Review

Development of New Synthetic Reactions for Nitrogen-Containing Compounds and Their Application

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Nitrogen-containing compounds are core parts not only of natural and synthetic medicines but also of biologically active compounds including natural products. This review focuses on the development of new synthetic reactions for nitrogen-containing compounds *via* three methodologies: the reductive photocycloaddition reaction of enamides, radical addition reaction, and nucleophilic addition reaction. Newly developed reactions were successfully applied to the synthesis of various types of nitrogen-containing compounds including medicines, lead compounds to new drugs, natural alkaloids, and others.

Key words photocycloaddition; radical addition; thiol addition; imine; total synthesis

1. Introduction

Nitrogen-containing compounds are found in many biologically active synthetic targets, including natural products and designed pharmaceuticals and they thus attract considerable attention from synthetic chemists. However, direct and more efficient synthesis of various types of amine compounds is surprisingly underdeveloped; comparison with methods for other heteroatom-containing compounds reveals a long-standing scientific problem. As a first step in making the chemical synthesis of organic compounds more efficient, greater use of simple addition reactions should be emphasized. In this context, we have been developing a novel synthetic strategy based on rather environmentally benign addition reactions involving the photochemical reaction, radical reaction, and domino reaction. Additionally, we have succeeded in the synthesis of various types of amine including alkaloids, amino acids, aminocyclitols, lactams, *etc.*

2. Reductive Photocycloaddition Reaction and Its Synthetic Application

Enamide photocyclization has been established as one of the most useful reactions for the construction of various types of six-membered lactams, which are key precursors for cyclic amines found in many natural products and medicines.[1—5] Under three different reaction conditions, one common enamide **1** undergoes the respective photocyclization to afford three different types of lactam **2**, **3**, and **4**, in good yields which involve different oxidation levels (Chart 1).

Among them, a breakthrough has been achieved with the discovery of the useful procedure of reductive photocyclization.[6] Considering two functional groups such as iminium and enolate moieties in the structure of intermediate **A**, we irradiated the enamide **1** in the presence of $NaBH_4$ in solvent systems including 10% methanol and found that the reductive photocyclization proceeded effectively to afford hydrogenated lactams **4** that carry aliphatic double bonds suitable for further functionalization. Thus reductive photocyclization consists of a reductive dearomatization strategy and can directly transform a flat aromatic motif into a 3-D (three dimensional) nonaromatic structure, providing a powerful strategy for the rapid chemical synthesis of complex molecules.

2.1. Synthesis of Yohimbine Alkaloids The enamide **5** with a methoxy group was prepared by simple acylation of harmalane and then irradiated in the presence of $NaBH_4$. The reductive photocyclization proceeds smoothly to afford the homogeneous product **6** in good yield which contains an enol ether moiety in the terminal ring and therefore was readily converted to the corresponding ketone **7** upon acid treatment.[7] Then **7** was stereoselectively converted to the respective stereoisomers of two conjugated enones **8** and **9** only by changing the reaction conditions. Regioselective introduction

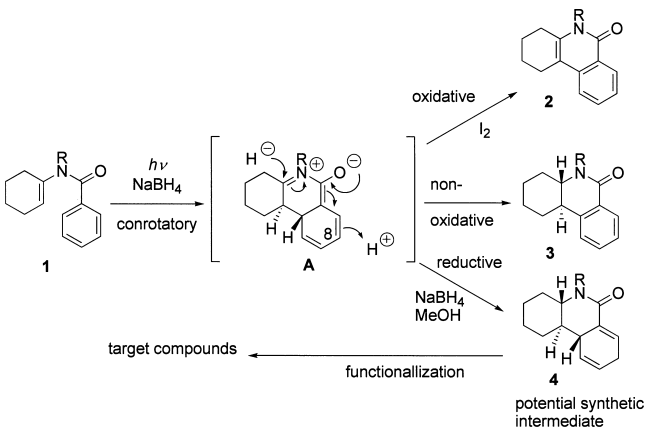

Chart 1. Enamide Photocyclization under Three Different Conditions

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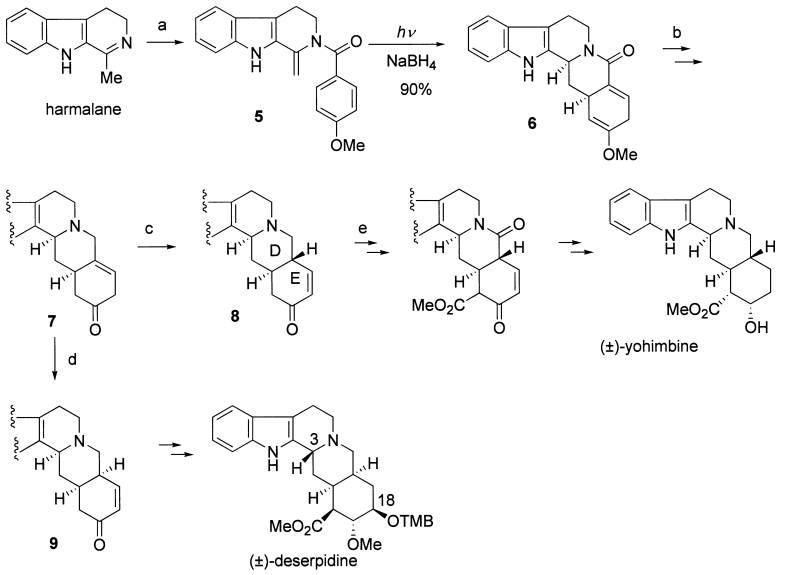

Chart 2. Synthesis of Yohimbine Alkaloids

of the ester group into **8** by acylation with Mander reagent (cyanoformate), and transformation of the functional groups, completed the total synthesis of (±)-yohimbine (Chart 2).[8,9] The generality of this synthetic methodology for indole alkaloids including reductive photocyclization was elegantly confirmed by another synthesis of (±)-deserpidine which was achieved simply by adding steps for the introduction of an additional oxygen function at the 18-position and for epimerization at the 3-position.[10,11]

2.2. Synthesis of Heteroyohimbine and Related Alkaloids To synthesize modified heteroyohimbines *via* one common methodology, we introduced a furan ring into the enamide structures **10** which was subjected to reductive photocyclization to afford new ring systems containing a dihydrofuran ring at the terminal position (Chart 3). Reductive photocyclization of the enamide **10a** prepared from harmalane and 2-furoyl chloride proceeded smoothly to afford the homogeneous lactam **11a** with a dihydrofuran in 94% yield.[10,12] To furnish a two-carbon unit, the introduction of an acetyl group into the ring junction of **11a** under kinetically controlled conditions followed by the ring-opening reaction of the dihydrofuran ring gave the acetyl lactam ester **12**. Transformation of the functional group involving selective reduction of three carbonyl groups led to the synthesis of (±)-corynantheine.[13] Additionally, we achieved the formal total synthesis of (±)-ajmalicine by preparing δ-lactone **13** starting from the common key intermediate **11b**.[14] Following almost the same strategy, dihydrofuran **11c**, prepared from a 3,4-dihydroisoquinoline derivative, was successively transformed to the lactam ester **14** that was already converted into (±)-emetine.[15]

2.3. Synthesis of Related Alkaloids The tetrahydrofuran derivative **16a** was prepared by reductive photocyclization of enamide **15a**, followed by the catalytic hydrogenation of the resulting dihydrofuran compound. Then **16a** carrying a β-alkoxylactam structure underwent the retro-Michael reaction to give α,β-unsaturated lactam **17a** by treatment with lithium diisopropylamide (LDA). The Michael addition of 2-lithioacetate to lactam **17a**, followed by transformation of the functional groups, synthesized (±)-hirsuteine and other related alkaloids (Chart 4).[16] The conversion of tetrahydrofuran **16a** to Michael adduct **18** was simplified to one-pot

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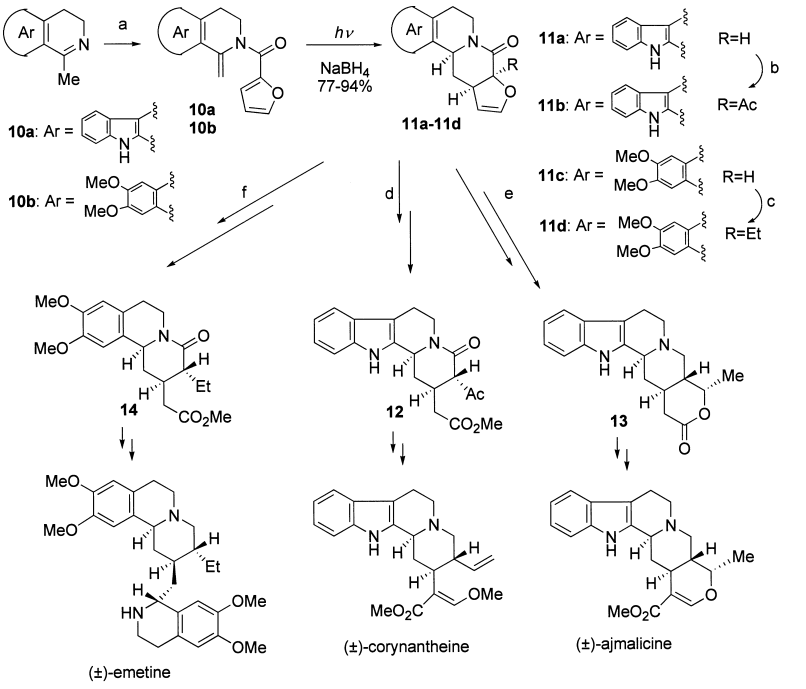
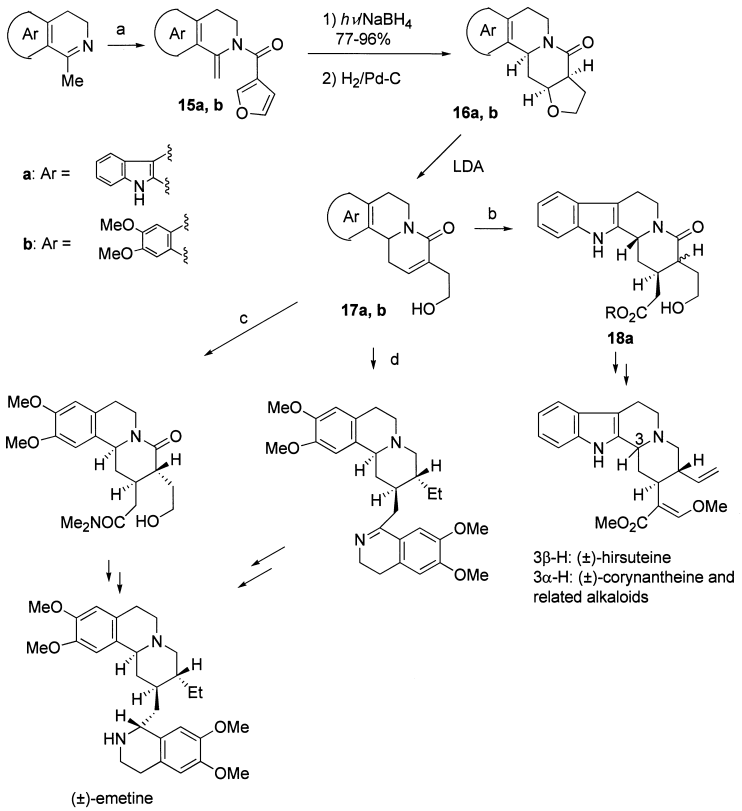


Reagents and conditions: (a) 2-furoyl chloride, Et_3N; (b) (1) LDA, (2) Ac_2O; (c) (1) LDA, (2) EtI; (d) (1) 15% H_2SO_4, (2) DMSO, Ac_2O (3) Zn-AcOH, (4) CH_2N_2; (e) (1) Lawesson's reagent, (2) Raney-Ni, (3) $NaBH_3CN$, HCl, (4) $NaBH_4$, (5) *p*-TsOH; (f) (1) 15% H_2SO_4, (2) PCC (3) Ca, liq. NH_3, (4) CH_2N_2

Chart 3. Synthesis of Heteroyohimbine and Related Alkaloids



Reagents and conditions: (a) 3-furoyl chloride, Et_3N; (b) $LiCH_2CO_2t$-Bu; (c) $LiCH_2CONMe_2$; (d) 3,4-dihydro-6,7-dimethoxy-1-(lithiomethyl)isoquinoline

Chart 4. Synthesis of Other Monoterpenoids and Related Alkaloids

procedure using furopyridone **16a** itself as a substrate, which we term the elimination-addition reaction. Analogously, the same strategy involving reductive photocyclization of enamides **15b** and elimination-addition reaction of the photocyclized lactams **16b** using 2-lithioacetamide or 1-(2-lithiomethyl)isoquinoline was successfully applied to the synthesis of (±)-emetine.[17]

The formal synthesis of (±)-eburnamine,[18] (±)-quinine,[19] and (±)-desmethoxycuanzine[18] was also achieved *via* almost the same synthetic strategy involving reductive photocyclization of enamides and elimination-addition of the common intermediate of tetrahydrofuranyl lactam (Fig. 1).

2.4. Synthesis of Ergot Alkaloids Reductive photocyclization of enamide **19**, easily prepared from tricyclic tetralone, proceeded very smoothly to afford the desired lactam **20** with a dihydrofuran moiety in high yield.[20] The dihydrofuran ring in **20** was cleaved in two ways to afford intermediates **21** and **22** for the synthesis of ergot alkaloids (Chart 5). First, osmium tetroxide oxidation of this dihydrofuran ring of **20** in the presence of trimethylamine *N*-oxide, followed by glycol-cleavage, gave a key intermediate, 9α-hydroxy-8β-aldehyde **21**. Oxidation of the formyl group, dehydration of the hydroxyl group, and other transformation of the functional groups completed the 9-ergolene type of alkaloids such as (±)-methyl lysergate.[20] On the other hand, reduction of the formyl group to carbinol and methyl groups, followed by the conventional functionalization, completed the synthesis of the 8-ergolene type of ergot alkaloids such as (±)-isofumigaclavine[4] B and (±)-lysergol.[4] Second, direct ring cleavage of the dihydrofuran ring of **20** by ozonolysis, followed by reduction with $LiAlH_4$, afforded the *cis*-9α-hydroxy-8α-carbinol **22** which was effectively converted to the 8-ergolene type of ergot alkaloids such as (±)-elymoclavine and others.[21,22]

2.5. Synthesis of Pseudodistomin Alkaloids The synthetic potential of the dearomatization strategy involving reductive photocyclization of enamides has been demonstrated in the efficient synthesis of monocyclic alkaloids such as pseudodistomins.[23] The enamide **23** was prepared by acylation of thioimidate with 2-phenyloxazole-4-carbonyl chloride and subjected to reductive photocyclization to form the dihydrooxazole lactam **24**, which carries a protected *cis*-amino alcohol moiety suitable for the construction of the desired alkaloids. The introduction of a three-carbon unit to **24** was achieved by photochemical conditions in the presence of allyltributyltin, leading to the stereoselective formation of allyllactam **25**. Transformation of the functional groups in **25** using conventional methods led to the synthesis of acetates

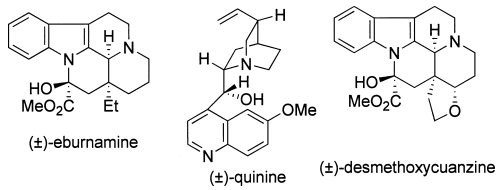


Fig. 1. Synthesized Miscellaneous Alkaloids

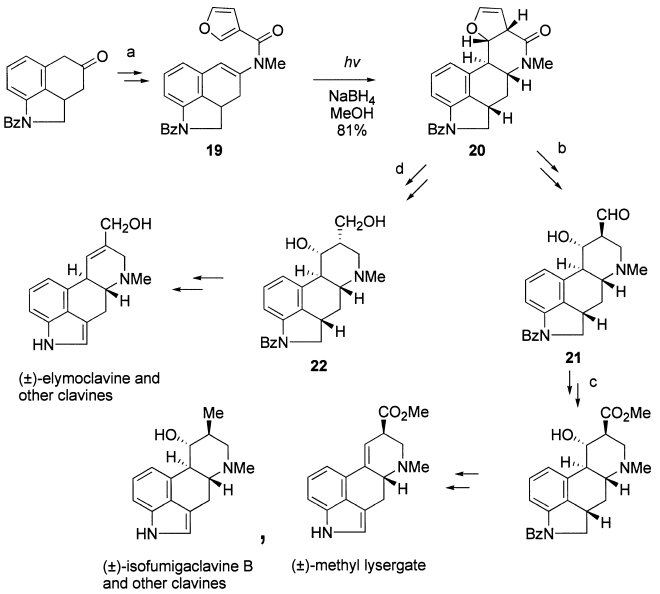


Chart 5. Synthesis of Ergot Alkaloids

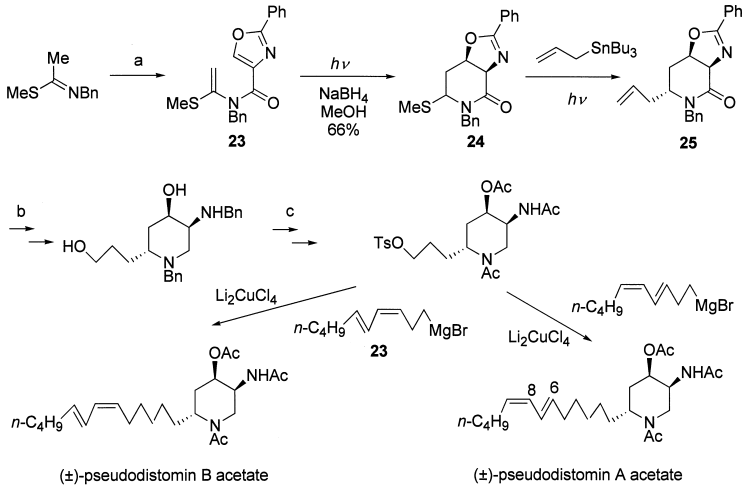


Chart 6. Synthesis of Pseudodistomin Alkaloids

of (±)-pseudodistomins A and B and the tetrahydro derivatives (Chart 6).[24,25] Our first synthesis of an acetate of natural alkaloids provided concrete evidence for the structure, particularly the 6,8-diene part that was incorrectly proposed in the structure determination of natural products.

Thus we developed a potential construction method for various types of alkaloids using dearomatization methodology involving reductive photocyclization, which is an environmentally benign reaction.

3. Radical Addition Reaction and Its Synthetic Application

3.1. Intermolecular Radical Addition Reaction Radical reactions have emerged as a valuable tool for organic chemists, providing many advantages over ionic chemistry (Chart 7).[26—28] The intermolecular carbon radical additions to the carbon–nitrogen double bond of imine derivatives had received much less attention when we started our research.[29] Generally, the nucleophilic addition of organometallic reagents to the carbon–nitrogen double bond constitutes an extremely useful method for preparing a variety of amines. However, the addition of organometallic reagents is frequently plagued by the aza-enolization of the substrates with acidic α-hydrogens, poor electrophilicity of the imino group, and the formation of reductive coupling products.[30]

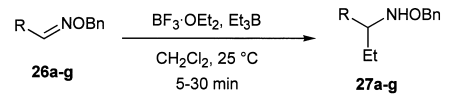
We expected that mild addition of a strictly neutral species such as an uncharged free radical would provide a highly general solution to the fundamental problems that are associated with the strong basicity of organometallic reagents. Among the different types of radical acceptors containing a C=N bond, the oxime ether and hydrazone are well known to be excellent radical acceptors because of the extra stabilization of the intermediate aminyl radical **B** provided by the lone pair on the adjacent heteroatom involving three electron π-bonding interactions.[31] Therefore we became interested in the development of a general, practical method for the carbon–carbon bond-forming reactions based on the intermolecular radical addition to imine derivatives for the synthesis of various types of amines as a final goal. Although the carbon–nitrogen double bond has attracted significant attention as an excellent radical acceptor in intramolecular radical cyclizations, the intermolecular radical addition to imine derivatives has not been widely studied except in some excellent work reported by Hart's,[32] Kim's,[33] Bertrand's,[34] and Friestad's groups.[35]

3.1.1. Addition to Imine Derivatives We initially explored the intermolecular addition of an ethyl radical to different types of aldoxime ethers **26**[36,37] and found an efficient method for preparing various types of alkoxyamines **27** *via* ethyl radical addition reaction in the presence of $BF_3 \cdot OEt_2$ as a Lewis acid even in the case of the aliphatic aldoxime ether with sensitive α-hydrogens (Chart 8). This newly found radical reaction has several advantages over the conventional organometallic reactions that require rigorous reaction conditions such as carefully dried reagents, solvents, and apparatus. In agreement with the general advantages of the radical reactions over the anion reaction, the present radical method will be useful because of the exceptional tolerance of functional groups such as aromatic, heterocycle, alcohol, acetal, ester, and amide moieties.

3.1.2. Reactivity of Imine Derivatives Since glyoxylic imine derivatives are convenient starting materials for the synthesis of natural and unnatural α-amino acids and related compounds through ene reactions, cycloadditions, or nucleophilic additions of organometallic reagents or enolate anion equivalents,[38] we turned our attention to radical addition to glyoxylic imines that have three electrophilic positions and thus the drawback of nonregioselective ionic reactions. Therefore we explored the intermolecular carbon radical addition to glyoxylic oxime ether **28** as an alternative synthetic route to allow ready access to a wide range of aliphatic α-amino acids (Chart 9).[39,40] In the absence of $BF_3 \cdot OEt_2$, good chemical yields were also observed even at −78 °C in the radical addition of *sec*- and *tert*-alkyl radicals to glyoxylic oxime ether **28**, which is activated by an electron-withdrawing substituent. It is important to note that the radical addition took place regioselectively at the imino carbon to give the desired *C*-alkylated product **29**. Radical addition to glyoxylic oxime ethers is not only a very promising approach to the synthesis of aliphatic α-amino acids but also complements the nucleophilic addition of organometallic reagents.[41—43]

We found that electron-deficient *N*-sulfonylimines **30** exhibit excellent reactivity toward nucleophilic alkyl radicals even in the absence of strong Lewis acids.[44] The reaction of *N*-sulfonylimine **30** proceeded in dichloromethane at 25 °C using alkyl iodides as a radical precursor and triethylborane as a radical initiator to give the alkylated product **31** in good to excellent yields.

3.1.3. Iodine Atom-Transfer Reaction Considering that radical reactions including atom- and group-transfer



a: R = Et (95%), **b**: R = Ph (93%), **c**: R = 2-MeO-C_6H_4 (93%), **d**: R = 4-HO-C_6H_4 (96%), **e**: R = 2-HO-C_6H_4 (41%), **f**: R = 3-Thiophenyl (57%), **g**: R = PhCH=CH (62%)

Chart 8. Radical Addition to Oxime Ethers

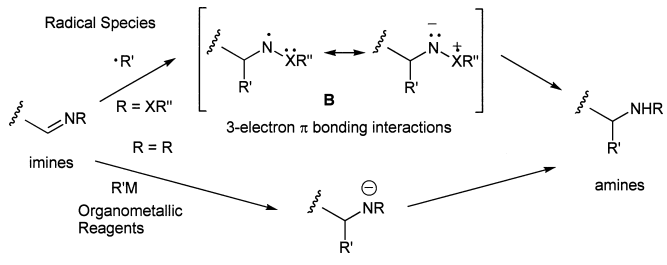


Chart 7. Nucleophilic Addition *vs.* Radical Addition

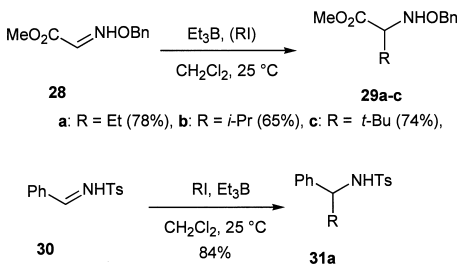


Chart 9. Radical Addition to Glyoxylic Oxime Ether and *N*-Tosylimine

processes or single-electron transfer (SET) processes are subjects of current interest, we started to examine the alkyl radical addition *via* a route involving the iodine atom-transfer process in the absence of tin hydride.[45] The alkyl radical addition reaction using *sec*- and *tert*-alkyl iodides proceeded smoothly in the absence of Bu_3SnH to give a good yield of alkylated product **29**. In contrast, the reaction with the unstable primary alkyl radicals such as methyl and isobutyl radicals gave significant amounts of the ethylated product **29a** as a result of the predominant addition of the ethyl radical generated from triethylborane. These observations suggest that the reaction involving the iodine atom-transfer process is an effective method when the stable tertiary and secondary alkyl radicals are employed. This radical reaction has a tremendous practical advantage over the stannyl radical-induced reaction, which requires a troublesome work-up to remove the tin residues from the reaction mixture. In this reaction, triethylborane acts multiply as a radical initiator, a Lewis acid, and a radical terminator, and therefore more than a stoichiometric amount of triethylborane is required (Chart 10).

3.1.4. Addition to Chiral Glyoxylic Oxime Ether We also succeeded in the first diastereofacial stereocontrol in the carbon radical addition to glyoxylic oxime ethers,[39,40] which is a convenient method for preparing a wide range of enantiomerically enriched α-amino acids. When the reaction was performed in dichloromethane at $-78\,^{\circ}C$ for 30 min with RI, Bu_3SnH, and triethylborane, a high degree of stereocontrol in the carbon radical addition to the glyoxylic oxime ether **32** was achieved using Oppolzer's camphorsultam as a chiral auxiliary (Chart 11). Excellent chemical yield and high diastereoselectivity were obtained in the reaction using not only secondary alkyl radicals such as *sec*-butyl and cyclohexyl radicals but also the bulky *tert*-butyl radical. The reductive removal of the benzyloxy group of the major diastereomer (*R*)-**33** and the subsequent removal of the sultam auxiliary with standard hydrolysis afforded the enantiomerically pure D-valine (*R*)-**34** without any loss of stereochemical purity. From the economic and ecologic points of view, we also developed the radical addition to oxime ether **32** in the absence of tributyltin hydride (Bu_3SnH).[40]

The potential application of our radical addition reaction to the oxime ether group was confirmed by the first total synthesis of (+)-penmacric acid[46,47] *via* the route involving the addition of alkyl radical generated from chiral iodoproline **35** to glyoxylic oxime ether **28**, which proceeded in a stereoselective manner only at the 3-position but not at the 1′-position to form the adduct **36**.[40] Transformation of the functional groups including removal of the hydroxyl group and introduction of the carbonyl group afforded (+)-penmacric acid (Chart 12).[48]

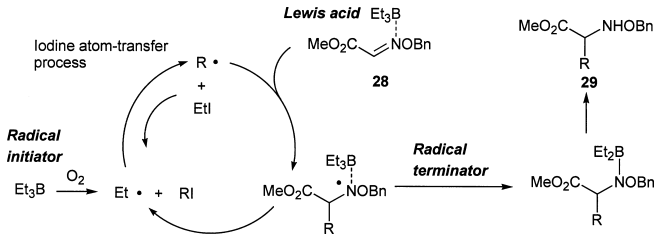


Chart 10. Possible Reaction Pathway

As our preliminary study on enantioselective radical reactions, we also investigated radical addition to oxime ether **28** in the presence of chiral Lewis acids[40] and found that the enantioselective isopropyl radical addition to **28** using (*R*)-(+)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) and $MgBr_2$ gave an excellent chemical yield of the valine derivative **29b** in 52% ee (Chart 13).

3.1.5. Synthesis of β-Amino Acids *via* Radical Addition to Chiral Unactivated Oxime Ether Following our studies on the synthesis of α-amino acids, we next investigated diastereoselective radical addition to unactivated oxime ethers (*R*,*Z*)-**38** bearing Oppolzer's camphorsultam for the synthesis of the enantiomerically pure β-amino acid derivatives (Chart 14).[49] The phase transfer-catalyzed monoalkylation of the active methylene in sultam derivative **37**, followed by alkyl radical addition to the resulting oxime ethers (*R*,*Z*)-**38** in the presence of alkyl iodides, triethylborane, and $BF_3 \cdot OEt_2$, gave the alkylated product **39** in moderate to good yield. The absolute configuration at the newly formed stereocenter of the ethylated product **39a** (R^1=Bn, R^2=Et) was determined to be *S* by X-ray analysis. Removal of the sultam auxiliary in **39a** afforded the enantiomerically pure α,β-dialkyl-α-amino acid **40** in 60% overall yield from **39** (Chart 14).

3.1.6. Addition to Chiral Nitrone Although nitrones have also evolved as a useful trap for short-lived reactive free radicals,[50] synthetically useful radical reactions are not available to our knowledge. We have developed a novel carbon–carbon bond-forming reaction for the first time by confirming the synthetic utility of nitrone as a radical acceptor in the intermolecular reactions with nucleophilic carbon radicals.[51] A high degree of stereocontrol and good chemical yields of desirably alkylated products **42a**—**d** were observed in the alkyl radical addition to chiral glyoxylic nitrone **41** using triethylborane and alkyl iodides (Chart 15). The absolute configuration of **42a** was assigned to be *R* by converting the product **42a** into *N*-Cbz-amino acid **43**.

3.1.7. One-Pot Synthesis of α-Amino Acid Derivatives The radical addition reactions of water-resistant imine derivatives would integrate a multistep reaction into a one-pot reaction.[52,53] Condensation of 2-hydroxy-2-methoxyacetic acid methyl ester **44** with benzyloxyamine proceeded smoothly to

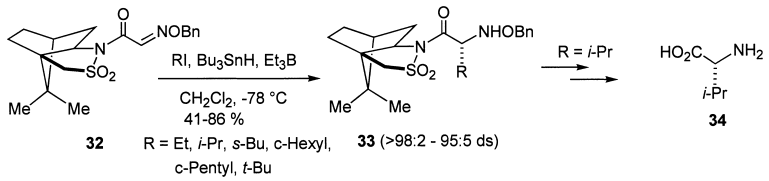
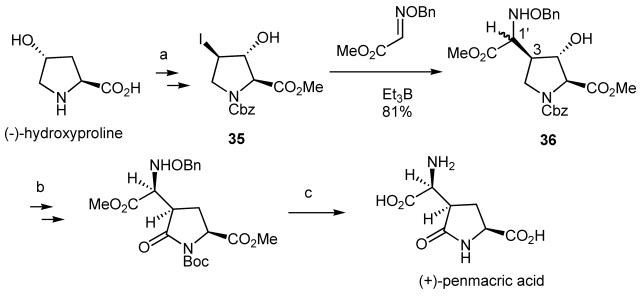


Chart 11. Diastereoselective Radical Addition

give the glyoxylic oxime ether **28** after being stirred at 25 °C for 24 h. To the reaction mixture in toluene at reflux were added alkyl iodide (RI) and triethylborane, and then the reaction mixture was stirred for 1 min. As expected, the one-pot reaction proceeded smoothly to give a good yield of alkylated products **29** when secondary alkyl iodides were employed (Chart 16). Alkylative amination of a few aldehydes **45** to **46** was also achieved using $BF_3 \cdot OEt_2$ as Lewis acid *via* the alkyl radical addition to oxime ethers generated *in situ* from aldehydes **45** and benzyloxyamine.[52]



Reagents and conditions: (a) (1) CbzCl, $NaHCO_3$, (2) concd. H_2SO_4, MeOH, (3) MeI, DEAD, PPh_3, (4) DBU, (5) *m*CPBA, 4,4'-thiobis(6-*t*-butyl-*o*-cresol), (5) MgI_2; (b) (1) H_2, $Pd(OH)_2$-C, $(Boc)_2O$, (2) TCDI, (3) Ph_3SnH, AIBN, (4) RuO_2, $NaIO_4$; (c) 3M HCl

Chart 12. Total Synthesis of (+)-Penmacric Acid

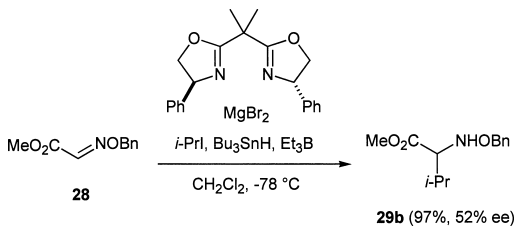
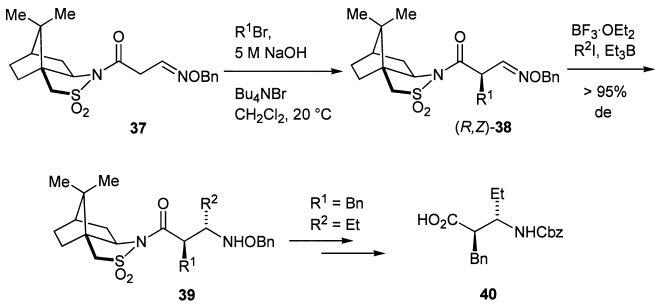


Chart 13. Enantioselective Radical Addition



R : Absolute configuration of newly-formed chiral center in **38**
Z : Geometry of oxime ether
R^1 = Bn, 4-NO_2-benzyl, Propargyl
R^2 = Et, *i*-Pr, c-Hexyl, c-Pentyl, *s*-Bu, *i*-Bu

Chart 14. Diastereoselective Radical Addition and β-Amino Acid Synthesis

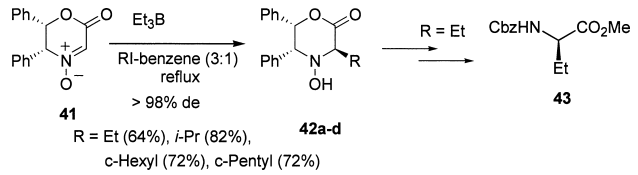


Chart 15. Radical Addition to Nitrone

3.1.8. Radical Reaction of Imine Derivatives in Aqueous Media The use of water as a solvent has generated considerable interest from both the economic and environmental points of view.[54] In principle, the reactions of strictly neutral species such as uncharged free radicals are not affected by the presence of water.[55—58] Therefore, employment of a moisture-resistant radical species would eliminate the cumbersome operations involved in conventional ionic reactions.

We reported the results of experiments to confirm the utility of imine derivatives in aqueous medium radical reactions.[59] The screening of several imines showed that oxime ethers **28** and **47** could participate in the aqueous medium radical reactions, particularly water-soluble oxime ether **47** carrying the carboxyl group worked well in only a 10-min reaction. Analogously, ethyl radical adducts **49** were prepared effectively from the corresponding imine substrates in aqueous media (Chart 17).

Another remarkable feature of this reaction is that employment of a water-resistant radical species successfully integrated a multistep chemical reaction into a one-pot three-component reaction, thus providing a convenient method for preparing the α-amino acids **51** in water from glyoxylic acid hydrate (Chart 18).[59] Comparison of the one-pot reaction either in organic solvent or in water is shown in Table 1, which exhibits the effectiveness of water as a medium in all categories including the formation of oxime ether, temperature at radical reaction, work-up procedure, and yield.[60]

3.1.9. In-mediated Radical Reaction We found for

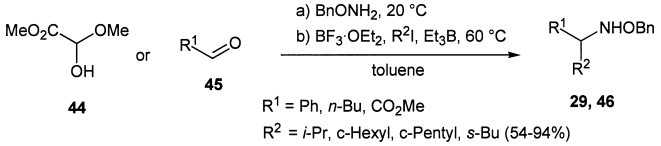


Chart 16. One-Pot Reaction

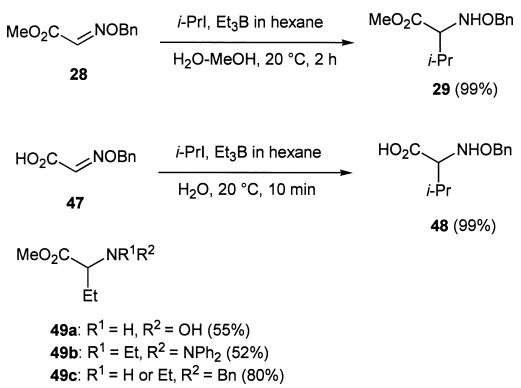


Chart 17. Radical Reaction in Aqueous Media

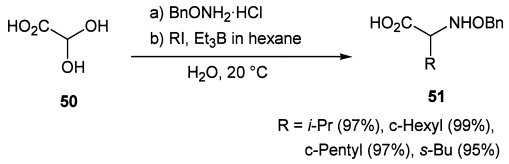


Chart 18. One-Pot Reaction in Aqueous Media

Table 1. Water *vs.* Organic Solvent

	in H_2O	in Toluene
Formation of oxime ether	2—3 h	20—30 h
Temp. at radical reaction	20 °C	Reflux
Work-up	No extraction	Extraction
Yield (%)	95—99	76—94

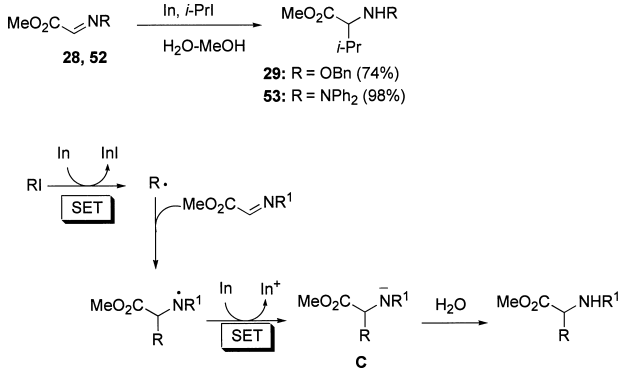


Chart 19. Indium-Mediated Radical Reaction and Possible Reaction Pathway

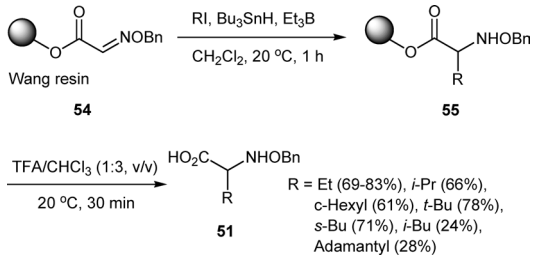


Chart 20. Solid-Phase Radical Addition

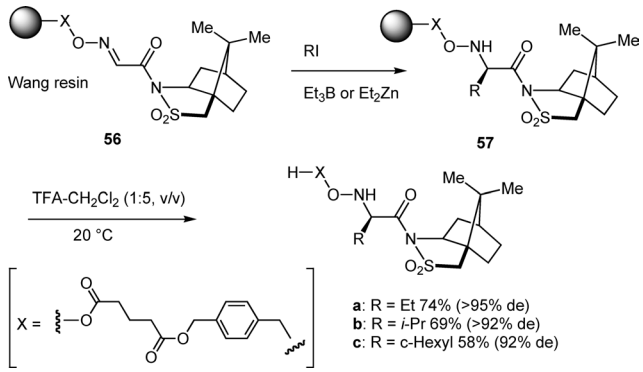


Chart 21. Diastereoselective Solid-Phase Radical Reaction

the first time an efficient carbon radical addition reaction to imine derivatives using indium metal as a single-electron transfer radical initiator. The first ionization potential of indium is close to that of sodium and lithium but indium is very stable in water.[61] Thus we investigated indium- and aqueous-mediated radical addition reaction to oxime ethers **28** and hydrazones **52** and found a novel synthetic method for α-amino and α-hydrazino acids. The result that practically no reaction of **28** occurred in the absence of water suggests that water is important for the activation of indium and for the proton-donor to the resulting amide anion **C**.[62] A plausible reaction pathway involves the SET reaction twice, as shown in Chart 19. Furthermore, the tolerance of hydrazone to the aqueous media provided practical one-pot synthesis of α-hydrazino acids and esters. As one of our related studies on radical reactions in water, zinc-mediated reaction of oxime ethers, hydrazones, and *N*-tosylimines in aqueous media was examined and found to be an efficient method for the preparation of amines and α-amino acids.[44,63]

3.1.10. Solid-Phase Radical Reaction Combinatorial chemistry has become a core technology for the rapid development of novel lead compounds in the pharmaceutical industry and for the optimization of therapeutic efficacy. Therefore the extension of carbon–carbon bond-forming radical reactions to solid-phase reactions would allow further progress in combinatorial organic synthesis.[60,64]

In addition to some reports on solid-state radical cyclizations using 2,2′-azobisisobutyronitrile (AIBN) or SmI_2 as a radical initiator,[65,66] Sibi's group reported the first studies on the solid-phase intermolecular radical reaction using allyl stannanes and AIBN.[67] To test the viability of triethylborane as a radical initiator on solid support, we first investigated the radical addition to the oxime ether **54** anchored to Wang resin and TentaGel OH resin (Chart 20). The reaction of **54** was run with RI, tributyltin hydride, and triethylborane in dichloromethane at 20 °C for 1 h. Not only secondary alkyl radicals but also a bulky *tert*-butyl radical worked well, allowing facile incorporation of structural variability. The solid-phase radical reaction will be particularly useful because the often tedious work-up to remove excess tin residues from the reaction mixture is eliminated in the solid-phase methodology by washing of the resin with solvents. Removal of solid support of radical addition products **55** afforded α-amino acid derivatives **51**.[68,69]

Diastereoselective alkyl radical addition to Wang resin-bound chiral oxime ether **56** proceeded in the presence of triethylborane and diethylzinc as an effective radical initiator at −78 °C to provide chiral adducts **57** after the removal of solid support (Chart 21).[70,71] The diastereomeric purity was found to be not less than 95% de. The solid-phase radical reaction was also effectively extended to the reaction of TentaGel OH resin-bound oxime ether in aqueous media.

3.1.11. Domino Radical Reaction Domino reactions that proceed sequentially through either ionic or radical species exhibit the sometimes problematic drawback of strictly settled reaction conditions for ionic reaction and polymerization for radical ones, although the domino reaction is generally known to be one of the most efficient synthetic methods.[72] On the other hand, a new combination of radical process and ionic process would be a promising approach as shown in a few examples[73,74] that employed enolate as an intermediate formed by radical addition reaction. We succeeded in a hybrid type of domino radical addition-aldol-type reaction of α,β-unsaturated oxime ether, providing a powerful synthetic approach to chiral γ-butyrolactones and γ-amino acids. Prior to exploring the new domino protocol, we first observed the regioselective carbon radical addition to the β-position of conjugated chiral oxime ether *E*-**58** carrying three radicophilic positions (Chart 22).[75] This is the first example of regioselective radical addition to conjugated oxime ether **58** that involves four electrophilic positions. The diastereomeric purity of **59a** was found to be not less than

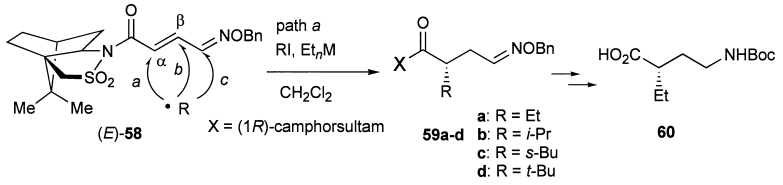


Chart 22. Radical Addition to Conjugated Oxime Ether and Conversion to γ-Amino Acid

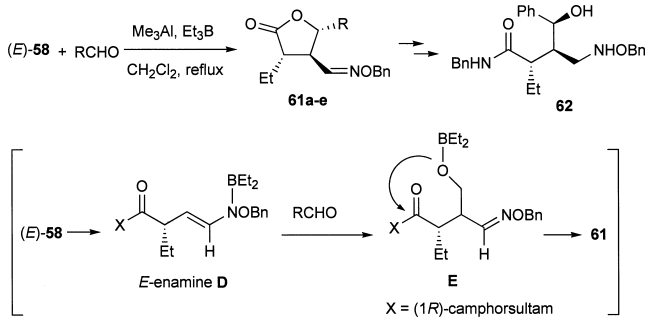


Chart 23. Domino Radical-Aldol-Type Reaction

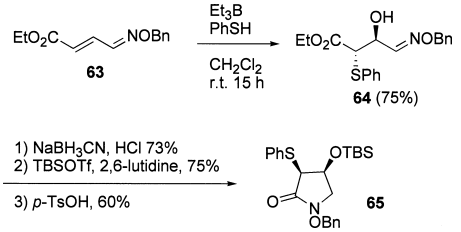


Chart 24. Radical Hydroxysulfenylation Reaction

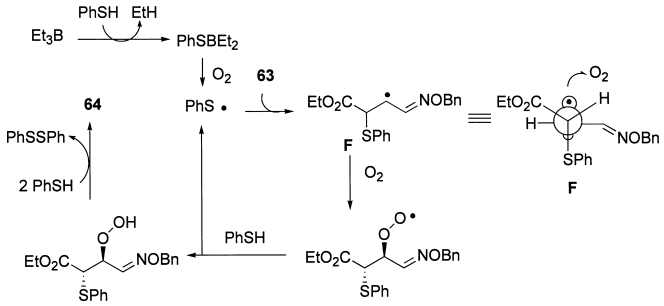


Chart 25. Possible Reaction Pathway of Radical Hydroxysulfenylation Reaction

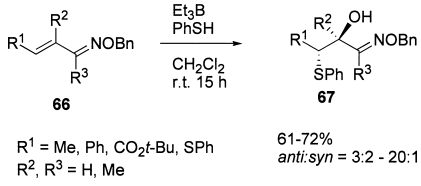


Chart 26. Radical Hydroxysulfenylation Reaction

95% de by ^{1}H-NMR analysis of the crude product. The absolute configuration at the newly formed stereocenter was determined to be *S* by converting the adduct **59a** into the authentic γ-amino acid **60**.[75]

The finding that triethylborane acts as an effective reagent for trapping the intermediate enaminyl radical to form the boryl *E*-enamine **D** prompted us to investigate the new domino reaction in the presence of an appropriate electrophile. We succeeded in the domino radical addition-aldol-type reaction of α,β-unsaturated oxime ether **58** using aldehyde as an electrophile, which was promoted in the presence of Me_3Al (1.2 eq) as a Lewis acid. The potentiality of the newly found domino radical-ionic reaction was confirmed by the asymmetric synthesis of various types of γ-butyrolactones **61** using different types of aldehydes (Chart 23). We also developed a domino reaction involving isopropyl radical addition *via* the iodine atom-transfer process, followed by the aldol-type reaction.[75]

3.1.12. Regioselective Hydroxysulfenylation of α,β-Unsaturated Imines During the course of our investigation[75] on the domino radical reaction described above, we developed a highly regioselective hydroxysulfenylation reaction of α,β-unsaturated imines **63** (Chart 24).[76] The reaction is characterized by mild conditions and simple operation and allows for regio- and stereoselective construction of a carbon–sulfur bond and a carbon–oxygen bond, providing a highly efficient synthetic approach to β-hydroxysulfides **64**.

Based on the weak bond dissociation energy[77] of the N–B bond as compared with the O–B bond and rapid formation[78] of $PhSBEt_2$ by the reaction of thiol and triethylborane, we started to investigate the reaction of conjugated imines **63** with thiol (3.5 eq) in the presence of triethylborane (0.5 eq) under atmospheric conditions and found a new hydroxysulfenylation reaction. The main *anti*-adduct **64** was firmly characterized by the conversion into γ-lactams **65**. The amounts of both thiols and triethylborane and the *anti*-stereostructure of main product **64** suggested a plausible reaction pathway *via* the conformation of sulfide intermediate **F** that is stabilized by homoconjugative interaction between the radical trigonal *p* orbital and the unoccupied sulfur 3*d* orbital (Chart 25).

Systematic study of the substituent effect using the substrates **66** disclosed that the conjugated imine moiety is a crucial functional group in this radical–radical type of domino reaction (Chart 26).[76]

3.2. Intramolecular Radical Addition Reaction Free radical-mediated cyclization has been developed as a powerful method for preparing various types of cyclic compounds *via* carbon–carbon bond-forming processes.[79] Although a number of extensive investigations into the radical reaction have been reported in recent years, the majority of those employed methods utilizing conventional radical acceptors such as alkenes or typical radical precursors such as halides, selenides, and xanthates. One drawback in the traditional procedures using such radical acceptors and precursors is the loss of the inherent functional groups. Therefore we focused our efforts on radical addition-cyclization of **68** employing aldehydes, ketones, imines, and C–C multiple bonds as a rad-

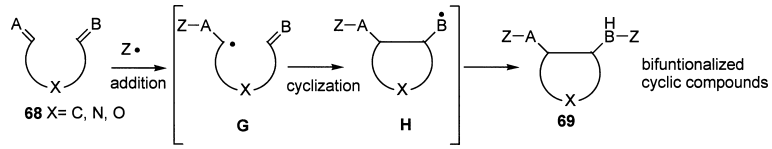


Chart 27. Radical Addition-Cyclization

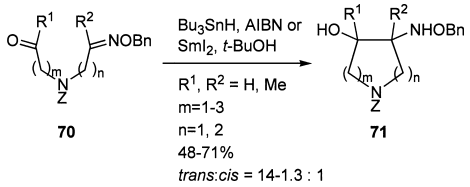


Chart 28. Radical Addition-Cyclization of Oxime Ethers

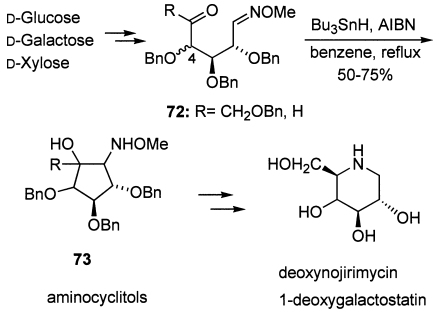
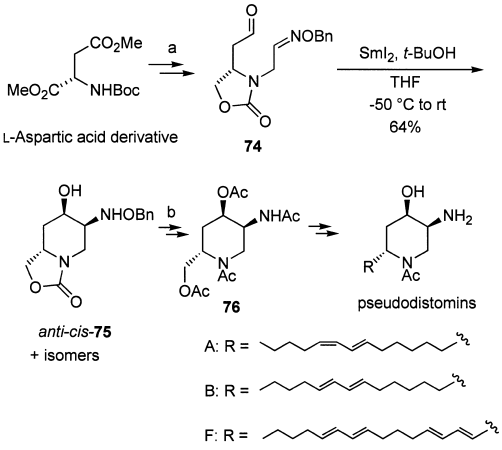


Chart 29. Radical Addition-Cyclization of Oxime Ethers Derived from Sugars



Reagents and conditions: (a) (1) $LiAlH_4$, (2) NaH, TBDMSCl, imidazole ; (3) chloroacetaldehyde *O*-benzyloxyoxime, NaH, (4) Bu_4NF, (5) DMSO, $(COCl)_2$, Et_3N, (5) MgI_2; (b) (1) H_2, $Pd(OH)_2$-C, (2) $Ba(OH)_2$, (3) Ac_2O, DMAP, pyridine

Chart 30. Synthesis of 2-Substituted 5-Amino-4-Piperidinols

ical precursor and/or an imino group as a radical acceptor and discovered the domino type of reaction *via* intermediates **G** and **H** which would provide bifunctionalized cyclic compounds **69** (Chart 27).[31,79,80]

3.2.1. Synthesis of Functionalized Cyclic Compounds *via* the Stannyl Radical Addition-Cyclization Reaction We have explored a new carbon–carbon bond-forming reaction based on the stannyl radical addition-cyclization of oxime ethers **70** tethered to a carbonyl group, which provides a synthetically useful method for the construction of cyclic amino alcohols **71** widely found in biologically active natural products (Chart 28).[81] The scope and limitation of the stannyl radical addition-cyclization of oxime ethers involving Bu_3SnH and AIBN were disclosed by our systematic study employing readily available starting compounds **70** in which two functional groups, oxime ether and carbonyl groups, are connected with a nitrogen atom with different carbon chains. These reactions were extended to the cyclization of the oxime ethers **70** to give the six- and seven-membered cyclic products **71**. We also investigated the SmI_2-induced reaction of oxime ethers **70** in the presence of *t*-BuOH as a proton donor in THF at from −78 °C to room temperature.[82,83] The addition of HMPA was found to be essential for successful seven-membered ring-forming cyclization to **71**, and the five-membered ring-forming reaction of **70** proceeded even in the absence of HMPA. As one of our related studies on the hetero-atom radical addition-cyclization reaction, we have also reported either stannyl or silyl radical addition reaction to olefins connected with oxime ether moiety in the same molecule.

3.2.2. Synthetic Applications to Natural Compounds The radical cyclization of oxime ethers connected with the formyl group provides a synthetically useful method for the construction of cyclic amino alcohols found in biologically active natural products such as (−)-balanol, pseudodistomins, amino cyclitols, and amino sugars (Chart 29). Stannyl radical addition-cyclization of oxime ethers **72** derived from D-glucose, D-galactose, and D-xylose proceeded smoothly to afford alkoxyamino alcohols **73**, which were effectively converted into two types of glycosidase inhibitors or its candidates such as aminocyclitols, 1-deoxynojirimycin, and 1-deoxygalactostatin *via* newly found reductive ring-expansion of *trans*-alkoxyamino alcohols **73**.[84]

Pseudodistomins and related compounds can be synthesized *via* radical reaction of oxime ether **74** prepared from L-aspartic acid (Chart 30).[85] Treatment of **74** with SmI_2 in the presence of *t*-BuOH underwent a smooth 6-*exo*-*trig* manner of cyclization to give the cyclized product **75** with other stereoisomers even in the absence of HMPA. Conversion of *anti*-*cis*-**75** to 2-substituted 5-amino-4-piperidinol **76**, which is regarded as a synthetic precursor of pseudodistomins, was readily achieved.[85]

(−)-Balanol, a potent protein kinase C inhibitor, consists of a benzophenone fragment **78** and a hexahydroazepine fragment **81** (Chart 31). The total synthesis of (−)-balanol was achieved *via* the preparation of a benzophenone fragment **78** based on a biomimetic oxidative anthraquinone ring cleavage starting from commercially available chrysophanic acid **77** and *via* the preparation of a hexahydroazepine fragment **80** based on either Bu_3SnH- or SmI_2-promoted radical cyclization of oxime ether **79**.[82]

3.2.3. Radical Addition-Cyclization-Elimination (RACE) and Total Synthesis of (−)-Martinellic Acid

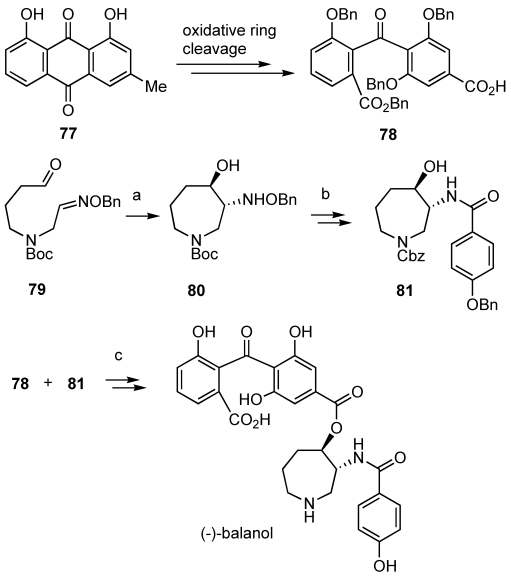
During the course of our investigation of stannyl radical addition-cyclization reactions of oxime ethers connected with carbonyl functionalities, we found an interesting reaction of conjugated systems.[86] Particularly the α,β-unsaturated ester group exhibited a very interesting reactivity in the radical chemistry of oxime ethers. Under the standard conditions, benzaldehyde oxime ether **82** carrying a conjugated ester moiety gave two types of products, **83** and **84**. The major product **83** was a tricyclic lactam and surprisingly the benzyloxy group was not present in the structure. Another minor product **84** was the bicyclic compound that was our initially expected product. We describe this reaction leading to NH-lactam **83** as RACE (Chart 32).[86]

Some additional reactions including deuterium incorporation suggested a tentative reaction pathway (Chart 33).[86] In the case of benzaldehyde oxime ether **82**, the stannyl radical would preferably attack the oxime ether group to generate stable benzyl radical **I**, which intramolecularly cyclizes to unsaturated ester. The resulting nucelophilic aminostannane **J** cyclizes to the ester group to form NH-lactam **83** and benzyl alcohol *via* intermediate **K**. The RACE reaction of an oxime ether carrying an unsaturated ester provides a novel method for the construction of pyrroloquinolines which opens a new approach to the total synthesis of martinelline alkaloids.[87,88]

Martinellines are alkaloids isolated in 1995 (Fig. 2) and found to show very interesting biological activities as non-peptidic Bradykinin receptor antagonists that will be good candidates for lead compounds in new drug discovery.[87] The skeleton of these alkaloids is a pyrroloquinoline, which is the first example found in an alkaloid structure. The total synthesis and synthetic studies on martinellines have recently been reported by several groups[89,90] and much attention has been paid to how to construct the pyrroloquinoline core stereoselectively.

Following our first formal synthesis of (±)-martinellines,[86] we employed pyroglutamate as a chiral source for our asymmetric synthesis of (−)-martinellic acid. According to the conventional manner, commercially available bromoester **85** and pyroglutamate **86** led to the formation of chiral substrate **87** for the RACE reaction *via* transformation of the functional groups. The RACE reaction of **87** proceeded to give a mixture of tetracyclic products **88**. The structure of the major product **88** was firmly established by X-ray analysis. Then, chemoselective reduction of three carbonyl groups in **88** and additional transformation of the functional groups gave trifluoroacetamide **89**. We developed a new route for the introduction of two guanidine groups. The Mitsunobu reaction of the hydroxyl group in **89** with isothiourea, followed by replacement of the methylthio group with the alkyl amine, gave the guanidine ester **90** in which the protective groups were removed to afford (−)-martinellic acid identical to the authentic sample based on comparisons of their spectral data except for the optical rotation (Chart 34).[89,90] Personal communication from the Merck group mentioned that natural alkaloid martinellic acid would be racemic and the absolute configuration was not characterized.[88] Our synthetic route involves 17 steps, which is shorter than those reported by other groups.[89,90]

3.2.4. Synthesis of Functionalized Cyclic Compounds



Reagents and conditions: (a) Bu_3SnH, AIBN, or SmI_2, HMPA;(b) (1) H_2, PtO_2, (2) *p*-benzyloxybenzoyl chloride, $NaHCO_3$; (c) (1) 2-chloro-1-methylpyridinium iodide, Et_3N, DMAP, (2) HCO_2H, Pd-black

Chart 31. Total Synthesis of (−)-Balanol

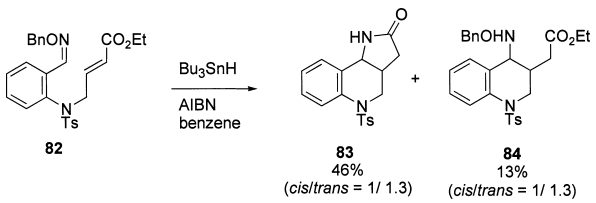


Chart 32. RACE Reaction

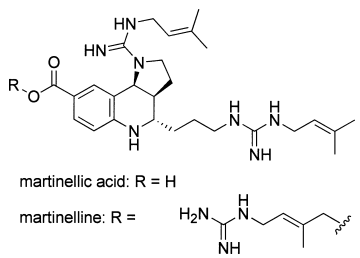


Fig. 2. Natural Martinellines

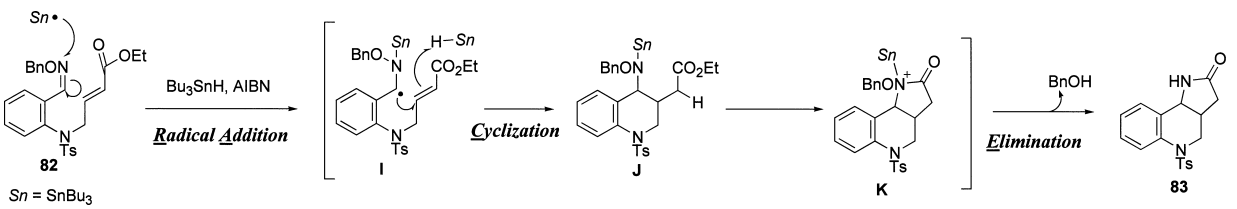
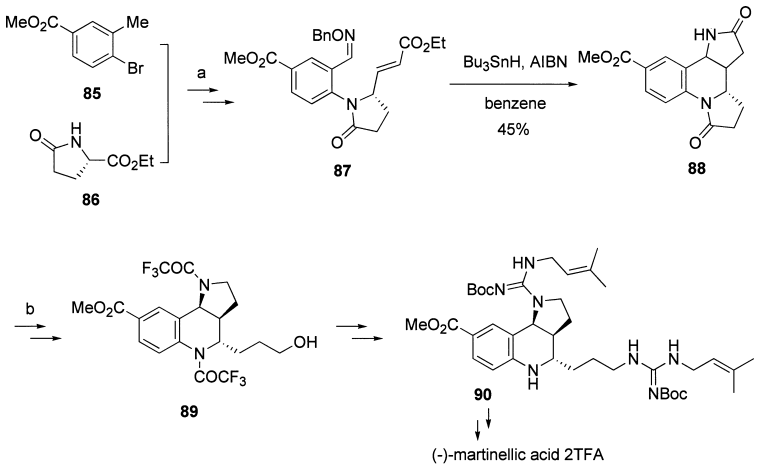


Chart 33. Possible Reaction Pathway of RACE Reaction



Reagents and conditions: (a) (1) $Pd_2(dba)_3$, Cs_2CO_3, xantphos, (2) $NaBH_4$, (3) DMSO, TFAA, Et_3N, (4) $Ph_3P{=}CO_2Et$; (b) (1) $LiBH_4$, THF, MeOH, (2) BH_3, THF, (3) TFAA, Et_3N, DMAP

Chart 34. Total Synthesis of (−)-Martinellic Acid

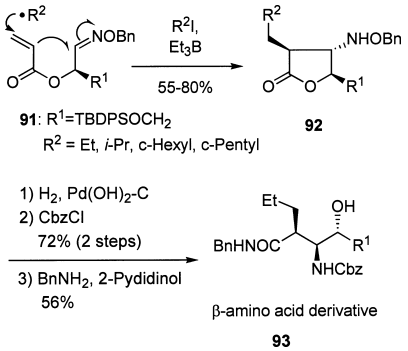


Chart 35. First Radical Mannich-Type Reaction

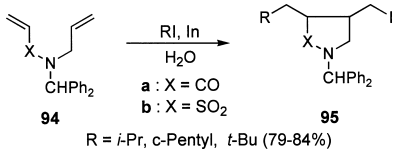


Chart 36. Indium-Mediated Domino Reaction in Water

***via* the Carbon Radical Addition-Cyclization Reaction** We developed the first radical Mannich-type reaction *via* carbon radical addition-cyclization reaction of substrate **91** having two different radical acceptors such as acrylate and aldoxime ether moieties (Chart 35).[91] A remarkable feature of this reaction is the construction of two C–C bonds and two chiral centers *via* a domino process even in the absence of toxic tin hydride or heavy metals *via* a route involving an iodine atom-transfer process. The reaction in refluxing toluene proceeded smoothly to give major diastereomers **92** in good yields along with a small amount of the other diastereomers. γ-Butyrolactone **92** was easily converted to a β-amino acid derivative **93** using standard methods. These reactions were successfully applied to the solid-phase radical reaction of oxime ethers.[92]

The domino reaction involving indium-mediated carbon radical addition-cyclization of olefinic acrylamide and sulfonamide **94** proceeded even in aqueous media. As described in intermolecular carbon radical addition, the nucleophilic carbon radical attacked more electrophilic acrylamide and sulfonamide parts, and then the resulting carbon radical cyclized to the terminal alkene part to form functionalized pyrrolidone and sultam **95** (Chart 36).[93]

Another type of alkyl radical addition-cyclization of oxime ethers carrying an appropriate leaving group proceeded smoothly to form the alkylated nitrogen-containing heterocyclic compounds (Chart 37).[94] Substrates **96** carrying two functional groups, on an electrophilic site and the other on a radical acceptor site, were expected to undergo carbon radical addition regioselectively at the oxime ether group to generate boryl amines **M**. The boryl amines **M** are also expected to undergo intramolecular ionic cyclization at the leaving group to form heterocycles **97**. If the same substrates **96** are treated with nucleophiles, two functional groups could react to form a complex mixture, which is a drawback of normal ionic reactions.

Treatment of oxime ether **98** carrying the tosyloxy group with Et_3B in the presence of $BF_3 \cdot Et_2O$ as a Lewis acid gave the desired product **99** in good yield.[95] In the presence of various types of alkyl iodides as radical precursors, the reactions also proceeded smoothly to form alkylated pyrrolidines **99**, except when using sterically hindered tertiary alkyl iodides. According to the recent report of Landais' group,[96] we employed the phenyl esters **100** and **101** because the phenoxy group is a better leaving group than the methoxy group. Under the standard radical conditions, **100** and **101** gave the expected lactams **102** and **103** in good yields (Chart 38). Based on these results, we then applied our method to the synthesis of a simple alkaloid, bgugaine and a synthetic key intermediate **104** for the poison frog alkaloids (Fig. 3).[95]

3.2.5. Synthesis of Functionalized Cyclic Compounds *via* the Thiyl Radical Addition-Cyclization Reaction As a complementary new method for radical generation that avoids the use of tin reagents, we have also explored the reactions based on sulfanyl radical addition-cyclization.[97,98] A combination of sulfanyl radical addition-cyclization of diene *Z*-**105** connected with hydroximate and subsequent conversion of the resulting cyclic hydroximate **106** to the lactone

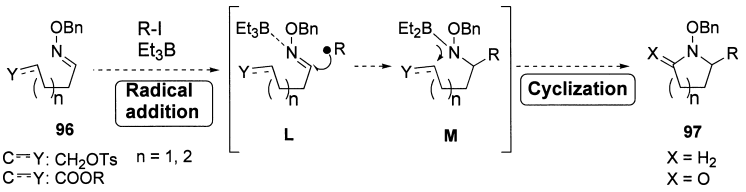


Chart 37. Domino Radical Addition-Cyclization

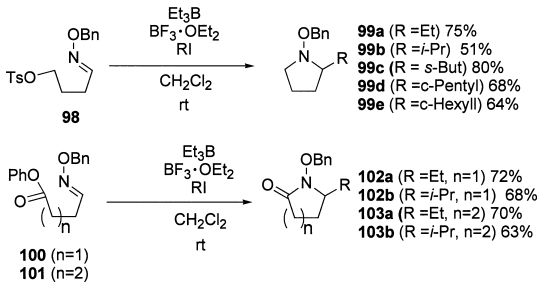


Chart 38. Radical Addition-Cyclization

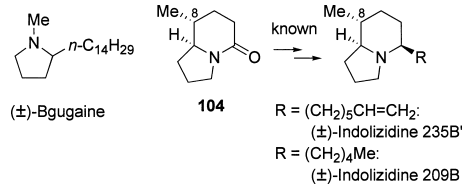


Fig. 3. Synthesis of an Alkaloid and a Key Intermediate

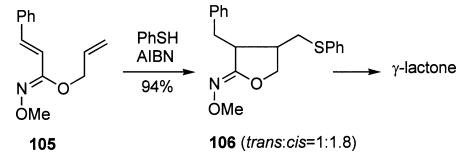
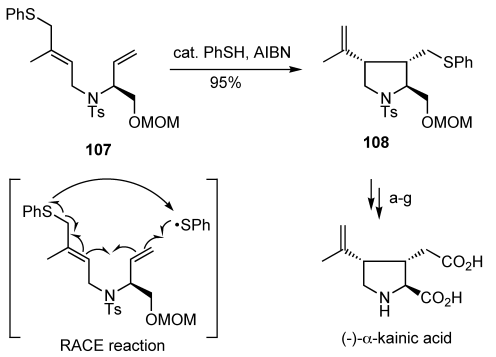


Chart 39. Sulfanyl Radical Addition-Cyclization

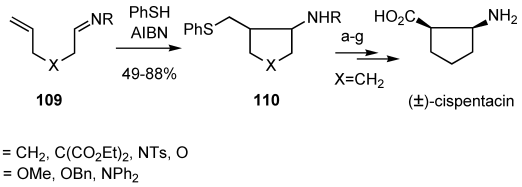


Reagents and conditions: (a) OXONE; (b) (1) MeLi, (2) $ClCO_2Me$; (c) Na-Hg; (d) TFA; (e) (1) PDC, (2) CH_2N_2; (f) LiOH; (g) Li-liq. NH_3

Chart 40. Asymmetric Synthesis of (−)-α-Kainic Acid

provides a novel method for the construction of α,β-disubstituted γ-lactones (Chart 39).[98] This method was successfully applied to the practical synthesis of (±)-oxo-parabenzlactone.

Following our synthesis of (+)-α-allokainic acid using the sulfanyl radical addition-cyclization of diene **107** derived



Reagents and conditions: (a) $LiAlH_4$; (b) $(Boc)_2O$, Et_3N; (c) *m*CPBA; (d) heat; (e) (1) 9-BBN, (2) H_2O_2, NaOH; (f) RuO_2, $NaIO_4$; (g) H^+

Chart 41. Sulfanyl Radical Addition-Cyclization

from D-serine or (*S*)-glycidol as a key step, we succeeded in more concise asymmetric synthesis of (−)-kainic acid *via* the route involving the sulfanyl RACE reaction of diallylamine **107** in the presence of a catalytic amount of thiophenol and AIBN (Chart 40).[99]

We also investigated the sulfanyl radical addition-cyclization of the alkenyl-tethered-imines **109** for the synthesis of rigidified β-amino acids.[100] In these reactions, the *cis*-isomers were preferentially formed, probably due to the effect of orbital symmetry reported by Beckwith.[101] The synthesis of the cyclic β-amino acid (±)-cispentacin from the cyclopentylamines *cis*-**110** prepared by our sulfanyl radical addition-cyclization was readily achieved by conversion of the phenylsulfanylmethyl group into a carboxyl group. The sulfanyl radical addition-cyclization strategy of the diyne substrate was successfully applied to the synthesis of the A-ring fragment of 1α,25-dihydroxyvitamin D (Chart 41).[102]

4. Stereoselective Addition of Thiols and Its Synthetic Application

Generally, nucleophilic addition reactions such as the Michael addition proceed in two-step processes with an initial attack of a nucleophile on electron-deficient olefin, followed by an electrophile on the intermediary enolate in its most stable conformation.[103] For example, most conjugate addition reactions to the Michael acceptors **111** and **113**, irrespective of the *E*- or *Z*-configuration in aprotic solvent, yield the same diastereomer of *erythro*-**112** as a result of the attack of an electrophile from the sterically and stereoelectronically preferable α-face of the enolate **N**, which is a rotational isomer of the less stable enolate **O** formed from *Z*-olefin **113**. Thus these reactions are stereoslective but not stereospecific.[104]

We investigated the addition of a small amount of lithium thiophenoxide to α,β-unsaturated carbonyl compounds **111** and **113** in the presence of a large amount of thiophenol as a proton source and found that the addition reaction of thiophenol to the *E*- and *Z*-substrates proceeds stereospecifically to give the respective *anti*-adducts, *i.e.*, *E*-**111** and *Z*-olefins **113** gave *erythro*-**112** and *threo*-adducts **114**, respectively

(Chart 42).[105,106]

4.1. Synthesis of (+)-Diltiazem As an extension of our stereospecific addition reaction of thiols to electron-deficient olefins, we developed the asymmetric construction of two contiguous stereocenters using the diastereoface differentiating addition reaction of thiols to chiral imides which allowed us to achieve asymmetric synthesis of an important cardiac drug, (+)-diltiazem (Chart 43).[107,108] The unsaturated chiral imide **115** was prepared by sequential reactions including condensation of glycolic acid chloride with lithiated Evans's chiral oxazolidinone, aldol reaction of the resulting imide with anisaldehyde, and dehydration *via* the corresponding mesylate. The addition reaction of 2-aminothiophenol to both chiral *E*- and *Z*-unsaturated imides **115** proceeded effectively to afford identical 2*S*,3*S*-adduct **116** in which the MEM group acted as a very interesting substituent effect in the transition state of the reaction. As the final steps to target compound **117**, the chiral auxiliary of **116** was smoothly removed by treatment with trimethylaluminum along with the concomitant lactam formation in one pot and without racemization. Deprotected hydroxylactam **117** had been transformed into (+)-diltiazem.[107]

4.2. Synthesis of (+)-PS-5 The newly found stereospecific addition of thiophenol to olefins was successfully applied to the synthesis of lactones and lactams. An example is the synthesis of (+)-PS-5 (Chart 44).[109] A combination of stereoselective addition of thiophenol to chiral imide **118**, prepared from unsaturated carboxylic acid and Evans's reagent, and subsequent intramolecular substitution of the corresponding sulfonium group with an *O*-alkylhydroxamate moiety in **120** has provided a new practical and stereoselective method for the construction of β-lactams **121** which has been successfully applied to the formal synthesis of the carbapenem antibiotic (+)-PS-5.[109]

4.3. Development of Olefin Inversion Encouraged by the newly found stereospecific *anti*-addition of thiols to olefins, we designed stereoselective olefin inversion *via* the route involving *anti*-addition of thiols followed by *syn*-elimination of the corresponding sulfoxide (Chart 45).[110] Theoretically, *anti*-addition of an appropriate additive to the trisubstituted olefins coupled with *syn*-elimination of the adduct or *syn*-addition and *anti*-elimination would furnish the isomerized olefins from either *E*- or *Z*-isomer. We developed a general and useful strategy for olefin inversion by combining *anti*-addition of thiol and *syn*-elimination of the corresponding sulfoxides **122** and **123**. Particularly, stereoselective formation of unstable *Z*-olefin **113** from stable *E*-isomer **111** would be a powerful synthetic method.

4.4. Synthesis of Isositsirikine Alkaloids The above-mentioned olefin inversion strategy was successfully applied to the total synthesis of isositsirikine alkaloids (Chart 46).[111,112] As described in Section 1 of this review, a common key intermediate of vinyl lactam **124** was prepared with the elimination-addition reaction of tetrahydrofuran **16a**, readily prepared by reductive photocyclization of enamide **15a**, with lithium acetate. Upon treatment with base, the vinyl derivative **124** was readily isomerized to the more stable 19*E*-conjugated lactam **125**. The 19*E*-ethylidene lactam **125** was treated with thiophenol in the presence of lithium thiophenoxide as base to afford the expected *anti*-adduct that was successively oxidized to the corresponding sulfoxide using *m*-CPBA. The sulfoxides obtained as an epimeric mixture were then subjected to thermal elimination, which furnished the homogeneous 19*Z*-lactam **126** quantitatively. Thus conversion of more stable 19*E*-olefin **125** to less stable 19*Z*-isomer **126** was overcome by our newly found method involving thiophenol addition and sulfoxide elimination. Back-conversion of 19*Z*-lactam **126** to the *E* isomer **125** was also achieved using the same methodology.

For the synthesis of isositsirikine alkaloids, the inversion from the 3β-hydrogen in **125** and **126** to 3α-orientation in **127** and **128** was accomplished *via* oxidation to the corresponding enamine derivative, followed by hydrogenation by $NaBH_4$ in AcOH which was established by Bohlmann's group.[113] Thus we provided all four stereoisomers of the intermediates: 3,15-*syn*-19*Z* **128**, 3,15-*anti*-19*Z* **126**, 3,15-*anti*-19*E* **125**, and 3,15-*syn*-19*E* **127**. Finally, we completed the

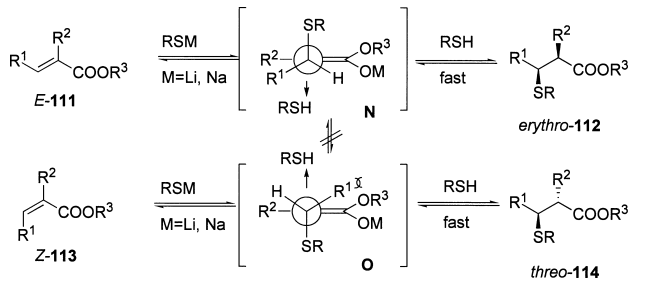


Chart 42. Stereospecific Nucleophilic Addition of Thiol

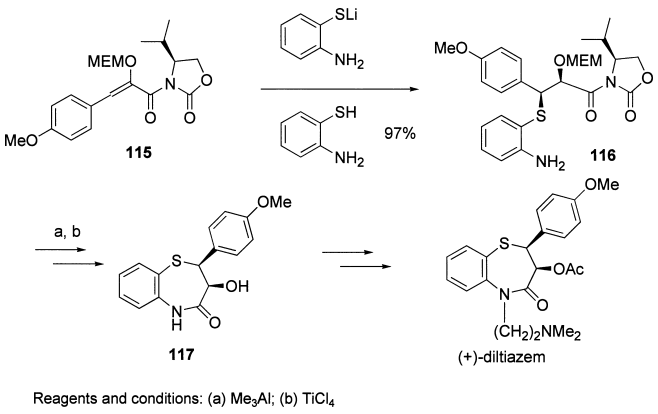


Chart 43. Synthesis of (+)-Diltiazem

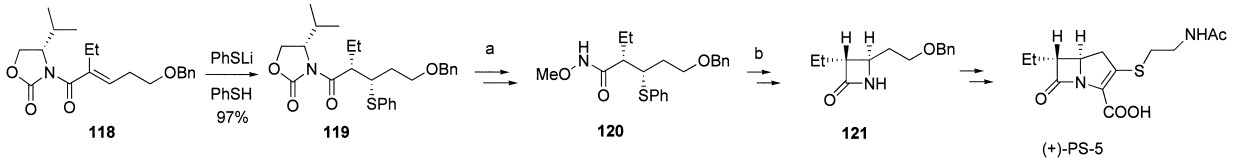


Chart 44. Synthesis of (+)-PS-5

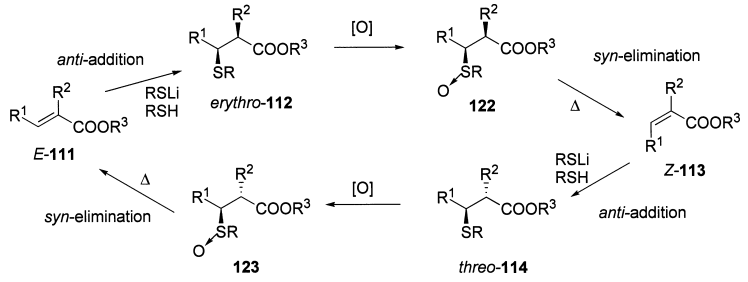


Chart 45. Olefin Inversion

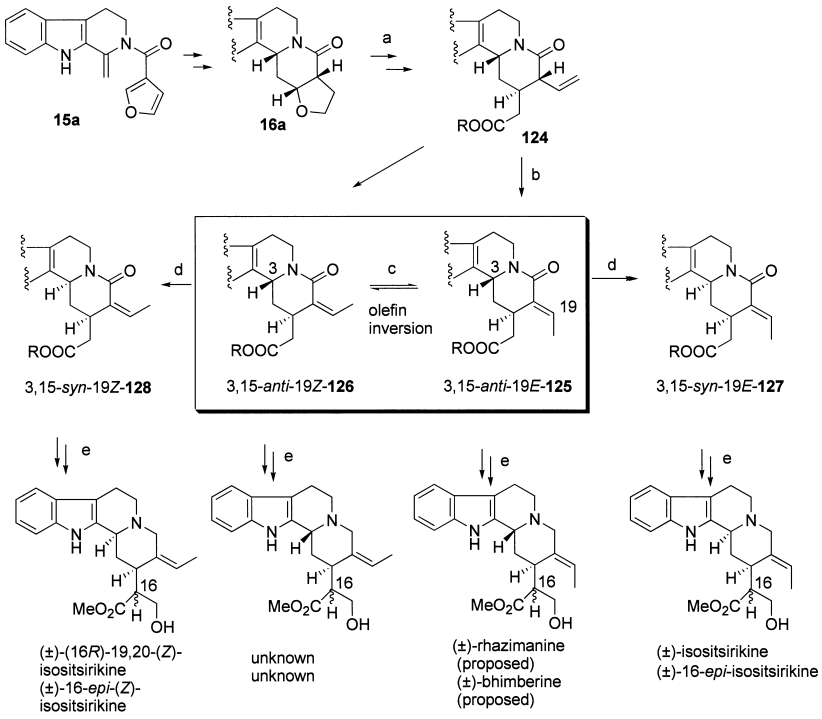


Chart 46. Synthesis of Isositsirikine and All Other Stereoisomers

total synthesis of eight possible stereoisomers of isositsirikines *via* the route involving transformations of the functional group, selective reduction of the lactam carbonyl group, introduction of the formyl group, and $NaBH_4$ reduction. Among them, isositsirikine, 16-epi-isositsirikine, (16*R*)-19-20-(*Z*)-isositsirikine, and 16-epi-(*Z*)-isositsirikine, were identical to the respective natural products but the final products derived from 3,15-*anti*-19*E* **125** were not identical to natural rhazimanine and bhimberine, and thus the structural elucidation requires reinvestigation.

5. Summary

We developed three efficient methodologies involving the reductive photocycloaddition reaction, radical addition reaction, and nucleophilic addition of thiols which were successfully applied to the synthesis of various types of amines. These findings will contribute to the development of new reactions and synthetic methodologies.

Acknowledgments I would like to express my sincere appreciation to my numerous coworkers whose efforts, persistence, and ability made possible the performance of the research work described. Names of collaborators in the present study are mentioned in the References.

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