Addition of Enolates and Azaenolates to α,β-Unsaturated Carbonyl Compounds

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1.5.2.4. Addition of Enolates and Azaenolates to *a*,*b*-Unsaturated Carbonyl Compounds

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The Michael addition [1], a well known key synthetic transformation, has recently emerged as an important method for stereoselective C-C bond formation [2, 369 - 371]. Two developments have contributed to a great extent:

a Methodology for the preparation of preformed enolates with well-defined double bond configuration was developed and it was shown that simple diastereoselection can be controlled, in many instances, through the use of these enolates [3].

b Various chiral auxiliaries and catalysts have been developed that allow diastereoface- and enantioface-selective Michael additions.

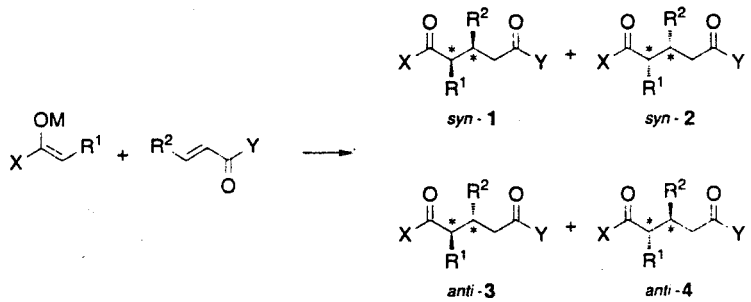
Enolates can add either 1,2 or 1,4 to Michael acceptors such as enones, the regiochemistry is dependent on a variety of factors that may be both electronic and steric in nature. With lithium enolates as Michael donors, some general trends in the regiochemistry can be observed [4, 5]. An increase of the bulk of the ***b***-substituent in the enone favors 1,2-addition, whereas a relatively large carbonyl substituent often increases the preference for 1,4-addition. In various cases more bulky enolates have a greater propensity for 1,4-addition. Softer enolates (for instance thioamide enolates) have a greater propensity for 1,4-addition than do harder enolates (oxoamides). With respect to the solvent, the presence of hexamethylphosphoric triamide (HMPA) generally favors 1,4-addition.

Furthermore, 1,2-addition is sometimes reversible, and in several cases leads to a 1,2 to 1,4 conversion at higher temperatures or when longer reaction times are used [6 - 14]. Finally the regiochemistry can be very sensitive to the reaction conditions.

1.5.2.4.1. *syn/anti* Selectivity

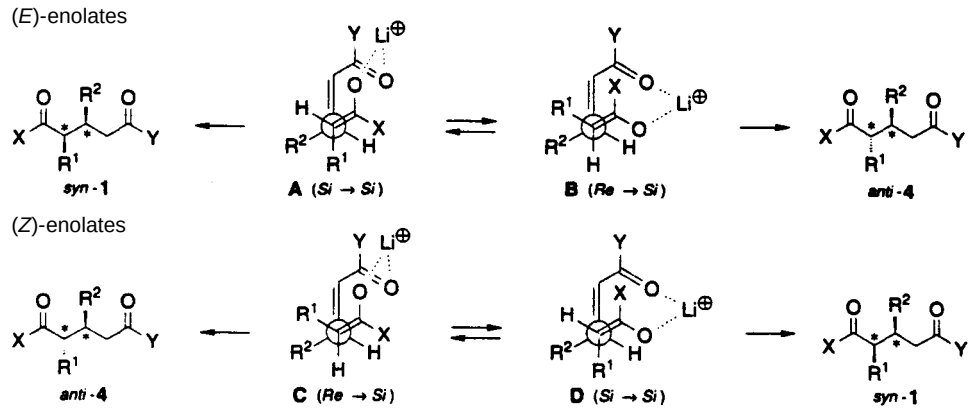
1.5.2.4.1.1. General Principles

In the Michael addition of achiral enolates and achiral Michael acceptors the basic general problem of simple diastereoselection (see Section D.1.5.1.3.2.), as described in Section 1.5.2.3.2. is applicable. Thus, the intermolecular 1,4-addition of achiral metal enolates to enones, ***a***,***b***-unsaturated esters, and thioamides, results in the formation of racemic *syn*-**1**,**2** and/or *anti*-**3**,**4** adducts.



X and Y achiral units - simple diastereoselectivity
X or Y chiral units - simple and induced diastereoselectivity

When chiral enolates or chiral Michael acceptors are used, for instance, when stereogenic centers are present in the substrate or when X or Y are chiral auxiliaries, both simple and induced diastereoselectivity is observed. This results, in principle, in the formation of four diastereomers **1** - **4**. The diastereoselectivity in the Michael addition of lithium enolates to enones can be rationalized by consideration of chelated transition states **A** - **D** [372].



Four different orientations are possible when the enantiofaces of (*E*)- and (*Z*)-enolates and an (*E*)-enone combine via a closed transition state, in which the olefinic moieties of the donor and the acceptor are in a *syn* arrangement. It should be emphasized that, a further four enantiomorphous orientations of **A** - **D** are possible leading to the enantiomers **2** and **3**. On the basis of extensive studies of Michael additions of the lithium enolates of esters (X = OR) and ketones (X = R) to enones (Y = R) it has been concluded:

1 With (*E*)-enolates model transition state **A**, leading to *syn*-adducts, is favored for large X or Y groups.

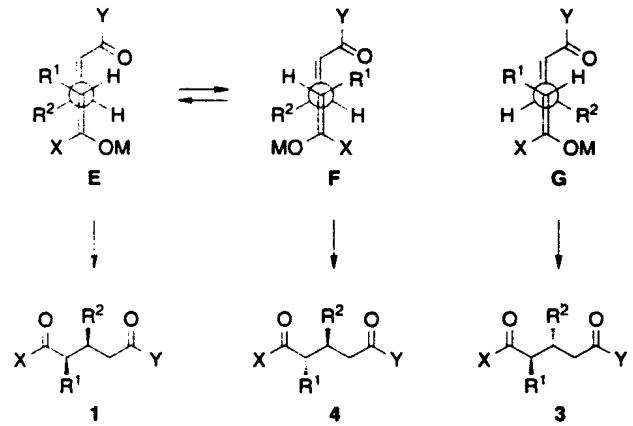
2 With (*Z*)-enolates model transition state **C**, leading to *anti*-adducts, is favored for large X or Y groups.

3 For small substituents X on the enolate the preference for **A** and **C** is diminished due to reduced unfavorable interactions of X.

4 For amide enolates (X = NR_2), with *Z* geometry, model transition state **D** is intrinsically favored, but, again, large X substituents favor the formation of *anti*-adducts via **C**.

Factors that influence the diastereoselectivity include the solvent, the enolate counterion and the substituent pattern of enolate and enone. In some cases either *syn*- or *anti*-products are obtained preferentially by varying the nature of the solvent, donor atom (enolate versus thioenolate), or counterion. Most Michael additions listed in this section have not been examined systematically in terms of diastereoselectivity and coherent transition state models are currently not available. Similar models to those shown in **A** - **D** can be used, however all the previously mentioned factors (among others) may be critical to the stereochemical outcome of the reaction.

Furthermore, in some cases the results may be rationalized by open (extented) transition states.



E, F: (*E*)-enolate/(*E*)-enone
G: (*E*)-enolate/(*Z*)-enone

for references see p 2148

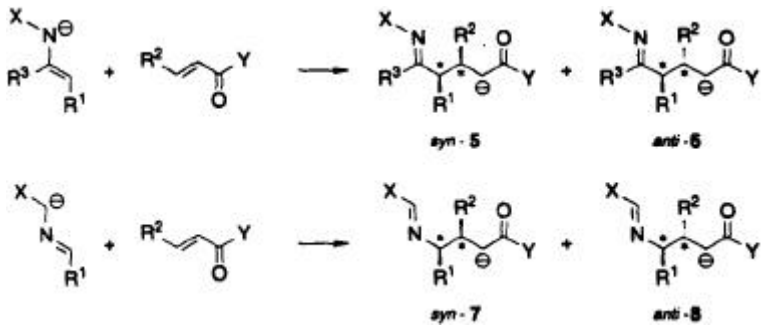
Structures **F** and **G** are two model transition states for the reaction of an (*E*)-enolate with an (*E*)-enone. Although the same *syn* and *anti* diastereomeric pairs are formed as in the case of the closed transition states, the ratios will in general be different.

The major difference, when compared with simple diastereoselection in aldol-type additions, is the *E*- and *Z*-geometrical isomers of the Michael acceptor. Model transition state **G** shows one of the orientations of the enantiofaces of an (*E*)-enolate with a (*Z*)-enone. These additions, again, result in the same *syn/anti*-adducts, as in the case of an (*E*)-enone, but the substituent interactions will be different.

A variety of Michael donors such as ketones, esters, thioesters, amides, lactones and lactams may be used and in all of these cases the problems of stereoselectivity apply.

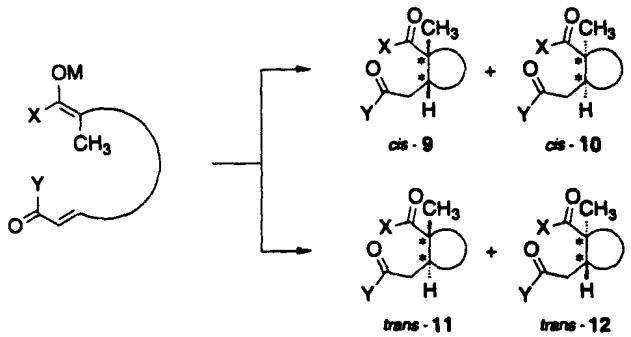
With a sufficiently active donor, the separate generation of metal enolates is not required. Thus, 1,4-addition may be mediated by stoichiometric or catalytic amounts of base.

Closely related to the 1,4-additions of enolates are the reactions of 1- and 2-azaallyl anions.



Several attractive methods, leading to *syn*-**5**,**7** or *anti*-**6**,**8**-adducts, with excellent diastereoselectivities have been developed using azaallyl-type Michael donors derived from hydrazones, imines, nitriles and lactim ethers.

The intramolecular Michael addition of an achiral metal enolate is similarly subject to simple diastereoselection.



X and Y achiral units - simple diastereoselectivity
X or Y chiral units - simple and induced diastereoselectivity

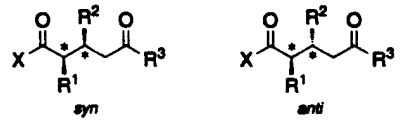
Racemic *cis*-**9**,**10** or *trans*-**11**,**12** substituted ring systems are obtained; in many instances high diastereocontrol is found.

1.5.2.4.1.2. Intermolecular Additions

1.5.2.4.1.2.1. 1,5-Diketones and *d*-Oxo Esters

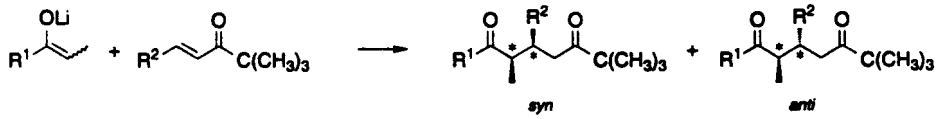
Via Enolate Addition to Enones

Lithium enolates of various ketones [15 - 17], esters [18], thioesters [19] and amides [20] react with enones to form either *syn* or *anti* ***a***,***b***-disubstituted 1,5-diketones, ***d***-oxo esters or their derivatives.



Excellent chemical yields, high regio- and, in several cases, high diastereoselectivities are observed. A correlation between enolate geometry and product stereochemistry is found, with (*Z*)-enolates producing *anti*-adducts and (*E*)-enolates yielding *syn*-adducts preferentially, if these reactions are performed with kinetic control (see Table 1, entries 1 - 10) [21 - 23].

Table 1. 2,3-Disubstituted 1,5-Diketones from Addition of Lithium Enolates to Enones



Entry [a]	R^1	R^2	*E*/*Z*	d.r. [b] (*syn*/*anti*)	Yield (%)	Ref
1	*i*-Pr	C_6H_5	4:96	4:96	88	17
2	$C(CH_3)_3$	C_6H_5	< 1:99	< 1:99	70	17
3	C_6H_5	C_6H_5	87:13	83:17	78	17
4	$OC(CH_3)_3$	CH_3	*Z* [c]	13:87	73	18
5			*E* [d]	95:5	85	18
6	$OC(CH_3)_3$	$C(CH_3)_3$	*Z* [c]	< 3:97	25	18
7	$OC(CH_3)_3$	*i*-Pr	*E* [d]	92:8	87	18
8			*Z* [c]	7:93	88	18
9	$OC(CH_3)_3$	C_6H_5	*E* [d]	94:6	95 [e]	18
10			*Z* [c]	11:89	76	18
11		C_2H_5	*Z*	37:63	95	33
12		*i*-Pr	*Z*	27:73	65	33
13		$C(CH_3)_3$	*Z*	< 3:97	70	33
14		C_6H_5	*Z*	9:91	69	33

[a] More examples can be found in refs 15 - 37.
[b] Determined by GC.
[c] Compounds are prepared according to the typical procedure.
[d] Compounds are prepared using the typical procedure omitting HMPA.
[e] mp 44 - 45 °C.

***tert*-Butyl (2*R**,3*R**)-2,3,6,6-Tetramethyl-5-oxoheptanoate [R^1 = $OC(CH_3)_3$; R^2 = CH_3]; Typical Procedure[18]:** Via the *Z*-enolate: an oven dried Schlenk tube equipped with a rubber septum is flushed with argon and charged with 0.66 mL (1.0 mmol) of butyllithium (1.5 N in hexane). The Schlenk tube is cooled to 0°C (ice/salt) and 0.12 g (1.1 mmol) of diisopropylamine are added slowly by a syringe. This mixture is stirred for 15 min and the rubber septum is replaced by a glass stopper. The hexane and the excess diisopropylamine are removed under reduced pressure. After the flask is filled with argon the stopper is replaced with a septum and 0.47 g (4.3 mmol) of HMPA and 2.5 mL of THF are added. This solution is immediately cooled to - 78 °C and 0.14 g (1.1 mmol) of tert-butyl propanoate are added quickly by syringe. After stirring for

for references see p 2148

30 min 0.126 g (1.0 mmol) of 2,2-dimethyl-4-hexen-3-one in 0.5 mL of THF are added over 10 min. After stirring for 15 min the mixture is quenched with 10 mL of sat. aq NH_4Cl. The resulting mixture is diluted with 10 mL of water and extracted four times with 10 mL of diethyl ether. The combined ether layers are washed six times with 8 mL of water and once with 10 mL of brine. Drying over $MgSO_4$ and evaporation of the solvent gives the *anti*-adduct as a clear oil; yield: 0.19 g (0.73 mmol, 73%).

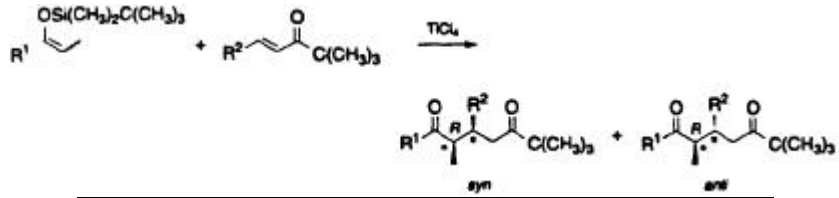
The enolate geometry can be controlled, in the case of esters, by the addition of HMPA; without HMPA the enolate has predominantly the *E*-geometry, while with HMPA mainly *Z*-geometry is observed. Similar additions with magnesium and zinc enolates are observed [24 - 32, 373, 374].

Amides, in general, form (*Z*)-enolates when treated with lithium diisopropylamide in THF, their 1,4-adducts with enones are mixtures of *syn*- and *anti*-isomers, with the *anti*-isomer moderately favored. With phenyl-substituted enones relative high *syn* selectivity is seen, whereas high *anti* preference is observed with *tert*-butyl-substituted enones. The *syn/anti* ratio's are only slightly influenced when these 1,4-additions are performed, either under kinetically or thermodynamically controlled conditions [33] (Table 1, entries 11 - 14). Lactam enolates, with *E*-geometry due to the constraints of the cyclic system, also predominantly give *anti* selectivity, but larger amounts of 1,2-adducts than usually observed.

Enolates of thioamides, which have *Z* geometry, give better *anti* selectivity than their corresponding oxygen analogs. Thiolactam enolates give higher proportions of *syn*-adducts than lactams, especially in reactions with enones with bulky substituents. Furthermore, there is a counterion effect, which leads to increasing *anti* selectivity in the order lithium < sodium < potassium [34 – 37, 375, 376].

The Lewis acid promoted 1,4-addition of silyl enolates to enones under kinetic control opens up flexible routes to 1,5-dicarbonyl compounds which often give high yields and good diastereoselectivities. With silyl enolates, it is possible to use pure (*E*)- or (*Z*)-enolates, which have an advantage over the in situ prepared ester metal enolates (*vide supra*). An investigation of the diastereoselectivity of the 1,4-addition to enones showed that silyl enolates from ketones (*E* or *Z*) show a general tendency for *anti* selectivity. This ranges from modest (1.5:1) for those from aliphatic ketones to high selectivities (> 20:1) for those from aromatic ketones (Table 2, entries 1 - 7). With silylketene acetals high *syn* selectivity is reached using *tert*-butyl enones. The *syn/anti* ratios are independent of the enolate structure [38] (Table 2, entries 8 - 11).

Table 2. 2,3-Disubstituted 1,5-Diketones form Addition of Silyl Enolates to Enones



Entry[a, b]	R^1	R^2	*E* or *Z*	d.r. (*syn/anti*)	Yield (%)	Ref
1	C_2H_5	CH_3	*E*	11:89	59	35
2			*Z*	13:87	57	35
3	*i*-Pr	CH_3	*E*	33:67	81	35
4			*Z*	15:85	63	35
5	$C(CH_3)_3$	CH_3	*E*	31:69	10	35
6	C_6H_5	CH_3	*E*	< 5:95	69	35
7			*Z*	27:73	77	35
8	$OC(CH_3)_3$	CH_3	*Z*	99:1	88	38
9	$OC(CH_3)_3$	*i*-Pr	*Z*	96:4	87	38
10			*E*	98:2	76	38
11	$OC(CH_3)_3$	C_6H_5	*Z*	98:2	77	38

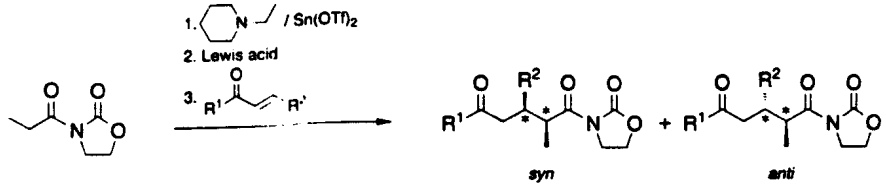
[a] All reactions were carried out following the typical procedure, entries 1 - 7 using tin(IV) chloride and entries 8 - 11 using titanium(IV) chloride as catalyst. [b] More examples can be found in refs 38 - 44.

***tert*-Butyl (2*R**,3*S**)-2,3,6,6-Tetramethyl-5-oxoheptanoate [$R^1 = OC(CH_3)_3$; $R^2 = CH_3$]; Typical Procedure[38]:** To a stirred solution of 126 mg (1 mmol) 2,2-dimethyl-4-hexen-3-one in 5 mL of CH_2Cl_2 at - 78 °C under an argon atmosphere is added 209 mg (1.1 mmol) of $TiCl_4$. After stirring for 10 min, 268 mg (1.1 mmol) of (*Z*)-1-(*tert*-butyldimethylsilyloxy)-1-*tert*-butyloxypropene in 1 mL of CH_2Cl_2 are added dropwise to the solution and the mixture is stirred for 3 h. The mixture is quenched with 5% aq K_2CO_3, filtered and extracted three times with 10 mL of ethyl acetate. After washing with water and brine and subsequent chromatography (silica gel, hexane/diethyl ether 2:1), the *syn*-adduct is obtained; yield: 325 mg (88%).

As Lewis acids, titanium(IV) chloride[39, 377, 378] or titanium(IV) isopropoxide in combination with titanium(IV) chloride can be used in stoichiometric amounts[40, 41], but triphenylmethyl perchlorate or chlorotriphenylmethane with tin(II) chloride offers a mild, catalytic alternative[42 - 46].

As an alternative, tin enolates are very useful in these additions. Usually they are prepared in situ from the amide using tin(II) trifluoromethanesulfonate and a base. They are subsequently reacted with an enone, catalyzed by a Lewis acid[47, 48] (see Table 3). With trimethylsilyl trifluoromethanesulfonate as a catalyst, in the presence of proline derived diamines *anti*-adducts are formed exclusively[49] (see Section 1.5.2.4.3.1.).

Table 3. 3-(1,5-Dioxoalkyl)-2-oxazolidinones from Addition of Tin Enolates to Enones[47]



R^1	R^2	Lewis acid	d.r. (*syn/anti*)	Yield (%)
CH_3	CH_3	$(CH_3)_2HSiCl$	5:95	56
CH_3	CH_3	$(CH_3)_3SiCl$	29:71	56
CH_3	C_6H_5	$(CH_3)_2HSiCl$	92:8	77
		$(CH_3)_3SiCl$	29:71	78
C_6H_5	CH_3	$(CH_3)_2HSiCl$	25:75	85

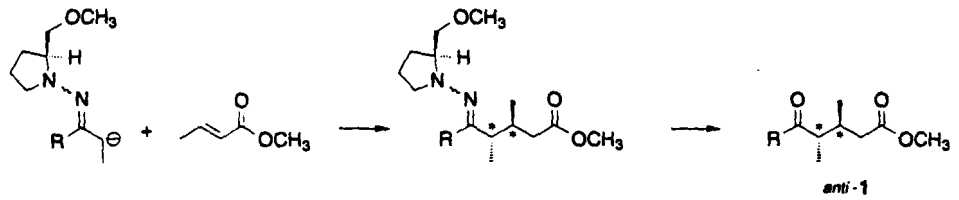
[a] More examples can be found in refs 45-49.

Via Enolate Addition to *a*,*b*-Unsaturated Esters

Although the methodology described so far produces ***d***-oxo esters via diastereoselective enolate additions to enones, the same product may be obtained via an alternate sequence, i.e., addition of ketone or aldehyde enolates to ***a***,***b***-unsaturated esters or amides. Enolates of ketones are known to react with ***a***,***b***-unsaturated esters to give the Michael adducts[50], however, the study of simple diastereoselectivity has, so far, been limited to special cases (MIMIRC reactions, Section 1.5.2.4.4.).

The use of hydrazone or enamine derivatives of ketones or aldehydes offers the advantage of stereocontrol via chelated azaenolates. Extremely useful synthetic methodology, with consistently high *anti* selectivity, has been developed using azaenolates based on (*S*)- or (*R*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP or RAMP)[51 - 58] (Enders method, see Section 1.5.2.4.2.2.3.). An example which illustrates the efficiency of this type of Michael addition is the addition of the lithium azaenolate of (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazone of propanal (R = H) to methyl (*E*)-2-butenoate to give the *anti*-isomer (an *l* adduct) in 80% yield with a diastereomeric ratio > 98:2.

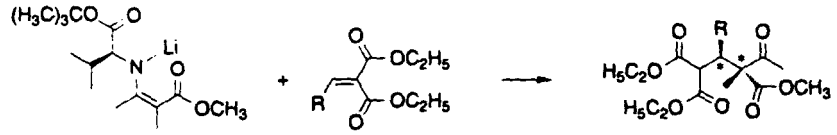
for references see p 2148



1: *methyl 3,4-dimethyl-5-oxoalkanoates*
R = H; *methyl* (3R*,*4*S*)-*3,4-dimethyl-5-oxopentanoates*; yield: 80%; d.r. [(3*R**,4*S**)/(3*R**,4*R**)] 98:2

The aldehyde or ketone functionalities in the Michael adducts are restored by ozonolysis of the hydrazone moiety resulting in *anti*-3,4-disubstituted-5-oxoalkanoates **1**.

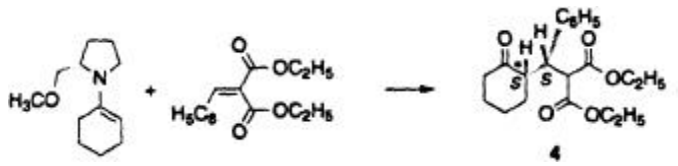
Two closely related methods for the diastereoselective preparation of ***d***-oxo esters have been developed. The first method uses the chelated lithio enamine **2**. These Michael donors are readily available from the *tert*-butyl ester of L-valine and ***b***-oxo esters. The Michael addition of this lithio enamine **2** to 2-(arylmethylene)propanedioates, followed by hydrolytic removal of the auxiliary, provides ***d***-oxo esters with contiguous quaternary and tertiary carbon centers with high diastereoselectivity [59, 60].



2 **3**

3: *5-ethyl 1-methyl 2-acetyl-3-aryl-4-*(*ethoxycarbonyl*)*-2-methylpentanedioate*; yield: 72 %;
d.r. [(2*R*,3*R*)/(2*S*,3*R*)] 93:7 to 99.5:0.5

The second method is based on the optically active enamine formed from (*S*)-prolinol methyl ether and cyclohexanone. This enamine reacts spontaneously with 2-(arylmethylene)propanedioates to give, after hydrolysis, the 2-{(*S*)-aryl[(*S*)-2-oxocyclohexyl]methyl}propanedioates **4** in 35 - 76% yield with d.r. 94 : 6 - > 97 : 3 [61].



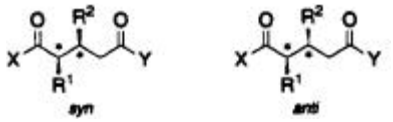
4

4: *diethyl 2-*{(S)-[(S)-*2-oxocyclohexyl*]*phenylmethyl*}*propanedioate* [61]; yield: 70%;
d.r. [(*S*,*S*)/(*S*,*R*)] > 97.5:2.5; 95% ee

A limited number of examples only exist for the Michael addition of lithium enolates to ***a***,***b***-unsaturated amides; high stereocontrol was observed in only a few cases [62 - 67, 379].

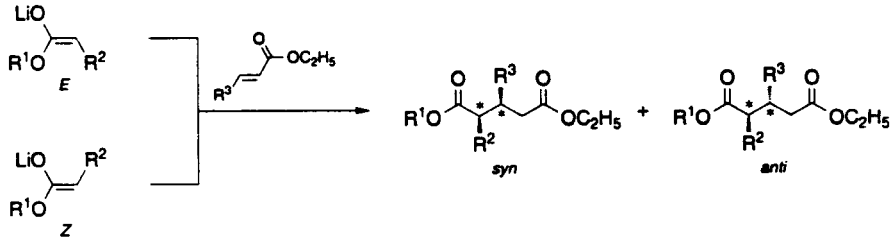
1.5.2.1.1.2.2. Glutarates via Enolate Addition to *a*,*b*-Unsaturated Esters

Closely related to enolate additions to enones is the diastereoselective 1,4-addition of lithium enolates of esters, thioesters and amides to ***a***,***b***-unsaturated esters. These reactions provide *syn*- or *anti*-2,3-disubstituted glutarates (pentanedioates).



The enolates of esters add, under kinetically controlled conditions, to ***a***,***b***-unsaturated esters [68] (including ***b***-substituted unsaturated esters) to give high yields of pentanedioates [69, 70, 380]. Again, the geometry of the ester enolate is crucial to the final configuration of the adduct; the configuration of the adduct may be controlled by the addition of HMPA. The (*E*)-lithium enolate (without HMPA) gives a *syn*-adduct and the (*Z*)-lithium enolate (with HMPA) gives an *anti*-adduct [71] (see Table 4).

Table 4. Pentanedioates from Addition of the Lithium Enolates of Esters to ***a***,***b***-Unsaturated Esters



R^1	R^2	R^3	d.r. (*syn/anti*)	Yield (%)	Ref
C_2H_5	CH_3	CH_3	< 1:20[a]	82	71
C_2H_5	CH_3	Bu	< 1:20[a]	95	71
C_2H_5	CH_3	C_7H_{15}	< 1:20[a]	86	71
C_2H_5	CH_3	C_6H_5	1:15[a]	85	71
C_2H_5	C_2H_5	CH_3	< 1:20[a]	87	71
C_2H_5	C_2H_5	C_7H_{15}	< 1:10[a]	83	71
C_2H_5	C_6H_5	C_6H_5	< 1:20[a]	90	71
C_2H_5	C_8H_{17}	CH_3	< 1:20[a]	78	71
$C(CH_3)_3$	CH_3	CH_3	> 20:1	81	68
$C(CH_3)_3$	CH_3	Bu	> 20:1	82	68
$C(CH_3)_3$	CH_3	C_7H_{15}	> 20:1	80	68

[a] HMPA is added before enolate formation.

1-*tert*-Butyl 5-Ethyl (2*R,3*S**)-2,3-Dimethylpentanedioate; Typical Procedure [68]:**
To a stirred solution of 2.0 mmol of LDA in 3.3 mL of a 60:40 mixture of THF/hexane at - 78 °C under a nitrogen atmosphere is added 264 mg (2.0 mmol) of *tert*-butyl propanoate in 2 mL of THF. After 30 min stirring a solution of 168 mg (1.5 mmol) of ethyl (*E*)-2-butenoate in 1.5 mL of THF is added and the mixture is stirred for an additional hour at - 78 °C. The reaction is quenched by addition of sat. NH_4Cl. Extraction with diethyl ether, drying over NaCl followed by evaporation of the solvent and short path distillation gives the adduct; yield: 378 mg (1.2 mmol, 84%).

As an alternative to lithium enolates, silyl enolates or ketene acetals may be used in a complementary route to pentanedioates. The reaction requires Lewis acid catalysis, for example: aluminum trifluoromethanesulfonate (modest diastereoselectivity with unsaturated esters) [72 – 74]; antimony(V) chloride/tin(II) trifluoromethanesulfonate (predominant formation of *anti*-adducts with the more reactive ***a***,***b***-unsaturated thioesters) [75]; montmorillonite clay (modest to good yields but poor diastereoselectivity with unsaturated esters) [76]; or high pressure [77].

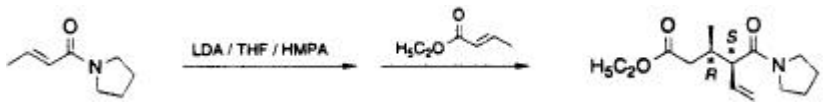
The Michael addition of lithium enolates of amides, which have preferentially the *Z* geometry, under kinetically controlled conditions to ***a***,***b***-unsaturated esters provides a highly

for references see p 2148

stereoselective route for the construction of vicinal stereogenic centers. Thus, the reactions of methyl (*E*)-2-butenoates with the lithium enolates of (*S*)-*N*-(1-oxopropyl)prolinol or 1-(1-oxopropyl)pyrrolidine gave the 1,4-adducts with *syn/anti* ratios of 87 : 13 and 100 : 0, respectively (see Section 1.5.2.4.2.2.1.).

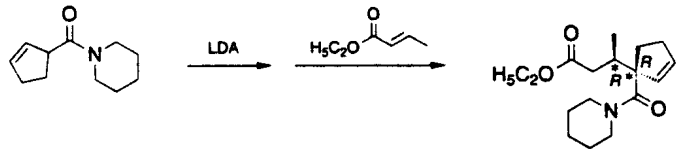
Bulky amides show, however, *anti* selectivity, i.e., trans-2,5-bis(methoxymethoxymethyl)-1-(1-oxopropyl)pyrrolidine gives a *syn/anti* ratio of 9 : 91 in the same reaction.

When the enolate of an ***a***,***b***- or a ***b***,***g***-unsaturated amide is used, it can react in an ***a*** or in a ***g*** fashion with ***a***,***b***-unsaturated esters, however, in most cases only ***a***-selectivity is observed. Using 1-(1-oxo-2-butenyl)pyrrolidine and lithium diisopropylamide at - 78 °C in a THF/HMPA mixture (1 : 1), high *syn*-selective formation of 3-alkyl-5-oxo-5-(1-pyrrolidinyl)-4-vinylpentanoates is achieved [78, 381, 382]. Related *syn*- or *anti*-selective additions of a vinylogous urethane also are known [79].



Ethyl (3*R,4*S**)-3-Methyl-5-oxo-5-(1-pyrrolidinyl)-4-vinylpentanoate; Typical Procedure [78]:**
To a stirred solution of 1.5 mmol of LDA in 3.5 mL of a 60 : 40 mixture of THF/hexane at - 78 °C under a nitrogen atmosphere are added 209 mg (1.5 mmol) of 1-(1-oxo-2-butenyl)pyrrolidine in 1.5 mL of HMPA. After 30 min 86 mg (0.75 mmol) of ethyl (*E*)-2-butenoate in 1.5 mL of THF is added and the mixture is stirred for an additional half hour at – 78 °C. The mixture is quenched by addition of sat. aq NH_4Cl. Extraction with diethyl ether is followed by drying over Na_2SO_4, followed by evaporation of the solvent and short path distillation to give the *syn*-adduct; yield: 123 mg (65%).

In general, the Michael addition of ***a***-substituted amide dienolates to ***a***,***b***-unsaturated esters is a method with great future potential for the diastereoselective construction of adjacent tertiary and quaternary stereogenic centers [80].

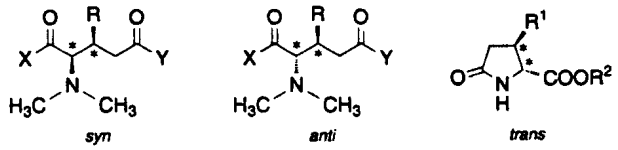


1

1: *ethyl* (*1*R*,***b***R*)-***b***-*methyl-1-*(*1-piperidinylcarbonyl*)-*2-cyclopentene-1-propanoate*; yield: 80%; d.r. [(1*R**,***b****R**)/(1*R**,***b***S*)] > 20:1

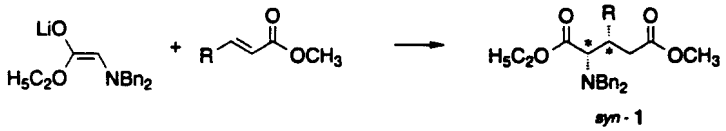
1.5.2.4.1.2.3. Glutamic Acid Derivatives via Enolate Additions to *a*,*b*-Unsaturated Esters

The addition of ***a***-amino-substituted lithium enolates to ***a***,***b***-unsaturated esters is a diastereoselective route to *syn*- or *anti*-glutamic acid derivatives and also to *trans*-substituted 5-oxo-2-pyrrolidinecarboxylates.



A convenient method for the stereoselective synthesis of *syn*-3-substituted glutamic acids is based upon the Michael addition of lithium enolates of *N*,*N*-dibenzylglycinates to ***a***,***b***-unsatu-

rated esters. These reactions are performed at - 78 °C in THF using lithium diisopropylamide to generate the (*E*)-enolate. The use of THF/HMPA [(*Z*)-enolate)] or other lithium amides as base results in mixtures of *syn*- and *anti*-adducts [81, 383].



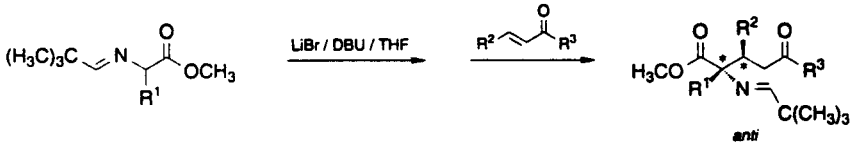
R = CH_3, Bu, *n*-C_7H_{15}
1: *1-ethyl 5-methyl 3-substituted* syn-*2-dibenzyl aminopentanedioate*; yield: 56-84%; d.r. 100:0

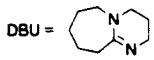
This method is complementary to the *anti*-selective Michael route to 3-substituted glutamates using 2-azaallyl anions derived from alkylidene protected glycine (see Section 1.5.2.4.1.1.).

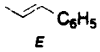
In general, metalated 2-azaallyl anions derived from imines of ***α***-amino esters serve both as Michael donors and as 1,3-dipolar reagents; the course of the reaction, as well as the stereochemical outcome depends upon the base and the reaction conditions [82, 83].

When 2,2-dimethylpropanal is used to prepare the azomethine moiety, the corresponding azaallyl anion may be obtained when 1,8-diazabicyclo[5.4.0]undec-7-ene/lithium bromide is used as base. The subsequent addition to various enones or methyl (*E*)-2-butenoate proceeds with *anti* selectivity, presumably via a chelated enolate. However, no reaction occurs when triethylamine is used as the base, whereas lithium diisopropylamide as the base leads to the formation of a cycloadduct, e.g., dimethyl 5-isopropyl-3-methyl-2,4-pyrrolidinedicarboxylate using methyl (*E*)-2-butenoate as the enone [84 - 89, 384].

Table 5. 3-Substituted Glutamates from the Addition of 2-Azaallyl Anions to Enones [84]





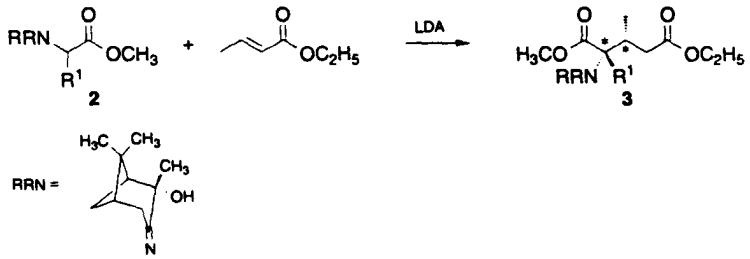
R^1	R^2	R^3	Time (min)	Temp. (°C)	Config. of Product	d.r. (*anti/syn*)	Yield (%)
H	CH_3	OCH_3	180	25	2*S**,3*S*	-	77
CH_3	CH_3	OCH_3	24	25	2*S**,3*S*	100:0	61
H	CH_3	CH_3	15	-5	2*S**,3*S*	100:0	80
H	C_6H_5	CH_3	15	-5	2*S**,3*R*	91:9	97
H		C_6H_5	30	-15	2*S**,3*R*	100:0	93

Dimethyl (2*S,3*S**)-2-[(2,2-Dimethylpropylidene)amino]-3-methylpentanedioate (R^1 = H; R^2 = CH_3; R^3 = OCH_3); Typical Procedure [84]:**
96 mg (1.1 mmol) of LiBr are added at 25 °C under a nitrogen atmosphere to a stirred solution of 157 mg (1.0 mmol) of methyl *N*-[(2,2-dimethylpropylidene)amino] glycinate in 3 mL of THF followed by stirrring for a few minutes. 100 mg (1.0 mmol) of methyl (*E*)-2-butenoate followed by 152 mg (1.0 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene are added and the resulting mixture is stirred for 10 min. The reaction is quenched with 10 mL of sat. NH_4Cl and the resulting mixture is extracted three times with 30 mL of diethyl ether. The combined ether layers are dried over $MgSO_4$ and evaporated to give the adduct; yield: 198 mg (0.77 mmol, 77%).

for references see p 2148

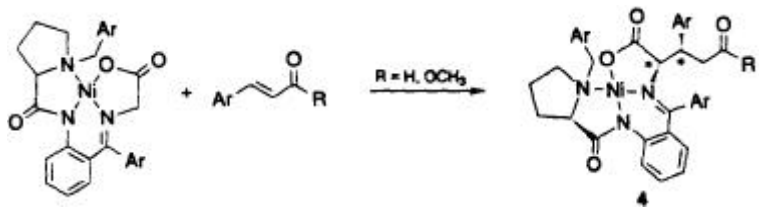
This method was extended to the diastereoselective synthesis of amino acid derivatives from the 1,4-addition of chiral nonracemic azaenolates derived from optically active imines to enones [90].

Ethyl (bornylideneamino)acetate (**2**) and the imines of (-)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone and glycine, alanine and norvaline methyl esters were particularly successful as Michael donors. The chiral azaallyl anions, derived from these imines by deprotonation with lithium diisopropylamide in THF at - 80 °C, add to various ***a***,***b***-unsaturated esters with modest to high diastereoselectivity (see Section 1.5.2.4.2.2.5.). Thus, starting with the imine **2**, (R^1 = CH_3) and ethyl (*E*)-2-butenoate, the ***a***,***b***-dialkylated glutamate derivative **3** is obtained as a single diastereomer in 90% yield [91, 92].



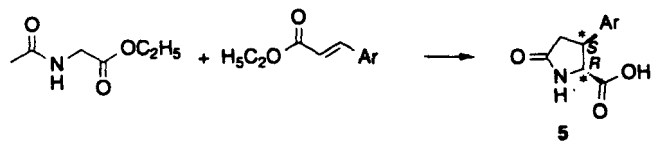
3: R^1 = CH_3; *1-methyl 5-ethyl* (2S,3R)-*2*-{[(*1*R,*2*R,5R)-*2-hydroxy-2,6,6-trimethylbicyclo*[*3.1.1*]*hept-3-ylidene*]*amino*}-*2,3-dimethylpentanedioate*; yield: 90%; ≥ 96% ee

Diastereoselective preparation of ***a***-alkyl-***a***-amino acids is also possible using chiral Schiff base nickel(II) complexes of ***a***-amino acids as Michael donors. The synthetic route to glutamic acid derivatives consists of the addition of the nickel(II) complex of the imine derived from (*S*)-*N*-[2-(phenylcarbonyl)phenyl]-1-benzyl-2-pyrrolidinecarboxamide and glycine to various activated olefins, i.e., 2-propenal, 3-phenyl-2-propenal and ***a***,***b***-unsaturated esters [93, 94].



d.r. (*syn* / *anti*) 66 : 34 - 92 : 8

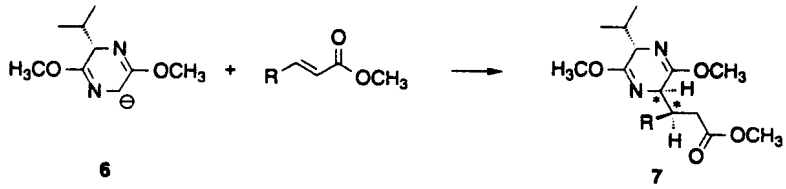
The addition of ***a***-(acylamino) esters to 3-aryl-2-propenoates, with sodium ethoxide in ethanol or sodium hydride in benzene as base, is a frequently ultilized procedure [95 - 99]. The initial Michael adducts cyclize to 3-aryl-5-oxo-2-pyrrolidinecarboxylic acids with modest to high *trans* diastereoselectivities [100].



5: (2R,3S)-*3-aryl-5-oxo-2-pyrrolidinecarboxylic acid*; yield: 5 - 70%; d.r. (*trans/cis*) 85:15-98.5:1.5

For related syntheses of *trans*-4-substituted or 3,4-disubstituted proline derivatives see refs 101 - 104.

An excellent method for the diastereoselective synthesis of substituted amino acids is based on optically active bislactim ethers of cyclodipeptides as Michael donors (Schöllkopf method, see Section 1.5.2.4.2.2.4.). Thus, the lithium enolates of bislactim ethers, from amino acids add in a 1,4-fashion to various ***a***,***b***-unsaturated esters with high diastereofacial selectivity (*syn/anti* ratios > 99.3:0.7 - 99.5:0.5). For example, the enolate of the lactim ether derivative **6**, prepared from (*S*)-valine and glycine, adds in a highly stereoselective manner to methyl (*E*)-3-phenyl-propenoate; a *cis/trans* ratio of 99.6:0.4 and a *syn/anti* ratio of 91:9, with respect to the two new stereogenic centers, in the product **7** are found [105, 106].



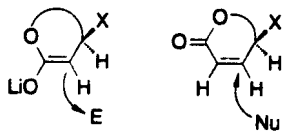
6 **7**

7: R = C_6H_5; *methyl* (2R*,5S*,***b***S*)-*2,5-dihydro-5-isopropyl-**b**-phenyl-2-pyrazinepropanoate*; yield: 92 %; d.r. [(2*R*,5*S*,***b****S*)/(2*R*,5*S*,***b****R*)/(2*S*,5*S*,***b****S*)/(2*S*,5*S*,***b****R*)] 200:2:1: < 0-5

In a modified procedure, these additions lead to ***b***,***g***- and ***g***,***d***-unsaturated amino acid derivatives with *cis/trans* selectivity > 99:1 and *syn/anti* diastereoselectivity > 99:1 (see Section 1.5.2.4.2.2.4.) [108].

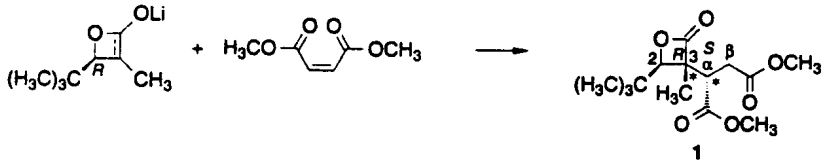
1.5.2.4.1.2.4. Lactones as Michael Donors or Acceptors

Lactones have been ultilized as donors, as well as acceptors, in Michael additions giving products with excellent diastereoselectivity. Once the ***p***-faces of the enolate or the ***a***,***b***-unsaturated lactone are effectively shielded by an appropriate substituent at a stereogenic center ***a*** to the olefin moiety, this results in the exclusive formation of the *trans*-adduct.



E = Michael acceptor, Nu = Michael donor

Michael addition of the enolate of (4*R*)-4-*tert*-butyl-3-methyl-2-oxetanone to dimethyl (*Z*)-butenedioate yields a single diastereomer. This provides a method to control two new vicinal stereogenic centers; one quaternary and one tertiary. The topicity of the addition is *u* with respect to the 3,3´-bond and *l* with respect to the 3´,4´-bond [109].



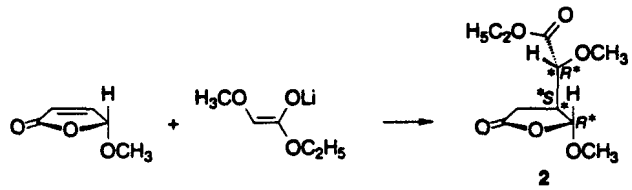
1

1: *dimethyl* (S)-***a***-[(2R*,3R*)-*2*-tert-*butyl-3-methyl-4-oxo-3-oxetanyl*]*butanedioate*; yield: 45 %; d.r. [(3*R*,3´*S*)/(3*R*,3´*R*)] 100:0

Efficient methods for the production of tetrahydro-5-oxo-3-furanalkanoates use chiral lactones based on 2(5*H*)-furanones as Michael acceptors [110-114] (see Section 1.5.2.4.1.2.5.). For

for references see p 2148

example, trans-diastereoselective addition of *tert*-butyl ***a***-lithio-***a***-methylthiopropanoate to 5-octyl-2(5*H*)-furanone to give *tert*-butyl ***a***-methylthiopropanoate-5-octyl-2(5*H*)-furanone in 93 % yield, was used in the synthesis of *dl*-avenaciolide [115]. Enolates of various esters such as ethyl propanoate, ethyl ***a***-methoxyacetate and ethyl benzeneacetate add to 5-methoxy-2(5*H*)-furanone with complete facial selectivity [116].



2

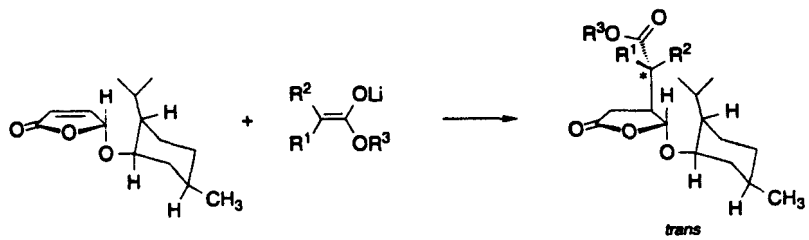
2: *ethyl* (αR*,*2*R*,*3*S*)-*tetrahydro-**a**,2-dimethoxy-5-oxo-3-furanacetate*; yield: 75 %

The geometry of the ester enolate dictates the configuration of the extracyclic asymmetric center; an (*E*)-enolate gives mainly an *anti*-adduct and a (*Z*)-enolate gives a *syn*-adduct. This is in accordance with the stereochemical results with *trans*-acyclic esters bearing in mind the fact that in this case a *cis*-unsaturated ester is present in the cyclic Michael acceptor.

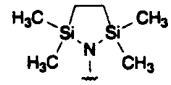
1.5.2.4.1.2.5. Auxiliary Control

Mainly sulfoxide groups are introduced as chiral auxiliaries for the modification of ***a***,***b***-unsaturated enones (see Section D.1.5.3.5.). Chiral imine derivatives have also been used (see Section D.1.5.3.1.). Various chiral alcohols, and in particular 8-phenylmenthol, have been successfully used as auxiliaries, mainly in two-fold Michael additions to ***a***,***b***-unsaturated esters.

In ***g***-alkoxyfuranones the acetal functionality is ideally suited for the introduction of a chiral auxiliary; simultaneously high ***p***-face selectivity may be obtained due to the relatively rigid structure that is present. With (+)- or (-)-menthol as auxiliaries it is possible to obtain both (5*S*)- or (5*R*)-***g***-menthyloxy-2(5*H*)-furanones in an enantiomerically pure form [293]. When the auxiliary acts as a bulky substituent, as in the case with the l-menthyloxy group, the addition of enolates occurs trans to the ***g***-alkoxy substituent. The chiral auxiliary is readily removed by hydrolysis and various optically active lactones, protected amino acids and hydroxy acids are accessible in this way [294, 295, 400].



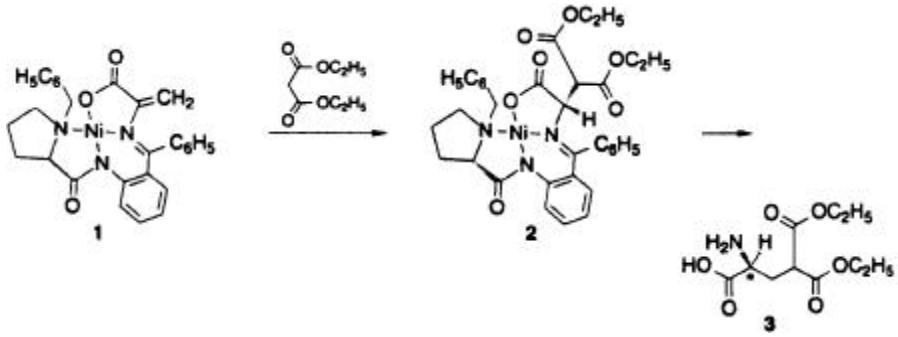
trans

R^1	R^2	R^3	d.r. (*trans/cis*)	Yield (%)	Ref
H	H	$C(CH_3)_2$	100:0	80 [a]	400
H	OCH_3	C_2H_5	100:0	73 [b]	400
H		CH_3	100:0	72	400
CH_3	CH_3	C_2H_5	100:0	97	400

[a] mp 101.4 - 102.2 °C. [b] mp 77.2 - 77.6 °C.

Ethyl (*a*R,2*R*,3*S*)-Tetrahydro-2-menthyloxy-*a*-methoxy-5-oxo-3-furanacetate; Typical Procedure [294, 295]: To a stirred solution of 11 mmol of LDA in 30 mL of THF are added under a nitrogen atmosphere at - 60 °C, 1.18 g (10 mmol) of ethyl methoxyacetate. After stirring for 0.5 h at - 60 °C the mixture is cooled to - 90 °C and 2.38 g (10 mmol) of (-)-menthyloxy-2(5*H*)-furanone in 30 mL of THF are added dropwise over a period of 0.5 h. After stirring for 1.5 h at -90 °C the mixture is quenched with 200 mL of sat. NH_4Cl, followed by extraction with diethyl ether, drying over Na_2SO_4, evaporation of the solvent, distilling of the lower boiling fractions and chromatography on silica gel (CH_2Cl_2); yield: 2.6 g (73 %); mp 77.2 - 77.6 °C (single isomer by ^{1}H NMR).

A proline derived chiral nickel complex **1** may be used instead of ***a***,***b***-unsaturated esters of lactones modified with a chiral alcohol as the Michael acceptor. The ***a***,***b***-unsaturated acid moiety in **1** reacts with various enolates to afford complexes **2** with diastereomeric ratios of 85:15 to 95:5. Hydrolysis of the imine moiety yields the optically active ***b***-substituted L-alanines. A typical example is shown [296].



3: (S)-*2-amino-4,4-bis*(*ethoxycarbonyl*)*butanoic acid*; yield: 80%; 80% ee

Recently, camphor-based oxazolines have been applied as chiral Michael acceptors [401, 402].

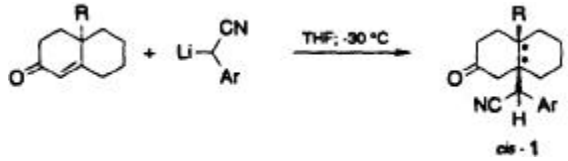
1.5.2.4.1.2.6. Azaallyl Michael Donors Derived from *a*-Substituted Acetonitriles

In addition to the examples described in the previous section, various azaallyl Michael donors, successfully used in diastereoselective 1,4-additions, may be obtained by lithiation of arene acetonitriles [117, 118], protected cyanohydrins [119 – 121, 385], and ***a***-amino- [122, 123] and ***a***-phosphino- [124, 125] substituted acetonitriles.

Lithiated areneacetonitriles react with ***a***,***b***-unsaturated ketones at low temperatures using short reaction times to give both 1,2- and 1,4-adducts. The 1,2-addition is reversible and under thermodynamic control (higher temperatures and longer reaction times) only the 1,4-adducts, i.e., ***d***-oxonitriles, are obtained. When lithiated arylacetonitrile is added to 2-substituted 2-cycloalkenones in THF or in THF/HMPA mixtures at – 70 - 0 °C, followed by protonation or alkylation under kinetically controlled conditions, predominantly *cis*- or *trans*-2,3-disubstituted cycloalkanones respectively, are obtained.

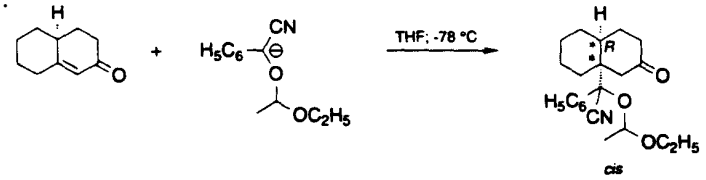
If the enone is part of a decalone system, i.e., a ***b***- and an ***g***-substituent are present, on reaction with lithiated areneacetonitriles in THF the exclusive formation of *cis*-substituted decalones is observed [126]. The diastereoselectivity at the exocyclic stereogenic center is, however, poor. Applications in the synthesis of anthracyclines are given in the literature [127, 128].

for references see p 2148



1: R = H; Ar = C_6H_5; cis-*octahydro-3-oxo-**a**-phenyl-3a-naphthaleneacetonitrile* [130] yield: 95%
R = CH_3; Ar = C_6H_5; cis-*octahydro-8a-methyl-3-oxo-**a**-phenyl-3a-naphthaleneacetonitrile* [130]; yield: 95 %
R = CH_3; Ar = 4-$CH_3OC_6H_4$; cis-*octahydro-**a**-(4-methoxyphenyl)-8a-methyl-3-oxo-3a-naphthaleneacetonitrile* [130]; yield: 95%

Protected cyanohydrins may be employed as acyl anion equivalents in 1,4-additions in the presence of HMPA [129]. For instance cyanohydrins prepared from arylaldehydes add in a 1,4-fashion under thermodynamic control (THF or THF/HMPA) to cyclohexenone, isophorone and decalone systems; in the latter case *cis*-octahydro-2(1*H*)-naphthalenones are exclusively obtained [130, 131].



***cis*-*a*-(Decahydro-3-oxo-3a-naphthalenyl)-*a*-(1-ethoxyethoxy)-*a*-phenylacetonitrile; Typical Procedure for the Reaction of *a*-Azaallyl Michael Donors with Enones [130]:**
To a stirred solution of 5 mmol of LDA in 4 mL of THF at - 78 °C is added under an argon atmosphere 0.97 g (5 mmol) of ***a***-ethoxyethoxybenzeneacetonitrile. The mixture is stirred for 0.5 h and subsequently 0.75 g (5 mmol) of hexahydro-2(1*H*)-naphthalenone are added followed by stirring at - 78 °C for 1 h. After this period the mixture is allowed to warm to 0 °C and stirred at that temperature for an additional hour, 20 mL of sat. aq NH_4Cl are added and the resulting mixture is extracted three times with 30 mL of diethyl ether. The combined ether layers are washed with water until neutral and dried over $MgSO_4$. The solvent is evaporated and the remaining solid material is recrystallized from ethanol to afford the adduct; yield: 1.55 g (90%); mp 168-169 °C.

1.5.2.4.1.3. Intramolecular Additions

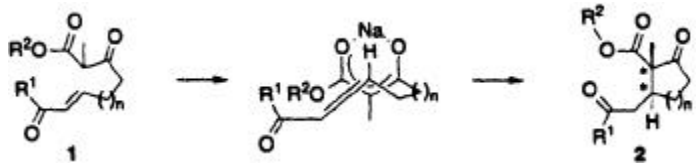
The intramolecular Michael addition of acyclic systems is often hampered by competing reactions, i.e., aldol condensations. With the proper choice of Michael donor and acceptor, the intramolecular addition provides a route to *trans*-substituted cyclopentanones, and cyclopentane and cyclohexane derivatives. Representative examples are the cyclizations of ***b***-oxo ester substituted enones and ***a***,***b***-unsaturated esters.

Addition of the chelated enolate of the ***b***-oxo ester moiety of a 2,8-dioxo-6-alkenoate **1** under thermodynamic control at 25 °C using stoichiometric or catalytic amounts of sodium hydride in benzene results in the formation of *trans*-2-oxo-5-(2-oxoalkyl)-1-cyclopentanecarboxylate **2** exclusively.

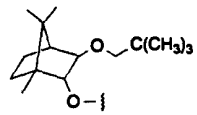
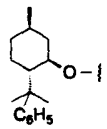
Chelation of the enolate and orientation of the acceptor chain away from the chelate, seems to be essential as the use of potassium *tert*-butoxide in *tert*-butyl alcohol (nonchelated enolate) results in a 1:1 mixture of *cis*- and *trans*-**2** [132, 133]. The diastereomeric ratio furthermore depends on the alcohol (R^2O) moiety [134 – 136, 386], whereas the use of zirconium(IV) isopropoxide also results in high *trans*-selectivity (*cis/trans* ratio, 1:25) [137].

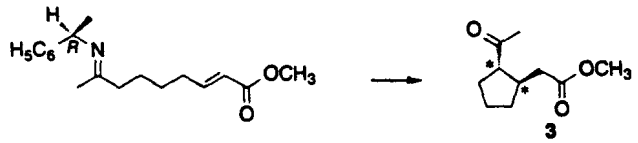
This intramolecular Michael addition, when followed by an aldol condensation provides a useful route to *trans*-octahydroindenes methylated in the ring fusion positions.

The diastereoselectivity of the intramolecular cyclization of acyclic imino-substituted enones, although predominantly *trans*, also strongly depends upon the conditions for cyclization, i.e., heat, pressure or Lewis acid [138, 387].



n = 1, 2

R^1	R^2	Yield (%)	(*cis/trans*)	d.r. [(*R*)/(*S*)]	Ref
OCH_3		85-95	0:100	7:93	134
OCH_3	OCH_3	85	8:92	-	133
CH_2OCH_3	OCH_3	62	0:100	-	137
CH_3	OCH_3	90	0:100	-	133
$OC(CH_3)_3$		85-95	0:100	92:8	134



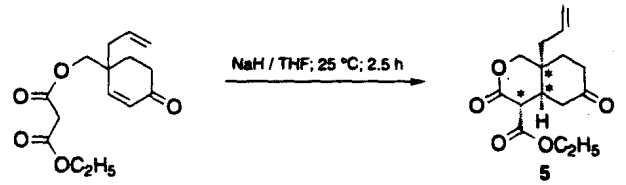
3: *methyl* (*1*R*,*2*S*)-*2-acetyl-1-cyclopentaneacetate*; yield: 60%
80 °C; 7.5×10^5 Torr: 58% op
20 °C; 9×10^6 Torr: 62% op
$MgBr_2$: 35 °C; 7.5×10^5 Torr: 29% op

The diastereoselective intramolecular Michael addition of ***b***-substituted cyclohexenones results in an attractive route to *cis*-octahydro-6*H*-inden-6-ones. The stereogenic center in the ***g***-position of the enone dictates the face selectivity, whereas the *trans* selectivity at C1,C7a is the result of an 6-*exo-trig* cyclization. *cis*-Octahydro-5*H*-inden-5-ones are formed as the sole product regardless of which base is used, e.g., potassium carbonate in ethanol or sodium hydride in THF, under thermodynamically controlled conditions [139, 140]. An application is found in the synthesis of gibberellic acid [141].

4: (*3*S*,*3a*R*,*7a*S*)-*3-acetyl-tetrahydro-3a-methyl-5*H-*inden-5-one*; yield: 70%; d.r. (*cis/trans*) 100:0

For a related diastereoselective route to spiro-fused bicyclooctanes, see refs 144-147. The construction of bicyclic compounds with a *cis* ring junction is also used in the formation of key intermediates, such as **5**, for forskolin [148, 149] and vernolepin [150, 151], see also ref 152.

for references see p 2148

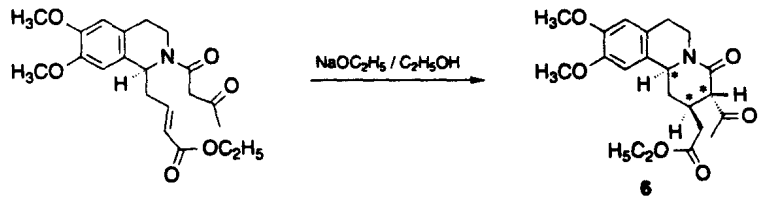


5

Ethyl (4*R,4a*S**,8a*S**)-Octahydro-3,6-dioxo-8a-(2-propenyl)-1*H*-2-benzopyran-4-carboxylate (5); Typical Procedure [150]:**

To a stirred slurry of 35 mg (0.87 mmol) of sodium hydride in 5 mL of THF under a nitrogen atmosphere at 0 °C is added 225 mg (0.80 mmol) of ethyl [4-oxo-1-(2-propenyl)-2-cyclohexenyl]methylpropanedioate in 3 mL of THF. After the evolution of hydrogen ceases the cooling bath is removed and the mixture is stirred for 2.5 h at 25 °C. The mixture is poured into cold 0.1 N aq HCl and then extracted three times with 10 mL of CH_2Cl_2. The combined extracts are washed with aq $NaHCO_3$ and water. After drying and evaporation of the solvent the crude product is recrystallized; yield: 197 mg (87%); mp 83-84 °C (diethyl ether).

A *trans* stereoselective intramolecular 1,4-addition was also used in the synthesis of (±)-emetine [153].



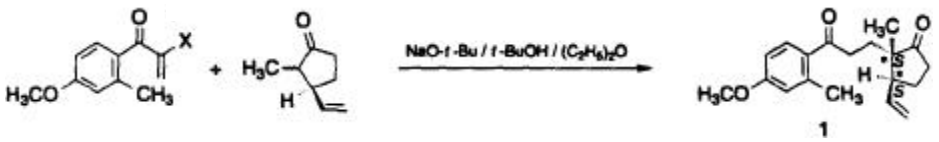
6

6: *ethyl* (2R*,3R*,*11b*S*)-*3-acetyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-4-oxo-2*H-*benzo*[a]*quinolizine-2-acetate*; yield: 63 % (single diastereomer)

1.5.2.4.2. Stereoselectivity Under the Influence of Chirality in the Donor

1.5.2.4.2.1. Substrate Control

Successful methodology for diastereoselective Michael additions with chirality in the donor is so far limited to chiral cyclic enolates. The stereocontrol is mainly due to shielding of one of the ***p***-faces of the enolate by the ring substituent that resides at the stereogenic center. The *trans*-diastereoselective Michael addition of (*S*)-2-methyl-3-vinylcyclopentanone illustrates this principle [154 - 157].

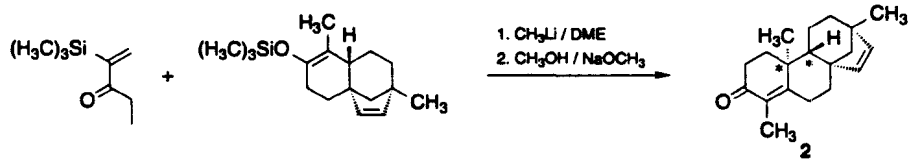


1

X = $Si(CH_3)_3$

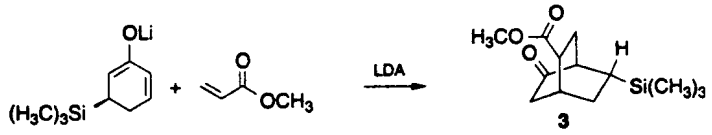
1: (2S,3S)-*2*-[*3*-(*4-methoxy-2-methylphenyl*)-*3-oxopropyl*]-*2-methyl-3-vinylcyclopentanone*; yield: 60 %

A very efficient method for annulations [158] is based on the addition of lithium or silyl enolates to ***a***-silylated enones as a key step. The diastereoselective 1,4-addition is followed by an aldol condensation. This procedure allows Michael additions under aprotic conditions, whereby the silyl substituent stabilizes the enolate of the Michael adduct preventing polymerization of the enone [159 - 163].



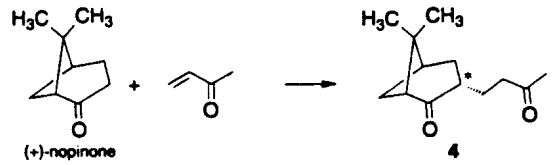
2: (*4a*S*,*4b*R*)-*4,4a,4b,5,6,7,8,8a,9,10-decahydro-1,4a,7-trimethyl-7,8a-etheno-2*(3H)-*phenanthrenone*; yield: 65% [163]

Using 3-substituted cyclohexanones the *trans*-diastereoselective synthesis of decalones and octahydro-1*H*-indenones may be achieved [164 - 169]. This method has been applied, for instance, in the synthesis of 19-norsteroids. In a related Michael addition the lithium enolate of (*R*)-5-trimethylsilyl-2-cyclohexenone reacts with methyl 2-propenoate selectively *trans* to the trimethylsilyl substituent. Subsequent intramolecular ring closure provides a single enantiomer of the bicyclo[2.2.2]octane [170] (see also Section 1.5.2.4.4.).



3: *methyl 3-oxo-5-*(*trimethylsilyl*)*bicyclo*[*2.2.2*]*octane-7-carboxylate*; yield: 73 %; d.r. 100:0; mp 47.5-48.5°C; $[\alpha]_D^{22}$ 98.0 (*c* = 1, $CHCl_3$)

The asymmetric Michael addition of chiral nonracemic ketone enolates has most frequently been used as part of the Robinson annulation methodology in the synthesis of natural products [171, 172]. The enolates are then derived from carbocyclic chiral ketones such as (+)-nopinone, (-)-dihydrocarvone, or (-)-3-methylsabinaketone.



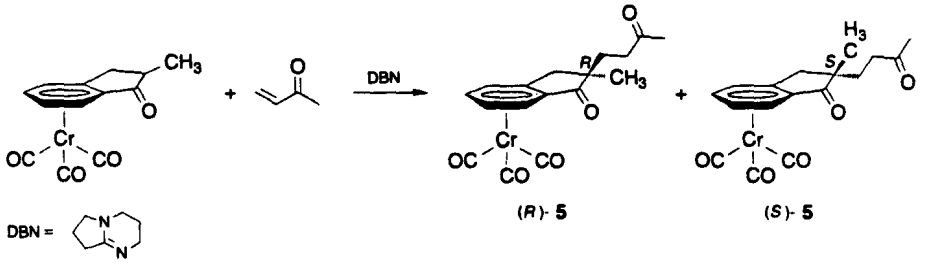
4: (*1*R,*3*S,*5*S)-*6,6-dimethyl-3-*(*3-oxobutyl*)*bicyclo*[*3.1.1*]*heptan-2-one*; yield: 87 %

By this method a ring may be constructed with a high degree of stereochemical control under thermodynamic conditions. This approach was used in the synthesis of (+)-***α***-cyperone [173, 174], eremophilane sesquiterpenoids [175, 176], the CD rings of steroids [177 - 179], (-)-ajmalicine [180], *O*-methylpisiferic acid [181] and (+)-pisiferol [182].

Methodology for the diastereoselective synthesis of vicinal quaternary and tertiary stereogenic centers has been developed using the lithium enolate of (4*R*)-4-*tert*-butyl-3-methyl-2-oxetanone [183] (see Section 1.5.2.4.1.2.4.).

In a rather different approach optically active chromium complexes of 2,3-dihydro-1*H*-indenone are used as chiral enolate precursors. These chiral complexes react with 3-buten-2-one in benzene using 1,5-diazabicyclo[4.3.0]non-5-ene as the base. The diastereomeric ratio of the product is the same irrespectively of whether the *exo*- or the *endo*-isomer of the chromium complex is used as a substrate; the chromium moiety dictates the configuration of the product [184, 185].

for references see p 2148



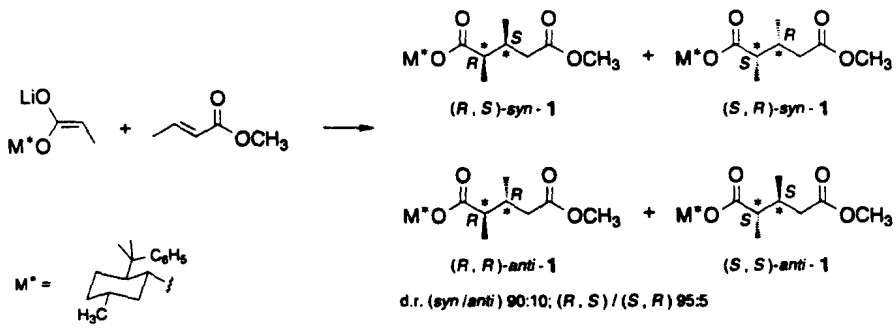
5: *tricarbonyl*[$\boldsymbol{h}^6$-*2,3-dihydro-1-oxo-2-*(*3-oxobutyl*)-*1*H-*indenyl*]*chromium*; yield: 90 %; ratio [(*R*)/(*S*)] 87:13

1.5.2.4.2.2. Auxiliary Control

Asymmetric Michael additions using chiral auxiliary containing donors have attracted widespread attention and various methods are now available that give high enantiomeric excess.

1.5.2.4.2.2.1. Chiral Esters and Amides

An efficient synthesis of optically active pentanedioates is possible using ester enolates based on chiral alcohols. This is illustrated by the addition of the lithium (*E*)-enolate of (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl propanedioate to methyl (*E*)-2-butenoate at -100 °C which shows simple and induced diastereoselectivity.



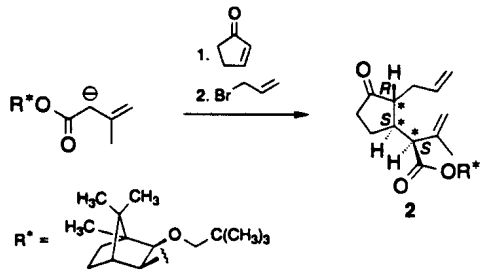
5-Methyl 1-[(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl] Propanedioate (1); Typical Procedure [186]:

To a stirred solution of 1.1 mmol LDA in 30 mL of THF are added 288 mg (1 mmol) of (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl propanoate under a nitrogen atmosphere at - 78 °C. After stirring for 30 min the mixture is cooled to - 100 °C (diethyl ether/liquid nitrogen bath) and 110 mg (1.1 mmol) of methyl (*E*)-2-butenoate in 3 mL of THF are added. The mixture is stirred for 3 h at - 100 °C before it is quenched with 30 mL of 1N acetic acid in THF. Extraction with diethyl ether followed by washing with aq $NaHCO_3$ and brine gives, after drying over Na_2SO_4 and evaporation of the solvent, the crude adduct. This adduct is purified by flash chromatography (silica gel, hexane/ethyl acetate 9:1) to give the product as a mixture of isomers; yield: 291 mg (0.75 mmol, 75%).

A diastereomeric ratio (*syn/anti*) of 90:10 is found, whereas within the *syn*-adduct the ratio between the (*R,S*)/(*S,R*)-isomers is 95:5. With methyl (*Z*)-2-butenoate the diastereomeric ratio (*syn/anti*) is 25:75, and in the *anti*-adduct the (*R,S*)/(*S,S*) ratio is 88:12 [186]. These results are consistent with a chelated transition state as shown in Section 1.5.2.4.1. This enantioselective Michael addition was used in the synthesis of 7,20-diisocyanoadociane [187].

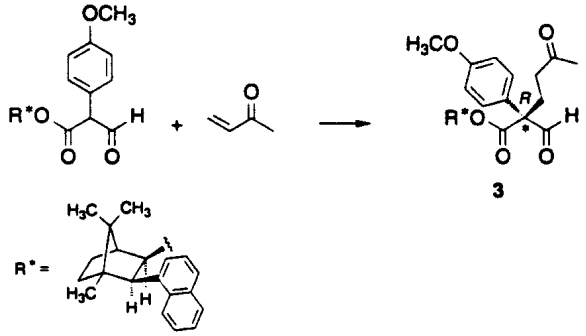
A number of chiral alcohols and amino alcohols have been applied as auxiliaries to enolates. The induction may be explained by the shielding of one of the faces of the enolate by a bulky alkoxy or aryl substituent. Representative examples, together with the results in diastereoselective 1,4-additions with different Michael acceptors, are given in the following.

The asymmetric 1,4-addition of the dienolate of the optically active camphor derived 3-methyl-3-butenoate to 2-cyclopentenone gives a mixture of four diastereomers. The major adduct was applied in the synthesis of (-)-khusimone [188].



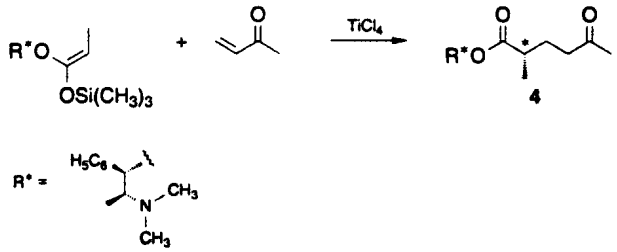
2: *2-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl* ***b****-methyl-****a****-[3-oxo-2-(2-propenyl)cyclopentyl]-****b****-butenoate*; total yield: 55%; d.r. [(1*S*,2*R*,***a****S*)/(1*S*,2*R*,***a****R*)/(1*R*,2*S*,***a****R*)/(1*R*,2*S*,***a****S*)] 67:7:13:3

The construction of quaternary stereogenic centers with high diastereoselectivity was used in the synthesis of (+)-*O*-methyljoubertiamine [189].



3: *4,7,7-trimethyl-3-(1-naphthalenyl)bicyclo[2.2.1]hept-2-yl 2-formyl-2-(4-methoxyphenyl)-5-oxohexanoate*; yield; 76%; d.r. [(*R*)/(*S*)] 95:5

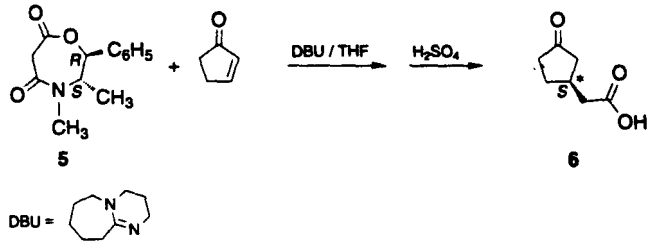
The (*E*)-trimethylsilylenolates of *N*-methylephedrine propanoates are useful as chiral propanoate equivalents in the titanium(IV) chloride catalyzed addition to enones. Although diastereoselectivities are high, this method suffers from low yields due to excessive polymerization [190].



4: (*1*R,*2*S)-*2-(dimethylamino)-1-phenylpropyl* (S)-*2-methyl-5-oxohexanoate*; yield: 20%; d.r. [(*S*)/(*R*)] 87:13

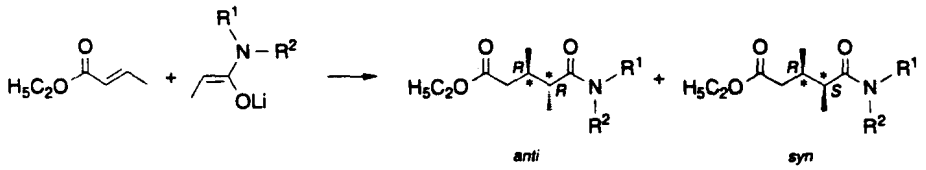
(-)-(1*R*,2*S*)-Ephedrine was used to make the chiral propanedioate derivative **5**. Both the yield and the enantioselectivity of the Michael reaction using this enolate precursor are base dependent, however, enantiomeric excesses as high as 96 % were achieved when 1,8-diazabicyclo[5.4.0]undec-7-ene was used as base [191].

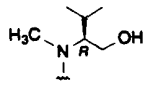
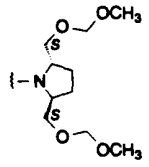
for references see p 2148



6: (S)-*3-oxocyclopentaneacetic acid*; yield: 43%; 96% ee

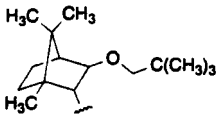
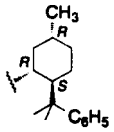
A variety of chiral amides as well as oxazolidones [388] and imidazolidones [389, 390] may easily be prepared from amino alcohols that are derived from amino acids [391, 392]. The addition of the lithium enolates of these amides under kinetically controlled conditions to ***a***,***b***-unsaturated esters yields optically active pentanedioates. Both *syn*- and *anti*-5-amino-5-oxopentanoates may be obtained with good diastereomeric ratios [192].



Amide Auxiliary	d.r. (*anti/syn*)	Yield (%)
	91:9	86
	13:87	84
	91:9	76

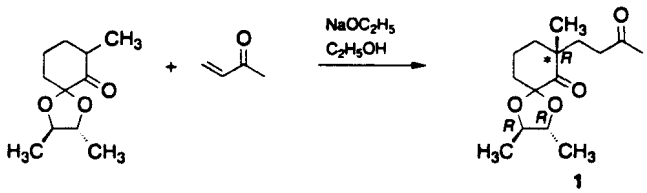
Ethyl (2*R,3*R**)-5-[(*R*)-(1-Hydroxymethyl-2-methylpropyl)methylamino]-3,4-dimethyl-5-oxopentanoate; Typical Procedure [192]:**
To a stirred solution of (1.5 mmol) LDA in 3.5 mL of THF/hexane (60:40) at - 78 °C under a nitrogen atmosphere are added 259 mg (1.5 mmol) of (*R*)-*N*-(1-hydroxymethyl-2-methylpropyl)-*N*-methylpropanamide in 1.5 mL of THF. After 30 min 86 mg (0.75 mmol) of ethyl (*E*)-2-butenoate in 1.5 mL of THF are added and the mixture is stirred for an additional 0.5 h at - 78 °C. The mixture is quenched by adding aq NH_4Cl. Extraction with diethyl ether, drying over Na_2SO_4 followed by evaporation of the solvent gives the adduct; yield: 185 mg (86%); d.r. (*syn/anti*) 9:91. The diastereomeric ratio is determined by ^{13}C NMR.

An interesting approach to *trans*-2,3-disubstituted cycloalkanones is offered by auxiliary controlled intramolecular Michael additions. The diastereoselectivity depends on the chiral alcohol used [193, 194]. When the borneol derivative **7** was used as substrate, a single diastereomer of **8** resulted when the reaction was performed at 25 °C under thermodynamic control with a catalytic amount of sodium hydride in benzene.

R*	d.r. [(2*S*,3*S*)/(2*R*,3*R*)]
	93:7
	8:92

1.5.2.4.2.2.2. Chiral Ketones

The application of auxiliary control in the asymmetric Michael addition of chiral enolates derived from ketones is rare; the only example known is the use of (2*R*,3*R*)-2,3-butanediol as an auxiliary. The ketal of (2*R*,3*R*)-2,3-butanediol with 3-methyl-1,2-cyclohexanedione reacts with 3-buten-2-one using as base a catalytic amount of sodium ethoxide in ethanol [195].



1: *6*-[(R,R)-*1,2-dimethyl-1,2-ethanediylbis*(*oxy*)]-*2-methyl-2*-(*3-oxobutyl*)*cyclohexanone*; yield: 78 %; d.r. [(2*R*)/(2*S*)] 72:28

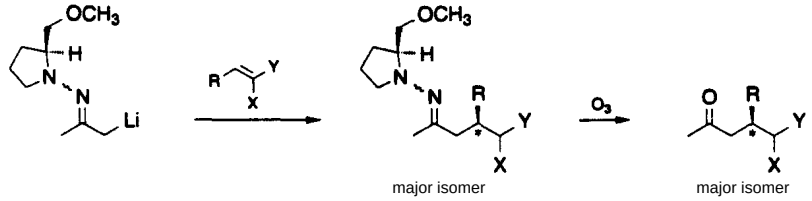
1.5.2.4.2.2.3. Enders Method Using Chiral Hydrazones

An excellent synthetic method for asymmetric C-C-bond formation which gives consistently high enantioselectivity has been developed using azaenolates based on chiral hydrazones. (*S*)- or (*R*)-2-(methoxymethyl)-1-pyrrolidinamine (SAMP or RAMP) are chiral hydrazines, easily prepared from proline, which on reaction with various aldehydes and ketones yield optically active hydrazones. After the asymmetric 1,4-addition to a Michael acceptor, the chiral auxiliary is removed by ozonolysis to restore the ketone or aldehyde functionality. The enolates are normally prepared by deprotonation with lithium diisopropylamide.

Thus, the lithiated SAMP hydrazones of various methyl ketones on addition to 2-(aryl-methylene)-1,3-propanedionates and propanedinitriles provide, after the removal of the auxiliary, (*R*)-2-(1-aryl-3-oxobutyl)-1,3-propanedioates and -propanedinitriles with high enantiomeric excess (> 95%) in 50-82% yield (see Table 6) [196, 197]. Using similar methods optically active ***d***-lactones (90% to ≥ 96% ee) are obtained [198].

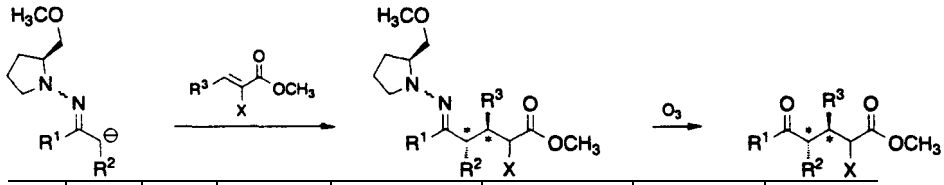
Excellent simple (90-100%) and induced diastereoselectivities (92-100%) were observed in the syntheses of 3,4-disubstituted 5-oxoalkanoates using, instead, various substituted aldehydes and ketones to prepare the chiral hydrazones.

for references see p 2148



R = alkyl, aryl; X = H, $COOCH_3$; CN; Y = $COOCH_3$, CN

Table 6. 5-Oxoalkanoates by Addition of Aldehyde or Ketone SAMP Hydrazones to Enones



R^1	R^2	R^3	X	Major Isomer	ee (%) or d.r. (*anti/syn*)	Yield [a] (%)	Ref
H	H	CH_3	H	*R*	≥ 96	43	198
H	H	C_2H_5	H	*R*	90	37	198
H	H	C_6H_5	H	*R*	≥ 96	51	198
H	CH_3	CH_3	H	3*R**,4*R**	98:2	58	198, 200
H	C_2H_5	C_6H_5	H	3*R**,4*R**	98:2	32	199
CH_3	H	CH_3	H	*R*	≥ 96	50	197
CH_3	H	C_6H_5	H	*R*	≥ 96	62	197
CH_3	H	C_6H_5	$COOCH_3$	*R*	≥ 95	72	196, 202
C_2H_5	H	CH_3	H	*R*	≥ 96	45	197
C_2H_5	CH_3	CH_3	H	3*R**,4*R**	98:2	40 [b]	199
C_2H_5	H	C_6H_5	$COOCH_3$	*R*	≥ 95	74	196, 202
C_6H_5	H	C_6H_5	$COOCH_3$	*R*	≥ 95	82	196, 202

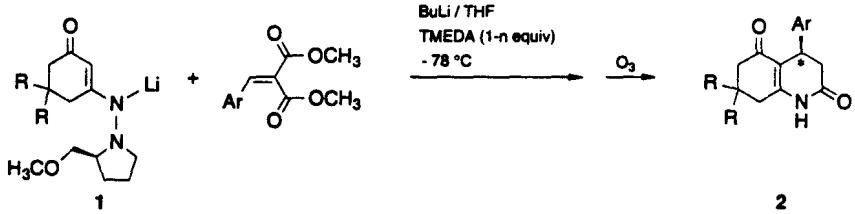
[a] For more examples see refs 196-202. [b] (*R*)-1-Amino-2-(methoxymethyl)pyrrolidine is used.

Methyl (3*R,4*R**)-3,4-Dimethyl-5-oxopentanoate; Typical Procedure [198]:**

To a stirred solution of 2.2 g (22 mmol) of diisopropylamine in 40 mL of THF are added dropwise at 0°C under argon 14 mL (22 mmol, 1.6 N in hexane) of butyllithium. After dropwise addition of 3.4 g (20 mmol) of (*S*)-2-methoxymethyl-*N*-propylidene-1-pyrrolidinamine, the mixture is stirred at 0 °C for 3 h, cooled to - 100 °C and a solution of 2.2 g (22 mmol) of methyl (*E*)-2-butenoate in 10 mL of THF is added. The reaction is stirred for 2 h at -100°C after which the mixture is allowed to warm to 0°C within 8-12 h. The mixture is then poured into 100 mL of sat. aq NH_4Cl and extracted three times with diethyl ether. After drying the organic layer over Na_2SO_4 and evaporation of the solvent the crude oily product is purified by silica gel chromatography (diethyl ether/pentane 50:50) to afford 4.3 g (16 mmol, 80%) of methyl (2*R**,3*R**)-5-[(*S*)-2-(methoxymethyl)-1-pyrrolidinylimino)-3,4-dimethylpentanoate. The pyrrolidine derivative is dissolved in 50 mL of CH_2Cl_2 and cooled to - 78 °C. A gentle stream of ozone is flushed through the solution. The reaction is followed by TLC (silica gel, diethyl ether/pentane) and when complete argon is flushed through the solution instead of ozone and the solution is subsequently warmed to 25 °C. Evaporation of the solvent and purification of the crude compound by chromatography on silica gel (diethyl ether/pentane) affords the adduct; yield: 1.8 g (58 % overall); bp 90-95 °C/1.3 Torr.

The addition of the lithium azaenolate of the SAMP hydrazone of propanal to methyl (E)-2-butenoate to furnish the (*S*,*S*,*S*)-adduct in 58% yield with ≥ 96% ee and de is illustrative for the efficiency of this asymmetric Michael addition [199]. Only the *anti*-isomer (an *l* adduct) is found. This methodology was used in the synthesis of pheromones of the small forest and red wood ant[200].

The Enders method has also been used as a key step in the synthesis of optically active *N*-heterocycles. The use of cyclic 1,3-diketones for the preparation of the SAMP or RAMP lithium azaenolates is shown by the synthesis of substituted 4,6,7,8-tetrahydro-2,5(1*H*,3*H*)-quinolinediones **2**. Michael addition of **1** with, for example, benzylidene propanedioates followed by removal of the auxiliary and lactamization gives **2** with ≥ 98 % ee [201].

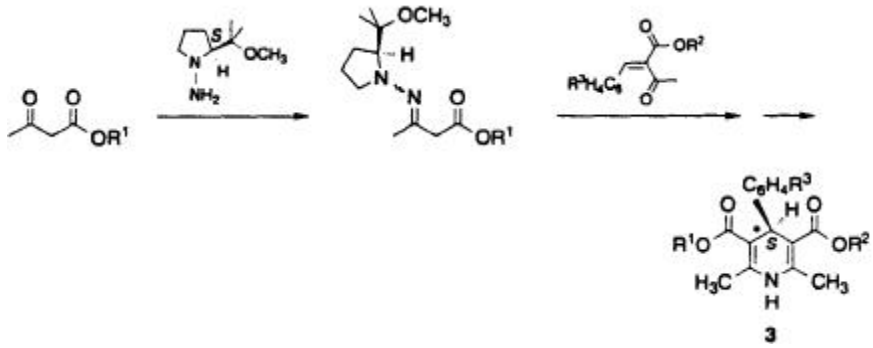


2: (R)-*4,5,6,7,8-tetrahydro-4-phenyl-2,5*(*1*H,3H)-*quinolinediones*

R	Ar	Ee (%) [a]	Con-fig.	Overall Yield (%)	mp (°C)	$[\alpha]_D^{20}$ (*c*, solvent)
CH_3	C_6H_5	≥ 98	*R*	50	218-9	-70.8 (1, EtOH)
CH_3	C_6H_5	≥ 98	*S*	51	218-9	+70.1 (1, EtOH)
CH_3	C_6H_5	0	*rac*	56	217-8	-
H	C_6H_5	≥ 98	*R*	50	230-1	-51.3 (0.3, EtOH)
H	C_6H_5	0	*rac*	60	230-1	-
CH_3	4-$CH_3OC_6H_4$	≥ 98	*R*	52	194-5	-65.5 (0.3, CH_3OH)
H	2,4-$Cl_2C_6H_3$	≥ 98	*R*	54	108-9	-36.5 (0.3, $CHCl_3$)
CH_3	3-$NH_2C_6H_4$	≥ 98	*R*	57	202-3	-82.7 (0.6, CH_3OH)

[a] ee determined by ^{1}H NMR [Eu(hfc)$_3$].

Enantioselective synthesis of Hantzsch 1,4-dihydropyridines was developed based on similar 1,4-additions of ***b***-oxoester derivatives to 2-(arylmethylene)-3-oxopropanoates. High enantiomeric excess (84-98%) was achieved when (*S*)-1-amino-2-(1-methoxy-1-methylethyl)pyrrolidine was used at the auxiliary [202].



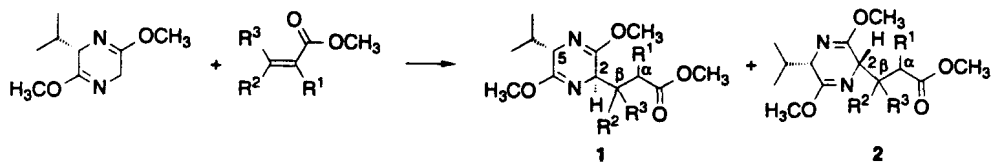
3: R^1 = Pr; R^2 = C_6H_5; R^3 = C_2H_5; *5-ethyl 3-*(*2-propenyl*) (S)-*1,4-dihydro-2,6-dimethyl-4-phenyl-3,5-dicarboxylate*; yield: 69%; 84% ee

3	R^1	R^2	R^3	ee (%)	Con-fig.	Overall Yield (%)	mp (°C)	$[\alpha]_D^{25}$ (*c*, acetone)
a	Pr	C_2H_5	H	84	*S*	69	105	+29.4 (1.1)
b	CH_3	*i*-C_3H_7	3,4-OCH_2O	85	*R*	71	130	+6.5 (1.3)
c	*t*-C_4H_9	$CH_3O(CH_2)_2$	3,4-OCH_2O	94	*S*	67	134	-17.0 (1.0)
c	$CH_3O(CH_2)_2$	*t*-C_4H_9	3,4-OCH_2O	≥ 96	*R*	67	134	+17.4 (1.0)
d	*t*-C_4H_9	C_2H_5	4-CH_3	92	*S*	64	140	+12.9 (1.0)
d	*t*-C_4H_9	C_2H_5	4-CH_3	91	*R*	65	140	-12.4 (1.0)
e	*t*-C_4H_9	CH_3	3,4-$(OCH_3)_2$	98	*S*	72	144	+14.4 (1.0)
f	*t*-C_4H_9	C_2H_5	3,4,5-$(OCH_3)_3$	≥ 96	*S*	70	152	+11.3 (1.0)
g	*t*-C_4H_9	C_2H_5	2-pyridyl	≥ 96	*S*	64	185	+2.0 (1.0)

for references see p 2148

1.5.2.4.2.2.4. Schöllkopf Method Using Chiral Bislactim Ethers

An extremely useful method for the asymmetric synthesis of substituted amino acids, in particular glutamic acids, is based on optically active bislactim ethers of cyclodipeptides. The lithium enolates of bislactim ethers (which are prepared easily from amino acids) undergo 1,4-addition to various ***a***,***b***-unsaturated esters to give ***b***-substituted 2,5-dihydropyrazinepropanoates [203 - 205] with high diastereofacial selectivity, ratio (*R*/*S*) > 140-200:1.



1 **2**

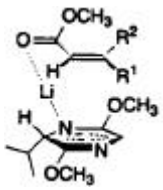
R^1	R^2	R^3	d.r. (**1**/**2**)	Isomeric Ratio	Yield (%)
H	H	H	> 98:2	[(2*R*)/(2*S*)] 200:1	42
H	CH_3	H	> 98:2	[(2*R*,***b***S)/(2*R*,***b***R)/(2*S*,***b***S)] 170:59:1	65
H	CH_3	CH_3	> 98:2	[(2*R*)/(2*S*)] 140:1	56
H	C_6H_5	H	> 98:2	[(2*R*,***b***S)/(2*R*,***b***R)/(2*S*,***b***S)] 200:20:1	92
H	H	C_6H_5	> 98:2	[(2*R*,***b***S)/(2*R*,***b***R)/(2*S*,***b***S)] 46:148:1	88
CH_3	H	H	98:2	[(2*R*,***a***S)/(2*R*,***a***R)/(2*S*,***a***S,2*S*,***a***R)] 98:98:1:1	68
H	4-$CH_3OC_6H_4$	H	98:2	[(2*R*,***b***S)/(2*R*,***b***R)/(2*S*,***b***S)] 88:8:1	85
H	4-pyridinyl	H	> 98:2	[(2*R*)/(***b***S)/(2*R*,***b***R)] 95:7	90

Methyl (2*R*,5*S*,*b***S)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-***b***-phenyl-2-pyrazinepropanoate; Typical Procedure [204]:**

To a stirred solution of 0.74 g (4 mmol) of (*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine in 20 mL of THF under a nitrogen atmosphere are added at - 70 °C, 2.6 mL (4 mmol, 1.55 N in hexane) of butyllithium and stirring is continued for 10 min. Then, a solution of 0.97 g (6 mmol) of methyl (*E*)-3-phenylpropenoate in 10 mL of THF is added. After 2-3 h a solution of 0.24 g (4 mmol) of acetic acid in 2 mL of THF is added and the mixture is allowed to warm to 25 °C. The solvent is removed in vacuo, the residual product dissolved in 10 mL of diethyl ether, then shaken with 10 mL of water, and the water layer extracted twice with 10 mL of diethyl ether. The combined diethyl ether extracts are dried over $MgSO_4$ and the diethyl ether is evaporated. The crude product is purified by bulb-to-bulb distillation to give the adduct; yield: 1.28 g (92%).

The adduct was a mixture of (2*R*,5*S*,***b***S)-, (2*R*,5*S*,***b***R)- and (2*S*,5*S*,***b***S)-isomers in a ratio of 90.5:9.0:0.5. bp 140 - 160 °C/0.045 Torr. The diastereomeric ratio was determined by GC-MS. The major adduct could be obtained diastereomerically pure by chromatography over silica gel (toluene/ethyl acetate 95:5) in 83 % yield.

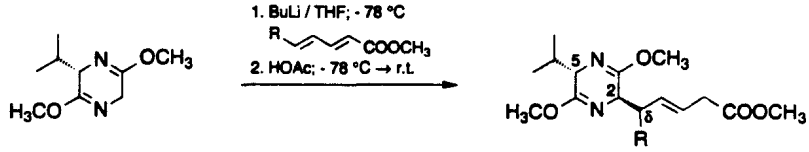
The stereochemical outcome may be rationalized via a lithium chelated ***p***-complex in which steric hindrance due to the isopropyl group and the R groups is minimized.



As an example the enolate of (*S*)-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine, prepared from (*S*)-valine and glycine, reacts with methyl (*E*)-3-phenylpropenoate and the (2*R*,***b***S)-isomer is obtained as the major diastereomer. The diastereofacial selectivity is reflected by a 2*R*/2*S* ratio of 99.6:0.4, whereas the high simple diastereoselectivity is shown by the diastereomeric ratio (*syn*/*anti*) of 91 : 9. Using methyl (*Z*)-3-phenylpropenoate the (2*R*,***b***R)-isomer is formed

exclusively. Hydrolysis and subsequent cyclization provides enantiomerically pure methyl (2*S*,3*S*)-5-oxo-3-phenyl-2-pyrrolidinecarboxylate and the chiral auxiliary valine may be recovered [203, 204]. This methodology was used in the synthesis of clausenamide [205].

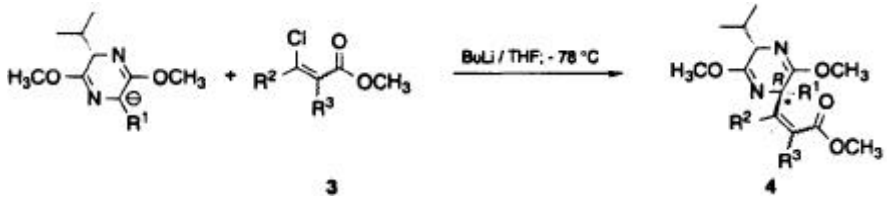
The (*S*)-valine based bislactim ether adds regioselectively in a 1,6-fashion to ***a***,***b***-***g***,***d***-unsaturated ***d***-substituted esters with both simple and induced diastereoselectivity exceeding 99:1. This provides, after hydrolysis, virtually enantiomerically pure dimethyl (*E*)-2-amino-3-heptene-1,7-dioates [206].



R	d.r. [(2*R*)/(2*S*)]	d.r. [(2*R*)/(***d*** [a])]	Yield (%)
H	> 99:1	-	52
CH_3	> 99:1	98.2:1.8	78
C_6H_5	> 99:1	> 99:1	70
4-pyridyl	> 99:1	> 99:1	68

[a] Configuration unknown.

In a further extension of this method, the enolate of the bislactim ether cyclo(L-Val-Gly) or cyclo(L-Val-Ala) were added to methyl (*Z*)-3-chloro-2-butenoate. The adduct is again a (*Z*)-***a***,***b***-unsaturated ester and was obtained as a single diastereomer (d.r. > 99:1) [207]. For further examples see references cited in the text.



3: R^1 = H; R^2 = CH_3; R^3 = H; *methyl* (Z)-*3*-[(2R,*5*S)-*2,5-dihydro-5-isopropyl-3,6-dimethoxy-2-pyrazinyl*]-*2-butenoate*; yield: 27%; d.r. [(2*R*,5*S*)/(2*S*,5*S*)] 99.5:0.5
R^1 = CH_3; R^2 = CH_3; R^3 = H; *methyl* (Z)-*3*-[(2R,5S)-*2,5-dihydro-5-isopropyl-3,6-dimethoxy-2-methyl-2-pyrazinyl*]-*2-butenoate*; yield: 73 %; d.r. [(2*R*,5*S*)/(2*S*,5*S*)] 99.5:0.5

R^1	R^2	R^3	Config. of Butenoate	d.r. [(2*R*,5*S*)/(2*S*,5*S*)]	Yield (%)
CH_3	H	H	*Z*	97.5:2.5	75
CH_3	H	H	*E*	99.0:1.0	34
CH_3	CH_3	H	*Z*	99.5:0.5	73
CH_3	CH_3	H	*E*	99.5:0.5	63
CH_3	C_6H_5	H	*Z*	> 99.5:0.5	66
CH_3	H	C_6H_5	*E*	99.0:1.0	61
CH_3	$(-CH_2-)_3$		*Z*	99.5:0.5	69
H	H	H	*Z*	> 150:1	27
H	H	C_6H_5	*E*	[a]	62
H	$(CH_2)_3$		*Z*	99.5:0.5	66

[a] Single isomer.

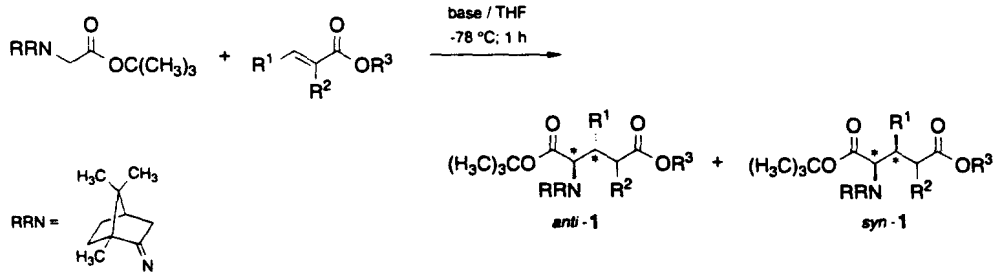
for references see p 2148

1.5.2.4.2.2.5. Chiral Imines and Enamines as Michael Donors

Several methods for asymmetric C-C bond formation have been developed based on the 1,4-addition of chiral nonracemic azaenolates derived from optically active imines or enamines. These methods are closely related to the Enders and Schöllkopf procedures. A notable advantage of all these methods is the ready removal of the auxiliary group. Two types of auxiliaries were generally used to prepare the Michael donor: [1] chiral ketones, such as camphor or 2-hydroxy-3-pinanone; [2] chiral amines, in particular 1-phenylethanamine, and amino alcohol and amino acid derivatives.

Chiral Ketones as Auxiliary

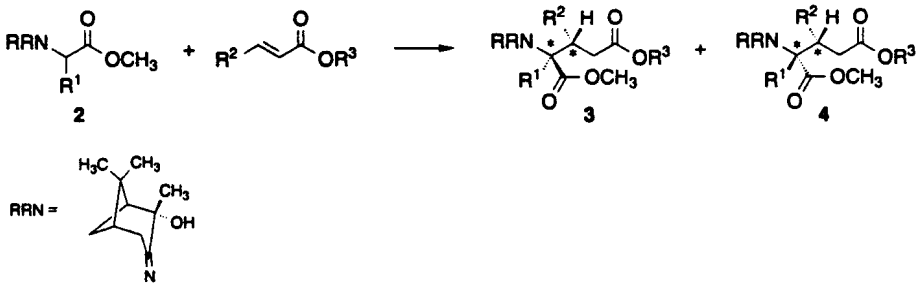
Addition of the imine of camphor and glycine, as the Michael donor, to ***a***,***b***-unsaturated esters yields, after removal of the auxiliary, *anti*-(2*R*)-3-substituted glutamates [208].



R^1	R^2	R^3	Base	Ratio (*anti/syn*)	d.r.	Yield (%)	Ref
H	H	*t*-Bu	LiBr/DBU		95:5	89	208
CH_3	H	*t*-Bu	LiBr/DBU	< 99: > 5	95:5	88	208
H	CH_3	CH_3	BuLi	< 95: > 5	95:5	53	209
CH_3	H	CH_3	LiBr/DBU	77:23	95:5	73	208

Using propenoates and 2-butenoates as Michael acceptors the highest diastereoselectivities are reached with *tert*-butyl esters. Lithium bromide and DBU in THF at room temperature are essential to generate the lithium enolate in these reactions. With the methyl esters the use of LiBr/DBU results in high induced diastereoselectivity at C-2 (> 95:5) but poor *anti* selectivity. It is remarkable that methyl 2-methyl-2-propenoate and dimethyl 2-benzylidene-1,3-propanedioate give a single 1,4-adduct, when butyllithium in tetrahydrofuran is used as the base and *tert*-butyl alcohol is added after generation of the enolate [209, 393]. The auxiliary group is readily removed by hydrolysis to provide *anti*-(2*R*)-2,3-substituted glutamates.

The imines of (-)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone and glycine, alanine and norvaline methyl esters were highly successful as Michael donors in the asymmetric synthesis of 2,3-disubstituted glutamates. The chiral azaallyl anions derived from these imines by deprotonation with lithium diisopropylamide in THF at - 80 °C undergo addition to various ***a***,***b***-unsaturated esters with modest to high diastereoselectivities [210, 394].

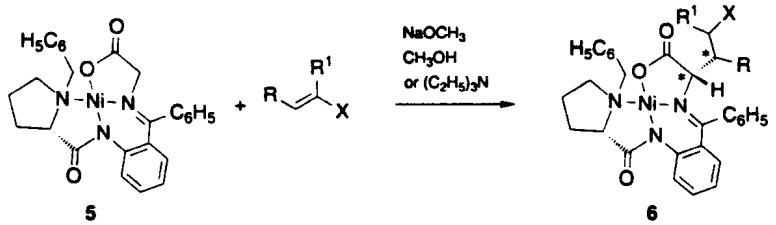


R^1	R^2	R^3	Ratio (**3**/**4**)	Yield (%)
H	H	CH_3	74:26	50
H	CH_3	C_2H_5	43:31:10:16	74
CH_3	H	CH_3	86:14	52
CH_3	CH_3	C_2H_5	100:0	90
Pr	CH_3	C_2H_5	100:0	80

1-Methyl 5-Ethyl (2*S*,3*R*)-2-(2-Hydroxy-2,6,6-trimethylbicyclo[3.1.1]hept-3-ylideneamino)-2,3-dimethylpentanedioate; Typical Procedure [210]:
To a stirred suspension of 2.3 mmol LDA in 20 mL of THF are added at - 80 °C under a nitrogen atmosphere 253 mg (1 mmol) of methyl 2-(2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]hept-3-ylideneamino)propanoate and the mixture is stirred for a further 30 min. After the addition of 114 mg (1 mmol) of ethyl (*E*)-2-butenoate the mixture is stirred at - 80 °C until the reaction is complete (followed by TLC on silica gel). The mixture is poured into 70 mL of sat. aq NH_4Cl and subsequently extracted three times with diethyl ether. The combined ether layers are dried over Na_2SO_4 and the solvent is evaporated. The crude adduct is purified by chromatography (silica gel, diethyl ether/hexane 66:34); yield: 330 mg (90%).

Based on the use of **2** (R^1 = H), metalated with two equivalents of potassium *tert*-butoxide in tetrahydrofuran, routes to (*S*)-phosphinotricin (79% ee) and glutamic acid (69% ee) were developed [211].

A related stereoselective route to glutamic acid derivatives consists of the addition of the nickel complex **5** to various activated olefins, i.e., 2-propenonitrile, 2-propenal and ***a***,***b***-unsaturated esters.



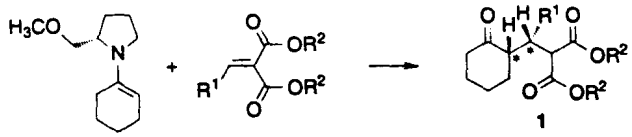
X	R	R^1	d.r.	Config. of Product	Yield (%)
$COOCH_3$	H	H	95-97:5-3	2*S*	89
CN	H	H	95-97:5-3	2*S* 2*R*	82 3.5
CHO	H	H	95:5	2*S* 2*R*	70 4
$COOCH_3$	H	CH_3	62:31:7	2*S*,4*R* 2*S*,4*S* 2*R*,4*S*	53 25 2.5
$COOCH_3$	C_6H_5	H	66:34	2*S*,3*R* 2*S*,3*S*	51 26

for references see p 2148

Under thermodynamically controlled conditions, using triethylamine as base for the addition of enones to **5** and sodium methoxide in methanol as base for the addition of (***a***,***b***-unsaturated esters, the diastereomeric ratios of **6** range from 95:5 to 97:3. The excellent diasteroselectivities are retained in the Michael addition of **5** to ***b***-substituted enones and esters, however, modest *syn/anti* selectivities are found [212, 213].

Chiral Amines as Auxiliary

The Michael additions of chiral cycloalkanone imines or enamines, derived from (*S*)-1-phenylethanamine or (*S*)-2-(methoxymethyl)pyrrolidine, are highly diastereofacially selective reactions providing excellent routes to 2-substituted cycloalkanones. This is illustrated by the addition of the enamine of (*S*)-2-(methoxymethyl)pyrrolidine and cyclohexanone to 2-(arylmethylene)-1,3-propanedioates to give, after hydrolysis, the (2´*S*,***a****S*)-oxodiesters in 35-76% yield with d.r. (2´*S*,***a****S*)/(2´*S*,***a****R*) 94 : 6 - > 97 : 3 and 80 - 95 % ee [214].

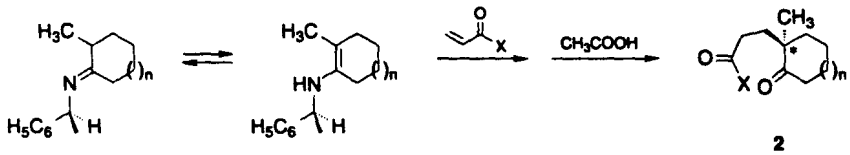


1

R^1 = C_6H_5, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 3,4-$(OCH_2O)C_6H_3$
R^2 = CH_3, C_2H_5

1: R^1 = C_6H_5; R^2 = CH_3; *dimethyl 2-*{(S)-[(S)-*2-oxocyclohexyl*]*phenylmethyl*}*-1,3-propanedioate*; yield: 76%; d.r. [(2´*S*,***a****S*)/(2´*S*,***a****R*)] > 97.5:2.5

A simple and apparently general synthesis of 2,2-disubstituted cycloalkanones with high enantiomeric excesses is based on the imines of (*S*)-1-phenylethanamine and 2-methylcycloalkanones. 1,4-Addition occurs via the tautomeric enamine and may be considered a deracemizing alkylation. A remarkably high regioselectivity is seen in the alkylation which takes place almost exclusively at the more substituted ***a***-position. The presence of an aryl substituent in the ***a***-position to the amine functionality in the chiral auxiliary appears to be essential to achieve high diastereofacial selection in the 1,4-addition [215]. Although no detailed experimental procedure has been published yet, the adduct is obtained by stirring a solution of the imine and enone in THF at room temperature for three days [216 - 219].

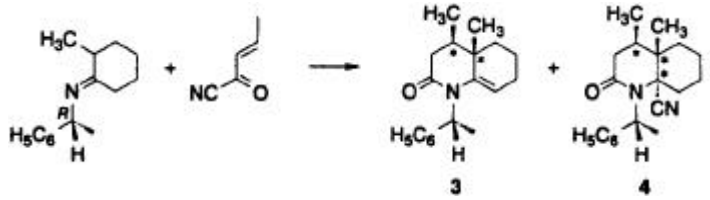


2

n = 0, 1

2: X = CH_3; (R)-*2-methyl-2-*(*3-oxobutyl*)*cycloalkanones*; n = 0; yield: 83%; 89% ee; n = 1; yield: 88%; 91% ee
X = OCH_3; *methyl* (R)-*1-methyl-2-oxocyclohexanepropanoate*; n = 0; yield: 79%; 90% ee; n = 1; yield: 81%; 90% ee

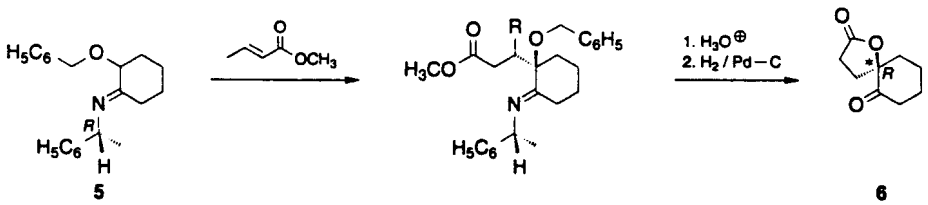
This methodology has been used in the synthesis of aspidosperma alkaloids [220, 221], the construction of an ABC ring precursor for steroids [222] and the preparation of an optically active phenanthrone in 93 % ee [223]. ***b***-Substituted Michael acceptors such as methyl (*E*)-2-butenoate are generally unreactive with *N*-cycloalkylidene-1-phenylethanamines, however (*E*)-2-butenoyl cyanide is a useful alternative. This is shown in the synthesis of enantiomerically pure *cis*-dimethyl substituted bicyclic lactams [224].



3: (*4*R*,*4a*S*)-*4,4a-dimethyl-3,4,4a,5,6,7-hexahydro-1*-[(R)-*1-phenylethyl-2*(*1*H)-*quinoline*; d.r. 100:0; mp 140 °C

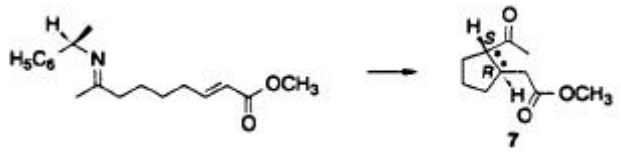
4: (*4*R*,*4a*S*)-*8a-cyano-4,4a-dimethyloctahydro-1*-[(R)-*1-phenylethyl-2*(*1*H)-*quinoline*; d.r. 100:0; mp 69 °C
Combined yield 50 %

An optically active spiro-annulated compound with excellent stereocontrol over the quaternary spirocenter is obtained from **5** which is prepared from 2-benzyloxycyclohexanone [225, 226].



6: (R)-*1-oxaspiro*[*4.5*]*decane-2,10-dione*; yield: 75%; 95% ee; mp 82-84°C

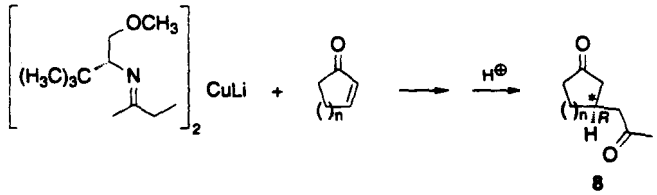
Furthermore, intramolecular cyclization of acyclic chiral imines, in which the imine and the enone groups are separated by alkyl chains, yield optically active cyclohexane and cyclopentane derivatives. *trans*-1,2-Disubstituted carbocyclic compounds are exclusively or predominantly formed with diastereomeric ratios in the range 80:20-100:0, strongly dependent on the conditions used to induce cyclization, i.e. heat, pressure or Lewis acid ($MgBr_2$) catalysis [227].



7: (*1*R,*2*S)-*methyl 2-acetylcyclopentaneacetate*; yield: 61 %; d.r. (*cis/trans*) 100:0; 62 % op (12 kbar)
Also obtained are:
methyl (*1*R,*2*R/S)-*2-acetylcyclohexaneacetate*; yield: 63 %; d.r. (*cis/trans*) 1:4; 92 % op (12 kbar)
methyl (S)-*3-oxocyclohexaneacetate*; yield: 68 %; 50 % op ($MgBr_2$, 0 °C)

Optically active 3-substituted cycloalkanones are prepared from prochiral cyclic enones using acyclic copper azaenolates [228]. For this purpose, ***b***-methoxyamines, such as the methyl ethers of (S)-valinol, (S)-phenylalaninol and (R)-*tert*-leucinol, were used to prepare the acetone imines. These imines are deprotonated with butyllithium, subsequent treatment with copper iodide gives the chiral copper azaenolate, presumably with a chelated homocuprate structure. Chiral copper/azaenolates undergo 1,4-addition to 2-cyclopentenone and 2-cyclohexenone to give after hydrolysis acetylcycloalkanones with optical purities ranging from 17-75 %. The highest optical yields are achieved with a *tert*-butyl group at the azaallyl stereogenic center and 2-cyclopentenone as the Michael acceptor [229]. Using this method a 3a-methylindanedione was obtained in 60 % ee [230].

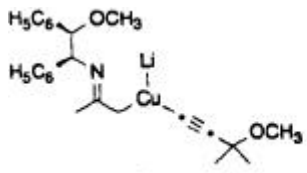
for references see p 2148



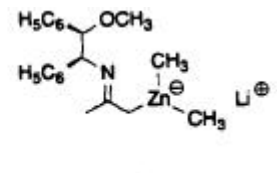
n = 1, 2
8: n = 2; (R)-*3*-(*2-oxopropyl*)*cyclohexanone*; yield: 89%; 75% op

(*R*)-3-(2-Oxopropyl)cyclopentanone; Typical Procedure [229]:
To a stirred solution of 855 mg (5 mmol) of the imine of (*R*)-1-(methoxymethyl)-2,2-dimethylpropylamine and acetone in 20 mL of THF at - 65 °C under a nitrogen atmosphere are added 3.1 mL (5 mmol, 1.6 N in hexane) of butyllithium and the resulting mixture is stirred for 30 min at - 65 °C, 475 mg (2.5 mmol) of copper(I) iodide are added and the mixture is stirred for another 30 min at - 65 °C, 205 mg (2.5 mmol) of 2-cyclopentenone in 10 mL of THF are added slowly and the mixture is stirred for 4 h at - 65 °C before it is poured into 50 mL of sat. aq NH_4Cl. Extraction with diethyl ether followed by drying over Na_2SO_4 and silica gel chromatography affords the adduct; yield: 234 mg (89%); 75% o.p.

In these reactions one equivalent of chiral azaenolate remains unused. This can be overcome when a mixed azaenol cuprate **9** is employed with an acetylide as nontransferable ligand or when a mixed azaenol-dimethylzincate **10** is used. Higher diastereoselectivities are achieved with zincates than with copper azaenolates and with (1*R*,2*S*)-2-methoxy-1,2-diphenylethanamine as auxiliary [231].

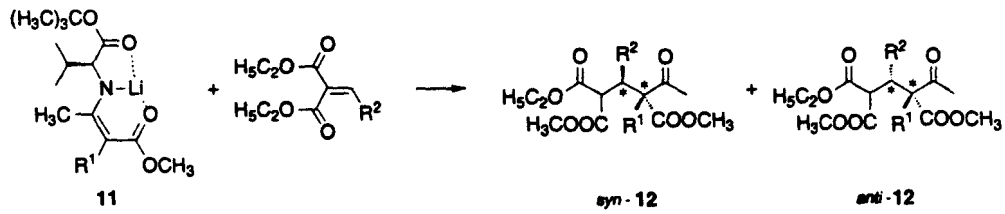


9
(**8** obtained with 71-82% ee)



10
(**8** obtained with 88-92% ee)

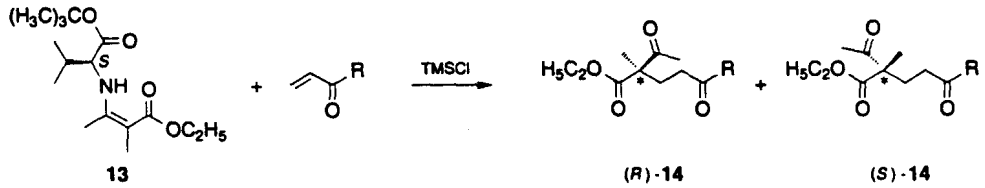
d-Oxo esters are accessible via the diastereoselective 1,4-addition of chiral lithium enamine **11** as Michael donor. The *tert*-butyl ester of L-valine reacts with a ***b***-oxo ester to form a chiral enamine which on deprotonation with lithium diisopropylamide results in the highly chelated enolate **11**. Subsequent 1,4-addition to 2-(arylmethylene) or 2-alkylidene-1,3-propanedioates at - 78 °C, followed by removal of the auxiliary by hydrolysis and decarboxylation of the Michael adducts, affords optically active ***b***-substituted ***d***-oxo esters [232] (for a related synthesis of 1,5-diesters, see Section 1.5.2.4.2.2.1.). In the same manner, ***d***-oxo esters with contiguous quaternary and tertiary carbon centers with virtually complete induced (> 99%) and excellent simple diastereoselectivities (d.r. 93:7 to 99.5:0.5) may be obtained [233, 234].



11 **syn-12** **anti-12**

R^1 = H, CH_3; R^2 = CH_3, C_6H_5
12: R^1 = H; R^2 = CH_3; *1-ethyl 5-methyl 4-acetyl-2-methoxycarbonyl-3-methylpentanedioate*; yield: 83 % d.r. (*syn/anti*) 93:7

Similar additions may be performed with the enamine **13**. However, with 3-buten-2-one or methyl 2-propenoate Lewis acid catalysis is needed to activate the Michael acceptor; chlorotrimethylsilane proved to be best suited for this purpose. A remarkable solvent effect is seen in these reactions. A change from THF to HMPA/toluene (1:1) results in a reversal of the absolute configuration of the product **14**, presumably due to a ligand effect of HMPA [235].



13 **(*R*)-14** **(*S*)-14**

R	Solvent	Config.	ee (%)	Yield (%)
CH_3	THF	*R*	87	66
	HMPA/toluene	*S*	50	38
OCH_3	THF	*R*	79	43
	HMPA/toluene	*S*	41	16

Ethyl (*R*)-2-Acetyl-2-methyl-5-oxohexanoate; Typical Procedure [235]:
To a stirred solution of 2 mmol of LDA in 30 mL of THF at - 78 °C under a nitrogen atomosphere are added 598 mg (2 mmol) of ethyl (*Z*)-3-[(*S**)-1-(*tert*-butoxycarbonyl)-2-methylpropylamino]-2,3-dimethyl-2-butenoate in 20 mL of THF. After stirring for 1 h at - 78 °C the resulting solution of the lithio enamide is added to a stirred solution of 210 mg (3 mmol) of 3-buten-2-one and 1.08 g (10 mmol) of chlorotrimethylsilane in 10 mL of THF at - 100 °C. The mixture is stirred at - 100 °C for 5 h before it is poured into 100 mL of 2.5 N HCl and extracted three times with diethyl ether. After washing with water and brine, drying over Na_2SO_4 and evaporation of the solvent the crude material is further purified by chromatography (silica gel, hexane/ethyl acetate 90:10); yield: 282 mg (66%); 87% ee [NMR using the chiral shift reagent $Eu(hfc)_3$].

1.5.2.4.3. Chiral Catalysts

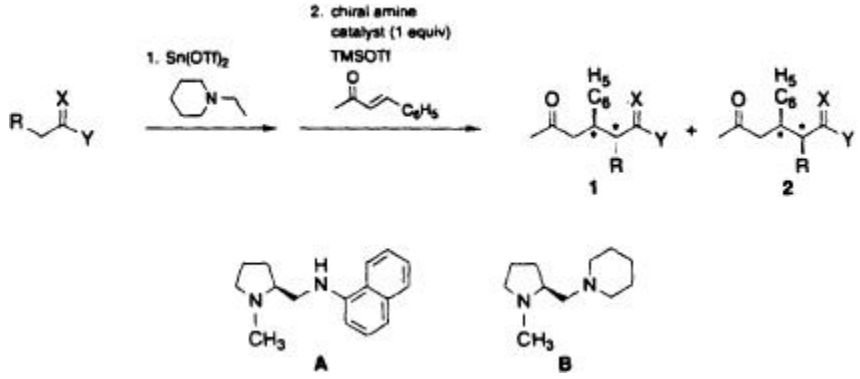
Methods for the catalytic enantioselective Michael addition have been developed using three different approaches:

1. via metal enolates under the influence of chiral ligands;
2. using chiral amines as bases;
3. using achiral bases in the presence of a chiral crown ether.

1.5.2.4.3.1. Metal enolates in the Presence of Chiral Amines

High enantioselectivities may be reached using the kinetic controlled Michael addition of achiral tin enolates, prepared in situ, to ***a***,***b***-unsaturated carbonyl compounds catalyzed by a chiral amine. The presence of trimethylsilyl trifluoromethanesulfonate as an activator is required in these reactions [236]. Some typical results, using stoichiometric amounts of chiral amine and various enolates are given below. In the case of the 1-(methylthio)-1-[(trimethylsilyl)thio]ethene it is proposed that metal exchange between the tin(II) trifluoromethanesulfonate and the ketene acetal occurs prior to the 1,4-addition [237, 395].

for references see p 2148



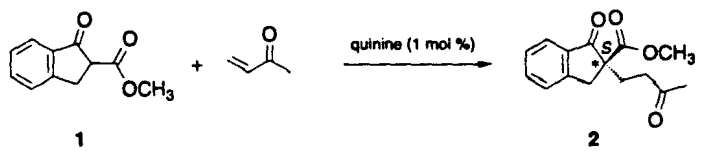
R^1	X	Y	Catalyst	d.r. (*anti/syn*)	ee [a] (%)	Yield (%)	Ref
H	S	SCH_3	**A** [b]	-	70	82	237
CH_3	O		**A** **B**	99:1 99:1	93 80	72 35	237 236

[a] At C-3.
[b] Also prepared using 1-methylthio-1-(trimethylsilylthio)-ethene with catalyst **A** (0.1 equiv) and $Sn(OTf)_2$ (0.1 equiv) in 82% yield and 70% ee [238].

(2*R,3*R**)-2-Methyl-1-(2-oxo-3-oxazolidinyl)-3-phenyl-1,5-hexanedione; Typical Procedure [237]:**
In an oven dried two-necked flask under an argon atmosphere are added 686 mg (1.64 mmol) of tin(II) trifluoromethanesulfonate. The flask is cooled to - 78 °C and 232 mg (2.06 mmol) of 1-ethylpiperidine in 4 mL of CH_2Cl_2 are added dropwise. After 10 min a solution of 194 mg (1.34 mmol) of 3-(1-oxopropyl)-2-oxazolidinone in 3 mL of CH_2Cl_2 is added dropwise to the stirring suspension, followed by 239 mg (2 mmol) of (*S*)-1-methyl-2-[(1-naphthalenylamino)methyl]pyrrolidine and stirring was continued at - 78 °C for 1 h. 77 mg (0.53 mmol) of 4-phenyl-3-buten-2-one and 220 mg (1.0 mmol) of trimethylsilyl trifluoromethanesulfonate are added successively to the mixture and after 2 h the reaction is quenched at - 78 °C with 10 mL of 10% citric acid. 10 mL of CH_2Cl_2 are added and the organic and aqueous phase are separated. The aqueous phase is extracted three times with 10 mL of CH_2Cl_2 and the combined organic layers are dried over $MgSO_4$, filtered and evaporated under reduced pressure. To completely hydrolyze the trimethylsilyl ether product the residue is dissolved in 5 mL of methanol and 1 mL of citric acid are added to this solution. After stirring for 1 h the reaction is quenched with 10 mL of phosphate buffer (pH 7). The organic layer is extracted three times with 10 mL of CH_2Cl_2 and the combined extracts are dried over $MgSO_4$. After evaporation of the solvent, the crude product is purified by chromatography (silica gel); yield: 111 mg (72%); 93% op.

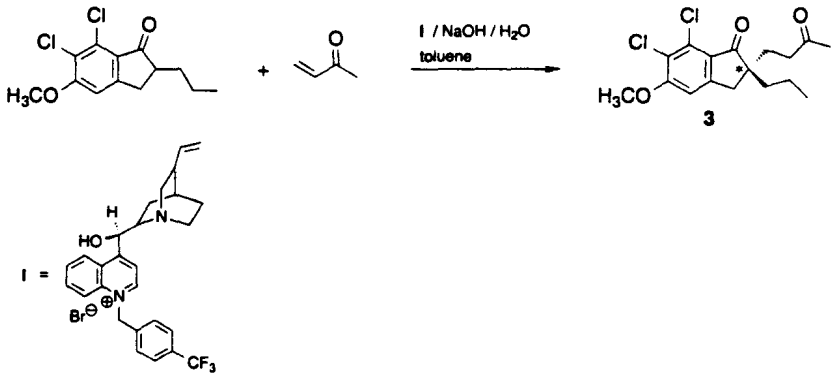
1.5.2.4.3.2. Chiral Amines as Bases

Chinchona alkaloids, such as quinine, are readily available quinuclidine chiral bases which have been used extensively in catalytic Michael additions [239 - 243]. Methyl-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (**1**) is most frequently used as the Michael donor in these studies. Enantioselectivities as high as 76% are reached in the additions to 3-buten-2-one. Modest enantioselectivities (≤ 67%) were also obtained with ethyl 2-oxo-1-cyclohexanecarboxylate and methyl 1,3-dihydro-3-oxo-1-isobenzofurancarboxylate [244, 245].



Methyl (*S*)-2,3-Dihydro-1-oxo-2-(3-oxobutyl)-1*H*-indene-2-carboxylate (2); Typical Procedure [245]:
2.1 g (31 mmol) of 3-buten-2-one and 65 mg (0.2 mmol) of quinine in 20 mL of CCl_4 are added to 3.8 g (20 mmol) of methyl 2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate in 230 mL of CCl_4 at - 21 °C. The solution is immediately thoroughly mixed and then stirred at - 21 °C for 8 d. The mixture is filtered through 60 g of silica gel. An additional 100 mL of ethyl acetate are used to elute all the products. The residue obtained after concentration of the eluates is further purified by short path distillation; yield: 5.1 g (99%); 76% op.

Polymer bound chiral quaternary ammonium hydroxides, hydrogen carbonates, fluorides and chlorides based on chinchona alkaloids have also been extensively investigated as chiral catalysts. The advantage of the use of a polymer bound catalyst is that it is easy removable. The enantiomeric excesses that are reached are however low [246, 247] to moderate [248 - 250]. Insertion of spacer groups between the alkaloid and the polymer backbone improves the stereoselectivity. The highest enantiomeric excess obtained by using polymer bound chinchona alkaloids as catalyst is 65 % in the reaction of **1** with 3-buten-2-one [251]; this enantioselectivity is in the same region as that found in the reaction with nonpolymer bound alkaloid. Phase transfer catalyzed reactions were performed using quaternary ammonium halides derived from chinchona alkaloids, such as *N*-benzylquininium bromide [252], an ephedrine-based catalyst [253] and a methionine-based catalyst [254]. A large excess of inorganic base was used and low enantiomeric excesses were found in the reaction of **1** with 3-buten-2-one. A substantial improvement in the phase transfer-catalyzed enantioselective Michael addition is possible with [4-(trifluoromethyl)phenylmethyl]cinchoninium bromide (**I**) as catalyst [255 - 258].

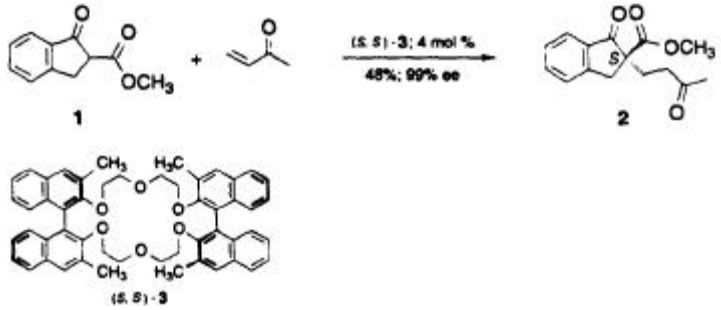


3: (R)-*6,7-dichloro-2,3-dihydro-5-methoxy-2-*(*3-oxobutyl*)*-2-propyl-1*H-*inden-1-one*; yield: 95%; 80% ee

1.5.2.4.3.3. Achiral Bases Complexed to Chiral Crown Ethers

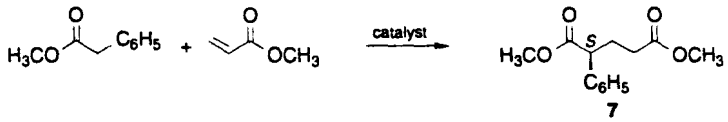
The highest enantioselectivities in the base-catalyzed Michael additions have so far been obtained using achiral bases complexed to chiral crown ethers. The addition of methyl 2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (**1**) to 3-buten-2-one using 4 mol % of a [1,1´-binaphthalene]-2,2´-diol derived optically active crown ether **3** in combination with potassium *tert*-butoxide as the base illustrates this successful method [259, 260]. It is assumed that the actual Michael donor is the potassium enolate complex of **1** and crown ether **3**.

for references see p 2148

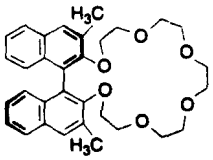
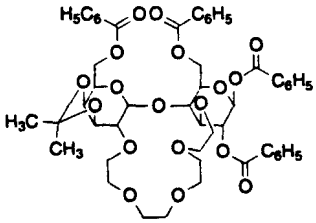
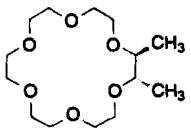


Methyl (*S*)-2,3-Dihydro-1-oxo-2-(3-oxobutyl)-1*H*-indene-2-carboxylate (2); Typical Procedure [259]**:**
In an oven dried glass flask under an argon atmosphere at - 78 °C, 950 mg (5 mmol) of methyl 2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate in 10 mL of toluene are added to 2.2 mg (0.2 mmol) of potassium *tert*-butoxide in 5 mL of toluene. 356 mg (0.2 mmol) of (*S*,*S*)-bis[3,3´-dimethyl-1,1´-binaphthalene]-2,2´-diol bis(diethyleneoxy) ether [(*S*,*S*)-**3**] are added, followed after 10 min by 700 mg (10 mmol) of 3-buten-2-one in 10 mL of toluene and the mixture is stirred for 120 h at - 78 °C after which it is poured into 35 mL of sat. aq NH_4Cl. The toluene layer combined with a toluene wash solution is dried over $MgSO_4$ and evaporated at 40 °C. The crude adduct is purified by chromatography over silica gel (CH_2Cl_2); yield: 624 mg (48%); 99% ee.

Various chiral crown ethers based on [1,1´-binaphthalene]-2,2´-diol, lactose or other chiral 1,2-diols were tested as catalyst in the addition of methyl benzeneacetate to methyl 2-propenoate using sodium amide or potassium *tert*-butoxide as the base. Some pertinent examples are given [261, 262, 396].



7: *dimethyl* (S)-*2-phenylpentanedioate*

Catalyst	ee (%)	Yield (%)	Ref
 (*S*, *S*)-**4**	83 (*S*)	80	259
 **5**	70 (*S*)	58	261
 **6**	81 (*S*)	95	263

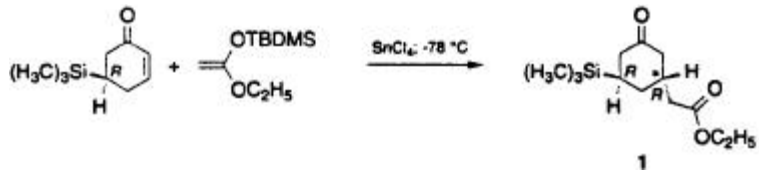
A remarkably high enantioselectivity of 81 % is achieved using the simple C_2-symmetric chiral crown ether **6** derived from (2*S*,3*S*)-butanediol [263].

1.5.2.4.4. Stereoselectivity Under the Influence of Chirality in the Acceptor

1.5.2.4.4.1. Substrate Control

Highly diastereoface selective Michael additions to chiral cycloalkenones and lactones have been developed [264]. The selectivity is, in general, due to the shielding of one of the diastereotopic faces by a substituent R at the stereogenic center in the ***g***- or ***d***-position (steric effect).

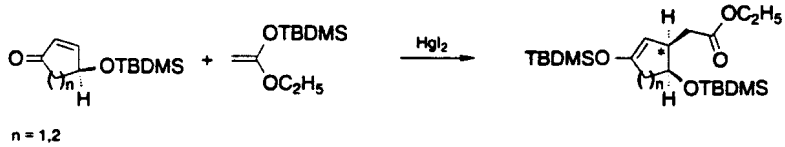
For example, using (*R*)-5-trimethylsilyl-2-cyclohexenone as the chiral Michael acceptor, optically active *trans*-3,5-disubstituted cyclohexanones **1** are obtained via a Lewis acid catalyzed addition of silylenol ethers or ketene acetals.



1: *ethyl* (*1*R,*5*R)-*3-oxo-5-*(*trimethylsilyl*)*cyclohexaneacetate*; yield: 95%; d.r. [(1*R*,5*R*)/(1*S*/5*R*)] 100:0

This procedure has been applied as a key step in the synthesis of (+)-ramulosin. Using dimethyl 1,3-propanedioate or cyanoacetate under basic conditions (20 °C, sodium methoxide) *trans*-adducts are obtained preferentially (diastereomeric ratios 2.5-10:1) [264].

Remarkable *cis* diastereoselectivity occurs in the addition of 1-alkoxy-1-(trialkylsilyloxy)-ethenes to ***g***-silyloxy-substituted cyclo-2-alkenones using mercury(II) iodide as a catalyst [265, 266]. C - C Bond formation *syn* to the electron-withdrawing silyloxy substituent has been attributed to the stabilization of the emerging ***s****-orbital at the ***b***-carbon by interaction with the ***s***(CH) bond at the ***g***-carbon atom [267].



Ethyl (1*R,6*S**)-3,6-Bis(*tert*-butyldimethylsilyloxy-2-cyclohexeneacetate; Typical Procedure [265, 266]:**
A solution of 4.5 g (19.9 mmol) 4-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone and 452 mg (1 mmol) of mercury(II) iodide is stirred at r.t. for 15 min and then cooled to - 78 °C. 5.03 g (24.8 mmol) of 1-ethoxy-1-(*tert*-butyldimethylsilyloxy)ethene are added dropwise during 15 min. The mixture is stirred at - 78 °C for 2 h, quenched with 302 mg (3 mmol) of triethylamine and allowed to warm to r.t. The mixture is filtered through a short (3 cm) column of silica gel (deactivated with a 5 % triethylamine solution in hexane/ethyl acetate, 10:1) eluting with hexane/ethyl acetate (10:1) and concentrated in vacuo. Purification of the crude material by flash chromatography (silica gel, hexane/ethyl acetate 30:1) gave the adduct as a colorless oil; yield: 7.98 g (18.7 mmol, 94 %); d.r. (*cis/trans*) 95.2:4.8.
Similarly prepared is:
From (*S*)-4-(*tert*-butyldimethylsilyloxy)-2-cyclopentenone; *ethyl* (*1*R,*5*S)-*5-*(tert-*butyldimethylsilyloxy*)-*3-triethylsilyloxy-2-cyclopenteneacetate*; yield: 92 %; 90 % ee

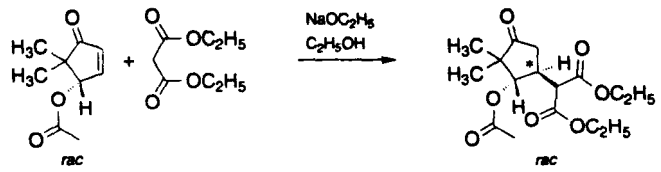
for references see p 2148

This method is especially useful as part of a three-component condensation of optically active ***g***-alkoxycyclopentenones leading to prostaglandin and compactin precursors [268].

Various diastereoselective Michael reactions are based on ***g***-bromo-, ***g***-alkyl-, or ***g***-alkoxy-2(5*H*)-furanones following the *trans*-face selectivity shown in Section 1.5.2.3.1.2. Thus the lithium enolates of esters such as ethyl propanoate, ethyl ***a***-methoxyacetate and ethyl ***a***-phenylacetate add to methoxy-2(5*H*)-furanone with complete face selectivity [269 - 273] (see Section 1.5.2.4.4.2.).

cis-Ring-fused decahydronaphthalenones can also be obtained with complete diastereoface selectivity [274 - 276].

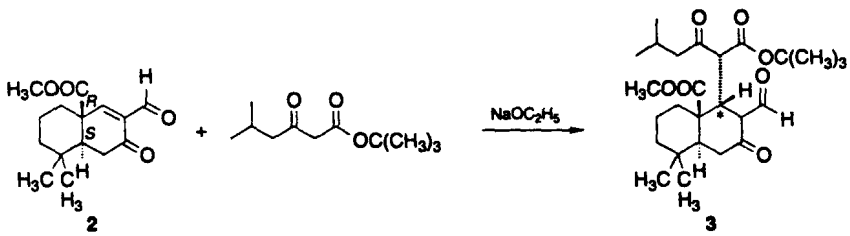
Optically active ***g***-alkoxycyclopentenones have become popular in the diastereoselective synthesis of *trans*-3,4-disubstituted cyclopentanones. The Michael addition to these cyclic enones catalyzed by sodium ethoxide in ethanol [277] or by potassium *tert*-butoxide [278, 279] proceeds under kinetic control *trans* with respect to the ***g***-substituent.



Diethyl *trans*-2-(5-Acetoxy-4,4-dimethyl-3-oxocyclopentyl)-1,3-propanedioate; Typical Procedure [277]:
A solution of 1.18 g (7 mmol) 4-acetoxy-5,5-dimethyl-2-cyclopentenone and 1.13 g (7.1 mmol) of diethyl 1,3-propanedioate in 0.8 mL of ethanol is added to a solution of 40 mg (1.7 mmol) of sodium in 4 mL of ethanol and stirred for 0.5 h at 25 °C. The mixture is acidified with 1 mL of acetic acid and poured into 10 mL of water. The resulting mixture is extracted three times with 10 mL of diethyl ether. The combined ether layers are washed with 10 mL of 5% aq $NaHCO_3$, 10 mL of brine and dried over Na_2SO_4. Evaporation of the solvent followed by chromatography (silica gel, benzene/ethyl acetate 30:1) affords the crude product which was recrystallized from hexane; yield: 478 mg (21 %); mp 65-66 °C.

Stereoselective *cis*-annulations of cyclopentenones are, however, possible using these procedures employing 1,3- or 1,4-bisMichael donors.

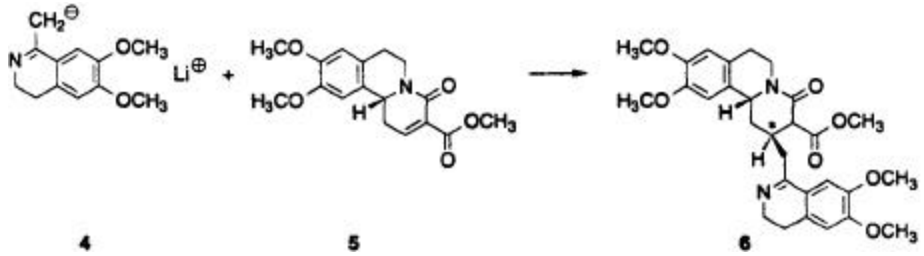
The quantitative and diastereoselective addition of the sodium enolate of *tert*-butyl 5-methyl-3-oxohexanoate to the Michael acceptor **2** was used in the synthesis of *O*-methyl pisiferic acid [280].



3: tert-*butyl*-*2*-[(*1*S,*4a*S,*8a*R)-*2-formyldecahydro-8-methoxycarbonyl-5,5-dimethyl-3-oxo-1-naphthalenyl*]-*5-methyl-3-oxohexanoate*; yield: 84%; d.r. 100:0

This type of 1,4-addition reaction has also been applied to optically active indenone derivatives in the synthesis of enantiomerically pure (C/D)-*trans*-dihydro-1*H*-indenones, precursors for nortestosterone [281]; see also refs 282, 283 and 397.

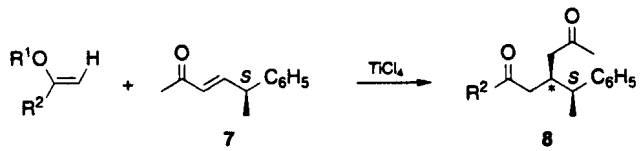
A further example concerns the *trans*-diastereoselective 1,4-addition of the lithium azaenolate **4** to the chiral Michael acceptor **5** under thermodynamic control [284]. This method has been applied in the synthesis of emetine [285 - 287].



6: *methyl* (2R,*11b*R)-*2,3,4,6,7,11b-hexahydro-2-*(*3,4-dihydro-6,7-dimethoxy-1-isoquinolinylmethyl*)-*9,10-dimethoxy-4-oxo-1*H-*benzo*[a]*quinolizine-3-carboxylate*; yield: 50 % (single diastereomer)

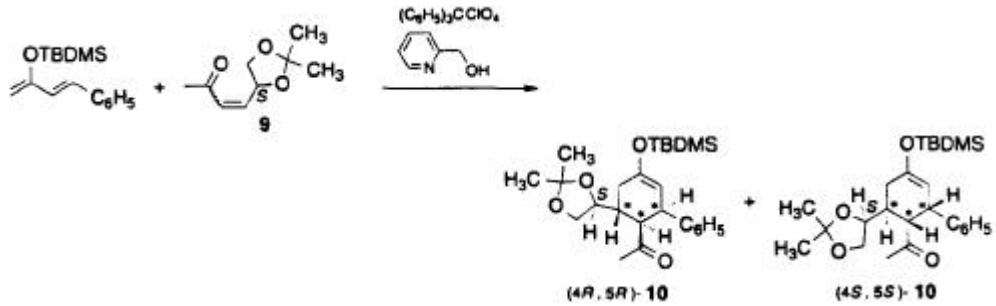
Useful methods for the nonauxiliary controlled diastereoselective 1,4-addition to acyclic chiral Michael acceptors are so far limited to two cases:

1 Chiral racemic ***g***-alkyl-substituted enones: the titanium(IV) chloride mediated addition of enol silanes and silylketene acetals to **7** shows high induced diastereoselection (diastereomeric ratios from 89:11 to more than 97:3) and the major isomer **8** results from addition of the enolsilane with *ul* topicity [288]. (*Re* face attack on the *S* enantiomer of **7**.)



8: R^1 = TBDMS; R^2 = $C(CH_3)_3$; *7,7-dimethyl-4-*[(S)-*1-phenylethyl*]-*2,6-octanedione*; yield: 59%; d.r. [(4*R*)/(4*S*)] 95:5
R^1 = TMS; R^2 = C_6H_5; *1-phenyl-3-*[(S)-*1-phenylethyl*]-*1,5-hexanedione*; yield: 60%; d.r. [(3*R*)/(3*S*)] 98:2

2 Optically active ***g***-alkoxy-substituted enones [289] or esters [290, 291, 398, 399]: for example the reaction of (*Z*)- or (*E*)-(*S*)-5,6-[isopropylidenebis(oxy)]-3-hexen-2-one with 2-(*tert*-butyldimethylsilyloxy)-4-phenyl-1,3-butadiene at - 78 °C using catalytic amounts (5 mol %) of triphenylmethyl perchlorate followed by a second (intramolecular) Michael addition gives optically active cyclohexanone derivatives (4*R*,5*R*)-**10** and (4*S*,5*S*)-**10**. If the enone has the *E* configuration the adduct is a mixture of isomers, whereas if the enone has the *Z* configuration only a single diastereomer is obtained. The higher diastereoselectivity in the case of (*Z*)-isomer can be attributed to conformational restriction due to allylic 1,3-strain [292].



10: *4-acetyl-1-*(tert-*butyldimethylsilyloxy*)-*5-*(S)-*2,2-dimethyl-4-dioxolanyl*]-*3-phenyl-1-cyclohexene*

Config. of **9**	Yield (%)	d.r. [(4*R*,5*R*)/(4*S*,5*S*)]
E	83	40:60
Z	83	

for references see p 2148

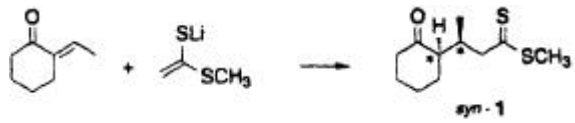
1.5.2.4.5. Formation of Stereogenic Centers After the Michael Addition Step

1.5.2.4.5.1. Intermolecular Additions

The enolate of the 1,4-adduct, obtained after the stereoselective Michael addition step, as discussed in the previous sections, may be quenched in situ with various electrophiles. The fact that additional stereogenic centers may be formed via such tandem Michael addition/quenching procedures, giving products with high diastereoselectivity in many cases, extends the scope of these methods substantially. Furthermore these procedures occasionally offer the possibility of reversing the *syn/anti* diastereoselection. In the next sections pertinent examples of diastereoselective inter- and intramolecular quenching reactions will be discussed.

Protonation

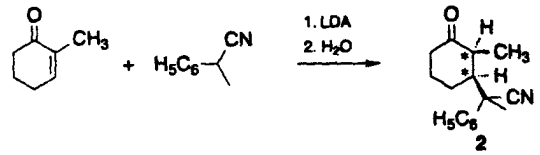
In contrast to the usual *anti* selectivity a remarkably high *syn* selectivity is observed in the addition of thioester enolates to 2-alkylidenealkanones [297]. The *syn* selectivity is probably due to a stereoselective internal autoprotonation of the resulting enolates by the dithioester ***a***-protons [298] in these cases where the prostereogenic centers reside exclusively in the enone part (see also Section D.2.1.).



1: *methyl **b**-methyl-2-oxocyclohexanepropanedithioate*; yield: 56%; d.r. (*syn/anti*) 96:4

The titanium(IV) chloride catalyzed addition of silylenol ethers to 2-substituted cyclopentenones stereoselectively yields trans-cyclopentanones [45, 46].

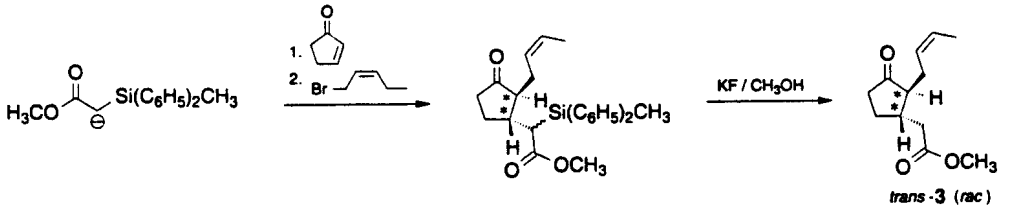
A diastereoselective route to *cis*-2,3-disubstituted cyclohexanones is based on the kinetically controlled protonation of the enolate obtained via the addition of an arylacetonitrile to 2-substituted 2-cycloalkenones in THF or in THF/HMPA mixtures at –70 - 0 °C [299, 300], see also refs 301, 302 and 403.



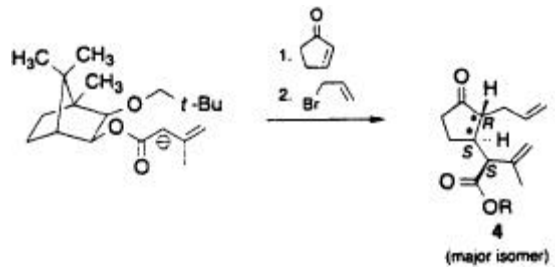
2: *3-(1-cyano-1-phenylethyl)-2-methylcyclohexanone*; yield: 80-95%; d.r. (*cis/trans*) 95:5

Alkylation

When the cyclic enone is unsubstituted, but the resulting enolate is quenched with an electrophile under conditions of kinetic control the *trans* adduct is formed exclusively [303]. Particularly successful is the sequential Michael addition/enolate alkylation in diastereoselective routes to *trans*-***a***,***b***-difunctionalized cycloalkanones and lactones [304 - 308]. The key steps in the synthesis of methyl (±)-jasmonate (**3**) [309, 310] (*syn/anti* diastereoselection) and (-)-khushimone (**4**) (*syn/anti* and induced diastereoselection) illustrate this sequence [311] (see also Section D.1.1.1.3.).



3: *methyl* (*1*R*,*2*R*)-*2*-[(Z)-*2-butenyl*]-*3-oxo-1-cyclopentanepentanoate*; yield: 54 %



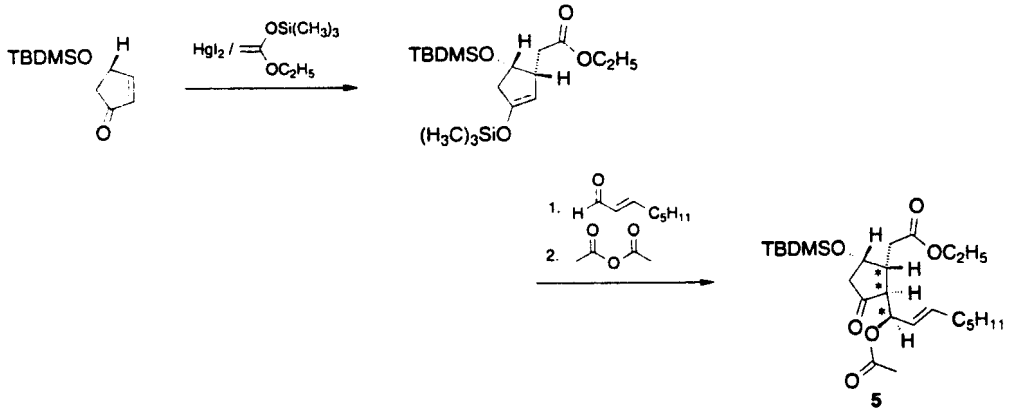
4: *2*-tert-*butoxy-1,7,7-trimethylbicyclo*[*2.2.1*]*hept-3-yl* ***b****-methyl*-[*3-oxo-2-*(*2-propenyl*)*cyclopentyl*]-***b****-butenoate*; yield: 55 %; d.r. [(1*S*,2*R*,***a****S*)/(1*S*,2*R*,***a****R*)/(1*R*,2*S*,***a****R*)/(1*R*,2*S*,***a****S*)] 67:7:13:13

For further examples with complete stereocontrol over two or three new stereogenic centers see refs 312 - 314.

Hydroxy Alkylations

These reactions imply an aldol condensation following the initial Michael addition. Two examples in which absolute stereocontrol over three or four new stereogenic centers is achieved in a single operation illustrate the potential of these methods.

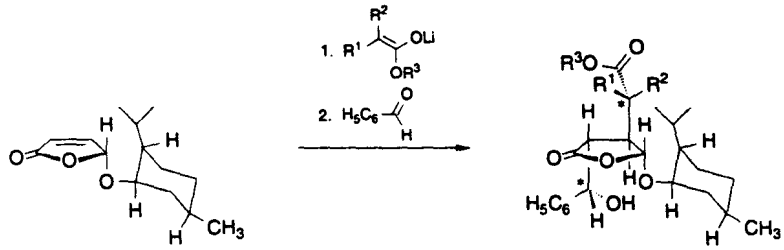
The asymmetric tandem dialkylation or three component condensation using optically active ***g***-alkoxycyclopentenones has been modified into a practical route to prostaglandin precursors. Thus, the addition of silylketene acetals using mercury(II) iodide as a catalyst proceeds with remarkable *cis* diastereoselectivity. The resulting cyclopentenone silylenolate can be alkylated diastereoselectively *trans* with respect to the ester group, using titanium(IV) chloride and an aldehyde [315, 316].



5: *ethyl 2-*{*2-*[(*5*S)-*1-acetoxy-2-octenyl*]-*5-*(tert-*butyldimethylsilyloxy*)-*4-oxocyclopentylacetate*; yield: 59 %; d.r. 100:0

for references see p 2148

The use of enantiomerically pure (*R*)-5-menthyloxy-2(5*H*)-furanone results in lactone enolates, after the initial Michael addition, which can be quenched diastereoselectively *trans* with respect to the ***b***-substituent. With aldehydes as electrophiles adducts with four new stereogenic centers are formed with full stereocontrol and the products are enantiomerically pure. Various optically active lactones, and after hydrolysis, amino acids and hydroxy acids can be synthesized in this way [317].



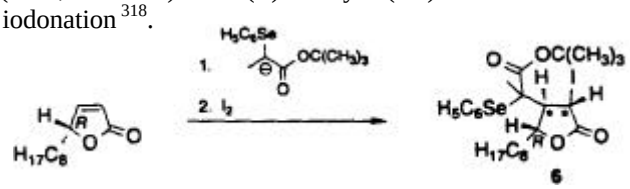
R^1	R^2	R^3	Yield (%)
H	H	$C(CH_3)_3$	93
H	NH_2	CH_3	65
H	OCH_3	C_2H_5	91
CH_3	CH_3	C_2H_5	93

Ethyl (*aR*,2*R*,3*S*,4*S*)-Tetrahydro-4-[(*S)-hydroxy(phenyl)methyl]-2-menthyloxy-*a*-methoxy-5-oxo-3-furanacetate; Typical Procedure [317]:**

To a stirred solution of 11 mmol of LDA in 30 mL of THF is added under a N_2 atmosphere at - 60 °C 1.18 g (10 mmol) of ethyl methoxyacetate. After stirring for 0.5 h at - 60 °C the mixture is cooled to - 90 °C and 2.38 g (10 mmol) of (-)-5-menthyloxy-2(5*H*)-furanone in 30 mL of THF is added dropwise over a period of 0.5 h. After stirring for 1 h at - 90 °C, 2 mL of freshly distilled benzaldehyde is added and the mixture is allowed to warm to - 45 °C over a period of 1.5 h. Quenching with 200 mL of a sat. NH_4Cl is followed by extraction with diethyl ether, drying over $NaSO_4$, evaporation of the solvent, distilling of the lower boiling fractions and chromatography on silica gel (CH_2Cl_2) to afford the adduct as an oil (single isomers by ^1H NMR); yield: 4.2 g (91 %).

Halogenation

This modification was used in the synthesis of (-)-avenaciolide. The key step is the *trans*-diastereoselective Michael addition of the lithium enolate of *tert*-butyl 2-(phenylseleno)propionate (THF, - 78 °C) to (*R*)-5-octyl-2(5*H*)-furanone and subsequent *trans*-diastereoselective iodonation [318].

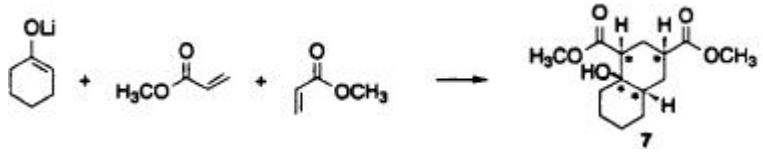


6: tert-*butyl 2-phenylseleno-2*-[(*2*R*,*3*R*,*4*S*)-*tetrahydro-4-iodo-2-octyl-5-oxo-3-furanyl*]*propanoate*; yield: 89 % (single isomer)

Michael Additions

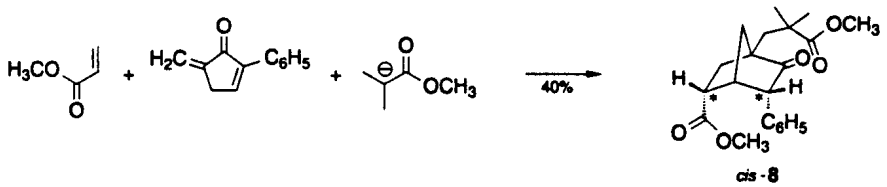
Michael additions followed by further Michael additions have become popular reactions and are usually referred to as Michael Michael Induced Ring Closure (MIMIRC) reactions. A three component Michael - Michael - aldol reaction of ketone enolates with acrylates can be achieved, resulting in the formation of six-membered ring compounds with good efficiency and high diastereoselectivites [319].

A complete diastereoselective triple Michael addition to form a bicyclic ring structure is also known. In this reaction the new ring is formed by a MIMIRC reaction (see also Sec-



7: *dimethyl* (*1*R*,*3*R*,*4a*S*,*8a*S*)-*decahydro-8a-hydroxy-1,3-naphthalenedicarboxylate*; yield: 79 % (single diastereomer)

tion 1.5.2.4.4.2.). The enolate which enters the MIMIRC reaction is formed by the addition of the ester enolate to a methylene-substituted cyclopentenone [320, 321].

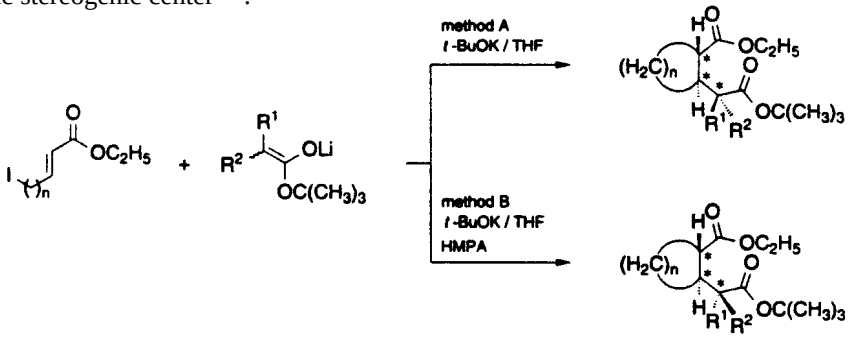


8: *methyl 3-*(*5-methoxycarbonyl-2-oxo-3-phenylbicyclo*[*2.2.1*]*hept-1-yl*)-*2,2-dimethylpropanoate* [320]; yield: 40 %; d.r. (*cis/trans*) 100:0

1.5.2.4.5.2. Intramolecular Additions

Alkylations

Consecutive Michael additions and alkylations can also be used for the diastereoselective synthesis of 5- and 6-membered ring systems. For instance when 6-iodo-2-hexenoates or 7-iodo-2-heptenoates are employed the enolate of the Michael adduct is stereoselectively quenched in situ to provide the cyclic compound with *trans* stereochemistry (> 94 : 6 diastereomeric ratio). As the enolate geometry of the Michael donor can be controlled, high stereoselectivity can also be reached towards either the *syn* or *anti* configuration at the exocyclic stereogenic center [322].

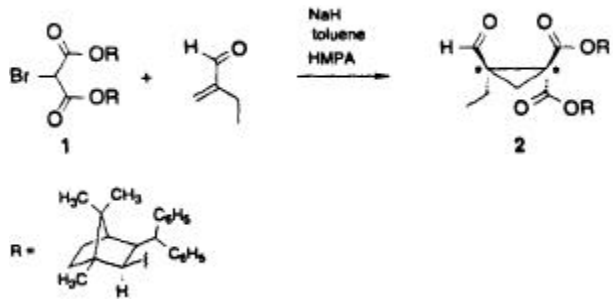


n	R^1	R^2	Method	Config.	d.r. (*trans/cis*)	Yield (%)
1	H	CH_3	B	***a****S**,1*R**,2*S**	100:0	89
			A	***a****R**,1*R**,2*S**	100:0	76
3	H	H	A	1*R**,2*S**	100:0	94
	H	CH_3	B	***a****S**,1*R**,2*S**	> 93:7	100
			A	***a****R**,1*R**,2*S**	> 93:7	95
	CH_3	CH_3	A		100:0	95
4	H	H	A	1*R**,2*S**	100:0	95
	H	CH_3	B	***a****S**,1*R**,2*S**	> 93:7	100
	CH_3	CH_3	A	***a****R**,1*R**,2*S**	> 100:0	80

for references see p 2148

***tert*-Butyl (*a*S*,1*R**,2*S**)-2-Ethoxycarbonyl-*a*-methyl-1-cyclopentaneacetate; Typical Procedure [322]:**
To a stirred solution of (1.5 mmol) of LDA in 3.5 mL of THF/hexane (60:40) at - 78 °C under a nitrogen atmosphere is added 198 mg (1.5 mmol) *tert*-butyl propanoate in 1.5 mL of HMPA. After 30 min 169 mg (1.5 mmol) of potassium *tert*-butoxide are added and the mixture is stirred for 10 min. Then 133 mg (0.5 mmol) of ethyl 6-iodo-2-hexenoate in 1.5 mL of THF are added and the mixture is stirred for an additional 0.5 h at - 78 °C. The reaction is quenched by adding sat. aq NH_4Cl. Extraction with ethyl acetate, drying over Na_2SO_4 followed by evaporation of the solvent and short-path distillation gives the adduct; yield: 135 mg (100%).

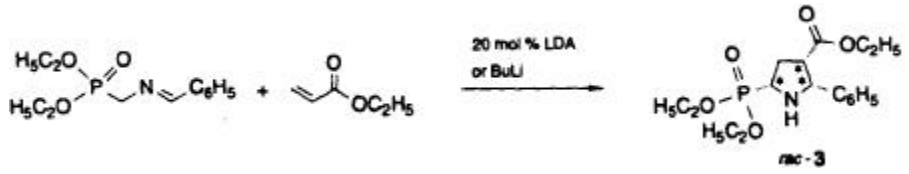
Cyclopropanes can be prepared via addition of enolates derived from ***a***-halo esters [323, 324] or acids [325] to an ***a***,***b***-unsaturated ester or enone followed by an intramolecular alkylation. Various examples show excellent *syn/anti* diastereoselection (diastereomeric ratios of 95:5) [326], and modest to high auxiliary induced diastereoselection [327, 328]. Double stereodifferentiation with diastereomeric ratios up to 67:33 have also been reported [329]. The stereoselectivity is strongly dependent on the reaction conditions, especially the solvent. A diastereomeric ratio of 90:10 in the addition of a chiral 2-bromo-1,3-propanedioate to 2-methylenebutanal was only achieved when HMPA was added and a 3-(diphenylmethyl)borneol derivative **1** used as auxiliary alcohol [330].



2: *bis*[*3*-(*diphenylmethyl*)-*1,7,7-trimethylbicyclo*[*2.2.1*]*hept-2-yl*] *2-ethyl-2-formyl-1,1-cyclopropanedicarboxylate*; yield: 83%; d.r. [(2*R*)/(2*S*)] 90:10

Metalated 2-azaallyl anions derived from imines of ***a***-amino esters or ***a***-amino phosphonates can serve both as Michael donors and as 1,3-dipolar reagents; the course of the reactions as well as the stereochemistry strongly depends upon the reaction conditions. Using triethylamine/lithium bromide [331], 1,8-diazabicyclo[5.4.0]undec-7-ene/lithium bromide or benzyltrimethylammonium methoxide [332] as bases the Michael adduct is prepared in high yield but it can be followed by a 5-*endo*-trig cyclization reaction to provide substituted pyrrolidines as mixtures of diastereomers [333 - 336].

When 2-azaallylphosphonates are used in the addition reaction with 2-propenoates only the cycloadducts were formed. Under kinetic conditions the more strained all-*cis* diastereomers are obtained in 95 % yield [337].



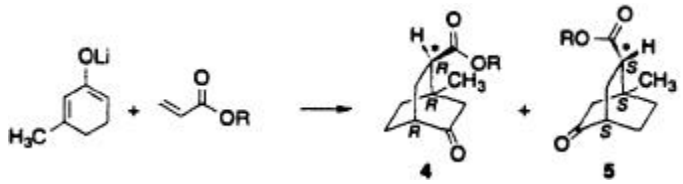
3: *ethyl* (*2*R*,*3*S*,*5*R*)-*5*-(*diethoxyphosphoryl*)-*2-phenyl-3-pyrrolidinecarboxylate*; yield: 95 %

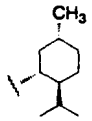
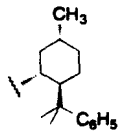
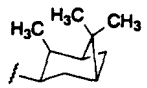
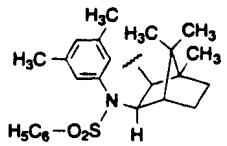
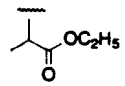
Michael Additions

When the enolate of an enone is brought into reaction with an enone, usually a carbocyclic system is prepared by two consecutive Michael additions (MIMIRC reactions). Due to the lower temperatures employed and the absence of diene polymerization these reactions are useful alternatives for Diels-Alder reactions and proceed in general with high diastereoselectivities. When neither enolate nor enone is cyclic a monocyclic system is formed [338] which can be converted into a bicyclic system when the Michael addition is followed by an aldol reaction [339]. When, however, the enolate is cyclic a bicyclic or a tricyclic system is formed [340, 341].

For instance a Michael addition with the kinetically favored cross-conjugated lithium dienolates, derived from cyclohexenones, usually results in a MIMIRC reaction to form a bicyclo[2.2.2]-octane [342, 343]. This reaction was the key step in the synthesis of sanadaol [344], eriolanin [345] and of isoeremolactone [346]. Related diastereoselective MIMIRC reactions were used in eremophilane sesquiterpene synthesis [347, 348] in additions to allene esters [349, 350] and in the preparation of khisilal [351] and khusitone [352]. Further examples see refs 353-357, and 405-407.

Optically active bicyclo[2.2.2]octanes can be obtained via diastereoselective MIMIRC reaction of lithium dienolates and ***a***,***b***-unsaturated esters of various chiral alcohols. Good yields (70-90%), high *endo* selectivities (> 95%) and diastereomeric ratios that depend on the auxiliary alcohol are found in these additions. The highest diastereomeric ratio reached was 18:82 using a camphor derived sulfonamide. The diastereomeric ratio could be improved (up to 9:91) by titanium(IV) chloride catalyzed addition of the corresponding silylenolates with the chiral ***a***,***b***-unsaturated esters [358].



R	d.r. (**4**/**5**)	Yield (%)
	33:66	71
	25:75	91
	45:55	67
	18:82	80
	25:75	90

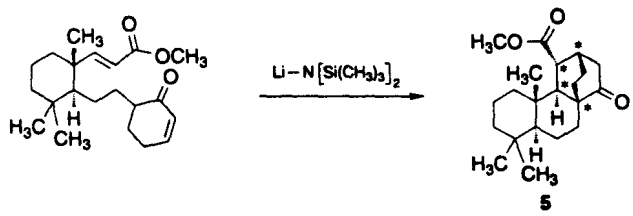
for references see p 2148

8-Phenylmenthyl 1-Methyl-5-oxobicyclo[2.2.2]octane-2-carboxylate; Typical Procedure [358]:
To a stirred solution of 12 mmol of LDA in 25 mL of a THF/hexane (4:1)mixture are added dropwise under argon at - 23 °C 1.16 g (10.5 mmol) of 3-methyl-2-cyclohexenone. This solution is stirred at - 23 °C for 1 h after which 2.86 g (10 mmol) of 8-phenylmenthyl 2-propenoate are added over a 15 min period. After 2 h at - 23 °C the mixture is quenched with water, extracted with diethyl ether, washed three times with 1N HCl, water and brine. After drying over Na_2SO_4 and evaporation of the solvent the crude adduct is obtained. Silica gel chromatography (pentane/diethyl ether); yield: 3.6 g (91 %); d.r. [(1*R*,2*R*,4*R*)/(1*S*,2*S*,4*S*)] 25:75 (^{1}H NMR); (1*S*,2*S*,4*S*)-isomer: mp 89 °C.

A further extension of the MIMIRC reaction is seen in the synthesis of enantiomerically pure cyclohexanones. A successful diastereoselective MIMIRC reaction with 2-(*tert*-butyldimethylsilyloxy)-4-phenyl-1,3-butadiene and an optically pure (*Z*)-***g***-alkoxy-substituted enone was performed using catalytic amounts (5 mol %) of triphenylmethyl perchlorate at - 78 °C [360, 408] (for a further example see Section 1.5.2.4.4.1.).

In this way cyclohexanones with two or three contiguous stereogenic centers are obtained under mild conditions, as compared to the Diels-Alder conditions or the strongly basic conditions of the lithium enolate MIMIRC reaction.

Finally, by a diastereoselective intramolecular double Michael reaction of a lithium dienolate to an ***a***,***b***-unsaturated ester moiety, a spiro-fused bicyclo[2.2.2]octane may be prepared. These MIMIRC form the key step in the synthesis of (±)-atisine [361] and (+)-atisirene [362 - 365].



5

6: *methyl* (3S,4R,4*a*R,4*b*S,8*a*S,10*a*R)-*dodecahydro-4b,8,8-trimethyl-1-oxo-1*H-*3,10a-ethanophenanthrene-4-carboxylate*; yield: 92% (single isomer); mp 145-149 °C

This type of reaction is best performed with lithium hexamethyldisilazanide as base in a mixture of hexane and diethyl ether under kinetic control at - 78 °C; the MIMIRC adducts are thus obtained as single isomers [366 - 368].

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