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Multicomponent Reactions

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Contents

Preface xiii

Contributors xv

1 Asymmetric Isocyanide-based MCRs 1
Luca Banfi, Andrea Basso, Giuseppe Guanti, and Renata Riva
1.1 Introduction 1
1.2 Racemization Issues 1
1.3 Asymmetric Passerini Reactions 2
1.3.1 Classical Passerini Reactions 2
1.3.2 Passerini-type Reactions 5
1.4 Asymmetric Intermolecular Ugi Reactions 6
1.4.1 General Remarks 6
1.4.2 Chiral Amines 8
1.4.2.1 \(\alpha\)-Methylbenzylamines 8
1.4.2.2 Ferrocenylamines 9
1.4.2.3 Glycosylamines 10
1.4.2.4 Esters of \(\alpha\)-amino Acids 12
1.4.3 Chiral Isocyanides, Carboxylic Acids and Carbonyl Compounds 13
1.4.4 Chiral Cyclic Imines 15
1.5 Asymmetric Intramolecular Ugi Reactions 17
1.5.1 With \(\alpha\)-Amino Acids 18
1.5.2 With Other Amino Acids 20
1.5.3 With Keto Acids 23
1.6 Other Asymmetric Isonitrile-based Multicomponent Reactions 24
1.6.1 Tandem Ugi or Passerini Reaction/Intermolecular Diels–Alder (IMDA) Cyclizations 24
1.6.2 Other Asymmetric Isonitrile-based Multicomponent Reactions 26
References 29

2 Post-condensation Modifications of the Passerini and Ugi Reactions 33
Stefano Marcaccini and Tomás Torroba
2.1 Convertible Isocyanides 33
2.2 I-MCR Post-condensation Reactions in Synthesis of Open-chain Products

2.2.1 Passerini 3CR + O-Deacylation 38
2.2.2 Passerini-3CR + N-Deprotection + O → N Acyl Migration 39
2.2.3 Ugi-4CR + Oxidation 41
2.2.4 Ugi-4CR + Hydrolysis 42
2.2.5 Ugi-4CR in Peptide Synthesis 42

2.3 I-MCR Post-condensation Reactions in the Synthesis of Heterocycles

2.3.1 Three-, Four-, and Five-membered Rings and their Benzo-fused Derivatives 44
2.3.1.1 Oxiranes and β-Lactams by Passerini-3CR + O- or N-alkylation 44
2.3.1.2 β-Lactams and Succinimides by Ugi-4CR + C-Alkylation 44
2.3.1.3 Furans, Pyrroles, and Indoles by Passerini-3CR or Ugi-4CR and Knoevenagel Condensation 45
2.3.1.4 Butenolides by Passerini-3CR and the Horner–Emmons–Wadsworth Reaction 46
2.3.1.5 Pyrroles and γ-Lactams by Ugi-4CR and Hydrolysis 47
2.3.1.6 Indazolinones by Ugi-4CR with N-deprotection and Aromatic Nucleophilic Substitution 48
2.3.1.7 Oxazole Derivatives and Imidazoles by Passerini-3CR or Ugi-4CR and Davidson Cyclization 49
2.3.1.8 2-Imidazolines, Imidazolidin-2-ones and Benzimidazoles by Ugi-4CR with N-Deprotection and Cyclization 50
2.3.1.9 Spiroimidazolones and Spirothioimidohydantoins by Ugi-4CR and Further Transformations 51

2.3.2 Six-membered Rings and Their Benzo-fused Systems 52
2.3.2.1 Pyridine Derivatives by Ugi-4CR and Aldol-type Condensation 52
2.3.2.2 Pyridazine Derivatives by Ugi-4CR and Knoevenagel Condensation 53
2.3.2.3 Phthalazine Derivatives by Ugi-4CR with N-Deprotection and Cyclization 53
2.3.2.4 Piperazines and Pyrazin-2-ones by Ugi-4CR and Cyclization 53
2.3.2.5 Ketopiperazines, 2,5-Diketopiperazines and Quinoxalines by Ugi-4CR with N-Deprotection and Intramolecular Amide Bond Formation 55
2.3.2.6 2,5-Diketopiperazines and Morpholines from Bifunctional Ugi-4CR Reagents 59

2.3.3 Seven-membered Rings and Their Benzo-fused Systems 59
2.3.3.1 Azepines by Ugi-4CR and Ring-closing Metathesis 59
2.3.3.2 1,4-Benzodiazepine-5-ones by Ugi-4CR with N-Deprotection and Aromatic Nucleophilic Substitution 60
2.3.3.3 1,4-Benzodiazepine-2,5-diones by Ugi-4CR with Convertible Isocyanides and UDC 61

2.3.4 Bicyclic Systems 62
2.3.4.1 Carbapenems and Carbacephems by Ugi-4CR and Dieckmann Condensation 62
2.3.4.2 Bycyclic Systems by Ugi-4CR and Cyclization  63
2.3.5 Polycyclic and Macrocyclic Systems  65
2.3.5.1 Polycyclic Orthoamides by Passerini-3CR  65
2.3.5.2 Polycyclic Systems via I-MCR and Intramolecular Diels–Alder Cycloaddition  65
2.3.5.3 Macrocycles by Passerini-3CR, Ugi-4CR and Ring-closing Metathesis  69
2.3.5.4 Macrocycles by Ugi-4CR and Nucleophilic Aromatic Substitution  69
References  72

3  The Discovery of New Isocyanide-based Multicomponent Reactions  76
Alexander Dömling
3.1 Introduction  76
3.2 New MCRs  80
3.2.1 What are New Reactions?  80
3.3 Random Discovery  82
3.4 Combinatorial MCR Discovery  85
3.5 Discovery by Design  87
3.6 The Union of MCRs  92
3.7 Outlook  94
References  94

4  The Biginelli Reaction  95
C. Oliver Kappe
4.1 Introduction  95
4.2 Mechanistic Studies  96
4.3 Reaction Conditions  97
4.4 Building Blocks  99
4.5 Synthesis of Combinatorial Libraries  101
4.6 Alternative Synthetic Strategies  103
4.7 Related Multicomponent Reactions  105
4.8 Asymmetric Biginelli Reactions  109
4.9 Conclusion  114
References  114

5  The Domino-Knoevenagel-hetero-Diels–Alder Reaction and Related Transformations  121
Lutz F. Tietze and Nils Rackelmann
5.1 Introduction  121
5.2 Two-component Reactions with an Intramolecular Cycloaddition  123
5.3 Three- and Four-component-domino-Knoevenagel-hetero-Diels–Alder Reaction  134
5.4 Synthesis of Azasteroids and Steroid Alkaloids  158
5.5 Domino-Knoevenagel-carbon-Diels–Alder Reactions  161
Acknowledgments  165
References  165
6 Free-radical-mediated Multicomponent Coupling Reactions 169
Mami Tojino and Ilhyong Ryu
6.1 Introduction 169
6.2 Hetero-multicomponent Coupling Reactions 171
6.3 Multicomponent Coupling Reactions Mediated by Group 14 Radicals 175
6.4 Multicomponent Coupling Reactions Involving Electron-transfer Processes 186
6.5 Conclusions 195
References 196

7 Multicomponent Reactions with Organoboron Compounds 199
Nicos A. Petasis
7.1 Introduction 199
7.2 MCRs Involving Amines and Aldehydes or Ketones 200
7.3 MCRs Involving Organoboron Compounds 202
7.3.1 Synthesis of Allylamines and Benzylamines 202
7.3.2 A New Three-component Process 203
7.3.3 Synthesis of ω-Amino Acids 205
7.3.4 Synthesis of Iminodicarboxylic Acid Derivatives 208
7.3.5 Synthesis of Peptidomimetic Heterocycles 209
7.3.6 Reactions with Other Carbonyl Components 210
7.3.7 Synthesis of Amino Alcohols 216
7.3.8 Synthesis of Amino Polyols and Amino Sugars 217
7.4 Summary and Conclusion 219
Acknowledgments 221
References 222

8 Metal-catalyzed Multicomponent Reactions 224
Geneviève Balme, Didier Bouyssi, and Nuno Monteiro
8.1 Introduction 224
8.2 Vicinal Difunctionalization of Alkenes and Acetylenes via Intermolecular Carbometallation 225
8.2.1 Difunctionalization of Unactivated Alkenes and Acetylenes 225
8.2.1.1 Carbopalladation of Norbornene and its Analogues 225
8.2.1.2 Carbometallation of Alkynes 226
8.2.2 Difunctionalization of Activated Alkenes 231
8.3 Reactions Involving π-Allyl Palladium Species as Intermediates 233
8.3.1 π-Allyl Palladium Species from Carbopalladation of Unsaturated Substrates 233
8.3.1.1 Carbopalladation of Conjugated Dienes 233
8.3.1.2 Carbopalladation of Non-conjugated Dienes 235
8.3.1.3 Carbopalladation of Allenes 236
8.3.1.4 Carbopalladation of Methylene cyclopropane and Bicyclopropyldiene 240
8.3.1.5 Palladium-mediated Reaction of Vinylic Halides with Alkenes 242
8.3.2 $\pi$-Allyl Palladium Species from Allylic Compounds 243
8.4 Cross-coupling Reactions of Terminal Alkynes with Organic Halides 244
8.4.1 Reactions Based on a Pd/Cu-catalyzed Coupling–Isomerization Process 244
8.4.2 Reactions Based on the In Situ Activation of Alkynes by a Sonogashira Coupling Reaction 245
8.5 Cyclofunctionalization of Alkynes and Alkenes Bearing Pendant Nucleophiles 246
8.5.1 Carbonucleophiles 248
8.5.2 Heteronucleophiles 250
8.6 Transition-metal-catalyzed Reactions Based on the Reactivity of Isonitriles 253
8.6.1 Three-component Synthesis of Indoles 253
8.6.2 Iminocarbonylative Cross-coupling Reactions 254
8.6.3 Titanium-catalyzed Three-component Synthesis of $\alpha,\beta$-Unsaturated $\beta$-Iminoamines 254
8.7 Pd/Cu-catalyzed Synthesis of Triazoles 256
8.8 Reactions Involving Imines as Intermediates 257
8.8.1 Grignard-type Addition of Acetylenic Compounds to Imines 257
8.8.1.1 Synthesis of Propargyl Amines 257
8.8.1.2 Synthesis of Quinolines and Isoquinolines 257
8.8.2 Addition of Organometallic Reagents to Imines 258
8.8.2.1 Alkylmetal Reagents 258
8.8.2.2 Allylmetal Reagents 259
8.8.3 Miscellaneous Reactions Involving Imines 259
8.9 Cycloadditions and Related Reactions 265
8.9.1 Synthesis of Substituted Arenes 265
8.9.2 Synthesis of Pyridines and Analogous Heterocycles 266
8.9.3 Related Reactions 267
8.10 Three-component Reactions Involving Metallocarbenes 268
8.11 Metathesis 269
8.12 Concluding Remarks 270
References 271

9 Catalytic Asymmetric Multicomponent Reactions 277
Jayasree Seayad and Benjamin List
9.1 Introduction 277
9.2 Mannich Reactions 277
9.3 Three-component Aldolizations 281
9.4 Three-component Tandem Michael–Aldol Reaction 281
9.5 Passerini Reaction 282
9.6 Strecker Reaction 284
9.7 Aza Morita–Baylis–Hillman Reactions 286
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.8</td>
<td>Domino-Knoevenagel-hetero-Diels–Alder-type Reactions</td>
<td>289</td>
</tr>
<tr>
<td>9.9</td>
<td>Three-component Hetero-[4+2]-cycloaddition–Allylboration Tandem Reaction</td>
<td>292</td>
</tr>
<tr>
<td>9.10</td>
<td>Addition of Alkylzincs</td>
<td>293</td>
</tr>
<tr>
<td>9.11</td>
<td>Alkyne Nucleophiles</td>
<td>294</td>
</tr>
<tr>
<td>9.12</td>
<td>Coupling of Alkynes, Imines and Organoboranes</td>
<td>295</td>
</tr>
<tr>
<td>9.13</td>
<td>Free-radical Reactions</td>
<td>295</td>
</tr>
<tr>
<td>9.14</td>
<td>Summary and Outlook</td>
<td>297</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>298</td>
</tr>
<tr>
<td>10</td>
<td>Algorithm-based Methods for the Discovery of Novel Multicomponent Reactions</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>Lutz Weber</td>
<td></td>
</tr>
<tr>
<td>10.1</td>
<td>Introduction</td>
<td>300</td>
</tr>
<tr>
<td>10.2</td>
<td>A Definition – What Are Novel MCRs</td>
<td>300</td>
</tr>
<tr>
<td>10.3</td>
<td>Unexpected Products Yield Novel MCRs</td>
<td>301</td>
</tr>
<tr>
<td>10.4</td>
<td>Experimental Designs to Search for New MCRs</td>
<td>302</td>
</tr>
<tr>
<td>10.5</td>
<td>Computational Methods of Finding Novel MCRs</td>
<td>306</td>
</tr>
<tr>
<td>10.6</td>
<td>Combinatorial Optimization of Reaction Conditions</td>
<td>308</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>309</td>
</tr>
<tr>
<td>11</td>
<td>Applications of Multicomponent Reactions in Drug Discovery – Lead Generation to Process Development</td>
<td>311</td>
</tr>
<tr>
<td></td>
<td>Christopher Hulme</td>
<td></td>
</tr>
<tr>
<td>11.1</td>
<td>Introduction</td>
<td>311</td>
</tr>
<tr>
<td>11.2</td>
<td>Hantsch (1882) and Biginelli (1893) Reactions</td>
<td>313</td>
</tr>
<tr>
<td>11.3</td>
<td>Passerini Reaction (1921)</td>
<td>315</td>
</tr>
<tr>
<td>11.4</td>
<td>Ugi Reaction (1958)</td>
<td>319</td>
</tr>
<tr>
<td>11.5</td>
<td>Constrained Ugi Adducts from Bi-functional Precursors</td>
<td>324</td>
</tr>
<tr>
<td>11.6</td>
<td>Gewald Reaction (1965)</td>
<td>332</td>
</tr>
<tr>
<td>11.7</td>
<td>Applications of MCRs to Process Development</td>
<td>335</td>
</tr>
<tr>
<td>11.8</td>
<td>Conclusions</td>
<td>336</td>
</tr>
<tr>
<td></td>
<td>Acknowledgments</td>
<td>337</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>337</td>
</tr>
<tr>
<td>12</td>
<td>Multicomponent Reactions in the Total Synthesis of Natural Products</td>
<td>342</td>
</tr>
<tr>
<td></td>
<td>Barry B. Touré and Dennis G. Hall</td>
<td></td>
</tr>
<tr>
<td>12.1</td>
<td>Introduction</td>
<td>342</td>
</tr>
<tr>
<td>12.2</td>
<td>Cyclopentane-containing Natural Products</td>
<td>343</td>
</tr>
<tr>
<td>12.2.1</td>
<td>Prostanoids</td>
<td>343</td>
</tr>
<tr>
<td>12.2.2</td>
<td>Others</td>
<td>350</td>
</tr>
<tr>
<td>12.3</td>
<td>Terpenoids</td>
<td>350</td>
</tr>
<tr>
<td>12.4</td>
<td>Polyenes and Polynes</td>
<td>360</td>
</tr>
<tr>
<td>12.5</td>
<td>Oxacyclic Natural Products</td>
<td>363</td>
</tr>
</tbody>
</table>
12.5.1 Cyclic Ethers 364
12.5.2 Lactones 366
12.6 Polyols and Polysaccharides 368
12.7 Lignans 371
12.8 Alkaloids 372
12.8.1 Indoles 374
12.8.2 Piperidines 374
12.8.3 Pyridines 381
12.8.4 Guanidiniums 382
12.9 Peptides 382
12.10 Other Natural Products 387
12.11 Conclusion 392
References 392

13 The Modified Sakurai and Related Reactions 398
Thomas Jacques, István E. Markó, and Jiří Pospíšil
13.1 Introduction 398
13.2 The Sakurai–Hosomi Reaction 399
13.3 The Silyl-modified Sakurai Reaction 405
13.3.1 History and Asymmetric Versions 405
13.3.2 Use in Total Synthesis 412
13.3.3 Deviance 413
13.3.4 Conclusions 416
13.4 Intramolecular Sakurai Condensation 416
13.4.1 Tetrahydropyran Rings 417
13.4.1.1 Dihydropyrans 418
13.4.1.2 Vinyl Tetrahydropyrans 426
13.4.1.3 exo-Methylene Tetrahydropyrans 429
13.4.2 Tetrahydrofuran Rings 438
13.4.3 Seven-, Eight- and Nine-membered Rings 441
13.4.4 Spiro Compounds 444
13.4.5 Nitrogen Atom-containing Analogues 446
13.4.6 Conclusions 449
References 450

Index 453
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 stereo-selective, 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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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.
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 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 $\alpha$-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].
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 isocyano group may account for this generally low stereoselectivity. A notable exception is the intramolecular reaction of chiral racemic ketoacid 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 isocyanoacetates also usually react with low stereoselectivity, the specially designed, camphor-derived, isonitrile 11

\[
\begin{align*}
\text{Scheme 1.2} \\
R^1 R^2 O & \quad + \quad \text{HO CO}_2 \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 1.3} \\
\text{cyHex–NC, Bu}_3 \text{N, MeOH} & \quad \text{reflux, 3h} \\
\end{align*}
\]

\[
\begin{align*}
\text{91%} \\
\end{align*}
\]
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].

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.
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 1.6](image1)

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 $e e s$, 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 $e e s$ are excellent with aromatic or $\alpha,\beta$-unsaturated aldehydes. On the other hand with aliphatic aldehydes they range from 35% to 74%. Also replacing $t$-butyl isocyanide with other isonitriles brings about a slight decrease of the $e e s$. 

![Scheme 1.7](image2)
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 \( \alpha \)-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 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\(_2\)Cl\(_2\) and Et\(_2\)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-
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 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 $\Delta G^\circ$ 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 reagents, the solvent and the temperature, but also on the structure of reagents. 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.
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
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 °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).

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 \textit{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 (\textit{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-\textit{d}-arabinopyranosylamine 29, which can be considered with good approximation the enantiomer of 27, but it is more easily synthesized (Scheme 1.13).

\begin{center}
\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_1.13}
\caption{Scheme 1.13}
\end{figure}
\end{center}

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-\textit{\beta}-d-glucopyranose 30 [38], 2,3,4,6-tetra-O-alkyl-\textit{\beta}-d-glucopyranosylamines 31 [39] and 1-amino-5-deoxy-5-thio-2,3,4-tri-O-isobutanoyl-\textit{\beta}-d-xylopyranose 32 [40] (Scheme 1.14).

\begin{center}
\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_1.14}
\caption{Scheme 1.14}
\end{figure}
\end{center}

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 CF₃CO₂H 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-amino acids 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 amino acids 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, R¹ 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].