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Recent Advances in Charge-Accelerated Aza-Claisen Rearrangements

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Abstract Aza-Claisen rearrangements (3-aza-Cope rearrangements) have gained an increasing interest in synthetic organic chemistry. Originally, the exceptionally high reaction temperatures of this hetero variant of the well-known 3,3-sigmatropic reaction limited their applicability to selected molecules. Since about 1970, charge acceleration enabled a significant reduction of the reaction temperature to be achieved, and cation- and anion-promoted rearrangements found their way into the syntheses of more complex molecules. The first total syntheses of natural products were reported. The development of zwitterionic aza-Claisen rearrangements allowed the reactions to be run at room temperature or below, and the charge neutralization served as the highly efficient driving force. After overcoming several teething troubles, the method was established as a reliable conversion displaying various stereochemical advantages. The first successful total syntheses of natural products incorporating the aza-Claisen rearrangement as a key step emphasized the synthetic potential. To date the aza-Claisen rearrangements are far from being exhausted. Still, an enantioselectively catalyzed variant has to be developed. This review summarizes one decade of investigation efforts in this area.

Keywords Aza-Claisen rearrangement · 3-Aza-Cope rearrangement · Chirality transfer · Asymmetric induction · Charge acceleration

Abbreviations

Acc	Acceptor
BINOL	Binaphthol
BOX	Bis(oxazolinyl)
Cy	Cyclohexyl
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAD	Dimethyl acetylene dicarboxylate
LiHMDS	Lithium hexamethyldisilazide
MCPBA	3-Chloroperbenzoic acid
MPA	Mycophenolic acid
PG	Protecting group
Pht	Phthaloyl
PMB	4-Methoxybenzyl
Proton sponge	1,8-Bis-(dimethylamino) naphthalene
TBS	TBDMS, *tert*-butyldimethylsilyl
TFA	Trifluoroacetic acid
TOSMIC	*p*-Toluenesulfonylmethyl isocyanide

1 Introduction

3,3-Sigmatropic rearrangements are defined as uncatalyzed processes to migrate a sigma bond of two connected allyl systems from position 1 to position 3. That means both allyl systems suffer from an allyl inversion. Though described for the first time in 1940, the Cope rearrangement can be considered as the basic type of such a process, since C–C bonds only are reorganized during the course of the reaction [1]. More than two decades earlier, in 1912, L. Claisen first described the rearrangement of aromatic allyl vinyl ethers to generate *o*-allyl phenols [2]. This so-called Claisen rearrangement is characterized by the replacement of the C3 carbon of the rearrangement system against a heteroatom X. The basic Claisen rearrangement bears X=O; consequently, such a process can be termed as a 3-oxa Cope rearrangement. Analyzing the literature, rearrangement systems displaying other heteroatoms X in position 3 can be found as hetero Claisen and 3-hetero Cope rearrangements. Focussing on systems with X=N, names such as aza- and amino-Claisen as well as 3-aza-Cope rearrangement occur in the literature. Furthermore, the term aza/amino Claisen rearrangement is widely used for nitrogen introduction processes rearranging 1-aza-3-oxy-Cope systems (imidates) to generate carbamates. Finally, the Fischer indole synthesis represents a special type of aza-Claisen rearrangement incorporating two N atoms in the 3 and 4 positions of the rearrangement system.

Intending to set a firm basis concerning the notion of the sigmatropic rearrangements, the following review will use the term Claisen rearrangement

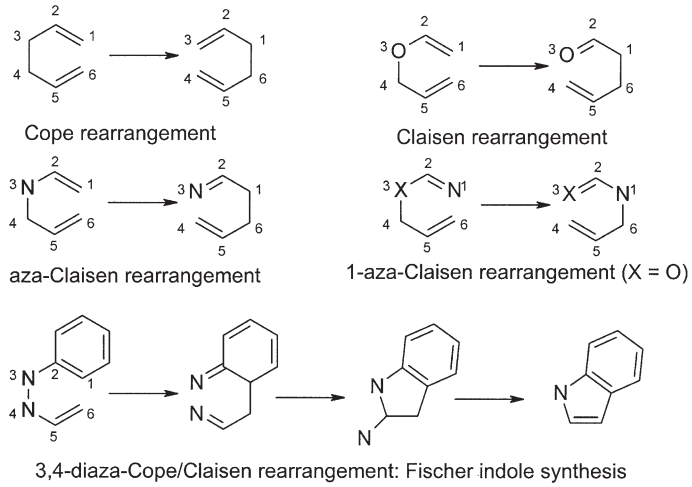


Fig. 1 Nomenclature of aza-Claisen rearrangements

for 3,3-sigmatropic core systems incorporating a heteroatom X in position 3, i.e., an aza-Claisen-type rearrangement is characterized by X=nitrogen (Fig. 1).

For a long period, aza-Claisen rearrangements were regarded as a sophisticated variant of the widely used oxygen analog. Because of the much more drastic reaction conditions, few applications have been published. Most investigation had been restricted to fundamental research on aza-Claisen rearrangements. About 25 years ago, the perception tended to change, because the nitrogen atom in the central position of the sigmatropic core systems was discerned as an ideal anchor for catalysts such as protons, Lewis acids, and for chiral auxiliaries in enantioselective rearrangements. Charge acceleration allowed a significant reduction of the reaction temperature, recommending the process now as a suitable key step in complex molecule syntheses. Finally, the development of very mild zwitterionic variants enabled the aza-Claisen rearrangement to be classified as a powerful method in synthetic organic chemistry. This review reports on recent advances in aza-Claisen rearrangements [3].

2 Aliphatic Simple Aza-Claisen Rearrangements

In analogy to the oxygen analogs, the simple aliphatic aza-Claisen rearrangements represent the basis of such reactions. Generally, the replacement of the oxygen offers two advantages. The vinyl double bond of the sigmatropic framework can be built up with a high *E* selectivity, since a bulky C1 substituent and the chain-branched nitrogen will adopt a maximal distance around the enamine moiety. Furthermore, only two valences of the nitrogen are occupied by allyl and vinyl substituents of the rearrangement system; the third one

potentially can bear an optically active subunit intending to run the rearrangement under the influence of an external chirality-inducing side chain (auxiliary control).

The major problem of the aza-Claisen rearrangement is the extremely high temperature, excluding the presence of a variety of functional groups, upon running the reaction. Uncatalyzed simple allyl vinyl amines undergo the 3,3-sigmatropic conversion at about 250 °C, while the somewhat more activated aromatic analogs require 200–210 °C [4]. Hence, charge acceleration was found to be a promising tool to achieve a significant decrease of the reaction temperature. Only 80–120 °C was required upon running the sigmatropic rearrangement in the presence of a proton and a Lewis acid. Alternatively, a comparable temperature-decreasing effect was observed after conversion of the central nitrogen into a peralkylated ammonium salt.

Intending to use the aliphatic simple aza-Claisen rearrangement to generate new C–C bonds, several prerequisites had to be considered. The first problem to be solved was the smooth and selective generation of the allyl vinyl amine backbone. The second challenge was the 3,3-sigmatropic reaction: the rearrangement should pass a single, highly ordered transition state to give rise to diastereoselective formation of the product. Since both reactant and product might suffer from imine–enamine equilibration, some difficulties concerning the unique sense of the rearrangement and the stable configuration of a stereogenic α center (with respect to the new imine) have to be taken into account.

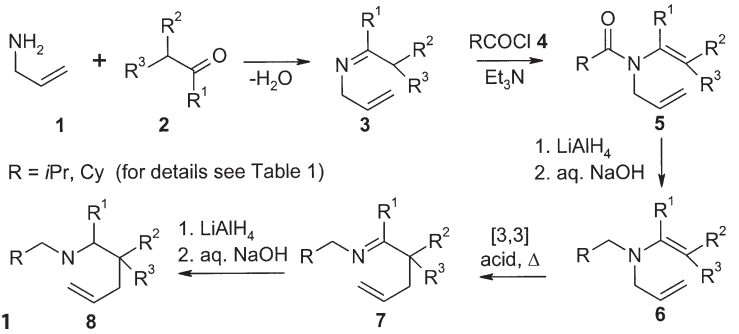
A set of systematic investigations has been published by Stille et al. [5]. Starting from allylamine **1**, an optimized three-step sequence of initial imine **3** formation with aldehyde **2**, *N*-acylation to **5** using acid chloride **4**, and subsequent $LiAlH_4$ reduction delivered the desired rearrangement systems **6** in 60–96% yield overall. Even though the enamide **5** formation was found to be unselective with respect to the vinyl double bond, the enamine **6** was isolated with substantially higher *E* selectivity pointing out some epimerization during the course of the reduction. The aza-Claisen rearrangement proceeded upon heating the enamines **6** to >100 °C (dioxane, toluene) in the presence of 0.3 to 0.8 eq. of HCl. Always, the intermediately formed imines **7** were reduced by means of $LiAlH_4$ to give the corresponding amines **8** as stable products. The success of the rearrangement strongly depended on the substitution pattern of the aldehyde **2** involved: branched starting material **6** (R^2, $R^3 \neq H$) underwent a smooth conversion to give the new amines **8**. In contrast, nonbranched derivatives (R^2 or R^3=H, small rings) suffered from competing reactions such as oligomerization and reductive amination [5a]. The replacement of the originally used HCl by different Lewis acids led to an extension of the original limitations. In the presence of one equivalent of Me_3Al a series of *N*-allyl enamines could be rearranged with high yield (Table 1, entries 1–6; Scheme 1) [5b].

The rearrangement of unsymmetrical allylamines **9** was investigated to exclude any competing 1,3-rearrangement during the course of the reaction. Allyl vinyl amines **10** were generated via condensation starting from allylamine **9** and isobutyraldehyde **2**. The substrates **10** were subjected to the acid-accel-

Table 1 [5]

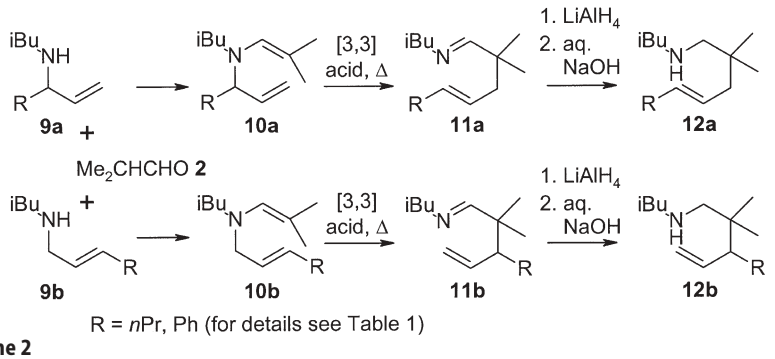
Entry	Educt	R/R′	R^1	R^2	R^3	Acid/yield (%)/dr			Ref.
1	**6**	*i*Pr/H	H	Me	Me	HCl/81	$TiCl_4$/71	Me_3Al/95	a,b
2	**6**	*i*Pr/H	H	Et	H	HCl/0	$TiCl_4$/0	Me_3Al/84	a,b
3	**6**[b]	*i*Pr/H	H	Ph	Me	HCl/77	$TiCl_4$/88	Me_3Al/92	a,b
4	**6**	*i*Pr/H	$(CH_2)_4$		H	HCl/99	$TiCl_4$/92	Me_3Al/96	a,b
5	**6**	*i*Pr/H	$(CH_2)_3$		H	HCl/10	$TiCl_4$/3	Me_3Al/83	a,b
6	**6**	Cy/H	H	Me	Me	HCl/85	$TiCl_4$/73	Me_3Al/99	b
7	**10a**	*n*Pr/H	H	Me	Me	HCl/69	$TiCl_4$/79	Me_3Al/80	c
8	**10a**	Ph/H	H	Me	Me	HCl/81	$TiCl_4$/80	–	c
9	**10b**	*n*Pr/H	H	Me	Me	HCl/76	$TiCl_4$/78	Me_3Al/87	c
10	**10b**	*n*Pr/H	H	Me	Me	–	–	Me_3Al/56	c
11[a]	**10c**	*n*Bu/H	$(CH_2)_4$		H	HCl/69 54:46	$TiCl_4$/72 55:45	Me_3Al/94 67:33	c,d
12	**10c**	*n*Bu/H	H	Et	H	–	–	Me_3Al/88 62:38	d
13	**10c**[b]	*n*Bu/H	H	Ph	Me	HCl/54 95:5	$TiCl_4$/48 80:20	Me_3Al/86 68:32	d
14[a]	**10c**	Me/Me	$(CH_2)_4$		H	HCl/98 [89:3]:8	$TiCl_4$/84 [65:11]:24	Me_3Al/98 [73:7]:20	d
15	**10c**	Me/Me	H	Et	H	–	–	Me_3Al/78 >98:2	d
16	**10c**[b]	Me/Me	H	Ph	Me	–	–	Me_3Al/95 >95:5	d

[a] Diastereoselective final DIBALH reduction.
[b] *E*:*Z*=86:14–90:10.



Scheme 1

erated rearrangement conditions. Smooth conversions led to the intermediates **11**, which were finally reduced with $LiAlH_4$ to give the stable amines **12.** Careful analyses (GC, ^1H NMR) of the products **12** indicated that all rearrangements proceeded stereospecifically (**a**→**a**, **b**→**b**). No crossover products originating from competing 1,3-sigmatropic and stepwise reactions could be detected (**a**→**b**, **b**→**a**) (Table 1, entries 7–10). The rearrangement of **10a** gave **11a** with exclusive *E* double bond geometry (Scheme 2) [5c].

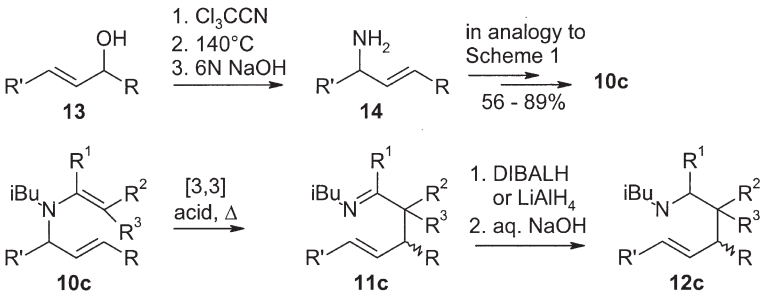


Scheme 2

The ability to generate defined configured allyl and enamine moieties in the 3,3-sigmatropic rearrangement framework raised the question of achieving internal and external asymmetric induction upon running aza-Claisen reactions [5d]. First investigations focused on conversions of type **10c** reactants (R=*n*Bu/R′=H). Allyl alcohols **13** were converted into the corresponding allylamines via Overman trichloroacetimidate rearrangement and a consecutive saponification resulting in allylamine **14** [6]. A three-step sequence (as displayed in Scheme 1) led to the allyl vinyl systems **10c** with high *E* selectivity concerning the enamine subunit and 56 to 89% yield.

Though the rearrangements of the reactants **10c** delivered single regioisomers, the products **12c** (R=*n*Bu/R′=H) were isolated as a mixture of diastereomers after the rearrangement reduction sequence. Likewise, the 3,3-sigma-

tropic process must have passed chair- and boat-like transition states or, alternatively, the products **11c** suffered from some epimerization via imine–enamine equilibrium (Table 1, entries 11–13). Intending to destabilize the boat-like transition states, the aza-Claisen systems **10c** (R=Me/R′=Me) were heated in the presence of an appropriate acid, and the rearranged crude imines **11c** were immediately reduced by $LiAlH_4$ and DIBALH. Analyzing the products **12c** (R=Me/R′=Me), substantially higher diastereoselectivities could be achieved, indicating the nearly exclusive passing of chair-like transition states during the course of the rearrangement. It was noteworthy that the conversion of the Ph/Me-substituted reactant **10c** (R^1=H, R^2/R^3=Ph/Me) displayed a comparatively high selectivity on generating **12c** even though **10c** was used as an *E*/*Z* vinyl amine mixture. Obviously, the presence of the acid allowed a fast *E*/*Z* interconversion prior to the sigmatropic process, enabling the isomer to be rearranged predominantly with minimized repulsive interactions. The second minor isomer found after running this special sequence was the corresponding *Z* olefin built up via a minor chair transition state (Scheme 3).

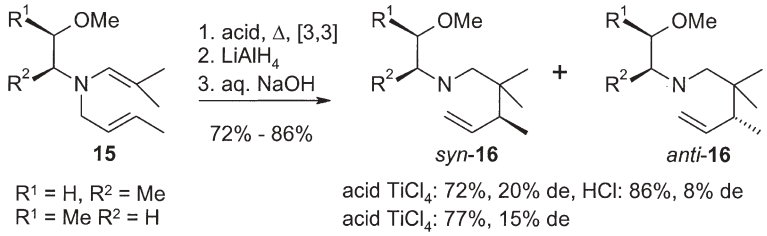


R = *n*Bu, R' = H and R = R' = Me (for details see Table 1)

Scheme 3

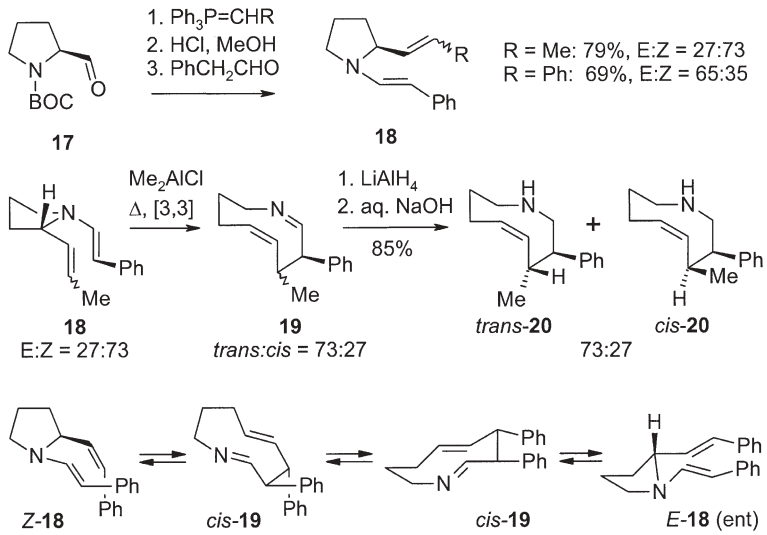
First investigations using a chiral substituent attached to the free valence of the nitrogen for efficient asymmetric induction gave disappointing results [5d]. The rearrangement of *N*-allyl enamines **15** in the presence of proton and Lewis acids produced *γ*,*δ*-unsaturated imines as mixtures of diastereomers with acceptable yield and regioselectivity. The de determined after the final $LiAlH_4$ reduction to amine **16** varied between 8 and 20%. The passing of a single transition state conformation failed. Further efforts investigating sterically more demanding auxiliaries to enable a more effective 1,5-asymmetric induction (1,4-induction including an intermediately built chiral ammonium center) were strongly recommendable (Scheme 4).

Finally, ring-expansion reactions starting from optically active 1,2-divinyl pyrrolidines **19** promised a smooth generation of nine-membered azonine derivatives **20** bearing defined configured centers and double bonds [5d]. Firstly, *N*-BOC prolinal **17** was converted into the divinyl pyrrolidine **18** via Wittig olefination (mixture of *E* and *Z* olefins), protective group removal, and a final con-



Scheme 4

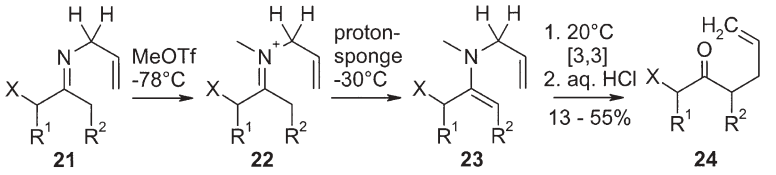
densation with phenyl acetaldehyde with 69% (R=Ph) and 79% (R=Me) yield. The rearrangement/$LiAlH_4$ sequence of **18** (R=Me) delivered the azonine **20** (via **19**) as a mixture of diastereomers; concerning the stereogenic centers, the olefin was exclusively *Z*, indicating the passing of a boat-like transition state. Since the final diastereomer pattern in **20** represented the same ratio as present in the starting material **18**, the result could be interpreted as a sigmatropic rearrangement characterized by a complete 1,3-chirality transfer. However, a thermodynamic reason cannot be excluded, since the reactant **19** and the intermediately formed *γ,δ*-unsaturated imines might have suffered from some equilibration as observed in several reactions discussed above. In contrast, subjecting the divinyl pyrrolidine **18** (R=Ph) to the rearrangement conditions, no azonine derivative **19** could be isolated. The *E*/*Z* mixture of diastereomers **18** was completely converted into the *E* material **18**. The result was rationalized by a reversible aza-Claisen rearrangement: the initial aza-Claisen reaction led to the nine-membered ring *cis*-**19** which, after appropriate conformational relax-



Scheme 5

ation, suffered from a final 1-aza-Cope rearrangement to regenerate the starting material *E*-**18**, but with inverse absolute configuration (not proven). This special result indicates that the unique sense of the aza-Claisen rearrangement should be taken into account when planning to use such a process as a key step in the total syntheses of complicated compounds (Scheme 5).

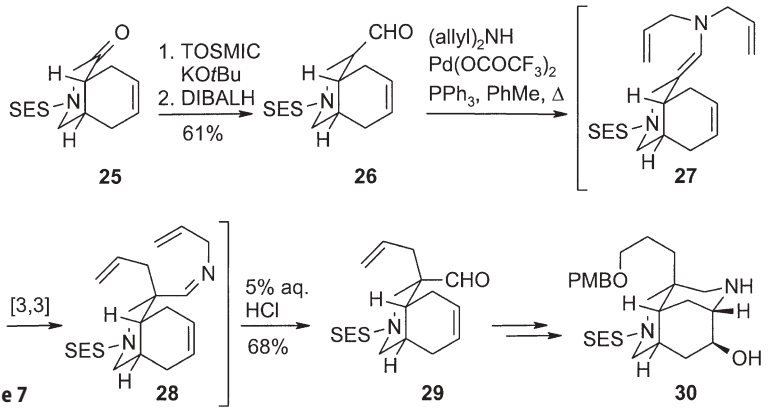
The regioselective enamine formation starting from unsymmetric ketimines **21** has been investigated by Welch [7]. Some simple ketones were converted into the corresponding *N*-allyl imines **21**. Treatment with methyl trifluorosulfonate at low temperatures caused *N*-methylation; the iminium salts **22** formed were then deprotonated by means of a proton sponge. Kinetically motivated deprotonation gave rise to the formation of the least substituted enamines **23**, which underwent aza-Claisen rearrangement upon warming up to room temperature. Acid hydrolysis gave the product ketones **24** with 13 to 55% yield (GC, NMR analyzed). The passing of a 3,3-sigmatropic process has been proven by deuterium labeling experiments (replacement of marked protons by deuterium) (Scheme 6).



Scheme 6

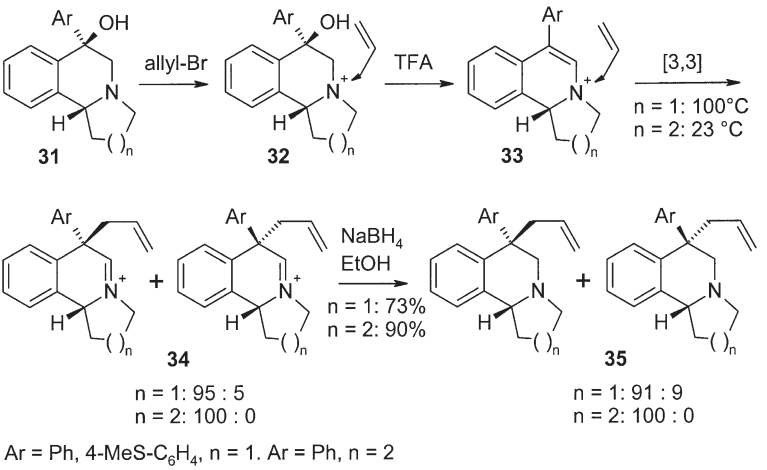
The synthesis of the tricyclic core of the cytotoxic marine alkaloid madangamine required an efficient method to generate the central quaternary carbon function. Weinreb employed an aza-Claisen rearrangement in the presence of a palladium catalyst [8]. After treatment of ketone **25** subsequently with TOSMIC and DIBALH, the carbaldehyde **26** formed was reacted with diallylamine in the presence of $Pd(OCOCF_3)_2/PPh_3$. Initially, the enamine **27** was formed, which underwent diastereoselective aza-Claisen rearrangement. The *γ*,*δ*-unsaturated imine **28** was cleaved with aqueous HCl and the corresponding aldehyde **29** was isolated in 68% yield. Several further steps allowed completion of the synthesis of the core fragment **30** of the natural product (Scheme 7).

Tetrasubstituted *N*-allyl enammonium salts underwent 3,3-sigmatropic rearrangements at ambient temperature or upon heating to about 80 °C. Maryanoff used such a reaction to generate tricyclic tetrahydroisoquinoline derivatives **35** bearing a quaternary center with defined configuration [9]. Initially, indolizidine **31** was allylated. The open-book shape of **31** forced the allyl bromide to attack the *exo* face, building up a chiral ammonium center with defined configuration in **32**. TFA-mediated H_2O elimination delivered the vinyl ammonium subunit in **33**. The quinolizidinine system **33** (n=2) rearranged



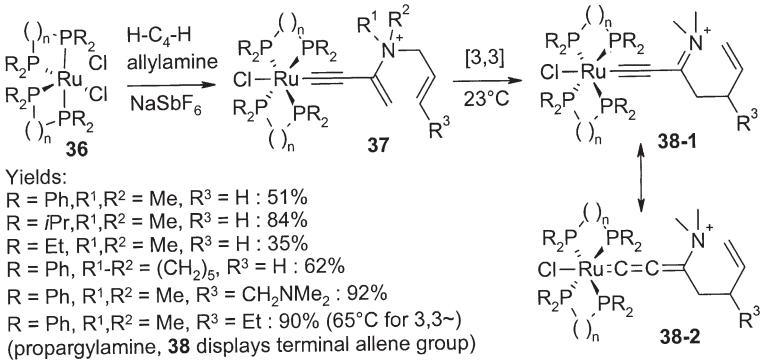
Scheme 7

slowly at 23 °C to give a single diastereomer **34** (n=2); $NaBH_4$ reduction gave the amine **35** (n=2) with 90% yield. The bridgehead H and allyl group exclusively displayed the *cis* arrangement, indicating a complete 1,3-transfer of the chiral information from the ammonium center toward the new quaternary carbon position. In contrast, the indolizidinine systems **33** (n=1) required higher reaction temperatures to induce the rearrangement. After about 2 h at 100 °C, iminium salt **34** (n=1) was formed as a 95:5 mixture of allyl/bridgehead H with *cis* and *trans* relative configuration. The final $NaBH_4$ reduction produced the indolizidinines **35** (n=1) in a 91:9 ratio of diastereomers and 73% yield. The loss of chiral information has been ascribed to a 5 to 10% portion passing a dissociative, nonconcerted reaction path at the elevated temperatures. This hypothesis was supported by deuterium labeling experiments (>90% allyl inversion) (Scheme 8).



Scheme 8

R. Winter reported on aza-Claisen rearrangements in transition metal complexes [10]. *Cis* ruthenium dichloride complexes **36** added butadiyne in the presence of nonnucleophilic $NaPF_6$ to generate a cationic butatrienylidene intermediate, which was trapped by a regioselective *γ*-addition of dialkyl allylamines to produce a vinyl allyl ammonium salt **37**. This material underwent an immediate aza-Claisen rearrangement. The formation of a resonance-stabilized iminium salt **38** was thought to serve as the driving force upon running this process. While most simple allylamines gave smooth reactions at ambient temperature, the rearrangement of sterically more demanding compounds failed. The rearrangement of a propargylamine proceeded at elevated temperature, and the product *β*,*γ*-allenylamine was obtained with 90% yield (Scheme 9). Extensive computational studies gave a somewhat reduced activation barrier of the allyl vinyl ammonium system compared to the uncharged analog [11].

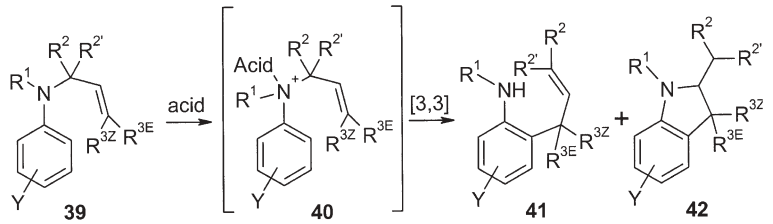


Scheme 9

3 Simple Aromatic Aza-Claisen Rearrangements

In analogy to the simple aliphatic aza-Claisen rearrangements, the aromatic systems required 200 to 350 °C reaction temperature to undergo the 3,3-sigmatropic conversion. Such drastic conditions often caused competing transformations such as the loss of the allylic moiety. Charge acceleration promised to run the process at lower temperatures making the reaction more attractive for extended synthetic use. Stille conducted the first systematic investigations concerning ammonium Claisen rearrangements [12]. Broad variation of suitable acids, solvent, concentration, and reaction time showed that $AlCl_3$, $ZnCl_2$, and $BF_3{\cdot}Et_2O$ in refluxing toluene (110 °C) and refluxing mesitylene (140 °C) led to the best results. The treatment of *N*-allylanilines **39** with the acid caused the formation of an intermediate ammonium salt **40**, which underwent the 3,3-sigmatropic rearrangement to generate the 2-allylaniline **41**. Bicyclic derivatives **42** were found in some attempts as a minor side product. 4-Alkoxy substituents

decelerated the rate, and the corresponding 3-alkoxy regioisomers enhanced the rearrangement. In this latter case, the regiochemistry could not be influenced, and mixtures of 1,2,3- and 1,2,5-trisubstituted products **41** were obtained. Detailed information is given in Table 2 (entries 1–9) (Scheme 10).



Scheme 10 For detailed information see Table 2

Ward reported on a mild proton-catalyzed variant of aromatic aza-Claisen rearrangements. A series of *N*-(1,1-disubstituted-allyl) anilines **39** were rearranged in the presence of 10 mol% of *p*-TsOH to give **41**. The reaction proceeded with complete allyl inversion. The formation of side products such as carbinols originating from a H_2O addition to the nascent double bond could be suppressed by running the conversion in aqueous acetonitrile. In agreement with the findings reported by Stille (*vide supra*), electron-withdrawing substituents Y in the *p*-position accelerated and electron-rich functional groups Y retarded the rearrangement (Table 2, entries 10–17, Scheme 10) [13].

Majumdar published several aza-Claisen rearrangements of 2-cyclohexenyl-1-anilines **39** ($R^{2'}$–R^{3Z}=$(CH_2)_3$, Table 2, entries 22–28) [14]. The reaction was carried out upon heating the reactant in EtOH/HCl. The corresponding 2-cyclohexenylanilines **41** were obtained with 50 to 90% yield. The cyclization to give indole derivatives **42** could be achieved in a separate step: treatment of the rearrangement products **41** with $Hg(OAc)_2$ in a suitable alcohol in the presence of acetic acid induced formation of the tetrahydrocarbazole **42**. The tricyclic products **42** were synthesized with 70–85% yield. Finally, carbazoles could be obtained after DDQ dehydrogenation.

Lai used a BF_3-catalyzed rearrangement of *N*-allylaniline **39** and *N*-allylindoline **43** as a key step in benzimidazole analogs **46** (X=N) and indole analogs **46** (X=C) of mycophenolic acid (MPA) [15]. MPA was known as an immunosuppressant and to have some antipsoriasis activity. With the intention of synthesizing metabolically more stable compounds, the replacement of the central isobenzofuranone subunit by an indole core was planned. Firstly, a suitable functionalized 7-alkyl indole **45** had to be generated. Upon heating of *N*-allylindoline **43** (R=H) in sulfolane to about 200–210 °C in the presence of $BF_3{\cdot}Et_2O$, the aza-Claisen rearrangement via **44** delivered 7-allylindoline **45** (R=H) in 47% yield. Generally, such reaction conditions enabled rearrangement of a set of aniline **39** (Scheme 10, Table 2, entries 18–21) and indoline deriva-

Table 2 [12–15]

Entry	Y	R^1	$R^2/R^{2'}$	R^{3E}/R^{3Z}	Acid/yield (%)			Ref.
1	H	Me	H	H/H	$AlCl_3$/68	$ZnCl_2$/45	$BF_3{\cdot}Et_2O$/58	12
2	H	Bn	H	H/H	$AlCl_3$/15	$ZnCl_2$/15	$BF_3{\cdot}Et_2O$/13	12
3	4-MeO	Me	H	H/H	–	$ZnCl_2$/58	$BF_3{\cdot}Et_2O$/55	12
4	4-MeO	Bn	H	H/H	–	$ZnCl_2$/53	$BF_3{\cdot}Et_2O$/35	12
5[a]	3-MeO	Me	H	H/H	–	$ZnCl_2$/70	$BF_3{\cdot}Et_2O$/99	12
6[a]	3-MeO	Bn	H	H/H	–	$ZnCl_2$/57	$BF_3{\cdot}Et_2O$/38	12
7[a]	3-MeO	*i*Bu	H	H/H	–	$ZnCl_2$/98	$BF_3{\cdot}Et_2O$/80	12
8[a]	3-MeO	Me	H	*n*Pr/H	–	$ZnCl_2$/70	$BF_3{\cdot}Et_2O$/75	12
9	4-MeO	Me	H	*n*Pr/H	–	$ZnCl_2$/50	$BF_3{\cdot}Et_2O$/79	12
10	H	H	Me/Me	H/H	*p*TsOH/70	–	–	13
11	H	H	Me/Et	H/H	*p*TsOH/53	–	–	13
12	H	H	Et/Et	H/H	*p*TsOH/90	–	–	13
13	H	H	$(CH_2)_5$	H/H	*p*TsOH/98	–	–	13

Conditions: 1–2 eq. $AlCl_3$, mesitylene 140°C, 1–2 eq. $ZnCl_2$, mesitylene 140°C, 1–2 eq. $BF_3{\cdot}Et_2O$, toluene 110°C, 10% *p*TsOH, MeCN/H_2O 10:1, 65°C, HCl, EtOH, reflux.

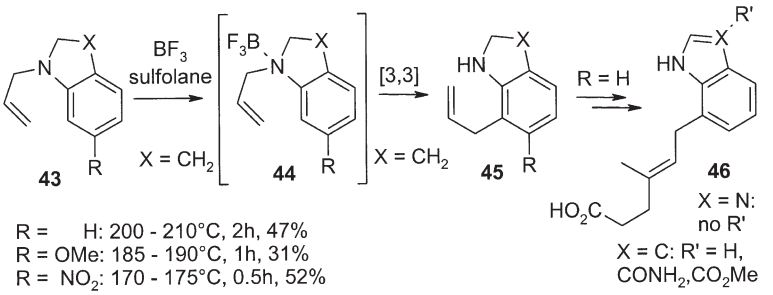
[a] Product: mixture of regioisomers, 1,2,3-and 1,2,5-trisubstituted anilines, ratios varying between 36:64 to and 17:83.

[b] Conditions: 1 eq. $BF_3{\cdot}Et_2O$, sulfolane, 160–195°C, 1 h.

Table 2 (continued)

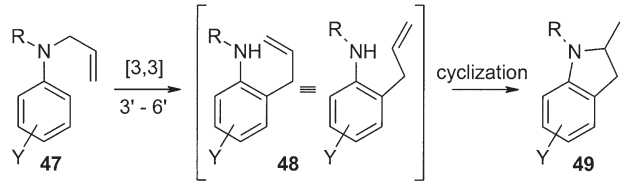
Entry	Y	R^1	$R^2/R^{2'}$	R^{3E}/R^{3Z}	Acid/yield (%)			Ref.
14	4-EtO_2C	H	$(CH_2)_5$	H/H	*p*TsOH/78	–	–	13
15	4-MeO	H	$(CH_2)_5$	H/H	*p*TsOH/88	–	–	13
16	H	H	Bn/H	H/H	*p*TsOH/95	–	–	13
17	4-EtO_2C	H	Me/Me	H/H	*p*TsOH/91	–	–	13
18[b]	2-NH_2	H	H/H	H/H	–	–	$BF_3{\cdot}Et_2O$/53	15a
19[b]	2-NO_2	H	H/H	H/H	–	–	$BF_3{\cdot}Et_2O$/57	15a
20[b]	2-MeO_2C	H	H/H	H/H	–	–	$BF_3{\cdot}Et_2O$/52	15a
21[b]	3-MeO	H	H/H	H/H	–	–	$BF_3{\cdot}Et_2O$/43	15a
22	H	Me	$(CH_2)_3$	$(R^{2'}–R^{3Z})$	HCl/90	–	–	14
23	4-Me	Me	$(CH_2)_3$	$(R^{2'}–R^{3Z})$	HCl/88	–	–	14
24	4-Br	Me	$(CH_2)_3$	$(R^{2'}–R^{3Z})$	HCl/50	–	–	14
25	2-Me	Me	$(CH_2)_3$	$(R^{2'}–R^{3Z})$	HCl/50	–	–	14
26	H	Et	$(CH_2)_3$	$(R^{2'}–R^{3Z})$	HCl/90	–	–	14
27	4-Me	Et	$(CH_2)_3$	$(R^{2'}–R^{3Z})$	HCl/90	–	–	14
28	4-Me	*i*Pr	$(CH_2)_3$	$(R^{2'}–R^{3Z})$	HCl/66	–	–	14

tives **43** (Scheme 11) in 31–52% yield. Several further steps allowed completion of the syntheses of three target molecules **46** (X=C) [15b,c] displaying different substitution patterns; one of them (R′=$CONH_2$) showed significant antitumor activity. One benzimidazole compound **46** (X=N) [15a] was synthesized via the same sequence starting from a nitrogen derivative of 2,3-dehydro-**45** (X=N). Recently, Ganesan employed such aza-Claisen rearrangement as a key step in the total synthesis of (+)-okaranine J, which displays potent insecticidal activity (Scheme 11) [15d].



Scheme 11

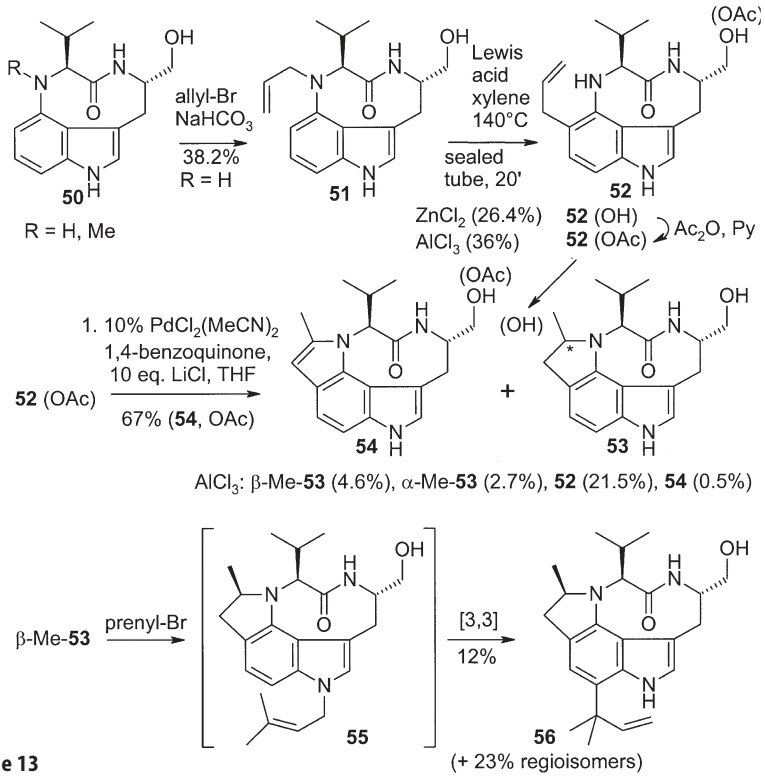
Microwave-assisted aza-Claisen rearrangements of *N*-allylanilines **47** proceeded in very short reaction times in the presence of Zn^{2+} montmorillonite as a catalyst [16]. In contrast to most of the (Lewis) acid-accelerated reactions a 3,3-sigmatropic rearrangement/cationic cyclization tandem process was passed to generate 2-methylindole derivatives **49** with high yield. The nonmicrovave-assisted reactions led to mixtures of simple rearrangement products **48** and rearrangement/cyclization products **49** (80 °C, 2 h) (Scheme 12) [16b].



Scheme 12

Teleocidines are known as tumor-promoting compounds characterized by an indolactam V core structure. Such indolactams adopt two stable conformations at room temperature. With the intention to investigate the biologically active conformer, Irie and Wender synthesized conformationally restricted analogs of indolactam V **50** (R=Me) [17]. Starting from desmethylindolactam

V **50** (R=H), the reaction with allyl bromide gave the corresponding *N*-allyl compound **51**. Heating of the material in the presence of substoichiometric amounts of $ZnCl_2$ gave the 5-allylated product **52** with 26.4% yield. Best results concerning a 3,3-sigmatropic rearrangement/cationic cyclization tandem reaction were achieved upon heating **51** to 140 °C (xylene) in the presence of $AlCl_3$: a mixture of **52**, *β*-Me-**53**, *α*-Me-**53**, and **54** was obtained in 29.3% yield and a 43:5.4:9.2:1 ratio. Furthermore, cationic cyclization to give **53/54** could be achieved by subjecting 5-allyl indolactam **52** to the $AlCl_3$-promoted reaction conditions (Scheme 13). The examination of tumor promotion resulted in a significant activity upon testing of *β*-Me-**53** and **54** [17a]. A substantial yield enhancement could be achieved by conducting the generation of the conformationally restricted indolactam analog **54** via a two-step procedure [17b]. After the rearrangement of *N*-allyl reactant **51** in the presence of 0.45 mol% $AlCl_3$ (sealed tube, 140 °C), the 5-allyl indolactam **52** was obtained in 36% yield. Then, the OH group of **52** was acetylated and the OAc-**52** was subjected to a Pd(II)-catalyzed amination to give OAc-**54** in 67% yield [18]. Tumor-promoting activity was enhanced after introduction of a terpenoid side chain. The reaction of *β*-Me-**53** with prenyl bromide led to the formation of a mixture of three regioisomers in about 35% overall yield. The generation of the 7-prenyl

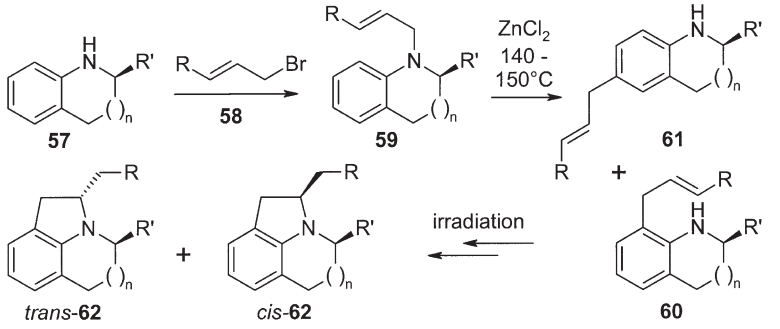


Scheme 13

compound **56** (one third of the adduct) was explained by the initial indole *N*-allylation (→**55**) and a subsequent aza-Claisen rearrangement. The direct C7 allylation would have built up the allyl-inverted analog only (Scheme 13).

Desmethylindolactam G (**50**, R=H, replace *i*Pr by H) was subjected to the same sequence (**50**→**54**). The first allylation step succeeded with 52% yield, but the aza-Claisen rearrangement/cationic cyclization gave only 9.5% of the product mixture **52**–**54** (replace *i*Pr by H).

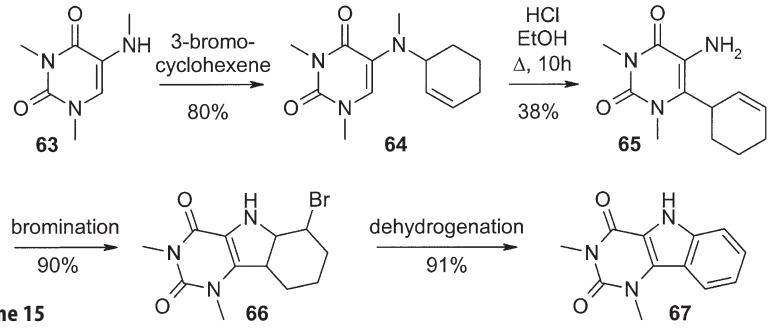
Photocyclization of allyl tetrahydroquinoline **60** (*n*=1) and allyl indoline **60** (*n*=0) delivered tricyclic compounds **62** with high regioselectivity. The reactant C-allyl systems **60** were produced by means of aza-Claisen rearrangements [19]. Initially, *N*-allylation succeeded upon treatment of the amine **57** with allyl bromide **58** to give the substrates **59**. Subsequent heating to 140–150 °C in the presence of $ZnCl_2$ caused the 3,3-sigmatropic rearrangements to **60**. The indole derivative **60** (*n*=0) was obtained in 42% yield along with 9% of the *p*-product **61** (*n*=0) generated via a final Cope rearrangement (for quinoline: no yield given, Scheme 14). It should be pointed out that the reactions incorporating the cinnamyl system (R=Ph) always produced compounds with a 3-phenyl side chain, indicating the passing of dissociative reaction paths prior to a 3,3-sigmatropic rearrangement.



Scheme 14

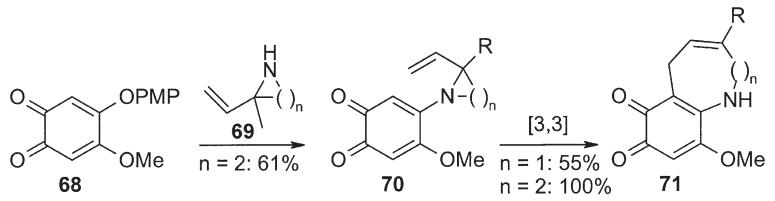
Pyrimidine annulated heterocycles fused at positions 5 and 6 to uracil were synthesized via a three-step sequence starting from uracil **63** [20]. Firstly, the reaction with 3-bromocyclohexene gave the *N*-allyl-vinyl core system **64** in 80% yield. Upon heating **64** in EtOH in the presence of HCl, aza-Claisen rearrangement gave rise to the C-cyclohexenyl uracil **65** in 38% yield. Final bromination (→**66**) and dehydrogenation steps (→**67**) allowed synthesis of the desired tricyclic fused uracil systems (Scheme 15).

Simple aromatic aza-Claisen rearrangement without charge acceleration by addition of an acid required other activating factors to enable the reaction to be run at acceptable temperatures. The reduction of ring strain was found to serve as a useful promoter to induce aromatic aza-Claisen rearrangement [21].



Scheme 15

4-Phenoxy-1,2-benzoquinone **68** was treated with 2-vinylazetidine **69** (*n*=2) and 2-vinylaziridine **69** (*n*=1). The azetidine adduct **70** (*n*=2) could be isolated in 61% yield. Heating in toluene induced aza-Claisen rearrangement to give the benzoquinone annulated azocine **71** (*n*=2) with 100% yield. In contrast, the corresponding aziridine adduct **70** (*n*=1) could not be trapped, and the azepine **71** (*n*=1) was isolated in 55% yield indicating an efficient aza-Claisen rearrangement run at ambient temperature (Scheme 16).



n = 1, R = H: **70** not detected, direct reaction to **71** at 23°C in MeCN
n = 2, R = Me: reaction **70** to **71** in PhMe, Δ.

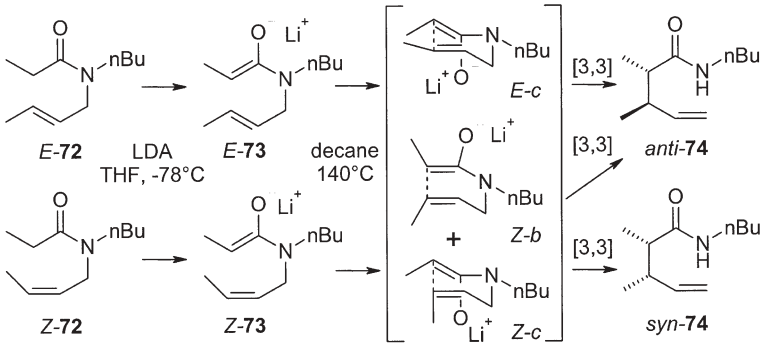
Scheme 16

4
Amide Enolate Rearrangements

The acceleration of simple aza-Claisen rearrangements by means of the addition of Lewis and proton acids offered the advantage of achieving a significant decrease of the originally very high reaction temperatures (>200 °C), enabling such a process to be employed in synthetically useful sequences. One major problem of the cation-mediated rearrangement was the potential passing of a dissociative reaction path via allyl cation and neutral enamine subunits. In several cases the regioselectivity of the sigmatropic reaction turned out to be a problem, since mixtures of 3,3- and 1,3-rearrangement products were found after running the conversion involving nonsymmetrical *N*-allyl moieties in the reactant core. The *N*-allyl amide enolate rearrangement promised to be much more flexible. In analogy to the oxygen analogs (Ireland ester enolate and silyl

ketene acetal rearrangement), relatively mild reaction conditions should be applicable. In contrast to the oxygen systems, the fragmentation to generate a ketene and an amide anion was unlikely to occur. Furthermore, the bulky nitrogen forced the nascent amide acetal to adopt the *Z* configuration, offering the advantage of achieving high internal asymmetric induction (high simple diastereoselectivity) upon forming the product *γ,δ*-unsaturated amides.

Basic systematic investigation of amide enolate rearrangements concerning reaction conditions and diastereoselectivity have been published by Tsunoda et al. [22]. *E* and *Z N*-crotyl propionic acid amides **72** were initially deprotonated with LDA at –78 °C in THF to form the corresponding *Z*-enolates **73** [22a,b]. After exchanging THF against a high-boiling nonpolar solvent, rearrangement was induced upon heating. The corresponding *anti γ,δ*-unsaturated amides **74** were generated with high yield. A high diastereoselectivity was achieved starting from the reactant olefin *E*-**72** via a chair-like transition state *E-c*. In contrast, the corresponding *Z* crotyl reactant *Z*-**72** gave the product **74** with high yield too, but with a low diastereoselectivity of *syn*-**74**:*anti*-**74**=63:37, indicating the passing of competing chair- and boat-like transition states *Z-c* and *Z-b* (Scheme 17).

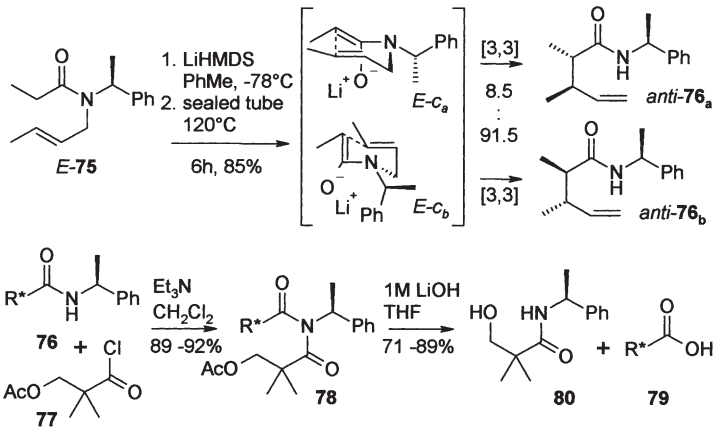


E-**73** into **74**: 135°C, 4h, 94% yield, ratio *anti*-**74**:*syn*-**74**: 99.4:0.6
Z-**73** into **74**: 148°C, 14h, 90% yield, ratio *anti*-**74**:*syn*-**74**: 37:63

Scheme 17

The high yield and the high internal asymmetric induction obtained via the rearrangement of *E*-**72** to *anti*-**74** raised a question concerning the efficiency of an additional external asymmetric induction [22a,b]. The best prerequisite provided amide **75** placing the chiral center of the phenethyl side chain (attached to the nitrogen) adjacent to the 3,3-sigmatropic rearrangement core system. The chiral auxiliary-directed rearrangement of the *N*-crotylamide *E*-**75** led to the corresponding *γ,δ*-unsaturated amides *anti*-**76** with 85% yield; no *syn*-**76** amides were found, indicating the exclusive passing of chair-like transition states *E-c*. The careful analysis of the product *anti*-**76** gave a composition of *anti*-$\mathbf{76_a}$:*anti*-$\mathbf{76_b}$ of 8.5:91.5. The outcome could be rationalized by the predominant passing of a chair-like transition state *E*-c_b causing the formation of

anti-**76**$_b$ with 83% de (Scheme 18). The removal of the auxiliary was succeeded by initial acylation of the secondary amide **76** with acid chloride **77**. Then, neighboring group-assisted saponification of **78** gave the optically active γ,δ-unsaturated acid **79** with 63–82% yield overall. The chiral auxiliary phenethylamine could be recovered in two further steps in 71% yield overall starting from **80** (Scheme 18). Investigating a series of chiral auxiliaries attached to amide *E*-**75**, most *S*-configured auxiliaries predominantly led to product *anti*-**76**$_b$ (yield: 66–90%, de: 70–84%). As an exception, (2*S*)-3,3-dimethylbutyl-2-amine resulted in *anti*-**76**$_a$ as the major product (38% yield, 80% de) [22c]. Recently, a related example has been published by Davies [22i].



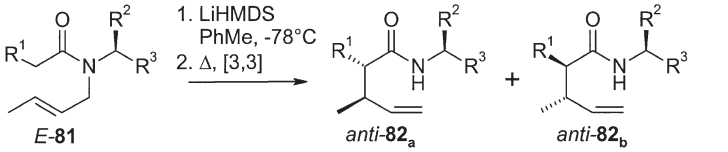
Scheme 18

Planning the employment of the amide enolate Claisen rearrangement as a key step in natural product total synthesis, the scope and limitations of the process were investigated [22d]. *N*-allylamino and α-hydroxy acetamides *E*-**81** were initially treated with base to generate the corresponding anionic species. If possible, lithium chelate formation (enolate O and α heteroatom) should fix the *Z* enolate geometry. The glycolic acid amides *E*-**81** (R^1=OH, OTBS) underwent smooth rearrangement upon heating to give the γ,δ-unsaturated amides **82** with 59–95% yield. The chiral auxiliary-directed rearrangements led to de values of 34 to 73%. The *N*-crotyl glycine derivatives displayed different reactivity *E*-**81** (R^1=NH_2, NHBOC). Despite varying the conditions, the NHBOC did not give any rearrangement product. In contrast, *E*-**81** (R^1=NH_2) underwent rearrangement at ambient temperature to build up **82** with 81–89% yield and 78% de after running the auxiliary-directed conversion (Table 3, Scheme 19).

First applications in total syntheses started from amide **83**. The rearrangement under standard conditions led diastereoselectively to amide **84** in 77% yield; no traces of other diastereomers were found. Amide **84** was converted

Table 3 [22]

Entry	R^1	R^2	R^3	Time (h)	*T* (°C)	Yield (%)	Ratio $\mathbf{82_a}$:$\mathbf{82_b}$	Ref.
1	OH	H	*n*Pr	15	80	74	50:50	d
2	OTBS	H	*n*Pr	15	100	59	50:50	d
3	NH_2	H	*n*Pr	4	23	81	50:50	d
4	NHBOC	H	*n*Pr	20	23–140	0	–	d
5	OH	Ph	Me	15	80	95	86:13	d
6	OTBS	Ph	Me	6	120	62	67:33	d
7	NH_2	Me	Ph	15	23	89	11:89	d

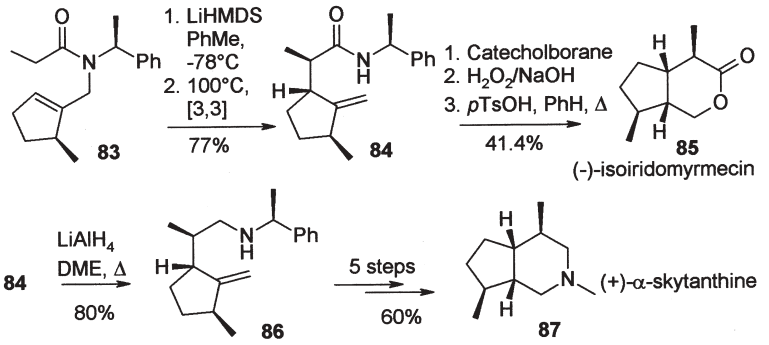


R^1 = OH, OTBS, NH_2, NHBOC. R^2 = H, R^3 = *n*Pr or R^2 = Me, R^3 = Ph (Table 3)

Scheme 19

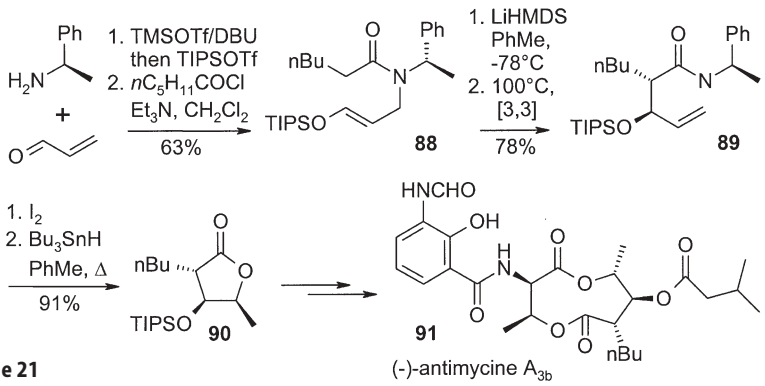
into (–)-isoiridomyrmecin **85** via diastereoselective hydroboration, oxidative workup, and a final lactonization in the presence of *p*-TsOH (41.4% yield over three steps) [22f]. Alternatively, $LiAlH_4$ reduction of **84** resulted in amine **86** (80%), and a final five-step sequence enabled (+)-α-skytanthine **87** to be synthesized with 60% yield (Scheme 20) [22g].

As an extension of the above-mentioned method, a successful rearrangement starting from silyl enol ethers as an electron-rich *N*-allyl moiety has been published. Allylamide **88** was synthesized in two steps starting from (+)-phenethylamine and acrolein via a condensation–acylation sequence. The auxiliary-



Scheme 20

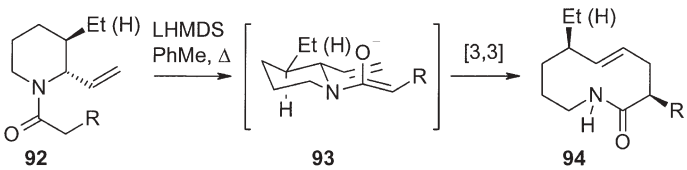
directed aza-Claisen rearrangement of **88** produced a mixture of two diastereomers; the major compound **89** was isolated by means of column chromatography. Iodocyclization and subsequent reductive removal of the halide resulted in γ-butyrolactone **90**, which served as the western half of the bislactone framework of antimycine A_{3b} **91**. Starting from **90** the total synthesis of **91** (component of antimycine A mixture: oxidoreductase inhibitor) was completed in several further steps (Scheme 21).



Scheme 21

The synthesis of the medium-sized lactam **94** started from 2-vinylpiperidine **92** [23]. The amide enolate aza-Claisen rearrangement led to the corresponding ten-membered ring lactam **94**. Reacting terminally unsubstituted olefins as in **92**, a complete 1,4-chirality transfer was observed, pointing out the highly efficient internal asymmetric induction. The stereochemical outcome of the process was rationalized by the passing of a chair-like transition state **93** minimizing repulsive interactions. As described above, the amide enolate in **93** should have been *Z* configured. One optically active azecinone **94** (R=Me, Et side chain) served as key intermediate in an asymmetric total synthesis of fluvirucin A_1 (Scheme 22).

Somfai enhanced the driving force of some amide enolate aza-Claisen rearrangements by choosing vinylaziridines as reactants [24]. The additional loss of ring strain offered the advantage of running most of the reactions at room temperature to synthesize unsaturated chiral azepinones. Various substitution

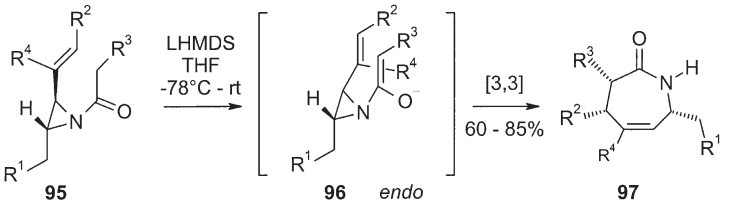


R = H (H): 40%, R = Me (H): 75%, R = OMe (H): 84%, R = Me (Et): 74%

Scheme 22

patterns were tested to investigate the scope and limitations of this process (Table 4). The stereochemical properties of the 3,3-sigmatropic rearrangement enabled the transfer of stereogenic information of easily formed C–N bonds completely to new C–C bonds by means of the highly ordered cyclic *endo* transition states **96**.The configuration of the allyl double bond was retained throughout the reaction. Furthermore, the defined enolate geometry of the in situ formed ketene aminal double bond caused a high internal asymmetric induction leading to one predominant relative configuration of the newly generated stereogenic centers.

Rearranging divinylaziridines **95**, the passing of a boat-like transition state **96** explained the stereochemical outcome of the reactions to give the azepinones **97** in 60 to 85% yield. The rearrangement of an α-branched amide **95** (replace CH_2R^2 by $CH(R^2)CH_3$, Table 4, entry 14) only required a higher reaction temperature of about 65 °C to induce the conversion. A single diastereomer **97** was generated bearing β-methyl and α-amino functions. Surprisingly, the α-NHBOC group was found to be replaced by a urea subunit, indicating a defined substitution during the course of the reaction (neighboring group-assisted cleavage of the BOC protective group). The reactant divinylaziridines **95** were synthesized via ex-chiral pool sequences starting from optically active α-amino acids (Table 4, Scheme 23).



R^1 = H, OBn, Bn, R^2 = H, Me, OBn, R^3 = H, Me, OBn, NHBoc R^4 = H, CH_2OBn (Table 4)

Scheme 23

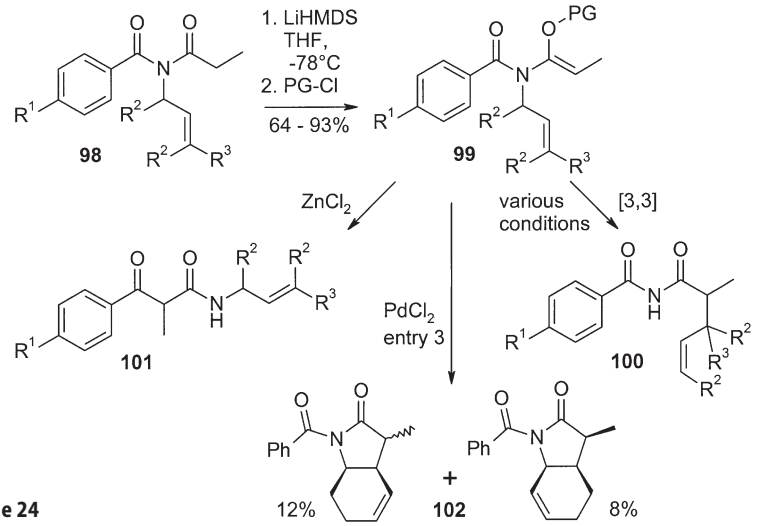
Neier et al. planned the development of a Diels–Alder cycloaddition/aza-Claisen rearrangement tandem process intending to construct up to four new stereogenic centers in a defined manner [25]. Initially, some test systems were checked but only a disappointing efficiency of such a sequence was found. Hence, cycloaddition and rearrangement were tested as separate reactions employing suitable model systems. Imides **98** (generated from the corresponding amides by *N*-acylation, 88–93%) were converted into the *Z*-*N*,*O*-ketene acetals **99** with 64–93% yield. The *N*-allyl amide acetals obtained were subjected to a set of different aza-Claisen rearrangement conditions to investigate the usefulness in regard to the planned tandem process, synthesizing imide **100** (Scheme 24).

Thermal aza-Claisen rearrangements were induced upon heating the reactant **99** in decalin to 135–190 °C. Though some product **100** could be obtained,

Table 4 [22]

Entry	R^1	Config./R^2	R^3	R^4	Yield (%)	Ref.
1	OBn	H	H	H	83	a
2	Bn	H	N	H	83	a
3	Bn	H	Me	H	85	a
4	Bn	H	OBn	H	81	a
5	Bn	H	NHBOC	H	76	a
6	H	α/CH_2OBn	H	H	73	a
7	OBn	α/Me	H	H	71	c
8[a]	OBn	β/Me	H	H	73	a
9	H	α/CH_2OBn	Me	H	60	c
10	OBn	α/Me	Me	H	64	c
11[a]	OBn	β/Me	Me	H	61	c
12	H	α/CH_2OBn	NHBOC	H	63	c
13	OPMB	H	H	CH_2OBn	85	c
14	Bn	NHBOC[b]	H	H	58	c

[a] Rearrangement of *Z*/*E*-olefin mixture (*Z*/*E*=1:13).
[b] Replace CH_2R^2 by $CH(R^2)CH_3$.



Scheme 24

best yields achieved were about 40%. The substituted allyl moieties in particular suffered from poor yield and the formation of diastereomer mixtures (Table 5, entries 2, 3). Lewis acid mediation was investigated by treating the reactants **99** with 0.7 mol% of $ZnCl_2$ in PhMe with heating to 85 °C. No product **100** was formed; β-ketoamides **101** were isolated pointing out the predomination of a competing reaction path. Further testing of various Lewis acids did not result in any rearrangement product **100**. The Overman rearrangement

Table 5 [25]

Entry	R^1	R^2	R^3	PG	Yield (%)[b]		
					>135°C	$ZnCl_2$, 85°C	$PdCl_2$
1	H	H	H	TBS	36	85	48
2	H	H	Me	TBS	13[c]	84	–
3	H	$(CH_2)_3$	H	TBS	11[c]	–	20[d]
4	Me	H	H	TBS	39	61	–
5	MeO	H	H	TBS	41	–	–
6	H	H	H	$P(O)(OEt)_2$	7	–	–
7	H	H	H	TES	40	–	–
8[a]	H	H	H	TBS	28	–	–

[a] Replace *N*-benzoyl by *N*-benzyl.
[b] Product **101**.
[c] Mixture of diastereomers.
[d] Cyclization products **102**.

conditions employed the soft electrophile $Pd(PhCN)_2Cl_2$ to accelerate the bond reorganization [26]. The reaction mechanism was rationalized likewise by a Pd(II)-catalyzed sigmatropic rearrangement or by a cyclization fragmentation sequence. However, rearrangement-type products should be formed. In the present investigations, the reaction of *N*,*O*-acetal **99** (entry 1, Table 5) gave some product **100** and 50 mol% Pd(II) catalyst was necessary to obtain a maximum yield of 48%. In contrast, the cyclohexenylamine derivative **99** (entry 3, Table 5) produced no amide **100**. Instead, bicyclic imides **102** were found with low yield, indicating the passing of a Pd(II)-mediated cyclization/β-hydride elimination tandem process (Table 5, Scheme 24).

5 Zwitterionic Aza-Claisen Rearrangements

Charge-accelerated ammonium and amide enolate aza-Claisen rearrangements allowed the originally very high reaction temperatures of 200–350 °C to be reduced to about 80–140 °C. Considering the significant nucleophilicity of some tertiary amines **103**, the addition to neutral electrophiles must cause an initial charge separation. Constructing such a zwitterion using an allylamine **103** as the nucleophile and a triple bond **104** or an allenic species **108** as an electrophile, the combination gives rise to an aza-Claisen rearrangement framework **105/109**. A consecutive 3,3-sigmatropic bond reorganization to **107/110** should profit from charge neutralization, holding out the prospect of a further decrease of the reaction temperature – a significant extension of the limitations in tolerating more complicated substitution patterns and functional groups within the

reaction as well as higher stereoselectivities seems to be achievable. Additional base and (Lewis) acid catalysis can be employed to support the reaction. One problem should be pointed out: the addition step of nucleophile **103** and electrophile **104/108** potentially is reversible. Consequently, the fragmentation of **105/109** to regenerate the reactants occurs not as a negligible process (entropy, charge neutralization). Intending to use the zwitterionic intermediate **105/109** for Claisen rearrangement, a sufficient lifetime of the charge-separated species must be taken into account to achieve the highly ordered transition state as a prerequisite of the 3,3-sigmatropic process. Analyzing the systems suitable for the intermolecular zwitterionic aza-Claisen rearrangement (addition/rearrangement tandem process), three combinations were found to be of interest (Fig. 2).

The first one can be described as the Michael addition of the *N*-allylamine **103** to an acceptor-substituted triple bond of **104** to form an intermediate *N*-allyl enammonium enolate **105** (alkyne carbonester Claisen rearrangement). The anion stabilizing group is placed in position 1 of the rearrangement core system. 3,3-Sigmatropic rearrangement delivers an iminium enolate **106**, which undergoes immediate charge neutralization to form an acceptor-substituted enamine **107**.

The second mechanism starts with addition of the *N*-allylamine **103** to the cumulated acceptor system of a ketene **108** (Acc=O) to form an intermediate *N*-allyl ammonium enolate **109** (ketene Claisen rearrangement) [27]. The anion stabilizing group is predominantly placed in position 2 of the rearrangement core system; resonance stabilization can place the anion in position 1, too. Then, 3,3-sigmatropic rearrangement gives rise to an iminium analog carboxylate (**110**, $Acc^-=O^-$), which represents the zwitterionic mesomer of the charge neutral amide **110** (Acc=O).

The third mechanism starts with addition of the *N*-allylamine **103** to the cumulated acceptor system of an allene carbonester **108** ($Acc=CHCO_2Me$) to form an intermediate *N*-allyl ammonium amide enolate **109** (allene carbonester Claisen rearrangement). The anion stabilizing group is exclusively placed

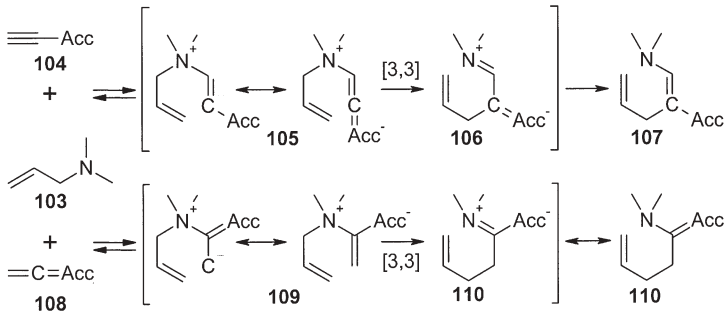


Fig. 2 Systems suitable for the intermolecular zwitterionic aza-Claisen rearrangement

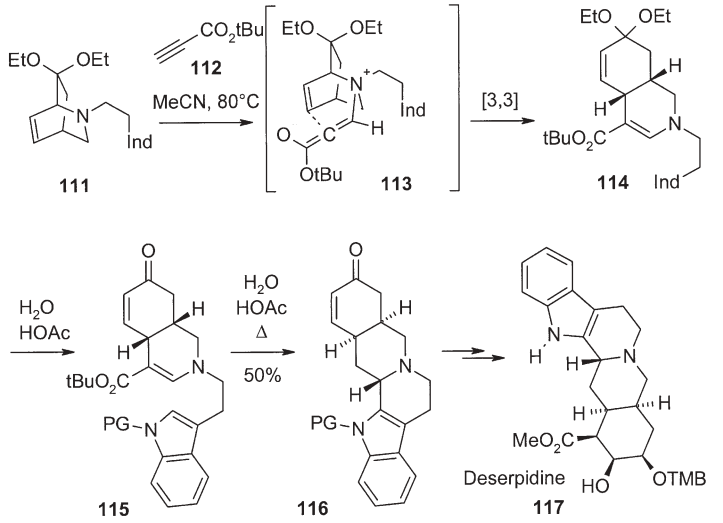
in position 2 of the rearrangement core system. Then, 3,3-sigmatropic rearrangement generates an iminium enolate (**110**, $Acc^{-}=CH^{-}CO_2Me$), which represents the zwitterionic mesomer of the charge neutral vinylogous amide **110** ($Acc=CHCO_2Me$).

All reaction mechanisms presented here should be understood as hypotheses to rationalize the outcome of the processes. Alternative explanations such as stepwise and dissociative mechanisms cannot be excluded. However, as long as the constitution and configuration of the product can be described as that of a 3,3-sigmatropic rearrangement, the present hypotheses seem acceptable.

5.1 Alkyne Carbonester Claisen Rearrangements

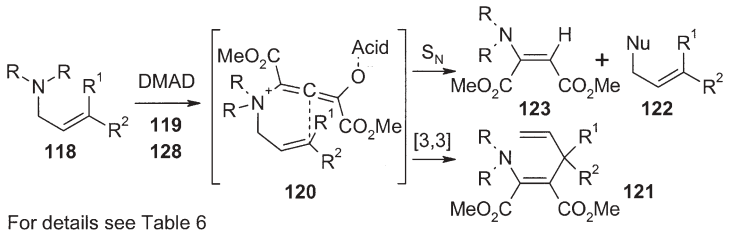
Mariano et al. developed alkyne carbonester Claisen rearrangements as key steps in alkaloid syntheses. A convincing application of such a process was published in 1990 describing the total synthesis of the Rauwolfia alkaloid deserpidine **117** [28]. Isoquinuclidene **111** was synthesized in several steps starting from a dihydropyridine. The heating of a mixture of amine **111** and propiolic ester **112** in MeCN at about 80 °C induced the addition rearrangement sequence to give the isoquinoline derivative **114**. Careful optimization of the reaction conditions improved a crucial role of the diethyl ketal function to obtain a smooth reaction. The addition of the alkynoic acid proceeded *anti* with respect to the ketal building up zwitterion **113** bearing the suitable 3,3-sigmatropic rearrangement framework. Without any indole protecting group (PG=H) only 39% of the desired product was obtained. Rearranging the sulfonamide of **111** ($PG=PhSO_2$), acceptable 64% yields of ketone **115** were achieved after consecutive cleavage of the ketal. Heating in aqueous acetic acid induced Wenkert cyclization to generate tetracyclus **116** as a mixture of three diastereomers. Several further steps allowed completion of the total synthesis of deserpidine **117** (Scheme 25).

Vedejs and Gingras investigated intermolecular aza-Claisen rearrangements of acetylene dimethyldicarboxylates **119** and methyl propiolate **128** and various acyclic and cyclic *N*-allylamines **118**, **124**, and **127** [29]. Proton and Lewis acids were found to accelerate the Michael addition step of the amine to the triple bond. Hence, the reaction temperature could be lowered to 23–0 °C in most of the experiments; optimized conversions were run at –40 to –60 °C. The reaction of allylamine **118** with DMAD **119** initially formed the Michael adduct **120**. The acid was thought to promote the addition and to stabilize **120**. A subsequent rearrangement enabled the isolation of enamine **121** in up to 99% yield. Acidic cleavage allowed removal of the enamine and buildup of the corresponding ketoesters. In the presence of a sterically demanding allyl system and, likewise, a nucleophilic counter-ion of the acid (e.g., benzoate from benzoic acid), the yield of rearrangement product **121** was decreased. A competing reaction activated the nucleophile to degrade the intermediate **120** by means of an S_N process. Up to 50% yield of enamine **123** and allyl compound **122** could be isolated (Scheme 26).

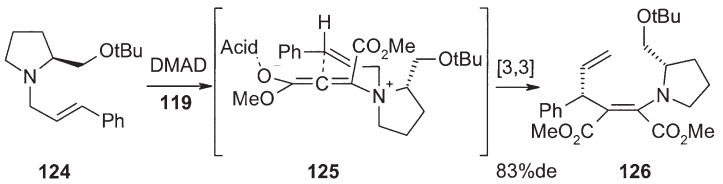


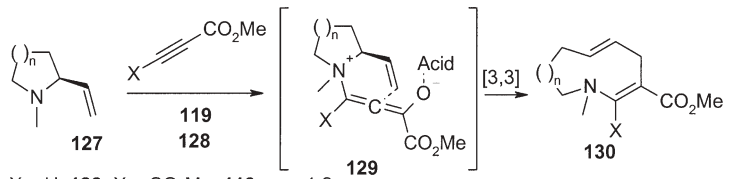
Ind = N-PG-3-Indoyl, yield **111** in **115**: PG = H: 39%, PG = $PhSO_2$: 64%

Scheme 25



For details see Table 6





X = H: **128**, X = CO_2Me: **119**. n = 1,2

Scheme 26

Table 6 [29]

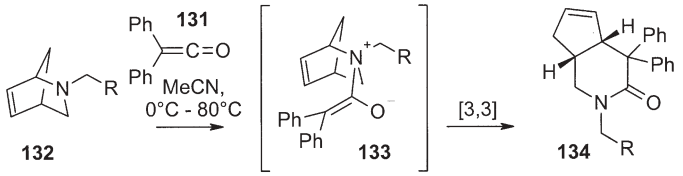
Entry	R	R^1	R^2	X	*T* (°C)	mol%/acid	Yield (%)
1	*n*Pr	H	H	CO_2Me	23	10/TsOH	99
2	*n*Pr	H	H	H	23	5/TsOH	95
3	*n*Pr	H	Me	CO_2Me	23	10/TsOH	95
4	$(CH_2)_4$	H	Me	CO_2Me	23	10/TsOH	89
5	$(CH_2)_4$	H	Ph	CO_2Me	23	5/TsOH	91
6	*n*Pr	Me	Me	CO_2Me	23	10/TsOH	64
7	$(CH_2)_5$	H	Ph	CO_2Me	23	10/TsOH	88
8	*n*Pr	Me	R[c]	CO_2Me	23	10/TsOH	73
9	*n*Pr	H	Me	CO_2Me	–40	27/$TiCl_2$(O*i*Pr)$_2$	66
10	*n*Pr	H	Me	CO_2Me	–40	27/(BINOL)$TiCl_2$	93
11	$(CH_2)_4$	H	Ph	CO_2Me	–40	10/$TiCl_2$(O*i*Pr)$_2$	83
12	$(CH_2)_4$	H	Ph	CO_2Me	–40	27/(BINOL)$TiCl_2$	92
13[a]	Et	H	Ph	CO_2Me	–60	10/$TiCl_2$(O*i*Pr)$_2$	83
14[b]	**124**			CO_2Me	–60	10/$TiCl_2$(O*i*Pr)$_2$	62
15	**127**	*n*=1		CO_2Me	–15	5.5/TsOH	57
16	**127**	*n*=2		CO_2Me	20	10/TsOH	71
17	**127**	*n*=2		H	65	–	71

[a] +25% AgOTf.
[b] +20% AgOTf.
[c] R=$CH_2CH_2CHCMe_2$.

Lewis acid catalysis offered the advantage of using chiral Lewis acid ligands with the intention of achieving some catalyst-directed asymmetric induction upon generating the enamine **121**. First experiments using (±)-BINOL catalyst (27 mol%) gave a significant rate acceleration, but no experiment with enantiopure material had been described. An auxiliary-directed asymmetric rearrangement was investigated starting from prolinol derivative **124**. The addition should have given the intermediate **125** bearing a chiral ammonium center. The consecutive 3,3-sigmatropic rearrangement gave the enamine **126** with 62% yield and 83% de, as determined after auxiliary cleavage/decarboxylation and final amidation with chiral 1-phenylethylamine. Here, the use of (+)-BINOL led to a slight decrease of the ee to about 80% (mismatched combination?). Ring expansions were studied upon rearranging 2-vinylpyrrolidine **127** (*n*=1) and piperidine **127** (*n*=2) with propiolic esters **119** and **128**, respectively. Best results were obtained using TsOH as accelerating acid. In most cases, NMR-scale experiments were conducted allowing generation of the medium-sized ring systems **130** via adduct **129** with 50–70% yield (Table 6, Scheme 26).

5.2
Ketene Claisen Rearrangements

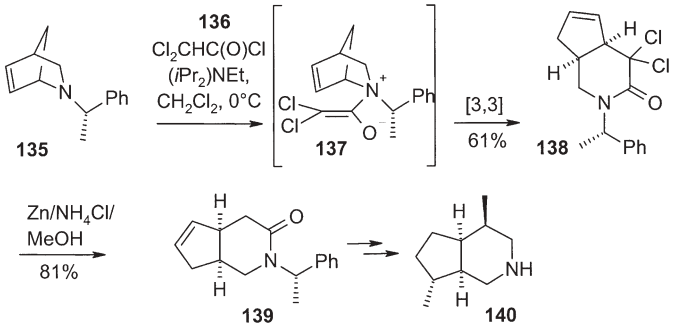
The *N*-allyl ammonium enolate Claisen rearrangement requires the addition of a tertiary allylamine to the carbonyl center of a ketene to generate the sigmatropic framework. The first crucial point of this so-termed ketene Claisen rearrangement is the formation of the ketene with a lifetime sufficient for the consecutive attack of the nucleophile and the avoidance of competing 2+2-cycloadditions. Roberts tested stable diphenylketene **131** [30]. *N*-benzyl azanorbornene **132** (R=Ph) was treated with diphenylketene **131** upon heating to reflux in acetonitrile for 6 days. The passing of the addition (→**133**) rearrangement sequence gave the desired bicyclic material **134** with 59% yield. Ultrasonication allowed reduction of the reaction time to 12 h (61% yield). At 0 to 23 °C, the sterically less hindered *N*-methyl derivative **132** (R=H) suffered from the intermolecular Claisen rearrangement to give **134** in 53% yield. The use of stable ketenes was mandatory, otherwise only 2+2 cycloadducts of ketene and olefin and degradation products were observed (Scheme 27).



R = Ph: 80°C, 6d, 59%. R = Ph, ultrasonication, 12h, 61%.
Scheme 27 R = H: 0°C - 23°C, 13h, 53%

A significant acceleration of the ketene reactivity could be achieved using electron-deficient species such as dichloroketene. Pombo-Villar described a rearrangement of optically pure *N*-phenethyl azanorbornene **135** to synthesize the α,α-dichloro-δ-valerolactam **138** [31]. At 0 °C in CH_2Cl_2, dichloroketene – generated in situ from dichloroacetyl chloride **136** and Hünig's base – was reacted with amine **135**. The addition step led to the hypothetical zwitterion **137**, which underwent immediate 3,3-sigmatropic rearrangement. The bicyclic enantiopure lactam **138** was obtained with 61% yield. Higher reaction temperatures led to tarry side products, and the yield was significantly decreased. The α,α-dichloro function of **138** could be reduced by means of Zn/NH_4Cl/MeOH to give the dechlorinated material **139**. Lactam **139** served as a starting material in a (–)-normethylskytanthine **140** synthesis (Scheme 28).

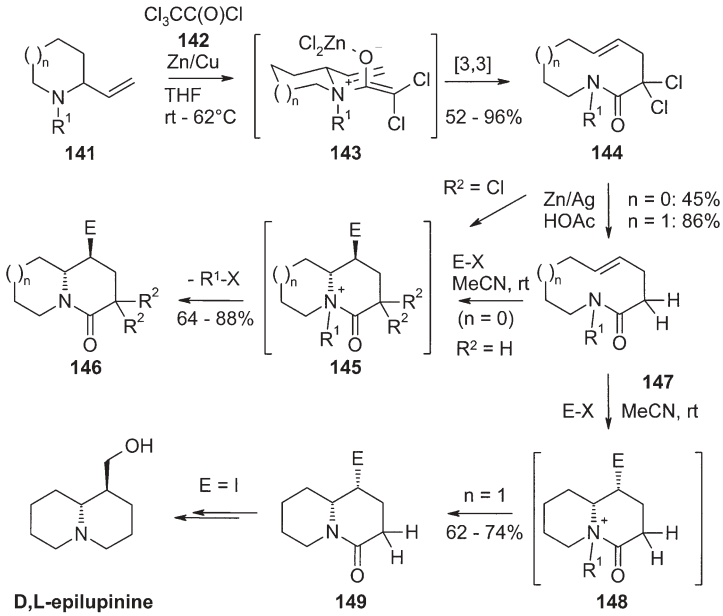
Edstrom used terminally unsubstituted 2-vinylpyrrolidine and piperidine, respectively, and dichloroketene to achieve the ring expansion to nine- and ten-membered lactams [32]. Starting from *N*-benzyl-2-vinylpyrrolidine (n=0) and piperidine (n=1) **141**, respectively, the ketene Claisen rearrangement using in situ generated dichloroketene led to the corresponding azoninone and azeci-



Scheme 28

none **144** (R^1=Bn) in 64 and 96% yield. Replacing the N protective group by the more electron-rich PMB substituent (R^1=PMB), the yields of **144** were observed to decrease to 52 and 54%, respectively. Here, Edstrom used trichloroacetyl chloride **142** and activated zinc to generate dichloroketene via a reductive dechlorination at 0 to 62 °C. Simultaneously, Lewis acidic $ZnCl_2$ was formed which might have activated the ketene and stabilized the zwitterionic intermediate **143** to support the rearrangement. Though the double bond included in the medium-sized ring was found to be exclusively *E* configured, both rearrangements suffered from a complete loss of chiral information because of the use of terminally symmetric substituted olefins in **141** (=CH_2) and ketenes **108** (=CCl_2, Acc=O) as reactants. The NMR spectra of the azecinone **144** (*n*=1) were characterized by the coexistence of two conformers. In contrast, the nine-membered ring **144** (*n*=0) was revealed as a single species. Both medium-sized lactams were used in transannular ring contractions to yield the corresponding quinolizidinones **146/149** (*n*=1) and indolizidinones **146** (*n*=0), respectively. The *E* double bonds suffered from an external attack of an electrophile (I^+, $PhSe^+$, Me_3Si^+) and the resultant onium ion underwent a regio- and stereoselective addition of the N center of the lactam to give an acylammonium salt **145**. Then, the benzyl group was removed (→**146**) by a von Braun-type degradation to form the corresponding benzyl halide. Surprisingly, the relative configuration of bridgehead hydrogen and the adjacent substituent were found to be *trans* on synthesizing quinolizidinones **149**. After dechlorination with Zn/Ag/HOAc to give the lactams **147**, the transannular ring contraction of the azoninone (*n*=0) took the expected path, generating indolizidinone **146** (R^2=H). In contrast, the analog reactions involving the azecinone **147** (*n*=1) gave bicyclus **149** by passing the hypothetical acylammonium ion **148** as a quasi-*syn* adduct of E and N at the double bond. Finally, the quinolizidinone **149** (*n*=1, E=I) were employed as a key intermediate in a total synthesis of D,L-epilupinine (Scheme 29, Table 7).

The mild reaction conditions and the obviously high potential driving force of the ketene Claisen rearrangement recommended the use of the process with more complex systems [33]. The first series of this type of reaction suffered from severe limitations (see Schemes 27–29, Fig. 3) [30–32]. On the one hand,



Scheme 29 n = 0, 1 R^1 = Bn, PMB, R^2 = H, Cl, E-X = PhSeCl, I_2, TMSI (Table 7)

Table 7 [28]

Entry	R^1	*n*	Yield (%) **144** (**147**)	Yield (%) **146** [**146**], (**149**)[a]		
				E=I	E=PhSe	E=TMS
1	Bn	0	64 (45)	88 [87]	79 [64]	72
2	PMB	0	52	–	–	–
3	Bn	1	96 (86)	85 (62)	84 (74)	–
4	PMB	1	54	–	–	–

[a] Yield: **146**: R^2=Cl, [**146**]: R^2=H, (**149**): R^2=H.

predominantly electron-deficient ketenes **108** added to the allylamines **103**, and useful yields of the amides were exclusively achieved by reacting dichloroketene [31, 32]. On the other hand, the rearrangement was restricted to either monosubstituted olefins in the amino fragment (**146**) or the driving force had to be increased by a loss of ring strain (**132**, **135**) during the process. The reaction path was rationalized as pointed out in Fig. 3. Initially, the ketene **108** was generated from a suitable precursor **150** (i.e., acid halide). Then, a reversible addition of the ketene **108** to allylamine **103** gave rise to the intermediate zwitterion **109**. Here, dichloroketene was found reactive enough to push the equilibrium toward adduct **109** and diphenylketene **131** was stable enough to

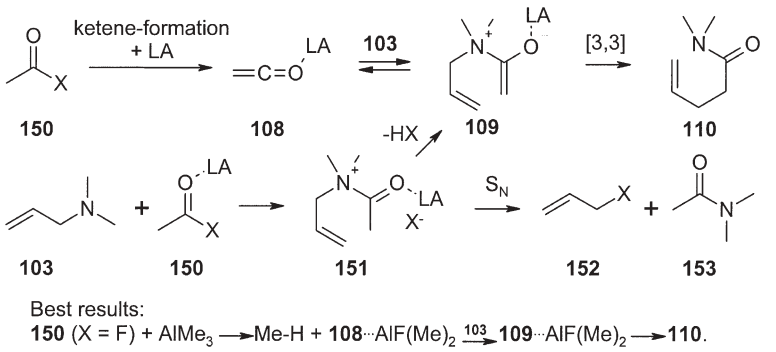


Fig. 3 Ketene Claisen rearrangements

survive several addition/elimination cycles without suffering from competing reactions (diketene formation, etc.). Finally, zwitterion **109** underwent the sigmatropic rearrangement to give amide **110** (Fig. 3). The careful analysis of a range of conversions indicated that two further competing processes have to be mentioned [33a,d]:

1. The tertiary amines **103** and the acid chlorides **150** (X=Cl) initially formed acylammonium salts **151**, which underwent a von Braun-type degradation by an attack of the nucleophilic chloride ion (X^-=Cl^-) at the allyl system to give allyl chlorides **152** and carboxylic acid amide functions **153** [34].
2. The reaction of acyl chlorides **150** led to the corresponding ketenes **108** while the allylamines **103** were deactivated as ammonium salts **103**-HCl (Schotten–Baumann conditions).

Three changes concerning the processing led to a pioneering surmounting of the limitations in converting allylamines **103** into the corresponding amides **110** [33a,d]:

1. Addition of stoichiometric amounts of a Lewis acid (LA), especially trimethyl aluminum to the reaction mixture. A range of α-substituted carboxylic acid halides **150** (X=Cl, F) as precursors of the ketenes **108** could be used, overcoming the restriction concerning the ketene component, but up to now, the rearrangement failed using α,α-difunctionalized carboxylic acid halides. The Lewis acid might have increased the acidity of the α-protons by interacting with the carbonyl group in **108**, **150**, and **151**, facilitating the formation of the intermediate zwitterions **109**, and/or the Lewis acid had stabilized the zwitterionic intermediate **109** suppressing the elimination of ketene **108**. Furthermore, allylamines **103** bearing 1,2-disubstituted double bonds could be successfully rearranged overcoming a restriction concerning the carbon framework [33a,b,d].
2. The replacing of the acyl chlorides **150** (X=Cl) by the corresponding acyl fluorides **150** (X=F) as the substituents of the ketenes **108**. The von Braun-

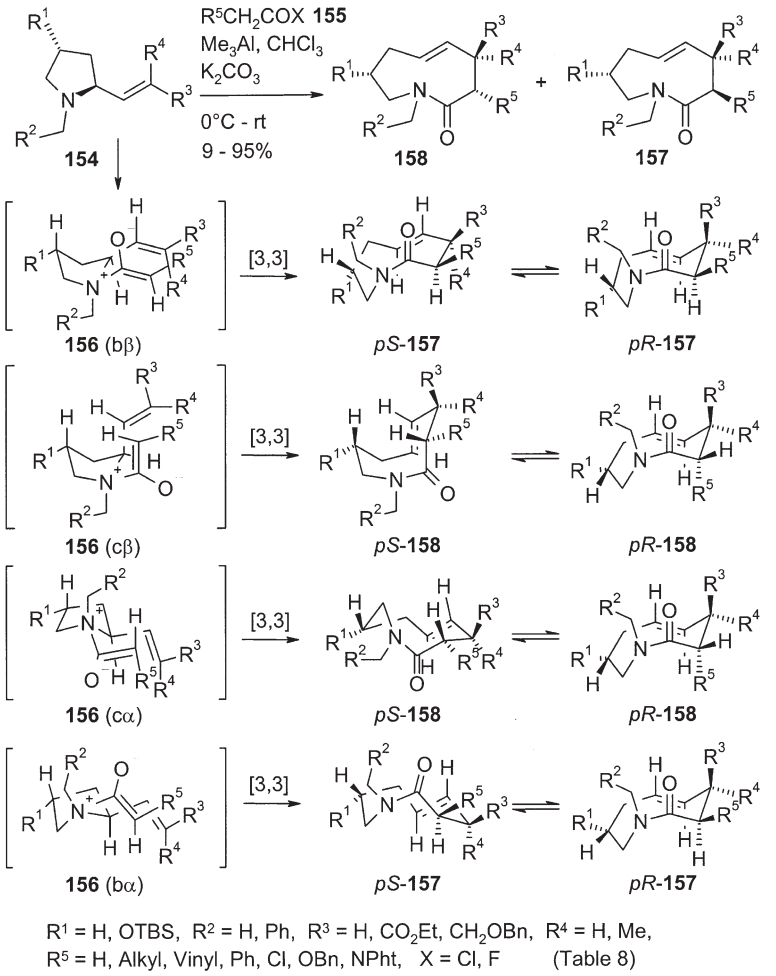
type degradation as the major competing reaction observed was efficiently suppressed. The fluoride counter-ion was known to be less nucleophilic but more basic. In the presence of trimethyl aluminum, the potential formation of a stable Al–F bond (F–$AlMe_2$, methane evolved) should have eliminated the fluoride as a latent nucleophile. The acyl fluorides **150** were found to be less reactive compared to the corresponding acid chlorides, causing some difficulties in the rearrangement with *n*-alkyl carboxylic acid derivatives. Such transformations needed longer reaction times, and the yield of the corresponding rearrangement products was moderate [33d,e].

3. The use of a second base to trap all proton acids generated during the course of the rearrangement. In most cases, a two-phase system of solid potassium carbonate as a suspension in dichloromethane or chloroform gave the best results, even though excessive HX formation during the course of the reaction could be avoided by employing the combination acid fluoride/Me_3Al (formation of methane and dimethylaluminum fluoride).

5.2.1 Stereochemical Results: 1,3-Chirality Transfer and Internal Asymmetric Induction

Employing the optimized reaction conditions upon running various reactions, the stereochemical advantages of the Claisen rearrangements were combined with an efficient synthesis of the azoninones **157** and **158** bearing defined *E*-configured double bonds in the medium-sized rings (Scheme 30) [33]. As is known for all Claisen rearrangements, a complete 1,3-chirality transfer was observed on treating *E*-allylamines **154** (R^1, R^4=H) with acetyl chloride **155** (R^5=H) [33a]. Both enantiomers of the core framework were constructed starting from the same L-(–)-proline derivative choosing either an *E* (R^4=H) or a *Z* (R^3=H) allylamine **154** [33f]. Furthermore, a high internal asymmetric induction could be observed involving α-substituted acyl halides **155** ($R^5 \neq$H) in the synthesis of the lactams. In most cases the diastereomeric excess was >5:1 in favor of the 3,4-*trans* lactam **156** (entries 4–14, Table 8). The phenylacetyl halide rearrangement (R^5=Ph, entry 7, Table 8) only gave a nearly equal mixture of *cis* and *trans* azoninones **157** and **158** (R^5=Ph). The stereochemical outcome of the rearrangement of **154** (R^1=H) was explained by the passing of a chair-like transition state **156** (cα) with minimized repulsive interactions and a defined *Z* enolate geometry (as is known for all amide enolates) [33b,d]. However the passing of the chair-like transition state **156** (cβ) could not be excluded: both **156** (cα) and (cβ) resulted in the same diastereomer *pS*-**158**!

Surprisingly, the rearrangement of the 4-*t*-butyldimethylsilyloxy-2-vinylpyrrolidines **154** (R^1=OTBS, R^3, R^4=H) took another course. The stereochemical outcome had to be rationalized by the passing of a boat-like transition state **156** (bβ) to give the 3,8-*trans* lactams **157** (R^1=OTBS, entries 15–19, Table 8). The corresponding *cis* product **158** (R^1=OTBS) resulting from the expected chair-like intermediate **156** (cβ) had only once been isolated as a minor compound



Scheme 30

(entry 17, Table 8). The completeness of the 1,4-chirality transfer should be pointed out [33]. Obviously, the configuration of the intermediately generated stereogenic ammonium center in **156** had to be considered: Rearranging the 2-vinylpyrrolidines **154** (R^1=H), the *N*-acylation should have been directed by the adjacent side chain to the opposite face of the five-membered ring to give **156** (*α*) (1,2-*anti* induction, as found analyzing appropriate acylammonium salts). Consequently, the rearrangement proceeded via a chair-like transition state **156** (c*α*), as known for the acyclic 3,3-sigmatropic reaction leading predominantly to lactams **158**. In contrast, the *N*-acylation of the 2,4-*trans* disubstituted pyrrolidines **154** (R^1=OTBS) were directed by the bulky silyl ether to generate a *syn* arrangement of vinyl and acyl group in an intermediate ammonium salt **156** (*β*) (1,3-*anti* induction, 1,2-*syn*). Then, an appropriate conformation to undergo a

Table 8 [33]

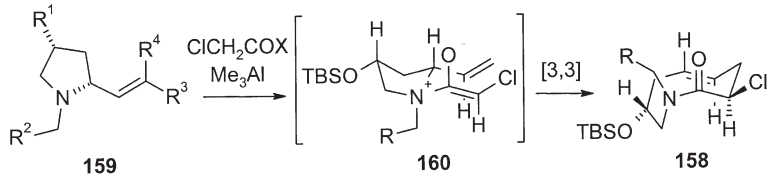
Entry	R^1	R^2	R^3	R^4	R^5	X	Yield (%)	Ratio **158:157**	Ref.
1	H	H	CO_2Et	H	H	Cl	70	–	a
		Ph				Cl	60		b
2	OTBS	H	CO_2Et	H	H	Cl	53	–	a
3	OTBS	H	CO_2Et[b]	H	H	Cl	47	–	a
4	H	H	CO_2Et	H	Me	Cl	77	>95:<5	b
		Ph[a]				F	73	>6:<1	d
5	H	Ph[a]	CO_2Et	H	CH_2CH_2Cl	F	51	>6:<1	d
6	H	H	CO_2Et	H	$CH{=}CH_2$	Cl	80	>95:<5	b
		Ph[a]				F	72	>3:>1	d
7	H	H	CO_2Et	H	Ph	Cl	32[c]	45:55	b
		Ph[a]				F	79	1:2	d
8	H	H	CO_2Et	H	Cl	Cl	72	>95:<5	b
		Ph				Cl	22	90:10	b
		Ph				F	81	90:10	d
9	H	H	CO_2Et	H	OBn	Cl	68	80:20	b
		Ph				Cl	30	80:20	b

[a] Rearrangement with acid chloride failed.
[b] Reaction with 2*R*-vinylpyrrolidine.
[c] Up to 50% of the reactant recovered.
[d] Only *pS*-diastereomers.

Table 8 (continued)

Entry	R^1	R^2	R^3	R^4	R^5	X	Yield (%)	Ratio **158:157**	Ref.
10	H	H	CO_2Et	H	NPht	Cl	35[c]	>94:<6	b
11	H	Ph	CH_2OBn	H	Cl	Cl	11	87:13	b
12	H	Ph[a]	H	Me	CH_2CH_2Cl	F	51	>6:1	d
13	H	Ph[a]	H	Me	Ph	F	87	1:>4	d
14	H	Ph	H	Me	Cl	Cl	9	1:1	d
						F	91	3:1	d
15	OTBS	H	H	H	Ph	Cl	17[c]	1:>10	c
		Ph				Cl	26[c]	1:>10	c
		Ph				F	95	1:>10	e
16	OTBS	H[b]	H	H	Cl	Cl	22	1:>10	c
17	OTBS	H	H	H	Cl	Cl	29[c]	1:>10	c
		Ph				Cl	20[c]	1:5	c
		Ph				F	92	1:>10	e
18	OTBS	Ph[a]	H	H	OBn	F	73	1:>10	e
19	OTBS	Ph	H	H	NPht	Cl	17	1:>10	c
20	H	Ph	H	H	Cl	F	77	1:1.4[d]	f

Claisen rearrangement presumably was the boat-like form **156** (bβ) with minimized 1,3 repulsive interactions resulting in the lactams **157**. However, the 2,4-*cis* disubstituted pyrrolidine **159** (R^1=OTBS, R^3, R^4=H) gave the expected lactam diastereomer **158** via a chair-like transition state conformation **160** (entry 16, Table 8) (Scheme 31).

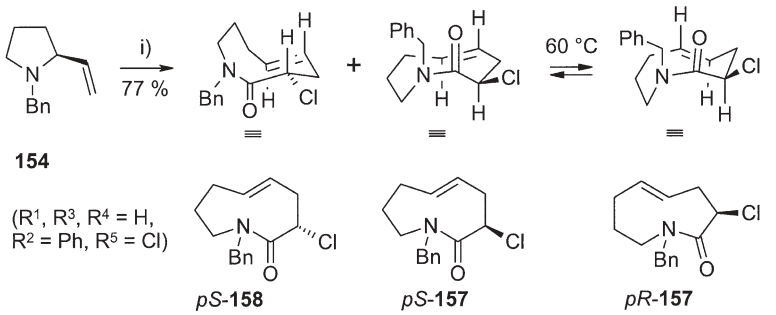


Scheme 31 R^1 = OTBS, R^2, R^3, R^4 = H, R^5 = Cl, X = Cl

The lactam and the olefin unit characterized the heterocyclic cores **157** and **158** as constrained ring systems, the conformations of which were found to be strongly dependent on the substitution pattern and the relative configuration of the stereogenic centers. The planar chiral properties of the medium-sized rings with internal *trans* double bonds had to be taken into account for analyzing the nine-membered rings [35]. The rearrangements of the 2*S*-vinylpyrrolidines **154** passing through a boat-like transition state **156** (b) effected initially the formation of the medium-sized ring with *pS* arrangement of the *E* double bond (*pS*-**157**). This planar diastereomer *pS*-**157** was obviously unstable: NMR and NOE analyses indicated the coexistence of one preferred *pS*-**157** and at least one additional minor conformation as a highly flexible equilibrium of some arrangements of the lactam function. Finally, the epimerization (flipping of the *E* double bond) to give the *pR* arrangement *pR*-**157** of the olefin with respect to the ring generated the most stable and rigid conformation. Preliminary force field calculations of the azoninones **157** and molecular mechanics calculations of the related *E*/*Z*-1,5-nonadiene confirmed these observations [36]. In contrast, the lactams **158** (R^4=H) generated via chair-like zwitterions **156** (c) were found to be generated directly in a stable *pS* arrangement of the *E* double bond *pS*-**158** (Schemes 30, 31). Nevertheless, a high activation barrier had to be passed to achieve the change of the planar chiral information (*pS*-**157**→*pR*-**157**). This fact allowed the isolation and the characterization of the conformers of the nine-membered rings (Schemes 30, 31) [33c,e,f].

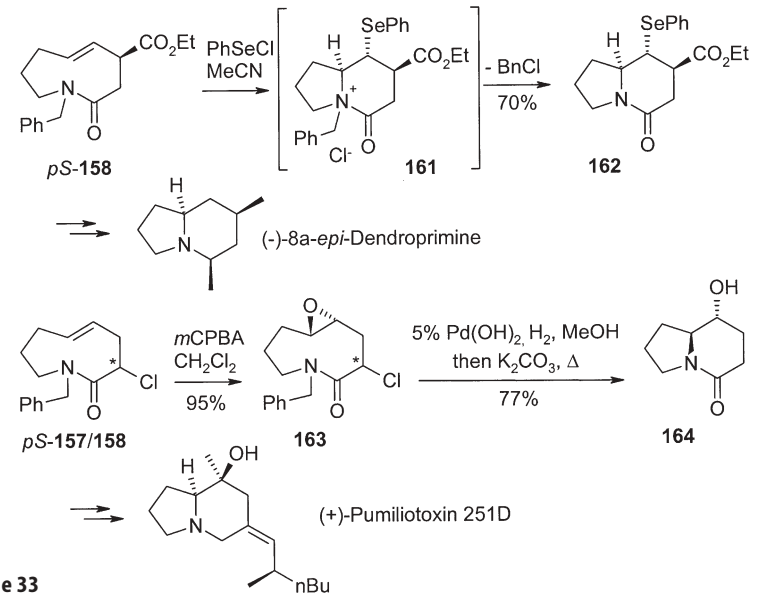
The proof of principle gave the aza-Claisen rearrangement of vinylpyrrolidine **154** (R^1, R^3, R^4=H, R^2=Ph) and chloroacetyl fluoride **155** (R^5=Cl) under standard conditions. A mixture of two diastereomers *pS*-**157** and *pS*-**158** was obtained in 77% yield and a ratio of 1.4:1, which could be separated by means of column chromatography and preparative HPLC. On handling these compounds, any warming up to 30–40 °C was avoided to maintain the planar chiral properties (*pS*) of the diastereomers resulting from the ring expansion. For testing the conformational stability of both compounds, the separated dia-

stereomers *pS*-**157** and *pS*-**158** were heated to about 60 °C [37]. After 3 to 10 h a second diastereomer *pR*-**157** occurred starting from *pS*-**157**, indicating the flipping of the double bond with respect to the ring. All spectral data of the new diastereomer *pR*-**157** were identical with those determined for lactam *pS*-**158** except the specific rotation proving the formation of the enantiomer. Lactam *pS*-**158** suffered the analogous process generating *pR*-**158** (enantiomer of *pS*-**157**), but the conversion was found to be incomplete. The relative arrangement of the double bond and the stereogenic center of the diastereomers was proven via NOE analyses. While the lactam *pS*-**158** was characterized by a single set of peaks (almost rigid conformation), the spectral data of lactam *pS*-**157** indicated the coexistence of two conformers (double set of peaks in ^{1}H and ^{13}C spectra) potentially originating from some mobility of the lactam function (Table 8, entry 20) (Scheme 32) [33f].



Scheme 32

The azoninones **157** and **158** with defined stereochemical properties served as key compounds in natural product syntheses. Firstly, the planar chiral information was used to generate stereospecifically new stereogenic centers depending on the defined conformation of the nine-membered rings [38]. Upon treatment of p*S*-**158** (R^1, R^4, R^5=H, R^2=Ph, R^3=CO_2Et) with PhSeCl in MeCN, the *anti* addition of $[PhSe]^+$ and the lactam lone pair to the double bond gave an intermediate acylammonium ion **161**, which suffered from immediate von Braun degradation to form benzyl chloride and the indolizidinone **162** as a single regio- and stereoisomer (ring contraction) with 70% yield. Several further steps allowed completion of a total synthesis of (–)-8-*epi*-dendroprimine [38a]. A mixture of p*S*-**157**/p*S*-**158** (R^1, R^3, R^4=H, R^2=Ph, R^5=Cl) was epoxidized by means of MCPBA to give the diastereomeric mixture of epoxy azonanones **163** with defined epoxide configuration (stereospecific cycloaddition). Chlorine and benzyl groups were removed by hydrogenation using Pearlman's catalyst to give a single hydroxyindolizidinone **164** after regio- and stereoselective intramolecular oxirane opening. Several further transformations enabled completion of a (+)-pumiliotoxin 251D synthesis (Scheme 33) [38b,c].



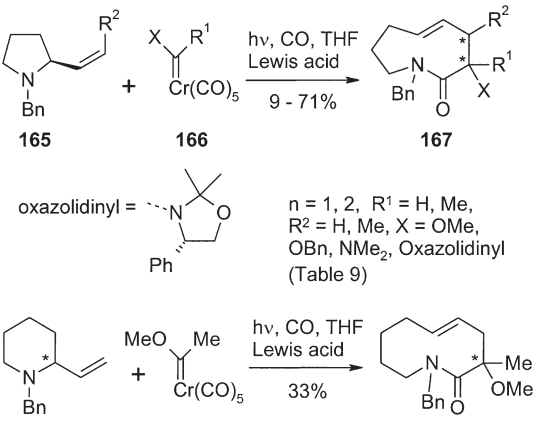
Scheme 33

An alternative pathway using a zwitterionic aza-Claisen rearrangement to generate azoninones was described by Hegedus [39]. 2-Vinylpyrrolidines **165** and chromium carbene complexes **166** underwent photochemical reactions in the presence of a Lewis acid to give the corresponding nine-membered ring lactams **167** bearing *E* double bonds in up to 71% yield. Though reactants and products suffered from some instability against Lewis acids, the presence of the zinc chloride or dimethylaluminum chloride was mandatory to start the rearrangement. In contrast to the classical ketene Claisen process, electron-rich ketene equivalents such as alkoxy or amino ketenes could be used, since the donor substituents stabilized the chromium carbene complex **166**. Furthermore, α,α-disubstituted lactams were synthesized but the stereoselectivity observed was low. The determination of the stereochemical outcome of the reaction proved that the 1,4-chirality transfer was not complete: a Mosher analysis of an appropriate azoninone gave a loss of about 10% of the chiral information. A chiral carbene complex **166** (R^1=oxazolidinyl) was found to have a negligible influence on the stereoselectivity of the rearrangement. Generally, the present variant of the rearrangement was found to be very sensitive to any steric hindrance. Additional substituents in any position (e.g., $R^2 \neq H$) led to a severe decrease of the yield and the stereoselectivity. Additionally, one example rearranging a 2-vinylpiperidine **168** was given. The corresponding azecinone **169** was formed in about 33% yield (Scheme 34). Some details are outlined in Table 9. In analogy to Edstrom's experiments [32], the nine- and ten-membered ring lactams **167** and **169** underwent regio- and stereoselective transannular ring contractions to give the corresponding indolizidinones and quinolizidinones, respectively (*vide supra* Scheme 29) (Scheme 34, Table 9).

Table 9 [39]

Entry	*n*	R^1	X	R^2	Lewis acid	Yield (%)	Ratio **167/169**
1	1	Me	OMe	H	$ZnCl_2$	71	–
2	1	Me	OBn	H	$ZnCl_2$	66	62% de[b]
3	1	$-(CH_2)_3-O-$		H	$ZnCl_2$	15	–
					Me_2AlCl	22	
4	1	H	NMe_2	H	Me_2AlCl	9	–
5	1	H	Oxazolidine[a]	H	$ZnCl_2$	19	74% de[b]
6	1	Me	OMe	Me	$ZnCl_2$	20	60% de[c]
7	1	Me	OBn	Me	$ZnCl_2$	40	33% de[c]
8	2	Me	OMe	H	Me_2AlCl	33	–

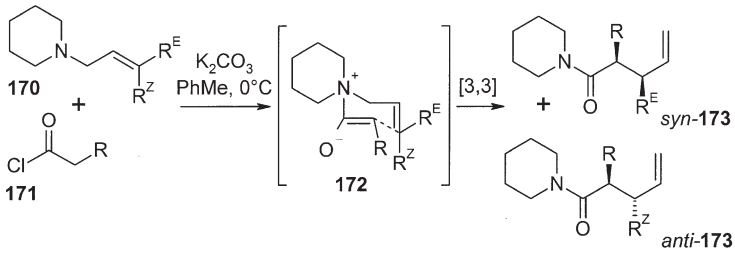
[a] Chiral oxazolidine.
[b] Determined via Mosher analysis of a derivative.
[c] Mixture of 3,4 diastereomers.



Scheme 34

First systematic efforts to investigate the internal asymmetric induction of ketene Claisen rearrangements have been published by Yu [40]. Some simple *E* and *Z N*-crotylpiperidines **170** were treated with propionyl, methoxyacetyl, and fluoroacetyl chloride **171**. Renouncing Lewis acid support, the reactants were combined in toluene at 0 °C in the presence of solid K_2CO_3 as a proton acceptor (Schotten–Baumann conditions). The piperidides **173** were isolated in 38–61% yield. The formation of side products (von Braun degradation) was not reported. All reactions were found to be highly diastereoselective. The stereochemical outcome could be rationalized by the initial formation of the zwitterion **172** with a defined double bond and a defined *Z*-ammonium enolate geometry because of steric and/or electronic reasons. The passing of a chair-like transition state gave rise to the formation of the *anti* product, *anti*-**173**,

starting from *Z*-**170** and the *syn* product, *syn*-**173**, starting from *E*-crotylpiperidine *E*-**170**. Alternatively, the use of the corresponding crotylpyrrolidines and the employment of in situ formed propionyl bromide gave somewhat lower yields and diastereoselectivities (Scheme 35).



E-**170**: R = Me (41% yield, *syn*/*anti* = 94:6), R = OMe (44%, 92:8), R = F (61%, 95:5)
Z-**170**: R = Me (38% yield, *syn*/*anti* = 3:97), R = OMe (39%, 5:95), R = F (57%, 4:96)

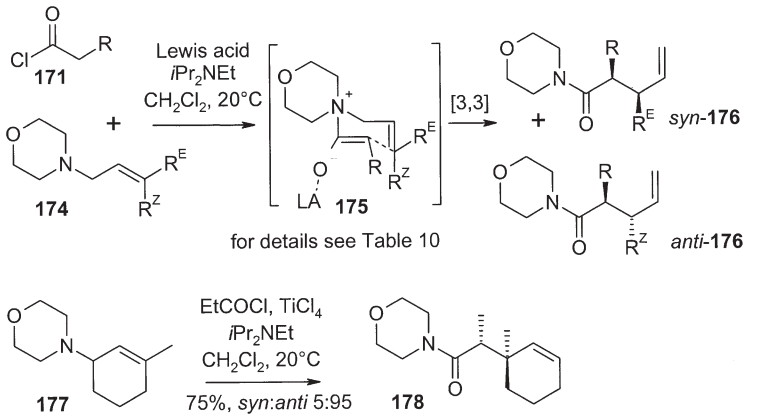
Scheme 35

A more recent systematic investigation of the internal asymmetric induction in ketene Claisen rearrangement was contributed by MacMillan [41]. *E* and *Z* *N*-allylmorpholine derivatives **174** were reacted with acid chlorides **171** in the presence of Hünig's base supported by 5 to 20 mol% of a Lewis acid (Einhorn conditions). The product *γ*,*δ*-unsaturated morpholine amides **176** were obtained with 70 to 95% yield. The conditions reported indicate the presence of a high concentration of nucleophilic chloride ions in the reaction medium. Though acid chlorides and tertiary amines tend to a rapid formation of *N*-acylammonium salts, even in the presence of substoichiometric amouts of a Lewis acid, no von Braun degradation-generating allyl chlorides and carboxylic acid morpholine amides were mentioned (Fig. 3). Best results were achieved running the rearrangement in the presence of $Yb(OTf)_3$, $AlCl_3$, and $TiCl_4$. As expected, a very high internal asymmetric induction was found in most experiments. Compared to the *Z* amine *Z*-**174** resulting in *anti*-**176** as the major compound, the corresponding *E*-configured reactants *E*-**174** gave somewhat higher yields and diastereoselectivities forming predominantly the *syn* amides *syn*-**176**. In accordance with previous reports the use of *α*-alkyloxyacetyl chlorides caused decreased diastereoselectivities of 86:14 to 90:10 [33, 43]. The stereochemical outcome could be rationalized by the intermediate formation of the zwitterion **175** with *Z* enolate geometry, which rearranged passing a chair-like transition state to give the desired product **176**. Furthermore, new quaternary carbon centers could be built up by means of the present protocol. The rearrangement of 3-ethyl-3-methyl-substituted allylamine *E*-**174** allowed generation of the corresponding amide *syn*-**176** with 72% yield and 99:1 *syn* selectivity (Table 10, entry 14). The cyclohexenylamine **177** could be converted into the amide **178** with 75% yield and 99:1 *syn* diastereoselectivity, too (Table 10, entry 15). Detailed information is outlined in Table 10 (Scheme 36).

Table 10 [41a]

Entry	R^E	R^Z	R	Lewis acid	Mol%	Yield (%)	Ratio *syn*:*anti*
1	Me	H	Me	$Yb(OTf)_3$	10	80	99:1
2	Me	H	Me	$AlCl_3$	10	90	99:1
3	Me	H	Me	$Ti(iOPr)_2Cl_2$	10	76	99:1
4	Me	H	Me	$TiCl_4$·2 THF	5	92	99:1
5	Ph	H	Me	$TiCl_4$·2 THF	10	76	99:1
6	Cl	H	Me	$TiCl_4$·2 THF	10	95	99:1
7	H	H	Me	$TiCl_4$·2 THF	10	95	–
8	H	Me	Me	$TiCl_4$·2 THF	20	74	5:95
9	Me	H	NPht	$TiCl_4$·2 THF	10	77	99:1
10	Me	H	SPh	$TiCl_4$·2 THF	10	81	92:8
11	Me	H	OBn	$TiCl_4$·2 THF	10	91	86:14
12	Cl	H	OBn	$TiCl_4$·2 THF	10	83	90:10
13	H	Cl	OBn	$TiCl_4$·2 THF	10	70	90:10
14	Et	Me	Me	$TiCl_4$·2 THF	10	72	99:1
15	Me	R[a]	Me	$TiCl_4$·2 THF	10	75	5:95

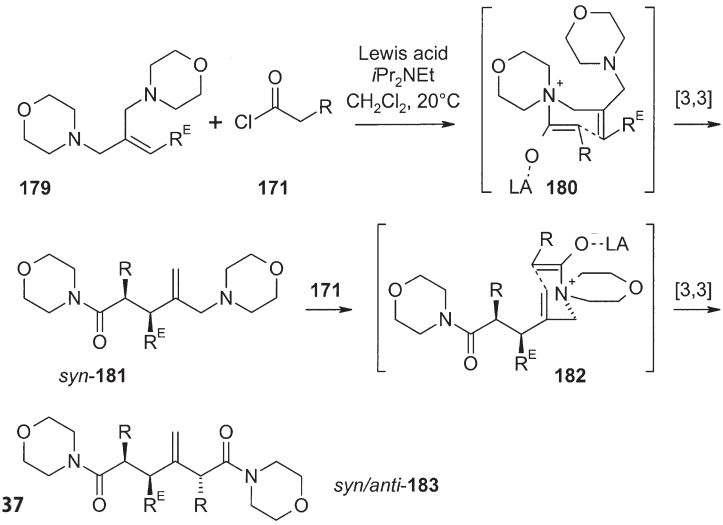
[a] Reactant **177**, product **178**.



Scheme 36

The present protocol enabled tandem ketene aza-Claisen rearrangements to be run [41b]. The reaction of allyl systems **179** bearing two allylamine fragments gave the corresponding diamides **183** with high yield and high simple diastereoselectivity as well as an excellent 1,3-asymmetric induction. The amount of Lewis acid had to be increased to about 200 to 400 mol%. The process was explained by two consecutive sigmatropic rearrangements. In the first step, the *E*-allylmorpholine moiety of **179** reacted with the ketene fragment from **171** passing the zwitterionic intermediate **180** displaying the well-known

Z-enolate geometry. The chair-like transition state gave rise to the formation of the *syn* intermediate *syn*-**181**. Then, the newly generated allyl morpholine in **181** suffered from a second rearrangement. The addition of another acid chloride **171** led to the zwitterion **182**, which was immediately transformed into the diamide *syn*/*anti*-**183**, passing a chair-like conformation with minimized repulsive interactions. High yields of 71 to 99% were reported; in most runs one major diastereomer could be detected with >92:8 diastereoselectivity. Detailed information is given in Table 11 (Scheme 37).



Scheme 37

Table 11 [41b]

Entry	R^E	R	Lewis acid	Mol%	Yield (%)	Ratio *syn*/*anti*:*anti*/*anti*
1	Me	Me	$Yb(OTf)_3$	200	97	98:2
2	Me	Me	$AlCl_3$	200	93	64:36
3[a]	Me	Me	MgI_2	400	70	98:2
4	Me	Me	$TiCl_4$·2 THF	200	93	98:2
5	Cl	Me	$Yb(OTf)_3$	200	98	99:1
6	OBz	Me	$Yb(OTf)_3$	200	86	91:9
7	CN	Me	$TiCl_4$·2 THF	200	78	97:3
8	SPh	Me	$TiCl_4$·2 THF	200	70	93:7
9	Me	Bn	$Yb(OTf)_3$	200	99	92:8
10	Me	NPht	$Yb(OTf)_3$	200	98	95:5
11	Me	OPiv	$TiCl_4$·2 THF	200	97	97:3
12	Cl	OPiv	$TiCl_4$·2 THF	200	84	95:5
13	OBz	OPiv	$TiCl_4$·2 THF	200	71	92:8

[a] Reaction at –20°C.

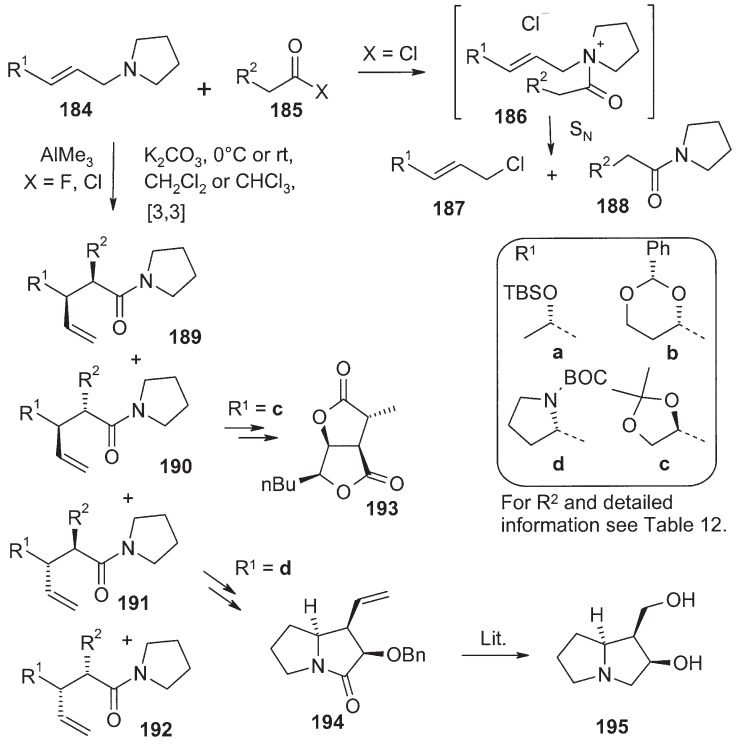
5.2.2
Stereochemical Results: External Asymmetric Induction/Remote Stereocontrol

The low reaction temperatures of the zwitterionic ketene aza-Claisen rearrangements recommended the process for further testing of the stereodirecting properties. An efficient external chiral induction within the addition rearrangement sequence requires not only a highly ordered transition state of the six core atoms, but also a defined arrangement of the external chiral subunit with respect to the rearrangement framework. Always, a single defined transition-state conformation causes a highly selective reaction [41b]. With the intention of achieving a maximal asymmetric induction via remote stereo control, the chiral information should predominantly be placed next to the nascent sigma bond formed during the course of the rearrangement and carrying the new chiral centers. A stereogenic center in the allylamine moiety adjacent to C3 fulfilled such a prerequisite. Particularly, defined C atom–heteroatom bonds offer the advantage of being potential excellent stereodirecting subunits. Since the electron-rich 1,2-vinyl double bond should attack the allyl system at position 6, an adjacent C–X (nucleophilic X) bond should adopt an *anti* arrangement with respect to the incoming donor. In other words, the extended C–X–σ^* orbital is *syn* coplanar positioned with respect to the attacking vinyl double bond. The transition state is stabilized by an additional delocalizing of some electron density in the empty *anti* binding orbital. Such weak electronic effects have been successfully used in ketene thia-Claisen rearrangements [42].

Allylamines **184** bearing an additional chiral center adjacent to C6 (R^1=**a**–**d**) were efficiently synthesized via short ex-chiral pool sequences starting from D-mannitol (→**c**), L-malic (→**b**), L-lactic acid (→**a**), and L-proline (→**d**) [43]. The treatment of such allylamines **184** with acid chlorides **185** (X=Cl), even in the presence of several Lewis acids (Me_2AlCl, $MeAlCl_2$, $ZnCl_2$, $TiCl_4$, $SnCl_4$, $Yb(OTf)_3$, etc.), suffered from the formation of varying amounts of von Braun degradation products **187** and **188** among the desired γ,δ-unsaturated amides **189**–**192**. The nucleophilic attack of the chloride at the intermediately formed acylammonium salt **186** sometimes predominated. Subjecting the allylamines **184** to α-monosubstituted acid halides **185** in the presence of Me_3Al, the desired rearrangement got the upper hand. Conducting the reaction at 0 °C in a two-phase system of CH_2Cl_2 and K_2CO_3, the degradation could be almost suppressed depending on the substitution pattern in **184** and **185**. Finally, the use of carboxylic acid fluorides **185** (X=F) in the presence of Me_3Al enabled the process to be run in the absence of nucleophiles [33d]. Since then, allyl halides **187** have not been found any more. Analyzing the stereoselection properties of the conversion to **189**–**192**, the 1,2-asymmetric induction was found to be mostly >90:10 in favor of the *syn* product – even in the presence of the nitrogen as directing function. The minor *anti* diastereomer only occurred in appreciable amounts if acetyl chloride **185** (R^2=H) was used as C2 source. Furthermore, the simple diastereoselectivity (internal asymmetric induction) was high, allowing the diastereoselective generation of two new stereogenic centers in a single step

bearing a variety of functional groups. The *γ,δ*-unsaturated amides **189–192** formed represented useful intermediates for natural product total syntheses, as demonstrated by completing the synthesis of (+)-dihydrocanadensolide **193** [43b] and the formal synthesis of (–)-petasinecin **194** (**195**=petasinecin) (Scheme 38) [33d]. Detailed information is summarized in Table 12.

The stereochemical outcome of the reaction could be explained by the passing of a clearly preferred transition state. Generally, the ketene equivalent (from **185**) and the allylamine **184** (R^1: **c**) combined to form a hypothetical intermediate acylammonium enolate with a defined *Z*-enolate geometry (in *b*-**189**, *c*-**190**, *c*-**191**), as is known for amide and acylammonium enolates. Adopting the chair-like conformations *c*, the *anti* arrangement of the attacking enolate and the guiding heteroatom (N and O at C6a) favored *c*-**190** facing *c*-**191**; the *anti*/*syn* product **190** was isolated as the major compound. Surprisingly, R^2 substituents characterized by extended Π-systems led to the *syn–syn* products **189** selectively. Here, the high remote stereocontrol must involve an alternative boat-like transition state conformation *b*-**189**. In Fig. 4 the hypotheses concerning **184** (R^1: **c**) are outlined. With respect to the inverted configuration of the directing center adjacent to C6 in **184** (R^1: **a**, **b**, **d**), **189–192** (R^1: **a**, **b**, **d**), the enantiomer stereotriads were formed.



Scheme 38

Table 12 [43]

Entry	R^1	R^2	X	Yield (%)	Ratio **189/190/191/192**	Ref.
1	**a**	H	Cl	84	–:1:2:–	a
2	**a**	Me	Cl	73	<1:<1:>15:<1	a
3	**b**	H	Cl	80	–:4:7:–	a
4	**b**	Me	Cl	74	<1:1:10:<1	a
5	**c**	H	Cl	82	–:3:2:–	a
6	**c**	Me	Cl	77	<1:9:1:<1	a
7	**c**	$ClCH_2CH_2$	Cl	74	3:7:<1:<1	b
8	**c**	*i*Pr	Cl	45	<1:97:<1:<1	b
9	**c**	$H_2C{=}CH$	Cl	62	<1:97:<1:<1	b
10	**c**	$H_2C{=}CH{-}CH{=}CH{-}$	Cl	60	97:<1:<1:<1	b
11	**c**	Ph	Cl	52	97:<1:<1:<1	b
12	**c**	Cl	Cl	82	2:96:<1:<1	b
13	**c**	OBn	Cl	83	9:86:<1:4	b
14	**d**	Me	F	78	<1:<1:>97:<1	c
15	**d**	Ph	F	85	<1:<1:>97:<1	c
16	**d**	Cl	Cl	24	<1:<1:>97:<1	c
17	**d**	Cl	F	76	<1:<1:>97:<1	c
18	**d**	OBn	F	68	<1:<1:>97:<1	c

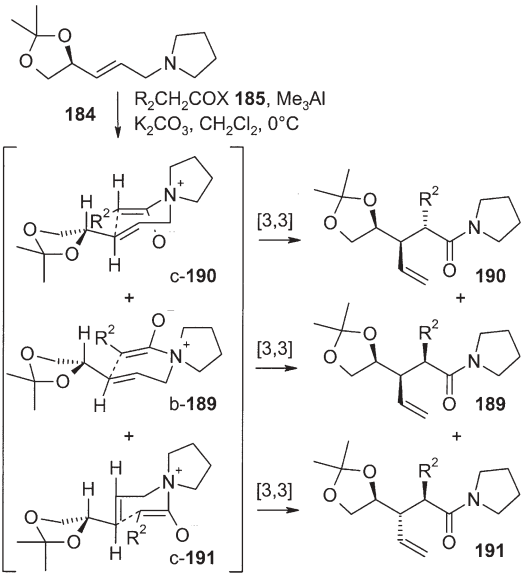


Fig. 4 Formation of enantiomer stereotriads of **184**

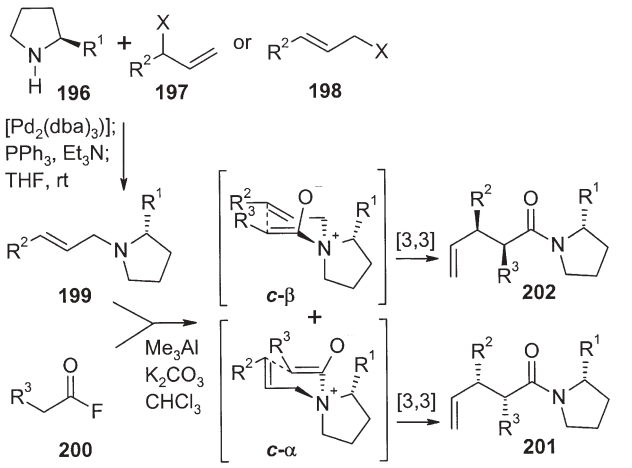
5.2.3
Stereochemical Results: External Asymmetric Induction/Auxiliary Control

Auxiliary-controlled 3,3-sigmatropic rearrangements represent an almost classical approach to introducing chiral information into a more complicated rearrangement system. The major advantage is a reliable control of the stereochemical outcome of the reaction. All products are diastereomers, e.g., the separation of minor compounds should be more or less easy and the well-known spectroscopic analyses will always be characterized by defined and reproducible differences. However, the auxiliary strategy requires two additional chemical transformations: the attachment and the removal of the auxiliary must be carried out in two steps. The efficiency of these steps influences the whole sequence. High yields and the avoiding of stereochemical problems are the prerequisites of each step. Furthermore, the synthesis and the recycling of an auxiliary have to be taken into account. Overall, a set of advantages and problems has to be considered before deciding on an auxiliary strategy.

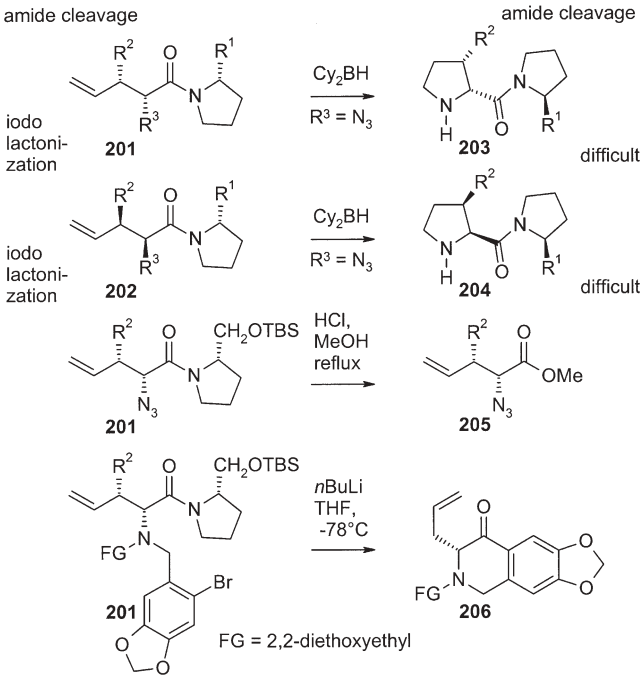
An aza-Claisen rearrangement enables a chiral auxiliary to be attached to the central nitrogen via the third binding valence next to the 3,3-sigmatropic framework. In analogy to the remote stereocontrol prerequisites mentioned above, a low reaction temperature was crucial to guarantee a restrained conformational mobility of the potential transition state. The system should be forced to take a single reaction path for obtaining a high diastereoselectivity.

The zwitterionic aza-Claisen rearrangement seemed to fulfill these prerequisites using L-(–)-proline derivatives **196** as chiral auxiliaries [44]. Several *N*-allyl pyrrolidines **199** were synthesized via a Pd(0)-catalyzed amination of the corresponding allyl mesylates **197** and **198.** Always, the double bond was *E* configured. The treatment with chloro and suitably protected α-amino acetyl fluorides **200** in the presence of solid K_2CO_3 and trimethyl aluminum in $CHCl_3$/0 °C led to the formation of the corresponding γ,δ-unsaturated amides **201** and **202.** Again, the charge neutralization served as an efficient driving force allowing the reactions to be conducted at such low temperatures. Especially, the use of azido acetyl fluoride **200** (R^3=N_3) enabled a subsequent reductive cyclization to generate D-proline/L-proline dipeptides **203**, allowing introduction of varying substituents in the new D-proline moiety (Schemes 39, 40, Table 13).

The removal strategy of the auxiliary should be chosen depending on the auxiliary and the substitution pattern of the amide **201/202.** Generally, the iodo lactonization as described by Tsunoda [22] and Metz [45] led to smooth cleavages of all types of amides. In particular, the prolinol auxiliaries (R^1=CH_2OTBS) offered further advantages. In the presence of acid-stable substituents R^2 and R^3, a neighboring group-assisted esterification (R^1=CH_2OTBS) with HCl/MeOH allowed conversion of the amides **201** into the corresponding esters **205.** Alternatively, the auxiliary can be used as a leaving group in an intramolecular metal organic reaction of **201** (R^3=CH_2–Ar–Br) to generate a cyclic ketone **206** without any loss of the chiral information (Scheme 40).



Scheme 39



Scheme 40

Discussing the stereochemical outcome of the Claisen rearrangements, two aspects had to be considered. On the one hand, the relative configuration of the new stereogenic centers was found to be exclusively *syn* in **201** and **202**, pointing out the passing of a chair-like transition state ***c*-α** and ***c*-β**, respectively, including a *Z*-acylammonium enolate structure (complete simple diastereoselectivity/internal asymmetric induction).

Table 13 [44]

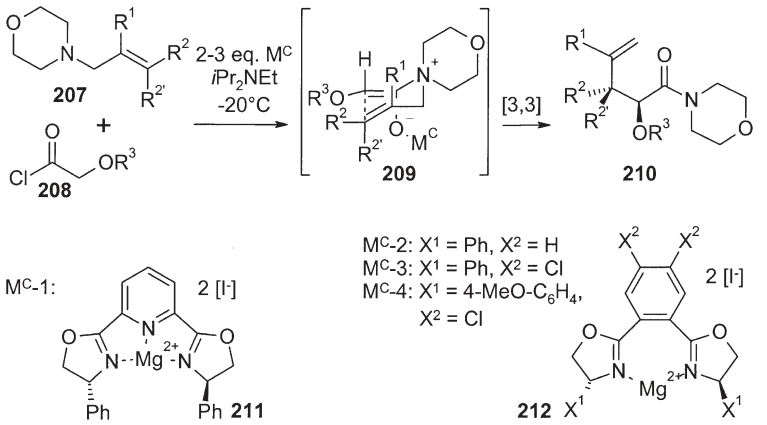
Entry	R^1	R^2	R^3	*T* (°C)	Yield (%)	Ratio **201/202**	Ref.
1	H	3,4-Methylenedioxyphenyl	Cl	0	36[a]	1:1	a
2	CO_2Me	3,4-Methylenedioxyphenyl	Cl	0	69	2:1	a
3	CO_2tBu	3,4-Methylenedioxyphenyl	Cl	0	50[a]	>95:5	a
4	CH_2OTBS	3,4-Methylenedioxyphenyl	Cl	0	72	>95:5	a
5	CO_2Me	3,4-Methylenedioxyphenyl	N_3	0	77	4:1	a
6	CO_2Me	4-Methoxyphenyl	N_3	0	13[a]	1:1	a
7	CH_2OTBS	3,4-Methylenedioxyphenyl	N_3	0	87	>95:5	a
8	CH_2OTBS	4-Methoxyphenyl	N_3	0	57	>95:5	a
9	CH_2OTBS	Ph	N_3	0	91	>95:5	a
10	CO_2Me	H	NPht	0	74	1:1	b
11	CO_2Me	H	N_3	20	77	4:1	b
12	CO_2Me	H	N_3	0	77	7:1	b
13	CO_2Me	H	N_3	–20	77	9.5:1	b
14	CO_2Me	H	$(EtO)_2CHCH_2NBOC$	20	73	15:1	b
15	CH_2OTBS	H	N_3	0	77	>95:5	b
16	CH_2OTBS	H	HNBOC	0	6	–	b
17	CH_2OTBS	H	$(EtO)_2CHCH_2NBn$	0	0	–	b
18	CH_2OTBS	H	$(EtO)_2CHCH_2NBOC$	0	51[b]	>95:5	b
19	CH_2OTBS	H	$(EtO)_2CHCH_2NCbz$	0	75	>95:5	b
20	CH_2OBn	H	$(EtO)_2CHCH_2NBOC$	0	47[b]	>95:5	b

[a] Not optimized.
[b] Yield including four further steps.

On the other hand, the external asymmetric induction strongly depended on the chiral auxiliary. The careful analysis of the hypothetical zwitterionic intermediates ***c*-α** and ***c*-β** indicated the formation of a stereogenic ammonium center. In terms of the well-known 1,3-chirality transfer of 3,3-sigmatropic rearrangements, the present reaction allowed the chiral information to be shifted from the ammonium center (1) to the enolate C (3). The amide **201/202** α-carbon atom had been built up with a defined configuration after passing the above-mentioned chair-like transition state ***c*-α/*c*-β**, including a defined olefin geometry and the equatorial arrangement of the bulky (chain branch) part of the auxiliary. Consequently, the crucial step of the whole process must have been the diastereoselective addition of the ketene equivalent from **200** on generating the zwitterionic intermediates. Thus, employing the auxiliaries bearing the small proline methyl ester substituent (R^1=CO_2Me) in **199**, the reaction with nonhindered acid fluorides **200** gave the corresponding amides **201/202** with low or moderate diastereoselectivity indicating unselective *N*-acylation. In contrast, conversions at lower temperatures or with bulky substituted acid fluorides **200** resulted in significantly higher selectivities (more selective acylation). The use of reactant allylamines **199** bearing the bulky proline *tert*-butyl ester and the OTBS prolinol auxiliaries as R^3 was characterized by a high auxiliary-directed diastereoselectivity, indicating the passing of a defined acylation rearrangement path via ***c*-α**. At present, the OTBS prolinol (R^1=CH_2OTBS) is the auxiliary of choice because of the easy introduction, the high auxiliary-directed induction of chirality, the stability against a set of consecutive processes, and the simple cleavage by the neighboring group-assisted amide **201**–ester **205** conversion. Detailed information is summarized in Table 13 (Schemes 39, 40). The zwitterionic aza-Claisen rearrangement has been developed as a reliable method for synthesizing suitably protected nonnatural α-amino acid derivatives, e.g., C-allyl glycines type **205** and 3-arylprolines type **203**.

The major disadvantage of the classical auxiliary-controlled 3,3-sigmatropic rearrangements is still the requirement of two additional chemical transformations: the attachment and the removal of the auxiliary had always to be considered. The efficiency of these steps influences the usability of the whole sequence.

Since coordination of the Lewis acid metal salt at the core heteroatoms of the 3,3-sigmatropic system was found to accelerate the process, the proximity of the Lewis acid ligands should allow one to influence the stereochemical outcome of the rearrangement. Hence, the use of chiral ligands should cause an external chiral induction. In conclusion, a Lewis acid carrying chiral ligands should serve as a chiral auxiliary. The separate attachment and the final removal of the auxiliary could be saved, and the enantioselective Claisen rearrangement arose as a more straightforward process. Generally, such a reaction should be run in a catalytic sense, but the increased complexation ability of the product in comparison to the reactants mostly inhibited the release of the Lewis acid right after a rearrangement step until the aqueous cleavage. It is understood that the stereochemical properties of the products had to be carefully analyzed using chiral GC, HPLC, and derivatization techniques.



Scheme 41 For detailed information including R^1 - R^3 see Table 14

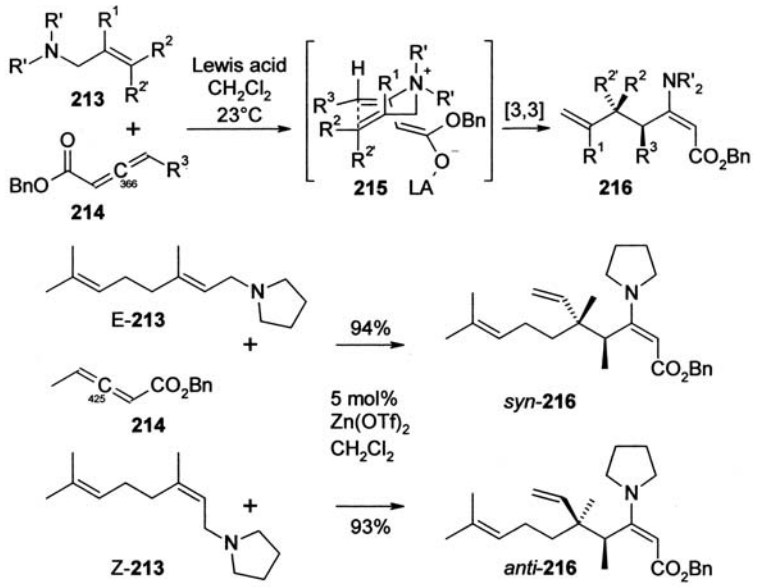
Table 14 [46]

Entry	R^1	R^2	$R^{2'}$	R^3	Eq. (M^C)	Yield (%)	de (%)	ee (%)
1	H	H	H	Bn	–	42	–	–
2	H	H	H	Bn	2.0 (1)	87	–	56
3	H	H	H	Bn	2.0 (2)	88	–	83
4	H	H	H	Bn	2.0 (3)	65	–	86
5	H	H	H	Bn	0.5 (4)	81	–	42
6	H	H	H	Bn	1.0 (4)	63	–	81
7	H	H	H	Bn	2.0 (4)	80	–	91
8	H	H	H	Ac	2.0 (4)	44	–	37
9	H	H	H	TBS	2.0 (4)	67	–	38
10	H	H	H	4-Cl-Ph	2.0 (4)	59	–	71
11	H	H	H	Ph	2.0 (4)	48	–	78
12	H	H	H	Me	2.0 (4)	28	–	80
13	Me	H	H	Bn	3.0 (4)	78	–	91
14	Ph	H	H	Bn	3.0 (4)	79	–	90
15	H	CH_2OBz	H	Bn	3.0 (4)	86	84	86
16	H	4-NO_2-Ph	H	Bn	3.0 (4)	82	98	97
17	H	CO_2Et	H	Bn	3.0 (4)	84	94	96
18	H	Cl	H	Bn	3.0 (4)	95	96	91
19	H	H	Cl	Bn	3.0 (4)	74	96	91
20	H	CO_2Et	Me	Bn	3.0 (4)	75	88	97

MacMillan [46] investigated the intermolecular aza-Claisen rearrangements treating *N*-allyl morpholines **207** with glycolic acid chlorides **208** in the presence of a chiral-chelated Lewis acid. The so-called magnesium BOX systems **211** and **212** gave the best results concerning yield (up to 95%) and chirality transfer (up to 97% ee) generating the amides **210**. Usually, 2–3 mol equiv of the chiral metal complexes **211** and **212** had to be employed to achieve satisfactory ee values. The glycolic acid framework seemed to play a crucial role in terms of asymmetric induction: A nonchelating α-oxygen substituent R^3 produced amides **210** with only moderate enantiomeric excess. In contrast, the use of benzyloxyacetyl chloride allowed very high ee values to be achieved. It seemed reasonable that this α-oxygen substituent enabled an efficient chelation of the chiral modified Lewis acid in **209** causing the high level of external chirality transfer. The substitution pattern of the allyl morpholine remained variable, and the use of *E* and *Z* olefin led to the defined formation of enantiomer amides **210** with comparable asymmetric induction. The scope and limitations are outlined in Table 14. Until now, the catalytic enantioselective aza-Claisen rearrangement involving substoichiometric amounts of the chiral information remained undiscovered (Scheme 41, Table 14).

5.3 Allene Carbonester Claisen Rearrangement

The third type of zwitterionic aza-Claisen rearrangement can be termed as *N*-allyl ammonium enolate Claisen rearrangement [47]. The first step of this tandem process was a Lewis acid-catalyzed Michael addition of a tertiary allylamine **213** to the β-carbon center of an allene carbonester **214**. The so-formed hypothetical zwitterion **215** must be characterized by a highly resonance-stabilized anion, and additional support should have given the O-coordinated Lewis acid. Then, the allyl vinyl ammonium moiety of **215** underwent a 3,3-sigmatropic rearrangement to give the unsaturated ester **216** bearing two new stereogenic centers in the γ and δ positions. The formation of the vinylogous carbamate in **216** and the charge neutralization served as potential driving forces, allowing such a reaction to be run at 23 °C. Best results were obtained using 5 to 10 mol% of $Zn(OTf)_2$.The products **216** were isolated with 75–97% yield and excellent diastereoselectivity of >98:2. Variation of the allylamine **213** and the allene substitution pattern in **214** gave a first insight into the scope and limitation of the transformation (Table 15). It should be pointed out that the present protocol enabled generation of defined quaternary centers. Furthermore, the double bond geometry of the allylamine **213** moiety allowed prediction of the stereochemical outcome of the reaction: The geranyl derivative *E*-**213** rearranged upon treatment with methyl pentadienoate **214** to give the *syn* product *syn*-**216** (methyl groups) with 94% yield and 98:2 dr. In contrast, the analogous reaction of nerylamine *Z*-**213** delivered the corresponding *anti* derivative *anti*-**216** (methyl groups) with 93% yield and 98:2 dr. The stereochemical outcome could be rationalized by the favored passing of a chair-like transition state in **215**; the vinyl



Scheme 42 For detailed information including R^1 - R^3 see Table 15

Table 15 (Reaction with 10 mol% $Zn(OTf)_2$) [47]

Entry	R′	R^1	$R^2/R^{2'}$	R^3	Yield (%)	Ratio *syn*:*anti*
1	$-(CH_2)_4-$	H	Me/H	Me	95	>98:2
2	$-(CH_2)_4-$	H	H/Me	Me	94	2:>98
3	$-(CH_2)_4-$	H	Ph/H	Me	97	94:6
4	$-(CH_2)_4-$	H	*i*Pr/H	Me	81	>98:2
5	$-(CH_2)_4-$	Me	H/H	Me	80	–
6	Me	H	Ph/H	Me	81	94:6
7	$-(CH_2)_5-$	H	Ph/H	Me	87	94:6
8[a]	$-(CH_2)_4-$	H	Me/H	Ph	86	97:3
9[a]	$-(CH_2)_4-$	H	Ph/H	Ph	94	94:6
10	$-(CH_2)_4-$	H	Ph/H	*i*Pr	94	94:6
11	$-(CH_2)_4-$	H	Ph/H	Cl	84	93:7
12	$-(CH_2)_4-$	H	Ph/H	$-CH_2CH=CH_2$	96	95:5
13	$-(CH_2)_4-$	H	Ph/H	H	84	–
14	$-(CH_2)_4-$	H	Me/H	PhtN	75	91:9
15[b]	$-(CH_2)_4-$	H	R/Me	Me	94	>98:2
16[b]	$-(CH_2)_4-$	H	Me/R	Me	93	2:>98

[a] Methyl ester.
[b] R=4-methyl-3-pentenyl, 5 mol% $Zn(OTf)_2$.

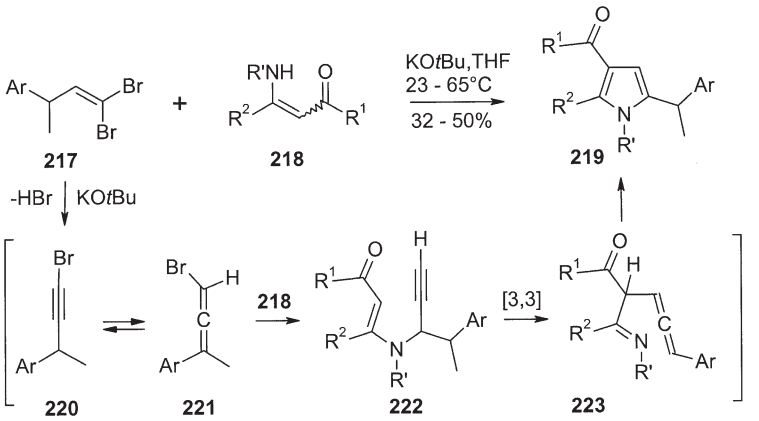
double bond should have been *E* configured because of the arrangement of R^3 and the bulky ammonium center with maximized distance. Enantioselectively catalyzed experiments will be reported in the future (Scheme 42, Table 15).

6 Alkyne Aza-Claisen Rearrangements

Propargylamines could serve as a suitable allyl moiety in aza-Claisen rearrangements. The 3,3-sigmatropic bond reorganization led to allenes, which easily underwent consecutive processes like nucleophile addition and cyclization in a tandem process.

Frey developed a pyrrole **219** synthesis starting from vinyl dibromides **217** and enamines **218** [48]. In the presence of a strong base (KO*t*Bu) an initial dehydrobromination of **217** led to an alkynyl bromide **220.** A consecutive equilibration was found to be crucial. Involving activating aryl substituents Ar (Ph, naphthyl), a reversible base-induced H shift should have formed the corresponding allene **221.** Without such a substituent, no cyclization took place. Then, the nucleophilic attack of the enamine **218** nitrogen proceeded to give the propargyl vinyl framework in **222** ready for the sigmatropic reaction. At 23–65 °C, the aza-Claisen rearrangement generated the *β,γ*-allenylimine **223** which underwent a final 5-exo-trig cyclization to produce the pyrrole **219.** The present procedure allowed 1,2,3,5 tetrasubstituted pyrroles to be built up with 32 to 50% yield overall including annulated bicyclic structures (Table 16, Scheme 43).

A related amination/rearrangement/cyclization tandem sequence had been introduced by Cossy [49]. Starting from cyclic epoxyketones **224** the reaction with propargylamines **225** caused an oxirane-opening condensation process to generate the enaminoketones **226.** Upon heating in toluene to reflux, aza-Claisen rearrangement delivered the intermediate allenyl imines **227**, which



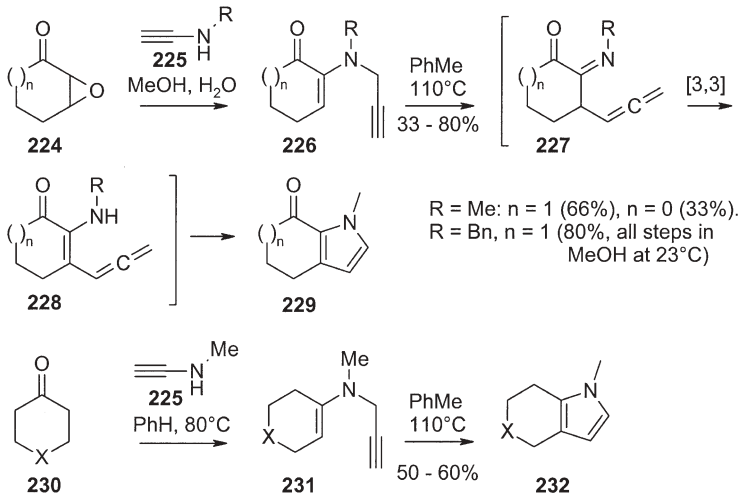
Scheme 43

Table 16 [48]

Entry	Ar	R′	R^1	R^2	Yield (%)
1	Ph	H	OMe	Me	45
2	Ph	Me	OEt	Me	32
3	Ph	Ph	OMe	Me	35
4	Ph	Bn	OEt	Me	50
5	Ph	Bn	Me	Me	35
6	Ph	Ph	$-(CH_2)_3-$		33
7	Ph	Ph	$-[CH_2C(Me)_2CH_2]-$		34

suffered from keto–enol tautomerism to **228** and a final cyclization to give the annulated pyrroles **229** with 33 to 80% yield overall. In contrast to all other reactions, the conversion of the *N*-benzyl propargylamine **224** (R=Bn) proceeded at ambient temperature; a best yield of 80% was obtained. The whole process could be run as a one-pot reaction without any heating. Furthermore, cycloketones **230** and propargylamines **225** gave rise to the formation of simple *N*-propargyl enamines **231**. The aza-Claisen rearrangements of these systems required significantly prolonged reaction times to achieve about 60 to 70% conversion of **231**. However, the corresponding pyrroles **232** were isolated in 50 to 60% yield recommending the procedure for further investigation (Scheme 44).

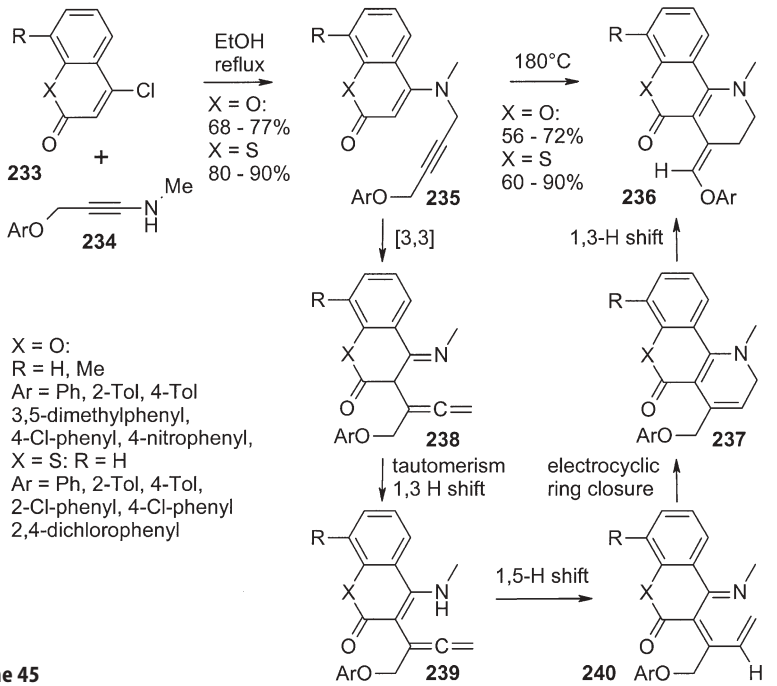
An uncatalyzed amination/aza-Claisen rearrangement/cyclization cascade described by Majumdar et al. was terminated by a final six-membered ring for-



Scheme 44

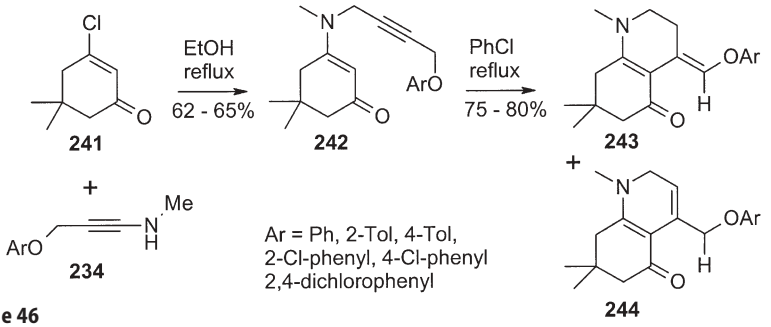
mation [50]. *N*-propargylenamines **235** were generated from vinylogous acid chlorides **233** and propargylamines **234** by means of a Michael addition–elimination process with 68–77% yield (X=O, coumarins) and 80–90% yield (X=S). Upon heating the propargyl vinyl amines in *o*-dichlorobenzene to about 180 °C, a cascade of rearrangement and cyclization steps allowed generation of the tricyclic products **236** and **237** with 56–72% yield (X=O) and 60–90% yield (X=S). Generally, the exocyclic olefin **236** was obtained as the major compound. If any, the material characterized by an endocyclic double bond **237** was isolated as a side product, which could be converted into **236** by prolonged heating (1,3-H shift). Though propargylamine **235** displayed a propargyl vinyl amine as well as a propargyl vinyl (aryl) ether subunit, the aza-Claisen rearrangement proceeded. The ether system remained untouched despite a broad variation of the aryl system. The reaction path was rationalized by starting with an aza-Claisen rearrangement to produce allene imine **238**. Imine–enamide tautomerism led to the vinylogous amide **239**, which suffered from a 1,5-H shift to build up 1-azahexatriene **240**. Then, an electrocyclic ring closure formed the dehydropiperidine **237**, which finally underwent double bond migration to give the coumarin derivative **236** as the major compound (Scheme 45).

Additionally, dimedone derivative **241** and propargylamine **234** could be combined to give the alkynyl vinyl amine **242**. The rearrangement/cyclization cascade could be induced upon heating until reflux in chlorobenzene. The an-



Scheme 45

nulated piperidines **243** and **244** were isolated with 75 to 80% yield. In analogy to the coumarin series, the product **243** displaying the exocyclic double bond was formed as the major product; the endocyclic olefin **244** was obtained as the side product (up to about 20%) (Scheme 46).



Scheme 46

7 Iminoketene Claisen Rearrangements

The iminoketene Claisen rearrangement has been investigated by Walters et al. [51]. Motivated by an early publication from Brannock and Burpitt in 1965 [52], *N*-allyl amides **245** were activated by means of a strong water-removing reagent like Ph_3PBr_2 and PPh_3/CCl_4. The dehydration at 20 °C led to a highly active hypothetical intermediate *N*-allyl iminoketene **246**, which underwent immediate aza-Claisen rearrangement to generate the product γ,δ-unsaturated nitrile **247**. The low reaction temperature of the present protocol recommended the process for further investigation. Extensive variation of the water-removing reagent and the conditions showed that the originally introduced activated triphenylphosphine produced the best results. Additionally, the combination of trimethylphosphite/iodine and Et_3N was found to be useful in reacting α-heteroatom-substituted amides (R^1=OBn, NPht, etc.). Quaternary centers in the α-position to the nascent nitrile functions (R^1, $R^{1'} \neq H$) were generated smoothly. Generally, alkyl OH groups were converted into the corresponding halides during the course of the reaction. In most cases oxygen substituents placed anywhere in the reactant resulted in moderate yields because of some side reactions, presumably caused by an oxygen–phosphorus interaction. For detailed information see Table 17.

The rearrangement of *E* and *Z* *N*-crotylamines **245** (R^3, *E* or *Z*=Me) gave the corresponding nitriles **247** with 82 and 68% yield, respectively. Disappointingly, the product was obtained as an inseparable mixture of *syn*/*anti* diastereomers **247** indicating a low simple diastereoselectivity. Obviously, the intermediate ketene imine fitted neither a chair- nor a boat-like conformation. Hence, a low axis-to-center chirality induction was operative, and *E* and *Z* reactants gave a

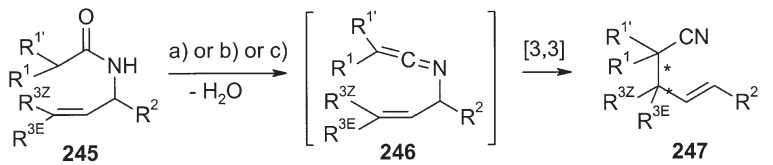
Table 17 [51]

Entry	R^1	$R^{1'}$	R^2	R^{3Z}	R^{3E}	Method	Yield (%)
1	Ph	H	H	H	H	b	89
2	Ph	H	H	H	H	a	94
3	Bn	H	H	H	H	a	67
4	Ph	Me	H	H	H	a	60
5	Ph	Ph	H	H	H	a	75
6	*p*-$MeOC_6H_4$	H	H	H	H	a	85
7	*p*-$F_3CC_6H_4$	H	H	H	H	a	73
8	MeO_2CCH_2	H	H	H	H	a	69
9	Et	H	H	H	H	a	36
10	BnO	H	H	H	H	c	40
11	Br-$(CH_2)_3$	H	H	H	H	b	30
12	Br-$(CH_2)_4$	H	H	H	H	b	45
13	MOMO	H	H	H	H	c	59
14	PhtN	H	H	H	H	b	78
15	PhtN	H	H	H	H	c	66
16	Me	H	–$(CH_2)_3$–		H	a	47
17	Ph	H	H	H	Me	c	82
18	Ph	H	H	Me	H	c	68
19[a]	*o*-$HOCH_2C_6H_4$	H	H	H	H	b	46

[a] Product: R^1=*o*-$BrCH_2C_6H_4$.

1.1:1 and a 1.6:1 ratio in favor of the major compound (isomer not determined, Table 17) (Scheme 47).

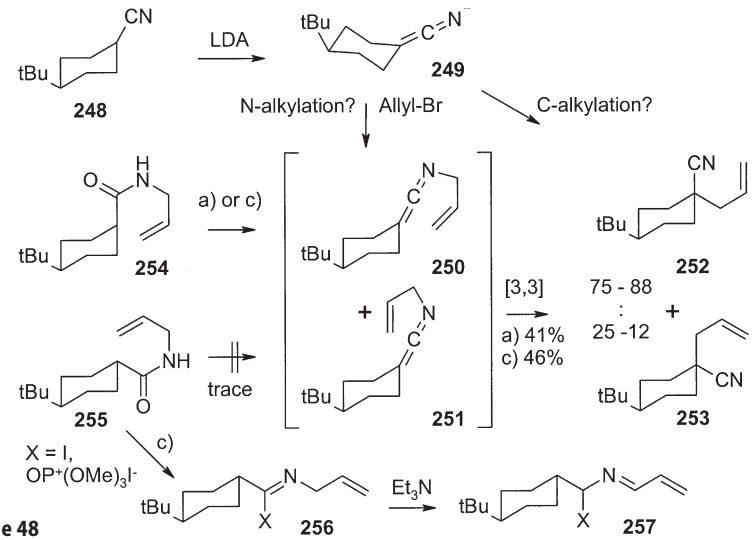
Further information concerning the stereochemical properties of the rearrangement were evaluated by submitting rigid cyclohexane derivatives **254/255** to the reaction conditions. In 1975, House described the allylation of a cyclohexyl cyanide **248** [53]. The initial deprotonation with LDA led to a ketene imine anion **249**, which was then treated with allyl bromide. Two potential paths rationalized the outcome: an *N*-allylation generated the intermediate ketene imines **250/251**, which underwent aza-Claisen rearrangement to deliver the nitriles **252/253**; alternatively, the direct C-allylation of **249** produced the nitriles,



a) Ph_3P, CCl_4, Et_3N, MeCN, 23°C. b) Ph_3PBr_2, Et_3N, CH_2Cl_2, 23°C.
c) $(MeO)_3P$, I_2, Et_3N, CH_2Cl_2, 23°C. For details see Table 17

Scheme 47

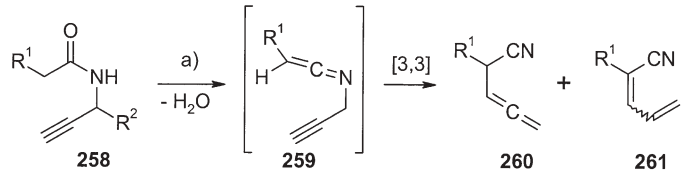
with the ratio of 88:12 in favor of the axial nitrile **252.** Walters presumed that the aza-Claisen rearrangement of the allyl amides **254** and **255** should have given the same nitriles **252/253** with comparable dr after passing the ketene imines **250/251.** In fact, the reaction of the axial amide **254** led to the corresponding nitriles with 41 to 46% yield and 75:25 ratio in favor of the axial nitrile **252.** In contrast, the equatorial amide **255** was converted into the imidate **256** and the azadiene **257**, and only traces of the nitriles **252/253** were found. It seemed reasonable that the iminoketene Claisen rearrangement was sensitive to sterically encumbered situations. The formation of the ketene imines **250/251** starting from axial amide **254** represented a sterically favored process leading to the nitriles **252/253.** In contrast, the formation of the ketene imines **250/251** starting from equatorial amide **255** must have been disfavored and the system gave rise to the formation of the competing products **256/257** (Scheme 48).



Scheme 48

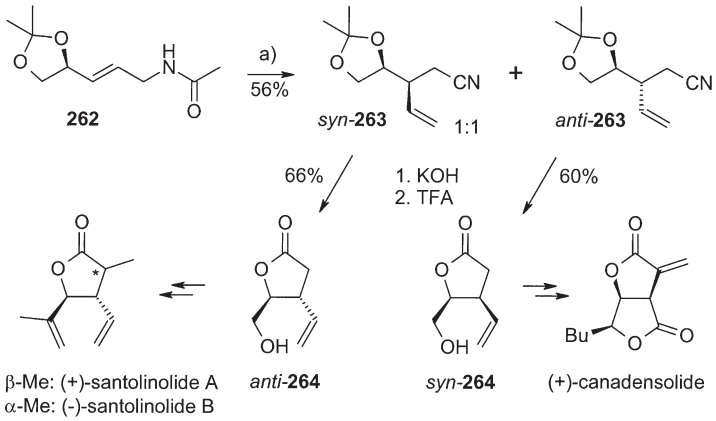
Preliminary investigations were undertaken rearranging propargylamides **258.** In the presence of an alkyl substituent R^1 (R^1=Bn, Et), the use of standard reaction conditions caused dehydration to give intermediate **259.** The final aza-Claisen rearrangement delivered allenylnitrile **260** with moderate yield. The reaction cascade of the phenyl derivative **258** (R^1=Ph) suffered from a final double bond migration to give the $\alpha,\beta,\gamma,\delta$-unsaturated nitrile **261** (56% yield) (Scheme 49).

In 1993, a first application of the Walters protocol in natural product syntheses was reported [54]: *N*-allylamide **262** could be converted into a 1:1 mixture of the diastereomer nitriles **263** with 56% yield. Despite the mild reaction conditions, no external 1,2-asymmetric induction (remote stereo control) was operative when conducting such a rearrangement. The diastereomers were sep-



Scheme 49

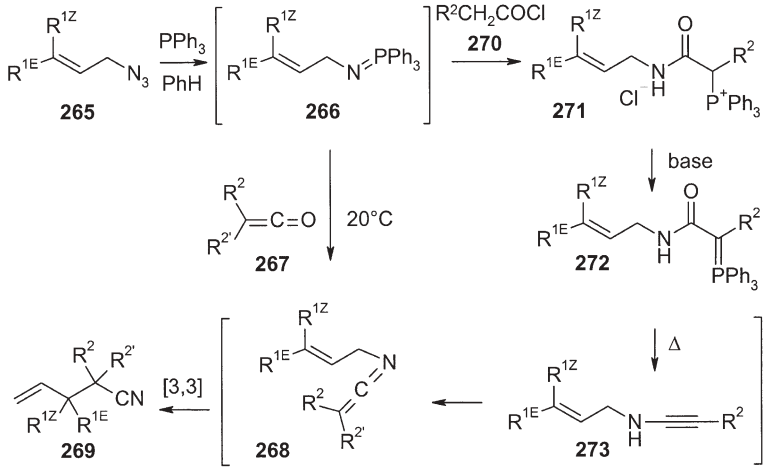
arated and the cleavage of the nitriles allowed the lactones **264** to be built up. The *syn* lactone *syn*-**264** was involved as a key intermediate in a (+)-canadensolide total synthesis. The *anti* lactone *anti*-**264** enabled completion of the total syntheses of (+)-santolinolide A and (–)-santolinolide B via several further steps (Scheme 50).



Scheme 50

At the same time as Walters' publications concerning iminoketene Claisen rearrangements, Molina reported on a related process [55]. *N*-allyl azides **265** were subjected to a Staudinger reaction to generate phosphine imines **266.** Then, the addition of stable ketenes **267** (synthesized separately) caused an aza-Wittig reaction to give iminoketenes **268,** which underwent immediate aza-Claisen rearrangement to produce the *γ,δ*-unsaturated nitriles **269** (method A). The driving force of the cascade was high enough to generate two adjacent quaternary carbon centers. The diastereoselectivities observed on generating the nitriles varied between 1:1 and about 4:1; the configuration of the major compound was not determined.

Alternatively, phosphine imines **266** were treated with various phenylacetyl chlorides **270** (method B). Surprisingly, phosphonium salts **271** were isolated with 25 to 97% yield, which could be deprotonated by means of a base to build up the corresponding phosphoranes **272** (66–89% yield). Upon heating to



Scheme 51 For detailed information see Table 18

Table 18 [55]

Entry	R^{1E}	R^{1Z}	R^{2}	$R^{2'}$	Method	*T* (°C)	Yield (%)
1	Ph	H	Ph	Ph	A	20	51
2	Ph	H	Ph	Et	A	20	48
3	Ph	H	*p*-Tolyl	Ph	A	20	44
4	Me	H	Ph	Et	A	20	55
5	Me	Me	Ph	Ph	A	20	47
6	H_2C=CH	H	Ph	Ph	A	20	60
7	H_2C=CH	H	Ph	Et	A	20	41
8	Me	Me	Ph	H	B	140	55
9	H_2C=CH	H	Ph	H	B	130	57
10	H_2C=CH	H	*p*-Cl-C_6H_4	H	B	115	29
11	H_2C=CH	H	*p*-F-C_6H_4	H	B	120	69
12	Ph	H	Ph	H	B	125	60
13	Ph	H	*p*-Cl-C_6H_4	H	B	90	25
14	Ph	H	*p*-F-C_6H_4	H	B	130	59

90–130 °C nitriles **269** were formed in 25 to 60% yield. This outcome was explained by an initial extrusion of Ph_3P=O to generate ynamines **273**. The consecutive isomerization delivered iminoketenes **268**, which underwent the usual iminoketene Claisen rearrangement to produce the nitriles **269**. Detailed information is given in Table 18 (Scheme 51).

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