

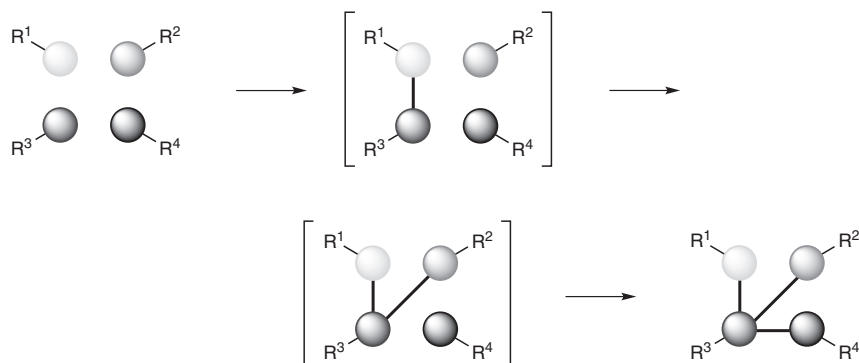
## Abstracts

p 5

### 1.1 Relative Reactivities of Functional Groups as the Key to Multicomponent Reactions

*T. J. J. Müller*

Multicomponent reactions are based upon the concept of consecutive transformations where intermediates created in the preceding step react with additional reaction partners. Based on the type of intermediate involved, multicomponent reactions can be categorized as following polar or nonpolar mechanisms. However, there are two outstanding functionalities that dominate hitherto known multicomponent reactions: the carbonyl and the isocyanide groups. Nonetheless, multicomponent reactions from the relatively young fields of organometallic chemistry and radical chemistry are quickly catching up, simultaneously enabling unusual multicomponent reaction sequences. Multicomponent reactions inherently allow for a high degree of building-block diversity and, therefore, they are perfectly suited for diversity-oriented syntheses and for inventing new types of one-pot syntheses for exploring huge structural and chemical dimensions in manifold applications.



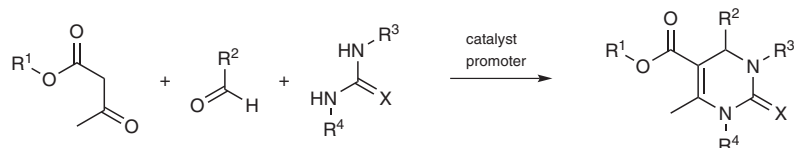
**Keywords:** organic reactivity · reactive functionalities · diversity-oriented synthesis

p 29

### 1.2.1.1 Third Component 1,3-Dicarbonyl Compound (with Ureas: Biginelli Reaction)

*V. A. Chebanov, N. Yu. Gorobets, and Yu. V. Sedash*

This chapter is devoted to a comprehensive analysis of the literature data concerning multicomponent Biginelli heterocyclization and contains descriptions of the diverse synthetic approaches to 1,4-dihydropyrimidines, illustrated by general experimental procedures as well as typical and specific examples.

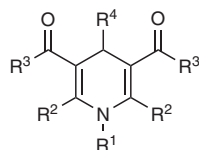


**Keywords:** multicomponent heterocyclization · Biginelli reaction · acid catalysts · organosilicon promoters · ionic liquids · ultrasonication · microwave-assisted synthesis · polymer-supported synthesis · solvent-free synthesis · stereoselective reaction

### 1.2.1.2 Third Component 1,3-Dicarbonyl Compound (with Ammonia or Amines: Hantzsch Pyridine Synthesis)

*J. J. Vanden Eynde and A. Mayence*

Aldehydes,  $\beta$ -dicarbonyl compounds, and a source of ammonia or, in fewer cases, an amine, react readily under mild conditions to yield 1,4-dihydropyridines. This procedure, as well as alternative routes to these heterocycles and structurally related analogues, including unsymmetrical compounds, are reviewed.

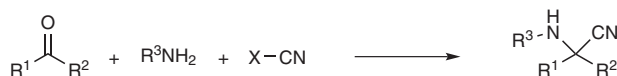


**Keywords:** aldehyde · ammonium acetate · combinatorial chemistry · 1,4-dihydropyridines · enamino ester · Hantzsch · microwave-assisted synthesis ·  $\beta$ -oxo ester · pyridine synthesis · solvent-free reaction

### 1.2.1.3 Third Component Cyanide (Strecker and Strecker-Type Reactions)

*M. Ayaz, F. De Moliner, G. A. Morales, and C. Hulme*

Under typical reaction conditions, the condensation of an amine, a carbonyl compound, and a cyanide ion source smoothly affords an  $\alpha$ -aminonitrile. The process has also been proven to be feasible in an asymmetric fashion and is thus widely exploited to provide enantiomerically pure products, which are predominantly converted into  $\alpha$ -amino acids.



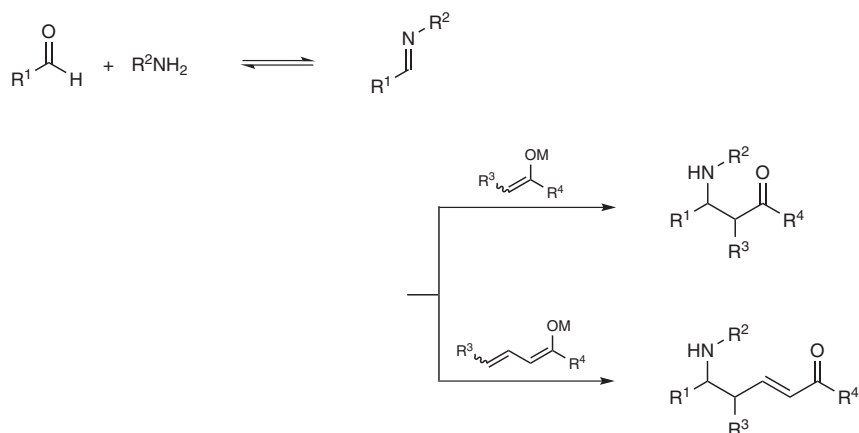
X = H, Na, K, TMS, Ac, SnBu<sub>3</sub>, etc.

**Keywords:** Strecker reaction · amines · carbonyl compounds · cyanides ·  $\alpha$ -aminonitriles ·  $\alpha$ -amino acids · asymmetric synthesis · Lewis acid catalysts · Brønsted acid catalysts

### 1.2.1.4 Third Component Enolizable Carbonyl Compound (Mannich Reaction)

*L. Bernardi and A. Ricci*

The three-component Mannich reaction between in situ generated imines and enolates gives rapid access to diverse  $\beta$ - and  $\delta$ -amino carbonyl compounds. The employment of tailored catalysts and promoters permits control of the regio-, chemo-, and stereoselectivity in both direct and indirect variants of the Mannich reaction.



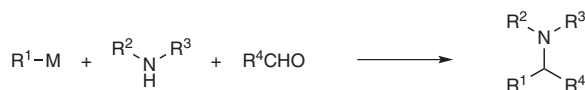
**Keywords:** aldehydes · amines · anilines · asymmetric catalysis · Betti reaction · Brønsted acid catalysts · C–C bond formation · imines · ketones · Lewis acid catalysts · Lewis base catalysts · Mannich reaction

p 165

### 1.2.1.5 Third Component Metal Alkyl or Aryl

*E. Le Gall*

Multicomponent Mannich-like reactions of preformed or in situ generated organometallic reagents, amines, and aldehydes provide a straightforward access to a range of nitrogen-containing derivatives including (diarylmethyl)amines,  $\beta$ -arylethylamines, homoallylic amines, propargylic amines, and  $\alpha$ -amino esters.



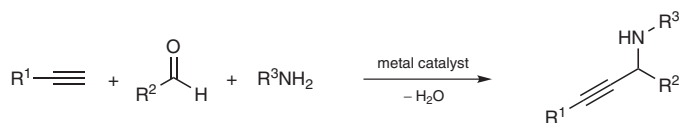
**Keywords:** aldehydes · amines · Barbier conditions · Mannich-like reaction · organometallic reagents

p 189

### 1.2.1.6 Third Component Alkyne

*W.-J. Yoo, L. Zhao, and C.-J. Li*

The metal-catalyzed  $A^3$ -coupling reaction (between an aldehyde, an alkyne, and an amine) is a versatile and powerful multicomponent process that leads to propargylic amines in a facile and atom-economical manner. This chapter describes the recent progress in this field and highlights the  $A^3$ -coupling reaction as a valuable synthetic tool in accessing complex molecules in a rapid and modular fashion.

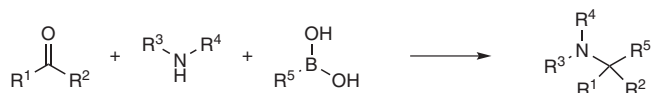


**Keywords:**  $A^3$ -coupling · aldehydes · alkynes · amines · metal catalysis

### 1.2.1.7 Third Component Boronic Acid (Petasis Reaction)

*B. Carboni and F. Berré*

Following the pioneering work by Petasis on the stepwise condensation between amines, aldehydes, and alkenyl- or arylboronic acids, the borono-Mannich reaction has been extended to a wide variety of carbonyl compounds, organoboranes, and amine partners. This three-component reaction allows the synthesis of a large variety of molecules with high levels of structural diversity. The use of chiral ligands as effective catalysts for the asymmetric version greatly expands the scope and utility of this important tool for the formation of new C–C bonds.

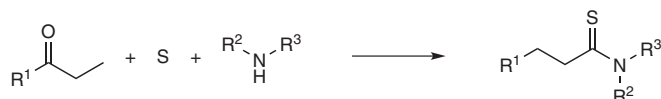


**Keywords:** amines ·  $\alpha$ -amino acids · boron compounds · carbonyl compounds · diastereoselectivity · enantioselectivity · heterocycles · natural products · sugars

### 1.2.1.8 Third Component Sulfur (Willgerodt–Kindler Reaction)

*Y. Huang and A. Dömling*

The Willgerodt–Kindler reaction (three-component coupling reaction of aldehydes or ketones, amines, and elemental sulfur) has been used to synthesize various thioamides. In this chapter are presented examples of Willgerodt–Kindler reactions reported since 2000, as well as discussion of their scope and limitations for the synthesis of thioamides.

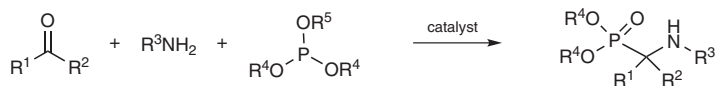


**Keywords:** Willgerodt–Kindler reaction · thioamides · sulfur · amines · aryl ketones · aldehydes

### 1.2.1.9 Third Component Phosphonate (Kabachnik–Fields Reaction)

*N. S. Zefirov, E. D. Matveeva, and M. V. Shuvalov*

This chapter reviews the latest advances in the synthesis of  $\alpha$ -amino phosphonates by the Kabachnik–Fields reaction, which greatly extend the range of applicability of the classical reaction. The recent interest in this area has in part been generated by the biological activity of this class of compounds.

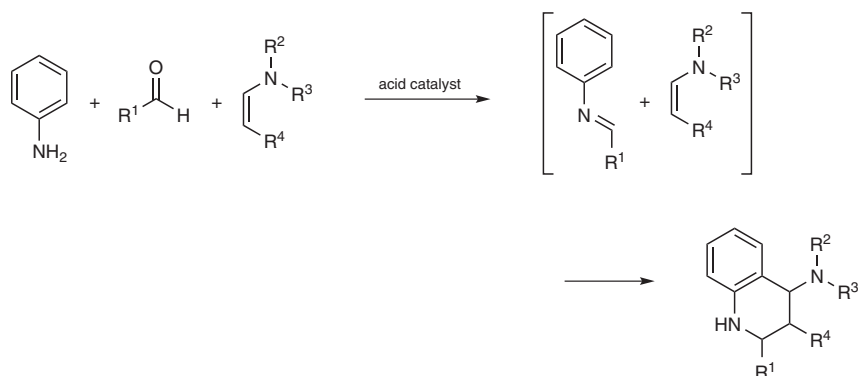


**Keywords:** acid catalysis · aldehydes · aldimines · amines ·  $\alpha$ -amino acids · asymmetric synthesis · azomethines · C–N bonds · C–P bonds · imines · ketones · Lewis acid catalysis · phosphites · phosphonates · phosphonic acids · phosphorylation · phthalocyanines

### 1.2.2 With an Enamine as One Component

*M. J. Arévalo and R. Lavilla*

The reaction of amines (normally aromatic) with carbonyl compounds and enamines under acid catalysis to yield multicomponent adducts is reviewed. The processes comprise mainly Povarov reactions, leading to tetrahydroquinolines, and also some transformations dealing with Pictet–Spengler processes involving indoles (as formal enamine derivatives) which yield gramine-type products and  $\beta$ -carbolines. The scope of these reactions is wide, allowing structural variations on each component; intramolecular versions and in situ generation of some components are also reported. The stereoselectivity varies from nonselective processes to highly diastereoselective transformations. The range of catalysts include Lewis and Brønsted acids. Recently, some catalytic enantioselective methods have been disclosed that enable the preparation of enantiopure compounds in a reliable manner.

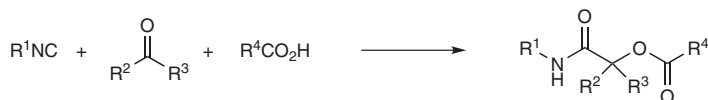


**Keywords:** amines · carbonyl compounds · enamines · Povarov reaction · Pictet–Spengler reaction · tetrahydroquinolines · indoles · gramines ·  $\beta$ -carbolines · Lewis acid catalysis · Brønsted acid catalysis

### 1.2.3.1 Third Component Carboxylic Acid (Passerini Reaction)

*R. Riva, L. Banfi, and A. Basso*

This chapter describes the scope and applications of the Passerini three-component reaction, including the classical reaction and its variants, stereochemical issues, post-condensation transformations, and applications to the synthesis of complex structures. The review focuses mostly on the literature published since 2003.

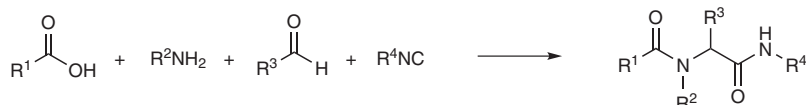


**Keywords:** Passerini reaction · isocyanides · acyl anion equivalent · acids · carbonyl compounds · depsipeptides ·  $\alpha$ -acyloxy amides · carboxamides · esters · heterocycles · medicinal chemistry · asymmetric synthesis

**1.2.3.2 Further Components Carboxylic Acid and Amine (Ugi Reaction)***L. A. Wessjohann, G. N. Kaluđerović, R. A. W. Neves Filho, M. C. Morejon, G. Lemanski, and T. Ziegler*

The Ugi reaction is the archetypal and arguably also the most frequently used multicomponent reaction. It can be seen as a variation of the Passerini reaction, in which the oxo component is substituted by an in situ formed imine or rather iminium species. It produces a (usually mono-*N*-alkylated) dipeptide, i.e. a peptoid-like backbone, found not only in peptides but also in many alkaloids and other heterocycles of biological importance. Beyond its value in combinatorial, heterocyclic, and medicinal chemistry, the Ugi reaction has in recent times gained increased acceptance because it can be considered environmentally friendly (water is the only formal byproduct), and is very easy to perform in almost any solvent, or even without solvent. It allows the rapid and predictable combination of four building blocks, even in the presence of water and air, if the reagents permit. Furthermore, the reaction is unusually insensitive to steric interference, rendering it ideal to generate otherwise difficult-to-reach crowded peptide moieties.

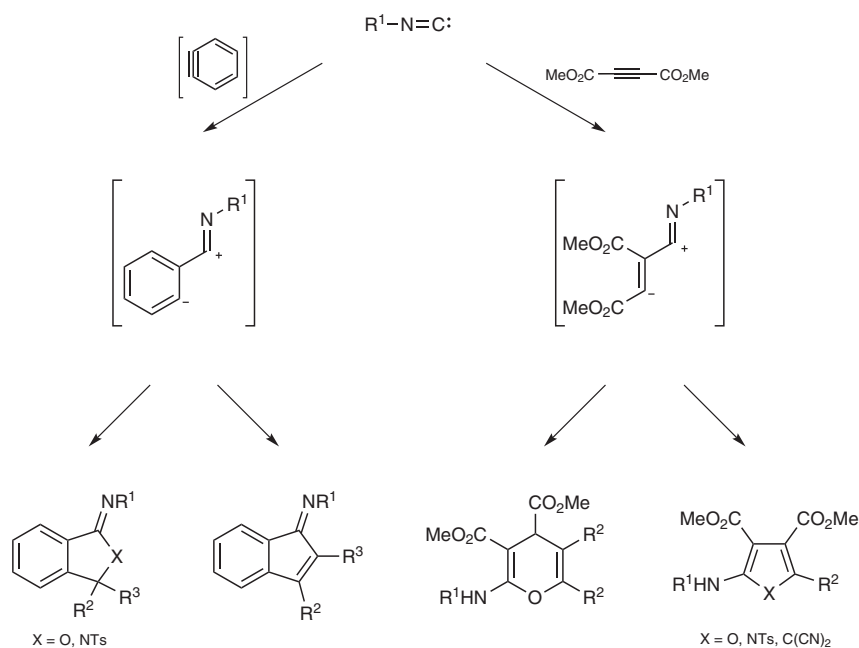
In this chapter, the focus is on the Ugi reaction in its classical four-component version (Ugi-4CR or U4CR), including related Ugi four-center, three-component reactions, i.e. Ugi four-component reactions with bifunctional building blocks.



**Keywords:** Ugi reaction · isocyanides · peptides · natural product synthesis · green chemistry · macrocycles · heterocycles

**1.2.3.3 Modifications of the Ugi Reaction***R. S. Menon and V. Nair*

On a very fundamental level, the Passerini reaction as well as the Ugi reaction involve the addition of an isocyanide to an electrophile (aldehyde or imine) and the subsequent interception of the resultant intermediate with a third component (acid). In a similar manner, addition of isocyanides to electrophilic alkynes generates 1,3-zwitterionic intermediates that can be intercepted by another reactant to afford valuable products in a one-pot, three-component reaction. Dimethyl acetylenedicarboxylate has been shown to participate exceedingly well in such three-component reactions. The isocyanide–dimethyl acetylenedicarboxylate derived zwitterion has been intercepted successfully with aldehydes, *N*-tosylaldimines, arylalkenes, and various enols to furnish 2-aminofurans, 2-aminopyrroles, aminocyclopentadienes, and aminopyrans as products. Arynes also behave as electron-deficient alkynes in such three-component reactions, allowing the synthesis of iminobenzo[*c*]furans, iminoisoindolines, iminoindenes, substituted pyridines, and isoquinolines. Related three-component reactions that involve formal [4 + 1] annulations of electrophilic entities (generated by the union of two stable reactants) and isocyanides afford valuable heterocycles as products. This class of multicomponent reactions stands out in the realm of isocyanide chemistry owing to the diversity of product scaffolds they directly afford.



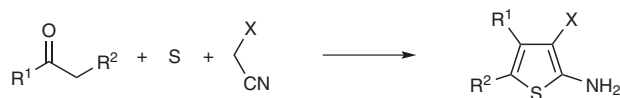
**Keywords:** isocyanides · 1,3-dipoles · dimethyl acetylenedicarboxylate · aryne · benzyne · aminofurans · aminopyrroles · alkynes

p 531 —

#### 1.2.4 Using a Nitrile and Sulfur as Nucleophiles (Gewald Reaction)

*Y. Huang and A. Dömling*

The Gewald three-component reaction of sulfur, cyanoacetic acid derivatives, and a carbonyl component yielding highly substituted thiophen-2-amine derivatives has seen diverse applications in synthetic chemistry. The scope and limitations, synthetic methodology, and combinatorial chemistry of Gewald products are summarized in this chapter.



**Keywords:** Gewald three-component reaction · thiophen-2-amine · sulfur · cyanoacetamide · malononitrile