Aminoacyl Benzotriazolides: Versatile Reagents for the Preparation of Peptides and Their Mimetics and Conjugates

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Professor Meike Niggemann of RWTH Aachen University, Germany, kindly suggested that we offer Ca(NTf₂)₂, a main-group-metal catalyst used to effect a number of synthetic transformations that typically require stoichiometric quantities of other Lewis acids. When utilized together with a catalytic quantity of Bu₄NPF₆, Ca(NTf₂)₂ can effectively catalyze regio- and stereoselective Friedel–Crafts alkylations, hydroarylations of alkenes, and cyclopropanations.


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ABOUT OUR COVER

Winslow Homer completed Breezing Up (A Fair Wind) (oil on canvas, 61.5 x 97 cm) in 1876, the U.S. centennial year. One of the most celebrated American artists of the nineteenth and early part of the twentieth centuries, Homer had little formal training as a painter, and seems to have developed his plein-air style of objective realism on his own. He was a prolific artist who excelled in several media and travelled widely, depicting a variety of themes, from battlegrounds of the Civil War to leisurely scenes of recreation.

An iconic American painting and one of Homer’s most celebrated works, A Fair Wind received wide acclaim when it was first exhibited in 1876, and was chosen by the U.S. Postal Service in 1962 for a commemorative postage stamp honoring the artist. This seascape touches upon a favorite theme of his, the struggles of man against powerful natural forces. Here the light sail boat is returning home with the day’s catch and a seemingly relaxed crew, unbothered or perhaps accustomed to the choppy waters. Unlike some of his later seascapes, this has a warm feel and more optimistic message,* perhaps meant to make a statement about the future of the young country following the uncertain and dangerous years of the Civil War.

This painting is a gift of the W. L. and May T. Mellon Foundation to the National Gallery of Art, Washington, DC.

* Homer included a traditional symbol of hope in this painting. Can you guess what it is? To find out, visit Aldrich.com/acta462
To efficiently synthesize peptides and peptidomimetics

Benzotriazole amino acids, or aminoacyl benzotriazolides, are versatile and efficient acylating reagents for synthesizing peptides and peptidomimetics. This methodology provides solid- and solution-phase techniques for accessing complex peptides and peptide conjugates and has been effective in many applications including:

- Polypeptidal benzotriazolides¹
- Peptidomimetics, such as aminoxypeptides², depsipeptides³ and heterocyclic peptidomimetics⁴
- Tagged peptides with fluorescent dyes as well as other labels⁵,⁶
- N-, O-, S-, and C-linked peptide conjugates⁶

References:
Keywords. benzotriazole; peptide synthesis; peptidomimetics; conjugates; methodology; coupling reagent.

Abstract. N-(Protected α-aminoacyl)benzotriazoles are efficient acylating reagents that offer many advantages in the preparation of peptides and their mimetics and conjugates. Advances in methodology, made possible by these novel reagents, have given rise to solution- and solid-phase preparative techniques for generating complex peptides and peptide conjugates, which are useful in the construction of diverse libraries of building blocks for medicinal chemistry.

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1. Introduction
Azolides are compounds in which an azole residue is attached to an acyl group. It has long been known that the azole nucleus in azolides can behave as a leaving group, and this property was explored widely by Staab as early as 1960. Katritzky and co-workers have reported that, of the azoles, benzotriazole is a particularly versatile synthetic auxiliary with attractive properties, easily inserted into or removed from molecules and endowing them with a range of useful reactivities. Much of this work has been summarized and, from 1985 to 2012,
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2. Synthesis of Aminoacylbenzotriazoles

Acylation benzotriazoles are versatile reagents in which the benzotriazol-1-yl (Bt) group serves as a surrogate for halogen and is easily displaced by nitrogen, sulfur, oxygen, or carbon nucleophiles. Acylbenzotriazoles are versatile reagents in which the benzotriazol-1-yl (Bt) group serves as a surrogate for halogen and is easily displaced by nitrogen, sulfur, oxygen, or carbon nucleophiles. Acylbenzotriazoles, however, offer numerous advantages over their halogen analogues since they are isolated in high yields, in crystalline form, are usually stable in air (and even to water for short periods at 20 °C), and are more reactive than the corresponding N-acylimidazolides. Thus, they can effect peptide coupling in H₂O–THF or H₂O–MeCN by using unprotected amino acids with the distinct advantage that, if the temperature is controlled, chirality within the component amino acids is preserved. Although synthesis of aminoacylbenzotriazoles requires protection of the α-amino function with either Boc, Fmoc, or Cbz (or by protonation); other common functional groups, especially OH but also SH, CONH₂, and CO₂H can be left unprotected.

2.1. From Fmoc- or Cbz-Protected Amino Groups

The first general method for the preparation of aminoacylbenzotriazoles involves the condensation of a protected amino acid with benzotriazole and thionyl chloride (1.0–1.2 equiv) in THF or DCM (Scheme 1, Part (a)). Excess benzotriazole is required to neutralize the two equivalents of HCl formed, and the method is not applicable to benzotriazolides containing the acid-sensitive Boc group. A wide range of amino acids may be used affording high yields. In addition, di-Bt derivatives are generated when aspartic acid, glutamic acid, or the S–S dimer of cysteine comprise the starting amino acids (Scheme 1, Parts (b) and (c)). The method is extremely versatile, and excess benzotriazole is easily removed by washing with either acid or base. Most significantly, chirality within the starting amino acids is retained in the majority of cases and the protected aminoacylbenzotriazoles may be stored at room temperature for many weeks.

2.2. From Boc-Protected Amino Groups

In cases where the amino acid is Boc-protected or sensitive to thionyl chloride, the sodium or trialkylammonium salt of the amino acid may be converted into the benzotriazolide by treatment with 1-(methanesulfonyl)benzotriazole (BtO₂MeS or BtMs) (Scheme 2). This clean, preparative method is enhanced in some cases by crystallization of the triazolide from water with concurrent removal of the water-soluble methanesulfonate byproduct. The thionyl chloride method can often be employed to prepare N-protected α-aminoacylbenzotriazoles (61–99%) without protection of potentially reactive side chains such as aliphatic OH (Ser, Thr), aromatic OH (Tyr), thiol SH (Cys), indole NH (Trp), and amide NH (Asn or Gln). There are, however, amino acids (e.g., His, Glu, Lys, and Asp) with side chains that do require protection (e.g., with Ts, Bn, or Cbz groups) in order to generate good yields of the benzotriazolides by reaction with either BtH–SOCl₂ or BtMs.²

3. Synthesis of Oligopeptidyl Benzotriazolides

All of the methods employed to prepare Fmoc-, Cbz-, and Boc-protected aminoacylbenzotriazoles may also be used to prepare N-protected benzotriazolides of dipeptides. Likewise, N-protected tri- through hexapeptides may be converted into the corresponding benzotriazolides (eq 1). Each benzotriazolide may then couple with amino acids or peptides to form N-protected tetra- through heptapeptides (vide infra).

4. Application to the Synthesis of Peptides

4.1. Natural Peptides and Isopeptides

A wide range of amino acids including many of those with additional, unprotected functional groups (Ser, Tyr, Cys, Trp, Pro, Asp, Glu, Lys, and Arg) coupled with N-protected aminoacylbenzotriazoles in aqueous acetonitrile (MeCN–H₂O, 7:3) at 20 °C to produce dipeptides in 47–98% yields (eq 2). Enantiopure dipeptides (L,L and D,D)
are obtained in high purity (>99% in most cases) without the use of chromatography, thus highlighting the significant utility of the method. However, protection of a carboxylic acid function as its benzyl ester is advantageous in some instances.

The synthesis of tripeptides is achieved by either a fragment-coupling procedure\(^{11,12,16}\) or by stepwise coupling.\(^{12,15}\) In the former, N-protected dipeptides are converted into their benzotriazole derivatives at –10 °C (in order to avoid racemization), which are then coupled with amino acids to form tripeptides (Scheme 3).\(^{15,18,19}\) Tri- and tetraptptides are similarly prepared in good yields (74–94%) by a stepwise procedure, but usually at a lower temperature (–10 °C) again to prevent racemization.\(^8\)

The first examples of penta-, hexa-, and heptapeptides prepared by the Bt technology were generated using microwave-assisted, solid-phase peptide synthesis (SPPS). In this technique, N-protected α-aminoacyl benzotriazoles were employed to attach Fmoc-protected α-aminoacyl groups to a Rink resin, which was then utilized for the synthesis of di- to heptapeptides in 20–68% yields.\(^{18,20,21}\) In contrast, amino acids are important in peptide and medicinal chemistry. Likewise, N-substituted peptides are important since they are constituents of cyclosporins\(^{26}\) and exhibit antibiotic,\(^{27}\) anticancer,\(^{28}\) and antiviral\(^{29}\) activities. Benzotriazole technology has proved valuable in the synthesis of hindered dipeptides from either N-protected Aib benzotriazoles and amino acids (Scheme 4, Part (a)) or C-terminus Aib dipeptides from N-protected aminoacylbenzotriazoles (Scheme 4, Part (b)) in isolated yields of 61–92%.\(^{11}\) This reaction has been applied to amino acids (or small peptides) containing free OH, SH, or indole NH groups, and proceeds with no detectable racemization (eq 3);\(^{11}\) it applies equally well to the synthesis of isopeptides.\(^{24}\)

**4.2. Difficult-to-Prepare Peptide Sequences**

Peptaibols, a group of antibiotics isolated from soil fungi, contain hindered amino acids such as 2-methylalanine (Aib), 2-ethylalanine, and 2,2-diethylglycine and, hence, α-substituted and α,α-disubstituted amino acids are important in antibiotic and medicinal chemistry.\(^{25}\) Likewise, N-substituted peptides are important since they are constituents of cyclosporins\(^{26}\) and exhibit antibiotic,\(^{27}\) anticancer,\(^{28}\) and antiviral\(^{29}\) activities. Benzotriazole technology has proved valuable in the synthesis of hindered dipeptides from either N-protected Aib benzotriazoles and amino acids (Scheme 4, Part (a)) or C-terminus Aib dipeptides from N-protected aminoacylbenzotriazoles (Scheme 4, Part (b)) in isolated yields of 67–92%.\(^{17}\)

It is well known that certain peptide sequences, particularly those containing valine (e.g., H-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-NH₂), are difficult to prepare, and the classical procedures are often characterized by low yields, aggregation, and β-sheet formation leading to racemization. The stepwise SPPS synthesis of difficult peptides utilizing N-protected aminocarbonylbenzotriazoles and microwave acceleration has been shown to facilitate amide-bond formation (22–37% yields, 89 to >99% purities) and to reduce aggregation.\(^{31}\)

**Scheme 3. Preparation of Tripeptides by Fragment Coupling** (Ref. 15,18,19)

**Scheme 4. Peptide Sequences with Sterically Hindered Amino Acid Residues from N-(Cbz α-aminoacyl)benzotriazoles.** (Ref. 17)
4.3 Cyclic Dipeptides (2,5-Diketopiperazines) and Tripeptides

Solution- and solid-phase (Scheme 5, Part (a)) Staudinger-type cyclizations afford efficient routes to hetero-2,5-diketopiperazines from protected dipeptide thioesters under microwave irradiation. However, attempts to synthesize cyclic tripeptides by this method resulted in the unprecedented cleavage of an amide group rather than a thioester to form 2,5-diketopiperazines again (Scheme 5, Part (b)), an observation that highlights the stability of a six-membered ring over its nine-membered analogue. Seven- and eight-membered-ring cyclic dipeptides can, however, be prepared in moderate-to-good yields by a Staudinger-type ring closure of a series of azido dipeptide thioesters (Scheme 5, Part (c)). The work was extended to the solution-phase synthesis of a ten-membered-ring cyclic tripeptide in 48% yield (Scheme 6).

5. Synthesis of Peptidomimetics

Peptidomimetics are small, protein-like molecules designed to mimic natural peptides by replacement of an amide bond or other element of the natural peptide. Clinical applications of bioactive natural peptides, for instance as hormones or enzyme inhibitors, have been limited by their susceptibility to rapid hydrolysis by peptidases. The corresponding peptidomimetics are not subject to this limitation, and, consequently, have been designed to exhibit high affinity for specific receptors, good metabolic stability toward endogenous proteases, greater oral bioavailability, and longer duration of action. To meet the need for good synthetic approaches to these peptidomimetics, flexible, high-yield, enantiospecific benzotriazole-mediated synthetic routes to six different structural types of peptidomimetics have been developed. These syntheses employ microwave-assisted benzotriazole acylation as the key step.

5.1 Aminoxypeptides

α-Aminoxo acids [RCH(ONH₂)CO₂H] are peptidomimetics that resist enzymatic degradation. Peptidomimetics as a class are of interest as bioisosteric α-amino acids and as analogues of β-amino acids. They have been used to prepare aminoxypeptides, α-aminoxy-α-hybrid dipeptides, and α-aminoxy-α,α-hybrid tripeptides from unprotected amino acids. This methodology has been extended to other aminoxoy-hybrid dipeptides and tripeptides starting from protected aminoxacyl benzotriazolides (Scheme 7).

5.2 Depsipeptides

Depsipeptides contain both amino acid and hydroxy acid units with amide and/or ester bonds. Natural depsipeptides exhibit antifungal, antimicrobial, and anti-inflammatory activities, and certain depsipeptides have been used in cancer treatment. A comparative study of standard coupling agents used to produce depsipeptides revealed variable yields and often long coupling times. N-Cbz(depsidipeptidoyl)benzotriazoles were found to be useful for coupling with amino acids (N-acylation)

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**Scheme 5.** Attempted Syntheses of Cyclic Tripeptides, Leading Instead to Cyclic Dipeptides (2,5-Diketopiperazines). (Ref. 30,31)

**Scheme 6.** Solution-Phase Synthesis of a Ten-Membered-Ring Cyclic Tripeptide. (Ref. 31)

**Scheme 7.** Preparation of Aminoxy and Other Peptides from α-Aminoxy Benzotriazolides. (Ref. 38)
and α-hydroxy acids (O-acylation) to give depsidi- and depsitripeptides in good yields under mild conditions (Scheme 8). This approach was applied to the preparation of unprotected depsidipeptides, which were converted into unprotected depsitripeptides.

5.3. Azapeptides
Azapeptides are peptidomimetics in which the α-CH group of one or more amino acid residues is replaced by a nitrogen atom. They are of interest for the generation of receptor ligands, enzyme inhibitors, and clinically approved drugs, and those with electrophilic moieties act as inhibitors of cysteine proteases. N-(N-Pg-α-Azadipeptidoyl)-benzotriazoles have been prepared from amino acid esters in four steps and 48–77% overall yields and utilized for the synthesis of N-Pg-azatripeptides, N-Pg-azatetrapeptides, and hybrid azapeptides (Scheme 9). This methodology proved valuable for the insertion of an aza-amino acid unit into an azatripeptide chain for the synthesis of the previously unknown aza-analogues of the endogenous opioid peptide neurotransmitter Leu-enkephalin, found in animals and humans.

5.4. Hydrazinopeptides
The replacement of an α-amino acid unit by a β-amino acid unit is a well-known strategy in the search for pharmacologically active peptides, and α-hydroxy acids (O-acylation) to give depsidi- and depsitripeptides in good yields under mild conditions (Scheme 8). This approach was applied to the preparation of unprotected depsidipeptides, which were converted into unprotected depsitripeptides.

![Scheme 8](image_url)

Scheme 8. Depsitripeptides from Cbz(depsidipeptidoyl)benzotriazoles. (Ref. 41)

![Scheme 9](image_url)

Scheme 9. Preparation of Azapeptides from N-(N-Pg-α-Azadipeptidoyl)benzotriazoles. (Ref. 45)
and replacement of the C\(^+\) and/or the C\(^-\) atom in such β-amino acid building blocks by a hetero atom offers an attractive extension of the β-peptide concept.\(^{47}\)

An alternate pathway to chirally pure α-hydrazino acids\(^{48}\) is based on microwave irradiation during the conversion of α-bromo acids into α-hydrazino acids by hydrazine hydrate. The corresponding benzotriazoles afford hydrazine hybrid peptides (Scheme 10).\(^{49}\)

5.5. *Heterocyclic Peptidomimetics*

1,2,4-Triazoles have been employed for the bioisosteric replacement of the amide bond,\(^{50}\) since 1,2,4-triazoles exhibit a wide range of antifungal and antibacterial activities.\(^{51}\) 3,5-Diamino-1,2,4-triazole has been coupled to di- and tripeptides at either ring or exocyclic nitrogens, using the benzotriazole methodology, to give potential building blocks for the preparation of peptidomimetics (Scheme 11).\(^{52}\)

5.6. *Cyclic Peptidomimetics*

In 2009, the benzotriazole methodology was extended to achieve cysteine S-acylation under mild conditions.\(^{53}\) This has now been employed to couple an N-acylbenzotriazole with cysteine to give a bis(N-acylcysteine), which, upon treatment with another equivalent of N-acetylbenzotriazole, affords cyclic peptide mimetics in 64–72% yields (Scheme 12).\(^{54}\)

6. *Synthesis of Tagged Peptides and Peptidomimetics*

6.1. *Fluorescent Labels*

Fluorescent labeling of biological systems is of great importance. There is also increasing interest in establishing methods for the incorporation of non-natural amino acids into proteins without suppression of binding ability.\(^{55}\)

6.1.1. Coumarin-Labeled Peptides and Peptidomimetics

Coumarins are constituents of many commercially important fluorescent dyes since they offer high-emission quantum yields, photostability, and good solubility in most solvents. Synthetic methods for the incorporation of coumarin into amino acids and peptides are now available. (Coumarin-3-ylcarbonyl)benzotriazoles react readily with a variety of aminoxy acids in aqueous acetonitrile at room temperature to form coumarin-labeled aminoxy acids.\(^{56}\) Coumarin-labeled amino acids have been prepared in a similar way\(^{57}\) and coumarin-labeled aminoxy hybrid peptides have been obtained in two steps from the respective benzotriazoles (Scheme 13).\(^{58}\) The 7-methoxycoumarin derivatives have quantum yields of 0.35–0.71 and may therefore be useful in peptide assays.

6.1.2. 6-Chloro-2,3-naphthalimides and Water-Soluble Fluorescent Tags

Organic fluorophores that contain a naphthalene nucleus are of interest since, on binding with a substrate, they often exhibit significant changes.
in their fluorescence spectra, quantum yields, and lifetimes in different solvents. The benzotriazole methodology offers access to new 6-chloro-2,3-naphthalimide derivatives (Scheme 14).58

6.2. Azo-Dye-Labeled Peptides
Azo-arene carboxylic acids are widely used as molecular switches in life sciences.79–81 The coupling of an azo-dye carboxylic acid to a biological moiety has, in many cases, required harsh conditions and given poor yields.82,83 In contrast, N-(4-arylazobenzoyl)benzotriazole and glycine in DMF–water at 20 °C give the coupled product in 99% yield. Similarly, other amino acids undergo this facile coupling (Scheme 15).84

7. Peptide Conjugates
Conjugates comprise peptides attached to another molecular skeleton, usually through either the carboxyl group (C-terminus) or the amino group (N-terminus) of an amino acid.

7.1. Conjugates of Sugars
Numerous naturally occurring carbohydrate conjugates link a sugar glycosidically to an α-amino acid unit of a peptide or protein. Considerable effort has been devoted to the synthesis of N- and O-linked glycopeptide conjugates utilizing both solution- and solid-phase methodologies.65–69 The benzotriazole methodology is advantageous for the solution-phase synthesis of chirally pure O-(α-aminoacyl)-70 and N-(α-aminoacyl)sugar conjugates.71 A typical procedure utilizes DMAP catalysis and microwave irradiation to give 82–92% yields of O- or N-coupled products (Scheme 16, Part (a)).72 The same benzotriazole-based method also provides a convenient and efficient route to Cbz-protected tri- and tetrapeptide conjugates with sugars (Scheme 16, Part (b)).72

7.2. Conjugates of Heterocycles
(α-Aminoacyl)amino-substituted heterocycles are of considerable importance as synthetic intermediates (e.g., for endomorphin-2 (EM-2) analogues),73 and because of their diverse biological activity (e.g., as inhibitors of bacterial RND efflux pump74–76 and of tumor necrosis factor-α converting enzyme (TACE) GW 333377). Until recently, only a few reports had described the preparation of α-aminoacyl conjugates

Scheme 13. Preparation of Coumarin-Labeled Aminoxy Hybrid Peptides. (Ref. 56)

Scheme 14. Preparation of 6-Chloro-2,3-naphthalimide and Water-Soluble Fluorescent Tags. (Ref. 58)

Scheme 15. Preparation of Azo-Dye-Labeled Amino Acids. (Ref. 64)

Scheme 16. Examples of (a) (α-Aminoacyl)sugar Conjugate and (b) Tetrapeptide Sugar Conjugate Synthesis. (Ref. 71,72)
of heterocycles by C- or N-acylation of heterocycles with amino acids. Kraus and co-workers\textsuperscript{39} reported that “N-acylation of weakly nucleophilic heterocyclic amines by protected amino acid is not a straightforward reaction which could be achieved under any standard coupling conditions”.

N-Aminoacyl benzotriazolides now enable the synthesis of chirally pure α-aminoacyl conjugates of heterocycles even from weakly nucleophilic heterocyclic amines by N-acylation in DMF under microwave irradiation.\textsuperscript{79} The analogous C-acylation of lithiated methylpyridine or methylquinolone in THF at –20 °C for 1–3 h with N-aminoacyl benzotriazolides gave the corresponding α-aminoacyl C-linked conjugates (Scheme 17).\textsuperscript{80} The convenient and efficient formation ofCbz-protected tri- (e.g., Z-1-Val-1-Phe-Gly-NH-(2-Pyr)) and tetrapeptide (e.g., Z-1-Phe-Gly-1-Leu-Gly-NH-(N-methylpiperazine)) conjugates with heterocyclic nuclei of biological importance succeeds under a variety of reaction conditions.\textsuperscript{72,80}

**7.3. Conjugates of Vitamins**
Recent approaches to enhance vitamin uptake include covalently bonding the vitamins to peptides. Water-soluble vitamins are usually transported into cells by potocytosis.\textsuperscript{81} Zhang and McCormick\textsuperscript{82} have proposed the delivery of vitamin B6 by receptor-mediated transport in eukaryotic cells with the amine of a peptide–vitamin conjugate, which facilitates the cell uptake of peptide and transport into the cytosol.\textsuperscript{82,83} The benzotriazole methodology enables the efficient coupling of amino acids and peptides to vitamins, again utilizing microwave irradiation to shorten reaction times and minimize epimerization.\textsuperscript{84}

Niacin and biotin benzotriazolides couple with free amino acids, dipeptides, and tripeptides (NET\textsubscript{3}, MeCN–H\textsubscript{2}O, µw, 70 °C) to give the corresponding bioconjugates 1 and 2 in yields of 43–81% and 35–82%, respectively (Figure 1).\textsuperscript{84} Amino acid and peptide conjugates of vitamin D3 (Figure 1, 3) are obtained by O-acylation of cholecalciferol withCbz-protected acylbenzotriazoles in the presence of DMAP in THF and under microwave irradiation (50 W, 70 °C) for 1–2 h.\textsuperscript{84} Amino acid and peptide conjugates of α-tocopherol (Figure 1, 4) are formed by O-acylation of α-tocopherol withCbz-protected acylbenzotriazoles under microwave irradiation (20 W, 50 °C, 0.3 h) in anhydrous DMF in the presence of potassium carbonate.\textsuperscript{84}

**7.4. Conjugates of Pharmaceuticals**
Improving the efficacy of therapeutics, particularly through enhanced local delivery to a diseased cell, is an important topic in pharmaceutical R&D. These techniques are helping to solve traditional drug delivery challenges, such as poor cellular uptake and/or non-specific toxicity.

The utilization of prodrugs that temporarily mask the acidic groups of NSAIDs may increase uptake and reduce irritation caused by direct contact.\textsuperscript{85,86} Indomethacin, diclofenac,\textsuperscript{87} ibuprofen, and naproxen,\textsuperscript{87,88} are among well-known NSAIDs that have been modified by linking to natural amino acids, as reported by numerous investigators. We have recently shown that ibuprofen and naproxen bioconjugates are readily

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**Scheme 17. α-Aminoacyl Conjugates of Amino-Substituted Heterocycles. (Ref. 79,80)**

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**Figure 1. Peptide Conjugates of Vitamins Prepared by the Benzotriazole Methodology. (Ref. 84)**

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**Scheme 18. Preparation of Peptide Conjugates of Pharmaceuticals. (Ref. 92,100)**
prepared by reacting NSAID benzotriazolides with amino acids and dipeptides in aqueous acetonitrile–triethylamine at 20 °C (Scheme 18, Part (a)).

Prodrugs formed by linking quinolone acids with amino acid esters are more lipophilic than the parent drugs,\textsuperscript{93,94} and show enhanced in vivo antibacterial properties\textsuperscript{95,96} with pronounced therapeutic effects against Pseudomonas aeruginosa,\textsuperscript{97} Escherichia coli,\textsuperscript{98} Staphylococcus aureus,\textsuperscript{99} and Salmonella typhimurium.\textsuperscript{100} Additional wide-ranging biological activities include anti-allergic,\textsuperscript{101} antihypertensive,\textsuperscript{102} bronchodilator,\textsuperscript{102} and binding to bovine serum albumin.\textsuperscript{92} Amino acid conjugates of quinolone antibiotics were prepared in 39–88% yields by coupling free amino acids with benzotriazole-activated oxolinic acid, nalidixic acid, cinoxacin, or flumequine (Scheme 18, Part (b)).\textsuperscript{100,101}

7.5. Conjugates of Plant Hormones
Indole-3-acetic acid (IAA), an indispensable plant hormone (auxin), also occurs naturally as “conjugates” linked to amino acids.\textsuperscript{103} Gene expression and cell division, elongation, and differentiation in plant tissue are all regulated by these indole-3-acetic acid auxins. Another endogenous plant hormone, indole-3-propionic acid (IPA), and its amino acid conjugates interact with serum albumin.\textsuperscript{104} Plant hormone benzotriazolides—prepared in 86–90% yields by standard treatment of indole-3-acetic acid and indole-3-propionic acid—coupled with diverse amino acids to give conjugates in 40–70% yields (Scheme 19).\textsuperscript{104}

7.6. Aminooxy Acid Conjugates of Peptidomimetics and Hydrazino Acid Conjugates
The benzotriazole methodology enables convenient and efficient synthesis of novel aminooxy acid containing conjugates even at hindered nucleophilic centers in steroids, terpenes, sugars, and nucleosides.\textsuperscript{105} The benzotriazolides of α-hydrazino acids were used to generate hydrazine acid conjugates through N-, O-, S- and C-acylations in good yields (49–88%).\textsuperscript{49}

8. Differential N-, O-, and S-Acylations
Isopeptides are used for the detection and capture of ubiquitinating and de-ubiquitinating enzymes using activity-based protein profiling (ABPP).\textsuperscript{106} The presence of an additional amino group in N-, O-, or S-acyl isopeptides generally increases their hydrophobicity, which is advantageous in effecting their purification by HPLC. The native peptides can then be generated from the corresponding N-, O-, or S-acyl isopeptides via an N to N,\textsuperscript{107} O to N,\textsuperscript{108} or S to N\textsuperscript{6,109,110} intramolecular acyl migration reaction. These findings have led to the synthesis of peptides containing difficult sequences.\textsuperscript{111}

8.1. S- and O-Acyl Isopeptides
S-Acyl isopeptides are usually less likely to aggregate in solution and therefore are easier to synthesize and purify relative to the corresponding native peptides. S-Acylation of protected cysteine-containing peptides was carried out in the presence of KHCO\textsubscript{3} at 20 °C in acetonitrile (Schemes 20, Part (a)).\textsuperscript{6,109,110} Selective S-acylation of cysteine was also carried out in acetonitrile–water mixture in the absence of base.

O-Acylation of protected serine and protected threonine with various N-Pg-(α-aminoacyl)benzotriazoles in the presence of disopropylethylamine in acetonitrile at 20°C for 12 h gave O-acylsorine and O-acylsithreonine dipeptides without racemization (Scheme 20, Part (b)). O-Acylisotyrosine tripeptides were also prepared in yields of 74–91% by reacting tyrosine-containing protected dipeptides with N-Pg-(α-aminoacyl)benzotriazole in the presence of DBU in acetonitrile at 20 °C for 12 h.\textsuperscript{24}
8.2. Ligation at a Distance

8.2.1. S to N Acyl Migration

The S to N acyl migration through various cyclic transition states was investigated by carrying out the ligation experiment on mono-isopeptides under microwave irradiation (50 W) at 50 °C for 1–3 h using 1 M NaH₂PO₄-NaHPO₄ phosphate buffer to maintain pH 7.3 (eq 4). The rates and yields of long-range S to N acyl transfers were found to depend significantly on the size of the macrocyclic transition state (TS), with the rates qualitatively following the TS ring-size trend 5 > 10 > 11 > 14, 16, 17 > 12 > 13, 15, 19 > 18 >>> 9 > 8.6,109,110

8.2.2. O to N Acyl Migration

The chemical ligation of serine isopeptide through O to N acyl transfer via 8- and 11-membered-ring transition states occurs without the use of an auxiliary group (eq 5).108 In contrast, threonine isopeptide failed to undergo acyl migration even under more basic conditions and longer reaction times.121 Chemical ligation studies of tyrosine isopeptides (µw, 50 W, 50 °C, 3 h, using 1 M phosphate buffer and DMF–piperidine) via 12- to 19-membered-ring cyclic transition states showed that intramolecular O to N acyl transfer occurs with 12- to 14-membered-ring TS’s under basic conditions and with 15- to 19-membered-ring TS’s in aqueous media.108

8.2.3. N to N Acyl Migration

Tryptophan isopeptides with α-, β-, or γ-amino acid units were synthesized, and the acyl migration from the indole nitrogen to the terminal NH₂ was studied under microwave irradiation. Intramolecular acyl transfer through 10-, 11-, and 12-membered-ring transition states was favored over that through a 7-membered-ring TS, and acyl migration occurred more readily in basic, nonaqueous media relative to aqueous buffered conditions (eq 6).107

9. Conclusions and Comparison with Alternative Methodologies

9.1. Carboxyl Group Activation by Isolation of an Intermediate

The most obvious method for activating the carboxyl group of an amino acid for peptide bond formation at room temperature or below is by forming the corresponding acid chloride.111 This type of activation has been carried out with chlorinating reagents such as pivaloyl chloride,114 phthaloyl dichloride,115 thionyl chloride,116 and oxalyl chloride.117 However, an amino acid chloride bearing an acid labile protecting group can easily racemize through the oxazolone, which limits the application of acid chlorides despite their high reactivity and low cost. Amino acid fluorides are less moisture-sensitive than acid chlorides, but the fluorinating reagents are expensive and hazardous, and the peptide-forming reactions require purification by chromatography.118

The acyl azide method of peptide coupling was developed about 100 years ago. It is not attractive for routine use because it involves four distinct steps, including two stable intermediates that require purification.119 An additional side reaction that occurs at higher temperature is rearrangement of the acyl azide into the alkyl isocyanate, which can react with nucleophiles to yield a peptide urea that is difficult to remove from the product.120 Recently, El-Faham and Albericio published a review on the use of different peptide coupling reagents including benzotriazoles.121

9.2. Carboxyl Group Activation without Isolation of an Intermediate

Besides acyl halides and acyl azides, other methods for peptide coupling include the use of various reagents, where the intermediates are not isolated. A traditional approach to form peptide bonds is the carbodiimide method, using dicyclohexylcarbodiimide (DCC). However, despite being compatible with solid-phase synthesis (SPS) that uses tert-butoxycarbonyl (Boc) chemistry, DCC is not compatible with the fluorenylmethoxycarbonyl (Fmoc) group. When DCC is utilized in solution, traces of the byproduct, DCU, are difficult to remove, even after passage through a chromatography column. Thus, DCC has been replaced by reagents such as diisopropycarbodiimide (DIC), N-ethyl-N’-(3-dimethylaminopropyl)carbodiimide (EDC), and N-cyclohexyl-N’-isopropylcarbodiimide (CIC), all of which are relatively soluble in DCM and therefore more suitable for Fmoc-SPS. Additives such as 1-hydroxybenzotriazole (HOBT), 1-hydroxy-7-azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), and others increase the efficiency of carbodiimide-mediated reactions and decrease the degree of racemization.122

Phosphonium reagents were developed to avoid racemization and side reactions that can occur with carbodiimide reagents. Coste et al. introduced chloro- and bromotris(dimethylamino)phosphonium hexafluorophosphate (ClPO₄ and BrO₄) as peptide-coupling reagents with noticeable racemization in the Young test.123 HOBT may be used in combination with (benzotriazol-1-yl)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) to suppress racemization. However, the intermediates formed in the coupling reaction are highly unstable and BOP is reported to be highly carcinogenic.124

The search for better coupling reagents based on DCC led to carbonyl diimidazole (CDI).125 Rapoport introduced the imidazolium...
reagent 1,10-carbonylbis(3-methylimidazolium) triflate (CBMIT) by bis-methylating CDI with methyl triflate. This reagent showed no sign of racemizing the amino acid residues in the presence of CuCl₂ or Cu(Ott)₂. However, CMBT is moisture-sensitive and, due to its polarity, the method is restricted to polar solvents such as nitromethane. The reactivity of these reagents also increases in the presence of additives like HOAc, HOBT, or DMAP.

Aminium or uronium reagents such as N-[[1H-benzotriazol-1-yl][1,2,3-triazolo[4,5-
1-yl] (dimethylamino)methylene]-N-methylthianaminium hexafluorophosphonate N-oxide (HBTU) and N-[[dimethylamino]-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylthiamaminium hexafluorophosphonate N-oxide (HATU) all react directly with the amine moiety of the amino acid residue to give a guanidine side product, which terminates the peptide chain. Benzotriazole offers an extremely useful alternative to all the above methods by affording a versatile range of coupling procedures under the mild conditions required to avoid racemization.

10. References

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Aminoacyl Benzotriazolides: Versatile Reagents for the Preparation of Peptides and Their Mimetics and Conjugates

Siva S. Panda, C. Dennis Hall, Eric Scriven, and Alan R. Katritzky*


About the Authors

Siva S. Panda was born in Orissa, India, and received his bachelor’s degree (B.Pharm.) in 2002 from the Roland Institute of Pharmaceutical Sciences, Berhampur, India, and his master’s degree (M.Pharm.) in 2005 from Manipal College of Pharmaceutical Sciences, Manipal, India. He then joined the Dabur Research Foundation, Sahibabad, India, as a research scientist for a period of one year and worked on the synthesis of Mitoxantrone, an anticancer drug. Siva obtained his Ph.D. degree in synthetic organic chemistry in 2010 under the supervision of Prof. Subhash C. Jain at the University of Delhi, Delhi, India. He is currently working as a postdoctoral associate with Prof. Alan R. Katritzky at the Center for Heterocyclic Compounds, University of Florida, Gainesville, FL, where his research involves the synthesis of novel peptides, peptide bioconjugates, peptidomimetics in solution, and ligation studies of various cyclic transition states in S to N, N to N, and O to N acyl migrations.

C. Dennis Hall retired from his academic position at King’s College, London, in 1999, and joined Prof. Katritzky’s research group at the University of Florida, where he serves as a group leader, administrator for the online journal ARKIVOC, and co-organizer of the Florida Heterocyclic and Synthetic Conferences (Flohet). Since joining Katritzky’s group, he has co-authored some 40 papers in the fields of heterocyclic chemistry, QSAR, insect control, and synthetic ion channels.

Eric Scriven is a native of Wales, U.K. After working at BISRA and Esso Ltd, he attended the University of Salford and graduated in 1965 with a degree in chemistry. He obtained his M.Sc. Degree from the University of Guelph, and his Ph.D. degree in 1969 from the University of East Anglia (with Prof. Katritzky). After postdoctoral years at the University of Alabama and University College, London, he was appointed Lecturer in Organic Chemistry at the University of Salford. There, his research interests centered on the reactivity of azides and nitrenes. He joined Reilly Industries in 1979, where he served as Director of R&D from 1991 to 2003. He is currently at the University of Florida. He has edited two books: Azides and Nitrenes: Reactivity and Utility (1984) and Pyridines: from Lab to Production (2013). He and Professor H. Suschitzky were founding editors of Progress in Heterocyclic Chemistry that has been published annually since 1989. He collaborated with Professors Katritzky and Rees as Editors-in-Chief of Comprehensive Heterocyclic Chemistry II (1996), and with Professors Katritzky, Ramsden, and Taylor on the third edition of the work. Currently, he is Publishing Editor of ARKIVOC, an online journal of organic chemistry free to readers and authors.

Alan R. Katritzky was educated at Oxford and Cambridge (Lecturer and Founder Fellow of Churchill College). Founder Dean of the School of Chemical Sciences at East Anglia from 1962, he transferred in 1980 as inaugural Kenan Professor to the University of Florida. His research in heterocyclic chemistry has covered inter alia N-oxides, benzotriazole methodology, electrophilic and nucleophilic substitutions, computational QSAR relationships, and peptide chemistry. He holds 14 honorary doctorates from 10 Eurasian countries and associate or foreign memberships of five national academies. He is Cavaliere Ufficiale (Italy) and Honorary Fellow of St. Catherine’s College, Oxford, and of the Polish and Italian Chemical Societies. Over 1,000 graduate students and postdocs have trained in his group. He created the not-for-profit Arkat USA, Inc., which organizes the Flohet Conferences and publishes the open-access journal ARKIVOC. Contributions to the secondary literature include editing Comprehensive Heterocyclic Chemistry (40 volumes in 3 editions), Advances in Heterocyclic Chemistry (106 volumes), Handbook of Heterocyclic Chemistry (3rd edition, 2010), and Heterocycles in Life and Society (2nd edition, 2011).
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91% yield

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\[
\text{Br}\text{O} \quad \text{WImC (2 equiv)} \quad \text{MeCN} \quad 80^\circ\text{C}, 24 \text{ h} \quad \text{OMe}
\]

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References:
Recent Advances in the Prins Cyclization

Sandro José Greco,* Rodolfo Goetze Fiorot, Valdemar Lacerda, Jr., and Reginaldo Bezerra dos Santos

Department of Chemistry
Federal University of Espírito Santo
Avenida Fernando Ferrari, 514
Goiabeiras, Vitória, ES 29075-910, Brasil
Email: sandro.greco@ufes.br

Abstract. The Prins reaction is often a key step in the synthesis of various heterocyclic rings that are important structural components of many classes of biologically active compounds and natural products. This review presents and discusses recent significant applications of this important reaction, and offers insight into its mechanism and regio- and stereochemical outcomes.

Keywords. Prins reaction; tetrahydropyrans; dihydropyrans; tetrahydrofurans; dioxanes; piperidines; azepines; lactones; spiro compounds; macrocycles; natural products.

1. Introduction
The Prins reaction is often related to the Kriewitz reaction, an example of which is the reaction of β-pinene with paraformaldehyde to produce an unsaturated alcohol through a thermal ene rearrangement (Scheme 1, Part (a)).1–3 When the reaction between an alkene and formaldehyde is conducted in the presence of an acid catalyst—such as the reaction of styrene with paraformaldehyde in the presence of aqueous sulfuric acid to give diol 1 (Scheme 1, Part (b))—it is called the Prins reaction. Numerous protic and Lewis acids are known to catalyze the reaction, and excellent reviews have been published on the early work.1–3 The products generally obtained in this condensation are formed as complex mixtures of 1,3-dioxanes, 1,3-glycols, tetrahydropyrans, and allylic and homoallylic alcohols, with the composition of the mixture being dependent on the specific experimental conditions employed (Scheme 1, Part (c)). In the presence of water, the intermediate carbocation leads to the formation of 1,3-glycols and 1,3-dioxanes, while 3-alkyl-4-halotetrahydropyrans are obtained through the intermediacy of the homoallylic alcohols.

Recent advances in the Prins cyclization play a key role in the synthesis of such important product classes as dihydrofurans, dihydropyrans, piperidines, and oxabicyclo and spiro compounds. This review presents a survey and a discussion of pertinent and interesting recent developments relating to the stereochemical course and mechanism of the Prins reaction and to its advantageous application in organic synthesis.

2. Mechanistic Considerations
The Prins cyclization involves a homoallylic alcohol, an aldehyde, and a Lewis acid. The latter acts as catalyst and, depending on experimental conditions, it can also serve as a source of a nucleophilic anion. In the presently accepted mechanism, the reaction is initiated by complexation of the Lewis acid with the aldehyde, which activates the carbonyl carbon toward attack by the hydroxyl group of the alcohol, generating the hemiacetal intermediate 2. Loss of the Lewis acid fragment from
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Sandro José Greco,* Rodolfo Goetze Fiorot, Valdemar Lacerda, Jr., and Reginaldo Bezerra dos Santos

(a) The Kriewitz Reaction

(b) The Prins Reaction

(c) Product Distribution in the Prins Reaction Is Dependent on Reaction Conditions

Scheme 1. Condensation Reactions of Olefins with Paraformaldehyde and the Dependence of Product Distribution on the Reaction Conditions. (Ref. 1–3)

Scheme 2. General Mechanism of the Prins Cyclization. (Ref. 2)

Scheme 3. Regioselectivity in the Prins Cyclization. (Ref. 4)

the hemiacetal forms the key oxonium ion intermediate, 3, which assumes the more stable chair conformation in which the substituents are pseudoaxial. Subsequent 6-endo cyclization of 3 selectively leads to secondary tetrahydropyranyl carbocation 4, which captures the halide to give rise to the 2,4,6-trisubstituted tetrahydropyran product (Scheme 2). 5

2.1. Regioselectivity for 5- vs 6-Membered Rings
When the double bond geometry in the homoallylic alcohol is switched from E to Z, tetrahydrofurans can be formed in competition with tetrahydropyrans. This regioselectivity can be studied by examining the stereochemistry of intermediates present in the accepted mechanism of this reaction. Under the Prins cyclization conditions, the Z homoallylic alcohol reacts with the activated aldehyde to give rise to oxonium ion 3. Two competing transition states can then be formed from 3: six-membered-ring transition state 6 has a 1,3-diaxial interaction between H and the substituent R1, while five-membered-ring transition state 8 has greater torsional and angular strains. When the R1 substituent is sufficiently large, an increase in the activation barrier of the process results, which slows the formation of tetrahydrofuran product 7 in favor of tetrahydropyran product 9 (Scheme 3). 6

2.2. Stereoselectivity of Nucleophile Capture at C4 of the Tetrahydropyran Ring
2.2.1. Alder’s Model: Equatorial Selectivity
On the basis of theoretical calculations employing Density Functional Theory (DFT), Alder and co-workers concluded that the all-cis 2,4,6-trisubstituted product of the Prins cyclization is favored by stabilization of the cationic intermediate 10 through hyperconjugation. When the hydrogen attached to the carbocation center is pseudoaxial, the empty p orbital of the positively charged carbon overlaps more efficiently with the coplanar σC–C and σ* C–C orbitals and with the orbital of the nonbonding electrons of oxygen. Nucleophilic attack thus occurs from the exo face (convex), leading to the 2,4,6-trisubstituted tetrahydropyran product with all three substituents in equatorial positions (eq 1). 5

2.2.2. Rychnovsky’s Model: Axial Selectivity
Rychnovsky investigated the capture of bromide and iodide at C4 of 10 by reacting α-acetoxy ester 11 with TMSBr, AcBr, HBr, or TMSI and lutidine in dichloromethane. High axial stereoselectivity at C4 was observed for the resulting Prins cyclization product 16 (Scheme 4). 6 In contrast, when SnBr2 was employed, the major product was the equatorial epimer 19. In the proposed mechanism, some Lewis acids; such as TMSBr, AcBr, and HBr; act as donors of bromide by forming the intimately associated ion pairs 14 and 15. The slightest movement (least motion pathway) in 15, results in Br– attacking C4 in the axial position (endo attack) to form 16. When SnBr2 is employed as the Lewis acid, the in situ formed [SnBr2]– in ion pair 17 is less nucleophilic than bromide, allowing separation of the ion pair by the solvent. In the resulting intermediate, 18, exo (convex) attack leads to the formation of product 19 with an equatorial bromine at C4.

2.3. Diastereoselectivity of the Prins Cyclization
Substituents at C2 and C6 of tetrahydropyrans formed by the Prins cyclization are preferentially cis. 7a Methodologies for forming the C2/C6 anti isomers are not well established. These isomers are present in some structures of natural products, such as the psymberins 7b and the apicularen. 7c Panek’s group has succeeded in synthesizing enantiomerically pure anti-2,6-dihydroxypyrans by the Prins cyclization with the aid of TMSOTf. 7d,e
Loh and co-workers investigated steric and electronic effects in the Prins cyclization of homoallylic anti-\(\text{O}-\)hydroxy esters, leading to 4-chloro-2,6-disubstituted THPs. This study demonstrated that groups with high electron density in the pseudoaxial position stabilize the oxonium ion by inductive electronic effects, and favor a transition state that forms the anti isomer, \(20\text{a};\) while steric effects favor the transition state leading to the syn isomer, \(20\text{b}.\) In both cases, equatorial attack of the nucleophile is preferred (Scheme 5).\(^8\)

### 3. Recent Synthetic Applications

Saturated six-membered-ring oxygen and sulfur heterocycles are features found in the structures of a variety of biologically important natural products such as polyether antibiotics, marine toxins, pheromones, and pharmaceutical agents. Tetrahydropyran is also the structural core of most carbohydrates, oligomers, and polymers, which play crucial roles in living organisms. It is therefore not surprising that considerable efforts have been expended toward developing facile and viable syntheses of tetrahydropryan-containing compounds.

#### 3.1. Substituted 1,3-Dioxanes

When olefins are condensed with aldehydes in aqueous solutions of mineral acid catalysts, alkylidioxanes (cyclic formals or acetals of 1,3-butadienol)s and 1,3-butadienols are formed. The distribution of these two products varies with the concentration of the solution of the acid catalyst and the reaction temperature. Amrute et al. studied the catalytic activity of \(\text{MoO}_3/\text{SiO}_2\) (7 wt %) in the Prins cyclization of a series of olefins with paraformaldehyde (2 equiv) in 1,2-dichloroethane at 80 °C.\(^9\) 72–90% conversions and 96–100% selectivities were observed for the corresponding 4-alkyl- and 4-phenyl-substituted 1,3-dioxane products. Du and Tian synthesized 1,3-dioxanes in moderate-to-high yields from formalin (aqueous formaldehyde), styrene derivatives, and trifluoromethanesulfonylic acid (\(\text{TiF}_3\)).\(^10\) The use of organic acid as catalyst for the Prins reaction was unprecedented. It is worth noting that this approach avoids the use of organic solvents by conducting the reaction in water, which makes it a more environmentally friendly process.

Yang and co-workers explored the use of water-stable and recyclable Brønsted acidic ionic liquids as environmentally benign catalysts for the Prins cyclization. The effectiveness of these ionic liquids was compared in the model reaction of styrene with formaldehyde at 94–96 °C, whereby \([\text{BMIM}][\text{HSO}_4]\) was found to be the most effective catalyst (eq 2).\(^11\) The 1,3-dioxane products were obtained in good yields, and the catalysts, after vacuum distillation at 80 °C, were recovered and reused in subsequent runs, thus reducing the risks to the environment by avoiding the use of organic solvents and enabling large-scale applications of the Prins cyclization.

#### 3.2. Spiro and Bicyclic Tetrahydropyrans (THPs)

Gaïs and co-workers have reported a modular asymmetric approach to spiroketal, spiroethers, and oxabicycles that employs a spiro- or bicycloannulation of \(\alpha\)-hydroxydihydropyrans. The synthesis included a stereoselective Ferrier-type O- and C-glycosidation, ring-closing metathesis, and stereoselective Prins cyclization as key steps. When \(\alpha\)-hydroxydihydropyrnan \(21\) was treated with \(\text{TiCl}_4\) in dichloromethane at \(-78^\circ\text{C}\), the regioisomeric spiro ethers \(22\) and \(23\) resulted from a Prins cyclization (eq 3).\(^12\)

Nakamura and co-workers have described a versatile method for the synthesis of 4-substituted 6-methyl-3-oxabicyclo[3.3.1]non-6-ene-1-methanol derivatives using a Prins-type cyclization reaction between aldehydes and O-protected or unprotected 4-methylcyclohexanols.\(^13\)

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**Scheme 4. Axial Selectivity in the Prins Cyclization.** (Ref. 6)

**Scheme 5. Diastereoselectivity of the Prins Cyclization.** (Ref. 8)
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3-ene-1,1-dimethanol (24). Under the optimized reaction conditions employing hafnium triflate, various aldehydes, including functionalized benzaldehydes and heteroaromatic aldehydes, afforded the cyclization products in high yields (eq 4).13 The zinc and lanthanum triflates form preferably spirodioxane 26.

3.3. Nitrogen Heterocycles via the Aza-Prins Cyclization
The Prins cyclization of homoallylic amines (the aza-Prins cyclization) takes place in a fashion similar to that of homoallylic alcohols, whereby the nonbonding electrons on the nitrogen initiate the sequence of reaction steps by attacking the electrophilic site of the aldehyde activated by an acid catalyst. The key intermediate of the aza-Prins cyclization is an iminium ion, in analogy to the oxonium ion. Piperidines are commonly found subunits in many biologically relevant molecules including alkaloids, and are attractive structural scaffolds for drug discovery.14 Subba Reddy showed that the BF$_3$•OEt$_2$ catalyzed aza-Prins reaction of benzaldehyde and N-tosyl-3-butenamine (a homoallylic amine), in the presence of anisole as solvent and nucleophile, produces the trans-2,4-diarylpiperidine in 83% yield.15,16 This is the first report of the preparation of 4-arylpiperidines via an aza-Prins–Friedel–Crafts reaction sequence.

The coupling of E- (27) and Z-3-hexene-1,6-ditosylamides with various aldehydes, including cinnamaldehyde (28) in the presence of 10 mol % Sc(OTf)$_3$ in 1,2-dichloroethane gave the corresponding trans- and cis-fused saturated pyrrolopyridines 29 and 30, respectively, in good yields by an intramolecular aza-Prins cyclization (eq 5).17 Other aromatic aldehydes such as benzaldehyde, para-anisaldehyde, and thioephene-2-carboxaldehyde were not effective substrates in the reaction. Ketones, such as cyclohexanone, failed to give the spirodiazacyclic bicyclic product. In contrast, aliphatic aldehydes; such as isovaleraldehyde (70%, trans:cis = 95:5), cyclohexanecarboxaldehyde (73%, trans:cis = 95:5), and propionaldehyde (66%); participated well in this reaction.

Camara et al. synthesized azepines fused to a naphthoquinone moiety by an intramolecular aza-Prins cyclization starting with an amino derivative, 31, of lapachol (Scheme 6).18 Products 32a and 32b were formed in 42% yield as a diastereomeric mixture, with a trans:cis ratio of about 7:3. The mechanism of C–C bond formation leading to 32a and 32b appears to resemble that of the intramolecular ene reaction between a carbonyl group and an alkene.19 The authors proposed that the formation of intermediates occurs through a Prins reaction, via nucleophilic attack of H$_2$O or MeOH at the isoprenyl double bond, possibly followed by a concerted attack onto the protonated carbonyl. The observed diastereoselectivity is possibly induced by steric hindrance of the 4-isopropyl and 3-hydroxy groups, despite the fact that the resulting seven-membered ring is conformationally less restricted than the corresponding six-membered ring. This synthetic method is important, since there are very few publications on the synthesis of such heterocyclic systems, which are of great interest in the scientific community because of their pharmacological applications.20,21

3-Azabicyclo[3.3.1]non-6-enes are structural motifs in many natural products and, with the proper choice of substituents, can serve as templates for complexity-generating transformations. Crasovan and co-workers have reported a facile synthesis of this ring system in a diastereomERICALLY pure form by an aza-Prins cyclization involving a δ,δ-unsaturated imine and an equivalent of BF$_3$•OEt$_2$ under microwave irradiation at 180 ºC for 1 h (Scheme 7).22 As in the mechanism proposed earlier by Overman for the aza-Prins cyclization employed in the total synthesis of (+)-nankakurines A and B,23 it is believed that the pair of nonbonding electrons on nitrogen participate in a regiospecific...
intramolecular deprotonation of the hydrogen vicinal to the initially formed carbocation in intermediate A.

Subba Reddy and co-workers have reported the synthesis of 2-aryl- and 2-alkyl-4-amidopiperidines in good yields and high selectivities by an aza-Prins–Ritter tandem reaction employing a slight excess of triflic acid in MeCN at 0 °C. It was observed that in the absence of triflic acid, no aza-Prins cyclization occurred even in refluxing acetonitrile. Other Brønsted acids—such as acetic acid, formic acid, and trifluoroacetic acid—were tested and, in all cases, the reaction proceeded rapidly at 0 °C; however, triflic acid provided the best conversion.

3.4. Synthesis of Furan Derivatives

Substituted dihydrofuranes (γ-butyrolactones or GBLs) are important intermediates in synthetic organic chemistry, and are commonly found as structural fragments in natural products, receptor ligands, and drug molecules. Compounds containing a GBL moiety exhibit pharmacological effects some of which are muscarinic (pilocarpine) and antimuscarinic (Kaiser lactones) activities, convulsant (picrotoxin, β-substituted GBL) and anticonvulsant (α-alkyl-substituted GBLs) activities, and the ability to modulate quorum sensing.

Gao and Canney reported a novel and concise approach for the synthesis of structurally diverse, substituted 5-(2-hydroxyethyl)-3,3-dihydrofuran-2(3H)-ones. This method relies on a modified Prins reaction that employs a catalytic amount of H3SO4 in glacial HOAc. In the proposed mechanism, acetic acid captures the initially formed oxonium ion formed after cyclization.

In analogy to the oxygen and nitrogen variants, the halo-Prins cyclization involves nucleophilic attack by halogen present in the reaction medium on the carbocation intermediate that arises from the oxonium ion formed after cyclization.

3.5. Synthesis of Halogenated Tetrahydropyrans: Halo-Prins Cyclization

In analogy to the oxygen and nitrogen variants, the halo-Prins cyclization involves nucleophilic attack by halogen present in the reaction medium on the carbocation intermediate that arises from the oxonium ion formed after cyclization.

3.5.1. Fluorinated THPs

The introduction of fluorine atoms into organic molecules alters in important ways their biological activity, solubility, hydrophobicity, metabolism, and bulk properties. However, few methods for the synthesis of fluorinated pyranyl motifs are known and, of these, the ones that employ BF3•Et2O and Et3NF•5HF as both Lewis acids and fluorine sources successfully achieve the Prins cyclization of homoallylic alcohols into fluorinated pyranyl motifs. When BF3•Et2O is utilized in stoichiometric quantities, it contributes fluoride ion to quench the intermediate carbocation, giving rise to the fluorinated products. As an example of this approach, O’Hagan and co-workers investigated the oxa- and aza-Prins reactions for the synthesis of 4-fluoropyrans and 4-fluoropiperidines starting from homoallylic alcohols and various aldehydes. The fluorinated THP products were obtained in good yields, but with only moderate diastereoselectivity. This method was extended to the aza-Prins reaction that utilizes N-tosylhomoolarylamins to generate the corresponding 4-fluoropyrrolidines.
O’Hagan’s group then investigated the Prins fluorination reactions under microwave conditions, and observed significantly reduced reaction times and higher conversions. However, there was a slight decrease in the diastereoselectivity of the reaction and, in some cases, an inversion of the diastereoselectivity. When a series of low-temperature (−20 °C) experiments were carried out in an attempt to improve the diastereoselectivity, dr increased from ~2:1 to 10:1 and yields remained good, but, not surprisingly, a significant increase in the reaction time was observed.

Prior to Loh and co-workers’ recent disclosure, all studies of the Prins fluorination reaction reported the almost exclusive formation of cis-2,6-disubstituted fluorinated di- or tetrahydropyrans. An efficient, highly diastereoselective synthesis of the trans-2,6-disubstituted counterparts—useful in the development of new pharmaceuticals—would be highly desirable. Loh’s group explored the Prins reaction of various allenic alcohols, e.g. 38, with a variety of aldehydes using different Lewis acids (LAs) and fluorine sources. Their research demonstrated that BF₃·Et₂O, acting both as an efficient Lewis acid and as a source of fluoride, gives the best results. The authors proposed a mechanism in which the Prins cyclization of the allenic alcohol takes place through a distorted chair transition state, in which a lone electron pair on the carbonyl oxygen of the ester group stabilizes the partial positive charge on the oxocarbonium carbon. This forces the carbonyl group to adopt an axial orientation, leading to the desired intermediate 40 and suppressing the generation of the undesirable intermediate 41.

In turn, intermediate 40 gives rise to the desired trans-2,6-disubstituted fluorinated dihydropyran 39, selectively (Scheme 10).

Saikia and co-workers have reported that TiF₄ can efficiently be employed for the stereoselective synthesis of substituted all-cis 4-fluorotetrahydropyran via the halo-Prins cyclization. A variety of aliphatic and aromatic aldehydes were reacted with a number of homoallylic alcohols to give good yields and high diastereoselectivities of the corresponding THPs. Moreover, acyclic and cyclic ketones were subjected to the reaction and found to be less reactive (5–6 h vs 2.5–4 h for the aldehydes), giving only moderate yields (50–70% vs 80–92% for the aldehydes). Cyclic ketones afford spiro compounds, as illustrated by the reaction of cyclohexanone, which leads to spirocyclic compound 42 in 70% yield (eq 6).

3.5.2. Chlorinated and Brominated THPs
InCl₃ has been demonstrated to be an excellent Lewis acid for the insertion of a chlorine atom at the 4 position of THPs by the Prins cyclization. For example, the InCl₃-promoted diastereoselective Prins reaction of 43 with benzaldehyde led to the pentasubstituted tetrahydropyran derivative 44 (essentially as a single product) in which five stereogenic centers (up-down-up-down-up) were controlled (Scheme 11, Part (a)). Subba Reddy and co-workers reported another example of the effectiveness of InCl₃, whereby the synthesis of cis-fused hexahydro-1H-furo[3,4-c]pyran scaffolds containing chlorine proceeded smoothly under mild conditions (Scheme 11, Part (b)).

FeCl₃ has been employed as an inexpensive, environmentally friendly, and stable Lewis acid to promote the halo-Prins cyclization of 3-buten-1-ol with several aldehydes. The cyclization affords the corresponding cis-4-halo-2-alkyltetrahydropyrans in generally excellent yields. The reaction works quite well with both aliphatic and aromatic aldehydes and, when FeBr₃ is employed, the 4-bromo-substituted analogue is formed. Liu and Loh have disclosed an efficient and highly stereoselective Prins cyclization leading to cis-2,6-dialkyl-3,4-dibromotetrahydropyran from terminal vinyl bromides. This method employs InBr₃ as the Lewis acid and TMSBr as the source of bromide ion.

Cascade reactions can be very powerful transformations in organic synthesis. The first examples of a Mukaiyama aldol–Prins (MAP) cascade cyclization reaction were reported by Rychnovsky’s group, whereby a very reactive allylsilane served as the internal nucleophile in a rapid and clean Prins cyclization. Rychnovsky and co-workers also described the use of simple alkene substrates in MAP cyclizations and the importance of selecting the appropriate Lewis acid to promote the reaction. The attraction of such a sequence is that it forms two new C–C bonds, a ring, and three new stereogenic centers. Initially, the Mukaiyama aldol addition and Prins cyclization with the simple alkene 45 was evaluated using previously optimized conditions. The reaction of 45 with 2.5 equiv of dihydrocinnamaldehyde in the presence
of BF₃•OEt₂ and 2,6-di-tert-butylpyridine (2,6-DTBP) at –78 °C led to the unexpected product 46 in 82% yield. The more powerful Lewis acids, TiCl₄ and TiBr₃, did not produce 1,3-dioxane 46 and gave the best yields of 47. TiBr₄ was particularly effective and gave adduct 47 in 72% yield (eq 7).

3.5.3. Iodinated THPs

The mild Lewis acidic nature of molecular iodine has been exploited by Yadav and co-workers in the first direct and metal-catalyst-free Prins cyclization of homoallylic alcohols with aldehydes for the rapid synthesis of highly substituted iododihydropyrans and iodothiopyrans in good yields and selectivities under neutral conditions. Other syntheses of highly substituted iododihydropyrans employed as an iodide source in the Prins cyclization of homoallylic and homopropargylic alcohols with various ketones leading to 2,2-disubstituted 4-iodotetrahydropyrans, spirocyclic 4-iodotetrahydropyrans, and spirocyclic 4-iodo-5,6-dihydro-2H-pyrylamyl carbocation by acetonitrile was detected.

The synthesis of 4-iodotetrahydropyrans by the Prins cyclization can also be performed in the presence of a combination of CeCl₃•7H₂O and LiI. This approach can be applied to both aldehydes and ketones, but requires a higher temperature (reflux in dichloroethane), with the best results achieved with 1 equiv of CeCl₃. In contrast, CAN and Ce(OTf)₃ were not effective and led to hydroxylated side products. Gallium triiodide (35 mol %) has also been employed for the synthesis of 4-iodotetrahydropyrans at room temperature in 10–25 min and in 82–89% yields.

3.6. Macrocyclization Involving the Prins Reaction

Oxacyclic macrodimers constitute an important class of natural products and are popular targets for synthetic chemists. Rychnovsky and co-workers introduced a new sequential dimerization–macrocyclization based on the Prins cyclization for forming symmetrical macrocycles. This approach is illustrated by the optimized conditions in the example in **equation 8**. A variety of Lewis acids, including other Re and non-Re ones, were investigated and found to be inferior to O₂ReOSiPh₃. Other reaction parameters; such as temperature, concentration, and substrate scope; were also examined: Both acetals and aldehydes were found to be viable substrates, whereas increasing the reaction temperature to 40 °C did shorten the reaction times but did not improve the yields. The usefulness of this strategy was demonstrated in a successful synthesis of a model for clavosolide A, a marine sponge metabolite.

![Scheme 10. Fluorinated Dihydropyrans by the Prins Cyclization of Allenic Alcohols. (Ref. 35)](Ref. 35)

![Scheme 11. Chlorinated THPs by the Prins Cyclization of Homoallylic Alcohols. (Ref. 4,39)](Ref. 4,39)
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About the Authors

Sandro José Greco was born in 1974 in Rio de Janeiro, RJ, Brazil. He received his B.Sc. degree in chemistry in 1997 and his M.Sc. and Ph.D. degrees in 2001 and 2005 from the Federal University Fluminense (Rio de Janeiro, Brazil), working under the guidance of Professor Sergio Pinheiro on studies of the use of terpenes and terpenoids in the enantioselective synthesis of potential anticholinergic agents, and on the synthesis of amino alcohol based, new chiral phase-transfer catalysts. In 2006, he joined Professor Maria D. Vargas’s group at the Federal University Fluminense as a postdoctoral researcher to work on the synthesis and pharmacological evaluation of new anticancer drugs containing the ferrocenyl group. He is currently an associate professor of organic chemistry at the Federal University of Espirito Santo, with research interests in the design and synthesis of potential bioactive compounds and the development of new organocatalysts and chiral phase-transfer catalysts for asymmetric synthesis.

Rodolfo Goetze Fiorot was born in 1974 in Rio de Janeiro, RJ, Brazil. He is currently pursuing his graduate-level studies in chemistry under the guidance of Professor Sandro J. Greco at the Federal University of Espírito Santo. His research investigations in the Laboratory of Organic & Medicinal Synthesis center on the development of multicomponent organic reactions of naphthoquinones.

Valdemar Lacerda, Jr. was born in 1975 in Goiânia, GO, Brazil. He received a B.Sc. degree in chemistry in 1997 from the Federal University of Goiás, where he worked in the laboratory of Professor Pedro Henrique Ferri. He received his M.Sc. degree in 2000 and his Ph.D. degree in 2004 from São Paulo University (Ribeirão Preto), working with Professor Maurício Gomes Constantino in organic synthesis and NMR studies. In 2004, he began working as a postdoctoral researcher at the NMR laboratory coordinated by Professor Gil Valdo José da Silva. In 2006, he joined the Department of Chemistry of the Federal University of Espirito Santo (ES State, Brazil) as an associate professor. His current research interests focus on organic synthesis, NMR studies, theoretical calculations, and petroleum studies. He has been Head of the Department of Chemistry since 2007, and is presently also a CNPq level 2 researcher.

Reginaldo Bezerra dos Santos was born in Matão, SP, Brazil, and obtained his B.Sc. degree in chemistry in 1986 from the Federal University of São Carlos (SP State, Brazil). He received his M.Sc. and Ph.D. degrees at the same University in 1990 and 1995, working under the supervision of Prof. U. Brocksom in the field of organic synthesis. In 1991, he accepted a position at the Federal University of Espirito Santo (ES State, Brazil) as an assistant professor in the Department of Chemistry, and was promoted to Associate Professor in 1995.
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