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Asymmetric [3.3]-Sigmatropic Rearrangements in Organic Synthesis

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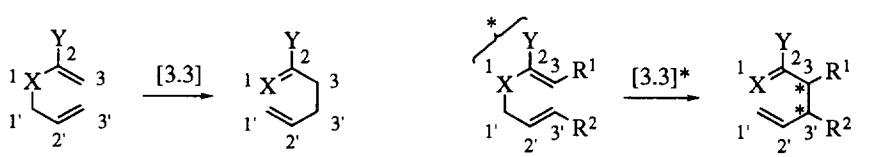
Contents

1 Introduction

In the recent past there has been a growing interest in asymmetric variants of sigmatropic rearrangements. Although numerous examples of [2.3][1] and [3.3]-rearrangements[2] *via* chirality transfer are known, only a few truly asymmetric [3.3]-sigmatropic rearrangements have been reported so far. In this report we wish to present a brief summary of such asymmetric [3.3]-variants. General formulae of classical and asymmetric [3.3]-sigmatropic rearrangements are given below.



Scheme 1. Prototypes of (asymmetric) [3.3]-sigmatropic rearrangements

As depicted in scheme 1, both groups X and Y can be varied, for example, X and Y can be a carbon atom as well as a hetero atom. The prototype of this large family of related reactions is the all carbon version, the Cope rearrangement,[3] discovered in 1940.[4] For the hetero variants of the Cope reactions Y is a carbon atom and X is a hetero atom like oxygen, nitrogen or sulfur. Among these, the versions where X is oxygen are probably the most important ones (Claisen rearrangements).

Since its discovery in 1912,[5] the Claisen rearrangement which was the first reaction of this type has become the most powerful tool for stereoselective C-C bond formation. The current popularity of the Claisen rearrangement has been achieved by the development of a great number of versions, such as the Carroll (1940),[6] Eschenmoser (1964),[7] Johnson (1970),[8] Ireland (1972),[9] and Reformatsky-Claisen (1973) rearrangement.[10] Some miscellaneous ionic variants also have been established, such as a ketene-Claisen version by Bellus and Malherbe (1978)[11] or a carbanion accelerated version by Denmark (1982).[12] The work of Bergmann (1935),[13] Lauer (1937),[14] Hurd (1938),[15] Arnold (1949),[16] Burgstrahler (1961)[17] and Marbet and Saucy (1967)[18] should also be mentioned.

Substitution at the carbon chain is possible in every position of the framework showing different effects concerning the stereochemical outcome of the rearrangement products. For example, the relative stereochemistry (*syn/anti*) at the newly generated adjacent stereogenic centres is controlled by the geometry of the double bonds (*E/Z*), if substituted at 3- and 3'-position. If there is a substituent at 1'-position, involving a stereogenic centre, this chirality can be transferred to 3- and/or 3'-position due to the highly ordered transition state (chirality transfer, immolative asymmetric synthesis). In asymmetric [3.3]-sigmatropic rearrangements the chirality information of a removable auxiliary at either X* or Y* or a chiral catalyst determines the stereochemical outcome of the reaction.

The [3.3]-sigmatropic Claisen rearrangements are exothermic, concerted pericyclic reactions which show a suprafacial reaction pathway according to the Woodward-Hoffmann rules. The [3.3]-rearrangements, especially those of acyclic systems, show a high preference for chairlike transition states. Due to these generally highly ordered transition states of [3.3]-sigmatropic rearrangements a high level of stereocontrol can be achieved. In cyclic systems, however, the stereochemistry of the rearrangements was usually explained by boatlike transition states. Furthermore, high product stereoselectivities can be realized by efficient control of the ketene acetal geometry, e.g. by solvent effects. Deprotonation with LDA/THF leads to the kinetically favoured (*Z*)-ester enolates, whereas the (*E*)-ester enolates are formed in the presence of THF/HMPA. The rearrangement of the (*Z*)-ester enolates or (*E*)-silyl ketene acetals afforded the *anti*-products, respectively, while *syn*-products are obtained by the rearrangement of the (*E*)-ester enolates or (*Z*)-silyl ketene acetals.

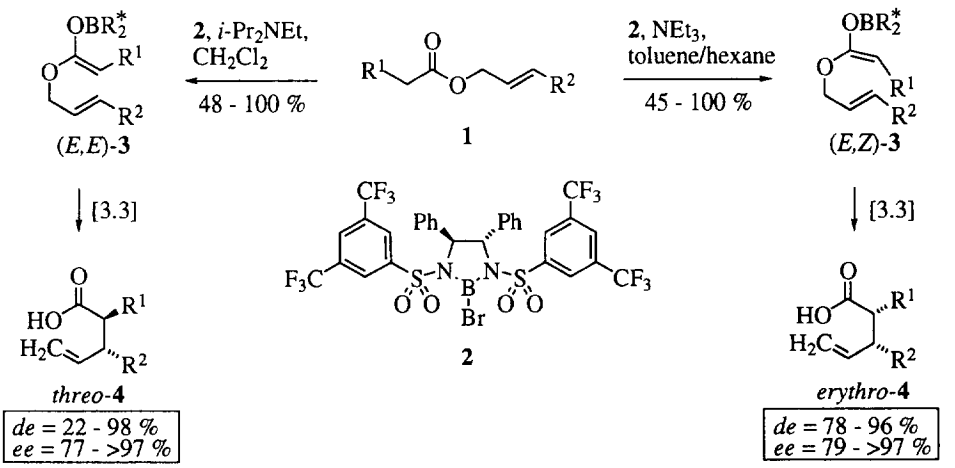
A great number of [3.3]-sigmatropic rearrangements with chirality transfer have been reported in recent years. In this short review we summarize the asymmetric variants of the [3.3]-sigmatropic rearrangements.

2 Ireland-Claisen ester enolate and related rearrangements

Since its introduction in 1972 the Ireland-Claisen rearrangement has become increasingly popular. It has found broad application due to the mild reaction conditions, the compatibility with differently functionalized structures and the high degree of stereoselection as a result of the highly ordered transition states and the efficient control of the ketene acetal geometry. The impact of the Ireland-Claisen rearrangement on modern synthetic methods is apparent from the large number of recent publications, the subsequent development of new variants and the numerous applications in bioactive and natural product synthesis.

2.1 Ireland-Claisen rearrangements

Corey et al. reported the first asymmetric enantioselective version of the Ireland-Claisen rearrangement using a chiral boron reagent.[19] The rearrangement of various allylic propionate and butyrate esters generally succeeded with good yields and excellent diastereo- and enantioselectivities (scheme 2).



Scheme 2. Enantioselective Ireland-Claisen rearrangement *via* chiral boron enolates according to Corey et al.

The achiral allylic esters **1** were converted with the enantiopure boron reagent **2** leading to the (*E,E*)-enolate (*E,E*)-**3** or (*E,Z*)-enolate (*E,Z*)-**3** depending on reaction conditions, respectively. The (*E,E*)-enolate (*E,E*)-**3** was formed in the presence of *i*-Pr_2NEt in CH_2Cl_2, whereas the (*E,Z*)-enolate (*E,Z*)-**3** was obtained by treating the ester **1** with NEt_3 in hexane/toluene. The enolates underwent rearrangement upon storage at 20 °C for 14 days leading to γ,δ-unsaturated acids. The enolates (*E,E*)-**3** afforded the *threo* acids **4** and the enolates (*E,Z*)-**3** led to the *erythro* acids **4** in good to excellent yields, good diastereomeric excesses and mostly

excellent enantiomeric excesses. Lower enantioselectivities were observed in the case of the allylic alcohol itself (R^2 = H). Furthermore, lower diastereoselectivities were obtained in the cases of R = Ph and R = SPh starting from the enolates (*E,E*)-**3**. The rearrangement of the respective enolates (*E,Z*)-**3**, however, afforded good diastereoselectivities. The high diastereoselectivities are based on the efficient control of the enolate geometry and the expected preference for a chairlike transition state. The scope of this enantioselective variant is shown in table 1 and 2.

Table 1. Enantioselective rearrangement *via* the enolate (*E,E*)-**3**

entry	R^1	R^2	yield [%]	*threo:erythro*[a]	*ee*[b] [%]
a	Me	Me	75	99:1	<97
b	Et	Me	79	98:2	95
c	Me	Me	75	91:9	>97
d	Et	Ph	72	91:9	>97
e	Ph	Ph	100	23:77	>97
f	SPh	Me	52	39:61	>97
g	Bn	H	70	–	82
h	CH_2-1-naphthyl	H	48	–	77

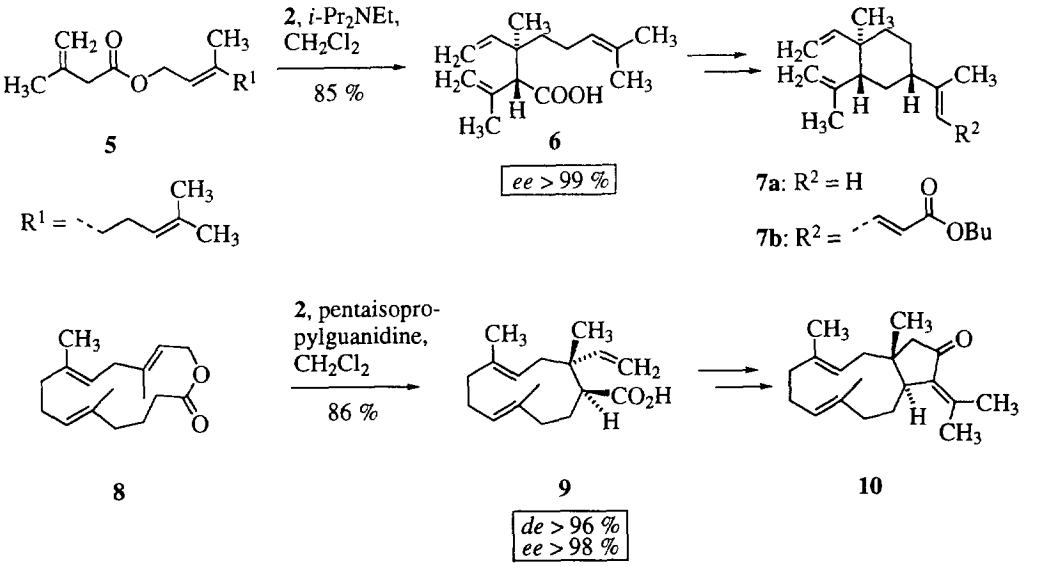
[a] The diastereomeric ratios were determined by GC analysis of benzyl or methyl esters; [b] The *ee* values were determined after reduction to the primary alcohol and conversion to the MTPA esters by ^{1}H NMR spectroscopy or by HPLC analysis of methyl esters using a Daicel OJ column.

Table 2. Enantioselective rearrangement *via* the enolate (*E,Z*)-**3**

entry	R^1	R^2	yield [%]	*erythro:threo*[a]	*ee*[b] [%]
a	Me	Me	65	90:10	96
b	Et	Me	79	89:1	>97
c	Me	Ph	88	96:4	>97
d	Et	Ph	69	95:5	>97
e	Ph	Ph	100	98:2	>97
f	SPh	Me	56	95:5	>97
g	SPh	Ph	45	91:9	>97
h	Bn	H	57	–	84
i	CH_2-1-naphthyl	H	63	–	79

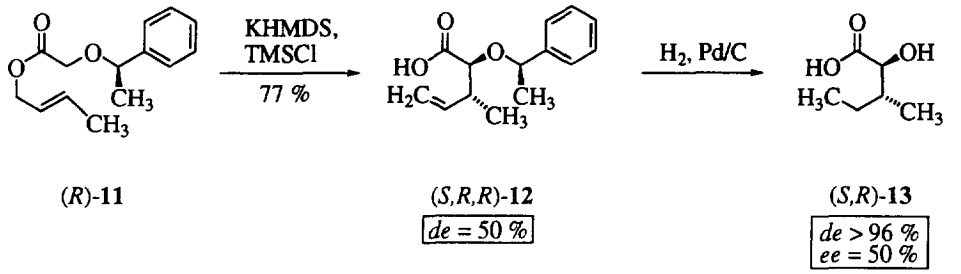
[a] The diastereomeric ratios were determined by GC analysis of benzyl or methyl esters; [b] The *ee* values were determined after reduction to the primary alcohol and conversion to the MTPA esters by ^{1}H NMR spectroscopy or by HPLC analysis of methyl esters using a Daicel OJ column.

The usefulness of this rearrangement methodology is apparent because of the excellent stereoselectivity and the easy recoverability of the chiral boron reagent. As an application of this rearrangement method the syntheses of the natural products *β*-elemene **7a**, fuscol **7b** and dolabellatrienone **10** have been developed (scheme 3).[20] Both **7a** and **7b** could be obtained in short syntheses *via* rearrangement of 3-methylenbutanoic acid geranyl ester **5** in the presence of the chiral boron reagent and NEt_3 as the key step. The rearrangement product **6** was obtained in 85 % yield and with an excellent enantiomeric excess (> 99 %). Furthermore, the first enantioselective synthesis of the marine diterpenoid dolabellatrienone **10** was achieved by the rearrangement of the 15-membered macrocyclic lactone **8**. It was treated with the chiral boron reagent and pentaisopropylguanidine at –78 °C for 8 h to form the boron enolate, which underwent rearrangement by keeping at 4 °C for 48 h. The acid **9** was produced in good yield with excellent diastereo- and enantioselectivity (*de* > 96 %, *ee* > 98 %).



Scheme 3. Synthesis of the natural products β-elemene **7a**, fuscol **7b** and dolabellatrienone **10** by enantioselective boron enolate mediated Ireland-Claisen rearrangement

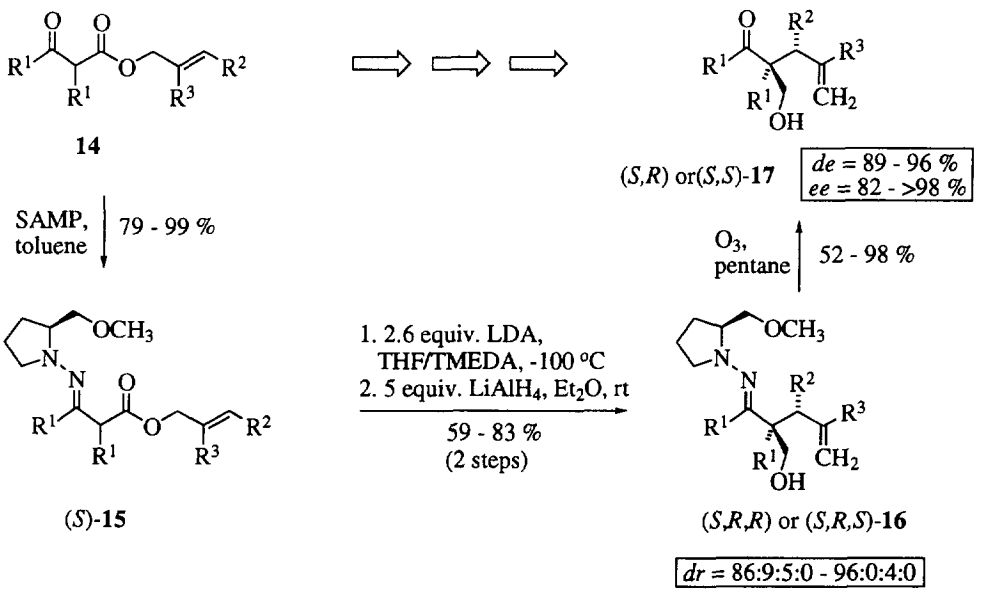
Kallmerten et al. described an auxiliary directed asymmetric Claisen rearrangement using chiral alcohols.[21] The allylic α-alkoxy ester (*R*)-**11** underwent rearrangement after deprotonation with KHMDS and subsequent silylation with TMSCl leading to α-alkoxy γ,δ-unsaturated acids (*S,R,R*)-**12** in good yield, complete *syn*-diastereoselectivity and a diastereoselectivity of 50 %. The excellent *syn*-diastereoselectivity can be explained *via* the expected chairlike transition state of the rearrangement.



(*R*)-**11** (*S,R,R*)-**12** *de* = 50 % (*S,R*)-**13** *de* > 96 % *ee* = 50 %

Scheme 4. Asymmetric Ireland-Claisen rearrangement using chiral alcohols described by Kallmerten et al.

A large number of examples confirming this regular course *via* the chairlike transition state which reacted with complete *syn* diastereoselectivity are reported by this group using racemic 1-phenylethanol. The chiral auxiliary was removed by hydrogenation affording α-hydroxyacid (*S,R*)-**13**. The enantiomeric acid (*R,S*)-**13** was accessible by the same procedure using the enantiomeric (*S*)-phenylethanol as auxiliary.



Scheme 5. Dianionic Carroll rearrangement using the SAMP/RAMP hydrazone methodology according to Enders et al.

Recently, we reported the first asymmetric Carroll rearrangement, which opened up an efficient novel C-C bond forming, intramolecular access to highly functionalized ketones **17** with vicinal quarternary and tertiary stereogenic centres of excellent diastereo- and enantiomeric purity (*de* = 89 - 96 %, *ee* = 82 - >98 %) using the SAMP/RAMP hydrazone methodology.[22] The β-ketoesters **14** were easily converted to the corresponding (*S*)-1-amino-2-methoxymethylpyrrolidine-(SAMP)-hydrazones (*S*)-**15** in excellent yields. Upon double deprotonation with LDA in THF/TMEDA (8/1), the intermediate dianions underwent the [3.3]-sigmatropic rearrangement by allowing the reaction mixture to warm up to room temperature. The crude rearrangement products were immediately reduced with 5 equiv. $LiAlH_4$ in diethyl ether leading to β-hydroxy-hydrazones (*S,R,R*)- and (*S,R,S*)-**16** in good yields (59 - 83 %), very good diastereoselectivities and excellent enantioselectivities. The diastereomeric ratios were determined to be *dr* = 86:9:5:0 - 96:0:4:0 (table 3). The cleavage of the chiral auxiliary was achieved by ozonolysis without epimerisation or concomitant oxidation of the terminal double bond leading to the β-hydroxyketones (*S,R*)- and (*S,S*)-**17** in very good yields (84 - >99 %), very good diastereo- (88 - 94 %) and good to excellent enantiomeric excesses (82 - >98 %). The yields for the hydrazones **17k,l** with the exocyclic double bond were somewhat decreased to 52 % or 57 %, respectively, since in these cases partial oxidation of the double bond was observed.

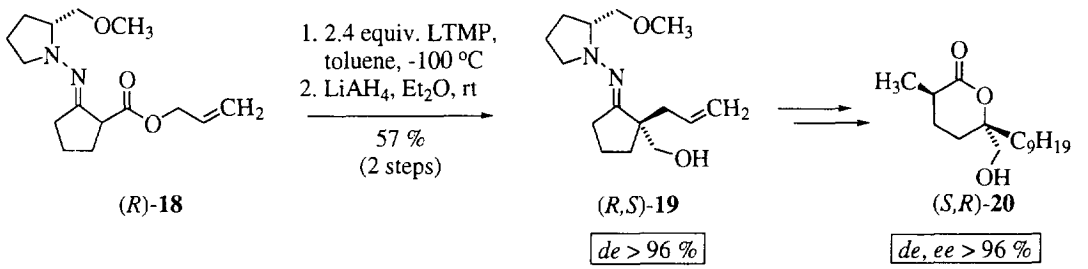
Table 3. Dianionic Carroll rearrangement leading to hydrazones (*S,R,R*)- or (*S,R,S*)-**16** and ketones (*S,R*)- or (*S,S*)-**17**

entry	R^1	R^2	R^3	yield **16** [%]	*dr*[a]	yield **17** [%]	*de*[b] [%]	*ee*[c] [%]	confg.
a	$(CH_2)_3$	*n*-Pr	H	81	88:7:5:0	84	89	86	(*S,R*)
b	$(CH_2)_3$	i-Pr	H	73	95:2:3:0	89	96	94	(*S,R*)
c	$(CH_2)_3$	*i*-Bu	H	62	94:2:4:0	91	91	96	(*S,R*)
d	$(CH_2)_3$	*i*-Pe	H	66	96:0:4:0	96	94	> 98	(*S,S*)
e	$(CH_2)_3$	*c*-Hex	H	83	96:0:4:0	93	93	> 97	(*S,S*)
f	$(CH_2)_4$	*n*-Pr	H	74	86:9:5:0	86	91	82	(*S,R*)
g	$(CH_2)_4$	*i*-Pr	H	69	94:0:6:0	95	89	> 98	(*S,R*)
h	$(CH_2)_4$	*i*-Bu	H	59	91:3:6:0	92	88	94	(*S,R*)
i	$(CH_2)_4$	*i*-Pe	H	64	93:1:6:0	98	88	98	(*S,S*)
j	$(CH_2)_4$	*c*-Hex	H	77	94:0:6:0	> 99	88	98	(*S,S*)
k	Me	$(CH_2)_4$		63	88:3:9:0	57	> 98[d]	> 96[d]	(*S,R*)
l	$(CH_2)_3$	$(CH_2)_4$		75	95:2:3:0	52	90	96	(*S,R*)

[a] The *dr* values were determined by ^{13}C NMR spectroscopy to be (*S,R,R*):(*S,S,S*):(*S,S,R*):(*S,R,S*)-**16a-c,f-h,k,l** and (*S,R,S*):(*S,S,R*):(*S,S,S*):(*S,R,R*)-**16d,e,i,j** = 86:9:5:0 - 96:0:4:0; [b] The *de* values were determined by ^{13}C NMR spectroscopy; [c] The *de* values were determined by ^{1}H NMR spectroscopy after conversion to the MPA esters; [d] Enriched by flash chromatography.

The rearrangement showed very high flexibility. The ketone fragment as well as the allyl alcohol moiety could be varied significantly. Both cyclic SAMP hydrazones and acyclic hydrazones might be used. Furthermore, not only primary aliphatic allylic alcohols but also endocyclic allylic alcohols could be employed.

The synthetic usefulness of this new asymmetric rearrangement method in the synthesis of bioactive and natural products was demonstrated by the synthesis of the antibiotic (–)-malyngolide (*S,R*)-**20**.[23] Herein the rearrangement of the RAMP hydrazone allylester (*R*)-**18** was used to generate the quarternary stereogenic centre. The resulting hydroxyhydrazone (*R,S*)-**19** was obtained with an excellent diastereomeric excess. After the cleavage of the chiral auxiliary, the C_9-chain elongation was achieved *via* oxidation of the terminal double bond by bishydroxylation, $NaIO_4$ cleavage, subsequent Wittig olefination and hydrogenation of the double bond in the presence of Pd/C. The tertiary stereogenic centre was generated diastereoselectively by α-alkylation. In the final step the enantiopure antibiotic was obtained by Baeyer-Villiger oxidation.



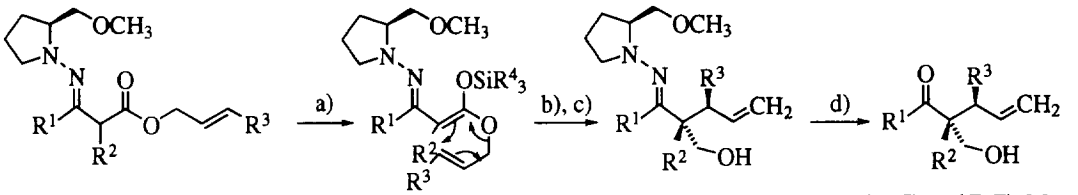
(*R*)-**18** (*R,S*)-**19** (*S,R*)-**20**

de > 96 % *de, ee* > 96 %

Scheme 6. Synthesis of the antibiotic (–)-malyngolide **20** *via* asymmetric Carroll rearrangement

The Carroll rearrangement could also be achieved in the presence of Lewis acids, for example *t*-butyldimethylsilyltriflate (TBSOTf) (scheme 7). The β-hydrazonoesters (*S*)-**21** were reacted with 1.3 equiv. TBSOTf and 1.5 equiv. Hünig's base leading to silyl ketene acetals (*S*)-**22**, which underwent rearrangement on warming up to room temperature. The crude silyl esters were reduced with 5 equiv. $LiAlH_4$ in diethyl ether leading to β-hydroxyhydrazones (*S,S,S*)- or (*S,S,R*)-**23** as a mixture of the four possible diastereomers in good yields (58 - 78 % over two steps). In comparison with the dianionic rearrangement the Lewis acid mediated Carroll rearrangement led to another diastereomer as the main product. In addition the main diastereomer of the dianionic rearrangement is the minor diastereomer of the Lewis acid mediated rearrangement. Oxidative cleavage of the chiral auxiliary led to ketones (*R,S*)- or (*R,R*)-**24** with only moderate enantiomeric excesses (58 - 78 %) for one enantiomeric pair, whereas the enantiomeric excess for the other enantiomeric pair was less then 25 %. This observation can be explained by the formation of an (*E/Z*) mixture of the silyl ketene acetals, in only one of which the chiral auxiliary is close to the newly formed C-C bond.

Another explanation for the observed stereochemistry starts with the assumption that the rearrangement does not occur *via* the regular chairlike transition state but with a partial boatlike transition state.



(*S*)-**21** (*S*)-**22** (*S,S,S*) or (*S,S,R*)-**23** (*R,S*) or (*R,R*)-**24**

dr = 2.3 : 1.1 : 1.1 : 1 - 7.2 : 2.1 : 1.3 : 1

de = 5 - 41 %
ee[1] = 39 - 86 %
ee[2] = 0 - 29 %

R^1 R^2 = Me, $(CH_2)_3$, $(CH_2)_4$
R^3 = Me, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *i*-Pe
SiR^4_3 = TMS, TIPS, TBS

a) R^4_3SiOTf, CH_2Cl_2 b) rt c) $LiAlH_4$, Et_2O, 54 - 78 % d) O_3, pentane, 78 - 96 %

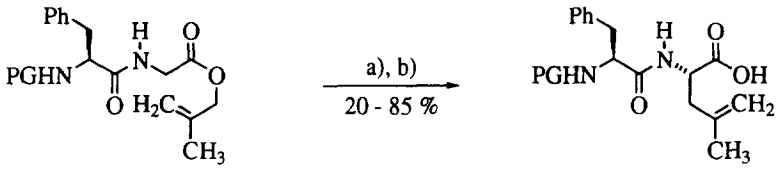
Scheme 7. Lewis acid mediated Carroll rearrangement using the SAMP/RAMP hydrazone methodology

Table 4. Lewis acid mediated Carroll rearrangement leading to hydrazones (*S,S,S*) or (*S,S,R*)-**23** and ketones (*R,S*) or (*R,R*)-**24**

entry	R^1	R^2	R^3	yield **23** [%]	*dr* [a]	yield **24** [%]	*de* [b] [%]	*ee*[1] [c] [%]	*ee*[2] [d] [%]
a	$(CH_2)_3$	*n*-Pr	H	58	3.7:3.5:3.4:1	84	19	57	1
b	$(CH_2)_3$	*n*-Bu	H	76	3.7:3.6:3.4:1	89	20	57	3
c	$(CH_2)_3$	*i*-Bu	H	78	4.0:3.5:3.2:1	90	16	60	4
d	$(CH_2)_4$	*n*-Bu	H	59	5.0:2.7:2.7:1	86	5	67	0
e	$(CH_2)_4$	*i*-Bu	H	67	7.7:4.0:3.4:1	87	8	77	8
f	$(CH_2)_4$	*i*-Pr	H	70	5.9:2.0:2.1:1	90	25	71	0
g	$(CH_2)_4$	*i*-Pe	H	66	7.2:2.1:1.3:1	87	41	76	24

[a] The *dr* values were determined by ^{13}C NMR spectroscopy, [(*S,S,S*):(*S,S,R*):(*S,R,S*):(*S,R,R*)]-**23a-f** and [(*S,S,R*):(*S,S,S*):(*S,R,R*):(*S,R,S*)]-**23g**; [b] The *de* values were determined by ^{13}C NMR spectroscopy; [c] The *ee* values were determined by ^1H NMR spectroscopy after conversion to the MPA esters, [(*R,S*):(*S,R*)]-**24a-f** and [(*R,R*):(*S,S*)]-**24g**; [d] The *ee* values were determined by ^1H NMR spectroscopy after conversion to the MPA ester, [(*S,S*):(*R,R*)]-**24a-f** and [(*S,R*):(*R,S*)]-**24g**.

Kazmaier et al. reported an ester enolate Claisen rearrangement leading to γ,δ-unsaturated α-amino acids **26**. The allylic esters **25** underwent rearrangement upon treatment with excess base in the presence of metal salts like $ZnCl_2$, $SnCl_2$, $CoCl_2$ or $AlCl_3$ and catalytic amounts of Pd(0)-compounds (scheme 8).[24]



25 **26**

de = 0 - 66 %

PG = Cbz, Ts

a) 1. 3.5 equiv. LDA, 1.2 equiv. MX_n, 10 % $Pd(PPh_3)_4$,
b) 2. CH_2N_2

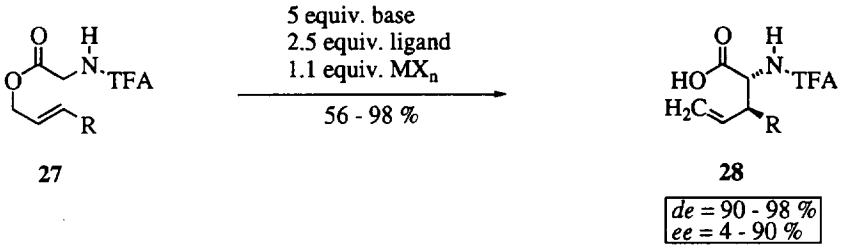
Scheme 8. Ester enolate Ireland-Claisen rearrangement using chiral amino acids as auxiliary according to Kazmaier et al.

The rearrangement could be explained by the formation of chelated enolates which underwent rearrangement. Because of the fixed enolate geometry and the expected chairlike transition state high degrees of diastereoselectivity were obtained. The best results concerning yield and diastereomeric excesses were obtained using tosyl protected amino acids as auxiliary (entry g,h). In the cases of the Cbz-protected amino acids only moderate asymmetric induction could be observed. Good yields were achieved in the presence of $ZnCl_2$ but with no stereoselection despite the fixed enolate geometry. In the presence of $SnCl_2$ better stereoselection could be observed but at loss of yield. The chiral amino acids which were used as auxiliary were not removed in any case.

Table 5. Ester enolate Ireland-Claisen rearrangement of chiral α-amino esters

entry	PG	MX_n	catalyst	yield [%]	*de* [%]	confg.
a	Cbz	$ZnCl_2$	–	28	24	(*S,S*)
b	Cbz	$ZnCl_2$	$PdCl_2$(cod)	20	30	(*S,S*)
c	Cbz	$ZnCl_2$	$Pd(PPh_3)_4$	75	0	(*S,S*)
d	Cbz	$SnCl_2$	$Pd(PPh_3)_4$	36	40	(*S,S*)
e	Cbz	$CoCl_2$	$Pd(PPh_3)_4$	35	30	(*S,R*)
f	Cbz	$AlCl_3$	$Pd(PPh_3)_4$	50	20	(*S,R*)
g	Ts	$ZnCl_2$	$Pd(PPh_3)_4$	85	65	(*S,S*)
h	Ts	$SnCl_2$	$Pd(PPh_3)_4$	82	66	(*S,S*)

In addition, Kazmaier et al. described an enantioselective rearrangement variant of chelated ester enolates which is depicted in scheme 8.



27 28

de = 90 - 98 %
ee = 4 - 90 %

Scheme 9. Enantioselective ester enolate Ireland-Claisen rearrangement according to Kazmaier et al.

Table 6. Enantioselective ester enolate Ireland-Claisen rearrangement using chiral bidentate ligands

entry	ligand	R	MX_n	yield [%]	*de*[a] [%]	*ee*[a] [%]	confg.
a	(S)-valinol	Me	Al(O*i*-Pr)$_3$	73	97	4	(2*R*,3*S*)
b	(−)-ephedrine	Me	Al(O*i*-Pr)$_3$	70	96	27	(2*R*,3*S*)
c	(+)-ephedrine	Me	Al(O*i*-Pr)$_3$	72	96	27	(2*S*,3*R*)
d	(−)-norephedrine	Me	Al(O*i*-Pr)$_3$	56	96	24	(2*R*,3*S*)
e	quinine	Me	$ZnCl_2$	95	90	10	(2*R*,3*S*)
f	quinine	Me	$MgCl_2$	98	91	69	(2*R*,3*S*)
g	quinine	Me	$CaCl_2$	73	96	65	(2*R*,3*S*)
h	quinine	Me	Al(O*i*-Pr)$_3$	70	98	86	(2*R*,3*S*)
i	quinine	H	Al(O*i*-Pr)$_3$	92	–	80	(2*R*)
j	quinine	Me	Al(O*i*-Pr)$_3$	98	98	86	(2*R*,3*S*)
k	quinine	Et	Al(O*i*-Pr)$_3$	88	98	88	(2*R*,3*S*)
l	quinine	*n*-Pr	Al(O*i*-Pr)$_3$	87	98	80	(2*R*,3*S*)
m	quinine	*i*-Pr	Al(O*i*-Pr)$_3$	72	98	88	(2*R*,3*S*)
n	quinine	*t*-Bu	Al(O*i*-Pr)$_3$	66	98	90	(2*R*,3*R*)
o	quinine	Ph	Al(O*i*-Pr)$_3$	97	98	79	(2*R*,3*R*)
p	quinidine	Me	Al(O*i*-Pr)$_3$	96	98	86	(2*S*,3*R*)
q	quinidine	Ph	Al(O*i*-Pr)$_3$	95	98	82	(2*S*,3*S*)

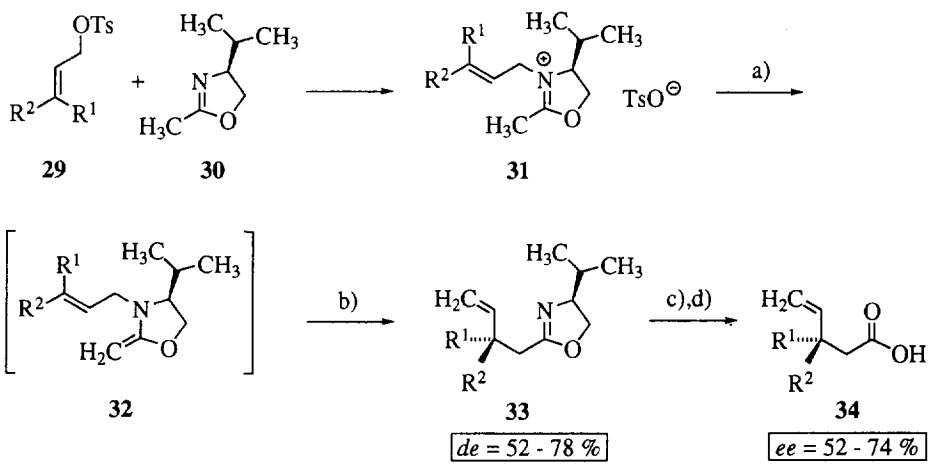
[a] The *de* and *ee* values were measured by GC analysis (Chira-Si-(L)-Val)

A high degree of asymmetric induction has been realized in the rearrangement of the corresponding chelated ester enolates **27** in the presence of Lewis acids like $ZnCl_2$, $CaCl_2$, $MgCl_2$ or Al(O*i*Pr)$_3$ and chiral bidentate ligands bearing the chirality information (scheme 9).[25] The best results are obtained with LHMDS as base and Al(*i*OPr)$_3$ as Lewis acid. Among the amino alcohol ligands quinine afforded the best results. In these

cases the *ee* values are ranging between 80 - 90 % (Table 6). Again, very high diastereoselectivities (>98 %) were observed due to the fixed enolate geometry of the chelated ketene acetal intermediates. The γ,δ-unsaturated α-substituted amino acids **28** were obtained in good to excellent yields.

2.2 Aza-Claisen rearrangements

Ireland-Claisen rearrangements in which one oxygen atom is replaced by a nitrogen atom are called Aza-Claisen rearrangements. There are two general possibilities of variation. On the one hand, N-allylamides can be used for the rearrangement process (X = N according to scheme 1). On the other hand, examples of the rearrangement of O-allylimidoesters were described (Y = N according to scheme 1). In both cases γ,δ-unsaturated amides were generated, but a different internal diastereoselectivity was observed. The rearrangement of N-allylamides led to the *syn*-configurated amides, whereas the *anti*-products were obtained by the rearrangement of O-allylimidoesters. The opposite geometry of the rearranged products is based on the different geometry of the double bond of the ketene acetals.



a) *n*-BuLi, THF, -78 °C, b) Decaline, 5h, 185 °C, c) Me_2SO_4 , d) KOH, aq. EtOH

Scheme 10. Aza-Claisen rearrangement of chiral N-allyl-N,O-ketene acetals according to Kurth et al.

The aza-Claisen rearrangement of N-allylic-N,O-ketene acetals has been known for quite some time and was introduced by Kurth et al..[26] In this procedure chiral oxazolines **30** were N-allylated by treatment with the allylic tosylates **29** and the resulting salts **31** deprotonated with *n*-butyl lithium to give the ketene acetals **32**, which were rearranged by heating in decaline without isolation. Then, the rearranged products **33** were hydrolyzed to give the γ,δ-unsaturated acids **34** in a few examples (scheme 10). Table 7 shows some of the

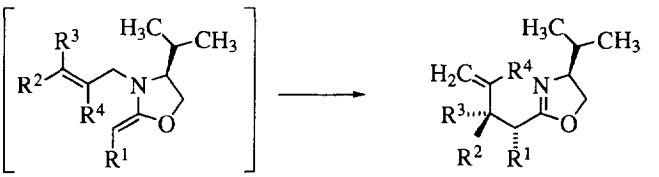
reported results. The starting oxazolines **30** were prepared by the common procedure of condensation of the appropriate imidate hydrochloride or free carboxylic acid with the requisite chiral aminoalcohol. Although the C- versus N-allylation is sometimes a problem employing tosylates the N-oxazolium salts were obtained in good yields. Furthermore, the salt formation required just a slight excess of the allylation reagents.

Table 7. Synthesis of γ,δ-unsaturated acids **34** according to Kurth et al.

entry	R^1	R^2	yield **33** [%][a]	*de* [%][b]	yield **34** [%][c]	*ee* [%]	confg. **34**	$[\alpha]_D$
a	H	Me	76	62	87	62	(*R*)	– 13.0
b	Me	H	75	74	81	72	(*S*)	+ 14.0
c	H	Me	71	52	85	52	(*R*)	+ 5.0
d	*i*-Pr	H	21	78	78	74	(*S*)	– 7.3

[a] Refers to the overall yield of **33** after chromatography starting from **30**; [b] The diastereomeric ratios were determined by HPLC of oxazolines **33** or ^{1}H NMR of the corresponding N-methyl oxazolinium salts; [c] Yield starting from **33**.

More examples of this rearrangement were reported, in which the auxiliary was not cleaved[27]. As depicted in scheme 11, the substitution pattern was varied in the oxazoline as well as in the allylic tosylate. The stereochemical outcome of the rearrangement of the N,O-ketene acetals was rationalized by a strongly preferred (*Z*)-configuration of the ketene acetal moiety. Furthermore, the N,O-ketene acetal face selectivity was based on the rapid nitrogen inversion prior to the rearrangement with an *anti* relationship between the N-allyl substituent and the isopropyl group of the chiral auxiliary. The results of representative examples of these rearrangements are listed in Table 8. This procedure also opened up the possibility to generate products with quarternary stereogenic centers.[28]



35 **36**

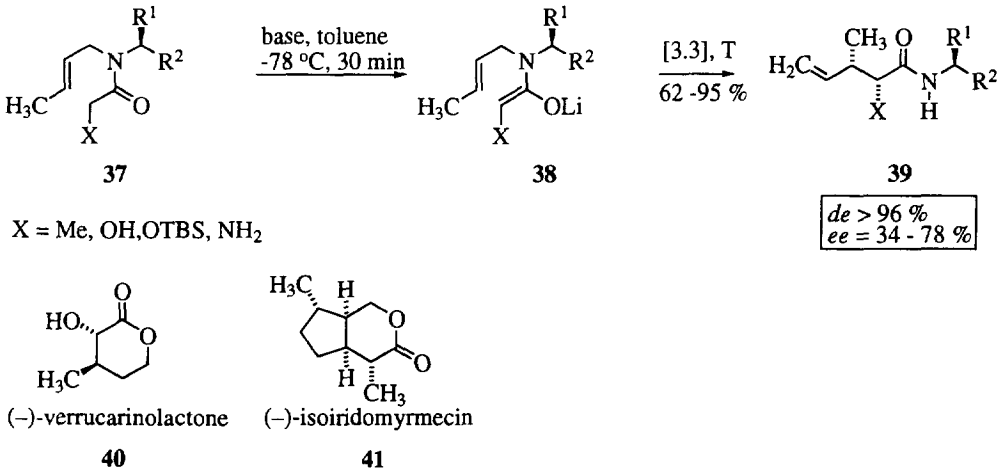
Scheme 11. Variation of the substitution pattern in the rearrangement of N-allylic N,O-ketene acetals

Table 8. Rearrangement of N-allyl-N,O-ketene acetals **35**

entry	R^1	R^2	R^3	R^4	yield **36** [%][a]	*dr* (*S,R,S*):(*S,S,R*):*S,R,R*):(*S,S,S*)[b]
a	$PhCH_2$	H	Me	Me	84	92:3:5:<1
b	$PhCH_2$	Me	H	Me	87	11:<1:87:2
c	$PhCH_2$	H	Me	H	82	83:2:13:2
d	$PhCH_2$	Me	H	H	84	17:2:79:2
e	Me	H	Me	H	73	82:2:14:2
f	Me	Me	H	H	75	15:2:81:2

[a] combined yield of the four oxazolines after chromatographic purification; [b] The diastereomeric ratios were determined by ^1H NMR spectroscopy of the corresponding N-methyl oxazolinium salts.

Tsunoda et al. reported the asymmetric [3.3]-sigmatropic rearrangement of N-allyl amides **37** using chiral amine derivatives as auxiliaries (scheme 12).[29] Upon deprotonation with different lithium amide bases the intermediate N,O-ketene acetals **38** underwent rearrangement by heating in a sealed tube leading to γ,δ-unsaturated α,β-substituted amides **39** in good yields, excellent *syn*-diastereoselectivities and moderate to good asymmetric induction. The results are listed in table 9.



Scheme 12. Aza-Claisen rearrangement of chiral N-allylic amides **37** according to Tsunoda et al.

The good asymmetric induction resulting from the aza-Claisen rearrangement of N-allylpropanamides could be extended to substituted amides **37** bearing a hetero atom in α-position (entry k-m).[30] In these cases the results concerning yield and diastereomeric ratios were as good as in the cases of the propionamide

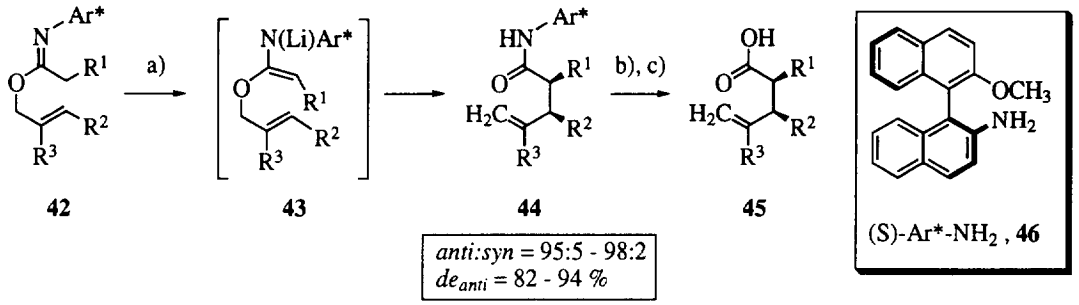
derivatives **37a-j**. As application to natural product synthesis the usefulness of these reaction could be proven by the development of the synthesis of (–)-verrucarinolactone **40** and (–)-isoiridomyrmecin **41**.[31] The rearranged γ,δ-unsaturated amide **37k** has been converted to the alcohol *via* hydroboration and subsequent cyclisation led to (–)-verricarinolactone. The flexibility of the rearrangement was demonstrated in the synthesis of (–)-isoiridomyrmecin, where an amide with an endocyclic double bond was rearranged in the key step leading to a product bearing an exocyclic double bond, which was converted to the natural product in four steps.

Table 9. Synthesis of γ,δ-unsaturated amides **39**

entry	R^1	R^2	X	base	solv.	T [°C]	t [h]	yield [%]	*dr*[a]
a	Me	Ph	Me	LDA	THF	120	6	66	77:21:1:1
b	Me	Ph	Me	LDA	THF	140	2	79	77:22:0:0
c	Me	Ph	Me	LDA	toluene	120	6	68	89:11:0:0
d	Me	Ph	Me	LHMDS	toluene	120	6	85	89:11:0:0
e	Me	$MeOC_6H_4$	Me	LHMDS	toluene	120	6	76	88:12:0:0
f	Me	2,6-$Me_2C_4H_6$	Me	LHMDS	toluene	120	6	90	87:12:2:0
g	Me	Naphthyl	Me	LHMDS	toluene	120	6	83	82:16.0:2
h	Et	Ph	Me	LHMDS	toluene	120	6	80	92:8:0:0
i	*i*-Pr	Ph	Me	LHMDS	toluene	120	6	76	85:15:0:0
j	Me	*t*-Bu	Me	*t*-BuLi	toluene	150	4	38	10:90:0:0
k[b]	Me	Ph	OH	LHMDS	toluene	80	15	95	13:86:0:1
l[b]	Me	Ph	OTBS	LHMDS	toluene	120	6	62	33:67:0:0
m	Me	Ph	NH_2	LHMDS	toluene	20	15	89	89:11:0:0

[a] The *dr* values were determined by LC or GLC analysis, confg. of the newly formed stereogenic centres(*R,S*):(*S,R*):(*S,S*):(*R,R*); [b] In these cases (*R*)-phenylethylamin was used as auxiliary.

An asymmetric aza-Claisen rearrangement of allylic imidoester enolates **43** was introduced recently by Metz et al..[32] As depicted in scheme 13, the rearrangement occurred after deprotonation with lithium diethylamide at 0 °C to give the amide products **44** in moderate yield, but with very good stereoselectivity. The anilides **44** then could be transformed into the corresponding unsaturated acids **45** without significant epimerisation in α-position to the carboxyl group *via* iodolactonization in the presence of water and reduction of the iodolactones. In this procedure the chiral auxiliary (*S*)-**46** could be recovered.



a) LDEA, THF, -78 ° C, b) I_2 , DME, H_2O, 20 °C, c) Zn, HOAc, reflux

Scheme 13. Aza-Claisen rearrangement of allylic imidoester enolates **43** reported by Metz et al.

The N-allylic imido esters **42** were prepared by formation of the amides of **46**, transformation into the corresponding imido chlorides by reaction with phosgene under mild conditions and finally reaction of the crude imido chlorides with a slight excess of the desired lithium alcoholates. The conditions and results for this rearrangement are listed in table 10.

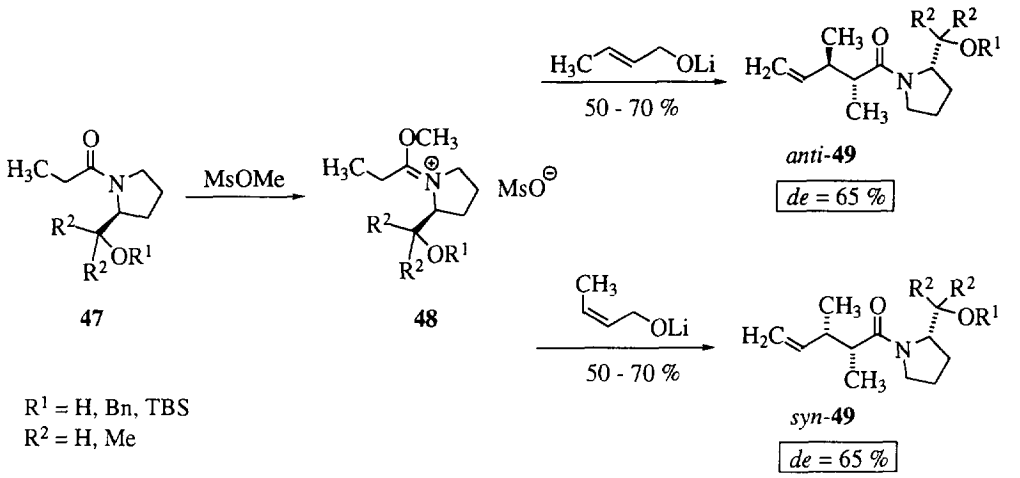
Table 10. Aza-Claisen rearrangement of allylic imidoester enolates **43** according to Metz et al.

entry	R^1	R^2	R^3	t (h)[a]	yield **44**[b] [%]	*anti:syn* [%][c]	de_{anti} [%][c]
a	Me	Me	H	5	78	98:2	94
b	Me	Et	H	8	60	97:3	94
c	Et	Me	H	10	59	95:5	94
d	Me	Me	Me	23	56	97:3	92
e	Me	Et	Me	40	43	95:5	92
f	Et	Me	Me	48	47	95:5	82

[a] Rearrangement time (0°C) after deprotonation; [b] Yield of all diastereomers of **44**; [c] According to ^{1}H NMR integration.

The common sequence of deprotonation/silylation for such rearrangements failed in this case. Whereas the N-silyl ketene acetals did not rearrange even at room temperature, the corresponding lithium azaenolates **43** reacted at 0 °C. The time for the rearrangement depended on the substitution pattern of the allylic double bond, the imidates reacted slowly within 1-2 days (entries d-f), partly they just needed a few hours (entries a-c). The high *anti*-selectivities were rationalized by a favoured $(Z)_{CC}$-configuration of the azaenolates and a preferred chairlike transition state. In addition to the relatively short reaction times it was suggested that it might be possible to further purify the crystalline anilides by simple recrystallization.

Welch et al. reported an asymmetric amide acetal Claisen rearrangement using chiral proline derivatives. The N-propionyl amides have been used to prepare asymmetric N,O-ketene acetals, which can be employed in the first room temperature amide acetale [3.3]-rearrangement (scheme 14).[33]



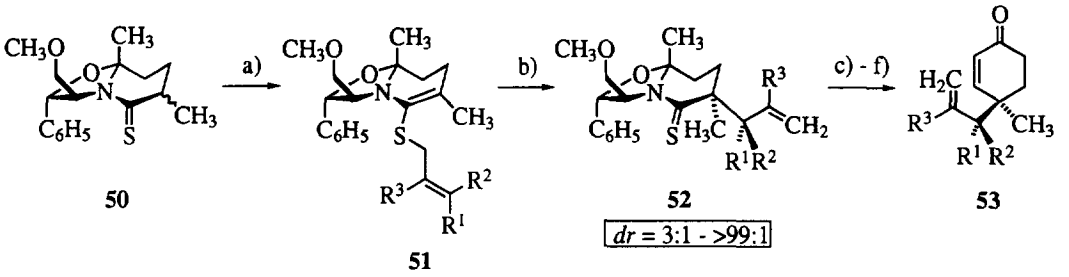
Scheme 14. Amide acetal rearrangement according to Welch et al.

N-propionyl derivatives **47** were converted into the ketene acetals by adding methyl trifluoromethanesulfonate. Treatment of the salts **48** with 3 equiv. of lithium salt of (*E*)- or (*Z*)-but-2-en-1-ol led directly to the formation of amides *anti*-**49** or *syn*-**49** as the major products of the rearrangement. The amide acetal Claisen rearrangement generated products in good yields but the stereoselectivity was only moderate with an average asymmetric induction of 4.7:1. The corresponding thioamides were reacted leading to products with the opposite configuration compared with the amides. Furthermore α-fluorinated compounds were rearranged according to this method but without any remarkable improvement of the stereoselectivity.[34]

2.3. Thia-Claisen rearrangements

Compared to the well-known oxygen analog the thia-Claisen rearrangement was given less attention. However, there are some interesting examples in this family of rearrangements, which shall be presented here.

As a result of employing chiral bicyclic lactams as auxiliaries in asymmetric synthesis, Meyers et al.[35] reported a highly stereoselective thia-Claisen rearrangement, as shown in scheme 15.



a)LDA, $R^1R^2C{=}CR^3CH_2X$, b) Δ, c) Et_3OBF_4, d) Red-Al, e) $HClO_4$, $EtOH/H_2O$, f) KOH, MeOH

Scheme 15. Thia-Claisen rearrangement of bicyclic S-allylic thiolactam systems **51** according to Meyers et al.

The lactam precursor was readily obtainable in enantiomerically pure form by a method elaborated previously in the Meyers group. After methylation in α-position and reaction with the Belleau reagent the thiolactam **50** was obtained in excellent yield. Then this compound was alkylated with different allylic halides at the sulfur atom to give **51**. The rearrangement of the N,S-ketene acetals **51** occurred in good yields with partly excellent diastereoselectivity as shown in table 11.

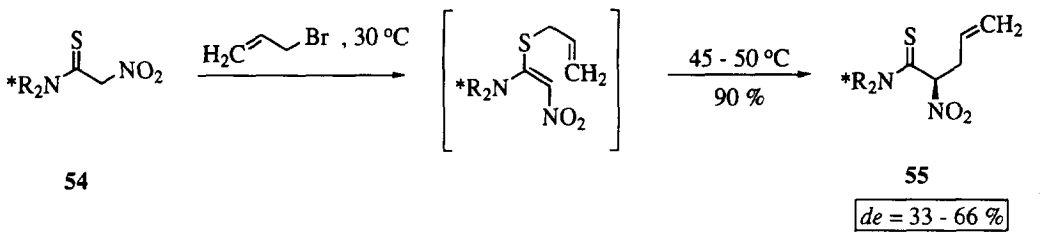
Table 11. Thia-Claisen rearrangements of bicyclic N,S-ketene acetals **51**

entry	R^1	R^2	R^3	T (°C)[a]	yield **52** [%]	*dr*[b]
a	H	H	Me	25	71	3:1
b	Me	H	H	25	79	91:9
c	Ph	H	H	140	48	>99:1
d	Me	Me	H	140	68	>99:1

[a] Rearrangements at room temperature were carried out in THF, otherwise xylene was the solvent employed; [b] The diastereomeric ratios were determined by capillary GLC and 300 MHz NMR integration of the benzylic proton in the oxazolidine ring.

The rearranged thiolactams **52b,d** were transformed into the corresponding cyclohexenone systems **53** in high enantiomeric purities to demonstrate the synthetic value of this process. It was suggested, that more complex substances with vicinal stereogenic quaternary centres, like trichodiene or bazzanene for example, might be successfully synthesized in an asymmetric manner by such a thia-Claisen rearrangement as key step.

An asymmetric thia-Claisen rearrangement under mild conditions was described by Rajappa et al..[36] As shown in scheme 16, chiral α-nitro substituted thioamides **54** reacted with allylbromide which rearranged to the allylic substituted product **55** upon rising the temperature of the reaction mixture.



54 55

de = 33 - 66 %

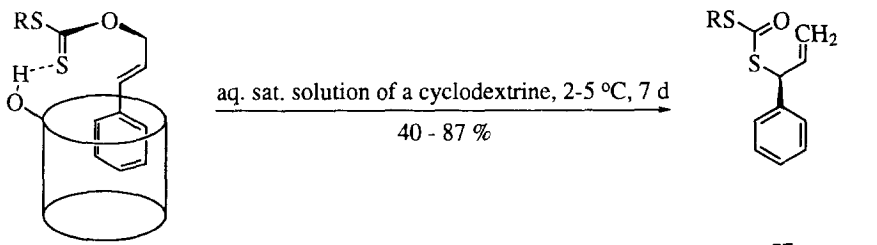
Scheme 16. Thia-Claisen rearrangement reported by Rajappa et al.

Table 12. Thia-Claisen rearrangement according to Rajappa et al.

entry	$^{*}R_2N$	yield [%]	*de* [%]	confg.[a]
a	(*S*)-proline ethylester	90	66	(*S*,*R*)
b	(*S*)-valine ethylester	–	33	(*S*,*R*)

[a] The configuration was deduced from NMR shift experiments.

Cyclodextrines were employed as source of chirality information in a thia-Claisen rearrangement of O-allylic xanthates **56**, reported by Hisano et al..[37] Although the enantioselectivities of the rearranged thioesters **57** were only low, this interesting version is depicted in scheme 17.



56 57

ee = 3 - 46 %

Scheme 17. Thia-Claisen rearrangement in the presence of cyclodextrines according to Hisano et al.

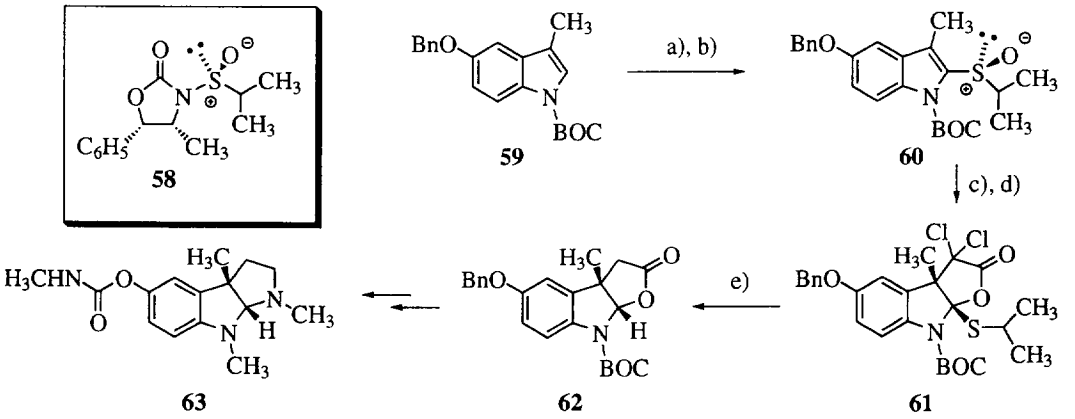
Table 13. Cyclodextrine-mediated asymmetric thia-Claisen rearrangement of allylic xanthates

entry	R	CD	yield [%]	$[\alpha]_D$	ee[a] [%]
a	Me	α	40	–	3
b	Me	β	80	+ 21.9	46
c	Me	γ	87	–	12
d	Et	β	80	– 17.7	10
e	Bn	β	67	– 8.8	11

[a] The *ee* values were determined by HPLC using a Daicel Chiracel OJ column (solvent: *n*-hexane-EtOH 8:2)

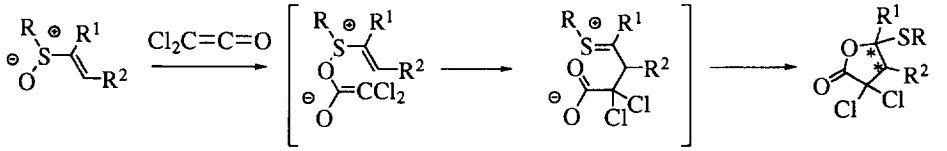
2.4 Miscellaneous Claisen rearrangements

The [3,3]-sigmatropic rearrangement of vinylic oxosulfonium enolates, sometimes called "additive Pummerer rearrangement", in combination with subsequent lactonization,[38] was employed in an asymmetric synthesis of precursors of the physostigmine alkaloids and aflatoxins by Marino et al..[39]



a) *s*-BuLi, b) **58**, THF, -78 °C, c) Zn/CuCl, THF, Δ, d) Cl_3CCOCl, THF, -5 °C, e) Bu_3SnH/AIBN, toluene, Δ

Proposed mechanism for the rearrangement in steps c) and d):



Scheme 18. Synthesis of Physostigmine according to *Marino et al.*

The chiral N-isopropylsulfinyloxazolidinone auxiliary **58** was prepared as single diastereomer from the corresponding oxazolidinone by the common *Evans* procedure. The reaction with the indole **59** gave the chiral vinylic sulfoxide **60** in high yield and with more than 95 % enantiomeric excess, which was subsequently transformed upon reaction with dichloroketene *in situ* to the thio-substituted lactone **61**. The physostigmine precursor **62** was obtained in moderate overall yield and with an *ee* value of 70 to 75 %. The precursor **62** was converted into the naturally occurring enantiomer of physostigmine **63** in eight steps.

The proposed mechanism for these reactions is also depicted in scheme 18. Interestingly, further extrapolations to larger alkyl groups for the sulfoxide did not result in higher asymmetric induction because of alternative reaction pathways of the sulfoxide. Although this method actually represents a chirality transfer process rather than an asymmetric [3,3]-rearrangement in the key step, it is listed here because the chiral starting material was synthesized under auxiliary control and the method itself is noteworthy.

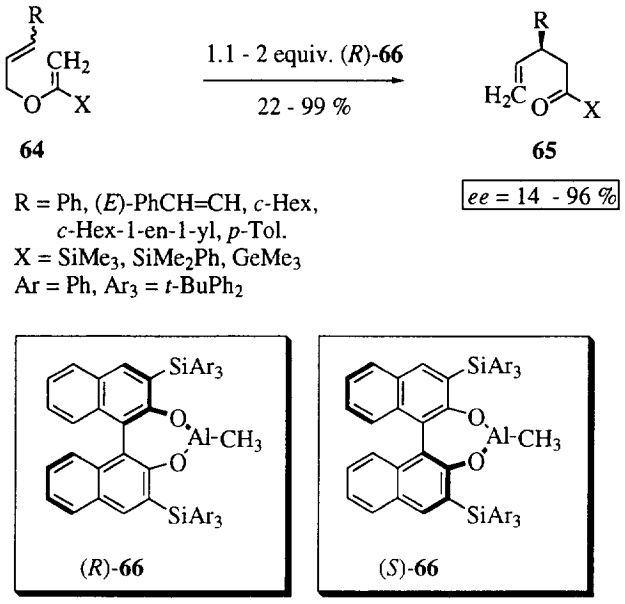
3. Cope rearrangements

The all-carbon version of the [3,3]-sigmatropic rearrangements, discovered by Cope et al. in 1940, generally is viewed as the prototype for this class of reactions, all other versions are formally derived by replacement of carbon by heteroatoms. Although the Cope rearrangement itself can be a powerful tool in the construction of stereogenic centres by chirality transfer reactions, the possibilities for asymmetric syntheses are limited here, compared to the heteroatom versions. To the best of our knowledge, no truly asymmetric Cope rearrangement has been reported yet.

3.1 Oxa-Cope (Claisen) rearrangements

The oxa-Cope rearrangement of allyl vinyl ethers, better known as Claisen rearrangement, was discovered as the first of all these rearrangements in 1912 by *Claisen et al.*.[5] Within the basic Claisen rearrangement, again, much effort was put in chirality transfer reactions. Accompanied by the development of the chiral Lewis acid catalysts, the interest then focussed on the possibility of enantioselective Claisen rearrangements.

H. Yamamoto et al. reported the enantioselective rearrangement catalysed by chiral organoaluminium reagents leading to acylsilanes and acylgermanes in moderate to excellent yield and mostly good enantiomeric excesses (scheme 19).[40] This flexible rearrangement variant allows the synthesis of both enantiomeric products by using one of the two possible chiral organoaluminium reagents (*S*)- or (*R*)-**66** as desired.



Scheme 19. Enantioselective Claisen rearrangement *via* chiral organoaluminium reagents described by H. Yamamoto et al.

The allyl vinyl ethers were prepared by treatment of the corresponding allylic alcohol with the appropriate silyl or germyl substituted allyl vinyl ethers in the presence of catalytic mercuric acetate. The chiral aluminium reagent (*S*)- or (*R*)-**66** was generated by treatment of the enantiomerically pure binaphthol derivative in toluene with $AlMe_3$/hexane at room temperature. The aluminium reagent **66** subsequently reacted with the allyl vinyl ether **64** at –20 °C for 25 h to furnish the rearrangement products (*S*)- or (*R*)-**65**. Table 14 lists the results of the rearrangement. The best *ee* values were obtained in the cases of the trimethylgermanyl allyl vinyl ethers **65n,o** and the dimethylphenylsilyl allyl vinyl ethers **65e,f**. Among the various trialkyl groups of the binaphthyl ligand the butyl diphenylsilyl group afforded the best results.

As shown in the table, ethers of (*E*)- as well as (*Z*)-allylic alcohols could be used. (*Z*)-allylic α-silylvinylethers **64p-v** produce the optically active acylsilanes with the same absolute configuration as these from the (*E*)-allylic α-silylvinylether. Based on these data the allylic α-silylvinylethers proceed by the way of a boatlike transition state. The more hindered Ar_3 = *t*-$BuPh_2$ seemed to destabilize the boatlike transition state as in these cases lower *ee* values were observed.

Furthermore, very recently the Yamamoto group reported the enantioselective rearrangement of non-silylated or germylated allyl vinyl ethers to γ,δ-unsaturated aldehydes in very good yields (63 - 97 %) and mostly very good enantioselectivities (61 - 92 %).[41] In these cases either binaphthtol derivatives or C_3-symmetric phenol aluminium reagents were used.

Table 14. Enantioselective Claisen rearrangement using chiral aluminium reagents.

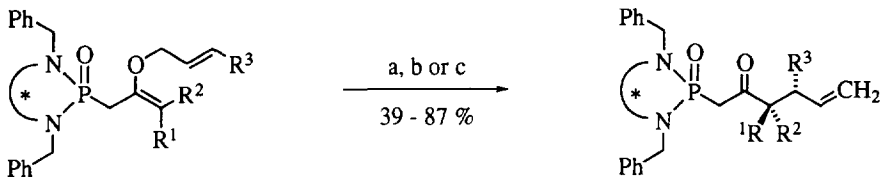
entry	R	X	$(E/Z)^a$	catalyst	yield [%]	ee^b [%]	confg.
a	Ph	$SiMe_3$	(*E*)	$Ar_3 = t\text{-}BuMe_2$	22	14	(*S*)
b	Ph	$SiMe_3$	(*E*)	Ar = Ph	86	80	(*S*)
c	Ph	$SiMe_3$	(*E*)	$Ar_3 = t\text{-}BuPh_2$	99	88	(*S*)
d	Ph	$SiMe_3$	(*E*)	Ar = Ph	85	80	(*R*)
e	Ph	$SiMe_2Ph$	(*E*)	Ar = Ph	65	85	(*S*)
f	Ph	$SiMe_2Ph$	(*E*)	$Ar_3 = t\text{-}BuPh_2$	76	90	(*S*)
g	*c*Hex	$SiMe_3$	(*E*)	Ar = Ph	79	61	(*S*)
h	*c*Hex	$SiMe_3$	(*E*)	$Ar_3 = t\text{-}BuPh_2$	84	71	(*S*)
i	*c*-Hex-1-en-1-yl	$SiMe_3$	(*E*)	Ar = Ph	83	96	(*S*)
j	*c*-Hex-1-en-1-yl	$SiMe_3$	(*E*)	$Ar_3 = t\text{-}BuPh_2$	96	60	(*S*)
k	*p*-Tol	$SiMe_3$	(*E*)	Ar = Ph	69	78	(*S*)
l	Me	$SiMe_3$	(*E*)	Ar = Ph	80	43	(*S*)
m	(*E*)-PhCH=CH	$SiMe_3$	(*E*)	Ar = Ph	40	60	(*S*)
n	Ph	$GeMe_3$	(*E*)	Ar = Ph	73	91	(*S*)
o	Ph	$GeMe_3$	(*E*)	$Ar_3 = t\text{-}BuPh_2$	68	93	(*S*)
p	Ph	$SiMe_3$	(*Z*)	Ar = Ph	56	78	(*S*)
q	Ph	$SiMe_3$	(*Z*)	Ar = Ph	77	67	(*S*)
r	Ph	$SiMe_3$	(*Z*)	$Ar_3 = t\text{-}BuPh_2$	64	58	(*S*)
s	*c*-Hex-1-en-1-yl	$SiMe_3$	(*Z*)	Ar = Ph	81	65	(*S*)
t	*c*-Hex-1-en-1-yl	$SiMe_3$	(*Z*)	$Ar_3 = t\text{-}BuPh_2$	76	50	(*S*)
u	*c*-Hex	$SiMe_3$	(*Z*)	Ar = Ph	44	75	(*S*)
v	(*E*)-PhCH=CH	$SiMe_3$	(*Z*)	Ar = Ph	70	58	(*S*)

[a] Configuration of the C=C double bond of the allylic alcohol moiety; [b] The *ee* values were determined by GLC analysis after conversion to the ketals of (2*R*,3*R*)-butanediol.

Denmark et al. reported an asymmetric carbanion accelerated Claisen rearrangement. Although a number of their investigations concentrated on the arylsulfonyl group to stabilize the carbanion, two asymmetric variants using chiral phosphonamides were decribed. The first method reported was based on chiral C_2-symmetric diamines (scheme 20).[42]

The phosphonamides **67** reacted readily at −20 °C to give γ,δ-unsaturated ketones **68** with good yields. A high degree of *syn/anti*-diastereoselectivity was obtained using *n*-BuLi as the base (entry g). In all other cases only one stereogenic centre was generated. However, the internal induction was very high but the relative

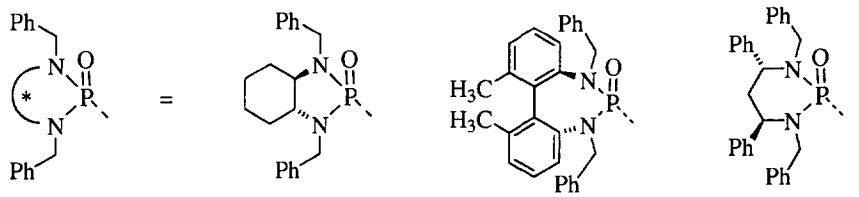
asymmetric induction with all three chiral phosphonamide structural classes **69a-c** was poor varying from 4 to 50 %. The rate of reaction follows solvent polarity.



67 **68**

de = 4 - 50 %

a: *n*-BuLi or LDA, THF
b: KH, DMSO
c: toluene, Δ



69a **69b** **69c**

Scheme 20. Asymmetric Claisen rearrangement using chiral C_2-symmetric phosphonamides according to Denmark et al.

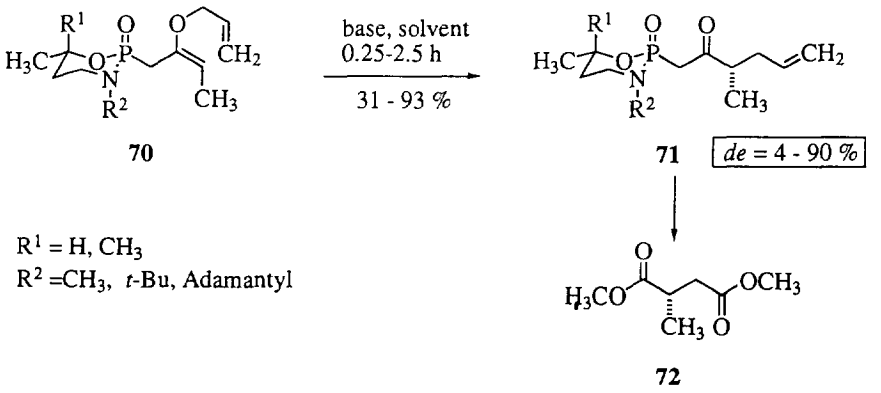
The excellent internal asymmetric induction observed for the phosphonamides is attributed to the strong preference for the chairlike transition state compared to the alternative boatlike transition state due to the nonbonding interactions with the N-benzyl groups. The chairlike transition state originates from the sickle shaped allyl anion, the chelation of the lithium atom, the pyramidality of the nitrogen atoms and the orientation of the benzyl groups.

Since the design of an appropriate auxiliary was seen to require a clear difference of the preferred orientation of nitrogen groups on either side of the phosphonamide or chemically dinstinct groups bearing substituents of highly disparate steric requirement another more potential auxiliary modified phosphorous stabilized method was developed using 1,3,2-oxazaphosphorinanes,[43] in which the two sides of the anion are highly differentiated because of the oxygen lone pair and the nitrogen *tert*-butyl group.

Table 15. Claisen rearrangement using chiral C_2-symmetric phosphonamides to form **68**

entry	R^1	R^2	R^3	base	solv	T [°C]	t [h]	*R_2PO	yield [%]	*syn:anti*	*dr*
a	Me	H	H	*n*-BuLi	THF	0	1	a	85	–	58:42
b	Me	H	H	LDA	THF	0	0.75	a	64	–	58:42
c	Me	H	H	KH	DMSO	20	2	a	79	–	31:69
d	Me	H	H	KH	DMSO	20	2	a	78	–	48:52
e	Me	H	H	none	toluene	110	2	a	81	–	62:38
f	*i*-Pr	H	H	*n*-BuLi	THF	0	1	a	74	–	57:43
g	Me	H	Me	*n*-BuLi	THF	0	1	a	74	97:3	57:43
h	Me	Me	Me	*n*-BuLi	THF	–20	1	a	85	–	60:40
i	Me	H	H	none	toluene	110	4	b	75	–	30:70
j	Me	H	H	*n*-BuLi	THF	0	1	b	39	–	75:25
k	Me	H	H	KH	DMSO	20	1	b	60	–	40:60
l	Me	Me	Me	*n*-BuLi	THF	–20	0.5	c	87	–	55:45
m	Me	Me	Me	none	toluene	110	0.5	c	87	–	75:25

As shown in scheme 21 the oxazaphosphorinanes **70** rearranged anionically under mild conditions in good yields leading to γ,δ-unsaturated ketones **71**. The degree of asymmetric induction was definitely higher than in the rearrangement of the C_2-symmetric phosphonamides.



Scheme 21. Asymmetric Claisen rearrangement using 1,3,2-oxazaphosphorinanes by Denmark et al.

The *de* values ranged up to 90 %. The absolute sense of asymmetric induction was determined by oxidative degradation of the rearrangement products (entry m-t) leading to the diester **72**.

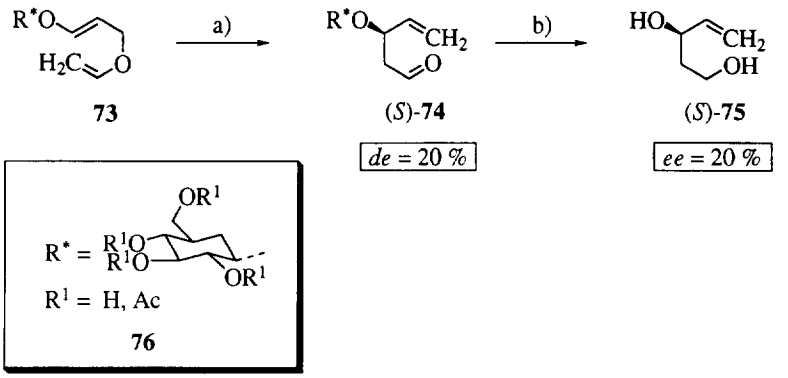
Furthermore, an example was decribed which allowed the generation of adjacent stereogenic centres with good internal and relative induction.

Table 16. Claisen rearrangement using 1,3,2-oxazaphosphorinanes to form **71**

entry	R^1	R^2	base	solvent	yield [%]	*de* [%]
a	Me	*t*-Bu	KDMSO	DMSO:THF 3:1	77	4
b	Me	*t*-Bu	KDMSO/LiCl	DMSO:THF 3:1	81	82
c	Me	*t*-Bu	LiDMSO	DMSO:THF 1:1	73	90
d	Me	*t*-Bu	LiDMSO	THF	64	88
e	Me	*t*-Bu	LiDMSO	Et_2O	31	80
f	Me	*t*-Bu	LiDMSO	THF	68	88
g	Me	*t*-Bu	*n*-BuLi	THF	51	90
h	Me	Adamantyl	none	toluene	93	20
i	Me	Adamantyl	LiDMSO	THF	58	88
j	Me	Adamantyl	LiDMSO	DMSO:THF 1:1	74	88
k	Me	Me	none	toluene	86	6
l	Me	Me	LiDMSO	THF	62	4
m	H	*t*-Bu	KDMSO	DMSO:THF 3:1	62	0
n	H	*t*-Bu	KDMSO/LiCL	DMSO:THF 3:1	77	30
o	H	*t*-Bu	KDMSO/2LiCl	DMSO:THF 3:1	69	60
p	H	*t*-Bu	KDMSO/6LiCl	DMSO:THF 3:1	78	80
q	H	*t*-Bu	KDMSO/12LiCl	DMSO:THF 3:1	65	78
r	H	*t*-Bu	LiDMSO	DMSO:THF 3:1	65	80
s	H	*t*-Bu	none	DMSO:THF 3:1	93	30
t	H	*t*-Bu	none/LiCl	DMSO:THF 3:1	90	28

Augé et al. described an asymmetric Claisen variant using the glucose auxiliaries **76**.[44] Both of the enantiomerically pure (*R*)- and (*S*)-diols **75** were prepared *via* this method with D-glucose or its acyl protected derivative as auxiliary. The rearrangement was carried out by heating the allyl vinyl ether **73** to 60 °C for 4 h in water and subsequent reduction with $NaBH_4$ leading to alcohols **75** with an moderate diastereomeric excess of 20 %. The chiral auxiliary was removed by enzymatic hydrolysis in the presence of β-glucidase. As mentioned

above, the rearrangement of the allyl vinyl ether with an α-glucose moiety as chiral auxiliary led to the (*R*)-**74**, whereas the enantiomeric (*S*)-compound was formed using the β-glucose moiety **76**.



a) MeONa, MeOH,
b) 1. NaOH, 60 °C, pH 12, $NaBH_4$, 2. Ac_2O, pyridine, 3. water, β-glycosidase

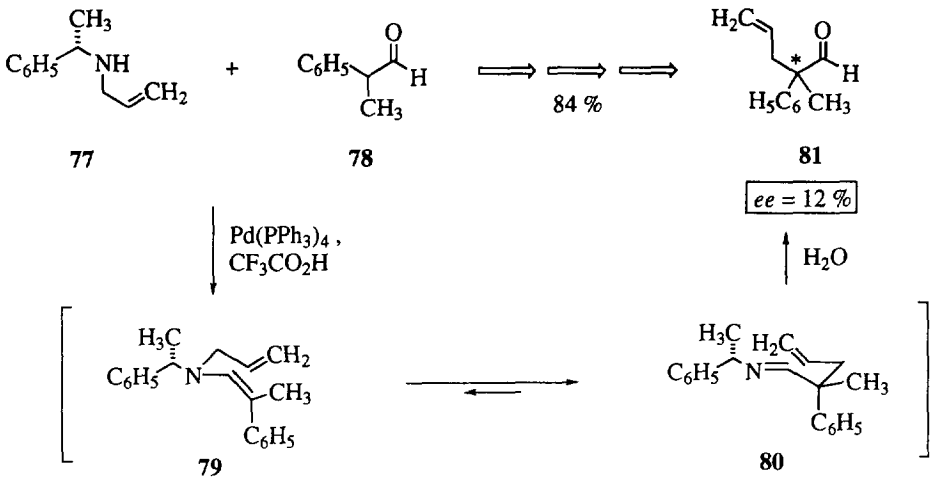
Scheme 22. Claisen rearrangement using carbohydrate auxiliaries according to Augé et al.

3.2 Aza-Cope rearrangements

Although changing from oxygen to nitrogen in hetero-Cope rearrangements gives a potentially powerful opportunity for the introduction of stereocontrol *via* a chiral amine auxiliary, examples with high asymmetric inductions are rather rare.

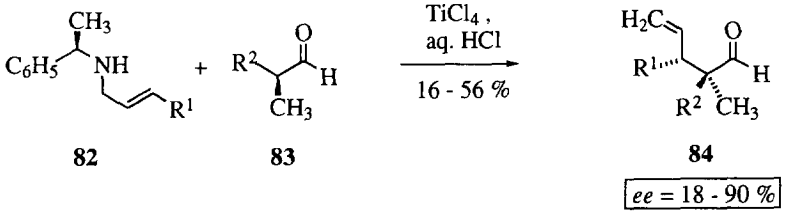
Like all of these rearrangements, the aza-Cope reaction can be carried out thermally or at lower temperatures by catalysis of various Lewis acids or transition metal complexes. In an example of Murahashi et al.,[45] depicted in scheme 23, the N-allylic enamine was generated and rearranged *in situ* to give the γ,δ-unsaturated aldehyde **81** in 84 % yield, but with an *ee* value of only 12 %.

Scheme 23 shows one drawback of the 3-aza-Cope rearrangement. To avoid side reactions of the N-allylic enamines, especially undesired [1,3]- instead of [3,3]-shifts, it is necessary to use geminally disubstituted enamine systems, which leads to the formation of quarternary carbon centres in the α-position of the rearranged imines. Unfortunately, this gives rise to problems for the stereoselectivity because the difference in the relative energies of the competing transition states involved decreases. Incidentally, the quarternary centre does not prevent the system from racemization, since the rearrangement is reversible, although the equilibrium lies far on the right side. In addition, the disubstituted enamines usually are obtained as mixtures of (*E*)- and (*Z*)-isomers and undergo further isomerization upon contact with the Lewis acid catalysts, which normally is a faster reaction than the rearrangement itself.



Scheme 23. Aza-Cope rearrangement of *in situ* generated N-allylic enamines according to Murahashi et al..

Despite these problems, there is one example of a double asymmetric 3-aza-Cope rearrangement with a high degree of stereocontrol reported by Bailey et al. as depicted in scheme 24.[46]



Scheme 24. Aza-Cope rearrangement of *in situ* generated N-allylic enamines mediated by titanium tetrachloride reported by Bailey et al.

The allylamine **82** was refluxed with the aldehyde **83** in toluene, then titanium tetrachloride was added to trigger the rearrangement, and finally the unsaturated aldehyde **84** was isolated after acidic hydrolysis. Table 17 lists the results of this reaction.

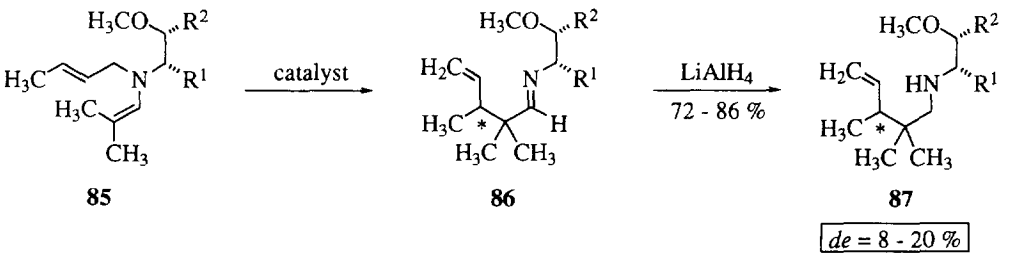
The relatively high inductions of this example to date could not be reached with isolated N-allylic enamines, even on formally the similar systems. Some examples are listed in table 17.

Table 17. Double asymmetric Aza-Cope rearrangement according to Bailey et al..

entry	R^1	R^2	solvent	T (°C)	catalyst	yield[b]	*de* [%][a]	*ee* [%][a]
a	H	Ph	toluene	110	$TiCl_4$	16	–	30
b	Me	Me	toluene	110	$TiCl_4$	48	–	18
c	Me	Ph	toluene	110	$TiCl_4$	56	72	81 (76)
d	Me	Ph	toluene	55	$TiCl_4$	46	70	90 (98)
e	Me	Ph	benzene	55	$TiCl_4$	18	40	1 (12)
f	Me	Ph	o-dichloro-benzene	179	none	44	50	15 (13)

[a] The diastereomeric ratios were determined *via* ^{19}F- and ^1H-NMR of the (*R*)-Mosher-esters of the corresponding unsaturated alcohols, obtained after $NaBH_4$ reduction of **84**. The diastereomeric ratios were corrected by comparison with the *de* from the ^1H-NMR of **84** . The absolute configurations were not determined. The *ee* values of the minor products were listed in parentheses; [b] The yields for **84** based on allylamines **82**. All reactions were conducted over a standard 24 h and not optimized.

The first attempts towards the asymmetric 3-aza-Cope rearrangement of isolated, chiral N-allylic enamines were reported by Stille et al. (scheme 25).[47] Starting from the corresponding primary amine auxiliaries the allylic amines were prepared *via* condensation with crotonaldehyde and subsequent chemoselective reduction with sodium borohydride. The enamines **85** then were synthesized by acid catalyzed condensation with isobutyraldehyde and azeotropic removal of the water. The rearrangement of the allyl enamines **85** occurerd by treatment with $TiCl_4$ forming the corresponding imines **86**. Although the removal of the auxiliary could be achieved by hydrolysis, the imines **86** were reduced to the amines **87** to determine the diastereomeric ratios.



85 **86** **87**

Scheme 25. Aza-Cope rearrangement of chiral N-allylic enamines **85** according to Stille et al.

The results for this asymmetric 3-aza-Cope rearrangement are shown in table 18. Stille et al. argued that the poor asymmetric induction in these rearrangements can be reasoned by an insignificant steric difference between the allylic and the enamine substituents in the competing diastereomeric transition states, because the

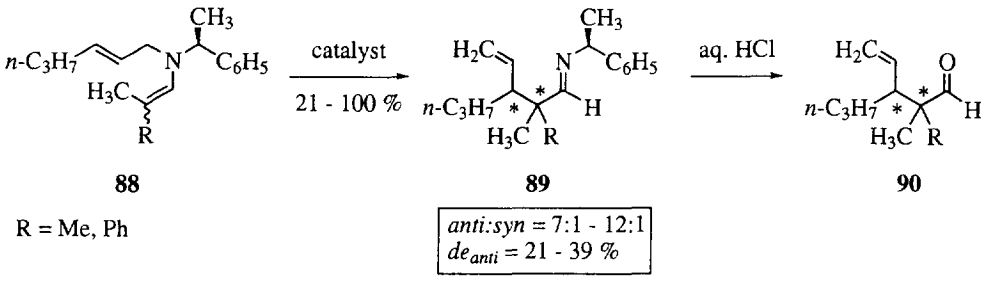
gauche-interactions do not provide the energy differences necessary to generate a preference for one transition state over the other. A solution to this problem would be the introduction of a substituent at the α-position of the allylic system, but then this is a chirality transfer reaction without the need of an additional auxiliary.

Table 18. Aza-Cope rearrangement mediated by catalysts

entry	R^1	R^2	catalyst	yield[a]	*de* [%]
a	Me	H	$TiCl_4$	77	15
b	H	Me	$TiCl_4$	72	20
c	H	Me	HCl	86	8

[a] Yield of unsaturated amine **87** based on allylic enamine **85**.

Independent from Stille's work we investigated the asymmetric 3-aza-Cope rearrangement.[48] Although various catalysts, auxiliaries and reaction conditions were tested, the diastereoselectivities were improved just moderately.



88

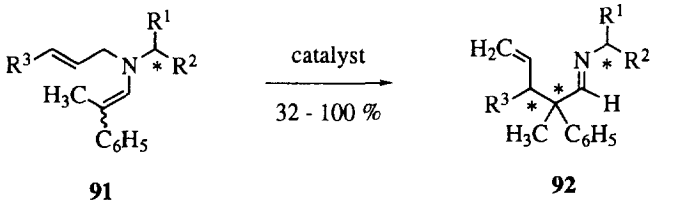
R = Me, Ph

89

anti:syn = 7:1 - 12:1
de_{anti} = 21 - 39 %

90

Scheme 26. Synthesis of γ,δ-unsaturated imines and aldehydes according to Enders et al.



91

92

anti:syn = 1.1 - 20:1
de_{anti} = 2 - 55 %

Scheme 27. Variation of the chiral amine auxiliary and the allylic substituents according to Enders et al.

Table 19. Catalysts employed for the Aza-Cope rearrangement

entry	R	catalyst	conditions	yield **89** [%][a]	*anti/syn*[b]	de_{anti} [%][c]
a	Me	$AlMe_3$	110 °C, 40 h	quant.	–	39
b	Me	$AlPh_3$	25 °C, 24 h	quant.	–	21
c	Ph	TMSTf	110 °C, 1 h	quant.	12:1	33
d	Ph	TMSTf	25 °C, 24 h	21	12:1	33
e	Ph	TMSTf (trace)	110 °C, 4 h	90	12:1	38
f	Ph	HTf	110 °C, 0.5 h	quant.	7:1	33
g	Ph	Bu_2BTf	110 °C, 0.5 h	quant.	9:1	33

[a] Yield based on **88**. If necessary, the products were purified by flash column chromatography (neutral Al_2O_3, ether/petrolether 1:1); [b] The relative ratios were determined by NMR spectroscopy, assigned by comparison with the *de* values of the corresponding aldehydes; [c] For the relative *de* values of the diastereomers see [b], the absolute configuration was not determined.

Table 20. Results of the asymmetric Aza-Cope rearrangements with different auxiliaries

entry	R^1	R^2	R^3	confg. **91**	conditions[a]	yield **92** [%][b]	*anti/syn*[c]	de_{anti} [%][d]
a	Me	*t*-Bu	*n*-Pr	(R)	I)	quant.	15:1	38
b	MOM	Et	*n*-Pr	(R)	I)	quant.	9:1	4
c	MOM	*i*-Pr	*n*-Pr	(S)	I)	quant.	9:1	7
d	MOM	*t*-Bu	*n*-Pr	(S)	I)	quant.	8:1	10
e	MOM	Bn	*n*-Pr	(S)	I)	quant.	9:1	2
f	MOM	Ph	*n*-Pr	(S)	I)	quant.	10:1	4
g	Me	1-Naphtyl	*n*-Pr	(S)	I)	quant.	12:1	38
h	Me	*t*-Bu	*n*-Pr	(R)	II), 280 °C,30 s	91	2:1	38
i	Me	*t*-Bu	*n*-Pr	(R)	II), 160 °C,8 h	60	3:1	55
j	Me	Ph	*n*-Pr	(S)	II), 160 °C,8 h	50	5:1	55
k	Me	Ph	Me	(S)	I)	quant.	14:1	33
l	Me	Ph	*n*-Bu	(S)	I)	quant.	10:1	33
m	Me	Ph	*i*-Pr	(S)	I)	32	20:1	33
n	Me	Ph	*t*-Bu	(S)	I)	none	–	–
o	Me	Ph	Ph	(S)	I)	quant.	1:1	33

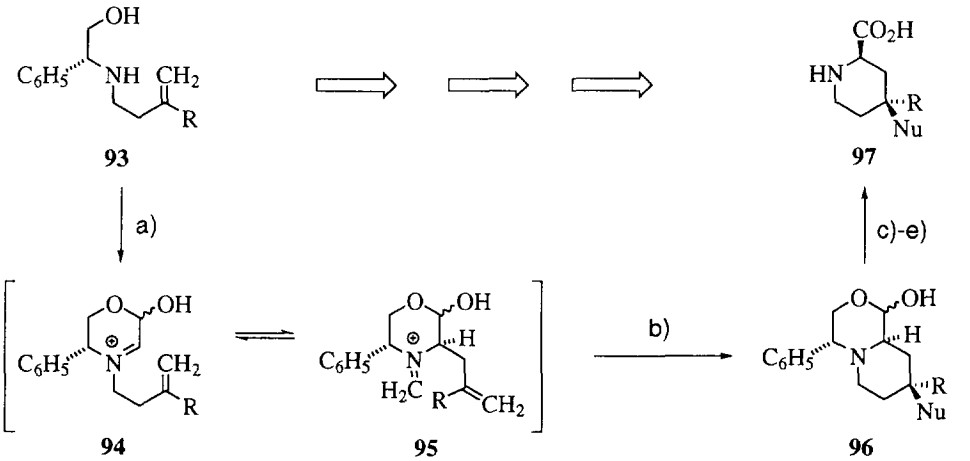
[a] Reaction conditions: I) catalyst TMSTf, 1h toluene 110°C, II) no catalyst, heating the pure substance under argon; [b] Yield based on **91**. If necessary, the products were purified by flash column chromatography (neutral Al_2O_3, ether / petrolether 1:1); [c] The relative ratios were determined by NMR spectroscopy, assigned by comparison with the *de* values of the corresponding aldehydes; [d] For the relative *de* values of the diastereomers see [c]; the absolute configuration was not determined.

One notable observation was the acceleration of the rearrangement by using trialkylsilyl or dialkylboron triflates as catalysts instead of titanium or aluminium reagents. The allyl enamines **88** and **91** underwent the rearrangement process in the presence of Lewis acids to give the imines **89** and **92** in mostly very good yield but with only modest diastereoselectivity. The imines **89** could be cleaved easily by addition of aqueous hydrochloric acid leading to the aldehydes **90** and amine hydrochlorides in good yields. Some typical examples are given in schemes 26 and 27 and the corresponding tables 19 and 20.

The N-allylic enamines **88** and **91** were prepared starting from the corresponding primary amine auxiliaries. Again, the allylic amines were synthesized by condensation with the appropriate α,β-unsaturated aldehydes and subsequent chemoselective reduction with sodium borohydride. The enamines then could be obtained in good to very good yield by Katritzky's method[49] through the mixed aminals with benzotriazole.

3.3. Miscellaneous Cope rearrangements

In addition to the 3-aza-Cope rearrangements of N-allylic enamines an aza-Cope rearrangement of γ,δ-unsaturated iminium compounds has been described. Because the equilibrium of this reaction usually is unfavourable, the rearrangement has to be combined with subsequent reactions of the product to become a valuable process. In the following example of Agami et al.[50] this goal was reached by an ene iminium cyclization, initiated by the attack of an added nucleophile, as depicted in scheme 28. The products are derivatives of the nonproteinogenic amino acid pipecolic acid.

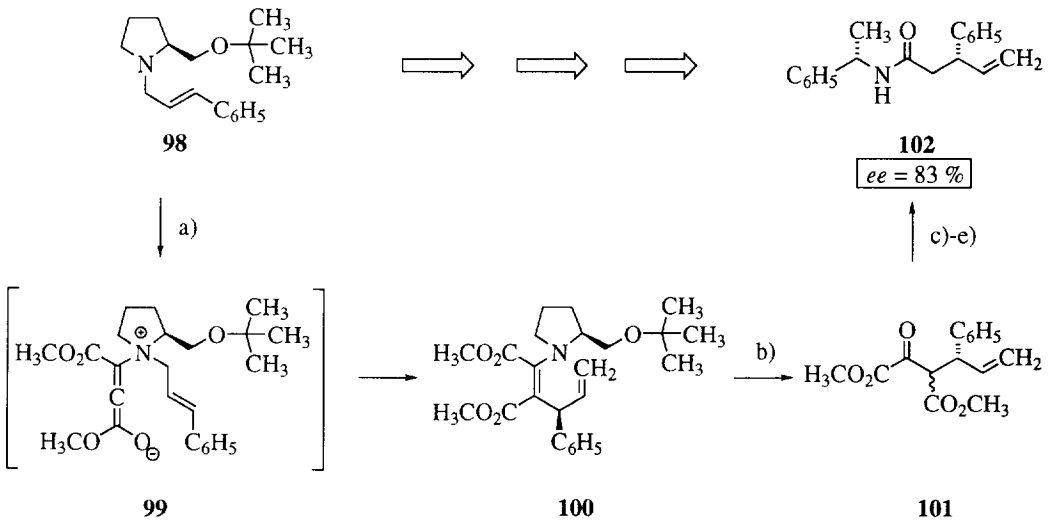


a) glyoxal, b) nucleophile, c) DMSO, $(COCl)_2$, NEt_3, d) CH_2=$CHCH_2OCOCl$, e) 6N HCl

Scheme 28. Synthesis of pipecolic acid derivatives by cationic aza-Cope rearrangement reported by Agami et al.

The tandem aza-Cope/ene iminium cyclization was totally stereoselective in all these examples, the reaction conditions depended on the substitution pattern of the homoallylic double bond. In case of unsubstituted N-homoallylic systems, the iminium moiety had to be generated from an amino thioether precursor in an anhydrous medium, whereas in the more favourable case, with R being methyl instead of hydrogen, cyclization occurred spontaneously in aqueous solution. Typical nucleophiles employed were azide, bromide, acetate or thiophenolate. The starting N-homoallylic aminoalcohols were prepared themselves *via* reaction of (*R*)-phenylglycinol with the appropriate homoallylic tosylate, which gave compounds **93** in moderate yields.

An asymmetric, cationic 3-aza Cope rearrangement has been reported by Vedejs et al..[51] As depicted in scheme 29, the chiral tertiary allylic amine **98** reacted with dimethyl acetylenedicarboxylate (DMAD) in a Michael-addition to give the allylic enamine system **99**, which isomerized after [3,3]-sigmatropic rearrangement to the enaminoester **100**. This substance could be hydrolyzed to the ketoester **101**, which then was cleaved and decarboxylated. Amidation with (*S*)-phenylethylamine *via* the mixed anhydride method finally gave amide **102** with a *de* value of 83 %.



a) DMAD, $TiCl_2(OiPr)_2$ cat. 10 %, AgOTf cat. 20 %, CH_2Cl_2, -60 °C, b) aq. H_2SO_4,
c) aq. NaOH, d) EtOCOCl, NEt_3, CH_2Cl_2, 0 °C, e) (*S*)-phenylethylamine

Scheme 29. Cationic 3-aza-Cope rearrangement according to Vedejs et al.

This notable rearrangement shows some important features to perform asymmetric aza-Cope reactions with a high degree of stereocontrol. Firstly, the *in situ* generated cationic allylic enamine was a very reactive

substance, which rearranged at a temperature of –70 °C to –60 °C, whereas the limit of common aza-Cope reactions is at about room temperature. Secondly, the rearrangement product readily isomerized irreversibly, which prevented a racemization at this stage and shifted the equilibrium to the right side.

Interestingly, the use of chiral catalysts with this system to improve the stereoselectivity by double asymmetric induction failed, just giving *ee* values of 80 % and 86 %, respectively. With achiral tertiary allylamines and chiral catalysts *ee* values of about 30 % were obtained.

4 Conclusion

We hope that this brief survey of asymmetric versions of [3.3]-sigmatropic rearrangements with some examples of applications in organic synthesis will not only summarize the possibilities of these reactions to date, but also show the interesting opportunities which are still possible. Especially, regarding to the rearrangements of prochiral substances with chiral catalysts, further developments should be possible and would make this stereoselective C-C bond formation *via* asymmetric synthesis even more attractive.

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