Multicomponent Reactions

Edited by Jieping Zhu, Hugues Bienaymé

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Preface

The length of a synthesis is dependent upon the average molecular complexity produced per operation, which depends in turn on the number of chemical bonds being created. Therefore, devising reactions that achieve multi-bond formation in one operation is becoming one of the major challenges in searching for step-economic syntheses. By today's standards, besides being regio-, chemo- and stereoselective, an ideal multi-bond-forming process should satisfy the following additional criteria: (a) readily available starting materials; (b) operationally simple; (c) easily automatable; (d) resource effective (personnel, time, cost etc); (e) atom economical; and (f) ecologically benign. Multicomponent reaction (MCR) processes, in which three or more reactants are combined in a single chemical step to produce products that incorporate substantial portions of all the components, naturally comply with many of these stringent requirements for ideal organic syntheses.

Multicomponent reactions, though fashionable these days, have in fact a long history. Indeed, many important reactions such as the Strecker amino acid synthesis (1850), the Hantsch dihydropyridine synthesis (1882), the Biginelli dihydropyrimidine synthesis (1891), the Mannich reaction (1912), and the isocyanide-based Passerini reactions (1921) and Ugi four-component reactions (Ugi-4CRs) (1959), among others, are all multicomponent in nature. In spite of the significant contribution of MCRs to the state of the art of modern organic chemistry and their potential use in complex organic syntheses, little attention was paid to the development of novel MCRs in the second half of the twentieth century. However, with the introduction of molecular biology and high-throughput biological screening, the demand on the *number* and the *quality* of compounds for drug discovery has increased enormously. By virtue of their inherent convergence and high productivity, together with their exploratory and complexity-generating power, MCRs have naturally become a rapidly evolving field of research and have attracted the attention of both academic and industrial scientists.

The development of novel MCRs is an intellectually challenging task since one has to consider not only the reactivity match of the starting materials but also the reactivities of the intermediate molecules generated *in situ*, their compatibility, and their compartmentalization. With advances in both theory and mechanistic insights into various classic bimolecular reactions that allow for predictive analysis of reaction sequences, the development and control of new reactive chemical

entities, and the availability of new technologies that activate otherwise ''inactive'' functional groups, we are optimistic that many new and synthetically useful MCRs will be developed in the coming years.

As enabling technology, the development and application of MCRs are now an integral part of the work of any major medical research unit. It is nevertheless important to point out that MCRs have contributed to drug development, from lead discovery and lead optimization to production, long before the advent of combinatorial technologies. The one-step synthesis of *nifedipine* (Adalat®), a highly active calcium antagonist, by a Hantsch reaction is a classic demonstration. A more recent example is the synthesis of piperazine-2-carboxamide, the core structure of the HIV protease inhibitor Crixivan®, by a Ugi-4CR. We believe that the impact of MCRs on both target-oriented and diversity-oriented syntheses will become stronger and stronger as we enter the post-genomic era in this new millennium.

In editing this book, we were fortunate to be associated with more than a dozen experts who were willing to devote the time and effort required to write their contributions. These distinguished chemists are highly knowledgeable in the area reviewed, have contributed to its development, and are uniquely able to provide valuable perspectives. We are truly indebted to all the authors for their professionalism, their adherence to schedules, their enthusiasm, and most of all, their high-quality contributions. We thank all of our collaborators at Wiley-VCH, especially Dr. Elke Maase for her invaluable help from the conception to the realization of this project.

We hope that this monograph will be of value to both expert and novice practitioners in this area, further stimulating the development and application of novel MCRs and providing an appropriate perspective with which to evaluate the significance of new results.

Gif-sur-Yvette and Lyon, France
September 2004

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1
Asymmetric Isocyanide-based MCRs

Luca Banfi, Andrea Basso, Giuseppe Guanti, and Renata Riva

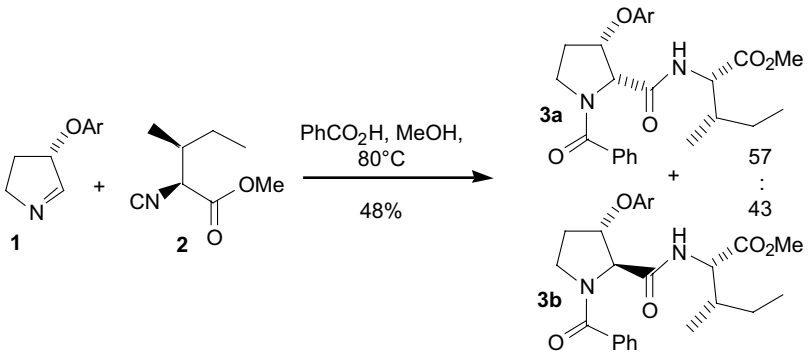
1.1
Introduction

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 α-alkyl substituent have been reported to be stereochemically unstable during Ugi condensation [3]. On the contrary, α-alkoxy substituted aldehydes do not racemize.



Scheme 1.1

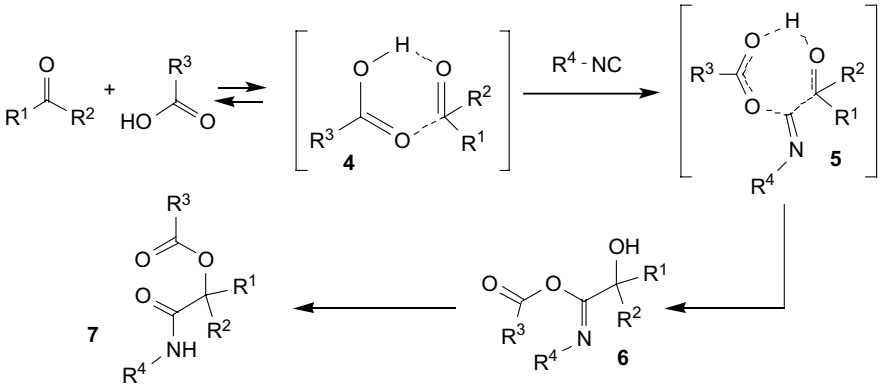
While enantiomerically pure α-substituted isocyanoacetates have been used in Passerini condensation without significant racemization [4–6], the same class of compounds is believed to be configurationally unstable under the conditions of U-4CRs [7]. However, one notable exception is the reaction shown 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 preformed 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 α-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 α-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

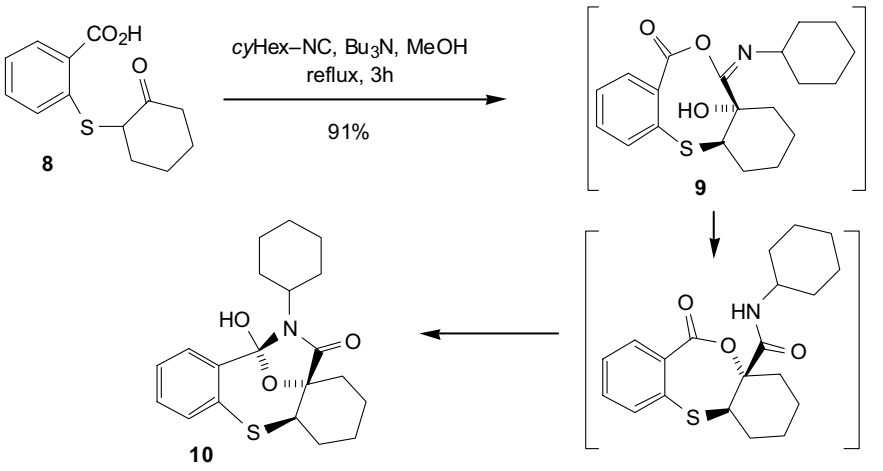


Scheme 1.2

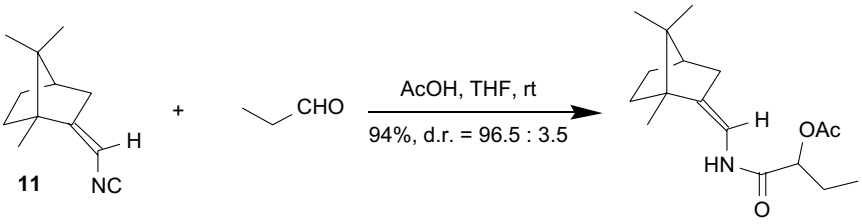
components are involved in rate-determining steps [12], in principle asymmetric induction may be achieved when at least one of them is chiral.

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 α stereogenic center, which often afford high stereoselectivity in other types of nucleophilic additions. The low steric requirement of the isocyano 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 α-substituted isocyanoacetates also usually react with low stereoselectivity, the specially designed, camphor-derived, isonitrile **11**



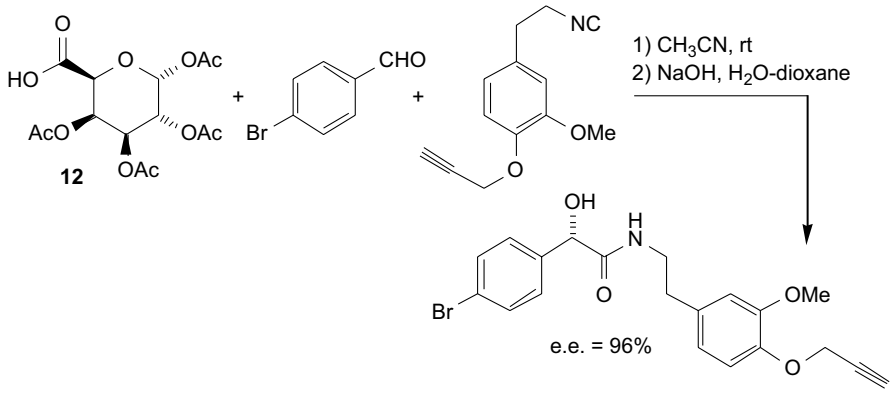
Scheme 1.3



Scheme 1.4

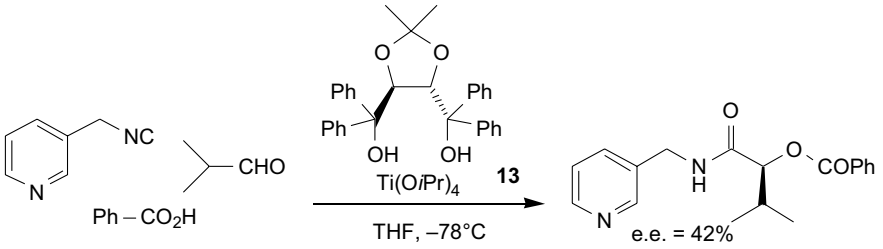
gives high asymmetric induction in the reaction with some aliphatic aldehydes [14] (Scheme 1.4). The chiral auxiliary may be removed after the condensation reaction to give a carboxylic acid or ester [15].

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

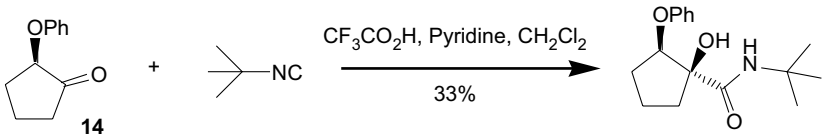
Finally a fourth way to achieve asymmetric induction in the Passerini reaction is by way of a chiral catalyst, such as a Lewis acid. This approach is not trivial since in most cases the Lewis acid replaces the carboxylic acid as third component, leading to α-hydroxyamides or to other kinds of products 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 *ee*s 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

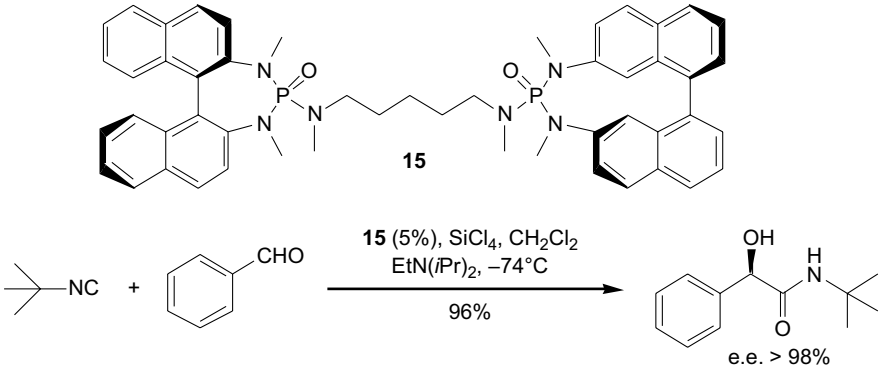
1.3.2 Passerini-type Reactions

When a mineral or Lewis acid replaces the carboxylic component in the Passerini reaction, the final products are usually α-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 *ee*s, 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 $SiCl_4$ 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 *ee*s are excellent with aromatic or α,β-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 *ee*s.



Scheme 1.8

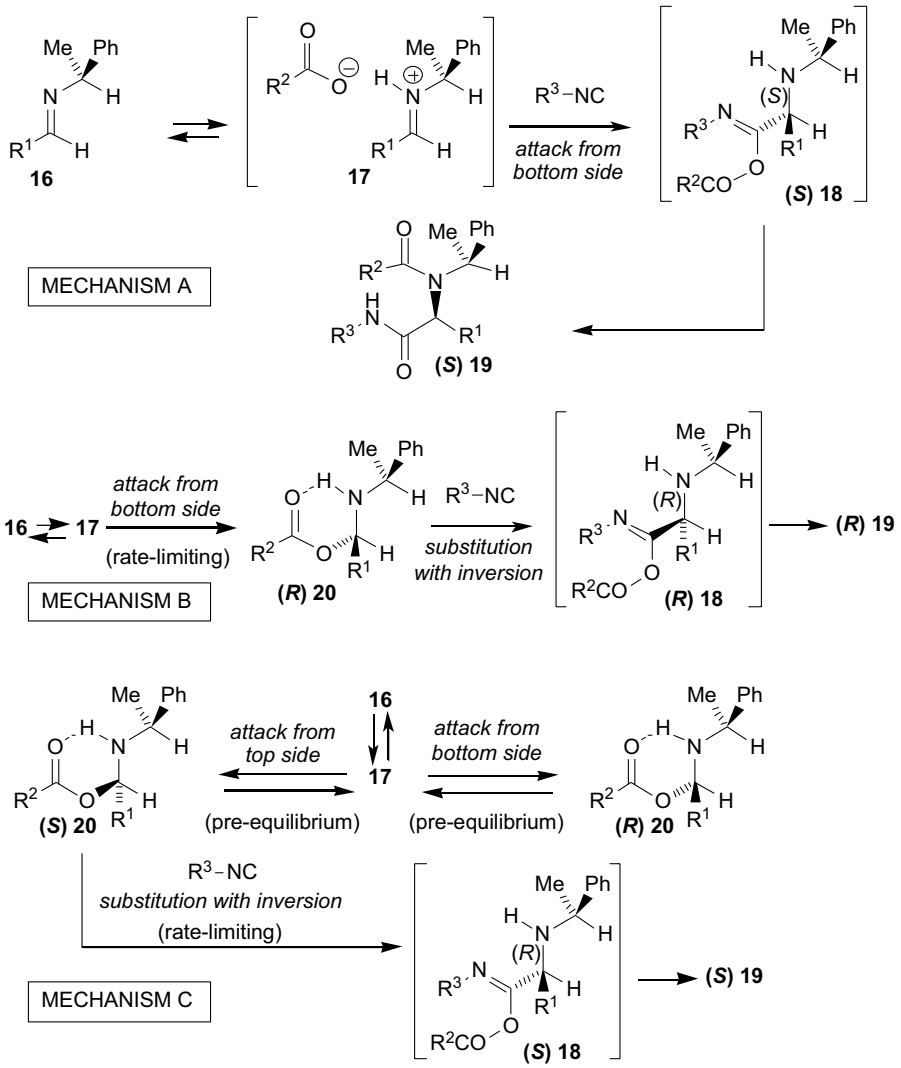
1.4 Asymmetric Intermolecular Ugi Reactions

1.4.1 General Remarks

The classical Ugi reaction [2] involves interaction of a carbonyl compound, an isonitrile, an amine and a carboxylic acid to obtain an α-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 isonitriles 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_2Cl_2 and Et_2O. 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*)-α-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 isonitrile 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^1 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 $\Delta G^{\neq}$ 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.

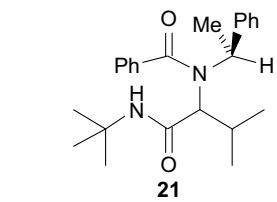
In any case, we must stress that these are at present only working hypotheses, not supported by unambiguous proofs. A better comprehension of the mechanism of U-4CRs, based on more solid grounds, is highly desirable for the development of efficient asymmetric modifications.

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

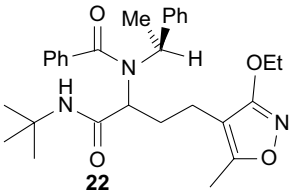
1.4.2.1 α-Methylbenzylamines

α-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.



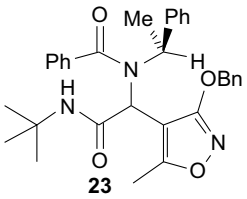
21

MeOH, –40°C, 0.10 M: (*S*) : (*R*) = 75 : 25
MeOH, –40°C, 2.0 M: (*S*) : (*R*) = 33 : 77



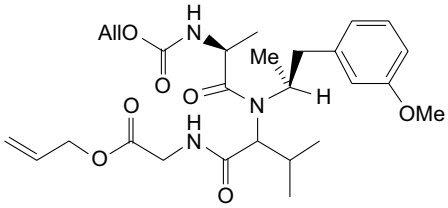
22

MeOH, 25°C, 0.58 M
(*S*) : (*R*) = 40 : 60



23

MeOH, 25°C, 0.40 M
(*S*) : (*R*) = 35 : 65



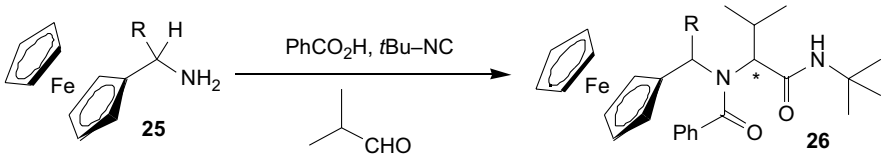
24

CF_3CH_2OH, –30°C, 0.50 M
(*S*) : (*R*) = 95 : 5

Scheme 1.10

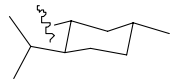
1.4.2.2 **Ferrocenylamines**

At the beginning of the 1970s Ugi et al. [29] reported the use of (+)-α-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 α-methylbenzylamine. Following this first study, different α-ferrocenylalkylamines have been employed [30, 31] and improvements in



25 **26**

Chiral aux.	Amine config.	R	Temp.	Conc. [M]	Solvent	Yield [%]	(*S*) : (*R*) (*)
25a	(*S*)	Me	–60°C	1.0	MeOH	n.r.	38 : 62
25a	(*S*)	Me	0°C	0.0375	MeOH	90	79 : 21
25b	(*R*)	*i*-Pr	–78°C	0.05	MeOH	97	99 : 1
25c	(*R*)	Menthyl	25°C	1.0	CF_3CH_2OH	46	82 : 18

Menthyl = 

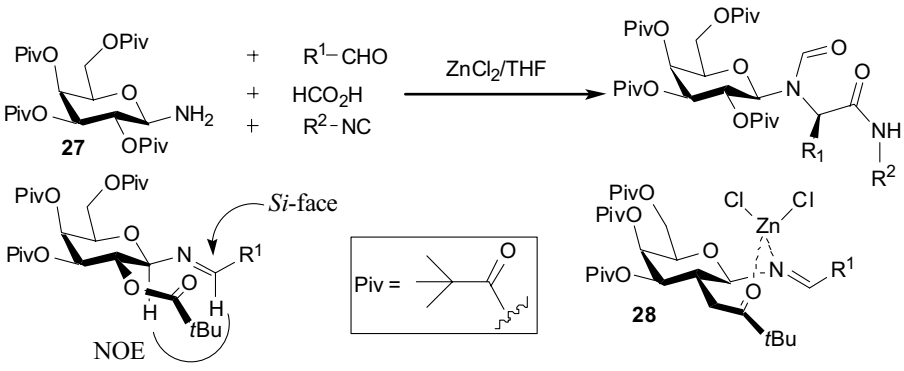
Scheme 1.11

diastereomeric excesses have been realized by substituting the methyl group with bulkier substituents, as in **25b** and **25c**. In particular, for R = *i*Pr, diastereomeric excesses up to 99% could be obtained working at −78 °C [31]. It is interesting to note that an overall reversal of stereoselectivity was obtained on passing from **25a** (R = 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-*β*-D-galactopyranosylamine **27** as chiral auxiliary in the preparation of *α*-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).



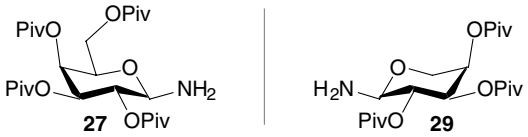
Scheme 1.12

Diastereomeric excesses were usually higher than 90% working between −25 °C and −78 °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).

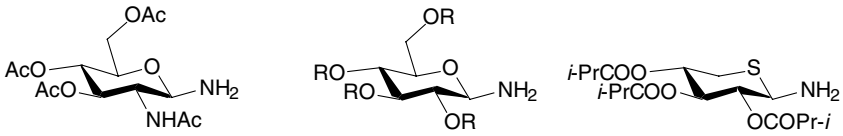
The substantial independence of the stereoselectivity from the structure of the aldehyde makes this methodology extremely convenient to prepare D-amino acid derivatives [35]. It has also been used for solid-phase syntheses [36]. However, some drawbacks can be envisaged, including the harsh conditions 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-α-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-β-D-glucopyranose **30** [38], 2,3,4,6-tetra-*O*-alkyl-β-D-glucopyranosylamines **31** [39] and 1-amino-5-desoxy-5-thio-2,3,4-tri-*O*-isobutanoyl-β-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_3CO_2H in the presence of $Hg(OAc)_2$. 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 α-amino Acids**

Esters of α-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 α-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 α-methylbenzylamine. In this case, R^1 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 α-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].