# 1   Introduction

## 1.1   Literature Syntheses of *C*-Allylglycine Derivatives

### 1.1.1   General

α-Amino acids are enjoying an unprecedented renaissance in virtually all disciplines of biology, medicine, biochemistry and chemistry. Amino acids are finding increasing utility in the synthesis of pharmaceuticals, agricultural products, the food industry and material science. The recent revolution in molecular biology and protein engineering technologies has opened vast new vistas for the intelligently designed use and incorporation of amino acids in numerous proteinaceous and non–proteinaceous materials. Among the numerous natural and non-natural amino acids, optically active *C*-allylglycine derivatives serve as versatile building blocks in organic synthesis. On one hand, the amino acid has been introduced into an oligopeptide chain to allow further transformation with the electron rich double bond,[1] on the other hand, this non-natural amino acid is used as a chiral starting material to construct a range of more complicated amino acids and alkaloids.[2] Although commercially available (*C*-allylglycine derivatives), the high price prevents the use of the material in bulk quantities. Thus, a range of synthetic approaches have been developed to obtain optically active *C*-allylglycine derivatives.

The synthetic strategies can be subdivided into electrophilic amination of ester and amide enolates,[3] nucleophilic substitutions of α-halogen carboxylic acids by amine reagents,[4]

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[1] (a) Fukami, T; Yamakawa, T.; Niiyama, H.; Amano, Y.; Kanada, F.; Ozaki, S.; Fukuroda, T.; Thara, M.; Yano, M.; Ishikawa, K. *J. Med. Chem.* **1996**, *39*, 2313. (b) Kurokawa, N.; Ohfune, Y. *Tetrahedron* **1993**, *49*, 6195. (c) Broxterman, Q.B.; Kaptein, B.; Kamphuis, J.; Schoemaker, H.E. *J. Org. Chem.* **1992**, *57*, 6286. (d) Baldwin, J.E.; Norris, W.J.; Freeman, R.T.; Bradley, M.; Adlington, R.M.; Long-Fox, S.; Schofeld, C.J. *J. Chem. Soc., Chem. Commun.* **1988**, 1128.

[2] (a) Voigtmann, U.; Blechert, S. *Synthesis* **2000**, 893. (b) Grossmith, C.E.; Senia, F.; Wagner, J. *Synlett* **1999**, 1660. (c) Gao, Y.; Lane-Bell, P.; Vederas, J.C. *J. Org. Chem.* **1998**, *63*, 2133. (d) Rutjes, F.P.J.T.; Schoemaker, H.E. *Tetrahedron Lett.* **1997**, *38*, 677. (e) Bossler, H.G.; Seebach, D. *Helv. Chim. Acta.* **1994**, *77*, 1124. (f) Seebach, D.; Beck, A.K.; Bossle, H.G.; Gerber, C.; Ko, S.Y.; Mutiashaw, C.W.; Naef, R.; Shoda, S.; Thaler, A.; Krieger, M.; Wegner, R. *Helv. Chim. Acta.* **1993**, *76*, 1564. (g) Baldwin, J.E.; Adlington, R.M.; Flitsch, S.L.; Ting, H.-H.; Turner, N.J.; *J. Chem. Soc., Chem. Commun.* **1986**, 1305.

[3] (a) Depew, K.M.; Kamenecka, T.M.; Danishefsky, S.J.; *Tetrahedron Lett.* **2000**, *41*, 289. (b) Rutjes, F.P.J.T.; Veerman, J.J.N.; Meester, W.J.N.; Hiemstra, H.; Schoemaker, H.E.; *Eur. J. Org. Chem.* **1999**. 1127. (c) Ahn. K.H.; Kim, S.-K.; Ham, C. *Tetrahedron Lett.* **1998**, *39*, 6321. (d) Kamenecka, T.M.; Danishefsky, S.J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2995; *Angew. Chem.* **1998**, *110*, 3166. (e) Hale, K.J.; Cai, J.; Delisser, V.; Manaviazar, S.; Peak, S.A.; Bhatia, G.S.; Collins, T.C.; Jogiya, N. *Tetrahedron* **1996**, *52*, 1047. (f) Oppolzer, W.; Tamura, O.; Deerberg, J. *Helv. Chim. Acta.* **1992**, *75*, 1965. (g) Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, J.F. *Tetrahedron* **1988**, *44*, 5525.

allylation of glycine enolates with allyl halides,[5] allylation of iminium salts with allyl metal compounds,[6] and rearrangements[7] (Figure 1.1). Generally, the optical activity of the allylglycine has been introduced by means of a chiral auxiliary ($X_c$).[4-7]
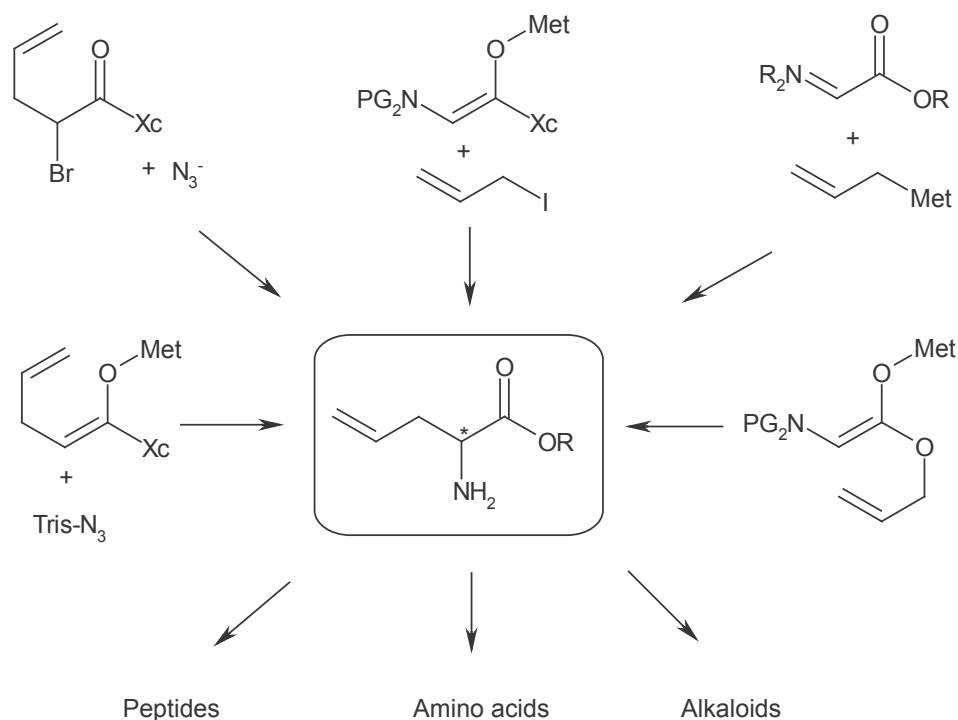


**Figure 1.1**: Literature syntheses of *C*-allylglycine derivatives

Some representative samples are shown as follows.

[4] (a) Kitagawa, O.; Hanano, T.; Kikuchi, T. *Tetrahedron Lett.* **1993**, *34*, 2165. (b) Evans, D.A.; Britton, T.C.; Ellman, J.A.; Dorow, R.L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

[5] (a) Meyers, A.G.; Schnider, P.; Kwon, S.; Kung, D.W. *J. Org. Chem.* **1999**, *64*, 3322. (b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (c) Juaristi, E.; Leon-Romo, J.L.; Ramirez-Quiros, Y. *J. Org. Chem.* **1999**, *64*, 2914. (d) Guillena, G.; Najera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3935. (e) Bull. S.D.; Davies, S.G.; Epstein, S.W.; Leech, M.A.; Ouzman, J.V.A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321. (f) Porzi, G.; Sandri, S.; Verrocchio, P. *Tetrahedron: Asymmetry* **1998**, *9*, 119. (g) Oppolzer, W.; Bienayme, H.; Genevois-Borella, A. *J. Am. Chem. Soc.* **1991**, *113*, 9660.

[6] (a) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R.G.; Joergensen, K.A. *J. Org. Chem.* **1999**, *64*, 4844. (b) Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *Heterocycles* **1998**, *47*, 765. (c) Kardassis, G.; Brungs, P.; Steckhan, E. *Tetrahedron* **1998**, *54*, 3471. (d) Loh, T.-P.; Ho, D.S.-C.; Xu, K.-C.;Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865. (e) Hanessian, S.; Yang, R.-Y *Tetrahedron Lett.* **1996**, *37*, 8997. (g) Kuraokawa, N.; Ohfune, Y. *Tetrahedron* **1988**, *44*, 5415.

[7] (a) Kazmaier, U.; Maier, S. *J. Org. Chem.* **1999**, *64*, 4574. (b) Kazmaier, U.; Krebs, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2012; *Angew. Chem.* **1995**, *107*, 2213.

### 1.1.2 Electrophilic Amination of Enolates

Evans and co-workers have devised a versatile and useful method to prepare a large variety of α-amino acids by highly diastereoselective azidations, this is shown in chapter 1.1.3 (page 5).

Oppolzer and co-workers[8] reported on a new sultam auxiliary, which was developed by Ahn's group[3(c)] to synthesize the optically active *C*-allylglycine derivative **1** (Scheme 1).
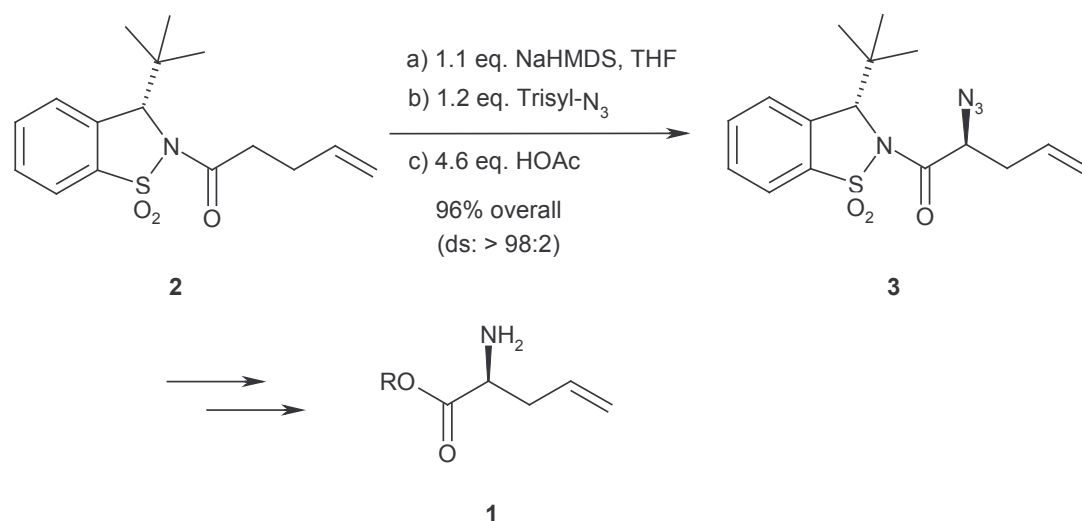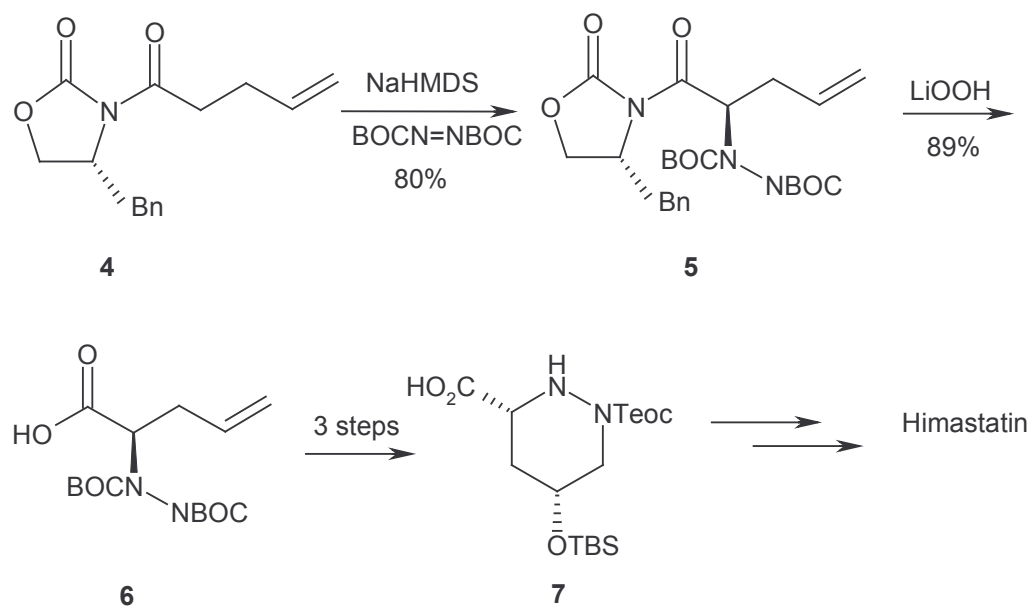


**Scheme 1**: Synthesis of a (*S*)- *C*-allylglycine derivative **1** by Oppolzer and Ahn

The *N*-acyl sultam **2** was deprotonated by treatment with NaHMDS at −78°C for 30 minutes, the azidation was carried out by using 2,4,6-triisopropylbenzenesulfonyl azide (trisyl-$N_3$), followed by treatment with HOAc to afford α-azido *N*-acyl sultam **3** in 96% yield with an excellent diastereoselectivity (>98:2). The optically active *C*-allylglycine derivative **1** was obtained after removal of the auxiliary and reduction of the azide.

In 1998 Danishefsky and his co-workers[3(a),(d),(g)] had completed the total synthesis of Himastatin.[9] The piperazine acid fragment **7** was generated from pentenoic acid derivative **4** via a (*R*)-*C*-allylglycine derivative **6** (Scheme 2). A sodium-enolate, achieved from compound **4** upon treatment with NaHMDS, stereoselectively reacted with di-*t*-butyl azodicarboxylate to give compound **5**. After removal of the auxiliary with LiOOH, the optically active (*R*)-*C*-allylglycine derivative **6** was furnished.

[8] Oppolzer, W.; Rodrinreguez, I.; Starkemann, C.; Walter, E.  *Tetrahedron Lett*. **1990**, *31*, 5019.

[9] (a) Lam, K.S.; Hesler, G.A.; Mattel, J.M.; Mamber, S.W.; Forenza, S.  *J. Antibiot*. **1990**, *43*, 956; (b) Leet, J.E.; Schroeder, D.R.; Krishnan, B.S.; Matson, J.A.  *J. Antibiot*. **1990**, *43*, 961; (c) Leet, J.E.; Schroeder, D.R.; Golik, J.; Matson, J.A.; Doyle, T.W.; Lam, K.S.; Hill, S.E.; Lee, M.S.; Whitney, J.L.; Krishnan, B.S.  *J. Antibiot*. **1996**, *49*, 299.

**Scheme 2**: Synthesis of the (*R*)-*C*-allylglycine derivative **6** by Danishefsky

The piperazine acid **7** was produced via 3 steps from the intermediate **6** and finally, Himastatin was synthesized.

### 1.1.3 Nucleophilic Amination of α-Substituted Acids

Evans and associates[4(b),10] have devised an elegant and practical route to α-amino acids by carrying out highly diastereoselective azidations and halogenations. In the azidation sequence, compound **8** was treated with KHMDS to give the illustrated potassium enolate **9**. After treatment with 2,4,6-triisopropylbenzenesulfonyl azide, the intermediate sulfonyl triazene **10** was decomposed by means of acetic acid quench to give the α-azido carboximide **11** in 78% yield. The diastereoselectivity of the reaction was 97:3 (Scheme 3).
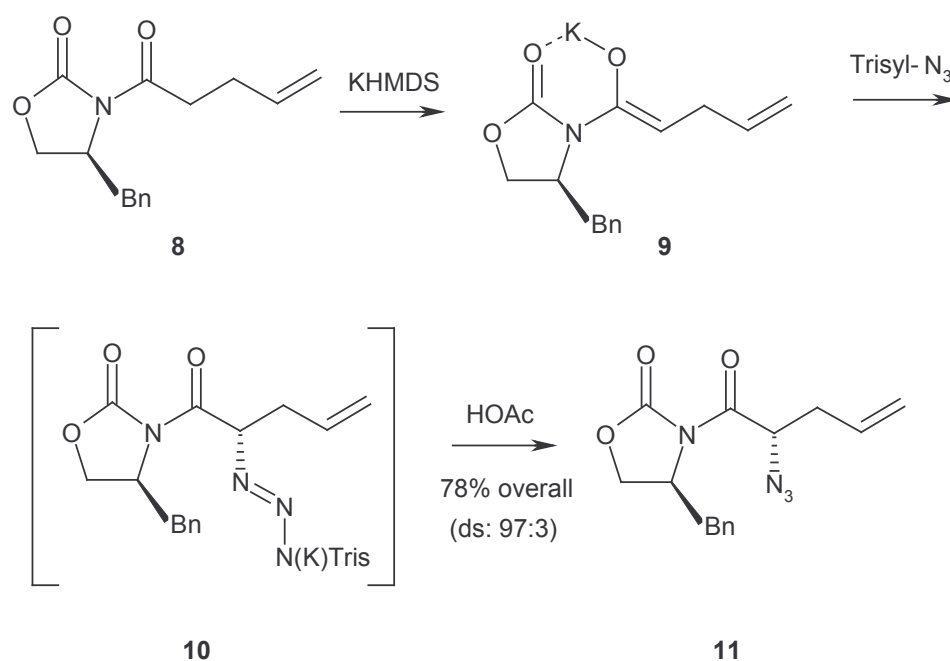


**Scheme 3**: Diastereoselective azidation by Evans

Analyzing the halogenation sequence, the diastereoselective bromination of the boron enolate **12** with *N*-bromosuccinimide was followed by stereospecific S$_N$2 azide substitution using tetramethyl-guanidinium azide. The resulting α-azido carboximide **14** could have been readily purified to high diastereomeric purity by chromatography on silicagel (Scheme 4). The overall yield via two steps was 83%, and the diastereoselectivity of the bromination was 94:6, that of the azide displacement was > 99:1.

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[10] (a) Evans, D.A.; Ellmann, J.A.; Dorow, R.L. *Tetrahedron Lett*. **1987**, *28*, 1123. (b) Evans, D.A.; Weber, A.E. *J. Am. Chem. Soc*. **1987**, *109*, 7151.
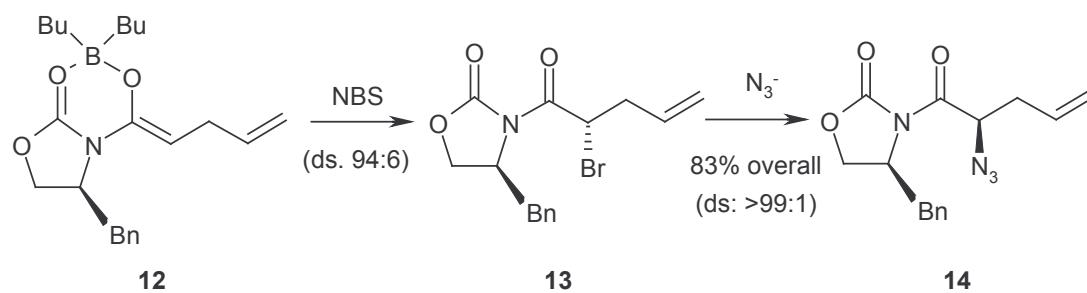
**Scheme 4**: Diastereoselective bromination and azide displacement by Evans

The α-azido carboximide products **11** and **14** have been shown to serve as versatile α-amino acid synthons that might be readily converted into α-amino acids as well as into *N*-protected α-amino acid derivatives. The racemization-free removal of the chiral auxiliary was achieved with high yield likewise by saponification and transesterification. The reduction and acylation of the azide functionality could be run before and after the auxiliary removal, respectively (Scheme 5).
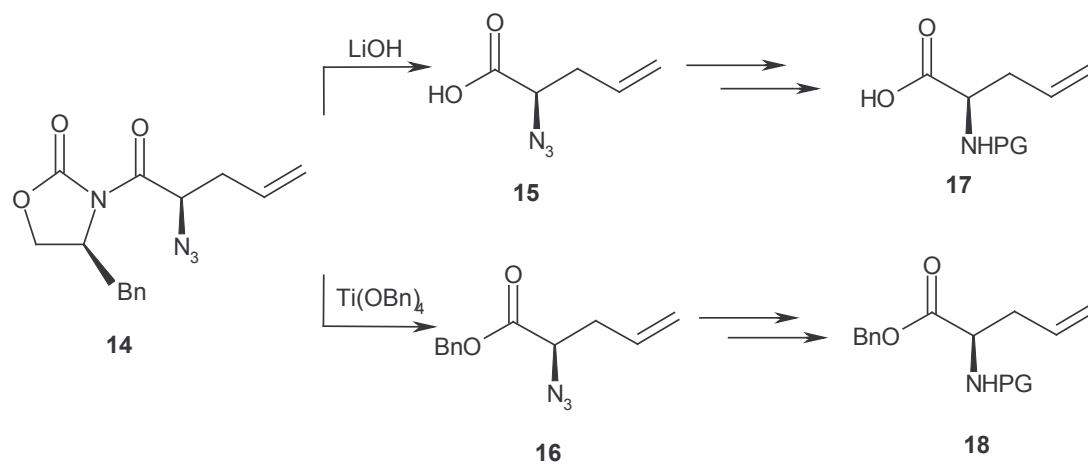


**Scheme 5**: Removal of the auxiliary and conversion into α-amino acid derivatives

### 1.1.4  Allylation of Glycine Enolate with Allyl Halides

In 1989, Najera and co-worker[5(d)] reported on the stereoselective allylation of glycine enolate under PTC (Phase Transfer Catalysis) conditions in the presence of DBU.
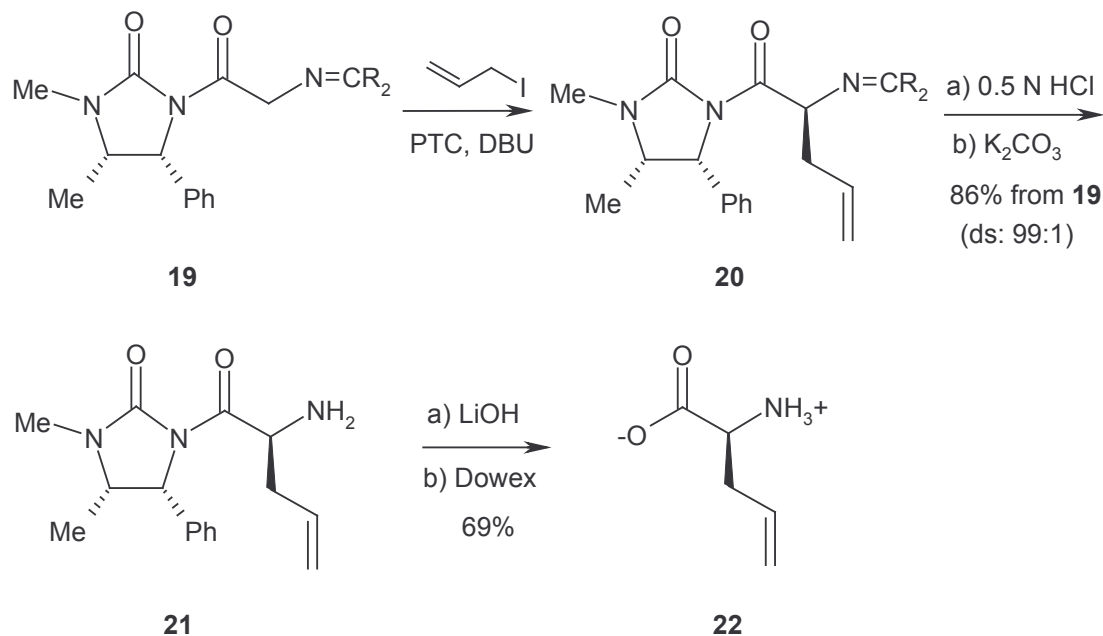
**Scheme 6**:  Synthesis of a (*S*)-allylglycine by Najera

As shown in Scheme 6, the glycine enolate, which was generated by treatment of compound **19** with DBU, attacked allyl iodide under PTC conditions to furnish the intermediate **20**. After hydrolysis of **20** with HCl and $K_2CO_3$, the allylglycine derivative **21** was provided in 86% yield with 99:1 diastereoselectivity. The corresponding (*S*)-allylglycine was obtained after removal of the auxiliary with LiOH followed by ion exchange chromatography (Dowex) with 69% yield.

Similar synthetic route was reported by Oppolzer and co-workers.[11] Instead of compound **19**, *N*-acylbornane-10,2-sultam was used as starting material (Figure 1.2).
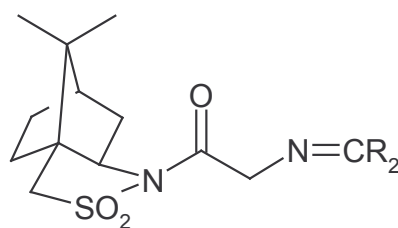
**Figure 1.2**: *N*-acylbornane-10,2-sultam

[11] (a) Oppolzer, W.; Morreti, R.; Thomi, S.  *Tetrahedron Lett*. **1989**, *29*, 6009. (b) Oppolzer, W.; Morreti, R.; Zhon, C.  *Helv. Chim. Acta* **1994**, *77*, 2363.

### 1.1.5 Allylation of Iminium Salts with Allyl Metal Compounds

Hanessian and co-workers[6(e)] used a chiral allyl metal reagent to achieve *C*-allylglycine derivative **25**. The general reaction for the enantioselective allylation of the α-ketoester oximes **23** is shown in Scheme 7.
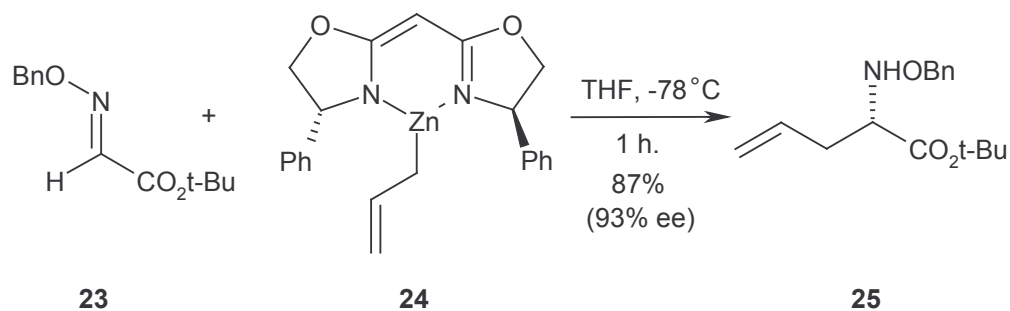


**Scheme 7**: Synthesis of a (*S*)-allylglycine derivative **25** by Hanessian

The phenyl substituted bis(oxazoline) allylzinc reagent **24**, prepared by Nakamura's method,[12] was reacted with oxime **23** in THF at -78 °C, and the corresponding *N*-benzyloxy allylglycine derivative **25** was obtained with 87% yield and 93% ee.

Kardassis and co-workers[6(c)] have generated a cyclic dipeptide **26** from *L*-proline and glycine after electrochemical oxidation. Catalysed by TiCl$_4$, the methoxy group of **26** could be exchanged with allyl trimethylsilane to afford **27** with 90% yield and 99% de. (Scheme 8). After hydrolysis with 6 N HCl, the (*R*)-allylglycine **28** was furnished with 62% yield.
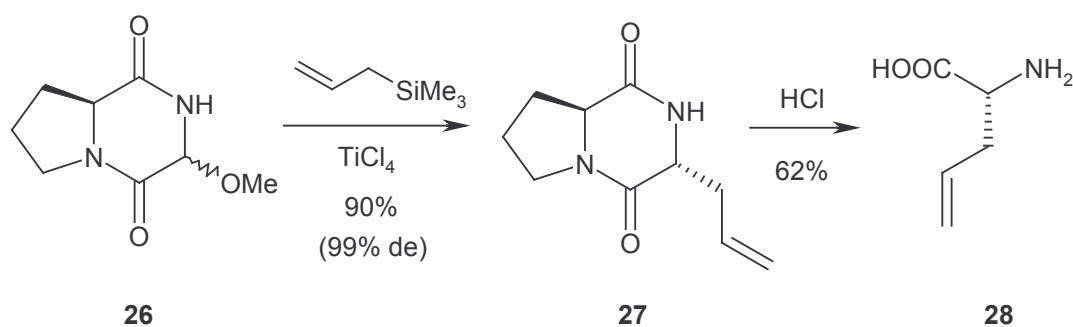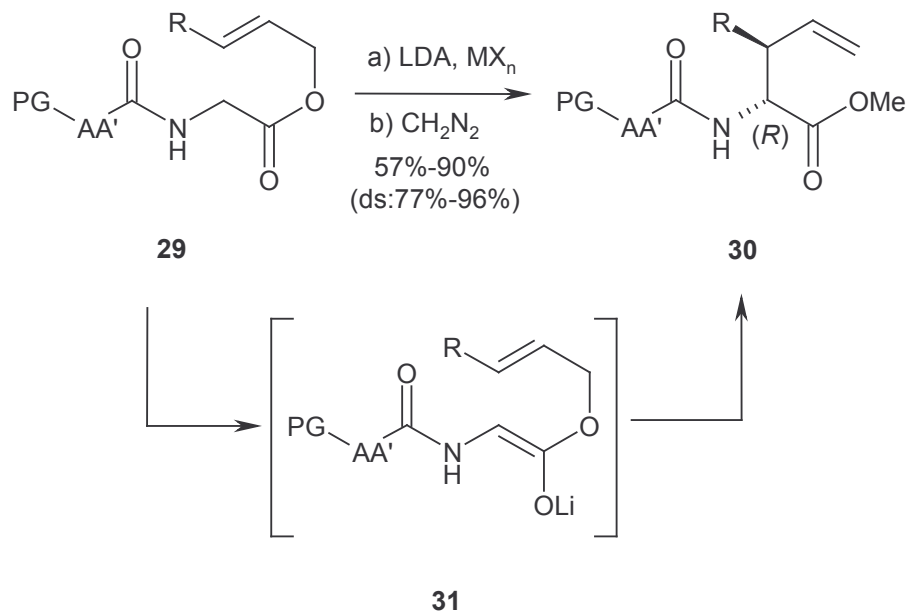


**Scheme 8**: Synthesis of a (*R*)-allylglycine **28** by Kardassis

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[12] Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179.

### 1.1.6 Synthesis of *C*-Allylglycine Derivatives via Claisen Rearrangement

Kazmaier and co-workers[7] have developed a chelate Claisen rearrangement to generate a dipeptide allylic esters (Scheme 9).



AA' = dipeptide,  M = metal, Al, Sn, Ti, Cu, Ni.

X = ligand,  R = Me, Ph

**Scheme 9**: Synthesis of dipeptide $\gamma,\delta$-unsaturated esters **30** by Kazmaier

Deprotonation of dipeptide crotyl esters **29** with LDA delivered the intermediate **31**, the Claisen rearrangement proceeded in the presence of a metal compound. The dipeptide $\gamma,\delta$-unsaturated ester **30** was obtained after esterification with diazomethane. The yields varied between 57% to 90%, and diastereoslectivities between 77% to 96%.

## 1.2    Zwitterionic Aza-Claisen Rearrangement

Focusing on the construction of optically active α-amino acids, a [3,3]-sigmatropic rearrangement should serve as a reliable reaction to generate such stereogenic center with high enantioselectivity. The Claisen rearrangement, including a variety of variants, is particularly valuable in organic synthesis as a method for the stereocontrolled construction of *trans* di- and tri- substituted carbon-carbon double bonds. [13] Because it requires high temperature (150-200°C), a significant number of thermolabile substances are excluded. Numerous new variants have been developed to overcome the disadvantage, among them, the variants of Eschenmoser,[14] Johnson[15] and Ireland[16] are very famous.

Because of the fact, that charge-acceleration enables a severe reduction of the reaction temperature, zwitterionic rearrangements occurred as the most promising protocol. The ketene-Claisen rearrangement, firstly reported by Bellus and Malherbe, [17] described the development of a zwitterionic thia-Claisen rearrangement. Mariano and co-workers firstly reported on zwitterionic aza-Claisen rearrangement.[18] As shown in Scheme 10, the tertiary allylamine **32** and propiolic ester combined to form the hypothetically zwitterionic intermediate **33**, which underwent rearrangement to furnish the product **34**. Two shortages had to be pointed out: the product is unstable and some stereochemical information is lost.
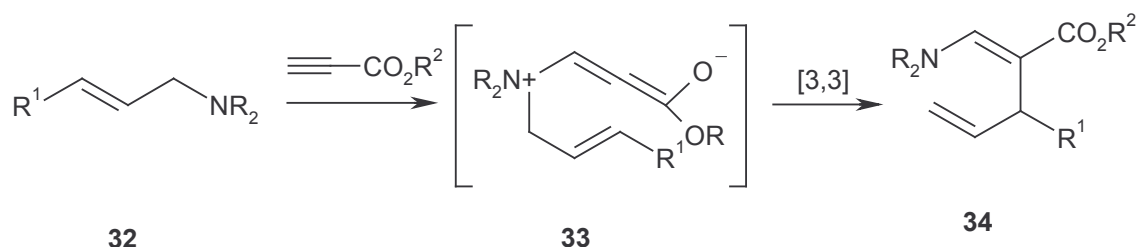


**Scheme 10**:  First zwitterionic aza-Claisen rearrangement by Mariano

[13] For some excellent reviews of the Claisen rearrangement, see: (a) Rhoads, S.J.; Raulins, N.R.  *Org. React.* (*N.Y.*) **1975**, *22*, 1. (b) Ziegler, F.A.; *Acc. Chem. Res*. **1977**, *10*, 227. (c) Bennett, G.B.; *Synthesis* **1977**, 589. (d) Hill, R.K. In *Asymmetric Synthesis*; Morrison, J.D., Ed., *Vol. 3*, Academic Press: New York, **1984**, p. 503. (e) Ziegler, F.A.  *Chem. Rev*. **1988**, *88*, 1423. (f) Kallmerten, J.; Wittman, M.D.  *Stud. Nat. Prod. Chem.* **1989**, *3*, 233. (g) Wipf, P.  In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I. Eds., Pergamon Press: New York, **1991**, *Vol. 5*, p. 827. (h) Frauenrath, H. *In Houben Weyl: Stereoselective Synthesis*, Vol. E21d; Helmchen, G.; Hoffmann, R.W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, **1995**, 3301-3756.
[14] (a) Wick, A.E.; Felix, D.; Stehen, K.; Eschenmoser, A.  *Helv. Chim. Acta.* **1964**, *47*, 2425. (b) Stehen, K.; Wick, A.E.; Eschenmoser, A.  *Helv*. Chim. *Acta*. **1969**, *52*, 1030.
[15] Johnson, W.S.; Wertheman, L.; Bartlett, W.R.; Brocksom, T.J.; Li, T.; Faulkner, D.J.; Petersen, M.R.  *J. Am. Chem. Soc*. **1970**, *92*, 741.
[16] Ireland, R.E.; Mueller, R.H.; Willard, A.K.  *J. Am. Chem. Soc*. **1976**, *98*, 2868.
[17] Malherbe, R.; Bellus, D.  *Helv. Chim. Acta*. **1978**, *61*, 3096.
[18] Chao, S.; Kung, F.-A.; Gu, J.-M.; Ammon, H.L.; Mariano, P.S.  *J. Org. Chem*. **1984**, *49*, 2708.

Since then, many examples of zwitterionic aza-Claisen rearrangements were reported by Kato,[19] Roberts,[20] Edstrom[21] and Pombo-Villar.[22]

All of them used a ketene and a tertiary allylamine, the rearrangement proceeded at 0°C to 25°C. Despite of the mild reaction conditions several side reactions, e.g. [2+2]-cycloadditions, decreased the yield of the rearrangement products.

Recently, the use of chiral auxiliaries to control the stereoselectivity of the zwitterionic aza-Claisen rearrangement[23] was intensively investigated, especially by Nubbemeyer and co-workers.[24] The zwitterionic aza-Claisen rearrangement of various *N*-allylamines with carboxylic acid fluorides[25] had been developed as a mild and efficient method to form γ,δ-unsaturated lactams or amides. Upon treatment of *N*-allylamines with carboxylic acid fluorides in the presence of solid $Na_2CO_3$ and $Me_3Al$ at –20°C to 20°C in $CH_2Cl_2$ or $CHCl_3$, the reaction took place smoothly to afford lactams or amides in good yield with high diastereoselectivity and enantioselectivity (Scheme 11).

[19] Ishida, M.; Muramaru, H.; Kato, S. *Synthesis* **1989**, 562.

[20] Roberts, S.M.; Smith, C.; Thomas, R.J. *J. Chem. Soc., Perkin Trans 1*. **1990**, *112*, 1493.

[21] (a) Edstrom, E.D. *J. Am. Chem. Soc*. **1991**, *113*, 6690. (b) Edstrom, E.D. *Tetrahedron Lett*. **1991**, *32*, 7233.

[22] (a) Cid, M.M.; Eggenauer, U.; Weber, H.P.; Pombo-Villar, E. *Tetrahedron Lett*. **1991**, *32*, 7233. (b) Cid, M.M.; Pombo-Villar, E. *Helv. Chim. Acta*. **1993**, *76*, 1591.

[23] (a) Vedejs, E.; Gingras, M. *J. Am. Chem. Soc*. **1994**, *116*, 579. (b) Baily, P.D.; Harrison, M.J. *Tetrahedron Lett*. **1989**, *30*, 5341. (c) Kurth, M.J.; Brown, E.G. *Synthesis* **1988**, 362. (d) Kurth, M.J.; Sorares, C.J. *Tetrahedron Lett*. **1987**, *28*, 1031. (e) Tsunoda, T.; Nishii, T.; Yoshizuka, M.; Yamasaki, C.; Suzuki, T.; Ito, S. *Tetrahedron Lett*. **2000**, *41*, 7667.

[24] (a) Nubbemeyer, U. *J. Org. Chem*. **1995**, *60*, 3773. (b) Nubbemeyer, U. *J. Org. Chem*. **1996**, *61*, 3677. (c) Diederich, M.; Nubbemeyer, U. *Angew. Chem.; Int. Ed. Engl*. **1995**, *34*, 1026; *Angew. Chem*. **1995**, *107*, 1095. (d) Laabs, S.; Scherrmann, A.; Sudau, A.; Diederich, M.; Kierig, C.; Nubbemeyer, U. *Synlett* **1999**, 25. (e) Sudau, A.; Münch, W.; Nubbemeyer, U.; Bats, J. *J. Org. Chem*. **2000**, *65*, 1710. (f) Sudau, A.; Münch, W.; Bats, J.; Nubbemeyer, U. *Chem. Eur. J*. **2001**, *7*, 611. (g) Laabs, S.; Münch, W.; Bats, J.; Nubbemeyer. U. *Tetrahedron* **2002**, *58*, 1317.

[25] Groß, S.; Laabs, S.; Scherrmann, A.; Sudau, A.; Zhang, N.; Nubbemeyer, U. *J. Prak. Chem*. **2000**, *342*, 1711.
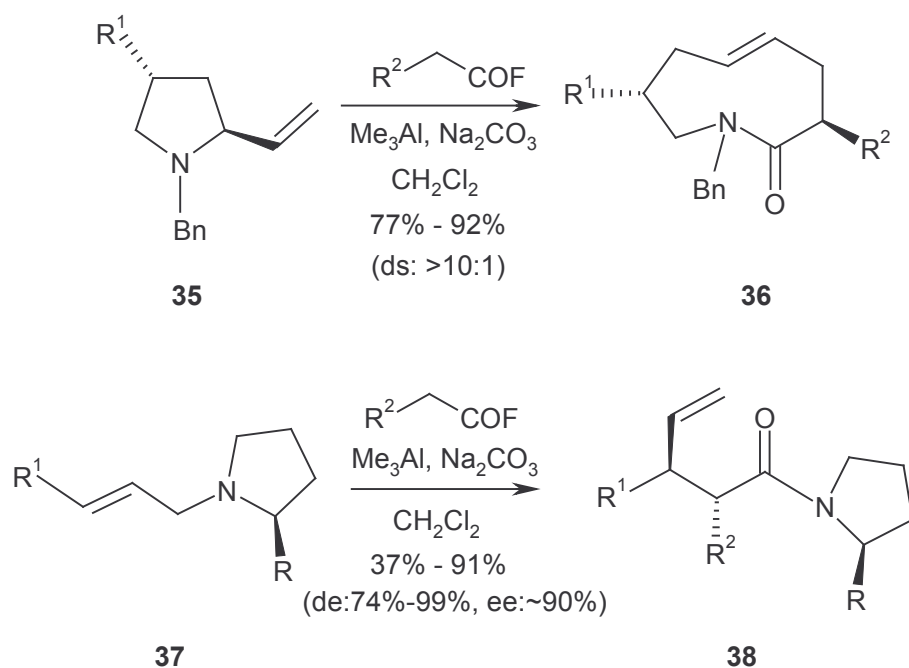
**Scheme 11**: Zwitterionic aza-Claisen rearrangement according Nubbemeyer's protocol

The *N*-allylamines, derived from *L*-proline, allowed to control the diastereoslectivity of the zwitterionic aza-Claisen rearrangement, the mechanism will be discussed in chapter 2. The *L*-proline derivative auxiliary could be easily removed without racemization of the new stereogenic centers. The lactams and amides, prepared via the zwitterionic aza-Claisen rearrangement, served as key intermediates in natural products synthesis[26] and in optically active non-natural α-amino acids syntheses.[24(g)] Furthermore, the absolute configuration of the α-position could be inversed from *R*- to *S*-configuration with high stereocontrol. (see chapter 2).

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[26] (a) Sudau, A.; Münch, W.; Bats, J.; Nubbemeyer, U. *Eur. J. Org. Chem*. **2002**, *19*, 3304. (b) Sudau, A.; Münch, W.; Bats, J.; Nubbemeyer, U. *Eur. J. Org. Chem*. **2002**, *19*, 3315.

## 1.3 Ring-Closing Olefin Metathesis

The highly efficient generation of optically pure *C*-allylglycines enables to use this amino acid in further syntheses. Especially the olefin moiety occurred as a versatile anchor for further C-C coupling reactions.

The development of well-defined catalysts for olefin metathesis[27] combining high activity, durability and excellent tolerance towards polar functional groups has revolutionized the field. The past decade has been characterized by a embrace of these reagents as tools for advanced organic and polymer chemistry and success of this development is witnessed by a plethora of elegant applications to the synthesis of natural and non-natural products.

Karl Ziegler discovered the catalysts,[28] in situ formed from certain transition metal salts and main group alkylating agents, to promote the polymerization of olefins under mild conditions. Since then, the research on mechanism of the olefin metathesis and the development of a new generation of catalysts or catalyst precursors were triggered. The mechanism of the ring-closing metathesis (RCM) was suggested by Chauvin[29] (Scheme 12). The most popular and versatile catalysts were tungsten and molybdenum alkylidene complexes **39**[30] developed by Schrock and co-workers as well as ruthenium carbene complexes **40**[31] (Figure 1.3) introduced by Grubbs and co-workers. Today, both reagents are commercially available. Their air sensitivity initiated the development of numerous more stable and more active catalysts.

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[27] For reviews of the olefin metathesis, see: (a) Fürstner, A. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3012. *Angew. Chem.* **2000**, *112*, 3140. (b) Ivin, K.J.; Mol, J.C. *Olefin* Metathesis *and Metathesis polymerisation*, Academic Press, San Diego, **1997**. (c) Dörwald, F.Z. Metal *Carbenes in Organic Synthesis*, Wiley-VCH, Weinheim, **1999**. (d) Fürstner, A. *Alkenes Metathesis in Organic Synthesis*, Springer, Berlin, **1998**. (e) Grubbs, R.H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (f) Schuster, B.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036. *Angew. Chem.* **1997**, *109*, 2124. (g) Fürstner, A. *Top. Catal.* **1997**, *4*, 285. (h) Amstrong, S.K. *J. Chem. Soc. Perkin Trans. 1* **1998**, 371. (i) Pariya, C; Jayaprakash, K.N.; Sarkar, A. *Coord. Chem. Rev.* **1998**, *168*. 1. (j) Grubbs, R.H.; Miller, S.J.; Fu, G.C. *Acc. Chem. Res.* **1995**, *28*, 446. (k) Schmlz, H.-G. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1833. *Angew. Chem.* **1995**, *107*, 1981. (l) Ivin, K.J. *J. Mol. Caalt. A.* **1998**, *133*, 1. (m) Randall, M.L.; Snapper, M.L. *J. Mol. Catal. A.* **1998**, *133*, 29. (n) Hashmi, A.S.K. *J. Prakt. Chem.* **1997**. *339*, 195. (o) Phillips, A.J.; Abell, A.D. *Aldrichimica Acta* **1999**, *32*, 75.

[28] Recent comprehensive treatise: Fink, G.; Mülhaupt, R.; Brintzinger, H.H. *Ziegler Catalysts*, Springer, Berlin, **1995**.

[29] Herisson, J.-L; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161.

[30] (a) Schrock, R.R.; Murdzek, J.S.; Bazan, G.C.; Robins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Oskam, J.H.; Fox, H.H.; Yap, K.B.; McCoville, D.H.; O'Dell, R.; Lichtenstei, B.J.; Schrock, R.R. *J. Orgnomet. Chem.* **1993**, *459*, 185. (c) Feldman, J.; Murdzek, J.S.; Davis, W.M.; Schrock, R.R. *Organometallics*, **1989**, *8*, 2260.

[31] (a) Nguyen, S.T.; Johnson, L.K.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (b) Nguyen, S.T.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1993**, *113*, 9858. (c) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R.H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039. *Angew. Chem.* **1995**, *107*, 2179. (d) Wu, Z.; Nguyen, S.T.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1995**, *117*, 5503. (e) Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
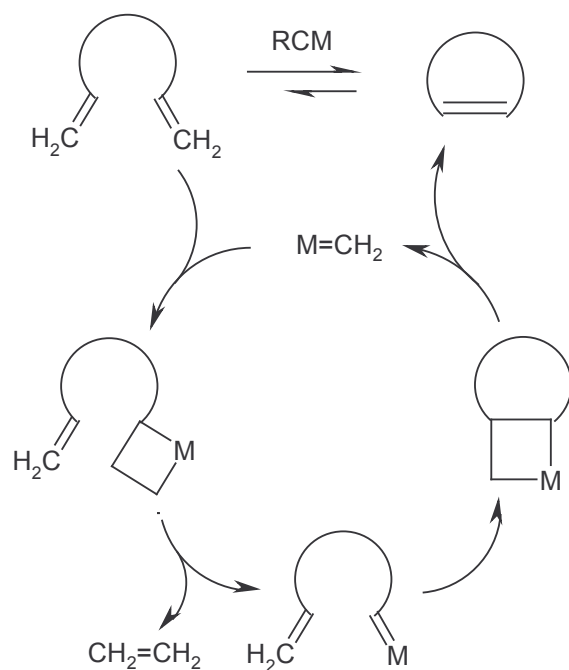
**Scheme 12**: Mechanism of RCM suggested by Chauvin



M = W, Mo                    R = Ph, CH$_2$Ph

**39**                            **40**
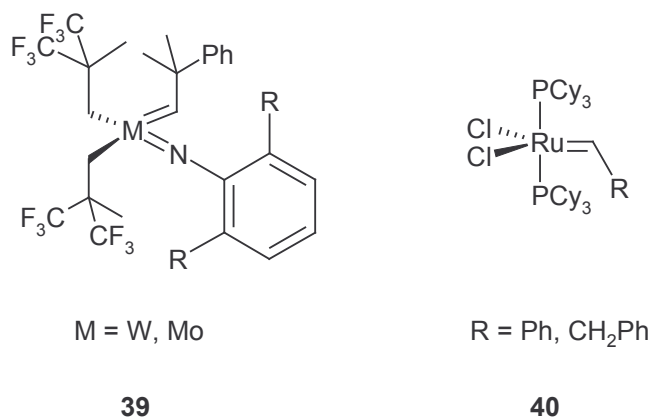
**Figure 1.3**:  Catalysts by Schrock and Grubbs

Because of its efficiency, high yielding and clean transformation character, the metathesis is gradually becoming one of the most important synthetic methods in organic synthesis.

The combination of zwitterionic aza-Claisen rearrangement and consecutive olefin metathesis occurred as a promising sequence to generate defined substituted and configured key compounds for natural product synthesis.

## 1.4 Amaryllidaceae-Alkaloids

Polycyclic alkaloids represent challenging targets to test the usability of Claisen rearrangement-ring closing metathesis sequences as key steps in total synthesis. Numerous alkaloids have been isolated from plants of the amaryllidaceae, especially from various Narcissus, Crinum, Haemanthus, Galanthus, Lycoris and Nerine species. Most of them were characterized by structurally related framework. At present, six groups of species had been distinguished as exemplified by the following:[32] Lycorine type, Ambelline type (from Amaryllis-, Ammocharis-, Brunsvigia- and Buphane-species), Hippeastrine type (from Amaryllis-, Brunsvigia-, Clivia- and Crinum-species), Tazettine type, Galanthamine type (from Amaryllis-, Cooperanthes- and Crinum-species) and Montanine type (from Haemanthus species).



(-)-Lycorine

(+)-Ambelline

(+)-Hippeastrine

(+)-Tazettine

(-)-Galanthamine

(-)-Montanine
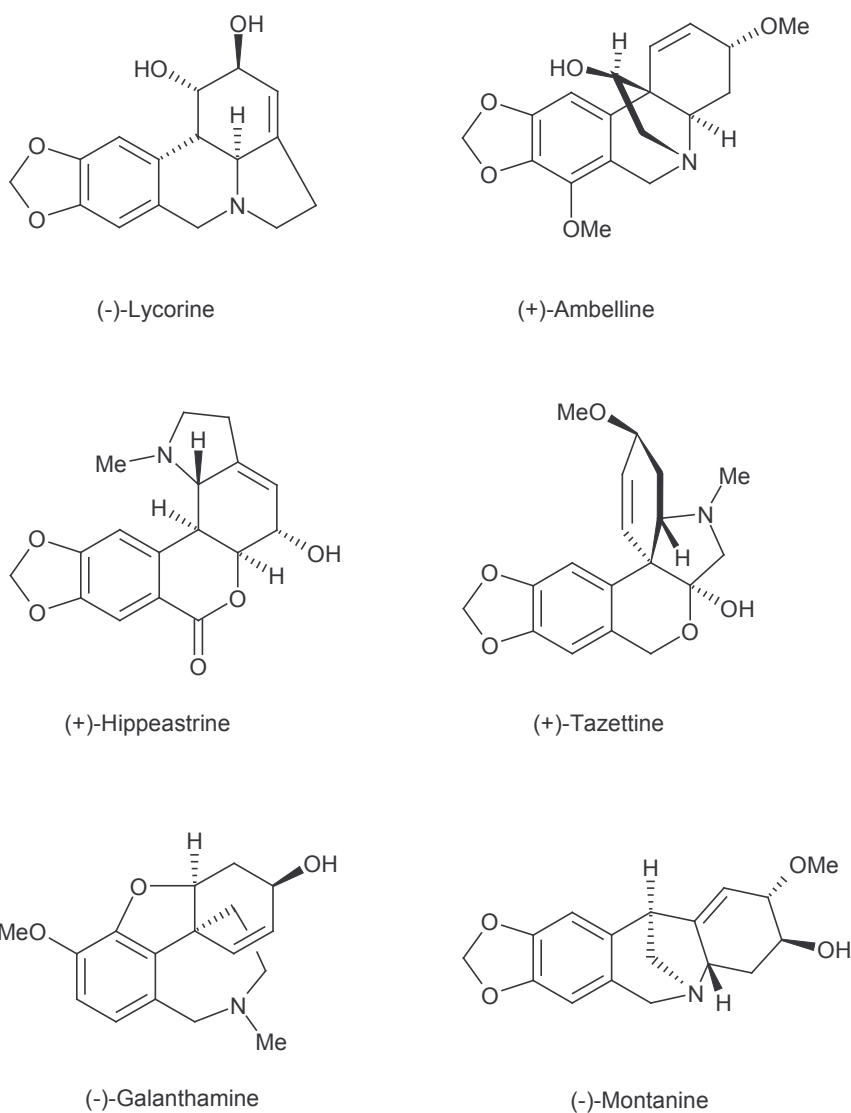
**Figure 1.4**: Six groups of the Amaryllidaceae alkaloids

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[32] Hesse, M. *Alkaloide, Fluch oder Segen der Nature?* Wiley-VCH, **2000**, p. 52-54.

Figure 1.4 shows the six representatives of the amaryllidaceae alkaloids, all of them contain piperonyl or 4-methoxyphenyl groups. Three of them (Lycorine, Ambelline and Montanine) display an isoquinoline structure.

The test of the biological and pharmacological efficacy of the amaryllidaceae alkaloids proved that they had cytotoxic and antibacterial efficacy,[33] and the efficacy depended strongly on their substitution patterns and configurations.

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[33] (a) Lewis, J.R. *Nat. Prod. Rep.* **1997**, *14*, 303. (b) Weniger, B. *Planta Med.* **1995**, *61*, 77.

## 1.5    Objectives

Optically active *C*-allylglycine derivatives are useful for the synthesis of alkaloids and peptides. Although a range of synthetic approaches have been developed to obtain optically active *C*-allylglycine derivatives, a mild and efficient zwitterionic aza-Claisen rearrangement had been developed by Nubbemeyer and co-workers promising a potential, much more flexible conversion upon building-up such α-amino acid derivatives.[24-26]

The first aim of this work is to synthesize optically active *C*-allylglycine derivatives using chiral auxiliary controlled stereoselective aza-Claisen rearrangement. The rearrangement is carried out with glycinyl fluoride derivatives and tertiary *N*-allylamine obtained from proline derivatives (Sheme 13). Always, the diastereoselectivity of each conversion has to be confirmed by means of different reagents.
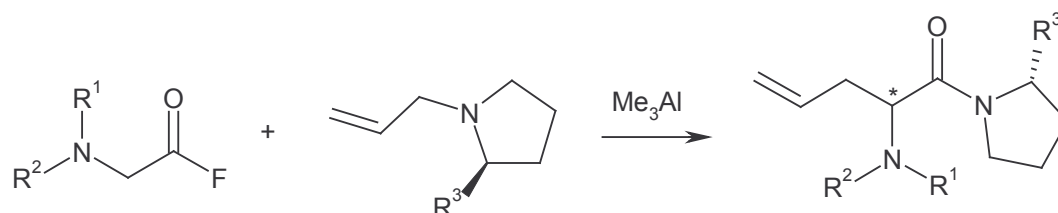


**Scheme 13**:    Zwitterionic aza-Claisen rearrangement with glycinyl fluoride derivatives and tertiary *N*-allylamine from proline derivatives

The second aim is to achieve smooth cleavage the auxiliary to obtain optically active isoquinolone derivatives and piperonyl containing acyclic ketone, as well as allylglycines displaying various *N*-substitution patterns.

The third aim is to introduce functional groups on above obtained isoquinolone and acyclic ketone to synthesize useful precursors for amaryllidaceae-alkaloid total syntheses (Scheme 14).
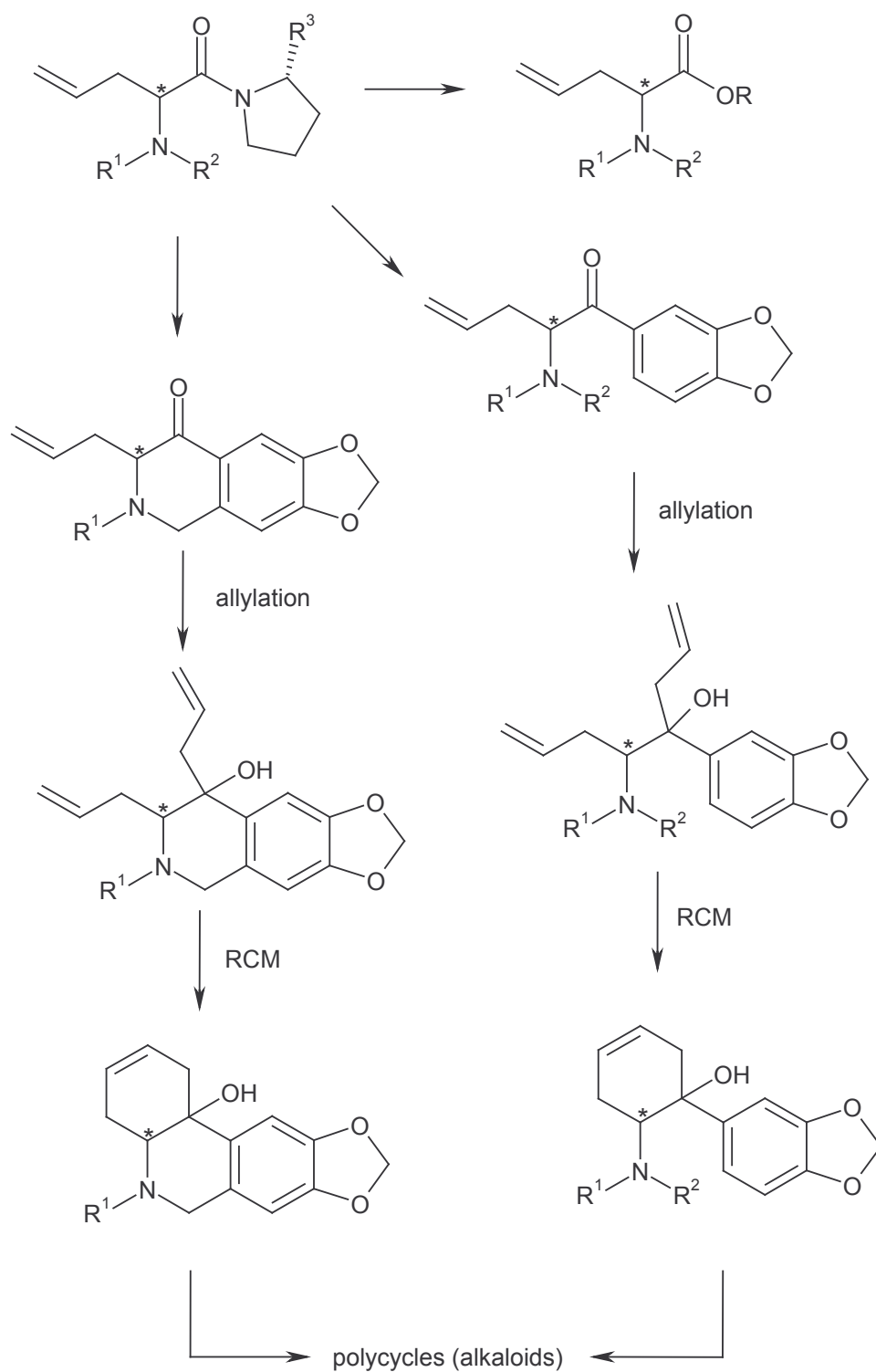
**Scheme 14**: Synthesis of the useful precursors for amaryllidaceae-alkaloid total syntheses