. Alternatively, a different starting conformation of the protonated imine, namely **34**, involving a hydrogen bond between the carboxylic oxygen and the iminic proton, has been suggested [43].

The most selective example is represented by the synthesis of 1,4-benzodiazepin-2,5-diones **37** via Ugi reaction with different  $\alpha$ -aminoesters. The use of aromatic aldehyde **35** leads in some cases to very high stereoselectivity in the preparation of intermediate **36**, and a single diastereoisomer is isolated after crystallization (Scheme 1.15) [43].



Scheme 1.15

## 1.4.3

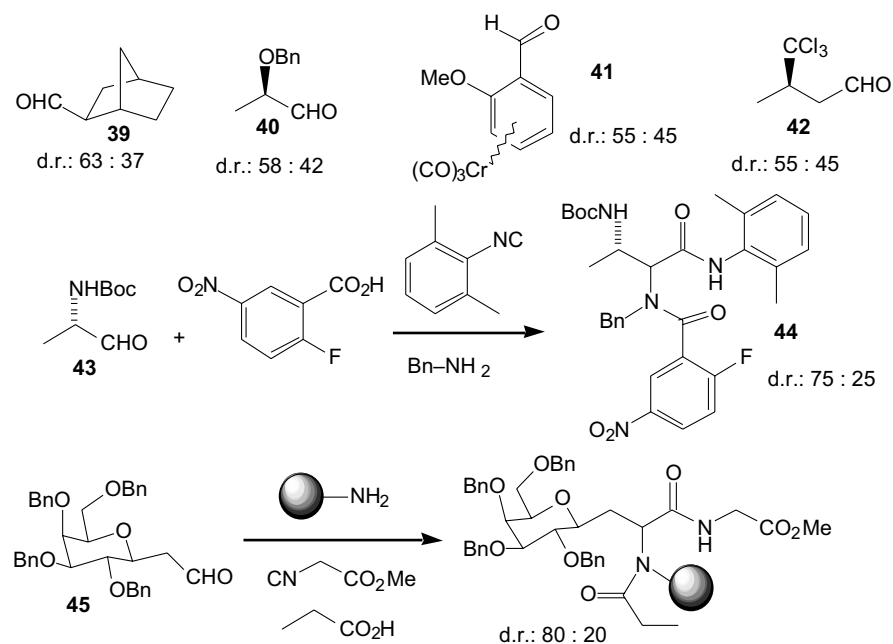
## Chiral Isocyanides, Carboxylic Acids and Carbonyl Compounds

As already mentioned in Section 1.4.1, chiral isocyanides usually give no induction at all in Ugi reactions. For example, when using chiral  $\alpha$ -substituted or  $\alpha,\alpha$ -disubstituted isocyanacetates [7, 27, 44], the two resulting diastereoisomers are

typically obtained in a 1:1 ratio. Even isonitrile **11** (Scheme 1.4), which affords excellent stereoselectivity in the Passerini reaction, is totally inefficient in asymmetric Ugi reaction and this fact has led the authors of that paper to suggest that the isocyanide may not be involved in the step that determines the configuration of the new stereocenter [14]. Finally, even isocyanoglucoses, despite their steric biases, only afforded stereoselectivity of between 50:50 and 57:43 in Ugi condensations with achiral aldehydes, amines and carboxylic acids [45].

At present no chiral carboxylic acid capable of significantly controlling the stereochemistry of the new stereogenic center has been reported [42, 46].

In most cases chiral carbonyl compounds also afford low stereoselectivity. As for the related Passerini reaction, even the use of aldehydes that are known to give excellent asymmetric induction in the reaction with other kinds of C-nucleophiles, results in low or moderate diastereoisomeric ratios. For example, both norbornyl aldehyde **39** [47] and  $\alpha$ -alkoxyaldehyde **40** [3, 48] gave *drs* lower than 2:1 (Scheme 1.16). The same happens with ortho-substituted chromium complex **41** [49], which usually leads to very high asymmetric induction in other nucleophilic additions. Finally,  $\beta$ -substituted aldehyde **42** [50] gave poor results as well.



Scheme 1.16

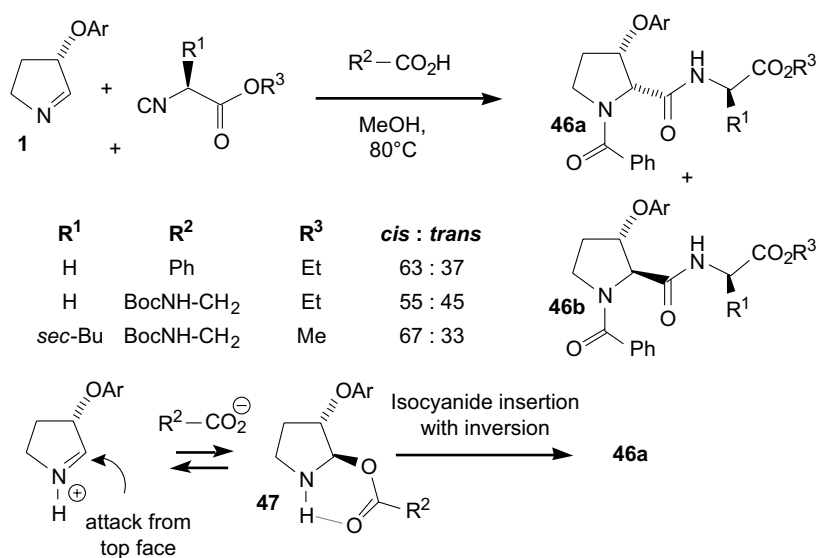
Protected  $\alpha$ -aminoaldehydes follow the same trend, although a notable exception is represented by the reaction of compound **43** with a bulky isocyanide, affording **44** in a 3:1 ratio (the relative configuration of the major product was not determined) [51].

Although various chiral glycosyl aldehydes with a direct attachment of the carbonyl group to the anomeric center showed low diastereoselectivity [52], a moderate stereoselectivity was observed in the condensation of **45** with methyl isocyanacetate, propionic acid and a solid-supported amine [53].

## 1.4.4

**Chiral Cyclic Imines**

Only a few examples of U-3CRs involving chiral cyclic imines have been reported to date.

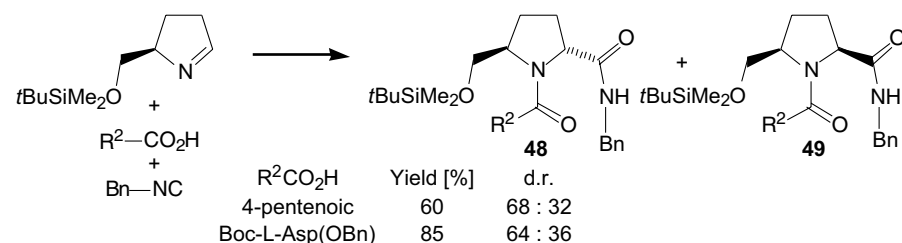


Scheme 1.17

Condensations employing 2-pyrrolines with the chirality on C-3 [8, 54] or C-5 [55] showed only moderate stereoselectivity.

In the first case the best combination of reagents gave a 2:1 cis:trans mixture (60% yield, Ar = *p*-cyanophenyl) [54]. To the best of our knowledge this represents the only example involving cyclic imines, in which the prevailing stereoisomer is the cis one. The observed stereoselectivity can be explained, according to the authors of that work if the reaction follows mechanism B or C to give preferentially the bicyclic hydrogen-bonded intermediate **47** after attack of the carboxylate from the side opposite to the OAr group. This intermediate, both kinetically and thermodynamically favored, finally undergoes insertion of the isocyanide with inversion to give the cis isomer.

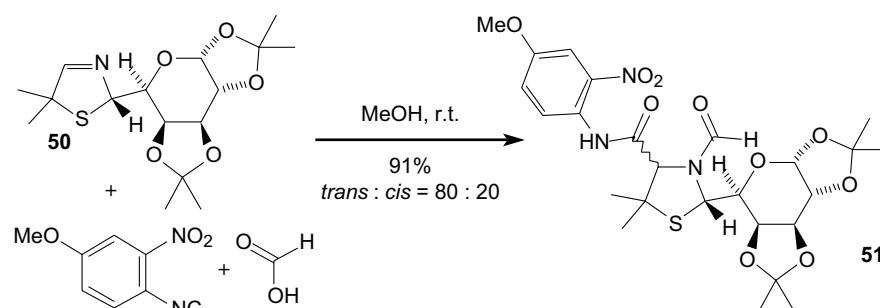
A reversal of stereoselectivity, with a ratio usually in the range 2:1, was observed when 5-substituted-2-pyrrolines were used [55]. 2,5-Pyrrolidines **48** and **49** (Scheme



Scheme 1.18

1.18) were therefore obtained, with the *trans* stereoisomer prevailing, employing a series of simple isocyanides and several acids or protected amino acids. However, when the bulky trityl group was present as protecting group on the pyrrolidine alcohol (instead of SiMe<sub>2</sub>tBu) the reaction was almost completely non-stereoselective.

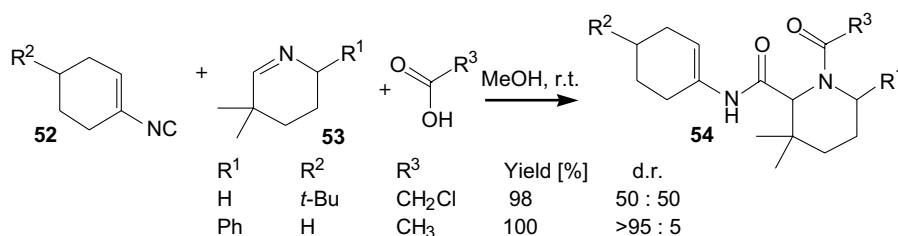
The enantiomerically pure 3-thiazoline **50**, obtained *via* Asinger reaction using a galactose-derived chiral auxiliary, was successfully submitted to an Ugi condensation affording the *trans* adduct **51** with good stereoselectivity, as reported in Scheme 1.19 [56].



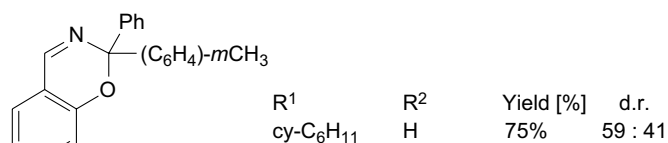
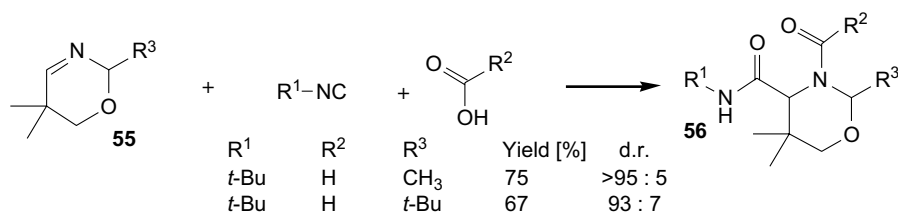
Scheme 1.19

The synthesis of 6-substituted pipercolic acid derivatives has been carried out, in most cases with excellent stereoselectivities (> 95:5 *trans*:*cis*) and yields, by U-3CR between six-membered cyclic imines **53**, carboxylic acids and the convertible isonitriles **52**. Representative examples are reported in Scheme 1.20. On the other hand, when the chirality was present only on the isocyanide no stereoselectivity was observed, as expected [57]. *In situ* treatment of enamides **54** with an appropriate nucleophile allowed the conversion into the final products. The same trend in stereoselectivity was observed when similar imines were condensed with isocynoacetic acid methyl ester and Boc-glycine to give a series of tripeptides [58].

Other cyclic imines involved in U-3CRs are represented by 2-substituted 2*H*-1,3-oxazines **55** [59]. In this case also, the reaction was found to be very stereoselective and gave protected homoserine derivatives **56** (Scheme 1.21). No information is



Scheme 1.20



Scheme 1.21

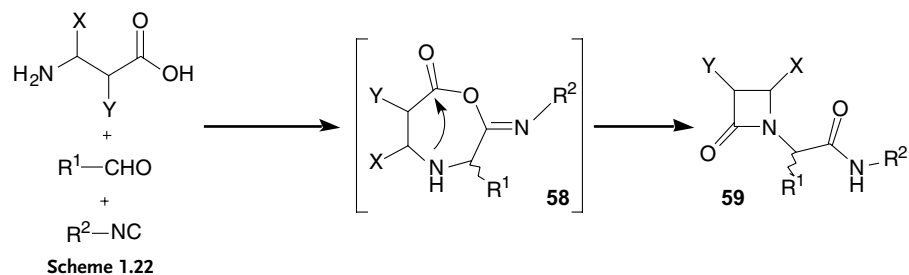
given about the relative configuration of the products. Interestingly, when 2*H*-1,3-benzoxazine **57** was employed, the stereoselectivity dropped to a 59:41 ratio.

In some cases, therefore, 1,3-induction in the Ugi reaction using cyclic imines seems to be excellent. However, further investigations should be performed in order to rationalize the results, although it is clear that the position of the chirality on the imine, together with the hybridization of the carbon atoms in the ring, seems to play an important role both with regard to the diastereoselectivity and in determining the preferred face during isonitrile attack.

## 1.5

### Asymmetric Intramolecular Ugi Reactions

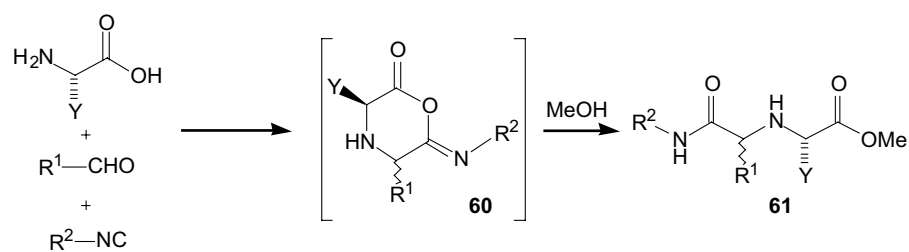
Intramolecular versions of the Ugi reaction, where two of the four functional groups involved belong to the same molecule, have attracted many scientists for their ability to generate various heterocycles relevant from a pharmacological point of view. Among others, reactions with  $\alpha$ - and  $\beta$ -aminoacids have been reported to generate interesting stereochemical outcomes. The possibility of generating  $\beta$ -lactam rings using  $\beta$ -aminoacids has been known since 1961 as the Ugi four-center-three-component reaction (U-4C-3CR) [60]; the postulated mechanism



Scheme 1.22

evolves through a seven-membered intermediate **58** to give the final compound **59** *via* a ring contraction step (Scheme 1.22) [61].

$\alpha$ -Amino acids can react following a similar path [62]; however, the six-membered ring intermediate **60** cannot evolve *via* a ring contraction, owing to higher steric tensions, but reacts with an external nucleophile (e.g. methanol used as the solvent), giving rise to an Ugi five-center-four-component reaction (U-5C-4CR) that generates an  $\alpha,\alpha'$ -iminodicarboxylic acid derivative **61** (Scheme 1.23).

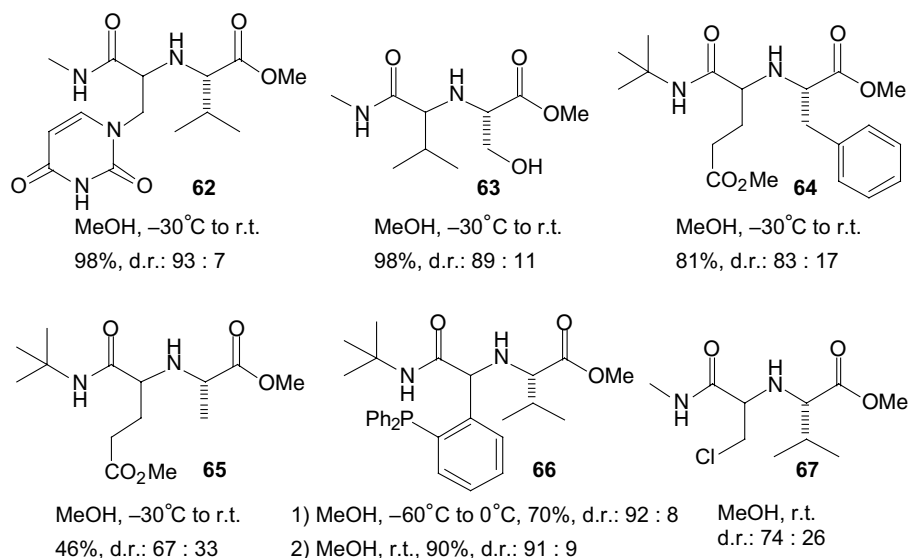


Scheme 1.23

### 1.5.1

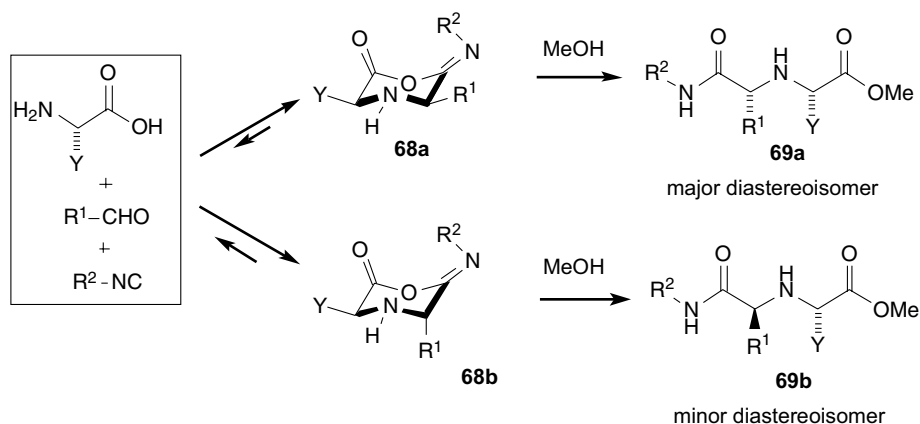
#### With $\alpha$ -Amino Acids

The U-5C-4CR with  $\alpha$ -amino acids typically leads to diastereoselectivities ranging from good to very good, as illustrated by the examples reported in Scheme 1.24, and has been exploited by different research groups [62–71]. Reactions are usually carried out at  $-30$  °C and the temperature is then left to rise to  $0$  °C or room temperature; however, it is worth noting that, by performing the same reactions at room temperature, the diastereoselectivity seems not to be affected (see for example compound **66** [64]). It is also interesting to note that diastereoselectivity usually increases when bulky amino acids (see for example compound **62** [62] using valine) and aldehydes (see for example compound **63** [67] using isobutyraldehyde) are used; similar considerations apply when comparing, for example, compounds **64** and **65** [69] or compounds **66** and **67** [70]).



Scheme 1.24

Sung et al. [71] attempted to explain the reasons for the observed stereoselectivities on the basis of the mechanism outlined in Scheme 1.25: it is assumed that the cyclic intermediate **68** is formed under thermodynamic control and can equilibrate to the more stable isomer before being attacked by the external nucleophile. When the amino acid has a bulky side chain (for example  $Y = i\text{-Pr}$ ), the cyclohexyl intermediate **68** will preferentially dispose this chain in the equatorial position. Between the two possible diastereoisomers, the most favored one will be that with  $R^1$  in the equatorial position **68a** and therefore this will be formed preferen-



Scheme 1.25

tially and will generate the major diastereoisomer **69a** after reaction with methanol. The size of Y and R<sup>1</sup> is important: in fact less bulky groups furnish a lower *de* [71].

Although it is reported that the U-5C-4CR can work well with nucleophiles other than methanol, such as primary or secondary amines, the only examples reported in the literature are those where trifunctional  $\alpha$ -aminoacids such as lysine [67] or homoserine [66] or bifunctional aldehydes such as glycolaldehyde [65] are employed. In these cases, the side-chain amino or hydroxy group acts as the nucleophile and opens the cyclic intermediate generating the corresponding lactams or lactones. A less nucleophilic solvent such as trifluoroethanol is usually employed, in order to maximize the intramolecular attack. The observed stereoselectivities are, apart from a few examples [66], usually not very high; this could be due to different factors: (a) the side chains of the  $\alpha$ -amino acids are not very bulky; (b) the intramolecular nucleophilic attack could be faster than the methanol attack and the cyclic intermediate could not equilibrate to the thermodynamically favored isomer; (c) the intramolecular nucleophilic attack on the more stable diastereoisomeric cyclic intermediate could be kinetically less favored.

Ketones react with  $\alpha$ -aminoacids in the same way [68], although reactions are reported to be slower; there is only one example with an unsymmetrical ketone (acetophenone) and the diastereomeric excess is not reported.

Finally, also N-alkylated  $\alpha$ -aminoacids such as proline, azetidincarboxylic acid or piperidincarboxylic acid give the U-5C-4CR but, apart from one example [62], diastereoselectivities are very poor [65].

### 1.5.2

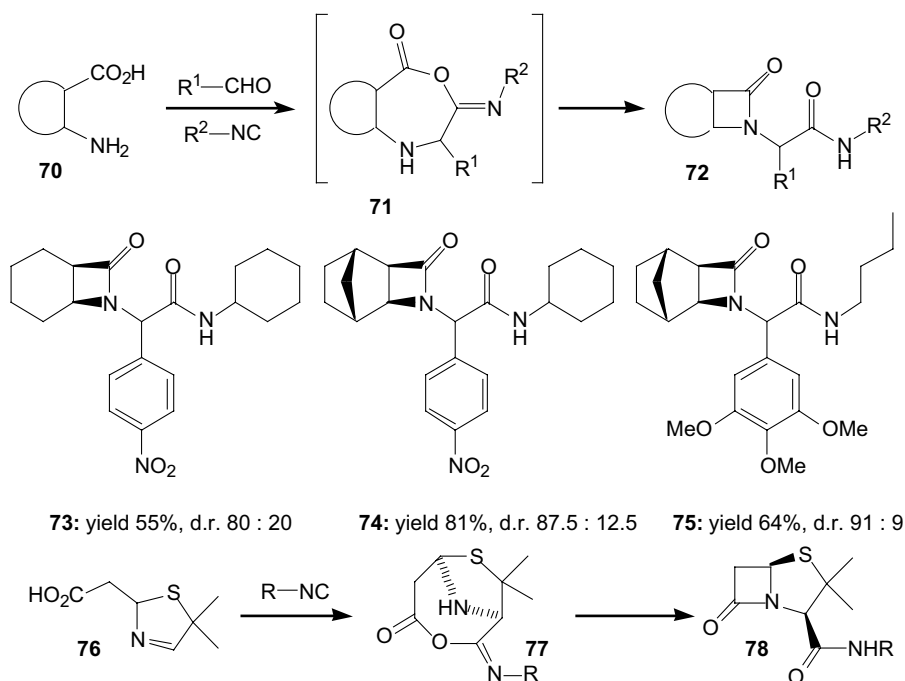
#### With Other Amino Acids

$\beta$ -Amino acids can react with aldehydes and isocyanides in a similar way; however, the seven-membered cyclic intermediate is sufficiently flexible to evolve to  $\beta$ -lactam *via* a ring contraction [60, 72]. When the stereogenic center is at the  $\alpha$  position, generally the diastereomeric excesses are low, owing to the greater distance between the pre-existing and the new stereocenters in the intermediate seven-membered ring. In these cases the two diastereoisomers are often obtained in a 1:1 ratio [61, 73]. Stereoselectivities are usually higher when the  $\beta$ -amino acids have a chiral carbon in the  $\beta$  position, in fact the final products are generated with diastereomeric excesses up to 70% [61, 74].

When the  $\beta$ -amino acid moiety is inserted into a monocyclic or bicyclic structure such as **70** and therefore possesses chiral centers at both the  $\alpha$  and  $\beta$  positions, high diastereoisomeric excesses are sometimes observed, as reported in Scheme 1.26 [75].

The higher rigidity of the bicyclic scaffolds could favor the preferential formation of one of the two diastereoisomeric intermediates **71** and therefore explain the observed selectivity for compounds **73–75**.

Also in the case of the cyclic Schiff base **76**, the bridged bicyclic nature of inter-

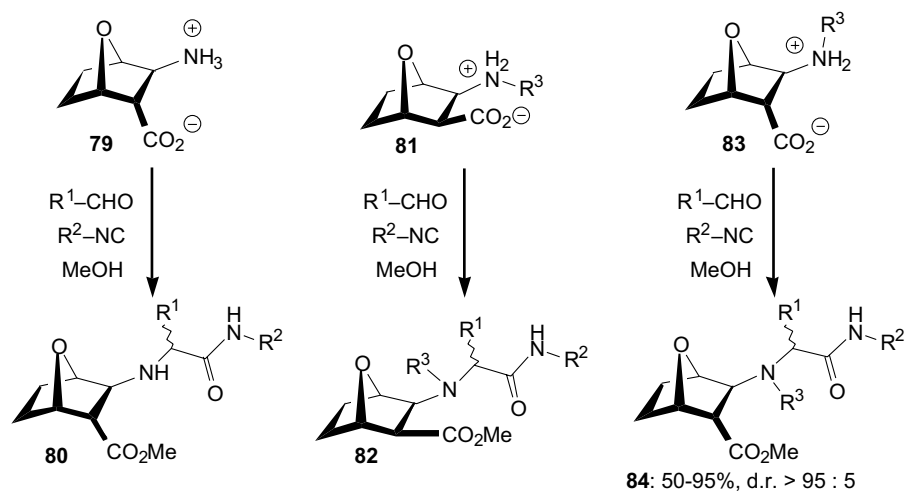


Scheme 1.26

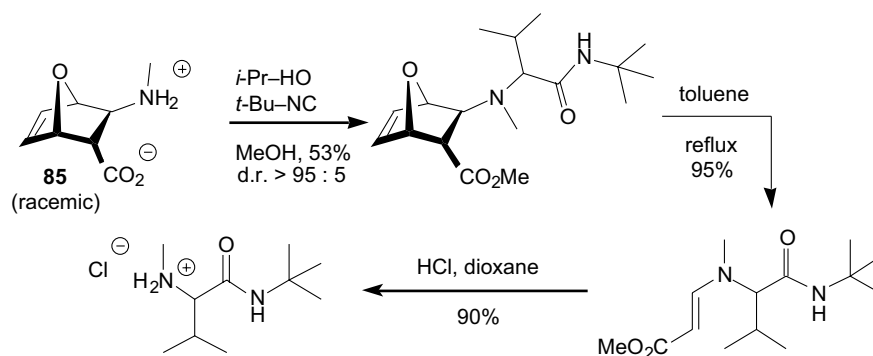
mediate 77 imposes a severe steric bias: as a result penicillanic derivative 78, having the same relative configuration as natural penicillins, is exclusively formed with complete stereoselectivity [76].

Bicyclic  $\beta$ -amino acids have also been used to study the chemical reactivity and stereochemical outcomes when the configuration of the carboxylic group is changed from exo to endo and when the nitrogen is alkylated [77]. The trans bicyclic  $\beta$ -amino acid 79 cannot evolve to the corresponding  $\beta$ -lactam *via* the U-4C-3CR, but generates the corresponding methyl ester 80 *via* the U-5C-4CR, in analogy with  $\alpha$ -amino acids. Similarly, N-alkylated cis and trans bicyclic  $\beta$ -amino acids 81 and 83 cannot undergo ring contraction and follow the U-5C-4CR path to give respectively 82 and 84 (Scheme 1.27). From the stereochemical point of view compound 83 is the most interesting: in fact only one diastereoisomer is observed with a wide variety of aldehydes and isocyanides. On the contrary, compounds 79 and 81 give high induction ( $dr > 95:5$ ) only in particular cases, the degree of stereoselectivity being strongly dependent on the structure of the isonitrile and aldehyde employed.

In order to develop a removable analogue of 83, unsaturated compound 85 was devised as a new chiral auxiliary that can be displaced at the end of the synthesis via a retro Diels–Alder reaction and subsequent acid treatment of the resulting enamine (Scheme 1.28).



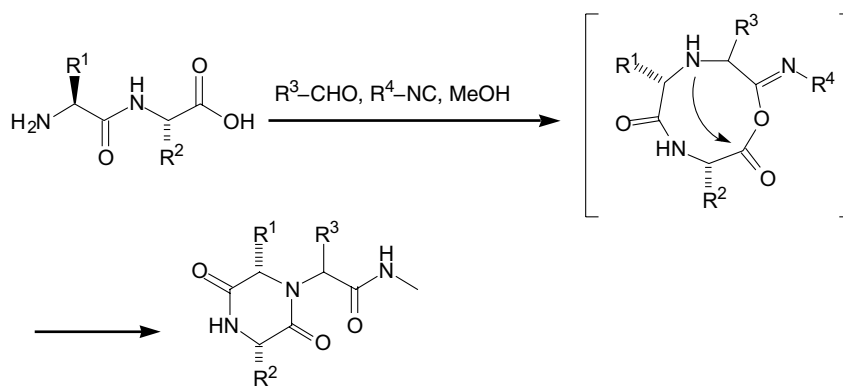
Scheme 1.27



Scheme 1.28

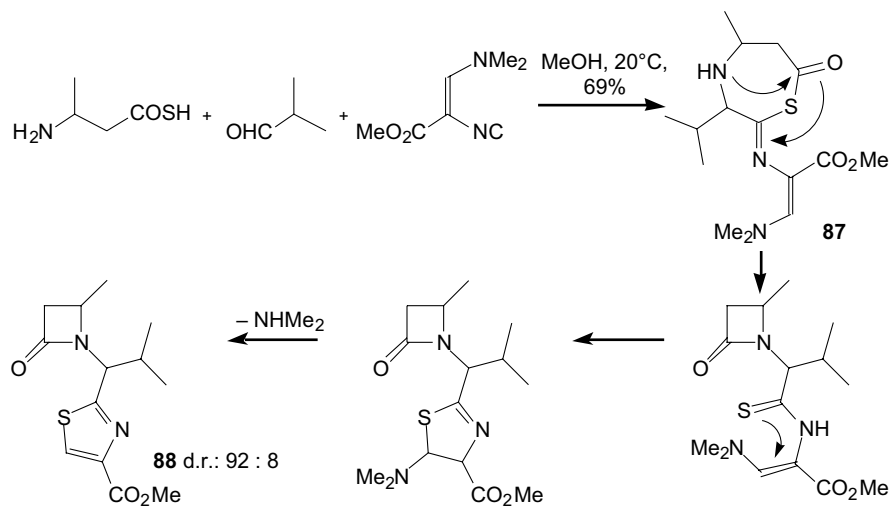
In the literature there is also an example of an intramolecular Ugi reaction with dipeptides used as bifunctional components, via their amino and carboxy groups [78] (Scheme 1.29). The postulated mechanism for this reaction, leading to *N*-substituted 2,5-diketopiperazines, is a U-4C-3CR characterized by the formation of a nine-membered cyclic intermediate that evolves to diketopiperazines **86** via ring contraction. Despite the ring size, the configurations of the two  $C_\alpha$  of the dipeptide have some influence on the newly generated stereocenter, and diastereomeric ratios up to 6:1 can be obtained.

$\beta$ -Aminothiocarboxylic acids react with aldehydes and 3-dimethylamino-2-isocyanoacrylic acid methyl ester following the pathway described for  $\beta$ -aminoacids, affording, after ring contraction of the seven-membered intermediate **87**, Michael-type cyclization and  $\beta$ -elimination,  $\beta$ -lactam **88** equipped with a thiazole



**86:** yield 21-87%, d.r. 60 : 40 to 86 : 14

**Scheme 1.29**



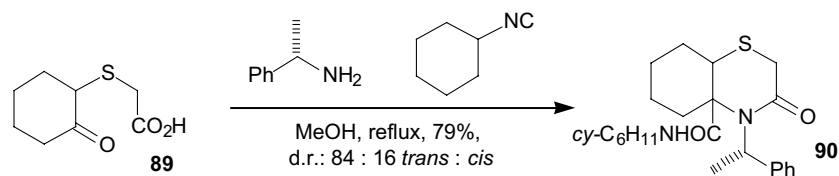
**Scheme 1.30**

ring in good yield (Scheme 1.30). The diastereoselectivity is excellent in contrast with the typical behavior of  $\beta$ -amino acids [79].

### 1.5.3

#### With Keto Acids

To the best of our knowledge only one example of diastereoselective intramolecular Ugi reaction employing a keto acid is known [80]. The condensation of acid **89** with (*S*)-1-phenylethylamine proved to be stereoselective, giving a mixture of the four possible diastereoisomers **90** in a 42:42:8:8 ratio, with the trans stereoisomers pre-



Scheme 1.31

vailing (Scheme 1.31). Other substrate combinations gave lower degrees of stereoselectivity.

## 1.6

### Other Asymmetric Isonitrile-based Multicomponent Reactions

#### 1.6.1

##### Tandem Ugi or Passerini Reaction/Intramolecular Diels–Alder (IMDA) Cyclizations

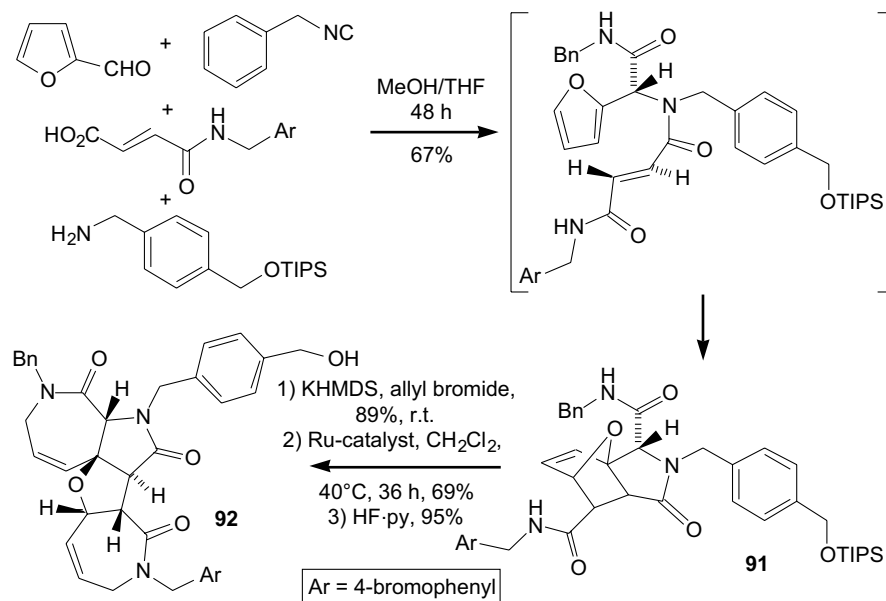
The possibility of coupling an Ugi-4CR or a Passerini-3CR with an *in situ* spontaneous, thermal or Lewis acid-catalyzed IMDA cyclization has been realized in a highly stereoselective manner by some research groups [81–83], allowing highly convergent syntheses of structurally complex compounds endowed with several heterocyclic rings. The stereoselectivity was, however, not displayed during the multicomponent reaction, but during the following IMDA cycloaddition of the intermediate  $\alpha$ -acylaminoamide or  $\alpha$ -acyloxyamide.

Toward this goal, a furane ring was included in the carbonyl or amine component, since this moiety will furnish a highly reactive diene for the following IMDA. In most cases 2-furaldehyde (or the corresponding 5-methyl derivative) was employed. The acid component was chosen in order to introduce an activated dienophile suited for the IMDA and was in turn a fumaric acid monocarboxyamide [82, 84], a maleic or fumaric acid monoester [84] or a 3-substituted propynoic acid [83]. Benzylamine (or a *para*-substituted derivative) [81–83] or *t*-butylamine [83] have been chosen as amine component for the Ugi reactions.

An example of this strategy is shown in Scheme 1.32 [82, 84]. On varying the isocyanide, the dienophile, the amine and the furaldehyde, analogues of **91** could be obtained in 70–89% yields and with *d.r.s* between 83:17 and 92:8. This Ugi/IMDA tandem methodology has been employed also in the solid phase, by anchoring the amine component to a suitable resin [82, 84].

In addition, the bisallylation of the two secondary amides of compound **91**, followed by treatment with an appropriate ruthenium catalyst, allowed a tandem ring-opening metathesis/ring-closing metathesis to give, after alcohol deprotection, the quite complex structure **92** [82].

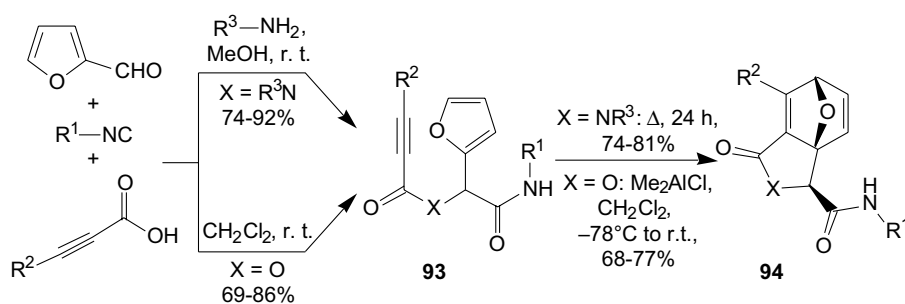
Interestingly, when the furane ring was present in the amine component, and



Scheme 1.32

benzaldehyde was used as the carbonyl partner, the tandem process was poorly stereoselective [84].

Both Ugi and Passerini reactions have been explored, using 3-substituted propynoic acids as dienophiles. The multicomponent adducts **93** have been submitted to IMDA under different conditions, depending upon the heteroatom X in the tether: Ugi adducts could be converted smoothly, usually under thermal conditions, to give **94** as the major stereoisomer (less than 10% of any other stereoisomer detected). On the contrary, Passerini adducts proved to be unreactive under thermal conditions, but reacted cleanly under Me<sub>2</sub>AlCl catalysis to give bicyclic lactones in a highly stereoselective way (Scheme 1.33) [83].



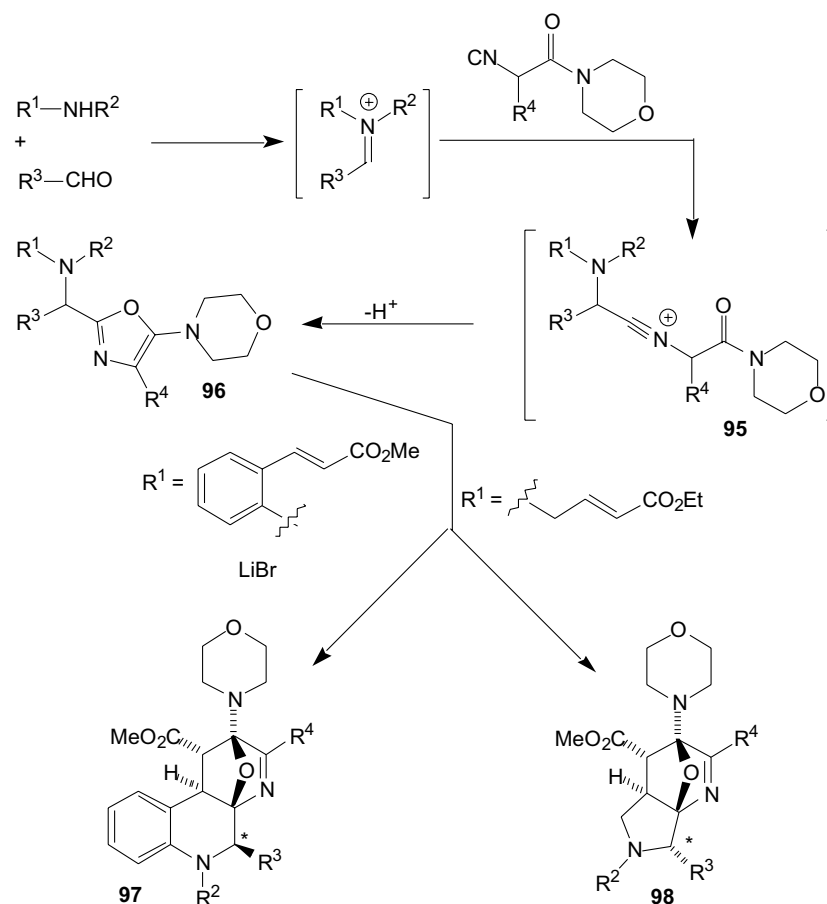
Scheme 1.33

## 1.6.2

## Other Asymmetric Isonitrile-based Multicomponent Reactions

The 3C-reaction between a primary or a secondary amine, an aldehyde and an isocyanacetamide affords 2,4-substituted-5-aminooxazoles (Scheme 1.34) [85]. Most probably, after formation of the initial imine or iminium species, the isocyanitrile reacts as a C-nucleophile to give intermediate **95** (Scheme 1.34), which undergoes an intramolecular nucleophilic attack by the amide oxygen to give the oxazole ring. During this reaction a new stereogenic center is created. In all cases, when enantiomerically pure isocyanides were employed, the corresponding oxazoles were obtained in racemic form. On the other hand a single example with a chiral amine component, namely proline methyl ester, was reported. In that case the *dr* was only 2.5:1.

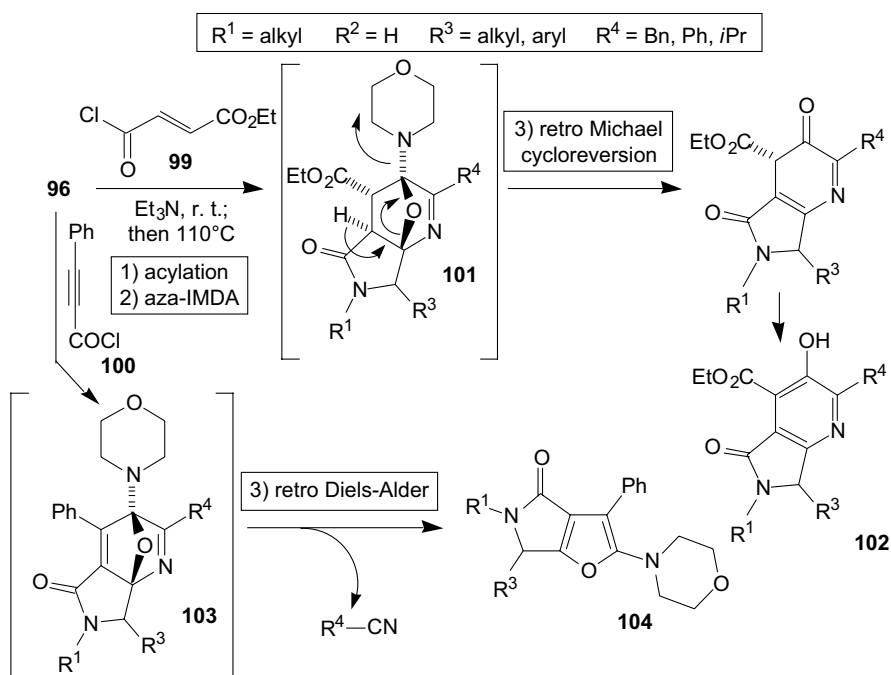
This new multicomponent reaction was coupled to IMDA, exploiting a strategy



Scheme 1.34

similar to that described in the previous paragraph [86–90]. When primary or secondary amines having a tethered electron-poor double bond were employed, oxazoles **96** cannot be isolated since they were directly converted into oxabridged derivatives **97** [86] or **98** [87] with the simultaneous creation of five stereogenic centers (Scheme 1.34). This is a consequence of a spontaneous aza-IMDA promoted by the presence of the electron-rich azadiene of the oxazole. In the case of compounds **97**, best results are obtained in the presence of LiBr as additive. The overall yields are good (42–78%) and the stereoselectivity is typically excellent. Only one relative configuration of the four stereogenic centers of the oxabridged ring is obtained. Thus only the aldehyde-derived stereogenic center (indicated with \* in the Scheme) gives rise to two epimers, with *drs* ranging from 3:1 to >95:5. Interestingly, the configuration of this center in the major stereoisomer is opposite for **97** and **98**.

Alternatively a two-step sequence was employed instead of a domino MCR-IMDA. Oxazoles **96** ( $R^2 = H$ ) were isolated and acylated with unsaturated acyl chlorides **99** and **100**, equipped with an electron-withdrawing substituent, in the presence of triethylamine. By heating to 110 °C, an aza-IMDA occurred (Scheme 1.35). However, in this case the oxa-bridged compounds **101** and **103** can not be isolated. Owing to the presence of  $\text{Et}_3\text{N}$ , further transformations occur, depending upon the type of unsaturation of the dienophile, leading to: (a) pyrrolo[3,4*b*]-pyridin-5-ones **102**, arising from a retro Michael cycloreversion promoted by the base [88]; (b) 5,6-dihydrofuro[2,3-*c*]pyrrol-4-ones **104**, arising from a retro Diels–



Scheme 1.35

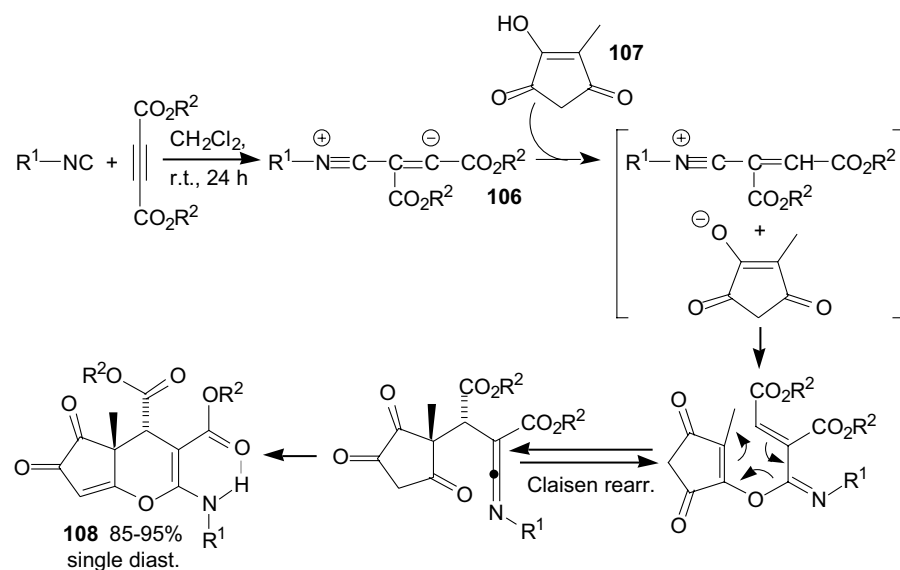
Alder reaction [89]. The latter compounds can be submitted again to a Diels–Alder reaction by treatment with maleimide and the resulting oxa-bridged intermediates, obtained as a mixture of diastereoisomers, can be transformed into hexasubstituted benzenes by thermal treatment. In these cases however, the possible asymmetric induction obtained during the cycloaddition is lost in the final part of the domino sequence.

The use of an  $\alpha$ -isocyanoacetamide instead of an  $\alpha$ -isocyanoacetate is essential in order to obtain oxazoles; when the latter compounds are employed, other condensations (Knoevenagel, Mannich), affording imidazolines or amidines, will take place [88]. This reaction has been explored for the preparation of a series of 2-imidazolines employing isocyanoacetates [91]. The reaction worked smoothly to give compounds **105a,b** (Scheme 1.36) with the *trans* isomer prevailing, provided that a racemic isocyanide with an acidic  $\alpha$ -proton and a sterically undemanding amine are used.

Pyrane derivatives were obtained through a stereoselective isocyanide-based multicomponent reaction. The reaction between an isocyanide, a dialkyl acetylene-



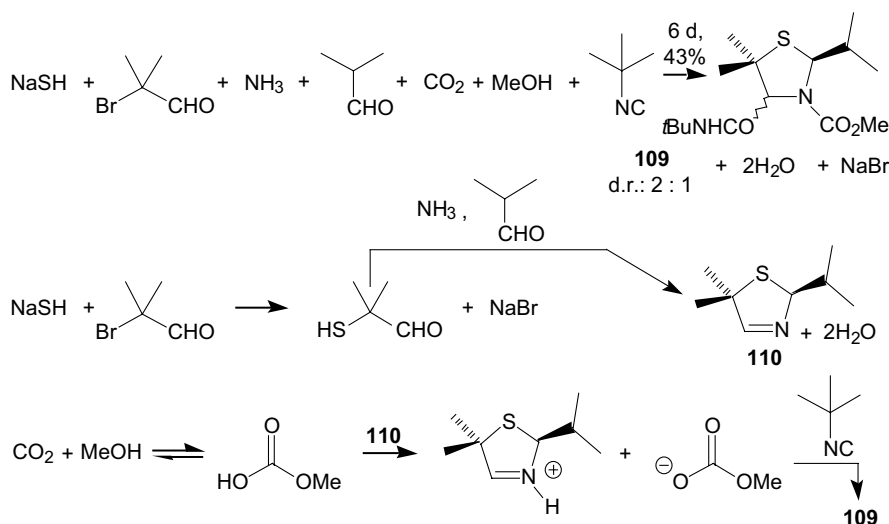
Scheme 1.36



Scheme 1.37

dicarboxylate and cyclopentanetrione **107**, allowed the preparation in excellent yields of a series of enaminoesters of general formula **108**, as single diastereoisomers [92]. The reaction most likely proceeds through the formation of zwitterionic intermediate **106**, followed by the nucleophilic attack of the enolate of **107** and a final Claisen rearrangement and cyclization, as depicted in Scheme 1.37. The relative stereoselectivity is controlled by the Claisen rearrangement step.

Finally, in the most complex multicomponent reaction involving isocyanides, the 7-CC proposed by Ugi in 1993 [93], a moderate diastereoselectivity, leading to a 2:1 mixture of epimeric thiazolidines **109** was observed. The reaction is a combination between an Asinger condensation, involving an  $\alpha$ -mercaptoaldehyde (generated from the  $\alpha$ -bromoaldehyde and  $\text{SH}^-$ ) and an Ugi-type 4-CC with a monoalkyl carboxylate as acid component (Scheme 1.38). Although the relative configuration of the major stereoisomer was not demonstrated, it is probably trans, in line with the results of Ugi condensation with chiral thiazolines, reported above in Scheme 1.19.



Scheme 1.38

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