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REVIEW

Dedicated to Full Member of the Russian Academy of Sciences Irina Petrovna Beletskaya for her prominent contribution to the development of organic synthesis and elaboration of numerous new catalytic reactions which inspired many chemists over the world

Ring-Closing Metathesis in the Synthesis of Cyclic α-Amino Acids*

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Abstract—The review summarizes recent advances in the synthesis of cyclic α-amino acids via intramolecular ring-closing metathesis of dienes and enynes.

INTRODUCTION

In the recent years, the use of intramolecular olefin metathesis in the synthesis of cyclic systems from linear dienes and enynes has developed extensively [1–6]. This method makes it possible to easily build up various carbo- and heterocycles, macrorings in peptides, and other biologically important structures [7, 8]. Rapid development of olefin metathesis originates from the discovery of a series of catalysts based on carbene molybdenum and ruthenium complexes [9–11], which show a high resistance toward atmospheric oxygen, protic solvents, and also various functional groups [12, 13].

The synthesis of sterically hindered α-amino acids which could considerably enhance conformational stability of peptides plays an important role in the design of new medicines. The most efficient approach to conformationally rigid peptides is based on introduction of medium-size cyclic α-amino acids (usually, 5–7-membered) into strategic positions of peptide chains [14, 15]. As a rule, this leads to significant improvement of pharmacological parameters of potential peptide medicines [16, 17]. Steric effects become even stronger when the α-hydrogen atom in amino acid is replaced by an alkyl group. Moreover, introduction of fluorine atoms or fluorinated alkyl groups into cyclic molecules may also be useful from the biological viewpoint. For example, α-fluoromethyl-substituted α-amino acids are known to be selective and irreversible inhibitors of pyridoxal phosphate-dependent enzymes, which possess a wide spectrum of biological properties [18]. In addition, the presence of fluorine atoms considerably facilitates study of conformational features of peptides with the aid of ^{19}F NMR spectroscopy.

* The original article was submitted in English.

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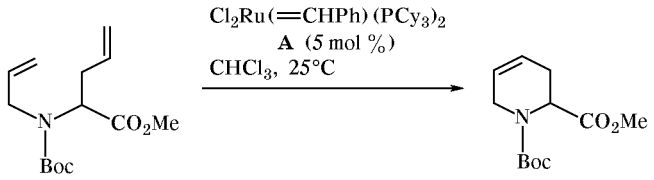
The present review considers the latest published data on the synthesis of cyclic α-amino acids and their derivatives and analogs by intramolecular ring-closing metathesis (RCM) of dienes and enynes.

2. RING-CLOSING METATHESIS OF FUNCTIONALLY SUBSTITUTED DIENES

2.1. Synthesis of Cyclic Amino Acids

Grubbs *et al.* [19] were the first to report on the synthesis of racemic dehydropipecolate **II** by cyclization of the corresponding *N*,α-diallylglycine derivative **I** in the presence of carbene ruthenium complex **A** [10, 11] (Scheme 1).

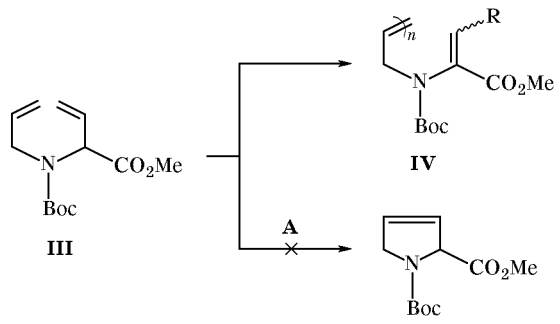
Scheme 1.



I **II**

A strong limitation of the RCM strategy as applied to the synthesis of cyclic amino acids was illustrated by the failure to obtain dehydroproline **IV** [19] (Scheme 2). The reaction of 1,6-diene **III** over the same catalyst afforded only a mixture of linear α,β-unsaturated esters. Presumably, this is explained by increased mobility of a fairly acidic α-proton in initial vinylglycine **III**.

Scheme 2.

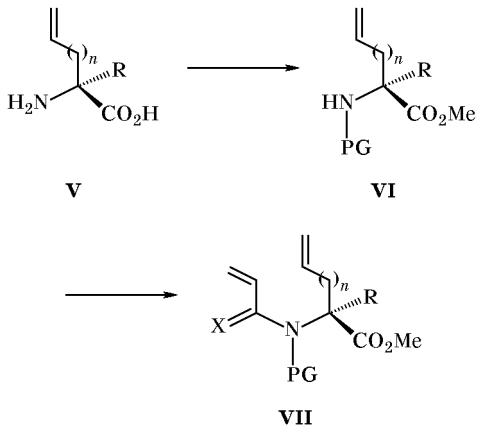


III **IV**

R = H, Me; *n* = 1, 2.

Rutjes and Schoemaker [20] successfully applied the RCM approach to obtain enantiomerically pure cyclic amino acids containing various functional and protecting groups. Initial optically active α-amino acids **V** can be prepared using enzymatic procedures for separation of the corresponding amino acid amides [21]. Intermediate protected esters **VI** were synthesized by esterification, followed by monoalkylation at the nitrogen atom. Finally, precursors **VII** for the RCM reaction were obtained by either N-acylation with 1.2 equiv of CH_2=CHCOCl (in the presence of 1.5 equiv of Et_3N) or N-alkylation of **VI** with allyl bromide (1.5 equiv; 2.5 equiv of $NaHCO_3$, LiCl; Scheme 3).

Scheme 3.



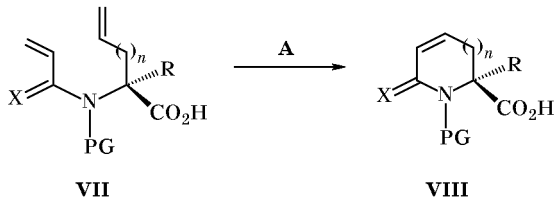
V **VI**

VII

R = H, Me; PG = PMB, $C_5H_5FeC_5H_4CH_2$, Boc, Bzl; X = O, H_2; *n* = 1, 2.

Ferrocenyl and benzyl derivatives **VI** (R = H) were specially prepared by esterification of **V** (R = H) and subsequent condensation with ferrocenecarbaldehyde or benzaldehyde; the resulting Schiff bases were reduced to amino acid derivatives **VI** with 1 equiv of $NaBH_3CN$ in the presence of 1 equiv of *p*-toluenesulfonic acid. Protected ester **VI** (PG = Boc) was obtained by N-allylation of the corresponding amino ester, followed by treatment with Boc_2O [20]. RCM

Scheme 4.



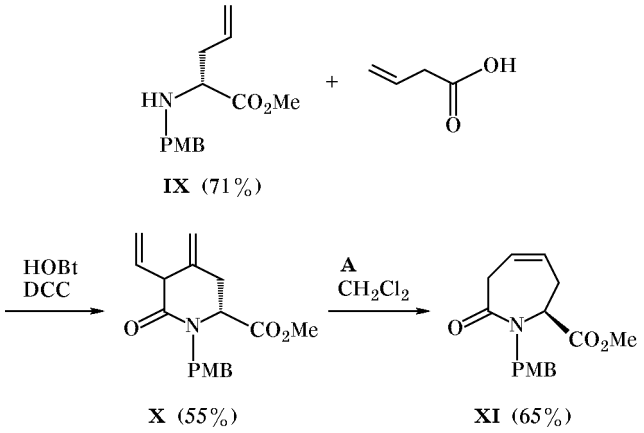
VII **VIII**

X	R	PG	*n*	Yield, %
H_2	H	PMB	1	54
H_2	H	$FcCH_2$	1	18
H_2	H	Boc	1	93
O	H	PMB	1	93
O	H	$FcCH_2$	1	89
H_2	Me	PMB	1	82

reaction of 1,7- and 1,8-heterodienes **VII** was successfully accomplished in the presence of complex **A** (5 mol %) at 40°C in CH_2Cl_2 to afford cyclic α-amino acid derivatives **VIII** (Scheme 4).

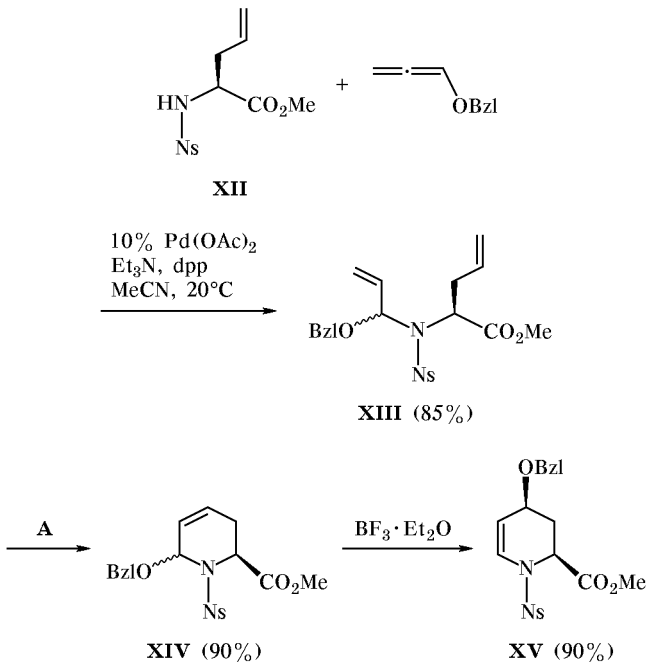
The position of the endocyclic double bond in azepine derivatives (*n* = 2) can be controlled by varying the substituents on the nitrogen atom. For example, treatment of compound **IX** with vinylacetic acid under standard conditions of peptide synthesis [1.05 equiv of 1-hydroxybenzotriazole (HOBt), 1.05 equiv of *N*,*N*′-dicyclohexylcarbodiimide (DCC)], gave 55% of compound **X** which undergoes ring closure to enantiomerically pure seven-membered lactam **XI** in the presence of complex **A** (Scheme 5). However, attempts to apply the same procedure to the synthesis of eight-membered cyclic derivatives were unsuccessful: in all cases, linear dimerization and polymerization products were formed [20].

Scheme 5.



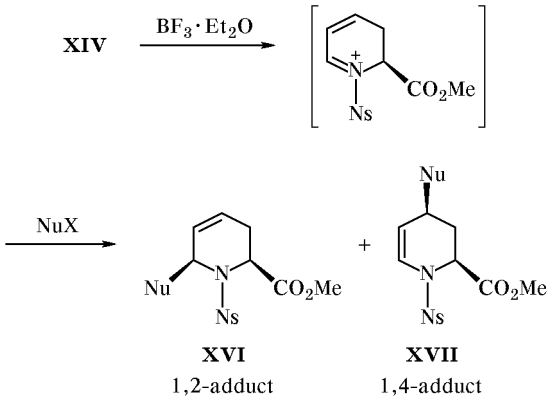
The same authors recently extended the scope of application of the above approach. The procedure was based on the formation of N,O-acetals via palladium-catalyzed reaction of *N*-4-nitrophenylsulfonyl(Ns)-α-allylglycine **XII** with benzyloxyallene [22] (Scheme 6). A stable 1:1 mixture of diastereoisomeric N,O-acetals **XIII** was subjected to intramolecular RCM reaction in the presence of complex **A**, and cyclic product **XIV** was thus obtained as a 1:1 mixture of *cis* and *trans* isomers. Treatment of that mixture with boron trifluoride–diethyl ether complex ($BF_3 \cdot OEt_2$) at –78°C in methylene chloride led to isomerization of **XIV** with formation of thermodynamically more stable N,O-acetal **XV**, which was a mixture of *cis* and *trans* isomers at a ratio of 8:1. The synthetic potential of acetal **XIV** was demonstrated by its reactions with various nucleophiles in the presence of Lewis acids. As a result, derivatives

Scheme 6.



of 6-substituted 4,5-dehydropipecolic acids **XVI** were mainly formed [22] (Scheme 7).

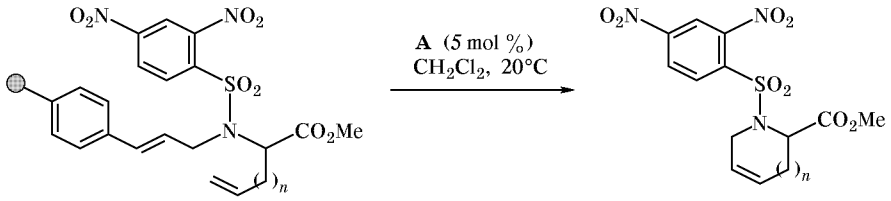
Scheme 7.



Nucleophile NuX	Nu	Ratio 1,2 : 1,4	Yield, %
$Me_3SiCH_2CH{=}CH_2$	$CH_2{=}CHCH_2$	75:25	79
$Bu_3SnCH_2CH{=}CH_2$	$CH_2{=}CHCH_2$	98:2	94
$Bu_3SnCH{=}C{=}CH_2$	$CH{\equiv}CCH_2$	100:0	75
$Me_3SiCH_2C(=CH_2)CH_2Cl$	$ClCH_2C(=CH_2)CH_2$	80:20	67
Et_3SiH	H	100:0	88

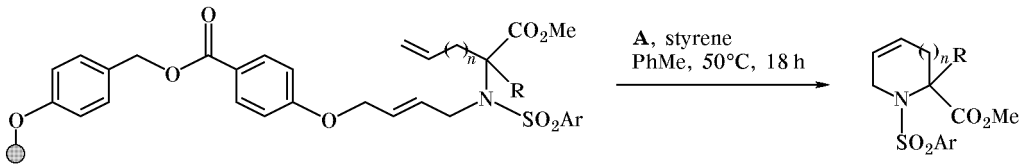
The viability of the Ru-catalyzed RCM metathesis as an efficient method for the preparation of dehydropipecolic (*n* = 1), azepine-2-carboxylic (*n* = 2), and azocine-2-carboxylic (*n* = 3) acid derivatives **XVIII**

Scheme 8.



XVIII

Scheme 9.



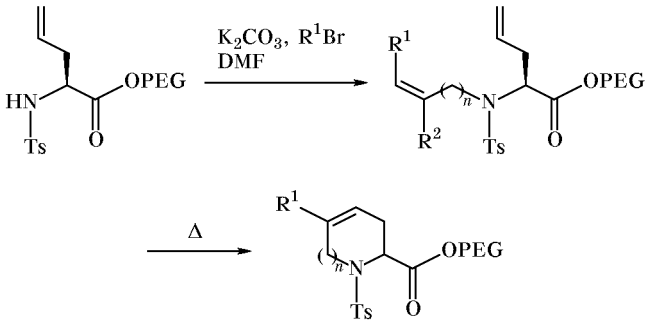
XIX **XX**

R = H, Me; Ar = *p*-$NO_2C_6H_4$; *n* = 1 (yield 80%), *n* = 2 (59%), *n* = 3 (12%).

was successfully demonstrated by Piscopio and co-workers [23] who applied a new solid-phase chemistry concept, cyclization–elimination (Scheme 8). Similar cyclizations were also effected by Veerman *et al.* [24] with immobilized homologous unsaturated amino acids **XIX**. As a result, the corresponding cyclic derivatives **XX** containing 6-, 7-, and 8-membered rings were obtained (Scheme 9); the latter were isolated in a low yield. A beneficial effect of addition of an equimolar amount of styrene was shown.

Varray *et al.* [25] recently reported on the synthesis of cyclic α-amino acid derivatives via RCM on a polyethylene glycol (PEG)-supported substrate. This method ensures efficient synthesis of optically active products **XXI** with various ring sizes. However, the procedure requires a relatively large amount of catalyst **A** (Scheme 10).

Scheme 10.



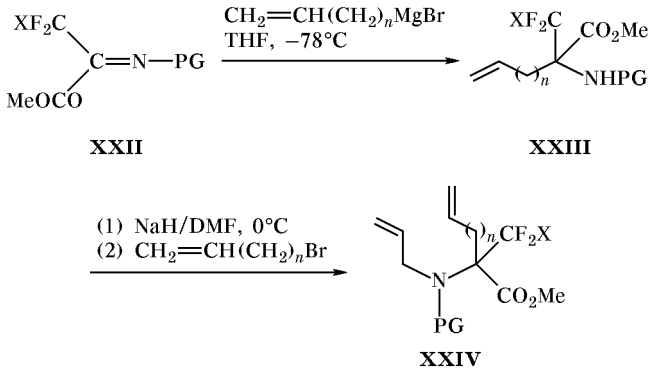
XXI

R^1	Catalyst, mol %	*n*	R^2	Yield, %
H	20	1	H	92
Ph	40	1	H	86
H	40	1	Me	95
H	40	2	H	90
H	40	3	H	82

2.2. Fluorinated Cyclic Amino Acids

Osipov and Dixneuf successfully applied the RCM methodology to the preparation of fluorinated amino acid derivatives. α-Amino acids **XXIV** having an XCF_2 group in the α-position and two alkene chains were synthesized via a two-step procedure, starting from electrophilic Schiff bases **XXII** with various protecting groups on the nitrogen atom (SO_2Ph, Boc, CBZ). Schiff bases **XXII** smoothly reacted with vinyl-, allyl-, and homoallylmagnesium bromides in THF to give amino acid derivatives **XXIII** in good yields. The latter were deprotonated

Scheme 11.

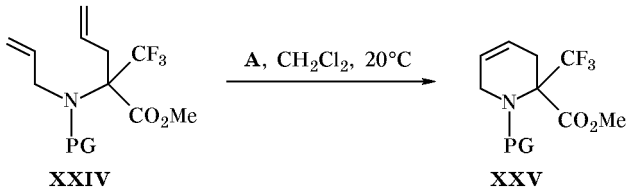


XXII **XXIII**

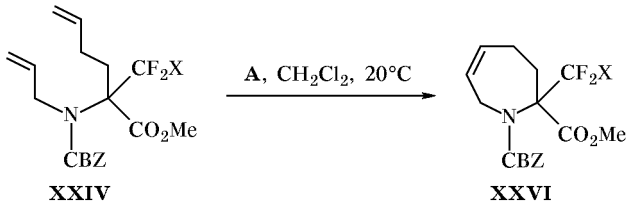
XXIV

with NaH, and the subsequent reaction with allyl or homoallyl bromide afforded 1,6-, 1,7-, and 1,8-heterodienes **XXIV** [26, 27] (Scheme 11). Intramolecular ring-closing metathesis of 1,7- and 1,8-heterodienes **XXIV** (*n* = 1, 2; *m* = 1, 2) occurred at room temperature in methylene chloride in the presence of 5 mol % of complex **A** to afford in high yields (>90%) derivatives of dehydropipecolic (**XXV**) and tetrahydroazepine-2-carboxylic acid (**XXVI**, **XXVII**) with an XF_2C group in the α-position [26, 27] (Scheme 12).

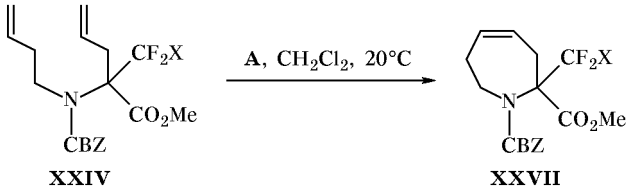
Scheme 12.



XXV, PG = SO_2Ph (93%), Boc (98%).



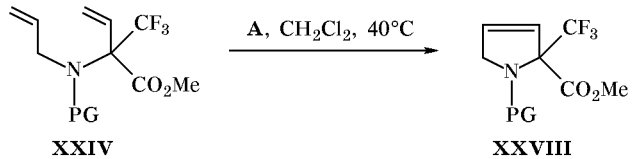
XXVI, X = F (95%), Cl (94%).



XXVII, X = F (96%), Cl (93%).

The position of double C=C bond in the seven-membered ring of **XXVI** and **XXVII** can be controlled by the length of the respective pendent chains in dienes **XXIV**. In contrast to the unsuccessful attempt by Grubbs to obtain proline derivatives (Scheme 2)

Scheme 13.

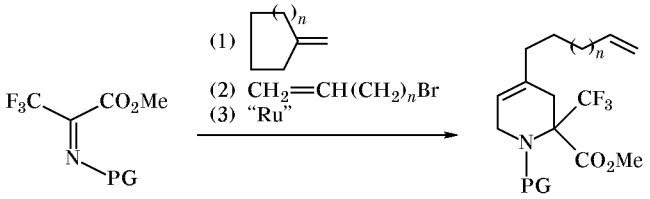


XXVIII, PG = SO_2Ph (45%), CBZ (50%).

[19], the absence of an acidic α-proton in vinylglycine structure **XXIV** (*n* = 0, *m* = 1) was crucial for the formation of the desired dehydroproline **XXVIII** (Scheme 13). Under standard RCM conditions (in the presence of 10 mol % of **A**), dienes **XXIV** underwent slow cyclization into proline derivatives **XXVIII** [26, 27] (Scheme 13).

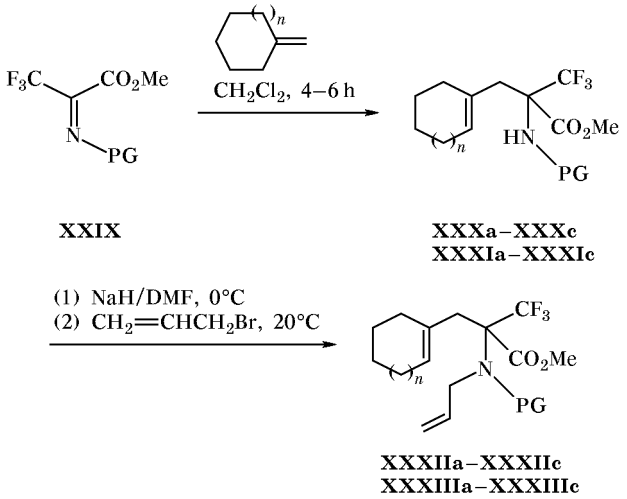
Cyclic α-amino esters with a pendent chain of various lengths but with a terminal double C=C bond were recently synthesized by two successive reactions: an ene reaction involving fluorine-containing Schiff base, followed by a ruthenium-catalyzed mixed ROM–RCM reaction [28] (Scheme 14).

Scheme 14.



Imines **XXIX** [29, 30] are highly electrophilic, and they readily react with methylenecyclopentane and methylenecyclohexane in the absence of Lewis acid as catalyst to give the expected ene reaction products **XXX** and **XXXI**. In order to perform RCM reaction, an allyl group was attached to the nitrogen atom, yielding dienes **XXXII** and **XXXIII** (Scheme 15).

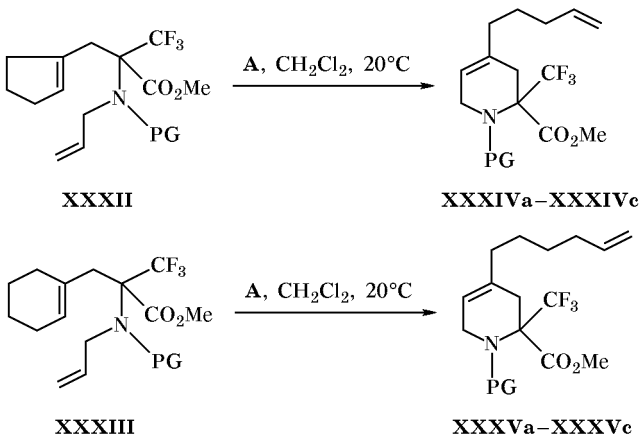
Scheme 15.



XXX, **XXXII**, *n* = 0; **XXXI**, **XXXIII**, *n* = 1; PG = SO_2Me (**a**), SO_2Ph (**b**), Boc (**c**); **XXXa** (yield 98%), **XXXb** (85%), **XXXc** (83%); **XXXIa** (68%), **XXXIb** (79%), **XXXIc** (71%); **XXXIIa**–**XXXIIc** (50–68%), **XXXIIIa**–**XXXIIIc** (52–66%).

Metathesis of alkenes **XXXII** and **XXXIII** in methylene chloride, promoted by the Grubbs catalyst (**A**, 10 mol %) led to products arising from tandem ring-opening and ring-closing metathesis reactions. In both cases, six-membered fluorinated amino esters **XXXIV** and **XXXV** were formed in 75 to 85% yield. The length of the pendent chain which is useful for further functionalization depended on the ring size of **XXXII** and **XXXIII** [28] (Scheme 16).

Scheme 16.



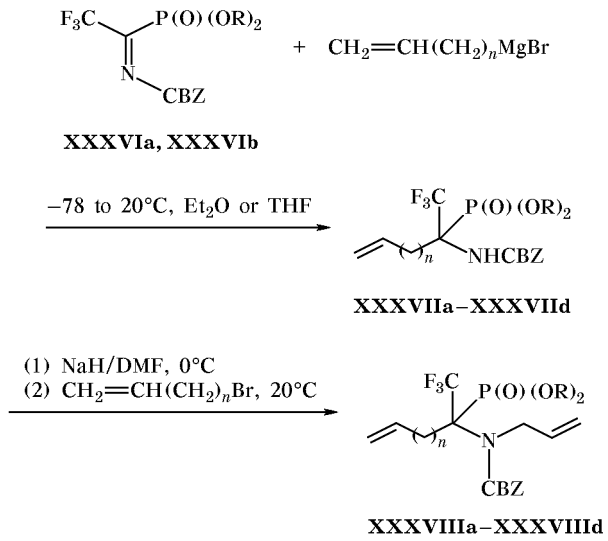
XXXII–**XXXV**, PG = SO_2Ph (**a**), SO_2Me (**b**), Boc (**c**); **XXXIV**, yield 77% (**a**), 85% (**b**), 79% (**c**); **XXXV**, yield 83% (**a**), 74% (**b**), 86% (**c**).

2.3. Cyclic α-Amino Phosphonates

α-Amino phosphonates are important analogs of α-amino acids, for they possess biological activity and thus attract interest from the viewpoint of medicinal chemistry [31]. Among these, (*R*)-phosphotyrosine, a natural product involved in two hypotensive tripeptides [32], unnatural α-amino phosphonates used as antibacterial compounds [32], and transition state analog inhibitors of proteolytic enzymes [33, 34]. In addition, cyclic α-amino phosphonates show potential to prevent rejection of transplanted tissues [35]. Their biological activities have stimulated search for cyclic α-amino phosphonates. Synthetic strategies adapted for cyclic α-amino acids can be directly transferred to cyclic α-amino phosphonates [27, 36].

Dienes **XXXVII** were prepared as potential substrates for cyclization to the key amino phosphonates via ring-closing alkene metathesis. As well as α-amino acid analogs, compounds **XXXVII** were synthesized by nucleophilic and then electrophilic addition to fluorinated Schiff bases $CBZN{=}C(CF_3)PO(OR)_2$ (**XXXVI**) [37–39] (Scheme 17). Dienes **XXXVII** were subjected to RCM in the presence of two catalyst precursors, $RuCl_2(=CHPh)(PCy_3)_2$ (**A**) and the ionic allenylidene complex $[RuCl(=C=C=CPh_2)(PCy_3)(p\text{-cymene})]OTf$ (**B**) [40, 41].

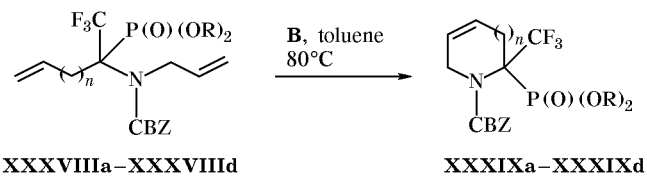
Scheme 17.



XXXVI, R = Me (**a**), Et (**b**); **XXXVIIa**–**XXXVIId**, R = Me, Et, *n* = 1, 2 (yield 66–74%); **XXXVIIIa**–**XXXVIIId**, R = Me, Et, *n* = 1, 2 (58–70%).

The reaction was carried out at 80°C in toluene. Under these conditions, complex **B** appeared to be more active than **A**. Actually, catalyst **B** was formed *in situ* by successive addition of PCy_3, AgOTf, and $HC{\equiv}CCPh_2OH$ to the ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ [25]. The diene conversion was complete within 6 h at 80°C, and a number of cyclic α-amino phosphonates were obtained: six-membered compounds **XXXIXa** and **XXXIXb** and seven-membered derivatives **XXXIXc** and **XXXIXd** (Scheme 18) [27, 36]. The success of this transformation also shows the tolerance of catalyst **B** toward a variety of functional groups. It should be emphasized that 6- and 7-membered cyclic phosphonates with the phosphorus atom included in the ring were prepared by RCM reaction with catalyst **A** and appropriate dienes [42].

Scheme 18.



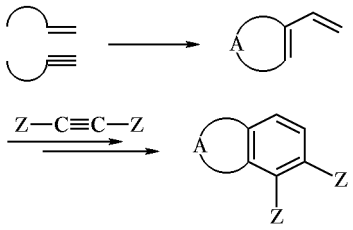
XXXIX, R = Me, *n* = 1 (**a**, yield 65%); R = Et, *n* = 1 (**b**, 69%); R = Me, *n* = 2 (**c**, 70%); R = Et, *n* = 2 (**d**, 61%).

3. SYNTHESIS OF α-AMINO ACID DERIVATIVES VIA RING-CLOSING METATHESIS OF ENYNES

3.1. Enyne Metathesis toward α-Amino Acids

Intramolecular metathesis of enynes corresponds to formation of a ring with an endocyclic double bond conjugated with exocyclic vinyl group, as shown in Scheme 19. It is called enyne metathesis since it is performed with alkene metathesis catalysts [43–45] but is also promoted by other catalysts such as platinum or palladium complexes for which another rearrangement mechanism is proposed [46–49]. Enyne metathesis products have a strong synthetic potential for further formation of polycyclic compounds via Diels–Alder reaction (Scheme 19).

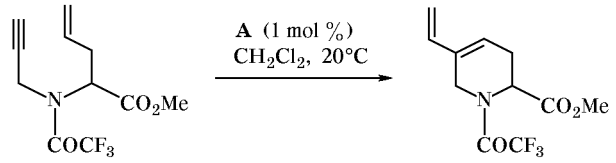
Scheme 19.



Both allyl- and 2-propynylglycine derivatives have been utilized for ring-closing enyne metathesis approaches toward cyclic α-amino acids. The first example reported by Mori *et al.* [50] was cyclization of α-allyl-*N*-(2-propynyl)glycine methyl ester promoted by catalyst **A** under ethylene atmosphere, which gave methyl 5-vinyl-4,5-dehydropipecolate in excellent yield (Scheme 20).

The same approach was later used for the preparation of dehydropipecolic acid derivatives having

Scheme 20.



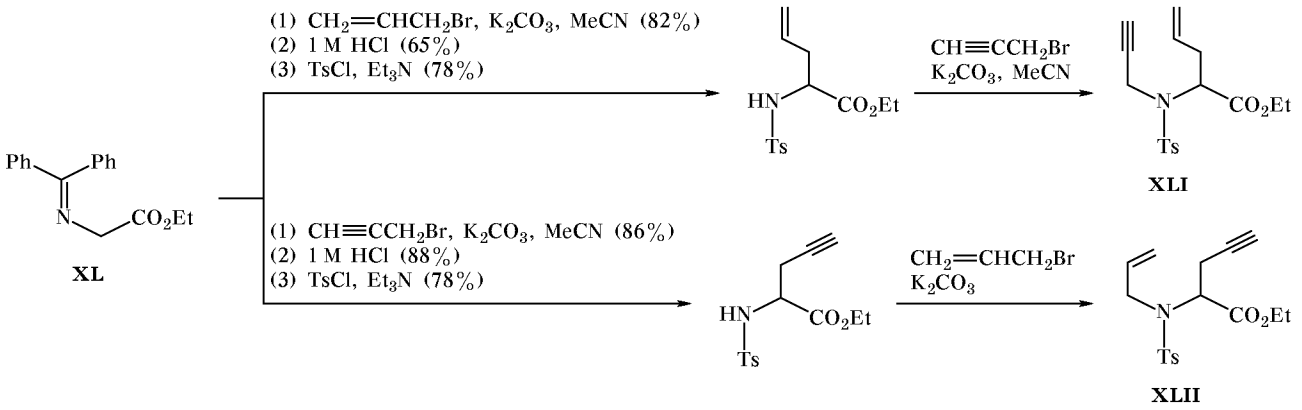
different protecting and functional groups. A variety of amino acid derivatives incorporating $N-C^{\alpha}$ bond into the linear arrangement of initial enyne have been synthesized via a four-step protocol starting from *N*-(diphenylmethylene)glycine ethyl ester (**XL**). The synthetic sequence includes C-allylation (or 2-propynylation) under basic conditions and reprotection of the amine function to give the corresponding tosyl derivatives, followed by N-alkylation with allyl or 2-propynyl bromide [51, 52]. Two types of enynes, **XLI** and **XLII** were thus obtained and brought into enyne metathesis with catalyst **A** (Scheme 21).

The transformation of **XLI** led to cyclic α-amino acids **XLIII** with a 1,3-diene structure [51, 52]. They reacted with diethyl acetylenedicarboxylate via Diels–Alder pattern, and (after aromatization by treatment with DDQ), bicyclic amino esters **XLIV** were obtained in good yields. Tricyclic derivatives **XLV** were synthesized with the use of 1,4-naphthoquinone as dienophile in the Diels–Alder reaction [51, 52] (Scheme 22).

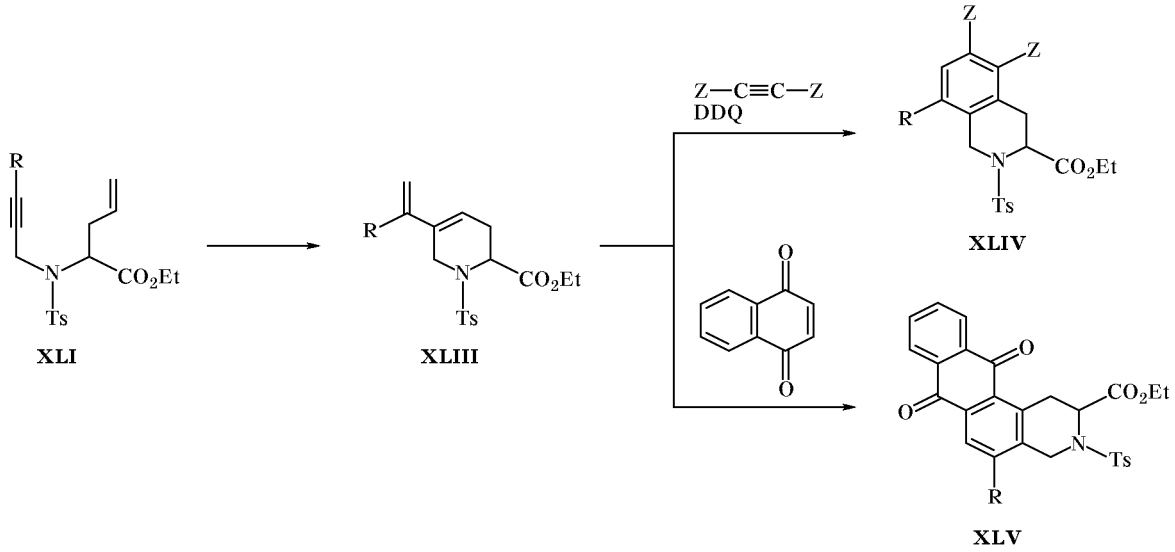
3.2. Synthesis of Fluorinated Amino Acids from Enynes

Enyne metathesis has recently been used for selective access to cyclic and bicyclic α-amino acid derivatives with a CF_3 or CF_2Cl group linked to the α-carbon atom. Such compounds were obtained in three steps starting from electrophilic fluorinated

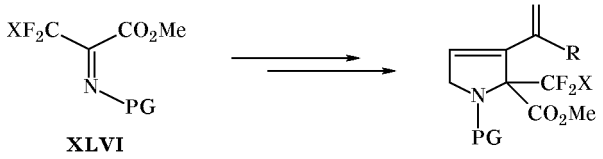
Scheme 21.



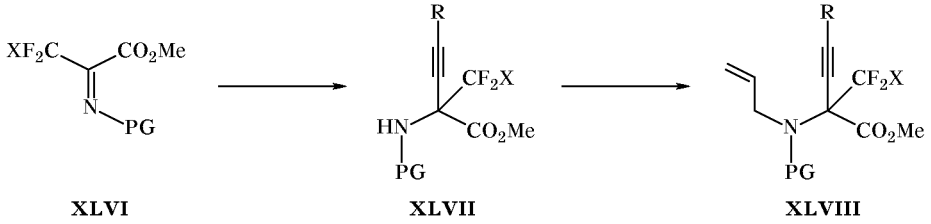
Scheme 22.



Scheme 23.

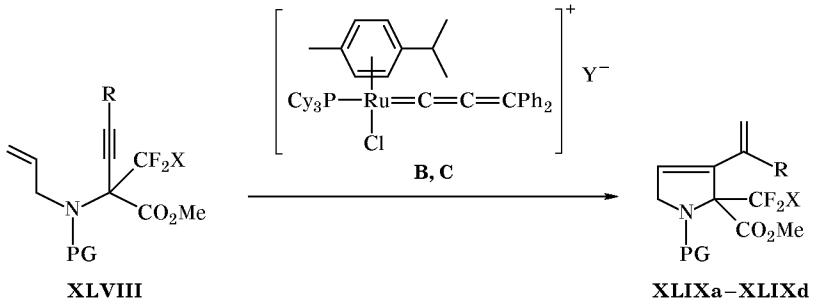


Scheme 24.



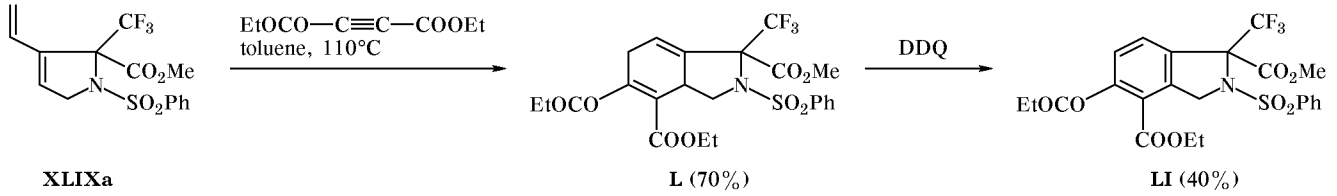
PG = Ts, SO_2Ph, CBZ; X = F, Cl.

Scheme 25.



XLIX, R = H, PG = SO_2Ph, X = F (**a**, yield 70%); R = *n*-Bu, PG = CBZ, X = F (**b**, 40%); R = CH_2OMe, PG = CBZ, X = F (**c**, 14%); R = H, PG = Boc, X = Cl (**d**, 56%).

Scheme 26.



XLIXa **L** (70%) **LI** (40%)

Schiff base (Scheme 23). Enynes **XLVIII** can be synthesized according to Scheme 24 by nucleophilic alkynylation of imines **XLVI** at the carbon atom and subsequent allylation of the nitrogen atom [53]. Metathesis of enynes **XLVIII** was effected with ionic allenylidene ruthenium catalyst **B** or **C** [12, 54], and fluorinated cyclic amino esters **XLIX** were obtained in good yields [53] (Scheme 25).

The Diels–Alder reaction of alkenyl-substituted cyclic α-amino ester **XLIXa** with diethyl acetylenedicarboxylate as dienophile afforded [4 + 2]-adduct **L**. The latter was dehydrated with DDQ to obtain bicyclic aromatic amino ester **LI** (Scheme 26).

4. CONCLUSION

Ring-closing alkene and enyne metathesis reactions catalyzed by alkylidene metal complexes have been used to obtain cyclic α-amino acid derivatives in which both amine and carboxylic acid (or carboxylate) functions are exocyclic [55]. These reactions are actually related to classical carbocyclizations via ring-closing metathesis of nonconjugated dienes and enynes, as long as both functions do not alter the catalyst activity. However, catalytic ring-closing reactions leading to cyclic amino acid derivatives with inclusion of the amino nitrogen atom inside the ring are usually more difficult to accomplish. Such reactions produce conformationally constrained cyclic amino acids which are more suitable for modification of peptide conformation than the previous ones [56, 57]. The present review summarizes the advances achieved in this direction with formation of a variety of 5-, 6-, 7-, and a few 8-membered amino acid derivatives, including the synthesis of cyclic α-amino esters containing a CF_3 or CF_2Cl at the α-carbon atom. The given data illustrate various general synthetic approaches useful for further developments.

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