ORGANIC REACTIONS

Volume 112

Organic Reactions

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INTRODUCTION TO THE SERIES BY ROGER ADAMS, 1942

In the course of nearly every program of research in organic chemistry, the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses*, they have not been subjected to careful testing in two or more laboratories. Each chapter contains tables that include all the examples of the reaction under consideration that the author has been able to find. It is inevitable, however, that in the search of the literature some examples will be missed, especially when the reaction is used as one step in an extended synthesis. Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required. Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy, the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

INTRODUCTION TO THE SERIES
BY SCOTT E. DENMARK, 2008

In the intervening years since "The Chief" wrote this introduction to the second of his publishing creations, much in the world of chemistry has changed. In particular, the last decade has witnessed a revolution in the generation, dissemination, and availability of the chemical literature with the advent of electronic publication and abstracting services. Although the exponential growth in the chemical literature was one of the motivations for the creation of *Organic Reactions*, Adams could never have anticipated the impact of electronic access to the literature. Yet, as often happens with visionary advances, the value of this critical resource is now even greater than at its inception.

From 1942 to the 1980's the challenge that *Organic Reactions* successfully addressed was the difficulty in compiling an authoritative summary of a preparatively useful organic reaction from the primary literature. Practitioners interested in executing such a reaction (or simply learning about the features, advantages, and limitations of this process) would have a valuable resource to guide their experimentation. As abstracting services, in particular *Chemical Abstracts* and later *Beilstein*, entered the electronic age, the challenge for the practitioner was no longer to locate all of the literature on the subject. However, *Organic Reactions* chapters are much more than a surfeit of primary references; they constitute a distillation of this avalanche of information into the knowledge needed to correctly implement a reaction. It is in this capacity, namely to provide focused, scholarly, and comprehensive overviews of a given transformation, that *Organic Reactions* takes on even greater significance for the practice of chemical experimentation in the 21st century.

Adams' description of the content of the intended chapters is still remarkably relevant today. The development of new chemical reactions over the past decades has greatly accelerated and has embraced more sophisticated reagents derived from elements representing all reaches of the Periodic Table. Accordingly, the successful implementation of these transformations requires more stringent adherence to important experimental details and conditions. The suitability of a given reaction for an unknown application is best judged from the informed vantage point provided by precedent and guidelines offered by a knowledgeable author.

As Adams clearly understood, the ultimate success of the enterprise depends on the willingness of organic chemists to devote their time and efforts to the preparation of chapters. The fact that, at the dawn of the 21st century, the series continues to thrive is fitting testimony to those chemists whose contributions serve as the foundation of this edifice. Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to contact the Editor-in-Chief.

PREFACE TO VOLUME 112

Looking for a Needle in a Haystack

Washington Irving, 1808

The preparation and identification of functional molecules with specific properties is a challenging and time-consuming process that is analogous to "finding a needle in a haystack," the modern version of Sir Thomas More's 1532 idiom looking for "a needle in a meadow." Interestingly, the idiom's origin can be traced to Arab and Chinese proverbs that date back over 2000 years in the latter case. The modern version is from 1808 in Part 20 of *Salmagundi* by Washington Irving and others and can be used to describe many aspects of scientific discovery, which is often an arduous and frustrating process. Consequently, developing methods that circumvent the challenges associated with conventional discovery methods aligns with science fiction author Keith DeCandido's notion of "just bring a magnet" to find the needle! For example, drug discovery inspired the development of high-throughput screening techniques that enable the simultaneous analysis of thousands of compounds to identify those with the right properties for lead development. In this context, the specific biological target behaves as the "magnet" to identify the so-called "needle." Although the requirement of analyzing many compounds may be counterintuitive, automation eliminates the mundane task of removing one straw at a time. Combinatorial synthesis is another excellent example of generating thousands of compounds to ensure the "haystack" contains the "needle" to permit detailed structure-activity relationship studies for lead optimization.

The *Organic Reactions* series is distinct in that it curates all the information on a specific transformation and thus provides a unique way of "finding a needle in a haystack." When founding *Organic Reactions* eighty years ago, Roger Adams recognized that much of the relevant information and know-how was often available; however, identifying and translating this uniformly across the chemical research landscape was quite challenging. Moreover, he appreciated that consistently organizing the data in a single venue had significant merit well before the advent of computers and the associated search engines. To this end, the authors generally tabulate all the known examples of a transformation to permit the interrogation of a proposed process, thereby allowing one to determine its feasibility on a specific substrate. Despite all the progress in chemical informatics, *Organic Reactions* still represents a unique resource that provides the proverbial "magnet" to "find the needle" and can thereby mitigate hours of arduous investigation. The chapters also delineate the mechanistic and experimental nuances that are equally important to the practicing synthetic organic chemist, which permits the development of adaptations to expand the scope and define the limitations of the process. The two chapters in this volume by Angelika Ullrich and Uli Kazmaier delineate half a century of the Ugi

and related reactions, which provide the community with an outstanding resource on this important multicomponent reaction and its associated variations.

The first chapter describes the classic four-component Ugi reaction, which combines a carboxylic acid, a carbonyl compound, an amine, and an isocyanide to prepare α-amino acids and peptides. The introduction provides an overview of the kinetic and thermodynamic features of three types of multicomponent reactions and their relevance to reactions that employ isocyanates. For instance, Passerini and coworkers described the first three-component process that combines an isocyanate with a carboxylic acid and a carbonyl compound to afford α-acyloxycarboxamides in the 1920s. An initial impediment to the broad adoption of the Passerini reaction was the limited availability of isocyanates, which Ugi resolved in 1958 by using a formamide dehydration reaction that ultimately led to the Ugi adaptation of including an amine as the fourth component.

The Mechanism and Stereochemistry section outlines the currently accepted mechanism that Ugi originally postulated in 1967, which is supported by kinetic data and calculations. The section also defines stereoselective Ugi reactions, which are rare since the reaction tends to afford mixtures of stereoisomers. Fortunately, this seeming drawback can in fact be an asset in drug discovery where both diastereoisomers may be of interest. Nevertheless, the chapter nicely documents the key to achieving good stereocontrol, which tends to rely on amines with cleavable chiral groups analogous to a classic chiral auxiliary.

The Scope and Limitations section is organized by the substrate (e.g., isocyanide, carbonyl compounds and preformed imines, carboxylic acids, and amines), which acts as an intuitive guide for selecting reaction conditions. For example, the type of isocyanide is subdivided into cleavable and convertible isocyanides, where the amide is not the desired product. The carbonyl component includes formaldehyde, aldehydes, and ketones, traversing the entire functionalization array from methylene to quaternary centers. The section on aldehydes with α-leaving groups permits access to β-functionalized α-amino acid derivatives. The carboxylic acid component is remarkably versatile, in that aryl, alkyl, and α,β-unsaturated acids can be employed. Finally, the process is optimal with primary amines, including ammonia, cleavable amines, unsaturated amines, hydrazines, and hydroxylamines. Notably, secondary amines do not undergo the acyl shift and are covered in the accompanying chapter on the modified Ugi reaction.

The Applications to Synthesis section describes selected applications for preparing drugs and drug-like molecules, including several natural products. The Comparison with Other Methods section compares the Ugi and Passerini reactions and briefly surveys the standard methods for preparing peptides and forming peptide bonds. The enormous Tabular Survey incorporates reactions reported through the end of 2012, covering the first fifty years of the Ugi reaction. The tables are arranged by isocyanide in order of increasing carbon count, followed by the carboxylic acid, carbonyl component, and amine, to permit the quick identification of the optimal combination for preparing a particular intermediate. This is an excellent chapter on an important transformation relevant to synthetic, medicinal, and bioorganic chemistry.

The second chapter on the modified Ugi reaction focuses on half a century of modifications that employ alternative reaction conditions and components, multifunctional substrates, and reactions that deploy more or less than four components. The key mechanistic and stereochemical aspects mirror the classic variant described in the preceding chapter.

The Scope and Limitations section is organized similar to the previous chapter (e.g., isocyanide, amine components, carbonyl compounds, and carboxylic acids). Variations in the isocyanide structure and the reaction conditions permit diversification of the reaction to form different types of products. This feature is exemplified by the reaction of isocyanoacetamides in the absence of a carboxylic acid to afford oxazoles, which then undergo a subsequent Diels-Alder reaction. The amine component includes secondary amines, diamines, hydrazines, hydroxylamines, and aziridines. In the case of diamines, the reaction can be modified to prepare six- and seven-membered heterocycles, while aziridines provide access to so-called "homo-Ugi" products. The carbonyl components used are similar to those in the preceding chapter, albeit with different outcomes based on the reaction conditions employed. Furthermore, this chapter includes reactions utilizing siloxycyclopropanes as precursors to the aldehyde components. The scope of the acid derivative is much more extensive and extends beyond conventional carboxylic acids (e.g., anhydrides, thiocarboxylic acids, hydrazoic acid, cyanic and thiocyanic acid, carbonic esters, etc.). Notably, suitably substituted aromatic and heteroaromatic alcohols and thiols undergo an Ugi-Smiles rearrangement. Another noteworthy Ugi variant is the use of bifunctional reagents in the form of amino-carboxylic acids, oxo-carboxylic acids, and formyl and keto amines, which also permit macrocyclization reactions that involve one or two Ugi reactions. The section on variations in the number of components is particularly interesting since the reaction can be conducted with more or less than four components. For instance, as many as eight components can be combined in a modified Ugi reaction, which provides unparalleled versatility.

The Applications to Synthesis section emphasizes natural product syntheses. The Comparison with Other Methods section compares some selected approaches to similar functionalities because of the diverse array of products that can be accessed using these variations. For instance, the merit of the Ugi reaction for preparing oxazoles and thiazoles is included to highlight the issues with the more classical approaches. The Tabular Survey incorporates reactions reported through the end of 2012 and mirrors the organization delineated in the previous chapter (e.g., isocyanide, carboxylic acid derivative, carbonyl component and amine, including preformed imines) followed by bifunctional and related multi-component reactions to enable identification of the optimal combination for preparing a particular intermediate. Overall, this outstanding chapter delineates important variations to the classic Ugi process and will be an excellent resource to the synthetic community.

I would be remiss if I did not acknowledge the entire *Organic Reactions* Editorial Board for their collective efforts in steering this volume through the stages of the editorial process. I want to thank Dr. Jeff Aubé and Dr. Paul R. Blakemore, who served as the Responsible Editors to marshal the chapters through the various phases of development. I am also deeply indebted to Dr. Danielle Soenen for her continued

and heroic efforts as the Editorial Coordinator; her knowledge of *Organic Reactions* is critical to maintaining consistency in the series. Dr. Dena Lindsay (Secretary to the Editorial Board) is thanked for coordinating the authors', editors', and publisher's contributions. In addition, the *Organic Reactions* enterprise could not maintain the quality of production without the efforts of Dr. Steven M. Weinreb (Executive Editor), Dr. Engelbert Ciganek (Editorial Advisor), Dr. Landy Blasdel (Processing Editor), and Dr. Tina Grant (Processing Editor). I would also like to acknowledge Dr. Barry B. Snider (Secretary) for keeping everyone on task and Dr. Jeffery Press (Treasurer) for ensuring that we remain fiscally solvent!

I am also indebted to past and present members of the Board of Editors and Board of Directors for ensuring the enduring quality of *Organic Reactions*. The specific format of the chapters, in conjunction with the collated tables of examples, makes this series of reviews both unique and exceptionally valuable to the practicing synthetic organic chemist.

P. Andrew Evans
Kingston
Ontario, Canada

ROBERT CHARLES KELLY

November 28, 1939 – May 22, 2022

Robert (Bob) C. Kelly was born in St. Joseph, Michigan, the son of Lester and Francis Kelly. He graduated Magna Cum Laude from Kalamazoo College in 1961 where he conducted undergraduate research with Professor Kurt Kaufman. Bob received a National Science Foundation Graduate Fellowship to attend Harvard University where he studied under the direction of Professor R.B. Woodward. After completing the first total synthesis of triquinacene (a theoretical precursor of dodecahedrane) and receiving his Ph.D. in 1965, Bob joined the Upjohn Company in Kalamazoo, Michigan.

Bob worked for the Upjohn Company and its successor companies in Kalamazoo (Pharmacia & Upjohn, Pharmacia, and finally Pfizer) for the next 38 years, retiring in 2003. Afterwards, he served as a consultant for a number of biotech companies. He was a life-long learner who always enjoyed both physical and mental challenges.

During his long career at the Upjohn Company Bob typically worked on the most challenging chemical problems at the company. These were usually associated with the synthesis of natural products and their analogs. Early in his career Bob helped develop the Upjohn synthesis of prostaglandins, which not only enabled the preparation of prostaglandin and prostacyclin analogs at the Upjohn Company, but also allowed the company to provide samples of various prostaglandins to researchers around the world when such precious compounds were in short supply. During this time Bob was part of the team that developed and published the well-known Upjohn dihydroxylation process to prepare *cis* vicinal diols from olefins using a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide. Earlier procedures had used a stoichiometric amount of osmium tetroxide, a highly toxic and expensive agent which caused severe work-up problems, or else employed catalytic procedures which typically also resulted in side products from the overoxidation of the desired alcohols.

After his work in the prostaglandin area, Bob worked in cancer research at Upjohn for a number of years, again focusing on various complicated natural products. He led the first synthetic effort to prepare the novel and potent antitumor agent CC-1065, which had been discovered several years earlier at Upjohn, and its analogs. This

work culminated in the first total synthesis of CC-1065 as well as ultimately three different clinical candidates, including, at the time, the most potent anticancer agent that had ever been published. Working with these highly potent anticancer compounds required the highest level of scientific skill and dedication to safety protocols. Later Bob worked on the semi-synthesis of taxol analogs resulting in a potent clinical candidate that was orally active. In subsequent years at what was by then Pharmacia & Upjohn (and Pharmacia), Bob worked in the infectious diseases area with an emphasis on the discovery of compounds to treat hepatitis C.

As might be expected given his chemistry expertise and determination, Bob rose through the scientist career ladder at the company becoming one of the few scientists at Upjohn to achieve the highest level of Distinguished Scientist in 1987. With each successive merger (typically resulting in new career path titles and levels), Bob was reaffirmed in his position at the top of the scientist career path. Bob also earned essentially every scientific honor at Upjohn, including the Upjohn Award (1973), the Fred Kagan Lead Finding Award (1986), and the Upjohn Award for Achievement in Science and Medicine (1988). During his career Bob had more than 80 patents and publications.

Bob was also active in the chemistry community at large. A 62-year member of the ACS, Bob was chair of the Kalamazoo Section in 1973. From 1988–1989 he was a member of the nominating committee to select candidates for Chairman-elect and for the Executive Committee of the Organic Division. Bob was also the Kalamazoo College Senior Independent Project (SIP) Coordinator for 17 years. The annual forum where seniors at Kalamazoo College give their SIP presentations is named the Robert C. Kelly SIP Symposium in his honor. He was an editor of *Organic Reactions* from 1988–1998.

Bob was an avid outdoorsman, enjoying fishing, hunting, backpacking, and sailing. He ran a number of marathons and played tennis until he was 80 years old. He was also an artisan, taking up basket weaving in his later years, creating works of art from scratch by felling trees himself and then fashioning them into wood strips for weaving.

As mentioned earlier, Bob looked forward to both mental and physical challenges. He was passionate, curious about nature, and highly competitive, but at the same time a humble man and a good mentor. In many ways Bob's life embodies the ideals expressed by Ralph Waldo Emerson: "The purpose of life is to be useful, to be honorable, to be compassionate, to have it make some difference that you have lived and lived well."

Bob is survived by his wife of 62 years, Sylvia Schaaf Kelly, his two children Sharon Sinton (wife of Mark Sinton) and Scott Kelly (husband of Patty Kelly), brother Dennis Kelly, and four grandchildren, Hannah and Helena Sinton and Stephen and Peter Kelly.

Paul A. Aristoff, Ph.D.
Fort Collins, Colorado

CONTENTS

ORGANIC REACTIONS

CHAPTER 1

A HALF-CENTURY OF THE UGI REACTION: CLASSIC VARIANT

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Edited by JEFFREY AUBÉ AND PAUL R. BLAKEMORE

CONTENTS

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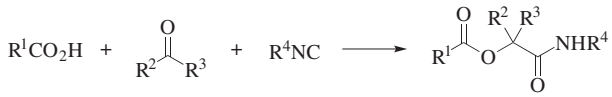
INTRODUCTION

Multicomponent reactions (MCR), defined as one-pot reactions that utilize more than three starting materials, are an interesting alternative to a multistep synthesis. The more components that can be involved in an MCR, the higher the potential diversity of the products that are formed, which explains the high popularity of MCRs in the construction of libraries of natural products and drug-like molecules.[1−6]

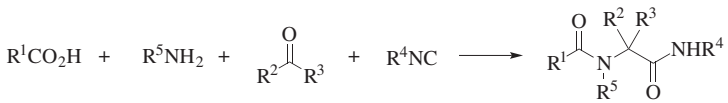
Multicomponent reactions can be divided into three major categories. In Type 1 reactions, starting materials, intermediates, and final products are in a dynamic equilibrium. The products generally cannot be isolated or they are obtained in low yields. Type 2 reactions also involve a dynamic equilibrium between starting materials and intermediates; however, the products are formed in a final irreversible step. For Type 3 reactions, the conversion of starting materials into products occurs by an irreversible sequence of subreactions. These MCRs are often described as tandem, domino, or sequential reactions.[7,8]

An important group of MCRs involves the use of isocyanides.[9–13] The first of these transformations was discovered in the 1920s by Passerini and coworkers, who investigated the synthesis of α-acyloxycarboxamides by combining carboxylic acids, carbonyl compounds, and isocyanides. Scheme 1 provides an example of this reaction, which is now called the Passerini three-component reaction.[14–18] This pioneering work ultimately set the stage for the development of related multicomponent reactions.[19]



Scheme 1

The utility of the Passerini reaction was initially limited by the availability of isocyanides. However, this changed in 1958 when Ugi and coworkers developed a general formamide dehydration protocol that could be used in the synthesis of a wide range of isocyanide products.[20–23] Ugi and coworkers also extended the Passerini reaction by adding an amine as the fourth component, which is now referred to as the Ugi four-component reaction (Scheme 2).[24] The Ugi reaction has been documented in numerous reviews.[4,5,13,25–48]



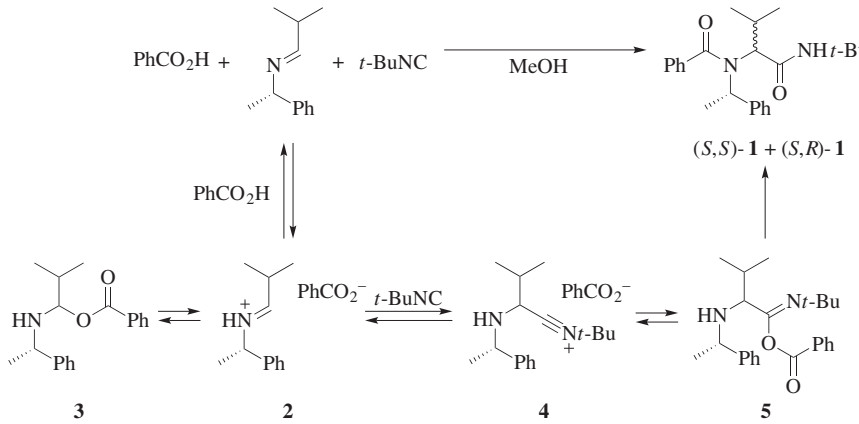
Scheme 2

The classic Ugi reaction is the four-component coupling process that combines a carboxylic acid, a carbonyl compound, an amine, and an isocyanide. This chapter reviews the development of the Ugi reaction over approximately half a century, from its initial discovery at the beginning of 1961 to the end of 2012. The application of this reaction to the synthesis of amino acid and peptide derivatives is also discussed, along with reactions in which the classic Ugi product undergoes, or is subjected to, further modifications. Related reactions that include the use of noncanonical or multifunctional components and Ugi reactions that involve fewer or more than four components are presented in *Organic Reactions* Volume 112b.[49] In this chapter, the term Ugi reaction refers specifically to the four-component coupling process. Modifications to the Ugi reaction that lead to heteroaromatic ring systems are excluded from this chapter.

MECHANISM AND STEREOCHEMISTRY

The mechanism of the Ugi reaction was first postulated in 1967 and is closely related to that delineated for the Passerini reaction.[50] Based on kinetic data and calculations performed on one of the first commercially available computers, Ugi

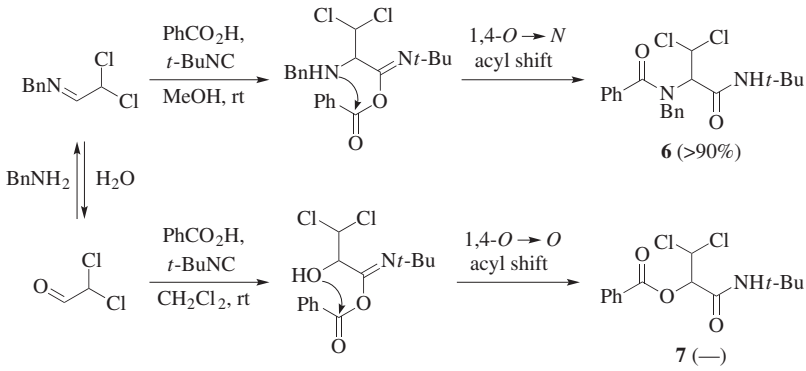
proposed a mechanism for the reaction of benzoic acid, isobutyraldehyde-(*S*)-α-phenylethylimine, and *tert*-butylisocyanide, which provides a diastereomeric mixture of amide **1** (Scheme 3).[51] Similar results are obtained when (*S*)-α-phenylethylamine and isobutyraldehyde are used in place of the preformed imine, thereby supporting the notion that imine formation is relatively fast in methanol. Once formed, the basic imine is protonated by the carboxylic acid to furnish iminium ion **2**, followed by reversible addition of the carboxylate counteranion to deliver aminal **3** in a nonproductive equilibrium process. Alternatively, the iminium ion **2** can be intercepted by the isocyanide component to generate a nitrilium cation (**4**), which can likewise react with the carboxylate anion to afford a different neutral intermediate (**5**). Up to this stage, all of the various reaction components are in a dynamic equilibrium; however, since compound **5** is an aza analog of a mixed anhydride (an imino anhydride) and possesses a free amino group in the α-position, it undergoes an intramolecular 1,4-*O*→*N* acyl transfer process to generate the final product **1**. Since the acyl transfer step is irreversible, the Ugi reaction is categorized as a Type 2 MCR (vide supra).[21]



Scheme 3

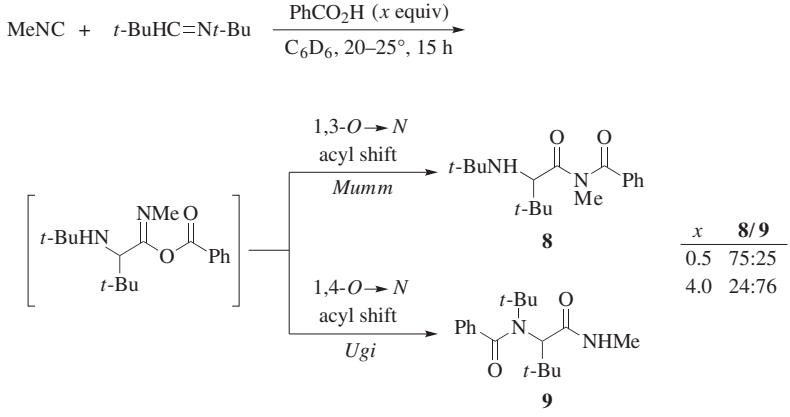
The positions of the equilibria in Scheme 3 depend heavily on concentration, temperature, and solvent.[51] In an analogous reaction of dichloroacetaldehyde in methanol, the expected Ugi product **6** is obtained in excellent yield, whereas the Passerini product **7** is preferentially formed when dichloromethane is used as the solvent instead (Scheme 4).[52] In the latter case, imine formation is very slow compared to the 1,4-*O*→*O* acyl shift, which is the final—and irreversible—step of the Passerini reaction.

The 1,4-*O*→*N* acyl shift of the Ugi reaction is slowed when a sterically demanding substituent occupies the α-position of the amine, as is the case in Scheme 5.[53–60] For these substrates, the Mumm rearrangement can become a competitive pathway, leading to the formation of unsymmetrical imide **8** via a 1,3-*O*→*N* acyl migration. The 1,4-*O*→*N* acyl shift (to give Ugi product **9**) is the only pathway catalyzed by



Scheme 4

the carboxylic acid component; therefore, the ratio of Mumm-to-Ugi rearrangement products (**8/9**) is dependent on the amount of carboxylic acid employed.[61]

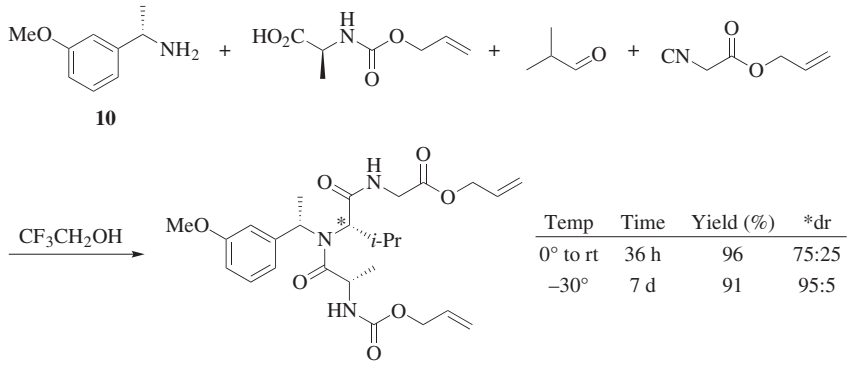


Scheme 5

Asymmetric Ugi Reactions

Diastereoisomers are formed when chiral components are used in the Ugi reaction, but often little or no stereoselectivity is observed in this process. The incorporation of chiral carboxylic acids,[62] carbonyl compounds,[40,62–70] or isocyanides[40,71–75] usually afford the Ugi products as 1:1 mixtures of diastereoisomers, even if several low-stereoinducing components are combined, albeit there are some exceptions.[76] For example, when performed at –30°, an Ugi reaction involving (*S*)1-phenylethylamine derivative **10** and *N*-alloc-protected (*S*)-alanine delivers the product with excellent diastereoselectivity (Scheme 6).[77]

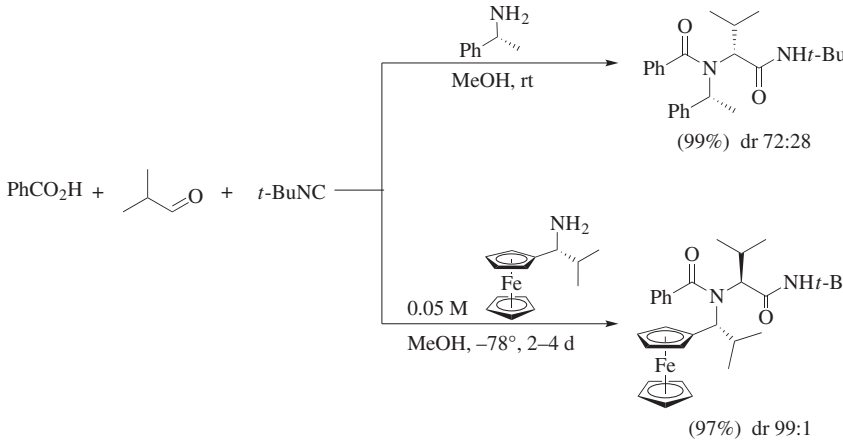
In general, the best diastereoselectivity is observed when chiral amines are used in asymmetric Ugi reactions. The most common amines employed are



Temp	Time	Yield (%)	*dr
0° to rt	36 h	96	75:25
–30°	7 d	91	95:5

Scheme 6

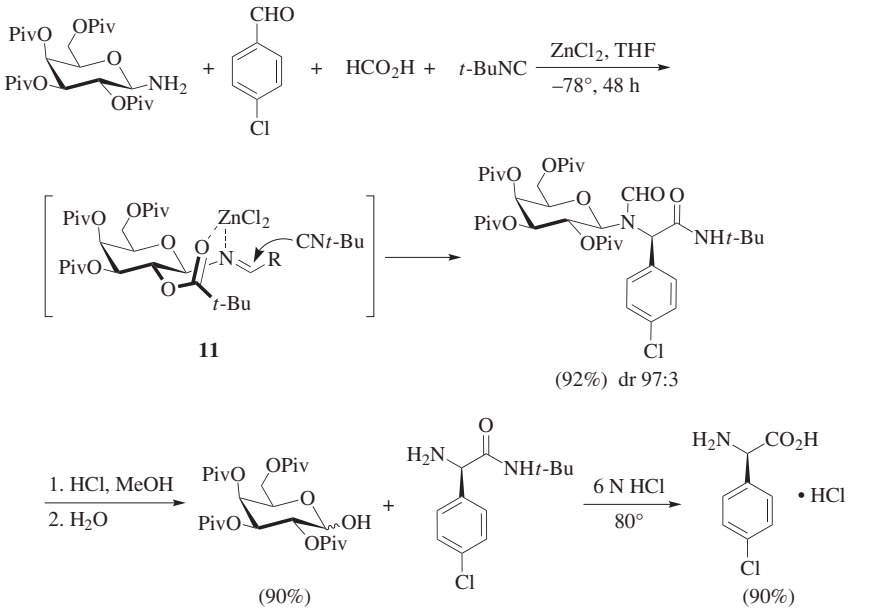
1-phenylethylamine derivatives,[78–81] α-ferrocenylalkylamines,[66,73,79,82–88] and glycosylamines.[89,90] These amines can be viewed as chiral ammonia equivalents if the chiral moiety can be removed after the completion of the Ugi reaction. An example of this strategy is outlined in Scheme 7, wherein 1-phenylethylamine affords diastereomeric ratios of up to 72:28, depending on the choice of reaction conditions.[66] Superior diastereoselectivities (dr 99:1) are achieved with chiral α-ferrocenylalkylamines,[81] which can be cleaved upon treatment with thioglycolic acid/trifluoroacetic acid[88,91] or formic acid.[79]



Scheme 7

Another amine that is commonly used in Ugi chemistry is *O*-tetrapivaloylated D-galactosylamine. In the presence of zinc(II) chloride and at very low temperature, this chiral amine reacts to afford the desired products in high yields and with excellent diastereoselectivities.[92,93] The stereochemical outcome of the reaction is explained by the formation of zinc-chelate complex **11**, which is

attacked from the least-hindered face by a nucleophilic isocyanide (Scheme 8).[94] Diastereomerically pure products can often be obtained by chromatography or crystallization. Cleavage of the carbohydrate moiety under weakly acidic conditions affords *O*-pivaloyl-galactose, which permits the regeneration of the chiral amine.[95] Treatment of the product with stronger acids, such as 6 N hydrochloric acid, can be used to generate the free (*R*)-amino acid salt.



Scheme 8

The corresponding (*S*)-amino acids can also be accessed with comparable diastereoselectivities by using the pseudoenantiomer D-arabinopyranosylamine.[92,96,97] Other chiral amines that have been successfully employed include *O*-alkylated D-glucopyranosylamines,[98] acylated glucosamine,[99,100] and amines derived from thiosugars.[101,102] The pivaloylated galactosylamine can also be coupled with a polymeric resin, such as the cleavable Wang resin,[103] for applications in parallel solid-phase synthesis.[104,105]

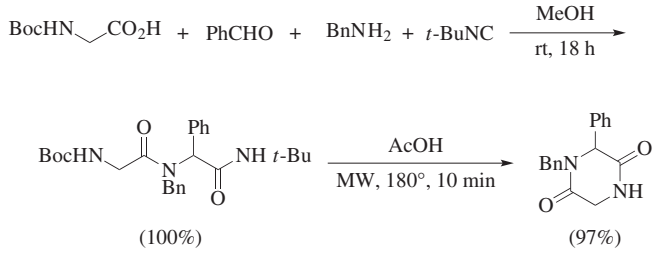
Although outside the scope of the present review, another example of an asymmetric Ugi reaction was reported in 2018.[106]

SCOPE AND LIMITATIONS

Although the Ugi reaction exhibits broad scope, special considerations are necessary when using particular types of isocyanides, carbonyl compounds, carboxylic acids, and amines. Each of the components of the Ugi reaction will now be discussed with respect to the scope and limitations of the process.

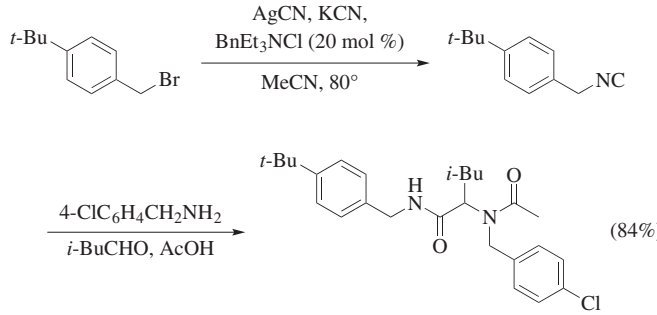
Isocyanides

With few limitations, the substituent on the isocyanide is selected based on the secondary amide product that is desired. The use of alkylisocyanides, including *tert*-butylisocyanide (resulting in *N*-*tert*-butyl secondary amides), is widespread in Ugi reactions. Although the resulting alkylamides are not generally cleaved, a common exception is cleavage of the amide via cyclization (Scheme 9),[107] as demonstrated in the synthesis of dioxopiperazines[107−109] and benzodiazepines.[108,110,111] Alkylamides can also be converted to the corresponding esters by nitrosation with dinitrogen tetroxide.[112−114]



Scheme 9

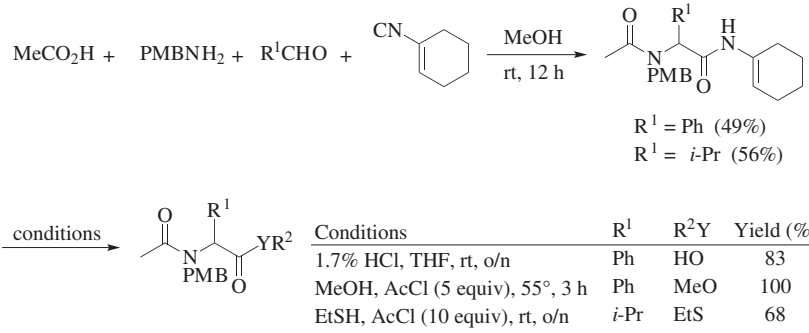
A wide range of functionalized and unfunctionalized isocyanides are commercially available. These compounds can also be prepared in situ by dehydration of formamides with triphosgene and triethylamine[115,116] or by treatment of an alkyl bromide with a mixture of silver cyanide and potassium cyanide (Scheme 10).[117,118] Once the isocyanide has been formed, the other three components can be added to the reaction flask, resulting in generally good-to-excellent yields of the Ugi products.[119] This convenient one-pot reaction sequence circumvents the isolation and handling of the isocyanides, which tend to have an unpleasant odor.



Scheme 10

Cleavable or Convertible Isocyanides. Isocyanides that facilitate cleavage of the amide bond are useful when a carboxylic acid is desired as the product.

A popular choice for a cleavable isocyanide is cyclohexenylisocyanide,[120] which is stable at −30° under argon for more than two months.[121] This reagent can be prepared by HI elimination from β-iodo-cyclohexylisocyanide[122] or by dehydration of cyclohexenylformamide.[22,121,123,124] The use of cyclohexenylisocyanide in the Ugi reaction furnishes cyclohexenylamides, which are susceptible to attack by a variety of nucleophiles; as a result, cyclohexenylisocyanide functions as a universal isocyanide synthon. Under slightly acidic conditions, the addition of water affords the free acid, whereas alcohols and thiols generate esters and thioesters, respectively (Scheme 11).[121] Higher yields of the products are obtained with more nucleophilic alcohols; the reaction does not proceed using phenols or amines. Cyclohexenylisocyanide is also used in solid-phase Ugi reactions to enable product modification (when anchored through a different component)[125] or to assist with product cleavage from the solid support (when anchored through a modified cyclohexenylisocyanide).[126]

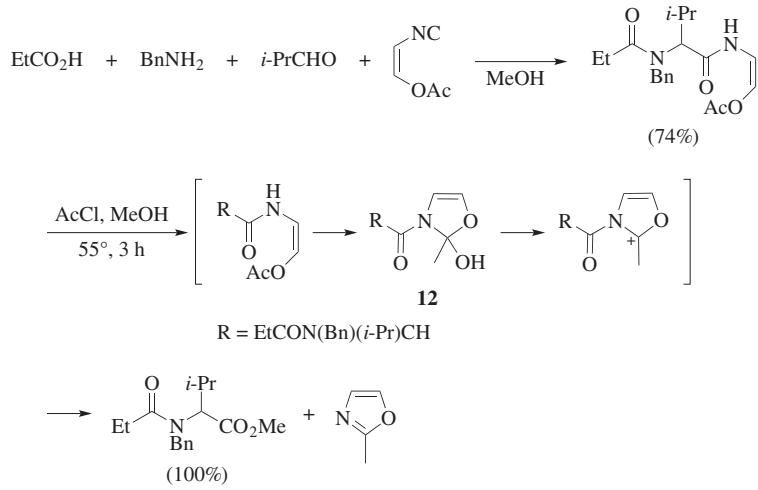


Conditions	R^1	R^2Y	Yield (%)
1.7% HCl, THF, rt, o/n	Ph	HO	83
MeOH, AcCl (5 equiv), 55°, 3 h	Ph	MeO	100
EtSH, AcCl (10 equiv), rt, o/n	*i*-Pr	EtS	68

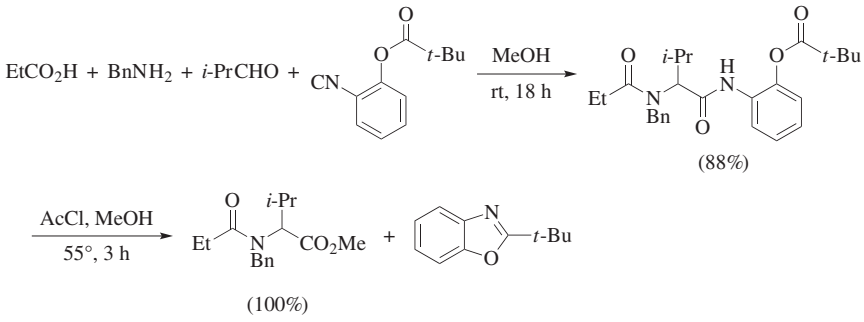
Scheme 11

β-Acyloxyvinylisocyanides do not smell as unpleasantly as other isocyanides and can be used in Ugi reactions to provide the expected enamide products in good yields (Scheme 12).[127] These products can be cleaved by treatment with HCl/MeOH, affording methyl esters in excellent yields through the likely formation of tetrahedral intermediate **12**. 2-Acyloxyphenylisocyanides are a class of aromatic analogs with similar attributes and applications in the Ugi reaction (Scheme 13).[128]

(β-Isocyanoethyl)alkylcarbonates, prepared from commercially available 4,4-dimethyloxazoline, are stable and can be stored at room temperature (Scheme 14).[129] When (β-isocyanoethyl)alkylcarbonates are used in Ugi reactions, the yields are typically very good, and the resulting amides can be cleaved under basic conditions.[129−131] This provides an alternate strategy for amide cleavage that might be particularly useful for acid-sensitive substrates. Deprotonation of the secondary amide likely results in the formation of *N*-acylated oxazolinone **13**, which is subsequently attacked by the liberated alkoxide to afford the corresponding alkyl ester. In the presence of water, the free acid is isolated instead.[129] The variable alcohol moiety (R) present in the (β-isocyanoethyl)alkylcarbonate affects whether *N*-acyloxazolinone **13** undergoes attack by the liberated alkoxide (RO^-).



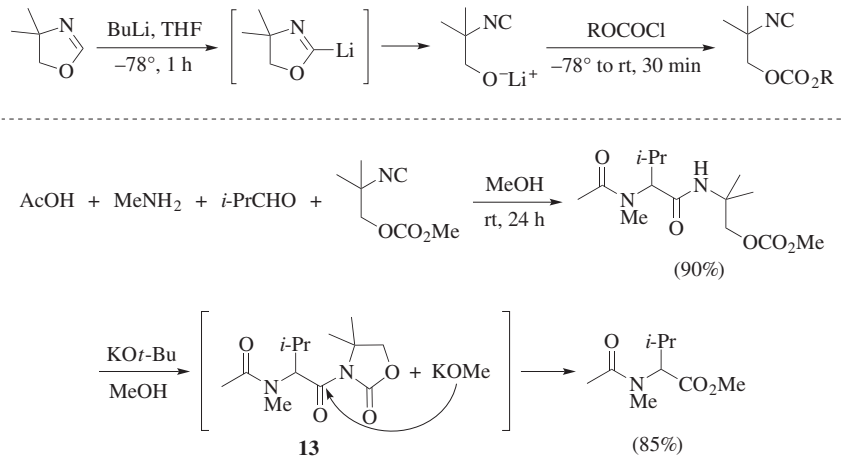
Scheme 12



Scheme 13

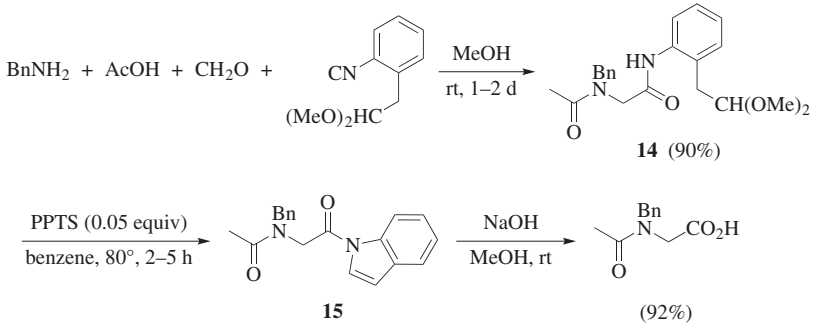
For example, when R = Ph, intermediate **13** can be isolated and subsequently treated with different nucleophiles; however, a more reactive alkoxide (e.g., MeO^-) attacks the amide bond to afford an ester, as depicted in Scheme 14. Treatment of **13** with thiols affords thioesters, whereas the addition of lithium borohydride reduces **13** to the corresponding alcohol.[132,133] The variable alcohol moiety (R) in the (β-isocyanoethyl)alkylcarbonate also enables Ugi reactions on solid support using a polymer-bound isocyanide. The resin-bound alcohol is cleaved, and the product is released into solution.[134] Alternatively, the isocyanide can be linked to a protein, allowing for the ligation of biomolecules[135] Similar results are obtained with 1-hydroxy-2-methyl-2-propyl isocyanide, which is odorless and shows good reactivity in the Ugi reaction; the corresponding *N*-(1-hydroxy-2-methyl-2-propyl) amide products are smoothly converted into esters by zinc triflate mediated solvolysis.[136]

2-(Dimethoxyethyl)phenylisocyanide is stable for weeks at 0°[137] and can be obtained in large quantities from 2-nitrotoluene via a five-step sequence. When this



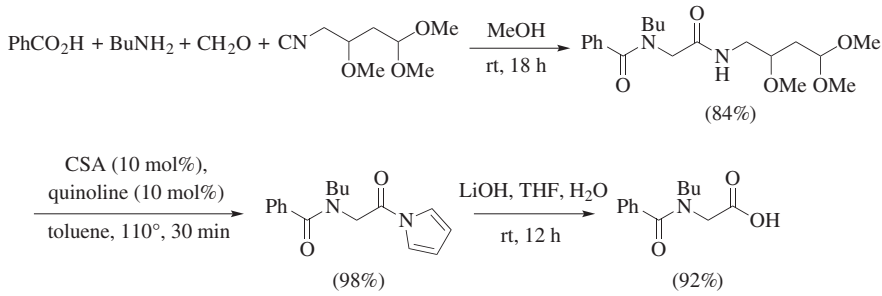
Scheme 14

isocyanide is used in Ugi reactions, the products are generally obtained in high yields,[138,139] and treatment with mild acid affords highly activated indolyl amides (Scheme 15).[140] The addition of various nucleophiles enables access to a broad spectrum of carboxylic acid derivatives, whereas reduction with sodium borohydride affords the corresponding aldehydes.[141] For example, treatment of the Ugi product **14** with catalytic PPTS delivers the indole **15**, which can then be subjected to basic hydrolysis to furnish the corresponding *N*-acyl amino acid in 92% yield over two steps.



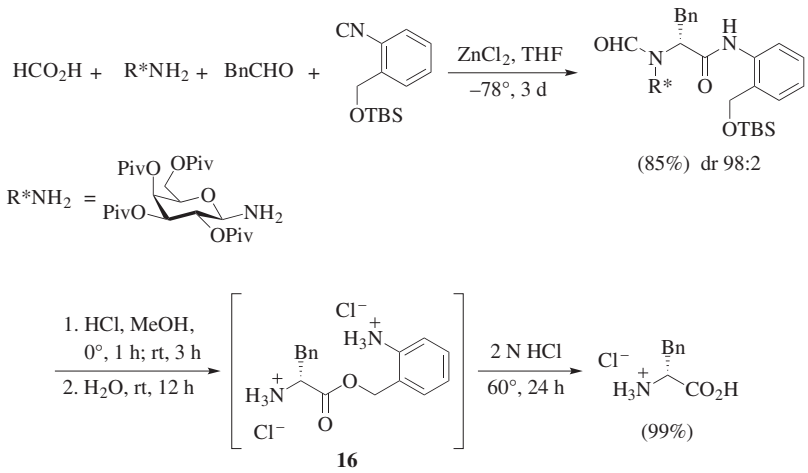
Scheme 15

4-Isocyano-1,1,3-trimethoxybutane is another versatile isocyanide. Heating the primary Ugi products with camphorsulfonic acid and quinoline at 110° results in cleavage of the acetal with concomitant cyclization to afford the activated *N*-acylpyrroles. Treatment of the latter with various nucleophiles affords esters, amides, alcohols, alkenes, and carboxylic acids (Scheme 16)[142] to provide an indication of the scope.



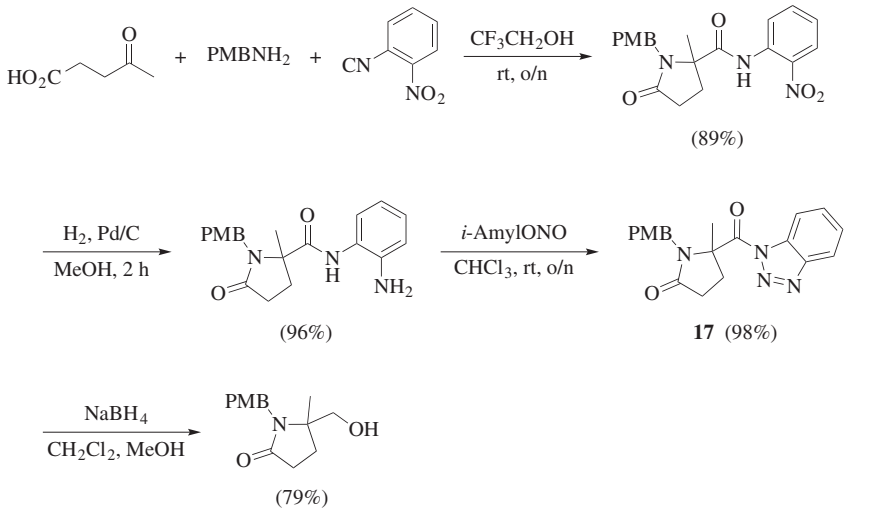
Scheme 16

Silyloxymethylphenylisocyanide is obtained from 2-aminobenzyl alcohol in three synthetic steps and can be used in conjunction with carbohydrate-based chiral amines to provide excellent diastereoselectivities in asymmetric Ugi reactions (Scheme 17).[143] Upon cleavage of the silyl protecting group, a nitrogen-to-oxygen acyl transfer gives rise to benzyl ester **16**, which is easier to hydrolyze than the original Ugi anilide.[144,145]



Scheme 17

2-Nitrophenylisocyanides can be prepared under standard conditions, but are not particularly stable.[22,146] Catalytic hydrogenation of the resulting Ugi products furnishes the corresponding 2-aminoanilides, which are subsequently converted into acylated benzotriazoles upon diazotization.[147,148] The acylated benzotriazole derivatives **17** can be treated with a wide range of nucleophiles including alcohols, amines, and thiols, or reduced to the corresponding alcohols as outlined in Scheme 18.[147] Interestingly, 2-nitrophenylisocyanides containing a 4-methoxy substituent are more stable,[149] making them more convenient Ugi components than the unsubstituted analogs.[150,151]



Scheme 18

2-Nitrobenzyl isocyanide is odorless, stable, convenient to prepare, and easy to handle. This isocyanide performs well in Ugi reactions, generating 2-nitrobenzylamide products that can be cleaved under acidic conditions.[152] Among the 2-isocyanopyridine derivatives, 2-bromo-6-isocyanopyridine is optimal: this reagent is nucleophilic enough to participate in Ugi reactions, and the resulting *N*-6-bromo-2-pyridyl amides exhibit good leaving-group ability under both basic and acidic conditions.[153]

Isocyanoacetates. Isocyanoacetates are useful for the synthesis of small peptides. In principle, chiral isocyanoacetates are available from the dehydration of *N*-formylated amino acid esters, but in many cases only racemic isocyanides are obtained.[154,155] The presence of a second electron-withdrawing group can lead to the epimerization of the stereogenic α-carbon, which can either occur during preparation of the isocyanide or the Ugi reaction.[124,156–160]

Isocyanoacetates are less nucleophilic than the corresponding alkyl isocyanides, often resulting in lower yields in Ugi reactions, especially when ketones are used. The reduced reactivity of these reagents can also lead to side reactions that arise from the increased α-acidity of isocyanoacetates. Weak bases, like the amine component in the Ugi reaction, can deprotonate the isocyanoacetate and generate a Mannich-type product (e.g., **18**), which undergoes cyclization to form an imidazoline (Scheme 19).[161] This side reaction can often be suppressed using preformed imines, which also reduce the risk of isocyanide racemization.[162]

Although the Ugi reaction is not generally efficacious for the preparation of enantiomerically pure peptides,[87,88] it has successfully been applied to the construction of a wide range of racemic peptides and peptide analogs as diastereomeric mixtures. The Ugi reaction is especially useful for preparing *N*-alkylated peptides,