Aldrichimica Acta

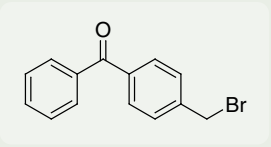
Volume 32, Number 3, 1999 (*Last issue in 1999*)

Ring-Closing Metathesis of Nitrogen-Containing Compounds: Applications to Heterocycles, Alkaloids, and Peptidomimetics

Are Two Phenyls Better than One? Synthesis and Applications of (R)-4-Diphenylmethyl-2-oxazolidinone

NewProducts

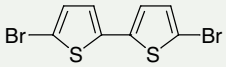
This benzophenone has been used to prepare several photoinitiators, including tetraalkylammonium salts, for acrylate polymerization.[1] It is also used to prepare photocleavable protein cross-linking agents.[2]



(1) Zhang, W. et al. *J. Org. Chem.* **1999**, *64*, 458. (2) Oatis, J.E., Jr.; Knapp, D.R. *Tetrahedron Lett.* **1998**, *39*, 1665.

44,938-5 **4-(Bromomethyl)benzophenone**, 97%

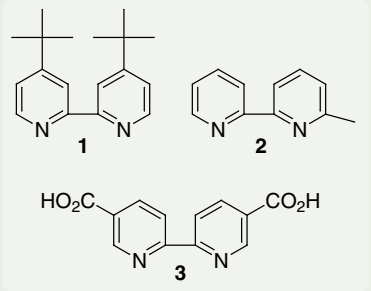
Oligothiophenes, with nonlinear optic and electrochemical applications, have been prepared from this brominated bithiophene.[1,2]



(1) Nakanishi, H. et al. *J. Org. Chem.* **1998**, *63*, 8632. (2) Roncali, J. *Chem. Rev.* **1992**, *92*, 711.

51,549-3 **5,5'-Dibromo-2,2'-bithiophene**, 99%

A variety of organometallic complexes have been prepared from these bipyridines. Compounds **1** and **2** are useful for the preparation of ruthenium complexes with increased solubility in organic solvents and modified redox properties relative to those of the complexes with unsubstituted bipyridine analogs.[1,2] Compound **3** has been utilized to prepare highly functionalized bipyridines.[3]



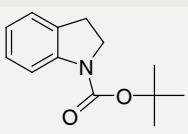
(1) Hadda, T.B.; Bozec, H.L. *Polyhedron* **1988**, 575. (2) Fabian, R.H. et al. *Inorg. Chem.* **1980**, *19*, 1977. (3) Penicaud, V. et al. *Tetrahedron Lett.* **1998**, *39*, 3689.

51,547-7 **4,4'-Di-*tert*-butyl-2,2'-dipyridyl**, 98% (**1**)

51,614-7 **6-Methyl-2,2'-dipyridyl**, 97% (**2**)

51,776-3 **2,2'-Bipyridine-5,5'-dicarboxylic acid**, 97% (**3**)

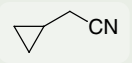
This compound is readily lithiated at C-7 using *sec*-butyllithium, and has been used to prepare a variety of 7-substituted indolines.



Meyers, A.I.; Milot, G. *J. Org. Chem.* **1993**, *58*, 6538.

51,014-9 ***tert*-Butyl indoline-1-carboxylate**, 98%

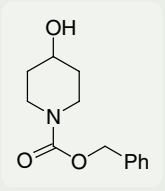
Important starting material for the preparation of cyclopropane-substituted heterocycles.[1,2]



(1) Li, Q. et al. *J. Med. Chem.* **1996**, *39*, 3070. (2) Kim, D.-K. et al. *ibid.* **1997**, *40*, 2363.

51,611-2 **Cyclopropylacetonitrile**, 97%

Useful synthon for the synthesis of biologically active quinolones[1] and fibrinogen receptor antagonists.[2]



(1) Cooper, C.S. et al. *J. Med. Chem.* **1992**, *35*, 1392. (2) Alig, L. et al. *ibid.* **1992**, *35*, 4393.

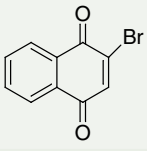
51,390-3 **Benzyl 4-hydroxy-1-piperidinecarboxylate**, 97%

This cyclopentadiene has been used as a diene in Diels–Alder reactions,[1] and for the preparation of fulvenes[2] and metallocenes.[3]

(1) Riemshneider, R.; Nehring, R. *Monatsh. Chem.* **1959**, *90*, 568. (2) Miyake, S. et al. *Macromolecules* **1995**, *28*, 3074. (3) Drewitt, M.J. *Chem. Commun.* **1996**, 2153.

49,498-4 ***tert*-Butylcyclopentadiene**, mixture of isomers

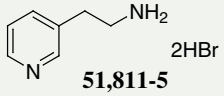
A number of anthraquinones and naphthoquinones have been prepared from this compound.[1,2]



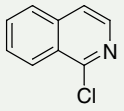
(1) Kesteleyn, B. et al. *J. Org. Chem.* **1999**, *64*, 1173. (2) Joshi, B.S. et al. *ibid.* **1994**, *59*, 8220.

51,030-0 **2-Bromo-1,4-naphthoquinone**, 98%

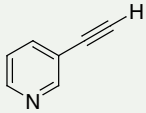
These heterocyclic synthons are widely used starting materials in medicinal chemistry.[1-4]



51,811-5



15,674-4



52,044-6

(1) Tucker, T.J. et al. *J. Med. Chem.* **1994**, *37*, 2437. (2) Moltzen, E.K. et al. *ibid.* **1994**, *37*, 4085. (3) Zhang, H. et al. *J. Org. Chem.* **1998**, *63*, 6886. (4) Hoffman, J.M. et al. *J. Med. Chem.* **1992**, *35*, 3784.

51,811-5 **3-(2-Aminoethyl)pyridine dihydrobromide**, 98%

15,674-4 **1-Chloroisoquinoline**, 95%

52,044-6 **3-Ethynylpyridine**, 98%

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About Our Cover

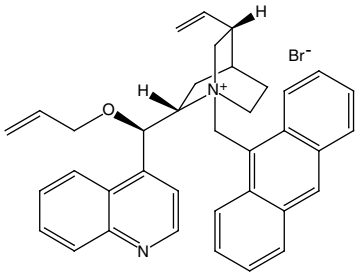
Jan Davidsz. de Heem's *Vase of Flowers* (oil on canvas, 27⅜ in. x 22¼ in.), painted about 1660, is a beautiful example of the delight that Dutch and Flemish seventeenth-century artists took in the natural world. The brilliant color, the soft texture of flower petals, the moist gleam of dew on leaves, and the detailed delineation of insects and small animals all contribute to the extraordinary illusionism of the painting. Moreover, the dynamic rhythms of the leaves, wheat stalks, peas, and flowers, and the small creatures crawling and fluttering in the air surpass mere description to make the objects represented seem almost to break through the surface of the picture. One can almost imagine the sweet scents of the flowers. The painting is far more than simply an extraordinary literal record of reality, however. It is an important expression of the imagination of the artist, who has overcome the laws of nature. Normally, this combination of flowers, fruits, and vegetables could not be in the same bouquet because they mature at different seasons of the year. Furthermore, these flowers will continue to bloom long after those in nature have withered and died. *Ars longa, vita brevis.* The painting is also filled with symbolic associations that would have been well understood in the seventeenth century. Insects and snails represent forces that are destructive of the beauties of nature. The transient loveliness of flowers is a reminder of the temporality of life. The morning glory, which opens at dawn and closes at dusk, symbolizes the light of truth.

This painting is part of the Andrew W. Mellon Collection at the National Gallery of Art, Washington, D. C.

"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President



Dr. Martin J. O'Donnell (IUPUI, Indianapolis) kindly suggested that we make *O*-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium bromide. This phase-transfer catalyst is useful for the enantioselective synthesis of α-amino acid derivatives.[1-3] A key step in the synthesis is the enantioselective alkylation of the enolate derived from *N*-(diphenylmethylene)glycine *tert*-butyl ester.

(1) O'Donnell, M.J. et al. *Tetrahedron* **1999**, *55*, 6347.
(2) O'Donnell, M.J. et al. *Tetrahedron Lett.* **1998**, *39*, 8775.
(3) Corey, E.J. et al. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

49,961-7 ***O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide**, 95%

36,448-7 ***N*-(Diphenylmethylene)-glycine *tert*-butyl ester**, 98%

Naturally, we made this useful catalyst. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Lab Notes

A Simple, Inexpensive Apparatus for Parallel Synthesis

In recent years, combinatorial chemistry[1] has emerged as an important component in drug discovery and as a technology that can increase the productivity of pharmaceutical research tremendously. Numerous synthesizers with varying degrees of automation are available commercially, both for solution- and solid-phase synthesis. Moreover, synthesis carried out in multiwell plates requires a liquid handling system and generates only a few milligrams of products.

In an attempt to increase the number of compounds synthesized, keeping in mind the cost, we designed a simple piece of equipment that is a modification of a vacuum manifold. Initially, we used a manifold with five arms (**Figure A**). Each arm is about 7 inches in length and serves as an air condenser; a reflux condenser is attached to the top of the manifold. The apparatus can be comfortably used for higher boiling solvents, especially when a common solvent is in use, with no overflow or drying of any flask. Later on, this apparatus was modified to accommodate a larger number (10) of reaction vessels (**Figure B**). Using this apparatus in an oil bath heated on a laboratory stirrer/hotplate, we carried out a series of solution-phase ester, amide, and guanidine syntheses in both 10-mL and 15-mL flasks. Each of the reaction flasks was charged with only 5–7 mL of reaction solution, and rigorous reflux was avoided to permit the refluxing solvent (e.g., xylenes) to condense completely in the 7-in. arm and thus avoid cross-contamination. We isolated a few hundred milligrams of each product in a relatively pure form (HPLC purity of guanidine derivatives >93%) with no cross-contamination. In the absence of fancier and more costly equipment, this apparatus can be used effectively for the synthesis of analogs with a common chemistry. It does not require any additional laboratory space and may also be suitable for solid-phase synthesis.

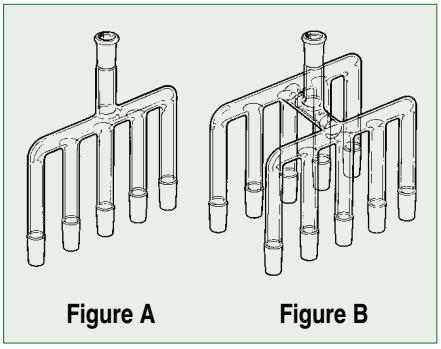


Figure A Figure B

References: (1) *Combinatorial Chemistry: Synthesis and Application*; Wilson, S.R., Czarnik, A.W., Eds.; John Wiley & Sons, Inc.: New York, NY, 1997 (**Z28,759-8**).

Seetharamaiyer Padmanabhan, Ph.D.
Cambridge NeuroScience
One Kendall Square, Bldg. 700
Cambridge, MA 02139, U.S.A.
E-mail: padman@cambneuro.com

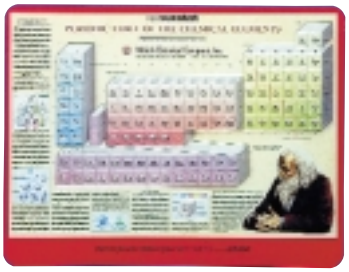
A Simple and Efficient Apparatus for Growing Crystals by Diffusion of Reacting Solutions

Growing crystals for X-ray diffraction analysis is often a challenging task. Several methods and techniques have been developed to grow good-quality crystals. Among them are the slow evaporation of saturated solutions,[1] cooling of saturated solutions, liquid diffusion, vapor diffusion, diffusion of reacting solutions,[2] and other more sophisticated methods such as crystal growing in gels.[3] In our research, we encountered difficulties growing suitable crystals of an organic host–guest complex using conventional methods. Layering one reacting solution on the other in a tube[2] gave crystals of some quality, but were too small for X-ray diffraction analysis. To overcome this problem, we designed a simple apparatus, which allows growing crystals of the complex during its formation reaction.

If compound **A** readily forms a crystalline complex with compound **B**, the size and quality of the crystals of the complex **AB** can be significantly improved by performing the reaction slowly. The apparatus shown in **Figure 1** is capable of extending the reaction time up to several weeks. The whole system is an easily made, single-piece glassware consisting of several parts:

Continued on page 90.

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, Aldrichimica Acta). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. **Z15,000-2**). If we publish your lab note, you will also receive an Aldrich periodic table turbo mouse pad (Cat. No. **Z24,409-0**). It is Teflon®-coated, 8½ x 11 in., with a full-color periodic table on the front. We reserve the right to retain all entries for future consideration.



Ring-Closing Metathesis of Nitrogen-Containing Compounds: Applications to Heterocycles, Alkaloids, and Peptidomimetics§

Andrew J. Phillips† and Andrew D. Abell
Department of Chemistry, University of Canterbury, Private Bag 4800
Christchurch, New Zealand
† Current Address: Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA
E-mail: aphillip+@pitt.edu
a.abell@chem.canterbury.ac.nz

Outline

1. Introduction

Olefin metathesis, a process by which alkylidene groups on alkenes are exchanged (**Figure 1**), was first reported in 1955 by Anderson and Merckling. Their seminal report described the polymerization of norbornene by titanium(II) species.[1] Despite its widespread use in industry as a method for producing higher olefins and polymers, it is only in recent times that the process has become more generally utilized. The generalization into synthetic organic chemistry has been driven primarily by the discovery of well-defined and functional-group-tolerant catalysts independently by Schrock and Grubbs.[2,3] The functional-group tolerance and reasonable stability of these catalysts have allowed their widespread use for ring formation. This review describes the applications of olefin metathesis to systems containing nitrogen functionality such as peptides, peptidomimetics, and azasugars, and covers the literature from January 1990 to December 1998. Recent reviews by Blechert, Armstrong, and Grubbs have surveyed other aspects of olefin metathesis in synthesis.[3]

2. Catalysts and Mechanism

At the present time there are two main types of catalyst in use (**Figure 2**). These are the molybdenum-based complex **1**, developed by Schrock and co-workers,[2] and the ruthenium-based complexes **2**, and in particular **3**, developed by Grubbs and co-workers.[4] Complex **1** has the major disadvantage of being particularly air- and moisture-sensitive, whereas **3** is not significantly affected by air, moisture, or other reaction impurities. Both catalysts are commercially available and details for their synthesis have been reported.[4d] It is worth noting that complex **3** is readily prepared by a short, one-pot sequence that is readily scalable to amounts as large as 10 g.[5] A number of other catalysts are also illustrated in Figure 2. Titanium carbenes such as **4** (presumably formed under the reaction conditions), which are more commonly utilized in olefination reactions, find occasional use.[6] Hoveyda and co-workers have recently reported the synthesis and some applications of ruthenium alkylidene **5**.[7] Although its scope has yet to be defined, this catalyst may well offer some advantages since it is stable to silica chromatography and thus can be recycled. It is worth noting that, although its rate of initiation is some 30-fold slower than that of carbene **3**, its rate of propagation is fourfold faster. Further investigations of carbenes that contain other nonphosphine ligands may yield even more useful catalysts.[8] In a similar vein, Grubbs and Nguyen have also reported the preparation of polystyrene–divinylbenzene-supported ruthenium carbenes and examined their activity and reuse.[9]

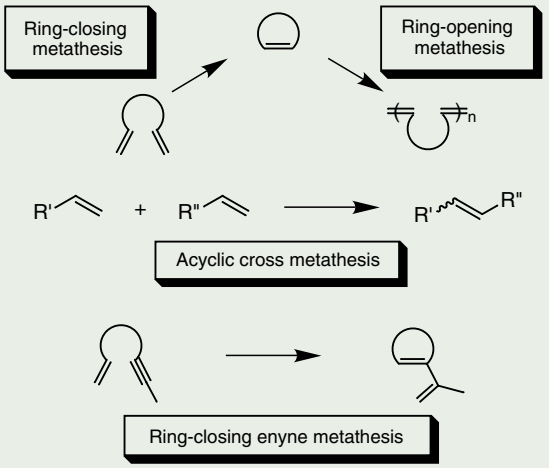


Figure 1. General types of olefin metathesis reactions.

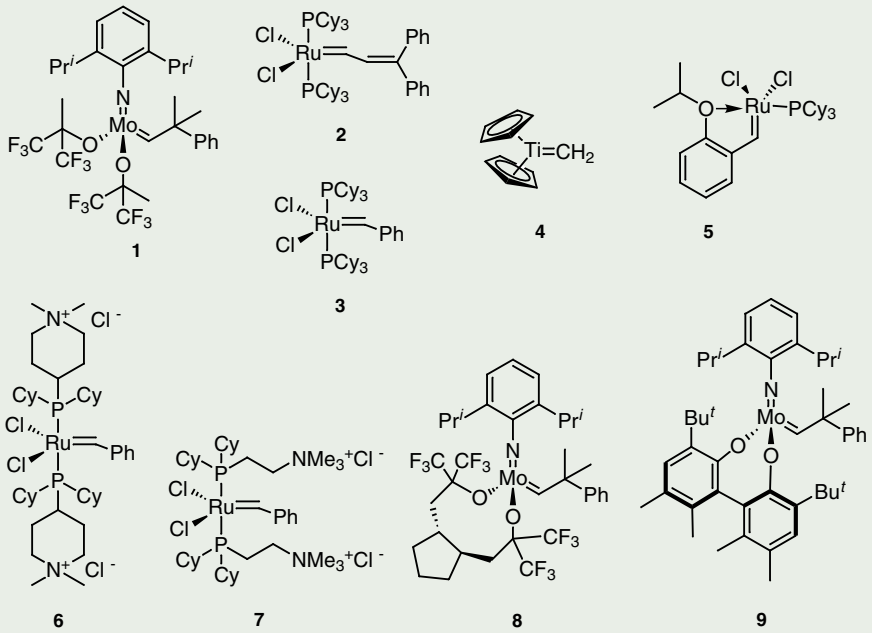


Figure 2. Catalysts used for olefin metathesis.

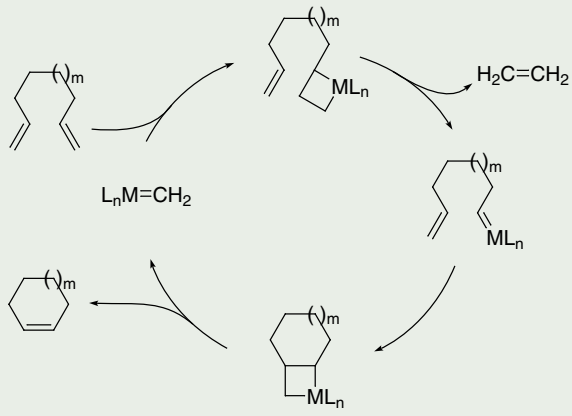


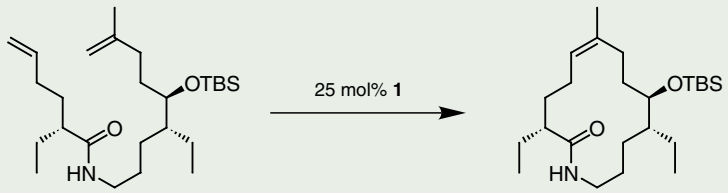
Figure 3. Schematic mechanism for ring-closing metathesis of acyclic dienes.

Catalysts that allow ring-closing metathesis (RCM) in methanol and water (complexes **6** and **7**) have recently been reported by Grubbs and co-workers.[10] The phosphine ligands of these catalysts contain quaternary ammonium salts, which confer enhanced solubility (and hence activity) in protic solvents. This study also revealed that the nature of the substrate has an important influence on the ease of cyclization. Phenyl-substituted substrates are claimed to be the best suited to cyclizations, since, as opposed to simple alkylidenes, they yield more stable benzylidene systems upon turnover. The exceptional activity of these catalysts in protic solvents should allow their ready application to systems of biological significance. Asymmetric ring-closing metathesis with chiral molybdenum carbenes **8**[11] and **9**[12] has been described but has yet to see widespread use. Several tungsten-based catalysts have also been described but have not been widely applied.[13] The preparation of imines by molybdenum-mediated metathesis has been reported recently.[14]

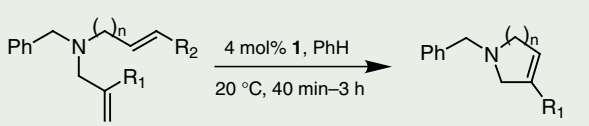
Most of the early work in olefin metathesis was performed using poorly defined catalyst systems and, even today, mechanistic studies on the ring-closing metathesis reaction remain scarce. This is primarily because of the difficulties involved in characterizing the species in these "classical" metathesis systems. However, there is some evidence that the reaction proceeds via metallacyclobutanes (**Figure 3**).[15] With the availability of well-defined catalysts, progress should now be more rapid on this front. In light of this, Grubbs has recently investigated the ring-closure of diethyl diallylmalonate by $H_2C{=}Ru(PCy_3)_2Cl_2$.[16] This study revealed that the major mechanistic pathway for this catalyst was via phosphine loss before metallacyclobutane formation.[17] Although this report is informative, care must be exercised in extending the results of this study to other catalyst systems. For the purpose of this review, the general mechanism illustrated in Figure 3 is adequate.

3. Scope and Functionality Tolerance

The body of literature that has emerged over the past three years has provided enough information to allow some guidelines to be formulated with respect to both ring size and compatible functionality. Catalysts **1–3** are all capable of catalyzing the formation of simple five-, six-, and seven-membered mono- and bicyclic rings. Eight-membered rings, as is the case for so many methods, remain more difficult to access by metathesis chemistry.[18] Nonetheless, examples do exist.[19] The formation of macrocycles is facile, and

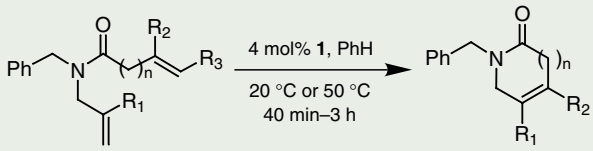


eq 1



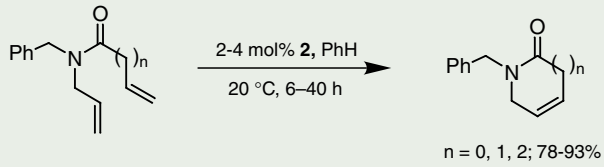
n	R_1	R_2	Yield (%)
1	H	H	86
1	Me	H	85
2	Me	Et	86
3	Me	H	73

eq 2



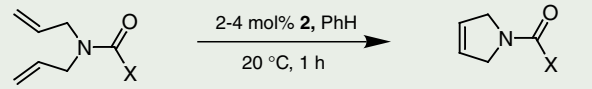
n	R_1	R_2	R_3	Yield (%)
0	H	H	Me	74
0	H	Me	Me	77
1	H	H	Et	80
2	H	H	H	87
2	Me	H	H	81

eq 3



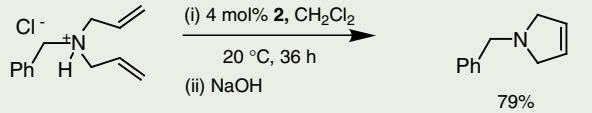
n = 0, 1, 2; 78-93%

eq 4



X = CF_3, 93%
X = *t*-BuO, 91%

eq 5



79%

eq 6

catalysts **1–3** have all been utilized in total syntheses of macrolides. Examples include the Hoveyda synthesis of fluvirucin (**eq 1**)[20] and the Danishefsky,[21] Nicolaou,[22] or Schinzer[23] syntheses of epothilones. In general, ruthenium alkylidenes **2** and **3** are less active than **1** with respect to the formation of trisubstituted alkenes, and incapable of cyclizations that form tetrasubstituted alkenes.[24] In contrast, **1** is capable of catalyzing the formation of tri- and tetrasubstituted bonds. Although appreciably sensitive to oxygen and water, molybdenum catalyst **1** is relatively tolerant of functionality in the substrate. At least in simple systems, this catalyst will tolerate ketones, esters, amides, epoxides, acetals, silyl ethers, some amines, and sulfides. Ruthenium catalysts **2** and **3** are remarkably tolerant of oxygen and moisture, and they will also tolerate substrates containing free alcohols, as well as the functional groups listed above for **1**. With catalysts **2** and **3**, some authors have noted difficulties in cyclizing substrates in which functional groups, that can potentially coordinate the metal center, are adjacent to the initially metathesized alkene. As a solution to this problem, Fürstner and Langemann have reported a procedure that involves the addition of Ti(*i*-PrO)$_4$ to these reactions.[25] Significant differences in the rates and yields of these reactions were noted.

The functional-group tolerance and ability of catalysts **5–8** to form cyclic structures of various sizes have yet to be fully explored. It is reasonable to assume that their compatibility with various functional groups will be similar to those of the original ruthenium and molybdenum catalysts. Their ability to form rings of various sizes is also expected to be similar, although the asymmetric processes may prove less efficient with some substrates.

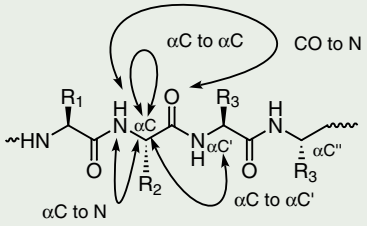
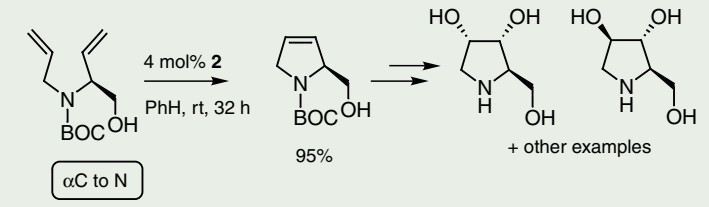
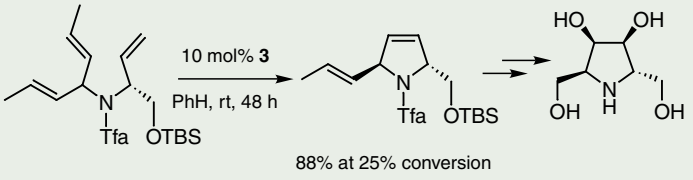


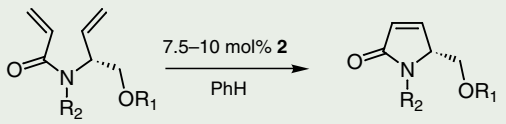
Figure 4. Nomenclature used to describe the cyclizations of peptidomimetics.



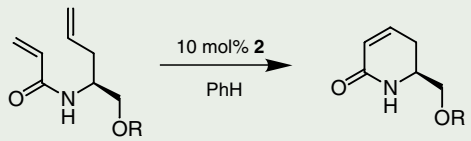
eq 7



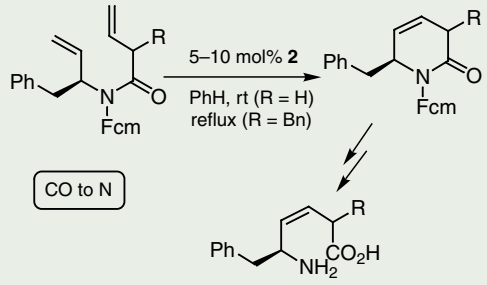
eq 8



eq 9



eq 10



eq 11

4. Applications to the Synthesis of Nitrogen-Containing Systems

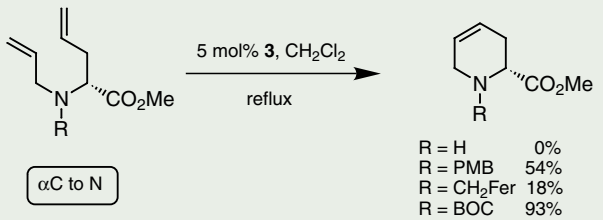
Due to their high catalytic activity and functional-group tolerance, catalysts **1–9** seem ideally suited to applications involving nitrogen. Many reports have appeared recently detailing ready access to a diverse range of compounds including peptidomimetics, peptide tertiary structure mimics, and azasugars. This growth of ring-closing metathesis (RCM) as a synthetic method for the preparation of nitrogen-containing compounds can probably be traced to 1992 and 1993 when several papers were published by Grubbs and co-workers on the synthesis of heterocycles by RCM.[26] In these papers, Fu, Grubbs, and Nguyen delineated the nitrogen-functional-group compatibility of catalysts **1** and **2**, along with their ability to form five-, six-, and seven-membered rings (**eq 2–6**). The remainder of this review will be devoted to presenting illustrative examples of the application of RCM to a number of these and related classes of compounds. For organizational purposes, we have classed the examples into three main groups that are defined by what the dienes are attached to:

(i) Cyclizations leading to heterocyclic structures. Here, the diene chain contains one or more nitrogen atom(s) such that cyclization gives rise to heterocycles, including pyrrolidines, piperidines, lactams, azasugars, and alkaloids. Systems that contain rings of 10 or more atoms are discussed under macrocyclic systems in part (iii).

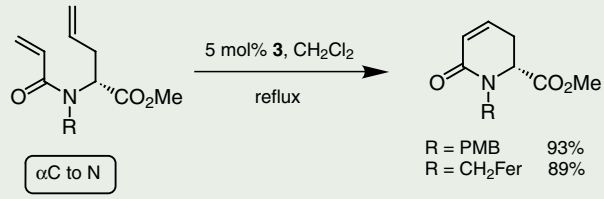
(ii) Cyclizations leading to carbocycles. Examples in this class give rise to carbocycles that contain a pendant nitrogen functionality.

(iii) Miscellaneous cyclizations. This section includes macrocyclizations, solid-phase methods, and various other applications.

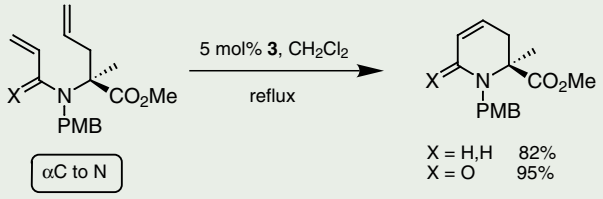
For some examples of peptidomimetics, we have tried to point out the relationship of the peptidomimetic to the peptide by denoting the atoms between which cyclization occurs relative to those of a simple peptide substrate.[27] This approach should prove useful to researchers working with peptidomimetics, whereby it is important to have systematic and documented methods for restraining the conformations of peptides and pseudopeptides. The nomenclature used is illustrated in **Figure 4**.



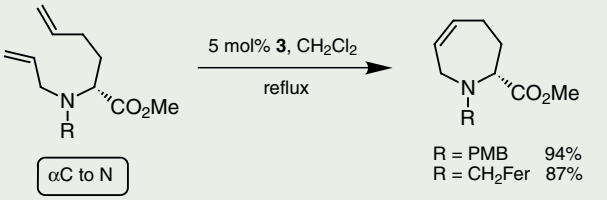
eq 12



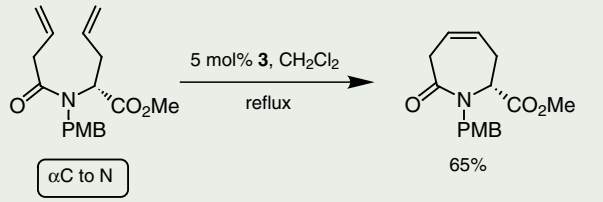
eq 13



eq 14



eq 15



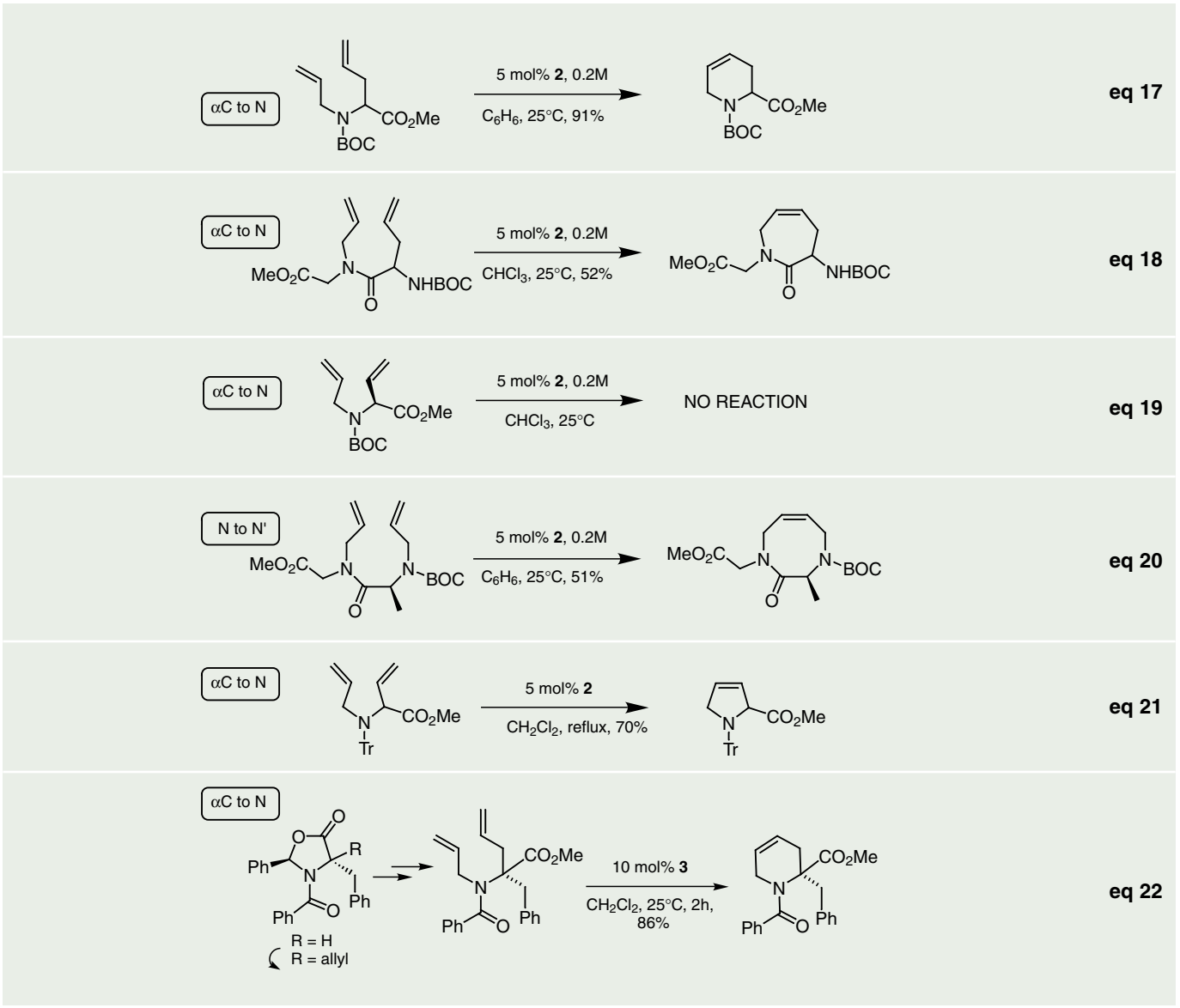
eq 16

4.1. Cyclizations Leading to Heterocycles: Pyrrolidines, Piperidines, Lactams, Azasugars, Alkaloids, and Related Compounds

There are a large number of examples of RCM involving substrates in which the diene linker contains a nitrogen atom. These types of cyclizations give access to a number of useful classes of compounds such as mono- and bicyclic pyrrolidine, pyrrolidinone, piperidine, and piperidinone ring systems. Many of these heterocycles are derived from amino acids, and offer a significant potential as peptidomimetics in which the torsion angle between the α carbon and the nitrogen of the amino acid is defined by the ring size and the position of the alkene. Some of these compounds are also important intermediates for the synthesis of azasugars and alkaloids.

A flexible synthesis of azasugars and homoazasugars has been reported by Blechert and Huwe (**eq 7** and **8**).[28] RCM of a vinyl glycine methyl ester derived diene, followed by stereoselective functionalization of the double bond, gave the desired sugar derivatives in good yields. The same group has also synthesized a number of five- and six-membered lactams using carbene **2** (**eq 9** and **10**).[29] Like many examples of metathesis cyclizations of this type, the yield of the cyclic product is dependent on the nature of the protecting group on nitrogen. In some cases, however, protection of the nitrogen is not necessary (**eq 10**). It is also interesting to note that increasing steric demand of the oxygen substituent in the example shown in eq 10 led to a marked increase in yield of the cyclic product (compare R = H, Bn, and Tr). The precursors in the pyrrolidinone series (**eq 9**) and the piperidinone series (**eq 10**) were synthesized from vinylglycine and allylglycine, respectively. Garro-Hélion and Guibé have reported an efficient sequence to *Z*-ethylenic peptidomimetics based on a related RCM chemistry.[30] Treatment of the acyclic dienes with **2** resulted in a smooth cyclization to the desired piperidinones; however, reflux in benzene was required in the case where R = Bn (**eq 11**). These compounds were then hydrolyzed to give the deprotected peptide isosteres.

Related work by Rutjes and Schoemaker has also resulted in the synthesis of a series of six- and seven-membered lactams and heterocycles (**eq 12–16**).[31] The yields of the RCM-derived tetrahydropyridines shown in **eq 12** were dependent on the nature of the

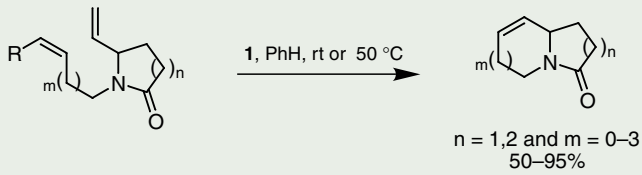


protecting group (R) on nitrogen. Without protection (R = H), ring closure was not observed, while BOC protection resulted in an excellent yield. The ease of cyclization of the acyclic amides shown in **eq 13** also proved to be dependent on the nature of the protecting group. The free amide (R = H) was sluggish, while the N-protected counterparts cyclized readily and in excellent yields. It has been suggested that an increase in steric bulk around the nitrogen leads to a more favorable transition state for ring closure.[31] The introduction of a methyl substituent α to the carboxyl group resulted in a marked increase in the ease of RCM (**eq 14**). The trifluoromethyl analogs have also been reported recently by Osipov, Dixneuf, and co-workers.[32] The homoallylglycine-derived acyclic systems shown in **eq 15** and **16** gave the corresponding seven-membered-ring heterocycles. The nature of N-protection proved to be less critical in these examples. A sequence based on the Ireland–Claisen rearrangement, followed by RCM, has been reported as a convenient means to construct similar systems.[33] The products shown in equations 12–16 are non-natural cyclic amino acid derivatives that deserve further study because of their interesting properties.

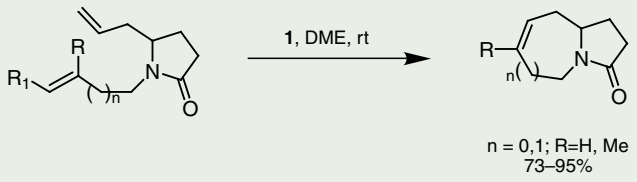
Grubbs and co-workers have also reported a number of applications of their Ru carbenes to peptide and heterocyclic chemistry. In a seminal paper, the application of carbene **2** to the synthesis of cyclic amino acids was reported (**eq 17–20**).[34] While six- and seven-membered cyclic amino acids were readily synthesized (**eq 17** and **18**), attempts to prepare a dehydroproline system were unsuccessful (**eq 19**). This was attributed to the acidity of the α hydrogen, although conformational effects and/or internal complexation of the carbene by the carbonyl group may also play a role. Recent work by Campagne and Ghosez[35] has shown that dehydroproline systems can be prepared, provided a triphenylmethyl (trityl) group is used as the protecting group on the nitrogen (**eq 21**). The original report by Grubbs and co-workers also included the synthesis of an eight-membered Ala–Gly dipeptide (**eq 20**).

The chemistry shown in **eq 12** and **eq 17** was recently extended by Abell and co-workers, who used a combination of Seebach's oxazolidinone chemistry and RCM in the synthesis of a phenylalanine mimic (**eq 22**).[36] This tetrahydropyridine system was designed to probe the constraints imposed by the six-membered ring on the torsion angle between the α carbon and the nitrogen. X-ray analysis demonstrated that this type of system has potential as a β-turn mimic.

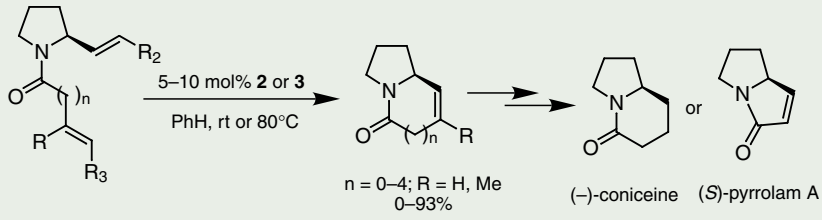
A number of groups have investigated the use of metathesis chemistry to form bicyclic systems. Martin and co-workers have shown the potential of RCM to form the ring systems found in a number of alkaloids (**eq 23** and



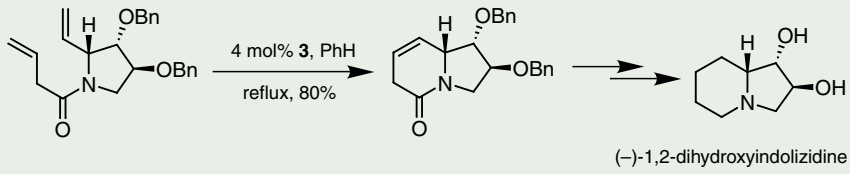
eq 23



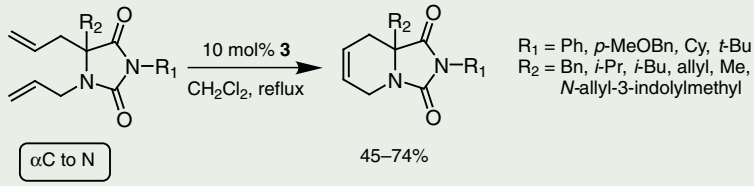
eq 24



eq 25



eq 26



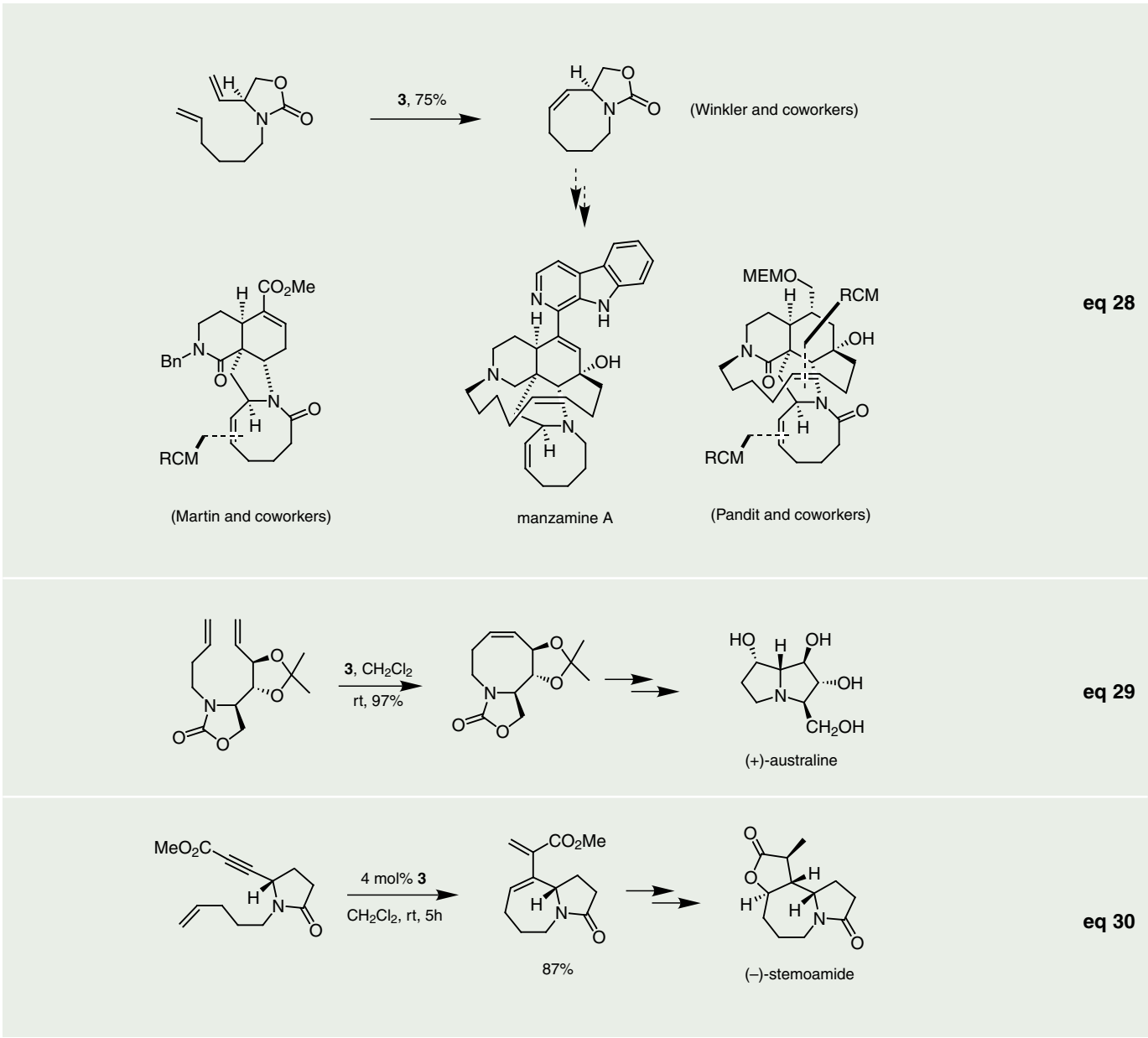
eq 27

24).[37] This work has demonstrated that a number of fused nitrogen heterocycles, including pyrrolizidines, indolizidines, and quinolizidines, can be readily prepared. Further examples of related bicyclic systems that have been synthesized using RCM are shown in **eq 25–27**.[38] Several of these examples have been used in the synthesis of simple alkaloids.

A number of medium-sized rings have been synthesized by RCM (**eq 28–30**). Seven-membered heterocyclic rings can be readily formed by RCM (see for example eq 15–16). However, reported syntheses of eight-membered rings tend to be on dienes attached or fused to other ring systems, i.e., the acyclic precursor is 'pre-organized' into a conformation that favors cyclization.[39] Early studies in this area by Grubbs and co-workers demonstrated the application of RCM to structures suitable for mitomycin and FR-900482 synthesis.[40] As part of studies directed toward the manzamine class of alkaloids, Winkler and co-workers investigated the synthesis of azocine rings by RCM (**eq 28**).[41] Advanced intermediates en route to manzamine A have been similarly cyclized by Martin's group using Mo carbene **1**, and by Pandit and co-workers using Ru carbene **2** (**eq 28**).[42] Magnier and Langlois have recently reported similar results.[43] An elegant synthesis of (+)-australine, utilizing RCM as the key step to form an eight-membered ring, has been reported by White and co-workers (**eq 29**).[44] As a further example, ring-closing enyne metathesis has been employed with impressive strategic gain in a concise synthesis of a key intermediate en route to (–)-stemoamide (**eq 30**).[45]

Some examples of diastereoselective RCM have recently been reported by Blechert and co-workers (**eq 31–33**).[46] The existing stereogenic center is used to control the cyclization of a diastereotopic diene. Control of which alkene is metathesized first is important, and the use of *trans*-disubstituted alkenes allows the initial reaction to be directed to the monosubstituted alkene. Levels of diastereoselection are modest when forming six-membered rings (**eq 31** and **32**), but are >70% with five-membered rings (**eq 33**). Interestingly, changing the catalyst from Mo carbene **1** to Ru carbene **3** allows some control of the relative diastereoselection (**eq 33**). This is probably related to the different spatial arrangements of various ligands around the different metal centers.

Pandit and co-workers have explored the applications of RCM of dienes appended to polysubstituted pyrrolidinones and piperidinones (**eq 34** and **35**).[47] In one such case (**eq 34**), a demanding five-membered-ring



cyclization was performed by using 50 mol% of catalyst **2**. These studies have expanded on an earlier report by the same group on a concise synthesis of castanospermine (**eq 36**), which demonstrated that, in some systems, α,β-unsaturated esters may be suitable substrates for metathesis.[48]

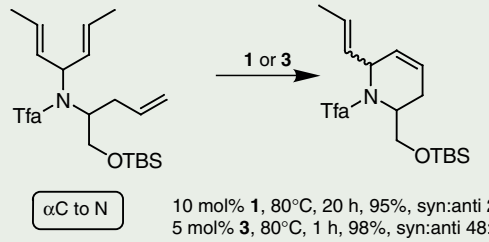
A number of other substrates, such as β-lactam-based dienes, have also been used to prepare interesting heterocycles by RCM (**eq 37** and **38**).[49]

4.2. Cyclizations Leading to Carbocycles

Although widely utilized for the synthesis of heterocycles, RCM has only been applied to a handful of systems that lead to carbocycles. This will undoubtedly be an area of growth over the next few years as more research groups employ RCM in carbocycle synthesis.

Hammer and Undheim have applied RCM to the synthesis of a number of five-, six-, and seven-membered carbocycles derived from (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (enantiomer of Schöllkopf's bislactim ether; see **eq 39** and **40**).[50,51] The results detailed in eq 39 indicate that, not surprisingly, the reaction is sensitive to steric interaction between the isopropyl group and the alkylidene. For example, the authors note that an allyl group syn to the isopropyl group is less reactive than when it is in the anti position. It is also worth noting that in these studies, five-membered rings were more difficult to form than either six- or seven-membered rings. The bislactims are readily hydrolyzed by dilute acid (0.2 M TFA, MeCN) to give an amino ester, where the α carbon is incorporated into a five-, six-, or seven-membered ring. Two recent reports have demonstrated the use of enones and hydroxymethylated dienes related to those in eq 39 and 40 as suitable RCM substrates within this strategy.[52] Further studies by Hammer and Undheim have also explored the applications of ruthenium-catalyzed, ring-closing enyne metathesis to systems derived from Schöllkopf's bislactim ether (**eq 41**).[53]

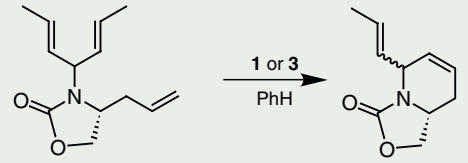
Kotha and Sreenivasachary have applied RCM to the synthesis of simple carbocyclic amino acids (**eq 42** and **43**).[54] Recently, Maier and Lapeva reported a synthesis of cyclohexenylamines that relies on RCM as the key step (**eq 44**).[55]



αC to N

10 mol% **1**, 80°C, 20 h, 95%, syn:anti 26:74
5 mol% **3**, 80°C, 1 h, 98%, syn:anti 48:52

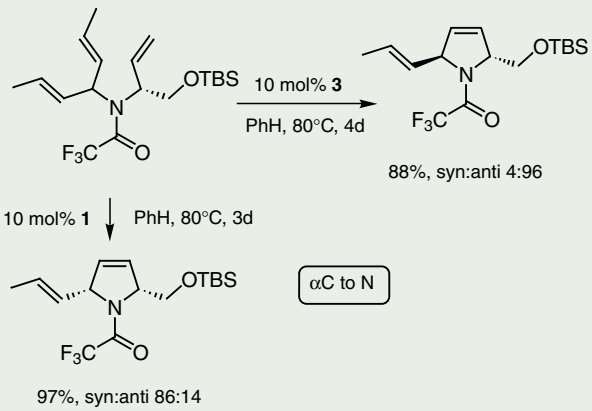
eq 31



αC to N

5 mol% **1**, rt, 24h, 88%, syn:anti 36:64
5 mol% **3**, rt, 2h, 90%, syn:anti 50:50

eq 32



88%, syn:anti 4:96

97%, syn:anti 86:14

eq 33

4.3. Miscellaneous Cyclizations: Macrocyclic Peptides, Solid-Phase Methods, and Other Applications

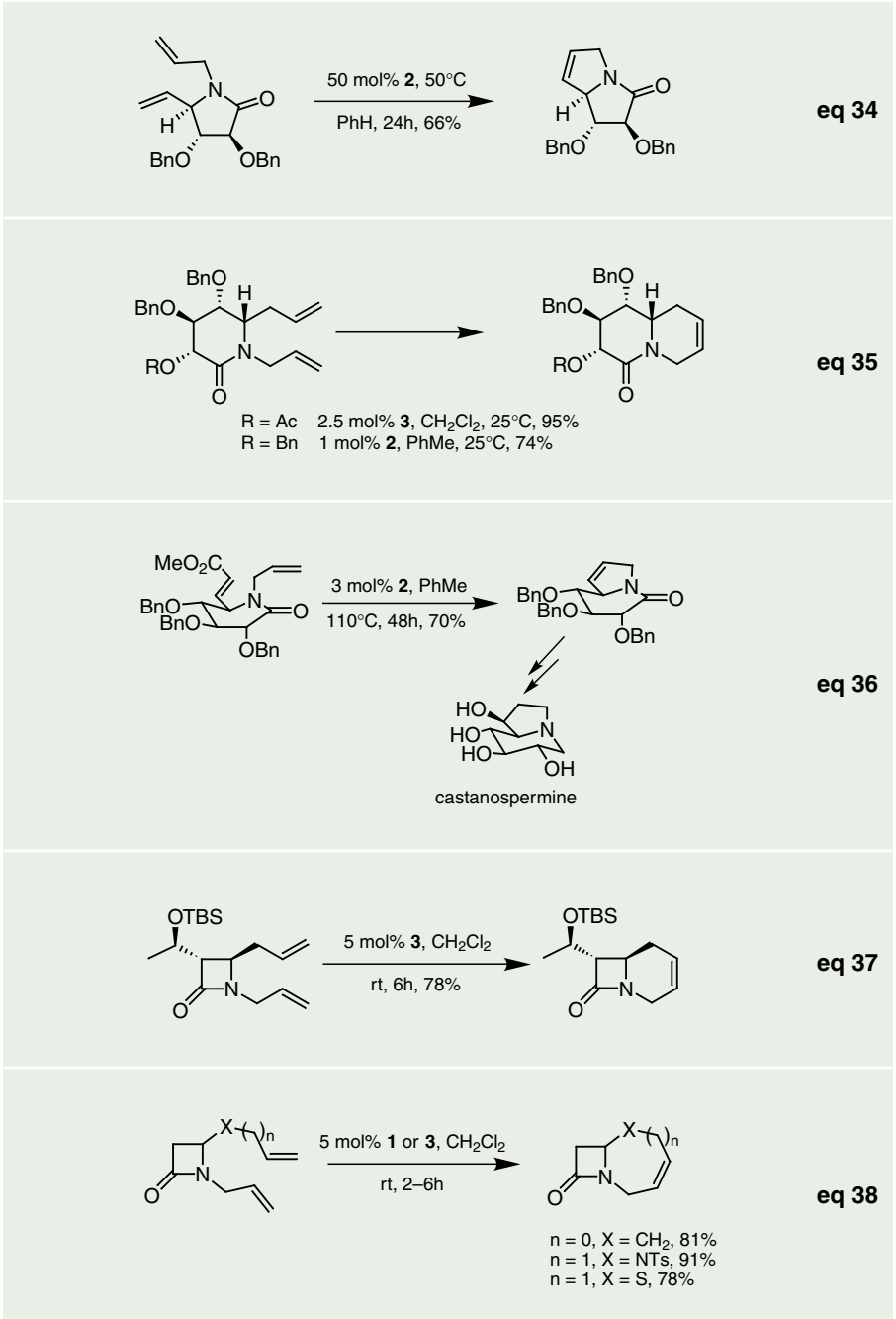
Miller, Blackwell, and Grubbs have described a number of applications of RCM to give rigid amino acids and macrocyclic peptides.[34] In this work (**eq 45** and **46**), a number of acyclic polypeptides were cyclized under high dilution to give 14- and 20-membered macrocycles. Several other polypeptides were cyclized, including a 14-membered tetrapeptide designed as a 'dicarba' analog of a disulfide β-turn motif (**eq 47**).[34] Initially, it had been thought that pre-existing conformational restrictions in the peptide backbone would be necessary to induce RCM cyclization.[56] However, the success of the cyclization shown in eq 47 demonstrates that this may not strictly be the case.

Williams and Liu have reported related studies in which a differentially protected 2,7-diaminosuberic acid derivative was prepared by RCM (**eq 48**).[57] Vederas and coworkers concurrently developed a similar route (**eq 49**).[58] 2,7-Diaminosuberic acids have been utilized in the synthesis of dicarba analogs of naturally occurring biologically active peptides.[59]

Several other research groups have utilized RCM in the synthesis of macrocyclic peptides. Katzenellenbogen and co-workers employed RCM as part of studies on a proposed Type 1 β-turn mimic (**eq 50**).[60] Here, the use of RCM on a dipeptide allowed the convenient synthesis of the 10-membered lactam in six steps. By comparison, a more traditional macrolactamization route to this compound required nine steps, and the RCM route had the added advantage of providing access to the (3*S*,10*S*) diastereoisomer, which was unobtainable by the original route.

Rich and co-workers have also reported a related synthesis of a macrocyclic pepsin inhibitor by RCM of a tripeptide-derived diene (**eq 51**).[61] The macrocyclic alkene and the fully saturated analog (derived from this compound by reduction) proved to be good inhibitors of *Rhizopus chinensis* pepsin (K_i 1.31 μM and 0.34 μM, respectively).

Acyclic dienes that are not derived from amino acids have also been shown to undergo macrocyclization by RCM. For example, Fuchs and co-workers reported such a macrocyclization in their synthesis of the tricyclic *ansa*-bridged core of roseophilin (**eq 52**).[62]



This reaction required very dilute conditions (0.5 mM) to avoid the formation of macrocyclic dimers.

In an impressive example of what the authors describe as 'supramolecular design by covalent capture', Clark and Ghadiri have synthesized a macromolecular peptide by an intermolecular RCM (**eq 53**).[63] Here, the two precursors are held in close proximity by hydrogen bonding between the amino acid side chains of the *N*-methyl cyclic peptides such that intermolecular RCM gives the macrocycle in an impressive yield of 65%. Another example of the use of RCM to give peptidic supramolecular structures was recently provided by Blackwell and Grubbs with the preparation of helical polypeptides.[64] Here, carbene **3** was used to prepare examples of heptapeptides in which the *i* and (*i* + 4) residues of the peptide are linked by RCM (**eq 54**). As noted by the authors, "The relative ease of introducing carbon–carbon bonds into peptide secondary structures by RCM and the predicted metabolic stability of the bonds renders olefin metathesis an exceptional methodology for the synthesis of rigidified peptide architectures". This area is one of exceptional promise given the compatibility of **3** with functional groups and solvents commonly found in peptide chemistry.

The products of RCM of amino acid based substrates have also been reported as key intermediates of important isosteric units. For example, Ghosh and co-workers have reported the cyclization of amino acid derived acrylate esters as part of a synthesis of hydroxyethylene isosteres that form the core units of an important class of HIV protease inhibitors (**eq 55**).[65] This work further demonstrates the usefulness of Fürstner and Langemann's procedure, which involves the addition of Ti(*i*-PrO)$_4$, in the case of substrates that may form stable, chelated carbene intermediates.

Although yet to be clearly defined, a substantial amount of the chemistry described in this review is applicable to solid-phase methods. Amongst the most impressive examples of the potential of this adaptation is the recent report by Nicolaou and co-workers of the synthesis of a library of epothilone analogs by a solid-phase RCM–cleavage strategy.[66] In the area of nitrogen-containing substrates, a number of groups have reported solid-phase adaptations of their syntheses using RCM. Blechert and co-workers have reported that their previous synthesis of five- and six-membered nitrogen heterocycles (**eq 9–11**) can be performed on solid-phase resins, such as Tentagel S and tritylpolystyrol (**eq 56–59**).[67] Examples have been reported where the resin is attached through either nitrogen or carbon, and, in all cases, the cyclizations appear to be slower than the corresponding solution-phase cyclizations.

An RCM–cleavage strategy for the synthesis of cyclic lactams has also been reported by van Maarseveen and co-workers (**eq 60**).[68] An essential feature of this work is the cleaving of the lactams from the resin in the course of RCM. The rate of RCM is, however, slow under relatively standard reaction conditions, a feature that the authors attribute to the immobilization of the carbene on the resin. This problem can be partly overcome by the addition of a terminal olefin such as 1-octene, although the yields are still modest. Piscopio and co-workers have reported a similar RCM–cleavage strategy for the solid-phase synthesis of pipecolinic acids and Freidinger lactams (**eq 61**).[69] In this report, the use of a cinnamyl alcohol resin appears to aid the cyclization–cleavage reaction. Further developments of this work have recently been reported.[70]

The synthesis of hexahydroisoindoles has been carried out on solid phase using Wang resin (**eq 62**).[71] Although no yields were reported, the authors described the synthesis of a library of 4200 (theoretical) compounds by this methodology. The equivalent solution-phase chemistry was also reported.

Grubbs and co-workers have demonstrated that RCM cyclization of polypeptides can also be performed on solid phase.[34] As noted by the authors, peptides of >5 residues in length

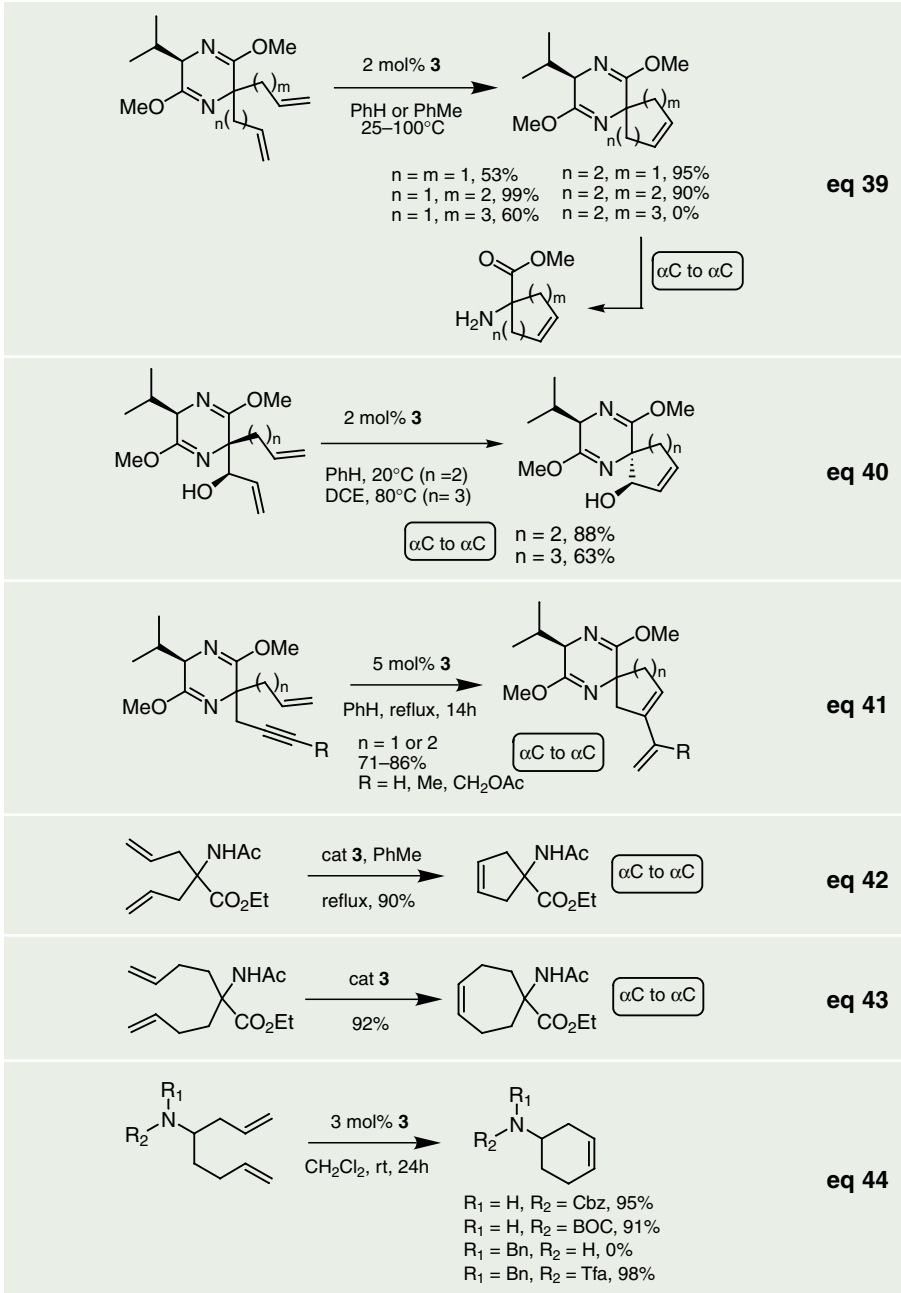
usually suffer from low solubility in solvents commonly used for RCM. However, the synthesis and RCM of these substrates was readily performed on a PEG/PS resin (**eq 63**).

5. Conclusions

Ring-closing metathesis has clearly reached the point where it is a reliable and relatively mature technique for the formation of a diverse range of ring structures. The mild conditions under which most reactions can be performed, along with the high functional-group tolerance of the current catalysts, mean that it is clearly of immense value in many areas of chemistry. The synthesis of N-containing compounds such as heterocycles and peptides has benefited from these features. Ring-closing metathesis also offers a new potential for strategic disconnections as is clearly evidenced by the synthesis of macrolides, where it provides a powerful alternative to traditional macrocyclization techniques. The future of ring-closing metathesis can almost certainly be bright as new catalysts and applications are discovered.

6. Acknowledgments

We thank the Marsden Fund of New Zealand (ADA), the New Zealand Public Good Science Fund (ADA), and the University of Canterbury (Doctoral Scholarship to AJP) for support of our research, and Professor Robert Grubbs for generous advice on RCM chemistry.



7. References and Notes

§ Abbreviations: Ac, acetyl; BOC, *tert*-butoxycarbonyl; Bn, benzyl; Cbz, benzyloxycarbonyl; DCE, dichloroethane; Fcm, ferrocenylmethyl; Fer, ferrocenyl; FMOC, 9-fluorenylmethoxycarbonyl; MEM, (2-methoxyethoxy)methyl; PCy_3, tricyclohexylphosphine; PMB, 4-methoxybenzyl; TBS, *tert*-butyldimethylsilyl; TFA, trifluoroacetic acid; Tfa, trifluoroacetyl; TIPS, triisopropylsilyl; Tr, triphenylmethyl; Ts, 4-methylphenylsulfonyl.

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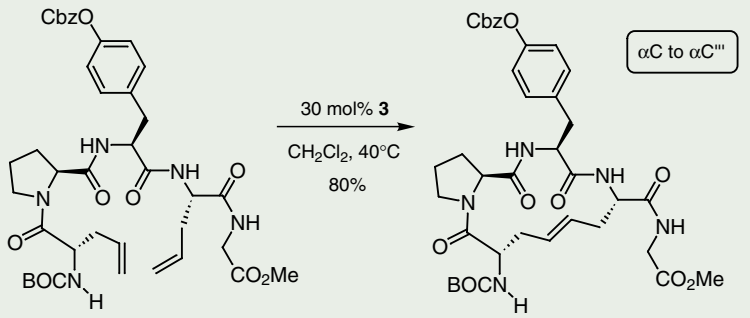

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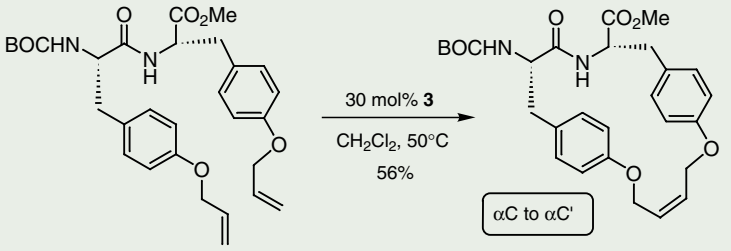

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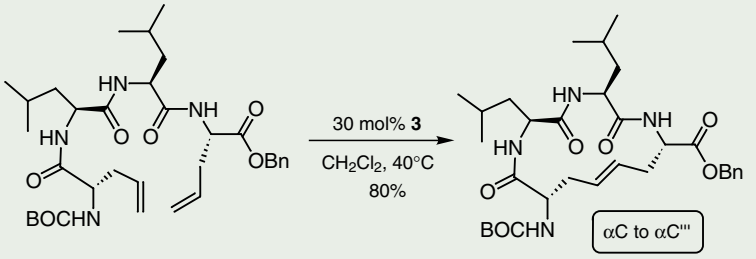

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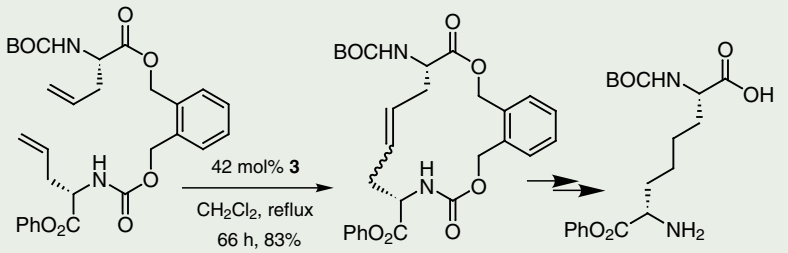

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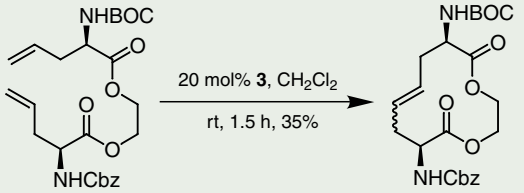

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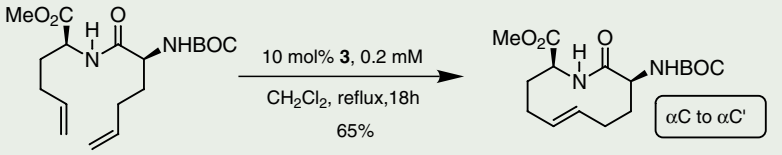

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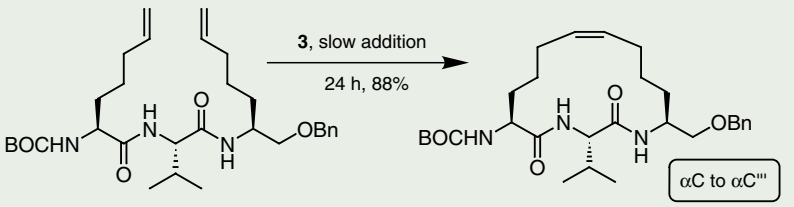

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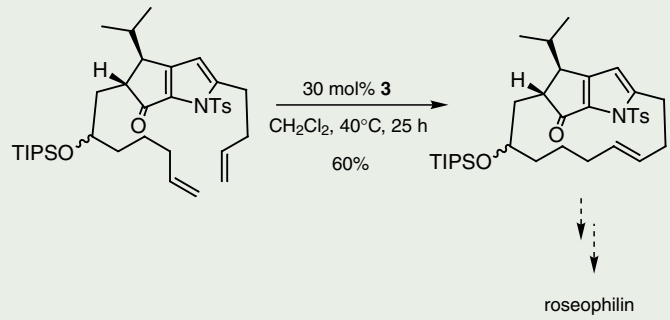

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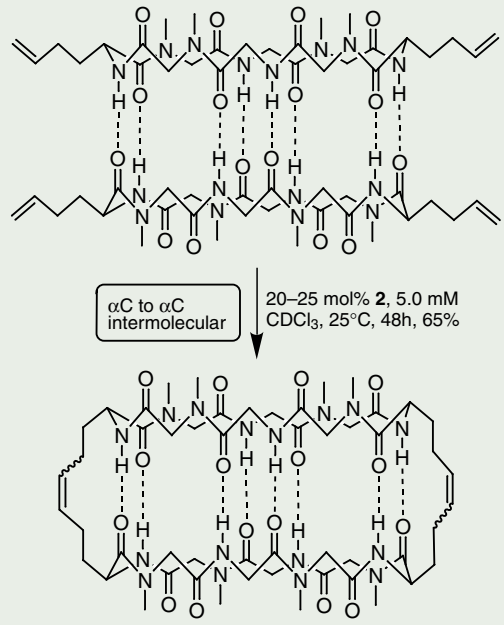

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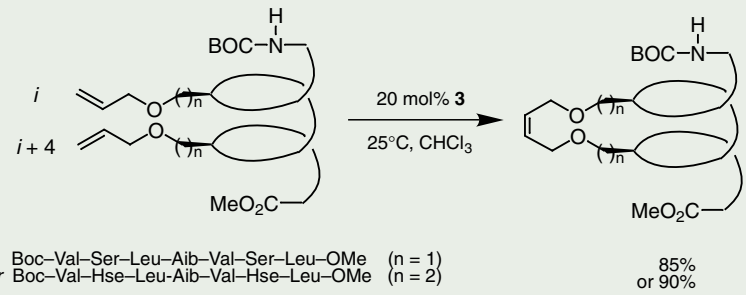

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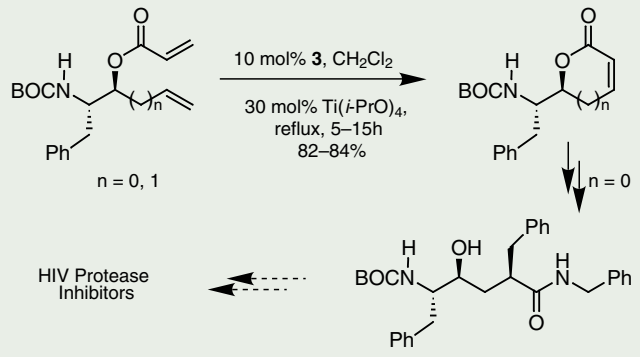

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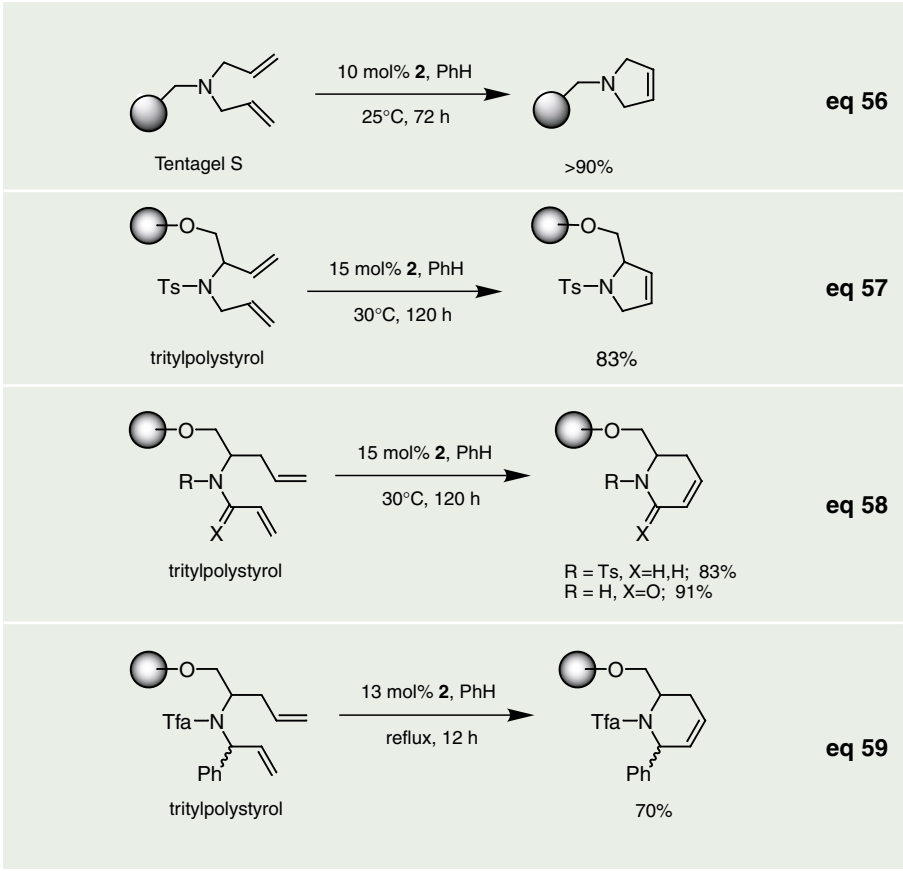

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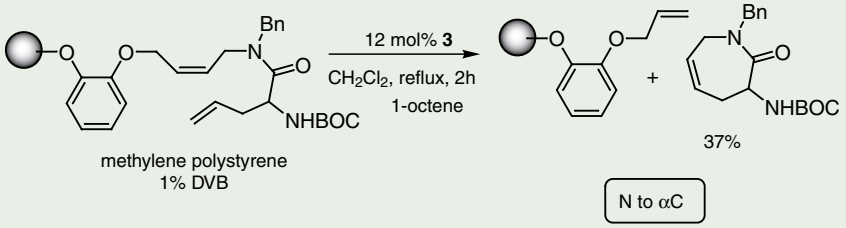

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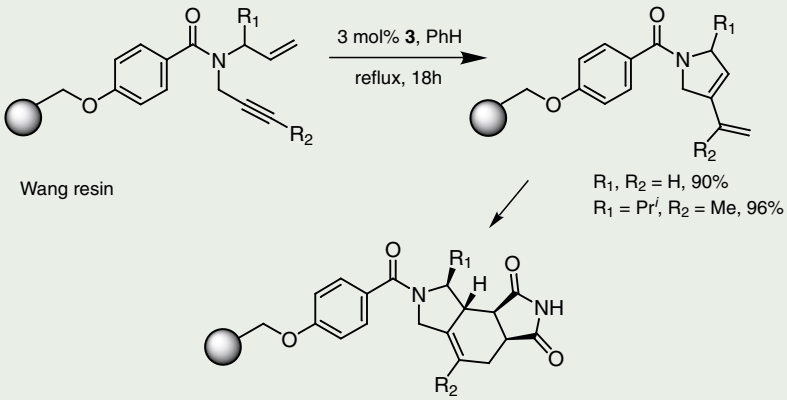

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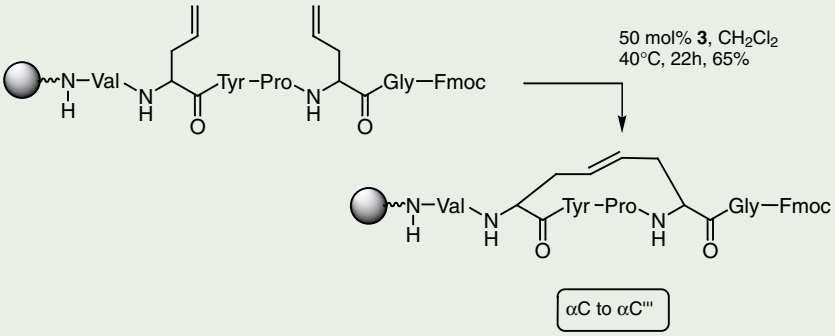

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About the Authors

Dr. Andrew Abell was born in 1960 in Adelaide, South Australia. He obtained a Bachelor of Science with First Class Honours in Organic Chemistry from the University of Adelaide in 1982. Dr. Abell received his Ph.D. from the same university in 1986 working with Dr. Ralph Massy-Westropp on aspects of terpenoid chemistry. Two years were then spent working as a postdoctoral fellow with Professor Sir Alan Battersby at the University of Cambridge, Cambridge, UK. In 1987, he took a position as a lecturer in chemistry at the University of Canterbury, where he is currently employed as a senior lecturer. Dr. Abell was awarded the New Zealand Institute of Chemistry Easterfield Medal in 1995 and a Senior Fulbright Fellowship in 1994, which was spent working at SmithKline Beecham Pharmaceuticals, King of Prussia, USA. He is also a recent recipient of a Royal Society of Chemistry Travel award for international authors. Dr. Abell has authored more than sixty publications and trained 15 Ph.D. students and 6 M.S. students. His current research interests include the design, synthesis, and biological properties of peptidomimetics.

Dr. Andrew Phillips was born in 1970 in Kawerau, New Zealand. In 1995, he obtained a Bachelor of Science with First Class Honours in Biochemistry from the University of Canterbury. The following year, he began a Ph.D. research program with Andrew Abell on the possible applications of ring-closing metathesis to the synthesis of the taxane diterpenoids. He is presently a postdoctoral associate with Professor Peter Wipf at the University of Pittsburgh. His current research interests include the applications of transition metals in organic synthesis, the synthesis of natural products, and the applications of organic synthesis to the investigation of biological processes such as cell signaling.

Lab Notes (continued from page 74).

(1) a crystallization chamber where crystal growth occurs; (2) curved tubes, which serve as gates that prevent the free flow of solutions into the crystallization chamber (as a result of the density difference between the two solutions and the pure solvent); and (3) side arms, which serve as reservoirs for the reacting solutions. Best results are obtained by using a seed crystal of the complex as follows: A small crystal seed is placed into the crystallization chamber. This chamber and the curved tubes are then filled with the pure solvent used in the reaction. The pure solvent serves as a buffer layer preventing the immediate mixing of the two reacting solutions. Separately prepared solutions of reactants **A** and **B** are carefully and simultaneously poured into the corresponding side arms. A smooth addition can be accomplished with the aid of disposable pipettes. The side arms are closed with rubber or plastic stoppers and the system is kept undisturbed for the period of time required for the complete mixing of the two components. Thus, mixing of the solutions occurs slowly in the reaction chamber only due to diffusion.

We used this system to prepare crystals of several complexes of organic hosts with guanidinium and alkylguanidinium salts.[4] The crystals grown in our apparatus, even without crystal seed, were about ten times larger in the edge dimensions (0.3 mm the smallest edge) than the crystals obtained in the vertical tube by layering the reacting solutions. For the apparatus with inner diameters of side arms and curved tubes of 12 mm and 4 mm, respectively, and a total volume of 7 mL, the whole crystal growing process takes about 2 to 3 weeks. After crystal growth has stopped, the stoppers are removed, and the crystals collected by pouring the solution into a beaker. If some crystals remain attached to the glass surface, they can be detached by gentle tapping with a piece of wood.

Our design can be very useful for growing crystals by diffusion of reacting solutions. Compared to the simple layering technique, it provides several advanced features such as smooth and independent-of-density gradient diffusion of the solutions leading to the formation of larger crystals, and the ability to use a crystal seed, since it can be simply placed into the crystallization chamber without special attachment techniques. The crystal growth and the major diffusion interface occur in the same chamber providing the shortest path between regions of local supersaturation and crystallization, thus minimizing the undesired spontaneous formation of many other nucleation sites.

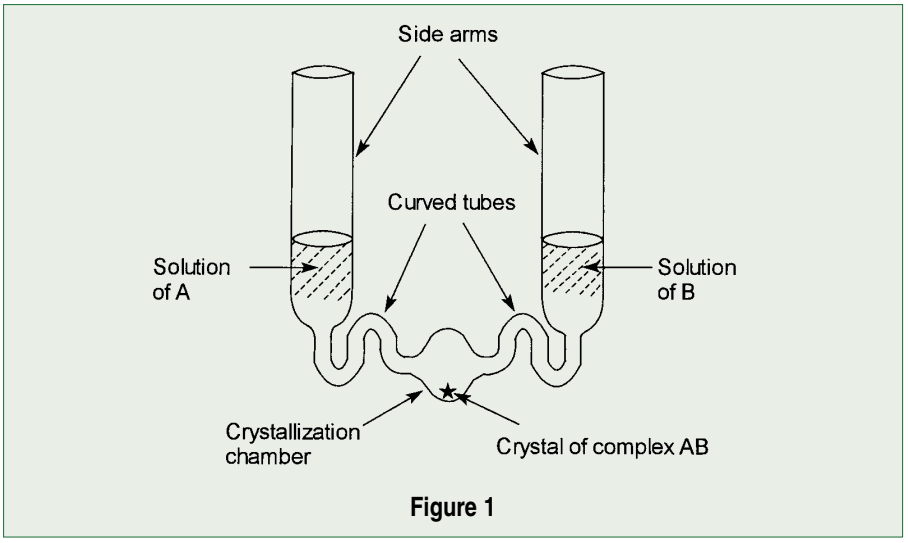

Figure 1

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Alisher B. Khasanov, Graduate Student
Department of Chemistry, MS 216
University of Nevada
Reno, NV 89557-0020
E-mail: akhasa@unr.edu

Editor's Note: Following publication of the lab note, *Maintaining a Constant Water Level in an Open, Warm-Water Bath* (*Aldrichimica Acta* **1999**, *32(2)*, 34), we received other suggestions on accomplishing the same thing. Chester J. Opalka of Albany Molecular Research, Inc. wrote to recommend the use of paraffin wax (e.g., **32,720-4**), which, he states, is easier to separate from the water after the bath has cooled. Jim Brien of Aldrich Techware recommends the use of polypropylene floating balls (**Z37,593-4**). Each of these three ideas, as well as the one recommending the use of polystyrene chips (Stronski, R.E. *J. Chem. Educ.* **1967**, *44*, 767), has its merits and drawbacks; for example the paraffin wax cannot be used if the bath temperature is lower than 56–80 °C. However, each is a lot simpler to carry out than some of the more complicated setups and devices recommended elsewhere in the literature.

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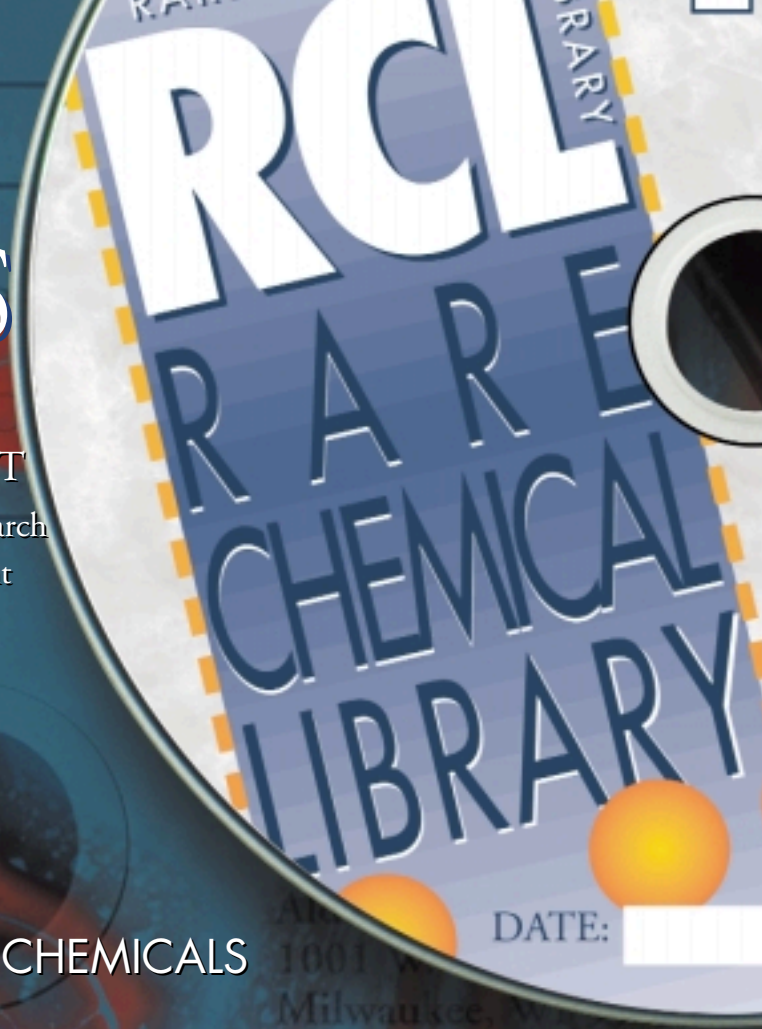

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Molecular Imprinting in Ultrathin Metal Oxide Films

Akira Suzuki
Cross-Coupling Reactions of Organoboron Compounds with Organic Electrophiles

Barry Trost
On Designing Chiral Space for Molecular Recognition in an Asymmetric Catalytic Reaction

For more information, please contact Professor P. V. Ramachandran at chandran@purdue.edu

Year 2000 ACS Award Recipients

Aldrich, a proud sponsor of three separate ACS awards, congratulates the following year 2000 recipients for their outstanding contributions to chemistry.

ACS Award for Creative Work in Synthetic Organic Chemistry

Professor Dennis P. Curran
University of Pittsburgh

Professor Curran has been selected to receive this award in recognition of his lasting impact and outstanding pioneering contributions to such wide-ranging research areas as synthetic radical chemistry, natural product synthesis, stereoselective organic reactions, fluorous chemistry, and others. To paraphrase a recent statement by an admiring colleague, Dennis is one of the most prominent synthetic organic chemists not only in the US, but also in the rest of the world. His loyalty to the University of Pittsburgh has given its chemistry department a top ranking.

ACS Award in Inorganic Chemistry

Dr. Edward I. Stiefel
Exxon Research and Engineering Co.

This award is a fitting tribute to Dr. Stiefel's pioneering research and outstanding achievements in Inorganic Chemistry. In the words of an enthusiastic colleague, Ed has made "significant and original contributions to Co-ordination Chemistry, Bioinorganic Chemistry, Inorganic Materials, and Catalysis", and is regarded as a "leading international authority" in these areas. Most noteworthy are his studies of transition metal sulfide complexes that have important biological and industrial applications, his synthesis of the first isolated metal complexes of the anti-Parkinsonism drug L-DOPA, and his discovery and development of the remarkable "induced internal electron transfer reactions" in which the addition of an external oxidant leads to reduction of the metal center.

Herbert C. Brown Award for Creative Research in Synthetic Methods

Professor Samuel J. Danishefsky
Sloan–Kettering Institute for Cancer Research and Columbia University

One of the leading synthetic organic chemists of the twentieth century, Professor Danishefsky was chosen for this award on the basis of his seminal contributions to the twin areas of synthetic methodology and total synthesis of complex molecules of biological significance. Notable examples of the former include the glycal assembly method for the synthesis of oligosaccharides and glycoconjugates, the Diels—Alder reaction of siloxydienes, and Lewis acid catalyzed cyclocondensation reactions. His accomplishments in the latter area include the total synthesis of paclitaxel, camptothecin, coriolin, and pancratistatin, to name only a few.

Congratulations to each and all!

Are Two Phenyls Better than One? Synthesis and Applications of (*R*)-4-Diphenylmethyl-2-oxazolidinone

Mukund P. Sibi
Department of Chemistry
North Dakota State University
Fargo, ND 58105, USA
E-mail: sibi@plains.nodak.edu

Outline

1. Introduction

Chiral auxiliaries have played a key role in the development of efficient and elegant routes to a variety of enantiomerically pure compounds (**Figure 1**).[1] Academics as well as the chemical industry have made extensive use of chiral auxiliaries in the synthesis of target molecules. The more commonly used auxiliaries are derived from either amino acids or terpenes. The availability of these naturally occurring materials in both enantiomeric forms makes them ideal starting materials. Oxazolidinones, readily available from chiral amino alcohols, have been the more popular auxiliaries.[2] Pioneering work from Professor David Evans's group has firmly established the utility of oxazolidinones as superior auxiliaries for a variety of bond constructions.[3]

Compounds **2–5** are generally successful in providing high levels of selectivity in a large number of transformations (alkylation, aldol, Diels–Alder, etc.). However, there are reactions in which they do not provide adequate selectivity. A notable transformation in this category is the conjugate addition reaction. While working on the preparation of unnatural amino acids from serine, we came upon an oxazolidinone which, we thought, was worth looking into as a chiral auxiliary. Our hypothesis was that, by placing a large group at the oxazolidinone 4 position, which extends its bulk to the β carbon in enoates, there was the potential for achieving a higher selectivity in transformations in which the traditional chiral auxiliaries did not perform satisfactorily. This account describes the preparation and utilization of a new oxazolidinone auxiliary, **1**, that is derived from diphenylalaninol. The chemistry described here is work from our laboratory only. Wherever possible, the advantages and disadvantages of the new auxiliary and its efficiency, as compared to that of the traditional compounds, will be highlighted.

2. Synthesis of (*R*)-4-Diphenylmethyl-2-oxazolidinone

Chiral oxazolidinones can be readily prepared from the corresponding amino alcohols. However, there are only a few enantioselective routes to the parent amino acid, diphenylalanine,[4] and most of these require several steps. We have prepared **1** in three steps from serine methyl ester hydrochloride (**Scheme 1**). Treatment of **12** with triphosgene and triethylamine provides oxazolidinone **13** in 95% yield. The desired aryl groups are introduced by reaction of **13** with phenylmagnesium bromide to furnish tertiary alcohol **14**,

which is then deoxygenated with Na/NH_3. The synthesis of **1** {mp: 135–137 °C, $[\alpha]_D^{20}$ = +37.1° (c = 1.0, CH_2Cl_2)} is amenable to scaleup, and we have typically prepared **1** in 25–50-g quantities.[5] Having reasonable quantities of the auxiliary on hand, we set out to evaluate its utility by examining three major types of reactions: alkylation, aldol condensation, and conjugate addition.

3. Alkylation Reactions

The synthetic utility of oxazolidinone **1** in stereoselective alkylations was explored first (**eq 1**).[6] Thus, treatment of **15**[7] with NaHMDS in THF at -78 °C produced an enolate, which, upon quenching with reactive alkyl bromides, furnished the alkylated products **16** in moderate-to-good yields and excellent diastereofacial selectivity. The stereochemical course of these reactions was established for one of the examples by $LiOH/H_2O_2$ hydrolysis of **16** (R = CH_2Ph) to afford a known carboxylic acid. In comparison, alkylation with benzyl bromide of the lithium enolate derived from the *N*-propionyl derivative of **2** proceeds in 92% yield and >99% de.[8]

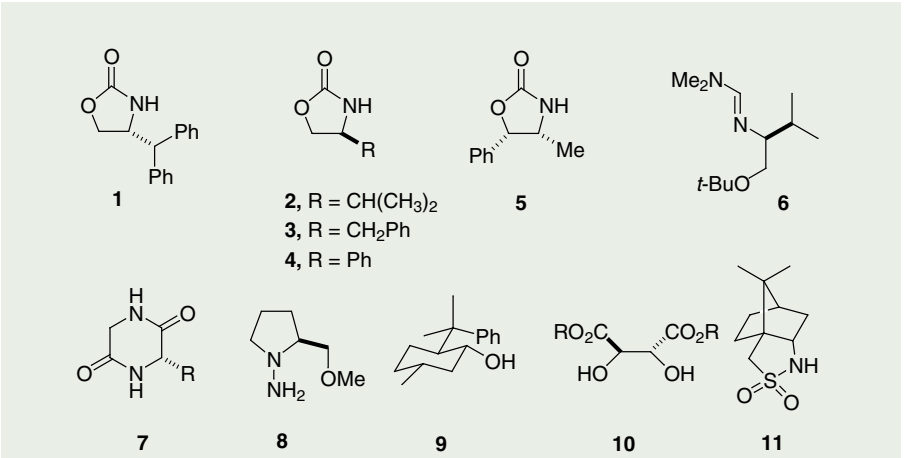
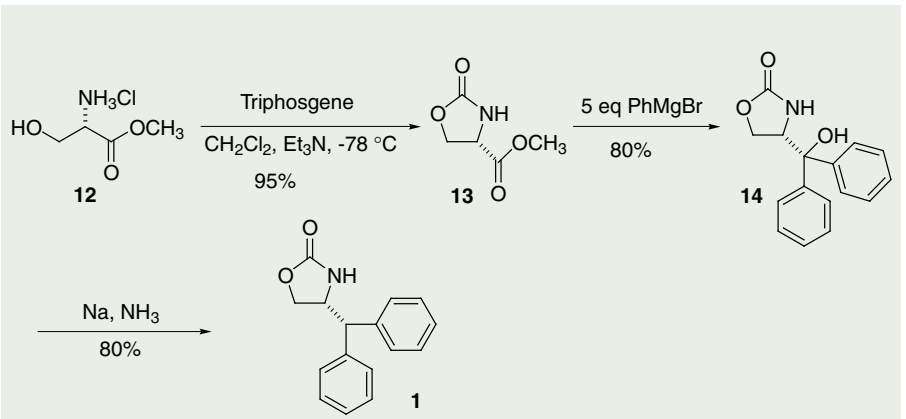
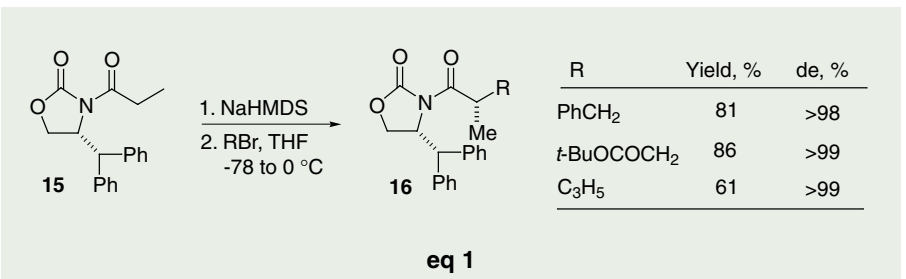


Figure 1. Some Commonly Used Chiral Auxiliaries.

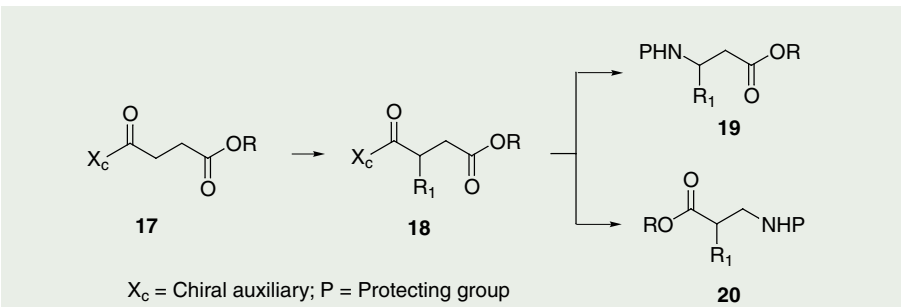


Scheme 1. Synthesis of the Chiral Auxiliary.



R	Yield, %	de, %
$PhCH_2$	81	>98
t-$BuOCOCH_2$	86	>99
C_3H_5	61	>99

eq 1



Scheme 2. Outline for the Synthesis of β-Amino Acids.

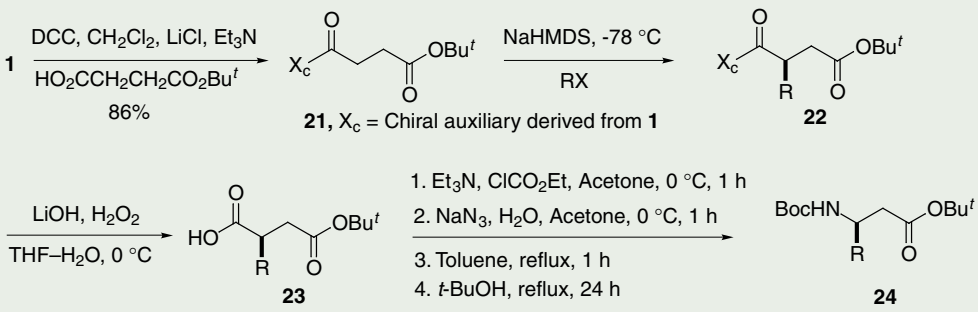
3.1. Synthesis of β-Amino Acids

Naturally occurring β-amino acids are compounds with an interesting pharmacological profile.[9] They are also found as components in a wide variety of biologically active compounds,[10] including peptides such as pepstatin.[11] β-Amino acids are also useful precursors in the synthesis of β-lactams.[12] Recently, α-substituted β-amino acids have received greater scrutiny, since they are important segments of bioactive molecules such as paclitaxel.[13]

We have evaluated the synthesis of β-amino acids in the context of a general methodology involving functionalization of linear dicarboxylic acid derivatives in a regio- and stereoselective manner. The succinate unit is an ideal fragment for the synthesis of a variety of natural products if substituents can be introduced regio- and stereoselectively onto the carbon framework.[14] Further selective conversion of one of the carboxyl groups to an amino functionality by a Curtius rearrangement provides access to β-amino acids. Alternatively, the lactonization strategy provides butyrolactone natural products (*vide infra*).

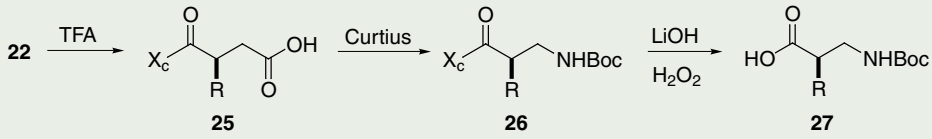
Scheme 2 illustrates our approach to β-amino acids wherein the starting material is a readily available succinate, **17**. The two carboxyl groups are differentiated by forming an ester at one end and attaching a chiral auxiliary to the other. With the two ends differentiated, the first step is a regio- and stereoselective alkylation at the carbon α to the imide functionality to furnish **18**. The second step involves the selective removal of either the imide or the ester functionality; this is then followed by a Curtius rearrangement of the free carboxyl group with retention of stereochemistry (if applicable). Thus, intermediate **18** serves as a common precursor for two different β-amino acids, **19** and **20**.[15]

Our methodology began with the attachment[16] of the mono-*tert*-butyl succinate[17] to oxazolidinone **1** (**Scheme 3**). Treatment of **21** with one equivalent of NaHMDS, followed by quenching with a reactive alkyl bromide, furnished **22** in good yield and diastereoselectivity.[18] In this reaction step, temperature and counterion played an important role in the generation of the enolate. When the reaction mixtures were warmed to above -48 ºC, after sodium enolate generation, cleavage of the chiral auxiliary was observed. The regioselectivity observed for the enolate generated from **21** may be attributed to the higher acidity of the hydrogens α to the imide as compared with those α to the ester group.[19] The next step involved the selective hydrolysis of the imide functionality. This was accomplished by treating **22** with $LiOH/H_2O_2$ to furnish **23**.[20] The key step in our methodology was the use



RBr	Yield **22**, % (de)	Yield **23**, %	Yield **24**, %
Benzyl bromide	83 (92)	90	83
Allyl bromide	72 (92)	88	80
(*E*)-1-Bromo-3-undecene	60 (97)	87	90
Cinnamyl bromide	73 (84)	80	78
Methyl iodide	83 (81)		

Scheme 3. Synthesis of β-Amino Acids.



R	Yield **25**, %	Yield **26**, %	Yield **27**, %
CH_2Ph	93	68	87
C_3H_5	97	69	98
CH_3	55	66	83

Scheme 4. Synthesis of Isomeric β-Amino Acids.

of the Curtius rearrangement to effect the one-pot conversion of the carboxylic acid group to the protected amino group with retention of stereochemistry (**23** to **24**).[21,22] Thus, the synthesis of β-amino acids was accomplished in four steps in good overall yields and high optical purities.

Intermediate **22** also served as a useful precursor for the synthesis of isomeric β-amino acids (**Scheme 4**). Selective deprotection of the *tert*-butyl ester functionality was achieved in high yields using trifluoroacetic acid. Curtius rearrangement followed by cleavage of the imide provided the isomeric β-amino acids in good yields (**26** → **27**).

3.2. Radical Allylations

The stereoselective introduction of functional groups into acyclic systems by free radical methods is often a challenge.[23] As has been amply demonstrated in the literature, as well as by the chemistry illustrated above, oxazolidinones provide high stereoselectivities in enolate alkylations. We were intrigued by the potential of oxazolidinones in radical chemistry, and wondered whether they would be equally suited for the introduction of the allyl group under a radical chain process. However, the use of oxazolidinone auxiliaries[24] in radical reactions has been hampered by the limited rotamer control that is available in the absence of Lewis acid additives.[25] Based on literature precedents for Diels–Alder reactions using oxazolidinone auxiliaries, we surmised that a proper combination of a chelating Lewis acid and the R group in the chiral auxiliary would allow for highly diastereoselective radical reactions. This would require that the radical react from a single rotamer (**28**) out of several possible rotamers (**28**–**31**) (**Figure 2**).

Radical allylations using several mono- and multidentate Lewis acids were tested (**Table 1**).[26] As expected, poor selectivity was observed with single-point-binding Lewis acids, such as BF_3•OEt_2. Of the Lewis acids examined, scandium and magnesium reagents resulted in the highest selectivities.[27] The sense of stereoinduction in the Lewis acid mediated radical allylation was the same as that of the enolate allylation, with the two reactions providing comparable diastereoselectivities.

The effect of the substituent at C-4 of the oxazolidinone ring was also examined. The results shown in Table 1 indicate that arylalkyl substituents provide the highest selectivities, and, of these, the diphenylmethyl and tritylmethyl groups give the best results. The traditional Evans auxiliaries derived from phenylalaninol and valinol gave good and low selectivities, respectively.

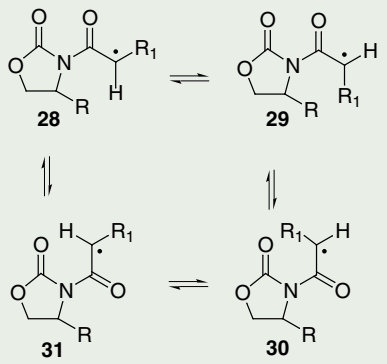
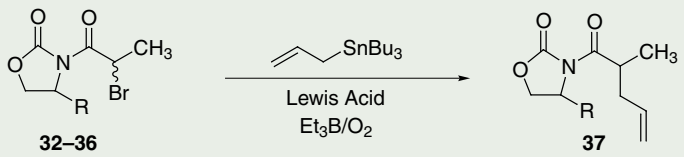


Figure 2. Rotamers of *N*-Acyloxazolidinones.

Table 1. Effect of Lewis Acid and Chiral Auxiliary on the Diastereoselectivity of Radical Allylations.



Compound (config.)	Lewis Acid	Reaction Conditions	Yield, %	Ratio (config.)[a]
32, R = $CH(Ph)_2$ (*R*)	None	-78 °C, CH_2Cl_2, 3 h	93	1:1.8 (*S*)
	$BF_3{\cdot}OEt_2$	-78 °C, CH_2Cl_2, 2.5 h	85	1:1.4
	$MgBr_2$	-78 °C, CH_2Cl_2, 2 h	94	≥100:1 (*S*)
	$Yb(OTf)_3$	-78 °C, THF, 2 h	86	5:1
	$Sc(OTf)_3$	-78 °C, ether, 2 h	94	≥100:1
33, R = CH_2CPh_3 (*R*)	$Sc(OTf)_3$	-78 °C, ether, 2 h	88	100:1 (*S*)
34, R = CH_2Ph (*R*)	$Sc(OTf)_3$	-78 °C, ether, 2 h	91	58:1 (*S*)
35, R = $CH(CH_3)_2$ (*S*)	$MgBr_2$	-78 °C, CH_2Cl_2, 2 h	85	2.8:1
36, R = Ph (*S*)	$MgBr_2$	-78 °C, CH_2Cl_2, 2 h	92	3:1

[a] The configuration of the major isomer at the newly formed chiral center.

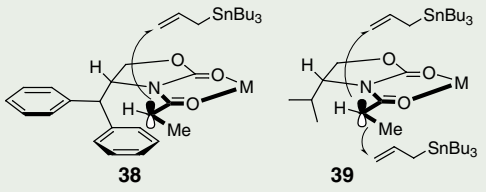


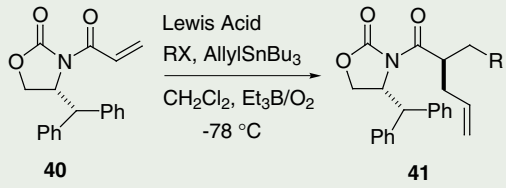
Figure 3. Models for Chiral-Auxiliary-Dependent Selectivity.

A model, **38**, that accounts for the observed selectivity is shown in **Figure 3**. In this model, the metal coordinates both carbonyl oxygens, and the allylic 1,3 strain favors the *s-cis* rotamer of the intermediate radical. Allylstannane addition to the chelated intermediate takes place from the face opposite the bulky oxazolidinone 4-substituent. The low selectivity observed for **35**, with an isopropyl substituent (see **39**), as compared to those for **32** and **34**, with diphenylmethyl and benzyl substituents, suggests that additional factors may, in conjunction with steric effects, be responsible for the high selectivities observed with these auxiliaries.[28]

Diastereoselective allylations were also achieved in a slightly different manner through radical addition to chiral oxazolidinone acrylate and trapping with allylstannane (**Scheme 5**).[29] In reactions with α,β-unsaturated substrates, the Lewis acid functions not only to control the rotamer populations, but also to increase the reactivity at the β carbon. After initial addition of the radical, an intermediate is generated at the α position and is trapped readily with allylstannane. It was found that magnesium bromide provides the highest selectivities (>100:1) in the tandem addition of isopropyl radical and trapping with allylstannane. A variety of radical precursors were employed to evaluate the scope of this methodology. Excellent diastereoselectivities resulted from alkyl radicals and acyl radicals, but the methoxymethyl radical appeared to interfere with the Lewis acid, in particular $MgBr_2$. Higher selectivities were attainable with $Yb(OTf)_3$ as a Lewis acid, presumably as a reflection of its higher coordinating ability. As in the case of the simple allylations discussed in Table 1, the highest diastereoselectivities were also obtained with auxiliary **1** in the tandem addition–trapping reactions.

4. Aldol Reactions

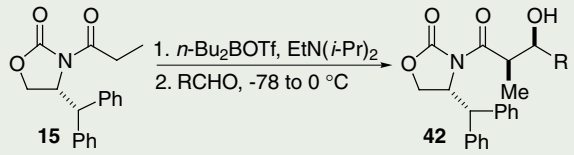
A major breakthrough in the total synthesis of complex natural products was the development of the stereoselective aldol reaction that uses boron enolates derived from *N*-acyloxazolidinones.[30] As a prelude to exploring the utility of **1** in the total synthesis of natural products, aldol reactions of **15** with representative aldehydes were examined (**eq 2**). The *Z* enolate of **15** was generated upon treatment with *n*-Bu_2BOTf followed by diisopropylethylamine in CH_2Cl_2 at 0 °C.[6] Quenching of the enolate with the appropriate aldehyde produced the syn aldol, **42**, in good yield. NMR and HPLC analyses of the crude reaction mixtures indicated that each aldol product was formed essentially as a single diastereomer. Crystallinity of all the aldol adducts was an advantage in their purification. The absolute stereochemistry of the aldol product was confirmed by hydrolysis of **42** to furnish the enantiomer of a known carboxylic acid in 90% yield, along with the chiral auxiliary (94%). In comparison, an aldol reaction of the *N*-propionyl derivative of **2** with benzaldehyde gave the product with >97% de. These results show that oxazolidinone **1** can be effectively employed in aldol reactions.



RX	Lewis Acid	Yield, %	Ratio[a]
CH_3I	$MgBr_2$	82	>100:1
i-PrI	$MgBr_2$	85	>100:1
t-BuI	$MgBr_2$	94	>100:1
$MeOCH_2Br$	$Yb(OTf)_3$	70	58:1
MeCOBr	$MgBr_2$	55	50:1

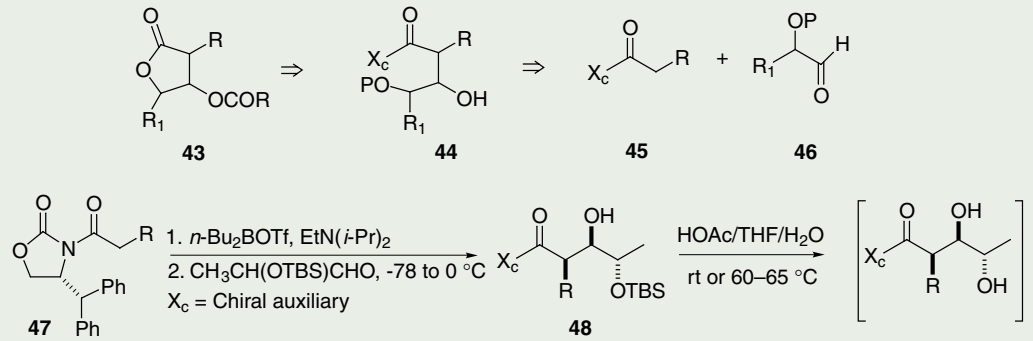
[a] Diastereomeric ratio (by ^1H NMR)

Scheme 5. Tandem Addition—Allylation.



RCHO	Product	Yield, %	de, %
PhCHO	R = Ph	83	98
Piperonal	R = $-C_6H_3(-OCH_2-O-)$	82	97
Hexanal	R = C_5H_{11}	84	97

eq 2



Overall Yields	
NFX-2: 49; R = C_6H_{13}	58%
NFX-4: 49; R = $(CH_2)_4CHMe_2$	49%
Blastmycinone: 50; R = C_4H_9, $R_1 = CH_2CHMe_2$	64%
Antimycinone: 50; R = C_6H_{13}, $R_1 = CH_2CHMe_2$	51%

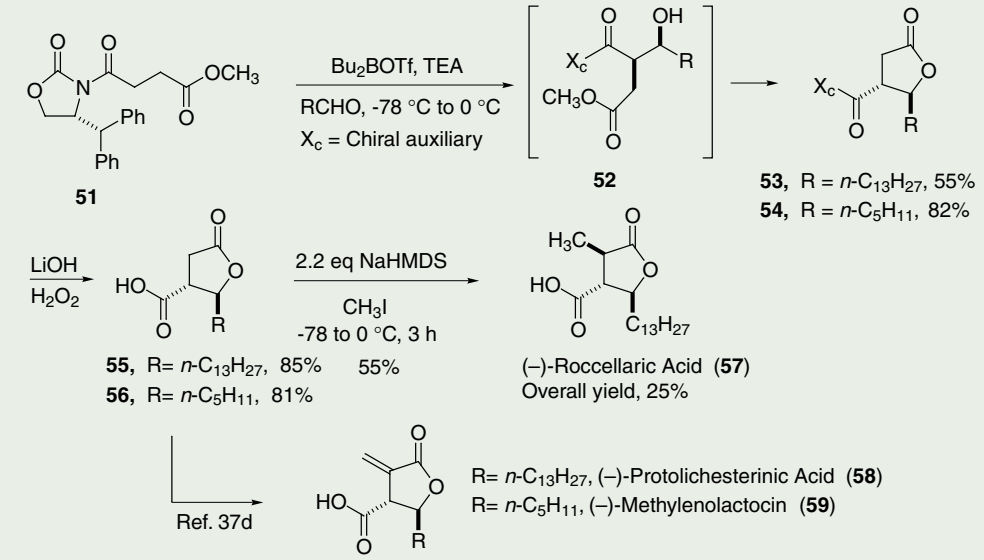
Scheme 6. Synthesis of Butyrolactone Natural Products.

4.1. Synthesis of Butyrolactone Natural Products

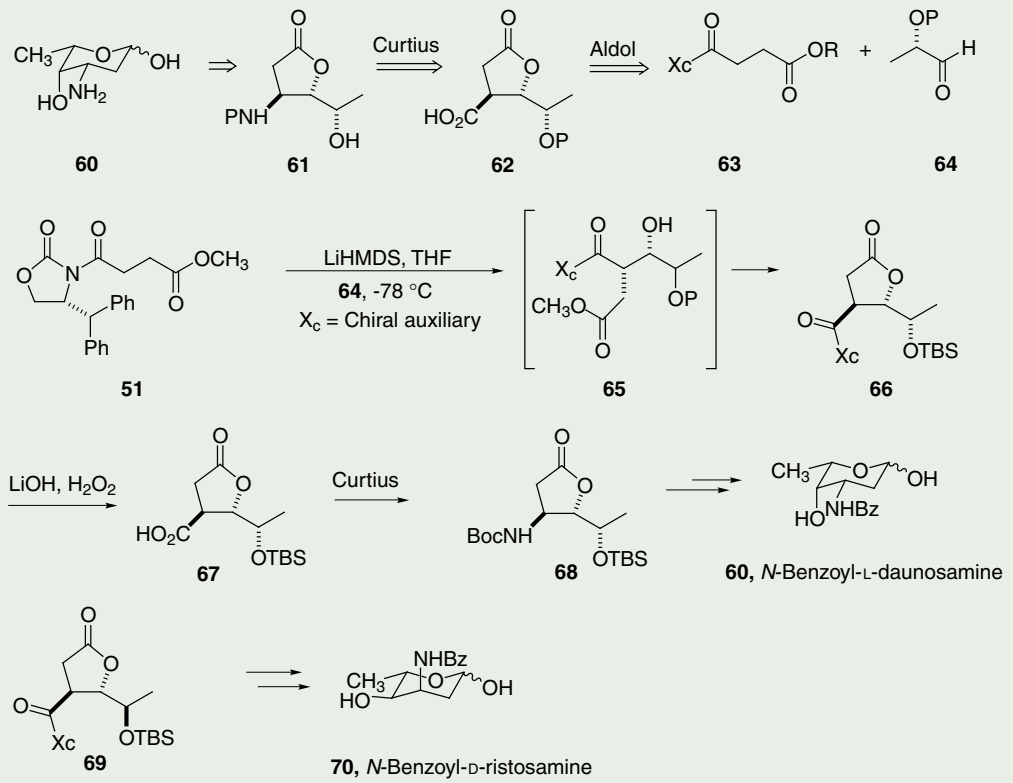
The development of new methodologies for the synthesis of butyrolactone natural products has received considerable attention.[31] The 3-alkyl-4-hydroxy-5-methyl-2(3*H*)-dihydrofuranone substructure is found in a wide variety of metabolites with very different origins.[32] Of these, the polyketide metabolites blastmycinone,[33] NFX-2,[34] antimycinone,[35] and NFX-4 contain short-to-medium-length carbon chains at the C-3 position.

The three contiguous chiral centers in blastmycinone and related compounds present a reasonable challenge for the development of new methodologies. We have been interested in exploring the aldol reaction between α-alkoxy aldehydes (**46**) and chiral *N*-acyloxazolidinones (**45**) as a method for the establishment of the stereotriad. The relative and absolute stereochemistries of the stereocenters would then be established by the nature of the aldol reaction (syn or anti) and by the resident chiralities of the auxiliary and the α-alkoxy aldehyde (**Scheme 6**).

The reaction of OTBS-lactaldehyde with the boron enolate derived from **47** gave the syn aldol product **48**.[36] Yields for the aldol product from several runs only averaged around 60%. Subsequently, enolate generation using modified conditions (Bu_2BOTf, Me_2NPh/Et_2O/0 °C/1 h; aldehyde/-78 °C to 0 °C/24 h) led to a reasonable improvement in chemical yields for the aldol products. Careful deprotection of the silyl group in **48** gave the hydroxy-lactones directly in good yields. These were then converted to the natural products by acylation. This strategy to the target



Scheme 7. Synthesis of Paraconic Acid Natural Products.



Scheme 8. Synthesis of Amino Sugars.

lactones has two key attributes: high overall yields and a small number of synthetic steps.

4.2. Synthesis of Paraconic Acid Natural Products

Paraconic acids (4-carboxy-γ-butyrolactones) are a small class of biologically active butyrolactone natural products.[37] Three members from this class, methylenolactocin, protolichesterinic acid, and roccellaric acid have received attention, since they exhibit antibiotic, antitumor,[38] antifungal, and growth-regulating properties. As discussed earlier, we were interested in the utilization of linear dicarboxylic acids for the synthesis of trisubstituted lactone natural products by cyclization and carboxyl differentiation.

Our synthetic strategy for these natural products was based on the selective aldol reaction at the α carbon of the imide (**Scheme 7**).[39] Using the well-established boron triflate mediated reaction of **51** gave the syn aldol product, **52**. This product could be

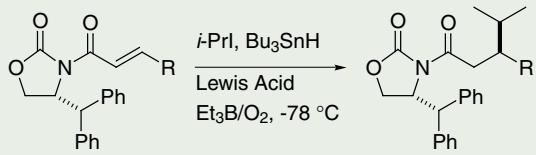
isolated prior to lactonization, but chemical yields suffered dramatically (40–45%); therefore, the cyclization was carried out without the isolation of **52**. The syn selectivity in the aldol reaction was established by converting the aldol products to compounds of known configurations. At this stage, we tried to introduce the desired methyl group at C-3 by metallation/alkylation of **53**. These experiments were unsuccessful: None of the desired products was obtained, and cleavage of the chiral auxiliary was observed along with several other unidentified products. Successful installation of the methyl group was possible with the acid derivative **55**. Treatment of **53** with in situ generated lithium hydroperoxide gave acid **55** as well as the chiral oxazolidinone **1**. Introduction of the C-3 methyl group with the desired β stereochemistry was carried out by dideprotonation followed by treatment with methyl iodide. The use of 2.2 equivalents of NaHMDS gave roccellaric acid only (β:α = >100:1) along with unreacted starting material (55% yield; 95% based on recovered starting material). The use of LiHMDS gave both diastereomers (β:α = 1:1) as well as some of the dialkylation product.[40] The overall yield of roccellaric acid was 25% over four steps.[41] Compounds **55** and **56** have been converted by Greene and co-workers to protolichesterinic acid and methylenolactocin, respectively.[37d]

4.3. Synthesis of Amino Sugars

The studies described above established two protocols for strategic bond formations: (1) selective functionalization α to the imide carbonyl in a differentially protected succinate, and (2) Curtius rearrangement in monosubstituted succinic acids with retention of configuration. We wanted to combine these two protocols for the synthesis of amino sugars. A number of clinically important anthracycline antibiotics contain a 3-amino-hexose unit as part of their structures. L-Daunosamine[42] (**60**) is the glycosidic component of naturally occurring anthracyclines daunomycin, adriamycin, and carminomycin;[43] and L-ristosamine is a component of the glycoprotein ristomycin.[44]

The key features of our synthetic strategy for daunosamine are: (1) the regio- and diastereoselective syn aldol reaction of a desymmetrized chiral succinate with an O-protected lactaldehyde (**63** + **64** to **62**), and (2) the Curtius rearrangement of the acid **62** to an advanced intermediate, **61** (**Scheme 8**). Further adjustments in the oxidation state of **61** lead to the target amino sugar. Additionally, D-ristosamine, the C-5 epimer of daunosamine, can also be prepared using the same methodology by using the O-protected (*R*)-lactaldehyde.

Table 2. Conjugate Radical Additions.



71, R = CH_3
72, R = Ph
73, R = CO_2Et

74, R = CH_3
75, R = Ph
76, R = CO_2Et

Model for the observed selectivity

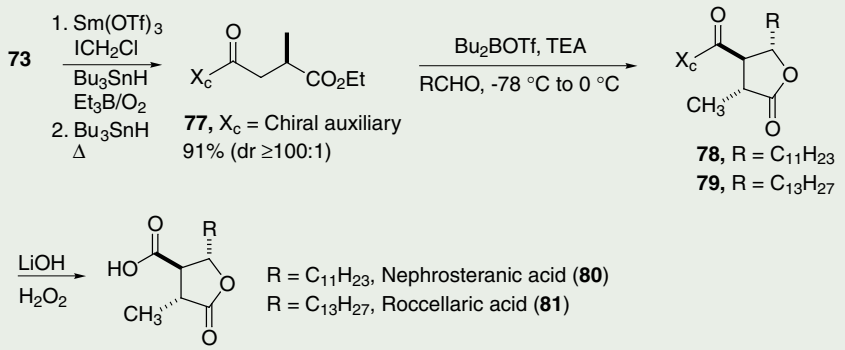
Oxazolidinone	Lewis Acid (eq)	Reaction Conditions	Yield, %[a]	Diastereomeric Ratio[b]
71	None	-78 °C, CH_2Cl_2/hexane	60	1.3:1
	$BF_3 \cdot OEt_2$ (1.0)	-78 °C, CH_2Cl_2/hexane	80	1.3:1
	$Sc(OTf)_3$ (1.0)	-78 °C, CH_2Cl_2/hexane/THF	90	15:1
	$Yb(OTf)_3$ (1.0)	-78 °C, CH_2Cl_2/hexane/THF	93[c]	25:1
72	$MgBr_2$ (1.0)	-78 °C, CH_2Cl_2/hexane/ether	90	20:1
	$Yb(OTf)_3$ (1.0)	-78 °C, CH_2Cl_2/hexane/THF	89[c]	45:1
	$Yb(OTf)_3$ (0.3)	-78 °C, CH_2Cl_2/hexane/THF	90	20:1
	$Lu(OTf)_3$ (1.0)	-78 °C, CH_2Cl_2/hexane/THF	90	50:1
73	$Mg(OTf)_2$ (1.0)	-78 °C, CH_2Cl_2	87	1:1
	$Sm(OTf)_3$ (1.0)	-78 °C, CH_2Cl_2/THF	95	29:1
	$Er(OTf)_3$ (3.0)	-78 °C, CH_2Cl_2/THF	91	71:1

[a] NMR yields. [b] Determined by 'H NMR. [c] Yield of purified material.

In contrast to the good chemical efficiency of the reactions of **51** and simple aliphatic aldehydes described above (see Scheme 7), the chemical yields in the boron-mediated aldol condensations with protected lactaldehydes were disappointing.[45] These results led us to examine reactions with lithium enolates, which have been shown to be more reactive.[46] Treatment of a THF solution of **51** with LiHMDS at -78 ºC furnished the lithium enolate, which was immediately reacted with a freshly prepared (*S*)- or (*R*)-*O*-TBS-lactaldehyde solution. We were delighted to find that these reactions gave a satisfactory chemical yield as well as high diastereoselectivity (**Scheme 8**). The aldol reactions were highly syn-selective: the absolute stereochemistry (non-Evans syn) obtained was the opposite of that observed in the boron-mediated aldol reaction (Evans syn). The diastereoselectivity in the aldol reaction was ~15:1. As has been reported in the literature,[47] ca. 14% of chiral auxiliary cleavage was observed in the lithium aldol reaction. The aldol adduct, **65**, underwent lactonization slowly, thus requiring acid catalysis. The imide could be conveniently deprotected to furnish the acid, **67**. In contrast to the Curtius rearrangement of the acyclic system **23**, the rearrangement of **67** to **68** was more facile with diphenylphosphoryl azide (DPPA). The synthesis was completed by a reduction–deprotection sequence, or by the reverse sequence. Yields of the target amino sugars by the former sequence were higher. Similarly, lactone **69**, the aldol–cyclization product from **51** and (*R*)-*O*-TBS-lactaldehyde, was converted to ristosamine. The overall yields of daunosamine and ristosamine were 18% in each case.

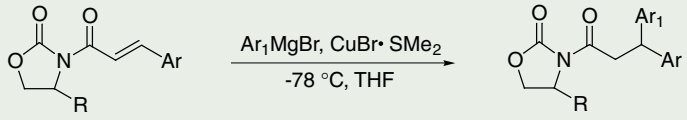
5. Conjugate Additions

Conjugate addition is one of the most important transformations in synthetic organic chemistry.[48] Diastereoselective conjugate additions to control stereochemistry at the β center have been approached in a number of ways. One approach utilizes chiral auxiliaries on the acceptor and yields products highly diastereoselectively. Another approach uses chiral nucleophiles (either chiral themselves or having chiral attachments), again highly selectively. Of the variety of chiral auxiliaries examined for conjugate addition, oxazolidinones have generally been inferior in terms of selectivity. Recently, several groups have undertaken a systematic study of various



Scheme 9. Conjugate Radical Addition to Fumarates. Synthesis of Paraconic Acid Natural Products.

Table 3. Diastereoselective Conjugate Additions. Effect of Chiral Auxiliary on Selectivity.



72, 82–86 **87–93**

Reactant	R	Ar	Prod.	Ar_1	Yield, %	de, %
72	$CH(Ph)_2$	Ph	**87**	3,4,5-$(MeO)_3C_6H_2$	85	88
82	$CH(Ph)_2$	3,4-$(OCH_2O)C_6H_3$	**88**	Ph	90	97
83	$CH(Ph)_2$	3,4,5-$(MeO)_3C_6H_2$	**89**	3,4-$(OCH_2O)C_6H_3$	88	95
83	$CH(Ph)_2$	3,4,5-$(MeO)_3C_6H_2$	**90**	3,4-(OCH_2O)-5-$MeOC_6H_2$	89	97
84	CH_2Ph	Ph	**91**	3,4-$(OCH_2O)C_6H_3$	80	28
85	CH_2Ph	3,4-$(OCH_2O)C_6H_3$	**92**	Ph	85	36
86	Ph	Ph	**93**	3,4-$(OCH_2O)C_6H_3$	90	92

auxiliaries in the addition of copper reagents to enoates.[49] Hruby has shown that the oxazolidinone derived from phenylglycinol provides high selectivity in the addition of aryl cuprates to cinnamates.[50] In the following section, we describe the use of **1** in conjugate additions to acyclic systems using radical and copper nucleophiles, and compare its effectiveness vis-à-vis the traditional oxazolidinones in controlling the stereochemistry at the β carbon.

5.1. Radical Conjugate Additions

When we initiated our study, examples of highly diastereoselective, intermolecular, conjugate radical additions in acyclic systems were rather sparse.[51] As discussed in section 3.2, we felt that, by utilizing a chelating Lewis acid and the proper choice of the C-4 substituent of the oxazolidinone, rotamer control should be feasible, and that there was potential for obtaining a high selectivity in the conjugate addition.

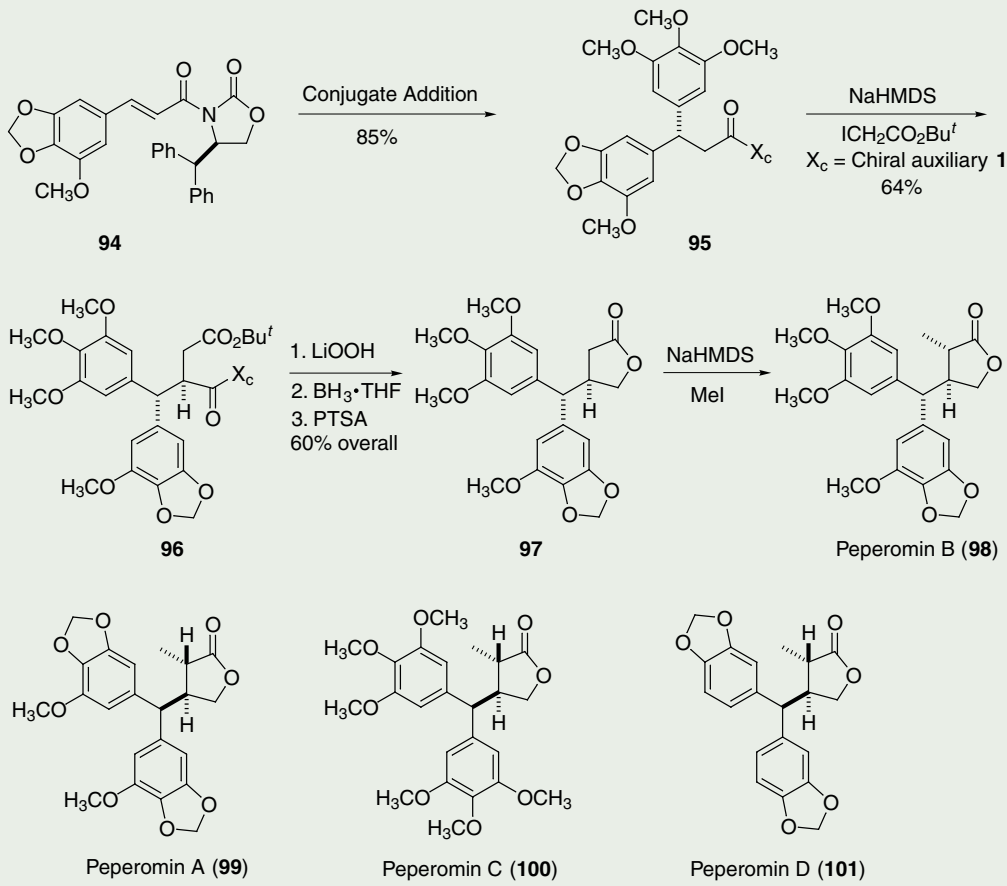
Intermolecular conjugate addition of the nucleophilic isopropyl radical to enoates **71**–**73**, derived from oxazolidinone **1**, in the absence and presence of various Lewis acids was investigated (**Table 2**).[52] After evaluating several Lewis acids, some trends emerged. Lanthanide Lewis acids provided the highest levels of selectivity, and the use of substoichiometric amounts of Lewis acids had a negligible effect on the stereoselectivity or reaction efficiency. It must be noted that the level of selectivity achieved through free radical conjugate addition to oxazolidinones rivals, if not surpasses, that obtained through ionic methodology.[50] Higher selectivities were observed for the less reactive cinnamates than for the more reactive crotonates in conjugate radical additions.

In a similar manner, conjugate radical additions to differentially protected fumarate **73** allowed access to functionalized succinates.[53] Regioselectivity in these radical additions is provided by preferential activation of the β carbon by the Lewis acid, which coordinates the imide carbonyl. These conjugate additions proceeded in excellent yields. High regio- and diastereoselectivity were observed with lanthanide and other Lewis acids, but little selectivity was seen in the absence of a chelating Lewis acid or with substoichiometric amounts of the Lewis acid. In general, the reactivity pattern was fumarate > crotonate > cinnamate. In contrast to the reactivity of crotonates and cinnamates in these reactions, where it was possible to use catalytic amounts of the Lewis acid, the fumarate substrate was orders of magnitude more reactive, and, hence, a highly selective radical addition to fumarate under catalytic Lewis acid conditions was not possible.

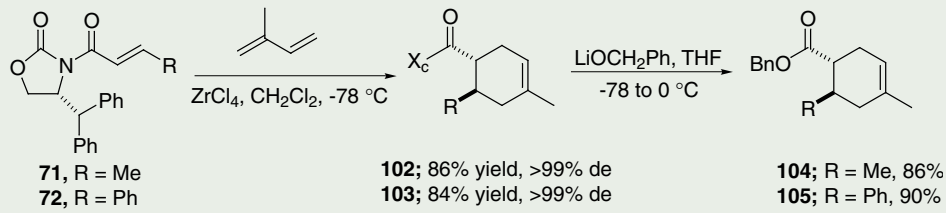
A model that accounts for the stereochemical outcome of the reaction is shown in Table 2. Upon chelation of the two carbonyls with the Lewis acid, their orientation becomes fixed. The Lewis acid also activates the β carbon toward addition of the nucleophilic radical species. A proper matching of the Lewis acid and the substrate, as well as the nucleophilicity of the radical, are the key factors in obtaining good chemical yields and high selectivities in the reaction. The stereochemistry of the product can be explained by postulating that the radical approaches from the face opposite the bulky diphenylmethyl substituent in the chelated intermediate. As was seen in the allylation experiments, replacement of the diphenylmethyl group by the smaller benzyl or isopropyl group (Evans auxiliary) results in much lower selectivities (~3:1). Similarly, the phenylglycinol-derived oxazolidinone is equally ineffective.

5.2. Synthesis of Paraconic Acid Natural Products

The difficulties we had with the introduction of the methyl group at C-3 (see section 4.2) led us to devise alternate approaches to the synthesis of paraconic acid natural products. The facile conjugate addition of nucleophilic radicals to fumarate **73** and the selective aldol reactions with succinates boded well for the new strategy. Conjugate addition of the chloromethyl radical to **73** gave the conjugate addition product in high chemical yield as a single isomer (**Scheme 9**). The chloro group was reduced at higher temperatures using radical conditions to furnish the methyl compound. Thus, we were able to install the remote chiral center in a highly selective manner. However, the direct introduction of the methyl group using methyl iodide was not possible. Boron triflate mediated, syn-selective aldol condensation of **77** with the respective aldehydes furnished **78** and **79** in high yields. Selective removal of the chiral auxiliary gave the natural products



Scheme 10. Synthesis of Peperomins.



Scheme 11. Diels–Alder Reactions.

(–)-nephrosteranic acid (**80**) and (–)-roccellaric acid (**81**). The natural products were synthesized in four steps in 53% and 42% overall yields, respectively. The key step in the total synthesis, the conjugate addition to **73**, once again illustrates the utility of **1** in controlling the stereochemistry at the β center.

5.3. Conjugate Addition of Copper Reagents

In connection with a project on the total synthesis of lignan natural products described in section 5.4, we became interested in exploring diastereoselective conjugate additions using copper reagents. To this end, we examined the addition of aryl Grignard reagents to the oxazolidinone-derived cinnamates, **72** and **82–86**, in the presence of Lewis acids and other additives (**Table 3**). The best reaction conditions involved the use of the Grignard reagent and the copper(I) bromide–dimethyl sulfide complex. NMR and HPLC analyses indicated that the diastereoselectivity was very high and was dependent on the oxazolidinone C-4 substituent: Chiral auxiliaries **1** and **4** gave the best selectivity, whereas **3** was far less selective—as reported by Hruby.[50,54] These experiments clearly show that **1** can shield the β carbon effectively in both radical and copper additions.

5.4. Synthesis of Peperomins

Recently, a novel and unusual class of lignans, peperomins, were isolated from *Peperomia japonica*[55] and from *Peperomia glabella*.[56] Using the conjugate addition protocol described in section 5.3, we have now developed an efficient route for the total synthesis of peperomins A–D.[57] This

synthesis relies on the use of functionalized succinates and their further elaboration into the target molecules.

Conjugate addition of the Grignard reagent derived from 1-bromo-3,4,5-trimethoxybenzene to **94** (Xc = **1**) in the presence of CuBr gave **95** in good yield and high selectivity (**Scheme 10**). Introduction of the acetic acid side chain was carried out by alkylation of the sodium enolate of **95** with *tert*-butyl iodoacetate to provide **96**. In this transformation, the chiral auxiliary determines the face selectivity. Selective manipulation of one of the carboxyls by hydrolysis, reduction, and lactonization furnished **97** in a good overall yield. The C-3 methyl group of the lactone was then installed by another alkylation with methyl iodide. The diastereoselectivity of this alkylation reaction was dependent on the base used and the C-4 substituent. The overall yield for the synthesis of peperomin B was ~25%. Lactones **99**–**101** were synthesized analogously in comparable overall efficiencies.

6. Diels–Alder Reactions

Another major reaction type in which oxazolidinone auxiliaries have been extensively utilized is the Diels–Alder reaction. In an excellent study, Evans[58] has shown that phenyl groups in the chiral auxiliary can participate in π stacking and lead to high diastereoselectivities. With this precedent in mind, we explored the Lewis acid mediated Diels–Alder reactions of **71** and **72** (**Scheme 11**).[6] Reaction of **71** with isoprene, using $ZrCl_4$ as a Lewis acid, furnished the cyclohexene **102** in 86% yield and >99% de. Analogous experiments reported in the literature, using **2** and **3** as chiral auxiliaries and diethylaluminum chloride as a Lewis acid, gave 68% and 91% de's, respectively.[59] Similarly, reaction of **72** with isoprene produced **103** as a single diastereomer in excellent chemical yield. The high diastereoselectivities observed in these Diels–Alder reactions indicate that the diphenyl auxiliary provides advantages similar to those of the auxiliary derived from phenylalanine in reactions where participation of the phenyl group in π-stacking interactions is important.

7. Conclusions

In answer to the question posed in the title, two phenyl groups in the auxiliary are definitely better for certain transformations. In general, they provide equal or better levels of selectivity than the traditional Evans auxiliaries (**2**–**5**). 4-Diphenylmethyl-2-oxazolidinone (**1**) is a more sterically demanding analog of **3**, provides high levels of diastereoselection, has potential for π stacking in a variety of reactions, and adds to the pool of useful chiral auxiliaries. In addition to practical advantages such as a three-step preparation, crystallinity, and ease of recovery, the new auxiliary **1** shows promise for providing high diastereoselectivity in more challenging synthetic transformations for which existing auxiliaries are unsatisfactory.[60]

8. Acknowledgements

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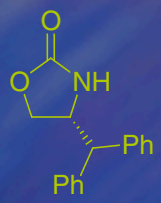
About the Author

Mukund Sibi hails from Bangalore, India. After undergraduate studies in Bangalore, he joined Hunter College, CUNY, and received his Ph.D. degree under the guidance of Prof. Robert Lichter. He carried out postdoctoral studies with Profs. Gordon Gribble (Dartmouth College), Victor Snieckus (University of Waterloo), and Robert Holton (Florida State University). He joined North Dakota State University in 1987, where he is currently Professor of Chemistry. His research interests include the development of new asymmetric processes, total synthesis of natural products, chiral catalysis, and nonfood uses of agricultural materials.

Oxazolidinone Chiral Auxiliaries



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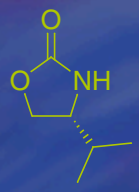

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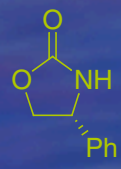

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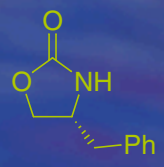

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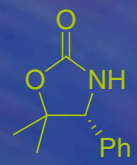

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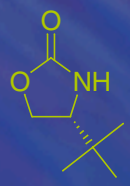

49,376-7

Chiral oxazolidinones similar to the one discussed by Professor Sibi in the preceding review, have found widespread use as auxiliaries in diasteroselective Michael additions, alkylations, aldol condensations, cyclopropanations, Diels–Alder, and other reactions. In addition, the auxiliaries are easily recycled under mild conditions, and most are available in bulk quantities. Aldrich offers a broad range of chiral oxazolidinones—a sampling is shown below—and amino alcohol precursors. Please call our Technical Services department at **800-231-8327** (USA) or visit us on the Web at www.sigma-aldrich.com to request your FREE copy of the *1998-99 Chiral Nonracemic Compounds* catalog.

For a recent review of the preparation, applications, and recycling of oxazolidinones, see Ager, D.J. et al. *Chem. Rev.* **1996**, *96*, 835.

49,470-4 *New!* **(*R*)-(+)-4-(Diphenylmethyl)-2-oxazolidinone**, 98%
49,469-0 *New!* **(*S*)-(−)-4-(Diphenylmethyl)-2-oxazolidinone**, 97%
33,994-6 **(*R*)-(+)-4-Isopropyl-2-oxazolidinone**, 99% (99% ee/GLC)
29,888-3 **(*S*)-(−)-4-Isopropyl-2-oxazolidinone**, 99% (98% ee/GLC)
40,245-1 **(*R*)-(−)-4-Phenyl-2-oxazolidinone**, 98%
37,669-8 **(*S*)-(+)-4-Phenyl-2-oxazolidinone**, 98%
30,097-7 **(*R*)-(+)-4-Benzyl-2-oxazolidinone**, 99%
29,464-0 **(*S*)-(−)-4-Benzyl-2-oxazolidinone**, 99%
45,070-7 **(*R*)-(−)-5,5-Dimethyl-4-phenyl-2-oxazolidinone**, 98% (99% ee/HPLC)
45,071-5 **(*S*)-(+)-5,5-Dimethyl-4-phenyl-2-oxazolidinone**, 98% (99% ee/HPLC)
49,376-7 *New!* **(*R*)-(+)-4-*tert*-Butyl-2-oxazolidinone**, 99%
44,051-5 **(*S*)-(−)-4-*tert*-Butyl-2-oxazolidinone**, 99%
29,889-1 **(4*R*,5*S*)-(+)-4-Methyl-5-phenyl-2-oxazolidinone**, 99% (99% ee/GLC)
34,052-9 **(4*S*,5*R*)-(−)-4-Methyl-5-phenyl-2-oxazolidinone**, 99% (99% ee/HPLC)
45,454-0 **(4*R*,5*S*)-(+)-*cis*-4,5-Diphenyl-2-oxazolidinone**, 98%
44,744-7 **(4*S*,5*R*)-(−)-*cis*-4,5-Diphenyl-2-oxazolidinone**, 98%
45,066-9 **(*R*)-(+)-4-Isopropyl-5,5-dimethyl-2-oxazolidinone**, 98%
45,067-7 **(*S*)-(−)-4-Isopropyl-5,5-dimethyl-2-oxazolidinone**, 98%
46,397-3 **(3a*S*-*cis*)-(−)-3,3a,8,8a-Tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one**, 98% (99%ee/HPLC)
46,396-5 **(3a*R*-*cis*)-(+)-3,3a,8,8a-Tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one**, 97% (99%ee/HPLC)
49,604-9 *New!* **(*S*)-(+)-4-(1*H*-Indol-3-ylmethyl)-2-oxazolidinone**, 98%
49,603-0 *New!* **(*R*)-(−)-4-(1*H*-Indol-3-ylmethyl)-2-oxazolidinone**, 98%

Some Other Products Mentioned in Professor Sibi's Review:

41,220-1 **L-Serine methyl ester hydrochloride**, 98%
12,423-0 ***tert*-Butyl bromoacetate**, 98%
19,035-7 **(*R*)-(−)-2-Phenylglycinol**, 98% (99% ee/GLC)
33,075-2 **Triphosgene**, 98%
D8,000-2 **1,3-Dicyclohexylcarbodiimide**, 99%
27,141-1 **Allyltributyltin**, 97%
26,147-5 **Dibutylboron triflate**, 1.0*M* solution in dichloromethane
23,050-2 **Copper(I) bromide-dimethyl sulfide complex**, 99%
17,875-6 **Diphenylphosphoryl azide**, 97%

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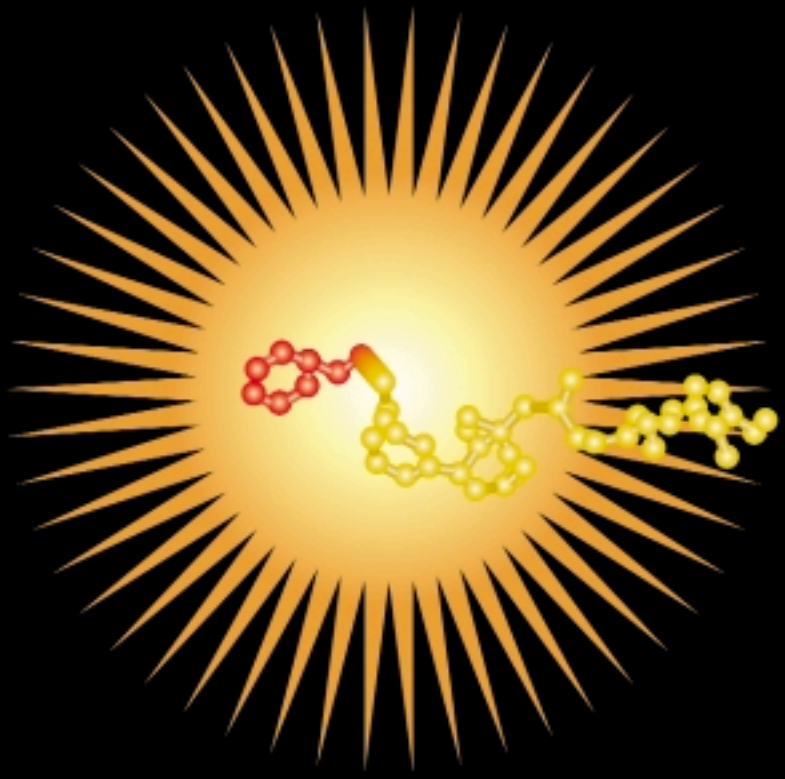

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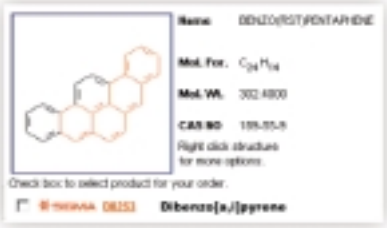

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Z25,750-8

Kirk-Othmer Concise Encyclopedia of Chemical Technology

4th ed., M. Grayson and D. Eckroth, Eds., John Wiley & Sons, New York, NY, 1999, 2,196pp. Hardcover. This abridged version of a 28-volume set contains information about 1,100 topics of interest to chemists.

Z41,246-5

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3rd ed., T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, NY, 1999, 784pp. Hardcover. Details the use of protecting groups in synthetic organic chemistry. Expanded by more than 50%, providing readers with a compendium of 1,050 of the most useful protective groups as well as 5,350 references to original publications.

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Z40,856-5

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M.P. Doyle, M.A. McKervey, and T. Ye, John Wiley & Sons, New York, NY, 1998, 652pp. Hardcover. This resource brings together a wealth of procedures for the synthesis and practical use of diazocarbonyl compounds. It features methods for the preparation of important catalysts and for applications of diazocarbonyl compounds within each of the main transformation categories—including in-depth coverage of cyclopropanation, C–H and X–H insertion, Wolff rearrangement, ylide formation, aromatic cycloaddition and substitution, and many other useful reactions.

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Z40,864-6

Stereoselectivity in Synthesis

T.-L. Ho, John Wiley & Sons, New York, NY, 1999, 448pp. Hardcover. Shows how to choose the best method for a given synthesis. Provides readers with a thorough understanding of stereoselectivity in organic and medicinal chemistry as well as the pharmaceutical, agricultural, and food industries.

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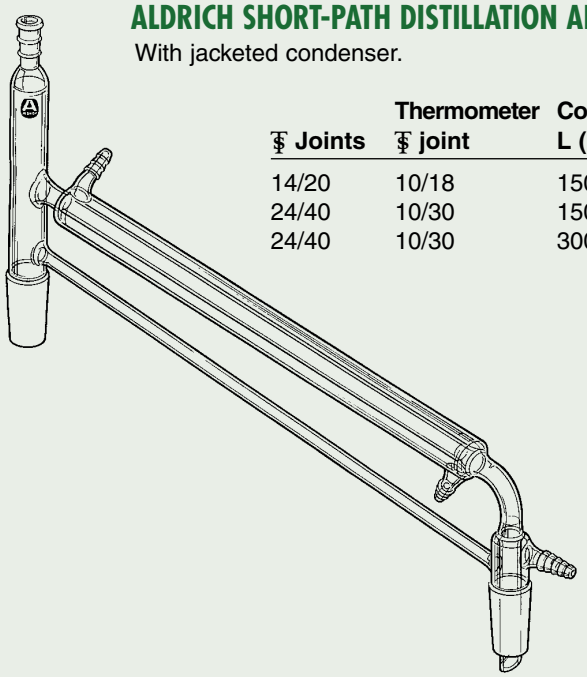

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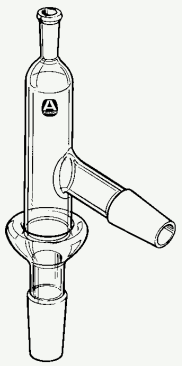

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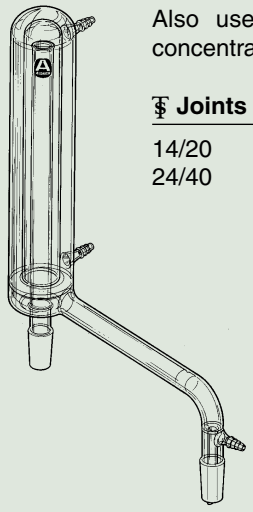

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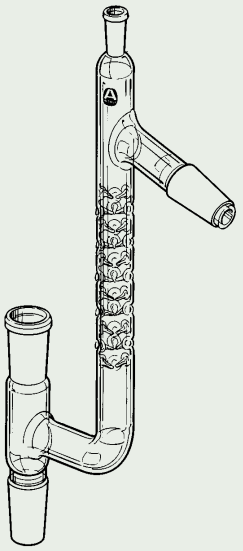

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Sigma-Aldrich Chimie S.a.r.l
L'Isle D'Abeau Chesnes
B.P. 701
38297 St.Quentin Fallavier
Cedex
Tel Numero Vert: 0800 21 14 08
Fax Numero Vert: 0800 03 10 52
E-mail: fradvsv@eurnotes.sial.com

Germany
(also SE Europe, the Baltics, Africa and the Middle East)
Sigma-Aldrich Chemie GmbH
Gruenwalder Weg 30
D-82041 Deisenhofen
Freecall Tel: 0800-5155 000
Freecall Fax: 0800-6490 000
Tel: +49(0)89-6513-0
Fax: +49(0)89-6513-1169
Export Department:
Tel: +49(0)89-6513-1807
Fax: +49(0)89-6513-1877
E-mail: DeOrders@eurnotes.sial.com

Greece
Sigma-Aldrich (o.m) Ltd.
72 Argonafton Str.
16346 Ilioupoli, Athens
Tel: 30-1-9948010
Fax: 30-1-9943831
E-mail: GRCustSV@eurnotes.sial.com

Hungary
Sigma-Aldrich Kft
1399 Budapest
Pf. 701/400
Magyarország
Tel ingyenes: 06-80-355-355
Fax ingyenes: 06-80-344-344
Tel: 06-1-235-9055
Fax: 06-1-235-9050
E-mail: info@sigma.sial.hu

India
Sigma-Aldrich Corporation
Bangalore location:
Survey No. 31/1, Sitharamapalaya
Mahadevapura P.O.,
Bangalore 560048
Phone: 91 80 852 4222
Fax: 91 80 852 4214

New Delhi location:
Flat No. 4082, Sector B 5/6
Vasant Kunj, New Delhi 110070
Phone: (011) 689 9826
Fax: (011) 689 9827
E-mail: sigma@del2.vsnl.net.in

Israel
Sigma-Aldrich Israel Ltd.
Park Rabin, Rehovot 76100
Toll Free Tel: 1-800-70-2222
Tel: 972-8-948-4222
Fax: 972-8-948-4200
E-mail: sigisr@sigma.co.il

Italy
Sigma-Aldrich S.r.l.
Via Gallarate 154
20151 Milano
Numero Verde: 800-827018
Tel: 02-33417.310
Fax: 02-38010.737
E-mail: itorder@eurnotes.sial.com

Japan
Sigma-Aldrich Japan K.K.
Higashi Nihonbashi Sky Bldg.
1-1-7 Higashi Nihonbashi, Chuo-ku
Tokyo 103-0012
Tel: 81-3-5821-3111
Fax: 81-3-5821-3170

Korea
Sigma-Aldrich Korea
Samhan Camus Annex, 10th Floor
17-26 Yoido-dong, Yungdeungpo-ku
Seoul, South Korea
Toll Free Tel: 080-023-7111
Toll Free Fax: 080-023-8111
Tel: 82-2-783-5211
Fax: 82-2-783-5011
E-mail: order@sial.co.kr

Malaysia
Sigma-Aldrich (M) Sdn Bhd
60, 60-1 Jalan Awan Jawa
Taman Yarl
Off Jalan Kelang Lama
58200 Kuala Lumpur
Malaysia
Tel: 03-7824181, 03-7808140
Fax: 03-7824067
E-mail: sigalm@po.jaring.my

Mexico
Sigma-Aldrich Química, S.A. de C.V.
Calle 6 Norte No. 107
Parque Industrial Toluca 2000
50200 Toluca, México
Teléfono sin costo: 01-800-007-5300
Teléfono en Toluca: (72)-76-1600
Fax sin costo: 01-800-712-9920
Fax en Toluca: (72)-76-1601
E-mail: mexico@sial.com

Netherlands
Sigma-Aldrich Chemie BV
Stationsplein 4 E
Postbus 27
NL-3330 AA Zwijndrecht
Tel Gratis: 0800 022 9088
Fax Gratis: 0800 022 9089
Tel: 078-620 54 11
Fax: 078-620 54 21
E-mail: nlcustsv@eurnotes.sial.com

Norway
Sigma-Aldrich Norway AS
Tevlingveien 23
1081 Oslo, Norway
Tel: 47 2317 6000
Fax: 47 2317 6010
E-mail: nororder@sial.com

Poland
Sigma-Aldrich Sp. z o.o.
Szelągowska 30
61-626 Poznań
Tel: (48-61) 823-24-81
Fax: (48-61) 823-27-81
E-mail: plcustsv@eurnotes.sial.com

Portugal
Sigma-Aldrich Quimica S.A.
(Sucursal em Portugal)
Aptdo. 131
2710 Sintra
Free Tel: 0800-202180
Free Fax: 0800-202178
E-mail, encomendas:
poorders@eurnotes.sial.com

Russia
Sigma-Aldrich Russia
TechCare Systems, Inc.
Makarenko Str. 2/21 Bldg. 1 Flat 22
Moscow 103062
Tel: 7-095-975-3321
Fax: 7-095-975-4792
E-mail: techcare@online.ru

Singapore
Sigma-Aldrich Pte., Ltd.
102E Pasir Panjang Road
#08-01, Citilink Warehouse
Singapore, 118529
Tel: (65) 271 1089
Fax: (65) 271 1571
E-mail: sapl@sialsea.com

South Africa
Sigma-Aldrich South Africa (Pty) Ltd.
Southern Life Industrial Park
Unit 16 & 17
CNR Kelly & Ackerman Streets
Jet Park, Boksburg 1459
Tel: (011) 397 8886
Fax: (011) 397 8859
E-mail: sigald@icon.co.za

Spain
Sigma-Aldrich Química S.A.
Aptdo. 161
28100 Alcobendas (Madrid)
Free Tel: 900-101376
Free Fax: 900-102028
Tel: 91-6619977
Fax: 91-6619642
E-mail, pedidos:
esorders@eurnotes.sial.com

Sweden
Sigma-Aldrich Sweden AB
Solkraftsvagen 14C
135 70 Stockholm
Tel (in Sweden only): 020-35 05 10
Fax (in Sweden only): 020-35 25 22
Outside Sweden Tel: 46-8-742 4200
Outside Sweden Fax: 46-8-742 4243
E-mail: sweorder@eurnotes.sial.com

Switzerland
Aldrich Chemie
A division of Fluka Chemie AG
Postfach 260
CH-9471 Buchs
Tel: 081-755 27 23
Fax: 081-755 28 40
Swiss Free Call: 0800 80 00 80
E-mail: Fluka@sial.com

United Kingdom
Sigma-Aldrich Company Ltd.
Fancy Road
Poole
Dorset BH12 4QH
Free Tel: 0800 717181
Free Fax: 0800 378538
Tel: 01202 733114
Fax: 01202 715460
E-mail: ukcustsv@eurnotes.sial.com

United States
Aldrich Chemical Company, Inc.
1001 West Saint Paul Avenue
Milwaukee, Wisconsin 53233
Toll Free Tel: 1-800-558-9160
Toll Free Fax: 1-800-962-9591
Tel: 414-273-3850
Fax: 414-273-4979
E-mail: aldrich@sial.com

Sigma Chemical Company
3050 Spruce Street
St. Louis, Missouri 63103
Toll Free Tel: 1-800-521-8956
Toll Free Fax: 1-800-325-5052
Tel: 314-771-5765
Fax: 314-771-5757
E-mail: sigma@sial.com