Chiral Homoenolate Equivalents, 6[◇]

Asymmetric Synthesis of β-Methylated Aliphatic Ketones via Lithiated 3-[(*S*)-2-(Methoxymethyl)pyrrolidino]hex-3-ene[☆]

Hubertus Ahlbrecht*, Rainer Schmidt[2], and Uwe Beyer[3]

Institut für Organische Chemie der Universität Gießen,
Heinrich-Buff-Ring 58, D-35392 Gießen, Germany
Fax: (internat.) +49(0)641/9934309
E-mail: hubertus.ahlbrecht@org.chemie.uni-giessen.de

Received October 16, 1997

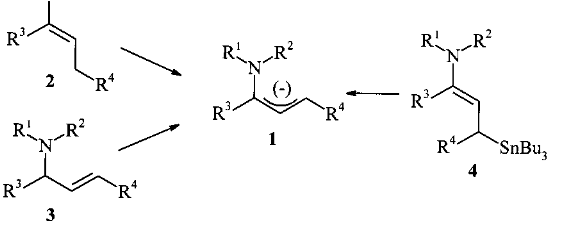
Keywords: Homoenolate equivalents, chiral / Alkylation / 1-Aminoallyl anions, chiral / β-Methyl ketones, chiral / Asymmetric synthesis

3-Substituted aliphatic ketones **10** have been obtained in excellent optical yields by alkylation of the aminoallyllithium compound *endo*-**8**, a homoenolate equivalent of hexane-3-one, using prolinol ether (SMP) as the chiral auxiliary. The intermediate *endo*-**8** was generated by tin–lithium exchange of the 3-stannylated enamine **7a** with butyllithium. An improved hydrolysis procedure for the resulting enamines is described. Some mechanistic implications with respect to the formation as well as the alkylation of *endo*-**8** are discussed.

Introduction

There are two general strategies for the construction of a carbon−carbon bond β to a carbonyl group, namely Michael addition of a carbon nucleophile to an α,β-unsaturated carbonyl compound, and the reaction of a carbon electrophile with a homoenolate equivalent using the umpolung methodology[4]. Because of its considerably greater synthetic flexibility compared with the Michael addition, the homoenolate route is very attractive. 1-Aminoallyl anions **1** as homoenolate equivalents are of particular interest in alkylation reactions because of their high nucleophilicity and γ-selectivity[5]. The generation of **1** by deprotonation of enamines **2** or allylamines **3** is, however, a limiting factor. Enamines prepared from aliphatic amines tend to be (*E*) configured, whereas, as pointed out previously[5], only (*Z*)-enamines obtained with *N*-methylaniline as the amino component can be metallated without difficulty. (*E*)-enamines require an activating substituent at the 1- and/or 3-position. The same holds for α-secondary allylamines.

Scheme 1



These limitations can be overcome by transmetallation of 3-stannylated enamines **4**[6], prepared by the condensation of 3-stannylated ketones with secondary amines[7]. Using this method, even non-stabilized 1-aminoallyl anions with purely aliphatic amino groups become available. One can use, for example, the (*S*)-2-methoxymethylpyrrolidine (SMP) group[8] as a chiral auxiliary, thereby generating a chiral homoenolate equivalent.

In this paper, we report on the asymmetric synthesis of β-methylated aliphatic ketones **10** by tin−lithium exchange of the 3-stannylated enamine **7a**, followed by alkylation of the resulting aminoallyllithium compound *endo*-**8**.

Preparation and Tin−Lithium Exchange

As shown in Scheme 2, the 3-stannylated ketone **6** was prepared by the addition of tributylstannyllithium to the α,β-unsaturated ketone **5**[7][9]. Tributylstannyllithium was generated in situ by treatment of a THF solution of tributyltin hydride with lithium diisopropylamide[10].

Condensation of the chiral auxiliary SMP with **6** by azeotropic distillation with benzene as the solvent and using a catalytic amount of *p*-toluenesulfonic acid, led to the formation of a mixture of both regioisomeric (*E*)-enamines **7a** and **7b** (**a**/**b** = 9:1), as reported previously[7]. However, we were unable to reproduce the high yield reported (91%)[7], especially when we performed large-scale preparations. The best yields that we could achieve were 56% (benzene as solvent) and 63% (toluene as solvent, less pure) using a fourfold excess of SMP.

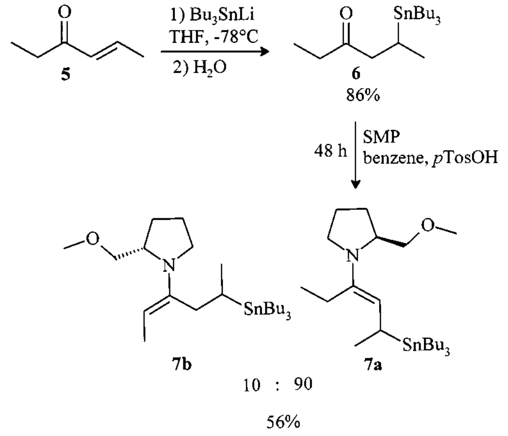
Tin−lithium exchange of morpholino enamines of type **7** can usually be achieved by treatment with butyllithium in THF for 15 h at −78°C[6]. With **7a**, however, the exchange

---

[◇] For Part V, see ref.[1].

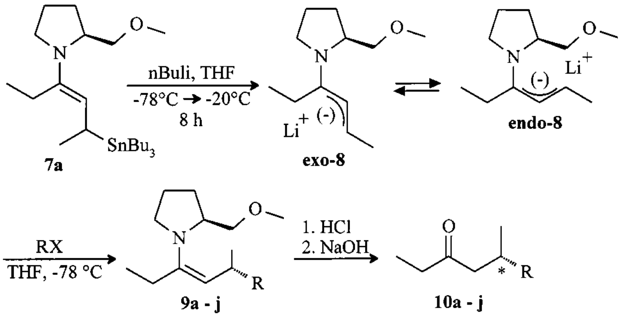
1434−193X/98/0707−1371 $ 17.50+.50/0

Scheme 2



reaction to **8** was incomplete even after 20 h. By raising the temperature to −10°C, complete exchange was observed after 5 h, but the formation of by-products was observed, the amount of these increasing with increasing temperature. Optimal results with regard to both yield and purity were obtained by adding the butyllithium at −78°C and then allowing the mixture to slowly warm to −20°C over a period of 8 h.

Scheme 3



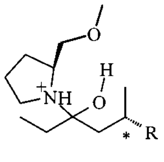
Alkylation and Hydrolysis

The blood-red coloured solution of **8**, obtained as described above, was cooled to −78°C once more, which resulted in a colour change to yellow-orange. The intermediate was then trapped with various alkyl halides to give the 3-alkylated enamines **9a−j** (see Table 1). Following non-aqueous work-up, ^{1}H- and ^{13}C-NMR spectroscopic analysis of these enamines showed them to be, without exception, (*Z*)-configured. In none of the reactions were any allylamines produced. This indicates that alkylation of **8** proceeds regioselectively without any competing α-attack.

Hydrolysis of enamines using a two-phase system such as diethyl ether/2 N HCl at room temperature is normally a clean and fast reaction[6]. However, in the case of SMP enamines, we often encountered difficulties in this step, necessitating extremely long reaction times and resulting in lower than expected yields. As we discovered, the reason for this unexpected behaviour was the formation of a water-soluble intermediate, which proved to be stable in the aqueous phase for hours. However, this intermediate could be instantly destroyed by adding sodium hydroxide until the aqueous phase was neutral. Hydrolysis was then completed within a few minutes and the ketones **10** were obtained in high yields.

A ^{13}C-NMR spectrum of the aqueous acidic solution, containing [D$_4$]methanol, showed a signal at δ = 101.9, i.e. within the range typical for the acetal carbon of *O*,*N*-acetals[11], whereas enamine and ketone signals were completely absent. The signals refering to the SMP moiety were slightly shifted and doubled compared to the free amine, e.g. OCH_2 (δ = 73.2, 73.3), NCH (δ = 65.9, 66.0), and OCH_3 (δ = 54.6, 55.2). In view of these findings, we favour the *N*-protonated amino hemiacetal structure **11** for the acid-stable and base-labile intermediate, probably stabilized in this particular case by an intramolecular hydrogen bond between the acidic hydrogens and the methoxy group (Scheme 4).

Scheme 4



11

A quick and quantitative hydrolysis could also be achieved by using a weaker acid, thereby preventing the formation of **11**, for example by adding a saturated aqueous ammonium chloride solution. However, the two-step procedure described above has an important advantage. The tetrabutyltin formed during the transmetallation step, which can usually only be removed with difficulty by chromatography[6], can in this case be easily extracted with diethyl ether, while the ketone **10**, masked as the protonated hemiacetal **11**, remains quantitatively in the acidic aqueous phase.

The alkylation reaction was further investigated by varying the size of the alkyl group and by using different leaving groups (see Table 1). Primary aliphatic alkyl chlorides were found to react as well as the corresponding bromides, albeit considerably more slowly. Since the yields of the ketones **10a−d** obtained in both cases were similar (entries 3−8), the use of bromides is preferred. In the case of ethyl iodide, the only iodide tested, the reaction proceeded very rapidly, but was accompanied by a number of by-products, such that the ketone **10a** could not even be isolated in this case (entry 2). Unsatisfactory results in alkylation reactions with alkyl iodides are typical for alkali metal salts of non-stabilized 1-aminoallyl anions[6]. Allylation, benzylation, and silylation were achieved in reasonable times, even with the chlorides, and the corresponding ketones **10e**, **10f**, and **10j** were obtained in high yields (entries 9, 10, and 14). Secondary alkyl halides also reacted. However, in this case, only the bromides could be used (entries 11 and 12). Finally, even the *tert*-butylated ketone **10i** was obtained by the reaction with *tert*-butyl bromide, but could not be isolated in pure form.

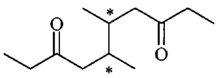
Table 1. 3-Chiral ketones **10** prepared by alkylation of the chiral homoenolate equivalent *endo*-**8**

Entry	**10**	RX	Reaction time [h]	Yield [%]	*ee* [%]	Configuration[c]
1	**a**	ethylbromide	4	78	≥ 98[a]	*R*
2	**a**	ethyliodide	2	32[b]	–	–
3	**b**	1-propylchloride	20	76	79	*R*
4	**b**	1-propylbromide	4	81	97	*R*
5	**c**	1-butylchloride	20	80	64	*R*
6	**c**	1-butylbromide	5	78	≥ 98[a]	*R*
7	**d**	1-heptylchloride	20	82	77	*R*
8	**d**	1-heptylbromide	5	83	≥ 98[a]	*R*
9	**e**	allylchloride	3	78	87	*R*
10	**f**	benzylchloride	4	76	97	*R*
11	**g**	isopropylbromide	20	68	65	*S*
12	**h**	cyclohexylbromide	25	46	49	*S*
13	**i**	*tert*-butylbromide	30	24[b]	–	–
14	**j**	trimethylsilylchloride	2	76	≥ 98[a]	*S*

[a] A second diastereomer was not observed. – [b] Not isolated; the yields given were determined by GLC. – [c] The descriptors given are based on the known absolute configuration of **10a** and **10g** (see refs.[15] and[16]).

As the major by-product in the last mentioned reactions (entries 11–13), and increasing in the series isopropyl-, cyclohexyl-, *tert*-butyl-, the dimerized ketone **12** (Scheme 5) was obtained with a diastereomeric ratio of 54 (*dl*):46 (*meso*), as determined by ^{13}C-NMR spectroscopy.

Scheme 5



12

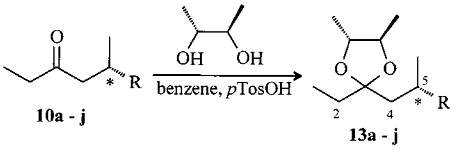
This dimerization also occurred following the treatment of *endo*-**8** with a half-equivalent of 1,2-dibromoethane[12]. This indicates that **8** probably undergoes a partial halogen–metal exchange with the alkyl halide in these reactions, and then the resulting species couples with unreacted **8** to give the bis(enamine) of the ketone **12**.

Diastereoselectivity

In some cases, the diastereoselectivities of reactions of alkali metal salts of SMP-substituted allyl anions containing aromatic groups could be determined by NMR spectroscopic analysis of the enamines obtained[1][13]. With the alkylated enamines **9**, however, this method proved unsatisfactory, since adequate separation of the signals in both of the diastereomers was only observed for the (*E*)-configured enamines and not for the (*Z*)-isomers. Therefore, a careful methanol-catalyzed (*Z*/*E*) isomerization had to be performed before determination could be carried out. With the enamines **9**, even this procedure was only successful with the 3-silylated derivative, since in the case of the alkylated enamines the separation of the partially overlapping signals was too small. Furthermore, besides (*Z*/*E*) isomerization, some regioisomerization with respect to the double bond also occurred.

In the case of 3-substituted phenylpropionaldehydes, cyclic *O*,*N*-acetals obtained with ephedrine could be used to determine diastereoselectivities[11]. However, this method could not be applied here, since *O*,*N*-acetal formation with ketones **10** and ephedrine failed. Nevertheless, it was possible to determine the enantiomeric purity of the chiral ketones **10a–h** and **10j** by ^{13}C-NMR spectroscopic analysis of their diastereomeric cyclic acetals **13a–h** and **13j**, which were obtained by condensation with (2*R*,3*R*)-(–)-2,3-butanediol (Scheme 6)[14].

Scheme 6



10a - j **13a - j**

The signals of the carbon atoms C-2, C-4, and C-5 were sufficiently separated in each of the compounds (see Table 2). The diastereomeric ratios could therefore be determined by comparison of the signal intensity. The more intense peaks consistently appeared at higher field for C-2 and C-4, and vice versa for C-5.

Table 2. ^{13}C-NMR signals (main diastereomer denoted by italics) of the cyclic acetals **13** used for determination of optical purity (100.6 MHz, C_6H_6/C_6D_6)

13	R	δ(C-2)	δ(C-4)	δ(C-5)
a	ethyl	32.0 *31.8*	44.9 *44.7*	*30.9* 30.7
b	*n*-propyl	32.1 *31.9*	45.3 *45.1*	*29.2* 29.0
c	*n*-butyl	32.1 *31.9*	45.4 *45.2*	*29.3* 29.1
d	*n*-heptyl	32.1 *31.9*	45.4 *45.2*	*29.3* 29.1
e	allyl	32.0 *31.9*	44.4 *44.3*	*29.1* 28.9
f	benzyl	32.0 *31.8*	45.3 *45.1*	*31.4* 31.2
g	isopropyl	32.1 *31.8*	42.3 *42.0*	*34.5* 34.2
h	cyclohexyl	32.1 *31.8*	*42.6* 42.3	*34.2* 33.9
j	trimethylsilyl	31.6 *31.3*	40.1 *39.5*	*15.6* 15.3

The results in Table 1 show that alkylation with primary alkyl bromides and benzyl chloride affords the chiral ketones **10a–d** and **10f** in an almost enantiopure state. With allyl chloride, which also proved very reactive in the alkylation of *endo*-**8**, the induction achieved was about 10% lower (entry 9). Only moderate optical purities were obtained with the considerably less reactive primary alkyl chlorides and secondary alkyl bromides, whereas the silylation (entry 14) was again highly stereoselective.

Absolute Configuration

There are only a few β-chiral ketones **10** where the relationship between optical rotation and absolute configuration is known, **10a**[15] and **10g**[16] being two of them. In both cases, the configuration of the laevorotatory compounds is that shown in Scheme 3. We assume the same configuration for all ketones **10** from the consistency of the sign of the rotation angle and the chemical shifts of their diastereomeric acetals **13**.

Mechanistic Considerations

Enamine **7a** was produced as a mixture of diastereomers (56:44) with (*E*) configuration of the double bond. After alkylation, almost diastereopure (*Z*)-enamines **9** were obtained. Therefore, the two diastereomeric 3-lithiated (*E*)-enamines to be expected from the initial tin-lithium exchange reaction must isomerize to give only one (*Z*)-configured lithium compound. In the light of earlier investigations, we prefer the structure **14** for the reactive intermediate, with the lithium ion fixed at one side of the allylic plane by chelation. Preferential metallo-inverse back attack of the alkylating reagent, as seen in other cases, would also explain the stereochemistry observed.

Interestingly, in the course of experiments aimed at investigating the temperature dependence of the diastereoselectivity using trimethylchlorosilane as the electrophile, we found that when the reaction was carried out at temperatures above −10 °C, some of the corresponding 3-silylated (*E*)-enamine was obtained. Since equilibration of the silylated enamines under the conditions of work-up can be ruled out, a fast and temperature-dependent equilibrium between *exo*-**8** and *endo*-**8** must exist. We confirmed it to be reversible, since a test sample warmed to 20 °C, whereupon it contained about 20% of the *exo*-isomer, gave only the (*Z*)-enamine when silylation was carried out after it had been recooled to −78 °C (see Table 3).

Normally, alkali metal salts of 1-aminoallyl anions show a strong preference for an *endo* orientation of the amino group. However, this rule seems to hold only for cases where the second substituent at the α-position is a hydrogen atom[17] or a group with acceptor properties such as cyano[18], phosphoryl[19], methoxycarbonyl[20], or phenyl[21]. With an alkyl group, which is itself a donor and strongly prefers the *endo*-position in salts of allyl anions[22], the situation seems to change, since now two donor substituents compete for the *endo*-position. Therefore, in principle, the aforementioned observed equilibrium can be understood.

In the case of the potassium salt of the 1-methylanilino-3-phenylallyl anion, we were able to measure the rate of this isomerization process and found half-lives in THF at 50 °C that varied from 2 to 13 hours, with a strong dependence on traces of oxygen present during the measurement[23]. The rate of isomerization of **8** was clearly much higher, since it occurred quantitatively even at low temperatures during the short period of cooling a probe from 20 °C to −78 °C. We attribute this rate enhancement to the presence of the methoxy group. During the isomerization process, localization of the negative charge of the allylic anion at the α-carbon is necessary, to give, in this case, a relatively unstable α-lithioamine. This unfavourable process is probably facilitated by the stabilization that results from chelation of the lithium ion by the methoxy group to give a six-membered ring.

In the case of the 3-silylated (*E*)- and (*Z*)-enamines, the diastereomeric ratio could be determined by ^{1}H-NMR spectroscopy by analyzing the doublet signals of the vinylic protons. The intermediate *exo*-**8** reacts much less selectively compared to *endo*-**8**, as is apparent from the low diastereomeric excess of only 9% (see Table 3). Analogous behaviour was observed in the case of the corresponding 3-phenyl-substituted compound, e.g. the potassium salt of the SMP-cinnamyl anion[11]. On the other hand, the selectivity of *endo*-**8** remains high even at elevated temperatures (see entry 3), as is evident from the high diastereomeric excess observed for the (*Z*)-enamine.

The addition of one equiv. of hexamethylphosphoramide strongly accelerated the tin−lithium exchange[6], but on the other hand, the stereoselectivity decreased drastically. In the presence of this cosolvent, a mixture of (*Z*)- and (*E*)-enamines (74:26) was obtained, even at low temperatures. In such a medium, poor asymmetric induction was observed with the *endo*-lithium compound as well (see entry 4).

Table 3. Dependence of diastereoselectivity on temperature and HMPA addition

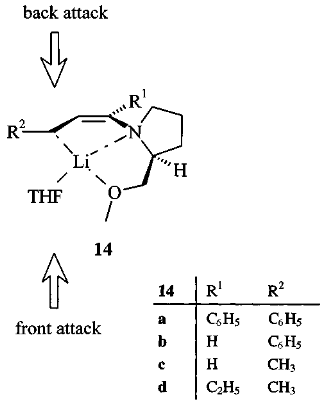
Entry	Transmet. temp. [°C]	Transmet. time [h]	Silylation temp. [°C]	Silylation time [h]	(Z)-**9j**[b] [%]	(*Z*)-**9j**[b] de [%]	(*E*)-**9j**[b] [%]	(*E*)-**9j**[b] de [%]	**10j** yield [%]	**10j**[d] ee [%]
1	−78 → −20	8	−78	2	100	≥ 98	0	–[c]	76	≥ 98
2	−78 → +20	8	−78	2	100	≥ 98	0	–[c]	58	≥ 98
3	−78 → +25	8	+25	0.5	80	≥ 98	20	9	51	76
4	−78/HMPA[a]	1	−78	2	74	25	26	27	62	25

[a] Addition of 1 equiv. of HMPA to a THF solution of **7a**. – [b] Determined by integration of the vinylic signals in the ^{1}H-NMR spectrum of **9j**. – [c] A second diastereomer was not observed. – [d] Determined by the signal height of carbon atom C-4 in the ^{13}C-NMR spectrum of **13j**.

As mentioned above, in order to explain the selectivities observed with alkali metal salts of 1-SMP-allyl anions, we propose the chelated contact ion-pair **14** as a model system, which reacts with alkyl halides via metallo-inverse back attack. In accord with this model, it was found that the tighter the structure of the reacting ion-pair, the higher the observed stereoselectivity.

The ion-pair structure can be externally influenced by a change of solvent. With stronger complexation of the cation by the solvent, the contact to the carbon becomes weaker and, therefore, back attack becomes less favoured. This explains why, in alkylation reactions of the less tight ion-pair of the strongly delocalized lithium salt of the SMP-1,3-di-

Scheme 7



14	R1	R2
a	C_6H_5	C_6H_5
b	H	C_6H_5
c	H	CH_3
d	C_2H_5	CH_3

Table 4. Dependence of the mode of asymmetric alkylation of **14** on internal and external factors

14	R1	R2	RX	TBME [% *ee*]	THF [% *ee*]	Ref.
a	C_6H_5	C_6H_5	CH_3I	77 (back)	76 (front)	[13]
b	H	C_6H_5	CH_3I	95 (back)	26 (back)	[11]
c	H	CH_3	C_4H_9Br	95 (back)[a]	95 (back)	[24]
d	C_2H_5	CH_3	C_2H_5Br	–	≥ 98 (back)	this work

[a] Potassium as counterion.

phenylallyl anion **14a**, variation of the solvent from the weakly solvating *tert*-butyl methyl ether (TBME) to strongly solvating THF favoured the frontside attack and even caused a reversal of the reaction mode (see Table 4)[13].

Internal factors point in the same direction. A reduction in the degree of delocalization by replacing one phenyl group of **14a** by a hydrogen atom (**14b**) favours the back attack[11]. However, the use of the more weakly solvating TBME as a solvent is again necessary to obtain high selectivity; the selectivity decreases in THF. Replacement of the second phenyl group of **14a** by an alkyl group, as in **14c**[24] and **14d**, clearly increases the tightness of the ion-pair, to such an extent that even in THF only back attack can occur. In this context, the influence of HMPA mentioned above is readily explained by our model, since such a strong complexing agent will be able to loosen even such a tightly bound ion-pair.

In conclusion, alkylation of the new chiral homoenolate equivalent *endo*-**8**, readily available by tin–lithium exchange of the 3-stannylated SMP-enamine **7a**, offers an efficient access to chiral 3-methylated aliphatic ketones **10** of high enantiomeric purity. The mode of asymmetric alkylation in this case, as well as in related cases, can be understood in terms of variations of the tightness of the chelated contact ion-pair **14** by internal or external factors.

Financial support by the *Deutsche Forschungsgemeinschaft (SFB 260)* and the *Fonds der Chemischen Industrie* is gratefully acknowledged. We thank *Degussa AG* for a generous gift of L-proline.

Experimental Section

GC: HRGC Mega 5300 (Carlo Erba), OV-101, l = 10 m, *i.d.* = 0.25 mm. – Specific optical rotations: Polarimeter 141 (Perkin-Elmer); $[\alpha]_D^T$ in degree·cm^2·10^{-1}·g^{-1}]. – Kugelrohr distillation: Glasrohrofen GKR-50 (Büchi). – MS: Mat-311A (Varian). – ^1H NMR: Bruker AC 200, Bruker AM 400; ^{13}C NMR: Bruker AM 400; internal standard TMS (δ = 0.00); first-order analysis of multiplets. – The boiling pressures given are only approximate; the boiling points refer to the oven temperatures and are about 20°C too high.

Reagents and Solvents: Argon (99.99%, Firma Messer-Griesheim) dried and freed from CO_2 by $CaCl_2$ and KOH, was used for all reactions requiring anhydrous and anaerobic conditions. – *THF:* Technical grade THF was stored for a few days over solid KOH, then decanted, distilled from fresh KOH, refluxed over Na/benzophenone, distilled once more, and stored in brown bottles under Ar and over Na. – *Benzene and Toluene:* The solvents were extracted with conc. H_2SO_4 until the H_2SO_4 was only slightly yellow. After refluxing over Na/benzophenone and distilling, they were stored under Ar and over Na. – *HMPA* was stirred for three days over CaH_2, distilled, and stored under Ar and over CaH_2. – *n-Butyllithium* in hexane (1.78 M) was obtained from the *Chemetall Gesellschaft, Frankfurt*. The content was determined by titration with diphenylacetic acid[25]. – L-*Proline* was obtained from *Degussa AG, Wolfgang*, and was dried over silica gel for 7 d. – *SMP* was synthesized according to ref.[11].

3-Stannylated Enamine **7**: A 100-ml single-necked flask containing a stirring bar was charged with benzene, 5-tributylstannyl-3-hexanone **6**[4], 4 equivs. of SMP, and a catalytic amount of *p*-toluenesulfonic acid hydrate. The flask was then fitted with a Dean-Stark trap (vol. 50 ml) equipped with a condenser and an argon inlet. The mixture was refluxed for 48 h, allowed to cool to room temperature, and the benzene was removed in a rotary evaporator. Purification by kugelrohr distillation afforded the enamines **7a** and **7b** in a ratio of 90:10, in 56% overall yield. b.p. 130°C/0.01 Torr. – For spectral data see ref.[7].

General Procedure for the Preparation of β-Methyl Ketones **10a–j**: To a solution of **7** (2.43 g, 5 mmol) in THF (10 ml) was added *n*-BuLi (3.1 ml of a 1.78 M solution in hexane, 5.5 mmol) at −78°C, and the mixture was allowed to warm to −20°C over a period of 8 h. On cooling to −78°C once more, the blood-red coloured solution changed to yellow-orange. The electrophile (6 mmol) was then added as a THF solution (2 ml), the mixture was stirred at −78°C until it became colourless (for reaction times, see Table 1), and was then allowed to warm to 0°C. HCl (4 M, 10 ml) was added, the resulting mixture was stirred for 1 min., and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 10 ml), neutralized with NaOH (2 M), stirred for 2 h, and reacidified in order to separate SMP as its ammonium salt. The mixture was extracted with diethyl ether (3 × 10 ml), the combined extracts were dried (Na_2SO_4), and concentrated in a rotary evaporator. Purification by kugelrohr distillation afforded the ketones **10a–j** as colourless, fruity smelling liquids.

5-Methyl-3-heptanone (**10a**): Alkylation of *endo*-**8** with ethylbromide gave 500 mg (78%) **10a**, b.p. 100°C/40 Torr. – *ee* ≥ 98%. – $[\alpha]_D^{20}$ = +5.31 (c = 4.20, benzene), $[\alpha]_D^{20}$ = −8.73 (neat) {ref.[15] $[\alpha]_D^{25}$ = +8.97 (neat), (*S*)-configuration}. – ^1H NMR (400 MHz): δ = 0.88 (t, 3 H, J = 7.4 Hz, $CHCH_2CH_3$), 0.88 (d, 3 H, J = 6.6 Hz, $CHCH_3$), 1.05 (t, 3 H, J = 7.3 Hz, $COCH_2CH_3$), 1.14–1.25, 1.27–1.38 (m, 1 H, $CHCH_2CH_3$), 1.93 (m$_c$, 1 H, CH), 2.21 (dd, 1 H, J = 15.7/8.1 Hz, COC*H*HCH), 2.34–2.50 (m, 3 H, CH_3CH_2COCHH). – ^{13}C NMR (50.3 MHz): δ = 7.8 ($COCH_2CH_3$), 11.3 ($CHCH_2CH_3$), 19.5 ($CHCH_3$), 29.7 (CH), 31.0 ($CHCH_2CH_3$), 36.5 (CH_3CH_2CO), 49.6 ($COCH_2CH$), 211.3 (CO). – $C_8H_{16}O$; HRMS: calcd. 128.1201; found 128.1207.

5-Methyl-3-octanone (**10b**): Alkylation of *endo*-**8** with 1-propylbromide gave 576 mg (81%) **10b**, b.p. 80°C/15 Torr. − *ee* 97%. − $[\alpha]_D^{20}$ = +5.84 (*c* = 4.930, benzene). − ^{1}H NMR (400 MHz): δ = 0.87 (d, 3 H, *J* = 6.6 Hz, CHC*H*$_3$), 0.89 (t, 3 H, *J* = 6.8 Hz, CH$_2$CH$_2$C*H*$_3$), 1.04 (t, 3 H, *J* = 7.3 Hz, COCH$_2$C*H*$_3$), 1.07−1.42 (m, 4 H, C*H*$_2$C*H*$_2$), 2.02 (m$_c$, 1 H, CH), 2.20 (dd, 1 H, *J* = 15.7/8.0 Hz, COCH*H*CH), 2.35−2.46 (m, 3 H, CH$_3$C*H*$_2$COC*H*H). − ^{13}C NMR (100.6 MHz): δ = 7.8 (COCH$_2$*C*H$_3$), 14.2 (CH$_2$CH$_2$*C*H$_3$), 19.9 (CH*C*H$_3$), 20.1 (CH$_2$*C*H$_2$CH$_3$), 29.1 (CH), 36.5 (CH$_3$*C*H$_2$CO), 39.3 (CH*C*H$_2$CH$_2$), 50.0 (CO*C*H$_2$CH), 211.6 (CO). − $C_9H_{18}O$; HRMS: calcd. 142.1358; found 142.1361.

5-Methyl-3-nonanone (**10c**): Alkylation of *endo*-**8** with 1-butylbromide gave 610 mg (78%) **10c**, b.p. 95°C/12 Torr. − *ee* ≥ 98%. − $[\alpha]_D^{20}$ = +8.48 (*c* = 6.520, benzene). − ^{1}H NMR (400 MHz): δ = 0.88 (d, 3 H, *J* = 6.7 Hz, CHC*H*$_3$), 0.89 (t, 3 H, *J* = 6.3 Hz, CH$_2$CH$_2$C*H*$_3$), 1.05 (t, 3 H, *J* = 7.3 Hz, COCH$_2$C*H*$_3$), 1.10−1.37 (m, 6 H, C*H*$_2$C*H*$_2$C*H*$_2$), 2.0 (m$_c$, 1 H, CH), 2.21 (dd, 1 H, *J* = 15.6/8.1 Hz, COCH*H*CH), 2.33−2.48 (m, 3 H, CH$_3$C*H*$_2$COC*H*H). − ^{13}C NMR (100.6 MHz): δ = 7.8 (COCH$_2$*C*H$_3$), 14.1 (CH$_2$CH$_2$*C*H$_3$), 19.9 (CH*C*H$_3$), 22.9 (CH$_2$*C*H$_2$CH$_3$), 29.2 (CHCH$_2$*C*H$_2$), 29.3 (CH), 36.5, 36.7 (*C*H$_2$COCH$_2$CH*C*H$_2$), 50.0 (CO*C*H$_2$CH), 211.6 (CO). − $C_{10}H_{20}O$; HRMS: calcd. 156.1514; found 156.1554.

5-Methyl-3-dodecanone (**10d**): Alkylation of *endo*-**8** with 1-heptylbromide gave 823 mg (83%) **10d**, b.p. 120°C/12 Torr. − *ee* ≥ 98%. − $[\alpha]_D^{20}$ = +10.06 (*c* = 6.520, benzene). − ^{1}H NMR (400 MHz): δ = 0.88 (t, 3 H, *J* = 6.8 Hz, CH$_2$CH$_2$C*H*$_3$), 0.88 (d, 3 H, *J* = 6.6 Hz, CHC*H*$_3$), 1.05 (t, 3 H, *J* = 7.3 Hz, COCH$_2$C*H*$_3$), 1.19−1.37 [m, 12 H, (CH$_2$)$_6$], 1.99 (m$_c$, 1 H, CH), 2.20 (dd, 1 H, *J* = 15.7/8.1 Hz, COCH*H*CH), 2.33−2.45 (m, 3 H, CH$_3$C*H*$_2$COC*H*H). − ^{13}C NMR (100.6 MHz): δ = 7.7 (COCH$_2$*C*H$_3$), 14.0 (CH$_2$CH$_2$*C*H$_3$), 19.9 (CH*C*H$_3$), 22.6 (CH$_2$*C*H$_2$CH$_3$), 27.0, 29.3, 29.7, 31.8 (CHCH$_2$*C*H$_2$*C*H$_2$*C*H$_2$*C*H$_2$), 29.3 (CH), 36.4, 37.0 (*C*H$_2$COCH$_2$CH*C*H$_2$), 49.9 (CO*C*H$_2$CH), 211.7 (CO). − $C_{13}H_{26}O$; HRMS: calcd. 198.1984; found 198.2020.

5-Methyl-7-octen-3-one (**10e**): Alkylation of *endo*-**8** with allylchloride gave 547 mg (78%) **10e**, b.p. 80°C/12 Torr. − *ee* 87%. − $[\alpha]_D^{20}$ = +8.37 (*c* = 19.750, benzene). − ^{1}H NMR (400 MHz): δ = 0.90 (d, 3 H, *J* = 6.2 Hz, CHC*H*$_3$), 1.04 (t, 3 H, *J* = 7.4 Hz, CH$_2$C*H*$_3$), 1.92−2.26 (m, 4 H, COCH*H*C*H*C*H*$_2$CH=), 2.32−2.52 (m, 3 H, C*H*$_2$COC*H*H), 4.92−5.05 (m, 2 H, =CH$_2$), 5.63−5.84 (m, 1 H, =CH). − ^{13}C NMR (100.6 MHz): δ = 7.8 (CH$_2$*C*H$_3$), 19.8 (CH*C*H$_3$), 29.0 (*C*HCH$_3$), 36.6 (*C*H$_2$CH$_3$), 41.2 (=CH*C*H$_2$), 49.0 (CO*C*H$_2$CH), 116.4 (=CH$_2$), 136.7 (=CH), 211.0 (CO). − $C_9H_{16}O$; HRMS: calcd. 140.1201; found 140.1182.

5-Methyl-6-phenyl-3-hexanone (**10f**): Alkylation of *endo*-**8** with benzylchloride gave 723 mg (76%) **10f**, b.p. 140°C/5 Torr. − *ee* 97%. − $[\alpha]_D^{20}$ = +13.60 (*c* = 3.64, benzene). − ^{1}H NMR (400 MHz): δ = 0.90 (d, 3 H, *J* = 6.5 Hz, CHC*H*$_3$), 1.01 (t, 3 H, *J* = 7.4 Hz, CH$_2$C*H*$_3$), 2.22 (dd, 1 H, *J* = 15.1/7.3 Hz, COCH*H*CH), 2.27−2.43 (m, 4 H, C*H*, CH$_3$C*H*$_2$, COC*H*HCH), 2.46 (dd, 1 H, *J* = 13.3/7.1 Hz, C*H*HC$_6$H$_5$), 2.56 (dd, 1 H, *J* = 13.3/6.6 Hz, CH*H*C$_6$H$_5$), 7.09−7.32 (m, 5 H, C$_6$*H*$_5$). − ^{13}C NMR (100.6 MHz): δ = 7.6 (CH$_2$*C*H$_3$), 19.7 (CH*C*H$_3$), 31.1 (CH), 36.4 (*C*H$_2$CH$_3$), 43.1 (*C*H$_2$C$_6$H$_5$), 48.8 (CO*C*H$_2$CH), 125.9 (C$_6$H$_5$, *para*), 128.1 (C$_6$H$_5$, *meta*), 129.1 (C$_6$H$_5$, *ortho*), 140.4 (C$_6$H$_5$, *ipso*), 211.1 (CO). − $C_{13}H_{18}O$; HRMS: calcd. 190.1358; found 190.1380.

5,6-Dimethyl-3-heptanone (**10g**): Alkylation of *endo*-**8** with isopropylbromide gave 483 mg (68%) **10g**, b.p. 90°C/15 Torr. − *ee* 65%. − $[\alpha]_D^{20}$ = +5.47 (*c* = 6.42, benzene), $[\alpha]_D^{20}$ = −9.01 (neat) {ref.[16] $[\alpha]_D^{25}$ = +8.87 (neat), (*R*) configuration}. − ^{1}H NMR (400 MHz): δ = 0.86, 0.88 (each d, 6 H, *J* = 7.0 Hz, C*H*$_3$CHC*H*$_3$), 0.91 (d, 3 H, *J* = 6.8 Hz, CH$_2$CHC*H*$_3$), 1.09 (t, 3 H, *J* = 7.3 Hz, CH$_2$C*H*$_3$), 1.59 (sept, 1 H, *J* = 7.0/2.1 Hz, CH$_3$C*H*CH$_3$), 1.98 (m$_c$, 1 H, CH$_2$C*H*), 2.22 (dd, 1 H, *J* = 16.0/8.8 Hz, COCH*H*), 2.37−2.54 (m, 3 H, CH$_3$C*H*$_2$COC*H*H). − ^{13}C NMR (100.6 MHz): δ = 7.9 (CH$_2$*C*H$_3$), 16.0 (CH$_2$CH*C*H$_3$), 18.4, 19.8 (*C*H$_3$CH*C*H$_3$), 32.4, 34.9 (*C*H*C*H), 36.5 (CH$_3$*C*H$_2$), 47.2 (CO*C*H$_2$), 211.9 (CO). − $C_9H_{18}O$; HRMS: calcd. 142.1358; found 142.1339.

5-Cyclohexyl-3-hexanone (**10h**): Alkylation of *endo*-**8** with cyclohexylbromide gave 419 mg (46%) **10h**, b.p. 140°C/5 Torr. − *ee* 49%. − $[\alpha]_D^{20}$ = +1.93 (*c* = 3.00, benzene) − ^{1}H NMR (400 MHz): δ = 0.83 (d, 3 H, *J* = 6.8 Hz, CHC*H*$_3$), 1.05 (t, 3 H, *J* = 7.3 Hz, CH$_2$C*H*$_3$), 0.88−1.28, 1.53−1.82 (each m, 11 H, *c*C$_6$*H*$_{11}$), 1.87−1.98 (m, 1 H, C*H*CH$_3$), 2.18 (dd, 1 H, *J* = 15.6/9.1 Hz, COCH*H*CH), 2.33−2.50 (m, 3 H, CH$_3$C*H*$_2$COCH*H*). − ^{13}C NMR (100.6 MHz): δ = 7.9 (*C*H$_3$CH$_2$), 16.7 (*C*H$_3$CH), 26.6, 26.7, 26.8, 29.1, 30.4 [-(CH$_2$)$_5$-], 34.3 (*C*HCH$_3$), 36.4 (CH$_3$*C*H$_2$), 42.9 [-CH$_2$*C*H(CH$_2$)$_4$-], 47.2 (CO*C*H$_2$CH), 212.0 (CO). − $C_{12}H_{22}O$; HRMS: calcd. 182.1671; found 182.1655.

5-Trimethylsilyl-3-hexanone (**10j**): Silylation of *endo*-**8** with trimethylsilylchloride gave 615 mg (76%) **10j**, b.p. 90°C/5 Torr. − *ee* ≥ 98%. − $[\alpha]_D^{20}$ = +11.15 (*c* = 6.27, benzene) − For spectral data see ref.[7].

Enamines **9a−j**. − *General Procedure*: A solution of **7** (0.97 g, 2 mmol) in THF (10 ml) was transmetallated and alkylated (silylated) according to the procedure described above. All solvents were then removed in an oil-pump vacuo and 20 ml of hexane was added. The precipitated lithium salts were allowed to deposit overnight and 5 ml of the clear pale-yellow solution was then transferred via syringe in a 25-ml single-necked flask. The solvent was again removed in an oil-pump vacuo. A part of the residue, containing the enamine **9** and tetrabutyltin, was dissolved in 1.5 ml of C_6D_6 and a NMR analysis was performed. The following ^{1}H- and ^{13}C-NMR signals of **9j** were used for determination of the (*E*/*Z*) ratio and the enantiomeric excess achieved, in dependence of external factors (see Table 3): ^{1}H NMR (400 MHz): δ = 4.15, 4.22 [d, 1 H, *J* = 10.9, 11.2 Hz, NC=C*H* (*E*)], 4.95, 4.96 [d, 1 H, *J* = 11.3 Hz, NC=C*H* (*Z*)]. − ^{13}C NMR (100.6 MHz): δ = 48.8, 49.0 [NCH (*E*)], 53.2 [NCH (*Z*)], 56.9, 57.0 [OCH$_3$ (*E*)], 58.4, 58.7 [OCH$_3$ (*Z*)], 74.3, 74.4 [OCH$_2$ (*E*)], 77.0 [OCH$_2$ (*Z*)], 105.8, 106.3 [=CH (*E*)], 122.9 [=CH (*Z*)], 141.4, 141.8 [=CN (*E*)], 144.1 [=CN (*Z*)].

Diketone **12**: A solution of **7** (2.43 g, 5 mmol) in THF (10 ml) was transmetallated as described above. A half equiv. of 1,2-dibromoethane (0.47 g, 2.5 mmol) was then added as a THF solution (2 ml) and the mixture was stirred for one hour at −78°C. The further hydrolysation and purification steps were the same as already described for the preparation of **10a-j**. Finally, kugelrohr distillation yielded 763 mg (77%) of the diketone **12** as a mixture of diastereomers (54:46), b.p. 140°C/5 Torr. − ^{1}H NMR (400 MHz): δ = 0.81 (d, 3 H, *J* = 6.6 Hz, CHC*H*$_3$), 0.85 (d, 3 H, *J* = 6.5 Hz, CHC*H*$_3$), 1.05 (t, 6 H, *J* = 7.3 Hz, 2 × CH$_2$C*H*$_3$), 1.98−2.10 (m, 2 H, 2 × C*H*CH$_3$), 2.18 (dd, 1 H, *J* = 15.8/8.9 Hz, COCH*H*CH), 2.24 (dd, 1 H, *J* = 15.9/8.5 Hz, COCH*H*CH), 2.31−2.52 (m, 6 H, 2 × CH$_3$C*H*$_2$COCH*H*). − ^{13}C NMR (100.6 MHz): δ = 7.8 (*C*H$_3$CH$_2$), 15.1, 16.9 (*C*H$_3$CH), 33.1, 33.5 (CH), 36.4, 36.5 (CH$_3$*C*H$_2$), 46.3, 47.5 (CO*C*H$_2$CH), 211.2, 211.3 (CO). − $C_{12}H_{22}O_2$; HRMS: calcd. 189.1620; found 189.1617.

General Procedure for the Preparation of Diastereomeric Acetals **13a−h** *and* **13j**[26]: A 25-ml single-necked flask containing a stirring bar was charged with benzene, the appropriate β-chiral ketone **10a−h** or **10j**, 2 equivs. of (2*R*,3*R*)-(−)-2,3-butanediol, and a catalytic amount of *p*-toluenesulfonic acid hydrate. The flask was then fitted with a Dean-Stark trap (vol. 7 ml) equipped with a condenser and an argon inlet. The mixture was refluxed for 24 h, allowed to cool to room temperature, and the benzene was removed in a rotary evaporator. The residue was redissolved in pentane and the resulting solution was washed with satd. aq. $NaHCO_3$ and 5% aq. $NaHSO_3$ solutions. The two aqueous washings were each back-extracted with 5 ml of pentane. The combined organic layers were dried with K_2CO_3 and concentrated in vacuo. The optical purities of the acetals were determined by ^{13}C-NMR spectroscopy without further purification, by comparison of the intensities of the signals attributable to C-2, C-4, and C-5 (deviations about ±1%).

☆ Dedicated to Professor *Dieter Seebach* on the occasion of his 60th birthday.

[1] Chiral homoenolate equivalents, part V: H. Ahlbrecht, A. Kramer, *Chem. Ber.* **1996**, *129*, 1161−1168.

[2] R. Schmidt, Diplomarbeit, University of Gießen, **1994**.

[3] U. Beyer, Ph. D. Dissertation, University of Gießen, in preparation.

[4] [4a] D. Seebach, *Angew. Chem.* **1979**, *91*, 259−278; *Angew. Chem Int. Ed. Engl.* **1979**, *18*, 239−258. − For the homoenolate problem, see: [4b] D. Hoppe, *Angew. Chem.* **1984**, *96*, 930−946; *Angew. Chem Int. Ed. Engl.* **1984**, *23*, 932−948. − [4c] N. H. Werstiuk in *Umpoled Synthons* (Ed.: T. A. Hase), Wiley, New York, **1987**, p. 173. − For other recent examples of chiral homoenolate reagents see: [4d] D. Hoppe, T. Krämer, J.- R. Schwark, O. Zschage, *Pure Appl. Chem.* **1990**, *62*, 1999−2006. − [4e] P. Beak, D. J. Gallagher, H. Du, S. A. Scott, *J. Am. Chem. Soc.* **1996**, *118*, 11391−11398. − [4f] M. Reggelin, H. Weinberger, M. Gerlach, R. Welcker, , *J. Am. Chem. Soc.* **1996**, *118*, 4765−4777. − [4g] M. Yus, F. Foubelo, L. R. Falvello, *Tetrahedron: Asymmetry* **1995**, *6*, 2081−2092. − [4h] J. D. Armstrong, III, J. C. McWilliams, N. Zheng, M. Bhupathy, R. P. Volante, P. J. Reider, *J. Am. Chem. Soc.* **1996**, *118*, 11970−11971. − [4i] . F. W. Jackson, M. J. Dunn, J. Pietruszka, D. Turner, *J. Org. Chem.* **1995**, *60*, 2210−2215.

[5] H. Ahlbrecht, *Chimia* **1977**, *31*, 391−403.

[6] H. Ahlbrecht, P. Weber, *Synthesis* **1992**, 1018−1025.

[7] H. Ahlbrecht, P. Weber, *Synthesis* **1989**, 117−120.

[8] For a recent review on the use of SMP as chiral auxiliary, see D. Enders, M. Klatt, *Synthesis* **1996**, 1403−1418.

[9] W. C. Still, *J. Am. Chem. Soc.* **1977**, *99*, 4836−4838.

[10] W. C. Still, *J. Am. Chem. Soc.* **1978**, *100*, 1481−1487.

[11] H. Ahlbrecht, D. Enders, L. Santowski, G. Zimmermann, *Chem. Ber.* **1989**, *122*, 1995−2004.

[12] [12a] D. E. Applequist, G. N. Chmurny, *J. Am. Chem. Soc.* **1967**, *89*, 875−880. − [12b] W. H. Glaze, C. M. Selman, A. L. Leroy Jr., L. E. Bray, *J. Org. Chem.* **1969**, *34*, 641−644.

[13] H. Ahlbrecht, H. Sommer, *Chem. Ber.* **1990**, *123*, 829−836.

[14] H. Wynberg, H. Hiemstra, *Tetrahedron Lett.* **1977**, *25*, 2183−2186.

[15] P. Pino, P. L. Luisi, *J. Chim. Phys. Physicochim. Biol.* **1968**, *65(1)*, 130−139.

[16] S. Pucci, M. Aglietto, P. L. Luisi, *Gazz. Chim. Ital.* **1970**, *100*, 159−174.

[17] [17a] G. Rauchschwalbe, H. Ahlbrecht, *Synthesis* **1974**, 663−665. − [17b] H. Ahlbrecht, J. Eichler, *Synthesis* **1974**, 672−674.

[18] H. Ahlbrecht, C. Vonderheid, *Synthesis* **1975**, 512−515.

[19] H. Ahlbrecht, W. Farnung, *Chem. Ber.* **1984**, *117*, 1−22.

[20] H. Ahlbrecht, H. Simon, *Synthesis* **1983**, 58−60.

[21] H. Ahlbrecht, G. Rauchschwalbe, *Synthesis* **1973**, 417−419.

[22] O. Desponds, L. Franzini, M. Schlosser, *Synthesis* **1977**, 150−152 and references cited therein.

[23] J. Eichler, Ph. D. Dissertation, University of Gießen, **1976**.

[24] C. Fröhlich, Ph. D. Dissertation, University of Gießen, in preparation.

[25] W. G. Kofron, M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879−1880.

[26] G. H. Posner, L. L. Frye, M. Hulce, *Tetrahedron* **1984**, *40*, 1401−1407.

[97311]