125. Synthesis of Optically Active Bifunctional Isoprenoid Building Blocks by Rhodium(I)-Catalyzed Asymmetric Allylamine to Enamine Isomerization[1])

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Dedicated to Dr. *Otto Isler* on the occasion of his 80th birthday

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The application of the known asymmetric allylamine to enamine isomerization methodology to bifunctional C_5-isoprenoid allylic amines of types **IId** and **IIe** *(Scheme 1)* is described. It is shown that a number of such substrates can be isomerized with enantioselectivities of > 90% ee using cationic Rh^I complexes containing (6,6′-dimethylbiphenyl-2,2′-diyl)bis(diphenylphosphine) (BIPHEMP; **9**) as asymmetry-inducing ligand (*Scheme 2, Tables 1* and *2*). Synthetically most useful is the isomerization of the benzyloxy derivative **10a** into the (*E*)-enamine **11a**. This isomerization proceeds with very high enantioselectivity (98–99% ee) and affords, after enamine hydrolysis, the optically active 4-(benzyloxy)-3-methylbutanals ((*R*)- or (*S*)-**12**) in chemical yields of *ca.* 90%. In conjunction, a short synthetic route to the starting material **10a** has been developed which has a Pd-catalyzed amination of isoprene epoxide (**30**) as the key step. Thus, convenient and practical access to the optically active aldehydes (*R*)- and (*S*)-**12** is now at hand. These aldehydes are useful optically active bifunctional building blocks for isoprenoid homologation.

1. Introduction. – Optically active, bifunctional isoprenoid C_5^*-synthons[3]) of type **I** are of interest for the synthesis of natural products containing terpenoid chains such as tocopherols, vitamin K_1, phytol, diphytanyl glycerophosphatides of halophilic bacteria, constituents of essential oils, insect pheromones *etc.* In the past, a number of synthetic equivalents for such synthons have been developed by a variety of methods. For example, the C_5^*-lactones (*S*)-**1** and (*S*)-**2** and their respective open-chain precursors have been obtained by fermentative transformations (*Leuenberger et al.* [1]) and, more recently, also by Ru^{II}-catalyzed asymmetric hydrogenations of precursors with a triply substituted double bond (*Takaya, Noyori* and coworkers [2]). Other C_5^*-building blocks were obtained *via* chemical resolutions (*e.g.* **3**; *Waard* and coworkers [3]) or *via* enzymatic kinetic resolutions (**4**; *Sih* and coworkers [4]). The masked C_5^*-building blocks **5** and (*S*)-**6** containing a styryl or 2-furyl moiety, respectively, as carbonyl 'protecting group' have been prepared by chemical resolution or by fermentative reductions (*Fuganti* and coworkers [5]). Finally, the access to optically active 2-methylglutarate or its ester derivatives **7** *via* asymmetric catalytic hydrogenations of itaconic acid or its esters has been investigated by several groups [6]. Further C_5^*-building blocks have been prepared by C_1-homologation of C_4^*-units [7] or by degradation of C_{10}^*- or C_6^*-building blocks [8].

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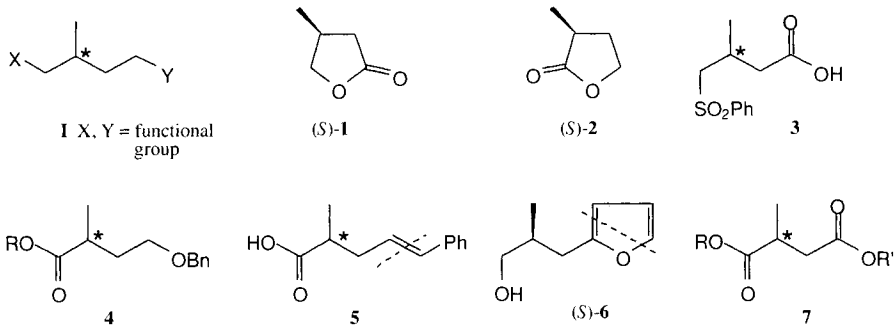
[3]) Asteriks will be used throughout this work to denote optically active entities as well as the number of centres of chirality combined in the entities.

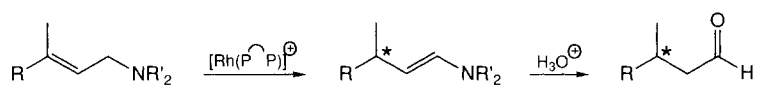


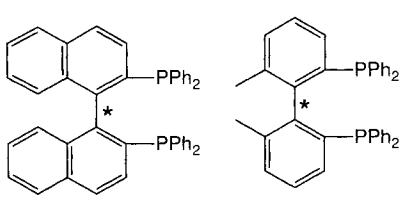
The utility of bifunctional isoprenoid C_5^*-building blocks **I** in syntheses has been demonstrated in a number of cases. In particular, the lactones (*S*)-**1** and (*S*)-**2** as well as the masked C_5^*-building blocks **5** and (*S*)-**6** have been applied to synthesize C_{15}^{**}- or C_{14}^{**}-side-chain derivatives of (*R,R,R*)-α-tocopherol *via* iterative isoprenoid homologation schemes $\{(C_5 \text{ or } C_4) + C_5^* + C_5^*\}$ (*Schmid* and *Barner* [9], *Zell* [10], *Fuganti* and coworkers [5]). Moreover, natural and unnatural dolichols have been synthesized using the optically active lactones **1** (*Suzuki et al.* [11]).

The present paper describes a new access to the series of bifunctional C_5^*-building blocks which is based on the application of the Rh^I-catalyzed asymmetric allylamine to enamine isomerization methodology [12]. The principal advantages of this methodology are *a*) the reliance on a catalytic reaction of proven efficiency, *b*) the predictable access to either product enantiomer in high enantiomeric purity by simply changing the catalyst configuration, and *c*) the direct access to γ-functionalized aldehydes of type **IVd/IVe** *(Scheme 1)* rather than acid derivatives, obviating the need for an additional reduction step prior to C,C bond formation in isoprenoid homologation schemes.

2. Isomerizations. – The Rh^I-catalyzed asymmetric allylamine to enamine isomerization methodology – developed by *Otsuka, Tani, Noyori* and coworkers [12] for the conversion of *N,N*-dialkylgeranylamines (**IIa**, *Scheme 1*) (or the corresponding (*Z*)-isomers, the *N,N*-dialkylnerylamines) into the optically active (*E*)-enamines **IIIa** of citronel-

Scheme 1



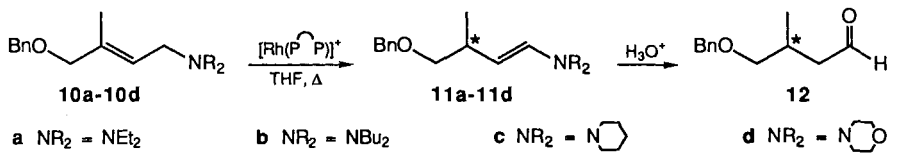


8 (BINAP) 9 (BIPHEMP)

a R = $(CH_3)_2C{=}CH{-}CH_2{-}CH_2$
b R = $(CH_3)_2C(OH)(CH_2)_3$
c R = Ph
d R = $R''OCH_2$
e R = $(R''O)_2CH$

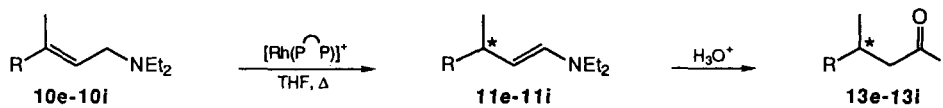
lal (**IVa**) – constitutes a highly efficient way to generate either configuration at the secondary C-atom Me*C*H. Cationic Rh^{I} complexes containing (1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine) (BINAP; **8**) have been found to be excellent catalysts both in terms of chemoselectivity as well as enantioselectivity for these isomerizations; they enable the (*E*)-enamines **IIIa** to be prepared in virtually quantitative yields and in enantiomeric purities of 96–99% ee [12]. In addition to the substrates **IIa**, only hydroxy analogues **IIb** and a cinnamyl derivative **IIc** have been investigated in asymmetric isomerization; the latter one afforded a somewhat lower ee of 90% [12e]. Recently, we have shown that (6,6′-dimethylbiphenyl-2,2′-diyl)bis(diphenylphosphine) (BIPHEMP; **9**) is

Scheme 2



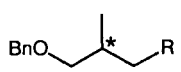
10a-10d **11a-11d** **12**

a NR_2 = NEt_2 **b** NR_2 = NBu_2 **c** NR_2 = N⟨⟩ **d** NR_2 = N⟨O⟩

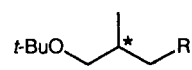


10e-10i **11e-11i** **13e-13i**

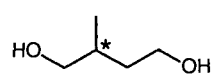
e R = *t*-BuOCH$_2$ **f** R = Me_3SiOCH_2 **g** R = $MeOCH_2OCH_2$ **h** R = AllylOCH$_2$ **i** R = $(MeO)_2CH$



12 R = CHO
14 R = CH_2NEt_2
15 R = CO_2H
16 R = (*R*)-CONH–CH(CH_3)–C_6H_4–*p*-NO_2
17 R = CH_2OH



13e R = CHO
18 R = CH_2NEt_2
19 R = CO_2H
20 R = (*R*)-CONH–CH(CH_3)–C_6H_4–*p*-NO_2



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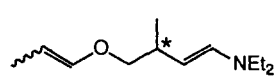
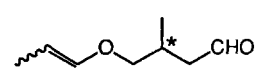
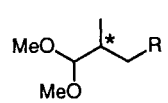
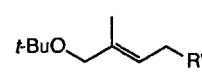


11h



13h





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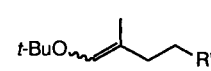

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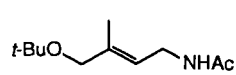
13i R = CHO
22 R = CH_2NEt_2



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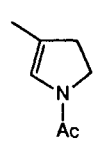

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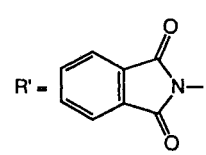


equally efficient as BINAP (**8**) as an asymmetry-inducing ligand for the isomerization of *N,N*-diethylnerylamine [13].

We have investigated now the application of the isomerization methodology to bifunctional isoprenoid derivatives of type **IId** and **IIe** and have found that such substrates are readily isomerized to afford optically active enamines of type **IIId** and **IIIe** and, after hydrolysis, the aldehydes of type **IVd** and **IVe**, respectively [14]. The results of these investigations *(Scheme 2)* are summarized in *Tables 1* and *2*. All isomerizations were carried out according to *Otsuka*'s procedure (THF solution, 60–100°) [12] using as catalyst cationic Rh^I complexes of the type [Rh(BIPHEMP)(cod)]ClO_4 or [Rh(BIPHEMP)(nbd)]BF_4 [13] and, in a few cases in the racemic series, [Rh(dppe)(nbd)]PF_6 or [Rh(dppe)(cod)]PF_6[4]). The amount of catalyst used was in the range of 0.3–1.0 mol-%. The enamines **11** formed from the allylic amines **10** were usually hydrolyzed directly with aq. AcOH solution to afford the corresponding aldehydes **12** or **13**. Side-products (**14**, **18**, and **22**) were formed under certain conditions (see below). In some cases and for different purposes (see below), derivatives of the aldehydes were formed (**12**→**15**→**16**; **12**→**17**; **13e**→**19**→**20**; **13e,h**→**1**, **13i**→**21**; see *Scheme 2*), or the intermediate enamine was directly converted to the diol (**11f,g**→**21**; see *Scheme 2*).

Table 1. *Isomerization of 4-Benzyloxy-Substituted Butenylamines*[a])

Entry	Substrate	Catalyst	Conditions		Aldehyde **12**		
			S/C[b])	Temp. [°] (time [h])	Yield[c]) [%]	ee[d]) [%]	Configuration[e])
1	**10a**	[Rh((*RS*)-**9**)(cod)]ClO_4	100	90 (38)	46		*RS*
2	**10a**	[Rh((*R*)-**9**)(cod)]ClO_4	200	75 (64)	73	99	*R*
3	**10a**	[Rh((*R*)-**9**)(cod)]ClO_4	320	65 (137)	86	99	*R*
4	**10a**	[Rh((*R*)-**9**)(cod)]ClO_4	370	65 (120)[f])	77[f])	98.5	*R*
5	**10a**	[Rh((*S*)-**9**)(cod)]ClO_4	85	85 (59)	54	98.5	*S*
6	**10a**	[Rh((*S*)-**9**)(cod)]ClO_4	200	75 (63)	76	98.5	*S*
7	**10a**	[Rh((*S*)-**9**)(cod)]ClO_4	320	60 (93)[g])	77[g])	99	*S*
8	**10b**	[Rh((*R*)-**9**)(cod)]ClO_4	85	75 (115)	48	99	*R*
9	**10c**	[Rh((*R*)-**9**)(cod)]ClO_4	100	75 (64)	52	99	*R*
10	**10d**	[Rh((*R*)-**9**)(cod)]ClO_4	100	75 (64)	42	93	*R*

[a]) All isomerizations were carried out in THF in sealed tubes at the temperature indicated or in stoppered *Schlenk* tubes (at 60°); substrate concentrations 0.5–2.0 mol **10**/l.

[b]) Molar substrate (S)/catalyst (C) ratio.

[c]) Isolated yield of aldehyde **12** after hydrolysis (50% $AcOH/H_2O$) and bulb-to-bulb distillation; GC purities 96–99%.

[d]) Determined according to the method of *Valentine et al.* [17] by oxidation to acid **15**, conversion to amide derivative **16**, and diastereoisomer analysis (*cf. Scheme 2* and *Exper. Part*). The ee's indicated generally are mean values of GC and HPLC diastereoisomer analyses; the accuracy of the values is estimated to be ±0.5%.

[e]) Determined by optical-rotation determinations: (+)-(*R*)-**12**, $[\alpha]_D^{20} = +11.7$ to $+12.5$ ($c = 3.8$–5.0, $CHCl_3$); (−)-(*S*)-**12**, $[\alpha]_D^{20} = -12.0$ to -12.2 ($c = 3.8$–5.0, $CHCl_3$).

[f]) 93% conversion by GC; 83% yield based on converted material.

[g]) 86% conversion by GC; 90% yield based on converted material.

[4]) cod = (*Z,Z*)-1,5-Cyclooctadiene; nbd = 8,9,10-trinorbornadiene; dppe = 1,2-bis(diphenylphosphino)ethane (= (1,2-ethanediyl)bis(diphenylphosphine)).

Table 2. *Isomerization of Various 4-Substituted Butenylamines*[a])

Substrate	Catalyst	Conditions		Conversion[c])	Isolated product			
		S/C[b])	Temp. [°] (time [h])	[%]		Yield[d]) [%]	ee[e]) [%]	Configuration[e])
10e	[Rh(dppe)(nbd)]PF_6[f])	100	100 (25)	95	**13e**	55		*RS*
10e	[Rh((*R*)-**9**)(nbd)]BF_4	180	110 (24)	94	**13e**	60	94[g])	*R*
10e	[Rh((*S*)-**9**)(nbd)]BF_4	200	110 (40)	quant.	**13e**	64	92.5	*S*
10e	[Rh((*S*)-**9**)(cod)]ClO_4	200	90 (48)	quant.	**13e**	67	94.5	*S*
10f	[Rh((*R*)-**9**)(cod)]ClO_4	50	80 (48)	n.d.	**21**[h])	50	96[i])	*R*
10g	[Rh((*R*)-**9**)(cod)]ClO_4	65	80 (48)	64	**21**[h])	19	96[i])	*R*
10h	[Rh((*RS*)-**9**)(cod)]ClO_4	150	75 (64)	quant.	**13h**[j])	61		*RS*
	[Rh((*R*)-**9**)(cod)]ClO_4	100	75 (87)	quant.	**13h**[j])	30	70[g])	*R*
10i	[Rh(dppe)(nbd)]PF_6[f])	200	100 (16)	44	**13i**	23		*RS*
10i	[Rh((*S*)-**9**)(nbd)]BF_4	100	90 (40)	79	**13i**	34	> 90	*S*

[a]) *Cf. Footnote a)* in *Table 1.*
[b]) Molar substrate (S)/catalyst (C) ratio.
[c]) Conversion by GC analysis.
[d]) Isolated yield of aldehyde **13** (or of other indicated derivative) after distillation, based on substrate **10**.
[e]) See text and *Exper. Part* for details about ee determination and configuration.
[f]) dppe = 1,2-bis(diphenylphosphino)ethane[4]).
[g]) Optical purity of derived lactone (*R*)-**1**.
[h]) In this case, the enamine **11** was converted into diol (*R*)-**21** by treatment with $NaBH_3CN$ in acidic soln.
[i]) Optical purity of diol (*R*)-**21**.
[j]) The allyloxy group was isomerized, in this case, to a prop-1-enyloxy group ((*E*/*Z*) 4:1).

A number of features of these isomerizations are worth discussing: *a*) The isomerizations occur with very high *regioselectivity*, *i.e.* only isomerization towards the allylic amino function at the tail end of the isoprene skeleton to afford an enamine is observed. The presence of the second allylic functionality (the O-substituent at the C(4) head end) apparently does not interfere and, in fact, we have found no indication of the formation of enol ethers in the isomerizations of the substrates of type **10**. However, when the dialkylamino function is replaced by an imido or an amido function, the mode of isomerization may change and isomerization towards the head end, *i.e.* towards the O-function can indeed occur. Thus, *e.g.*, isomerization (0.5% [Rh((*RS*)-**9**)(nbd)]BF_4, 110°) of the phthalimido substrate **23** proceeded exclusively towards the *t*-BuO group to produce the enol ether **24** ((*E*/*Z*) 85:15) in 94% yield *(Scheme 2)*. Similarly, treatment of the acetamido substrate **25** with 1% of [Rh((*RS*)-**9**)(cod)]ClO_4 at 90° afforded an 81% yield of pyrroline **26** *(Scheme 2)*, presumably *via* intermediate formation of an enol ether followed by cyclization and elimination of *t*-BuOH. It is interesting to note, that a 'reversed' type of substrate, the amine derivative **34** (see below, *Scheme 4*), containing a diethylamino function at the head end and a *t*-BuO function at the tail end proved to be completely inert under isomerization conditions at temperatures of up to 110°. Evidently, not only electronic but also steric effects are responsible for these differences in reactivity[5]).

[5]) Simple non-functionalized *N*-allylimides and -amides mostly undergo isomerization towards the N-atom (affording enimides or enamides) when treated with Rh, Ru, or Fe catalysts [15]. An exception is *N*-(3,3-dimethylallyl)phthalimide which affords *N*-(3-methylbut-3-enyl)phthalimide upon treatment with $Fe(CO)_5$ [15].

b) The *structural variation* of the O-functionality at C(4) revealed that a variety of protected oxy groups at C(4) are tolerated in the isomerization. Among them are the benzyloxy (BnO; substrates **10a–d**, *Table 1*), *t*-BuO (**10e**, *Table 2*), Me_3SiO (**10f**), $MeOCH_2O$ (**10g**), and the allyloxy group (**10h**). The last group was completely converted into a prop-1-enyloxy group under the isomerization conditions, and the reaction product, therefore, was the enol ether/enamine **11h** or its hydrolysis product, the enol-ether/aldehyde **13h** ((*E*/*Z*) *ca.* 4:1 for the enol-ether double bond; *Scheme 2*)[6]. An acetal moiety at C(4) such as that present in substrate **10i** *(Scheme 2)* is also well tolerated in the isomerization. Unsuitable C(4) functional groups proved to be the AcO group and the non-protected OH group; the acetylated derivative of amino alcohol **29a** (see below, *Scheme 3*) was inert under the isomerization conditions at temperatures of up to 110°, while the amino alcohol **29a** itself led to a multitude of products.

c) The *chemoselectivity* of the reactions is temperature dependent. At temperatures higher than those quoted in *Tables 1* and *2*, the yields of enamines (or of the derived aldehydes, respectively) were substantially reduced by side-reactions such as the formation of saturated amines (*e.g.* **14**, **18**, and **22**; *cf. Scheme 2*) and the formation of non-distillable, high-molecular-weight products. Presumably, the saturated amines are formed *via* transfer hydrogenation processes. It has not been investigated, whether, and if so to what degree, asymmetric induction took place in the formation of these saturated amines. Fortunately, lowering of the reaction temperatures led to a significant decrease of these side-reactions as shown in the case of the BnO derivative **10a** (13% of saturated amine **14** at 90°, 5% at 75°, 0% at 65°), while at the same time the yield of aldehyde **12** increased from 46 to 73 to 86%, respectively *(cf. Table 1)*.

d) The nature of the C(4) substituent has some but not a very pronounced effect on the *rate* of the isomerizations. Thus, the reaction temperatures required for the isomerization were in the range of 60 to 80° for all substrates with the exception of the *t*-BuO derivative **10e** which required a higher temperature (90–100°), presumably for steric reasons. Generally, the rates of isomerization of the bifunctional substrates of type **10** appeared to be lower than those of substrates of type **IIa**. The observation of *Otsuka* and coworkers [12] that rates of isomerizations are faster for cod than for nbd complexes holds true also for the bifunctional type of substrates (see *e.g.* isomerizations of **10e**, *Table 2*).

e) The *enantioselectivity* of the isomerizations is generally high, and asymmetric inductions of > 90% ee were observed for all substrates with one exception only. The highest asymmetric inductions of 98–99% ee were achieved with the BnO derivative **10a**. The dependence of the degree of asymmetric induction on the nature of the oxy substituent at C(4) is as follows: **10a** (BnO, 98–99% ee) > **10f** (Me_3SiO, 96% op) > **10e** (*t*-BuO, 94% ee) ≈ **10g** ($MeOCH_2O$, 94% op) > **10i** ($(MeO)_2$, > 90% ee) > **10h** (CH_2=$CHCH_2O$, *ca.* 70% op). Unfortunately, direct comparison of these values is limited by the different methods of analysis that had to be employed. Only the ee values for the isomerizations of the BnO and *t*-BuO derivatives **10a–d** and **10e**, respectively, were derived by highly accurate GC and HPLC diastereoisomer analyses. In these cases, the product aldehydes **12** and **13e** were converted, by analogy to the method developed by *Valentine et al.* [17] for the ee determination of citronellals (**IVa**, *Scheme 1*), to the amide

[6]) For transition-metal catalyzed isomerizations of allyl to prop-1-enyl ethers, see *e.g.* [12e] [16]. In most cases, the products are mixtures of (*E*)- and (*Z*)-enol ethers.

derivatives **16** and **20**, respectively, by Ag_2O or *Jones* oxidation (→**15** and **19**, resp.) followed by amide formation [18] with (*R*)-α-methyl-4-nitrobenzylamine *(cf. Scheme 2)*. The diastereoisomeric composition of these amide derivatives could readily be determined by either GC or HPLC analysis with an estimated accuracy of ±0.25% (±0.5% ee). In the isomerizations of the other substrates, either optical-rotation measurements (**10f**, **10g**, and **10h**) or ^{1}H-NMR analysis in the presence of a chiral shift reagent (**10i**) have been used for the determination of inductions (see *Exper. Part* for details). Therefore, these values of asymmetric inductions are of lower accuracy. The relatively low induction of only *ca.* 70% in the case of the allyloxy derivative **10h** was calculated based on the optical purity of lactone (*R*)-**1** obtained by *Jones* oxidation of aldehyde **13h**. This value, however, is somewhat uncertain, since (*R*)-**1** was obtained only in low yield and in a chemically impure state. The asymmetric induction shows little dependence on the nature of the dialkylamino substituent, as is demonstrated in the series of the BnO derivatives **10a–d** (*Table 1, Entries 2, 8, 9,* and *10*). The Et_2N, the Bu_2N, and the piperidino derivatives all led to 98–99% ee, the morpholino derivative **10d**, though, to a slightly reduced induction of 93% ee.

f) The assignments of *absolute configurations* were carried out by chemical correlations with known compounds *(cf. Scheme 2)*: (*S*)-**12**→(*S*)-**17** [5a] ($NaBH_4$, MeOH); (*R*)-**13e**→(*R*)-**1** [1] [9] (*Jones* oxidation, then TsOH, C_6H_6, Δ); (*R*)-**11f**→(*R*)-**21** [1] ($NaBH_3CN$, aq. AcOH); (*R*)-**11g**→(*R*)-**21** [1] ($NaBH_3CN$, aq. AcOH; then 2N HCl); (*R*)-**13h**→(*R*)-**1** [1] [9] (*Jones* oxidation); (*S*)-**13i**→(*S*)-**21** [1] ($NaBH_4$, MeOH; then 85% HCO_2H; then $NaBH_3CN$, pH 4). The direction of asymmetric induction with regard to substrate geometry ((*E*)-configuration) and ligand and product configurations is the same as for the isomerization of *N,N*-diethylgeranylamine with the BINAP or BIPHEMP ligands [12] [13].

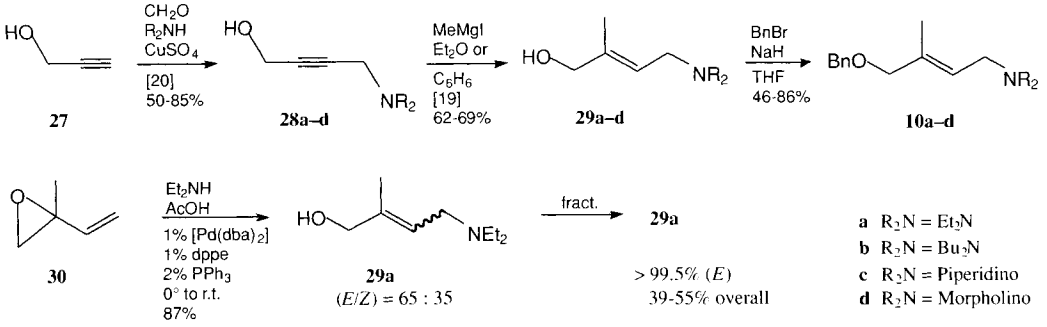
g) Preparatively by far the most useful example is the conversion of the BnO derivative **10a** *via* the enamine **11a** to its hydrolysis product, the aldehyde **12**. This conversion affords the highest inductions (98–99% ee) and highest chemical yields (up to 86%). Moreover, the isomerization substrate is readily available (see below). This isomerization has been conducted on a scale of 50–100 g using substrate/catalyst ratios of up to 1000:1, and asymmetric inductions of consistently 98.5–99% ee and chemical yields of 85–94% have been achieved[7]).

3. Synthesis of the Isomerization Substrates. – Since *Otsuka* and coworkers [12] have shown that the isomerizations of geometrical isomers of allylic amines of type **IIa** (*e.g.* of *N,N*-diethylgeranyl- and *N,N*-diethylnerylamine) proceed with strictly opposite asymmetric inductions and at virtually equal rates [12c], the configurational integrity ((*E*) or (*Z*)) of the allylamine isomerization substrates is an indispensable prerequisite to achieve high enantiomeric excesses. Consequently, either highly stereoselective methods for the construction of the trisubstituted double bond in the bifunctional substrates **10** or efficient separations of (*E*/*Z*)-isomer mixtures of such substrates were required, and special attention had to be given to the analysis of diastereoisomeric (geometrical) purities.

The *Grignard*-addition method of *Mornet* and *Gouin* [19] was broadly used for the synthesis of the unsaturated amino alcohols **29a–d** *(Scheme 3)*, since the starting materi-

[7]) We thank Drs. *E. Broger* and *Y. Crameri* at our department for carrying out these scale-up experiments.

Scheme 3



als, the aminobutynols **28**, can readily be obtained by a *Mannich* reaction of propargyl alcohol (**27**) [20], and since the addition of MeMgI to the triple bond proceeds with very high regio- and stereoselectivity (> 95% (*E*) by NMR as stated by *Mornet* and *Gouin* [19a]). In fact, we have determined by GC analysis that less than 0.5% of (*Z*)-isomer (if any) was formed in the methyl *Grignard* addition **28a**→**29a**. Independently, we have also shown that in the case of the addition of MeMgI to 4-(dimethylamino)but-2-yn-1-ol, only 0.6% of the (*Z*)-isomer was produced[8]).

In spite of its advantage with regard to selectivity, the *Grignard*-addition method is not very practical for larger-scale syntheses of amino alcohols **29**, because an excess (2–3 mol-equiv.) of *Grignard* reagent needs to be employed. For scale-up work, we developed a novel, non-stereoselective route to the key amino alcohol **29a**, which relies on a Pd-catalyzed ring-opening amination of isoprene epoxide (**30**→(*E*/*Z*)-**29a**; *Scheme 3*)[9]). Special reaction conditions are required in order to achieve good chemoselectivity in this amination reaction. The use of 1 mol-equiv. of AcOH in the presence of a several-fold excess of Et_2NH and the use of the chelating diphosphine dppe[4]) for the Pd-catalyst system[10]) is crucial for the success of this reaction. Under optimum conditions, yields of up to 87% of a 65:35 (*E*/*Z*)-mixture of amino alcohol **29a** were obtained. Subsequent fractionation of the (*E*/*Z*)-mixture allowed to separate the lower-boiling (*Z*)- from the higher-boiling (*E*)-isomer which eventually was obtained in 39–55% yield and with a geometrical purity of > 99.5% ((*E*)). The benzylation of amino alcohols **29a–d** as well as the formation of other derivatives of **29a** were performed according to standard procedures (see *Exper. Part*).

The *t*-BuO derivative **10e** was synthesized *via* the so-called 'abnormal' addition of *tert*-butyl hypochlorite to isoprene [23] to afford a 4:1 mixture of the two 1,4-addition products **32** and **33** (*Scheme 4*). Subsequent treatment with Et_2NH and chromatographic separation yielded 61% of the desired amine **10e** and 17% of amine **34**. The geometrical

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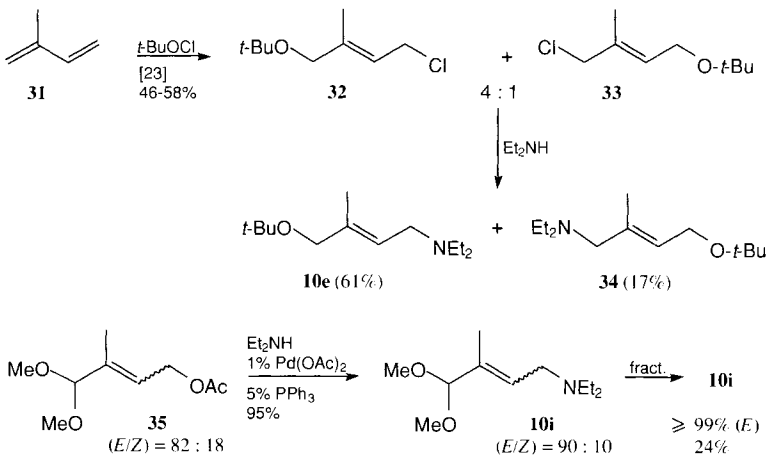
[8]) For reference, the (*Z*)-isomer was synthesized according to [21] by *Wittig* reaction of 2-acetoxyacetone (= 2-oxopropyl acetate) with [2-(dimethylamino)ethyl]triphenylphosphonium bromide.

[9]) Pd-catalyzed reactions of vinyl epoxides with C- and N-nucleophiles have been reported [22], but for isoprene epoxide (**30**), only reactions with C-nucleophiles have been investigated so far [22a].

[10]) 'Normal' conditions used for the amination of 2-vinyloxiranes ([$Pd(PPh_3)_4$]/Et_2NH; [$Pd(dba)_2$]/PPh_3/Et_2NH) [22] (dba = dibenzylideneacetone) afforded highly complex reaction mixtures and only low yields of **29a**. The role of AcOH, respectively of $Et_2NH_2(OAc)$ formed in the mixture, remains unclear at present.

Scheme 4



purity of **10e** was at least 98% (*E*) since the material obtained contained only two trace components in 1.5 and 2% by GC analysis. According to a GC/MS analysis, both these trace components were isomers of **10e**, but it could be neither proved nor excluded that one of them corresponded to the (*Z*)-isomer of **10e**. If this were the case then the 'true' enantiomeric excess in the isomerization of **10e** might have been higher by some 3–4% than the observed 94.5% ee.

The remaining dimethoxy-amine **10i** was synthesized *via* a Pd-catalyzed amination of allylic acetate **35** *(Scheme 4)*. This amination occurred with good but not sufficiently high *trans*-stereoselectivity, and a distillative fractionation was again required to obtain **10i** of ≥ 99% (*E*)-content by GC analysis.

4. Concluding Remarks. – The investigations presented in this paper show that the asymmetric allylamine to enamine isomerization methodology [12] can be readily applied to bifunctional C_5-isoprenoid substrates which contain an allylic dialkylamino function at the tail end and an allylic O-function at the head end. The allylic O-function causes no problems with regard to the regioselectivity of the isomerization but may contribute to a somewhat lower rate and lower chemoselectivity of the isomerization in comparison to simple allylic amines. Structural variation of the protected 4-oxy substituents is tolerated in the isomerization. Asymmetric inductions with cationic [Rh^I(BIPHEMP)] complexes are generally above 90% ee. By far the most favorable example is the isomerization of the BnO derivative **10a** because it affords the highest induction (98–99% ee) and the highest chemical yield (*ca.* 90%). The isomerization substrate **10a** and its precursor amino alcohol **29a** are readily available by the newly developed Pd-catalyzed amination of isoprene epoxide (**30**). Thus, the bifunctional C_5^*-aldehyde **12** is now readily accessible in both configurations in very high enantiomeric purity in only 3 steps starting from isoprene epoxide and can be considered to be a synthetically useful C_5^*-building block for isoprenoid homologation. An application of the isoprenoid C_5^*-building blocks **12** for the synthesis of all four optical isomers of *trans*-vitamin K_1 is presented in the following paper in this issue [24].

We would like to thank Dr. *M. Schmid* and Dr. *R. Barner* for helpful discussions. We also wish to thank our colleagues from the Central Research Units, *F. Hoffmann-La Roche AG*, for IR spectra (Mr. *A. Bubendorf*), NMR spectra (Dr. *G. Englert*, Dr. *W. Arnold*, Mr. *Y. Mercadal*), MS (Dr. *W. Vetter*, Mr. *W. Meister*), elemental analyses (Dr. *A. Dirscherl*†), optical-rotation measurements (Dr. *K. Noack*, Mrs. *J. Kohler*), and for GC and HPLC analyses (Dr. *M. Vecchi*†, Dr. *R. Maurer*, Mr. *W. Walter*, Mr. *E. Glinz*).

Experimental Part

The excellent experimental assistance of Mr. *Alfred Grieder* is gratefully acknowledged.

General. Cf. [13]. The syntheses of the cationic Rh^I complexes [Rh((*RS*-, *R*-, or *S*)-**9**)(cod)]ClO_4 and [Rh((*RS*-, *R*-, or *S*)-**9**)(nbd)]BF_4 were carried out as described in [13]. [Rh(dppe)(nbd)]PF_6 and [Rh(dppe)(cod)]PF_6 were purchased from *Strem Chemicals*. Anal. GC (substrates and reaction mixtures): *Carbowax 20 M* capillary column (50 m × 0.34 mm), carrier gas N_2; peaks are quoted with area-% with respect to the total of all peaks (= 100%); for mixtures, the components are listed in the order of increasing retention times. ^{1}H-NMR spectra: $CDCl_3$ solns. IR spectra: neat, unless otherwise noted.

1. Isomerization Substrates. – 1.1. *(E)-4-(Dialkylamino)-2-methylbut-2-en-1-ols* (**29a–d**). The amino alcohols **29a–d** were synthesized according to [19] by addition of MeMgI to the corresponding *4-(dialkylamino)but-2-yn-1-ols* (**28a–d**) which in turn were prepared by the procedure [20].

(E)-4-(Diethylamino)-2-methylbut-2-en-1-ol (**29a**). To a soln. of 1.40 mol of MeMgI in 1.2 l of Et_2O were added, at r.t. within 45 min, 56.4 g (0.40 mol) of **28a** [20]. The resulting suspension was heated under reflux for 8 h and then poured onto 37% HCl soln. (450 ml) and ice. The aq. phase was washed 3 times with Et_2O and made alkaline by addition of 50% NaOH soln., the resulting suspension extracted exhaustively with Et_2O in an apparatus arranged for continuous extraction, the extract dried (Na_2SO_4), filtered, and evaporated, and the residue distilled (10-cm *Vigreux* column): 46.7 g (72%) of **29a**. Colourless liquid. B.p. 45–57°/0.03 mbar. GC: purity 97%, containing 2% of **28a**. In larger-scale reactions, a simplified, non acidic workup procedure was applied, which consisted of hydrolysis of the reaction mixture with 50% NaOH soln., separation of the Et_2O phase from the aq. suspension by decantation and repeated extraction of the aq. suspension with Et_2O; yield after distillation, 84% of **29a**. IR: 3370 (br., OH); 2822 (N-alkyl); 1676 (C=C); 1383 (CH_3); 1069, 1020 (OH). ^{1}H-NMR (90 MHz): 5.5 (*t* with fine struct., J = 7, H–C(3)); 4.0 (*s*, CH_2(1)); 3.1 (br. *d*, J = 7, CH_2(4)); 2.5 (br. *s*, *q*, J = 7, OH, $(CH_3CH_2)_2N$); 1.7 (br. *s*, CH_3–C(2)); 1.05 (*t*, J = 7, $(CH_3CH_2)_2N$). MS: 157 (14, $M^{+\cdot}$), 142 (12), 126 (12), 86 (35), 73 (18), 58 (100).

(E)-4-(Dibutylamino)-2-methylbut-2-en-1-ol (**29b**). As described in [19c]. Yield 62%. B.p. 78–80°/0.05 mbar. GC: purity 92%.

(E)-4-Piperidino-2-methylbut-2-en-1-ol (**29c**). From **28c** [20] as described above for **29a**. Colourless liquid. Yield 60%. B.p. 76–78°/0.01 mbar. GC: purity 96%. IR: 3370, 3260 (br., OH); 2803 (N-alkyl); 1675 (C=C); 1368 (CH_3); 1022 (OH). ^{1}H-NMR (60 MHz): 5.55 (*t* with fine struct., J = 7, H–C(3)); 4.0 (*s*, CH_2(1)); 3.0 (br. *s*, OH); 2.95 (*d*, J = 7, CH_2(4)); 2.35 (*m*, CH_2NCH_2); 1.68 (br. *s*, CH_3–C(2)); 1.5 (*m*, 3 CH_2). MS: 169 (14, $M^{+\cdot}$), 168 (3), 152 (11), 138 (23), 136 (27), 110 (23), 98 (57), 85 (66), 84 (100). Anal. calc. for $C_{10}H_{19}NO$ (169.27): C 70.96, H 11.31, N 8.28; found: C 70.63, H 11.21, N 8.28.

(E)-4-Morpholino-2-methylbut-2-en-1-ol (**29d**). From **28d** [20] as described above for **29a** but with benzene as solvent instead of Et_2O (*cf.* [19c]). Colourless liquid. Yield 69%. B.p. 92–95°/0.01 mbar. GC: purity 96%. IR: 3400 (br., OH); 2816 (N-alkyl); 1678 (C=C); 1117 (C–O–C); 1070, 1001 (OH). ^{1}H-NMR (60 MHz): 5.55 (*t* with fine struct., J = 7, H–C(3)); 4.0 (*s*, CH_2(1)); 3.7 (*m*, CH_2OCH_2); 3.35 (br. *s*, OH); 3.05 (*d*, J = 7, CH_2(4)); 2.45 (*m*, CH_2NCH_2); 1.68 (br. *s*, CH_3–C(2)). MS: 171 (20, $M^{+\cdot}$), 170 (8), 154 (12), 140 (21), 124 (48), 100 (25), 87 (100). Anal. calc. for $C_9H_{17}NO_2$ (171.24): C 63.13, H 10.01, N 8.18; found: C 63.09, H 9.88, N 8.17.

1.2. *(E)-4-(Diethylamino)-2-methylbut-2-en-1-ol* (**29a**) via *Pd-Catalyzed Amination of Isoprene Epoxide* (**30**). To a soln. of 690 mg (0.12 mmol) of bis(dibenzylidenacetone)palladium, 628 mg (0.24 mmol) of Ph_3P and 478 mg (0.12 mmol) of dppe[4]) in 90 ml (0.866 mol) of Et_2NH were added at 0–10° 7 ml (0.12 mol) of AcOH and then, within 1 h, 10.0 g (0.12 mol) of *3,4-epoxy-2-methylbut-1-ene* (= 'isoprene epoxide'; **30**). The mixture was allowed to attain r.t. and stirred for 20 h. After dilution with 300 ml of Et_2O and addition of 3 ml of sat. K_2CO_3 soln., the mixture was thoroughly stirred, then dried (K_2CO_3 and Na_2SO_4), filtered, and evaporated. The residue (GC: **29a**, (*Z*/*E*) 23:77) was distilled through a 5-cm *Vigreux* column: 16.4 g (87%) of **29a** ((*Z*/*E*) 34:66). This material was fractionated on a 'Spaltrohr' column (*Fischer MMS 202*; bath temp. 140–150°/15 mbar) until the amount of the lower-boiling (*Z*)-isomer dropped below 0.5% in the distillation flask. Simple distillation of the residue then

afforded 7.3 g (39%) of **29a** ((*E*)) as colourless liquid. B.p. 120°/15 mbar. GC: purity 99%, containing $\leqslant$ 0.5% of (*Z*)-isomer. In a similar experiment, starting from 50.0 g (0.60 mol) of **30**, the crude material was distilled through a 25-cm *Vigreux* column to afford 70.0 g of impure **29a** ((*Z*/*E*) 57:43), b.p. 65–70°/0.01 mbar, and 25 g of pure **29a** ($\geqslant$ 99% (*E*)), b.p. 70°/0.01 mbar. Redistillation of the first fraction afforded an additional 27 g of pure **29a** ($\geqslant$ 99% (*E*)), b.p. 70–72°/0.01 mbar. Combined yield of **29a** ($\geqslant$ 99% (*E*)): 52 g (55%).

1.3. *Benzyloxy Derivatives* **10a–d**. *(E)-4-(Benzyloxy)*-N,N-*diethyl-3-methylbut-2-enylamine* (**10a**). To a suspension of 25.9 g (0.594 mol) of 55% NaH dispersion in mineral oil in 450 ml of THF was added, within 30 min at 60–65°, a soln. of 77.4 g (0.495 mol) of **29a** in 50 ml of THF. The mixture was heated under reflux until the H_2 evolution ceased (1 h). Then, at *ca.* 0–5°, 93.5 g (0.547 mol) of benzyl bromide were added dropwise, and the mixture was stirred overnight at r.t. The excess of NaH was destroyed by the addition of some ice cubes, then 200 ml of 25% HCl soln. were added. Neutral material was removed by washing twice with Et_2O. The aq. phase was cooled to 0° and made alkaline by the addition of 50% NaOH soln. Usual workup with Et_2O afforded 114.7 g of a yellow oil. This material was combined with 100.9 g of crude product obtained in an analogous experiment from 70.8 g (0.450 mol) of **29a**. Distillation through a 15-cm *Vigreux* column afforded 174.55 g (70.5%) of **10a** as a pale yellow oil, b.p. 91–98°/0.01 mbar (GC: purity 97%) and, from a forerun, 10.76 g (4.5%) of **10a** of 93% GC purity. IR: 2812 (N-alkyl); 1674 (C=C); 1605, 1586, 1496 (Ar); 1382, 1354 (CH_3); 1091, 1071 (C–O–C); 735, 697 (monosubst. benzene). ^{1}H-NMR (80 MHz): 7.35 (br. *s*, 5 arom. H); 5.6 (*t* with fine struct., J = 7, H–C(2)); 4.45 (*s*, Ph CH_2); 3.95 (*s*, CH_2(4)); 3.15 (br. *d*, J = 7, CH_2(1)); 2.55 (*q*, $(CH_3CH_2)_2$N); 1.7 (br. *s*, CH_3–C(3)); 1.05 (*t*, J = 7, $(CH_3CH_2)_2$N). MS: 172 (63, M^+), 171 (18), 157 (20), 129 (53), 128 (31), 126 (57), 124 (37), 91 (100). Anal. calc. for $C_{16}H_{25}NO$ (247.38): C 77.68, H 10.19, N 5.66; found: C 77.92, H 10.29, N 5.72.

(E)-4-(Benzyloxy)-N,N-*dibutyl-3-methylbut-2-enylamine* (**10b**) was prepared analogously from **29b**. After bulb-to-bulb distillation at *ca.* 150°/0.01 mbar, 46% yield. GC: purity 88.5%, containing 4% of **29b**. IR: 2804 (N-alkyl); 1675 (C=C); 1605, 1586, 1496 (Ar); 1092, 1070 (C–O–C); 734, 696 (monosubst. benzene). ^{1}H-NMR (60 MHz): 7.3 (br. *s*, 5 arom. H); 5.5 (*t* with fine struct., J = 7, H–C(2)); 4.45 (*s*, PhCH_2); 3.95 (*s*, CH_2(4)); 3.15 (br. *d*, J = 7, CH_2(1)); 2.4 (*m*, $[CH_3(CH_2)_2CH_2]_2$N); 1.7 (br. *s*, CH_3–C(3)); 1.6–0.7 (*m*, $[CH_3(CH_2)_2CH_2]_2$N). MS: 303 (1, M^+), 260 (18, $M - C_3H_7]^+$), 172 (16), 129 (13), 91 (100). Anal. calc. for $C_{20}H_{33}NO$ (303.49): C 79.15, H 10.96, N 4.62; found: C 79.53, H 11.02, N 4.93.

1-[(E)-4-(Benzyloxy)-3-methylbut-2-enyl]piperidine (**10c**) was prepared analogously from **29c**. After bulb-to-bulb distillation at *ca.* 140°/0.01 mbar, 84% yield. GC: purity 94%. IR: 2800, 2756 (N-alkyl); 1677 (C=C); 1605, 1586, 1496 (Ar); 1116, 1092, 1071 (C–O–C); 735, 697 (monosubst. benzene). ^{1}H-NMR (60 MHz): 7.3 (br. *s*, 5 arom. H); 5.6 (*t* with fine struct., J = 7, H–C(2′)); 4.45 (*s*, PhCH_2); 3.95 (*s*, CH_2(4′)); 3.0 (br. *d*, J = 7, CH_2(1′)); 2.4 (*m*, CH_2(2), CH_2(6)); 1.7 (br. *s*, CH_3–C(3′)); 1.7–1.2 (*m*, CH_2(3), CH_2(4), CH_2(5)). MS: 259 (8, M^+), 258 (5), 152 (35), 138 (23), 110 (10), 98 (35), 91 (100). Anal. calc. for $C_{17}H_{25}NO$ (259.39): C 78.82, H 9.71, N 5.40; found: C 78.72, H 9.76, N 5.68.

4-[(E)-4-(Benzyloxy)-3-methylbut-2-enyl]morpholine (**10d**) was prepared similarly from **29d**. After bulb-to-bulb distillation at *ca.* 130°/0.01 mbar, 86% yield. GC: purity 98.5%. IR: 2811 (N-alkyl); 1677 (C=C); 1604, 1585, 1496 (Ar); 1118, 1093, 1070 (C–O–C); 737, 698 (monosubst. benzene). ^{1}H-NMR (80 MHz): 7.35 (br. *s*, 5 arom. H); 5.65 (*t* with fine struct., J = 7, H–C(2′)); 4.5 (*s*, PhCH_2); 3.95 (*s*, CH_2(4′)); 3.75 (*m*, CH_2(2), CH_2(6)); 3.05 (br. *d*, J = 7, CH_2(1′)); 2.45 (*m*, CH_2(3), CH_2(5)); 1.7 (br. *s*, CH_3–C(3′)). MS: (16, M^+), 154 (29, $[M - PhCH_2O]^+$), 140 (78, $[M - PhCH_2OCH_2]^+$), 124 (34), 100 (15), 91 (100). Anal. calc. for $C_{16}H_{23}NO_2$ (261.37): C 73.53, H 8.87, N 5.36; found: C 73.57, H 9.08, N 5.56.

1.4. tert-*Butoxy Derivatives* **10e** *and* **34**. A 75:25 mixture of *(E)-1-(*tert-*butoxy)-4-chloro-2-methylbut-2-ene* (**32**) and *(E)-4-(*tert-*butoxy)-1-chloro-2-methylbut-2-ene* (**33**) was obtained by addition of *tert*-butyl hypochlorite to isoprene according to [23] ('abnormal addition' in the absence of a solvent). Yield 57%. At r.t., 27.1 g (0.1 mol) of **32**/**33** were added within 10 min to 70 ml of Et_2NH and stirred for 15 h. The resulting yellow suspension was treated with 400 ml of sat. NaCl soln. and Et_2O. The org. phase was separated and extracted with 15% HCl soln. (5 × 100 ml). The combined aq. phases were washed with Et_2O, made alkaline by the addition of 50% NaOH soln. and extracted with Et_2O (3 × 100 ml). The org. extracts were further processed as usual to afford 25.0 g of a pale yellow oil. GC: 20% of **34** and 77% of **10e**. Chromatographic separation on silica gel (800 g, Et_2O/Et_2NH 98:2) followed by bulb-to-bulb distillation at *ca.* 80°/0.05 mbar afforded 3.6 g (17%) of **34** and 13.0 g (61%) of **10e**.

*(E)-4-(*tert-*Butoxy)*-N,N-*diethyl-3-methylbut-2-enylamine* (**10e**): Colourless oil. GC: 1.9% unknown, 96.5% **10e**, 1.6% unknown. IR: 2806 (N-alkyl); 1676 (C=C); 1367, 1361 (CH_3); 1061 (C–O–C). ^{1}H-NMR (60 MHz): 5.55 (*t* with fine struct., J = 7, H–C(2)); 3.8 (*s*, CH_2(4)); 3.1 (br. *d*, J = 7, CH_2(1)); 2.5 (*q*, J = 7, $(CH_3CH_2)_2$N); 1.65 (br. *s*, CH_3–C(3)); 1.2 (*s*, *t*-BuO); 1.0 (*t*, J = 7, $(CH_3CH_2)_2$N). MS: 213 (11, M^+), 198 (9, $[M - CH_3]^+$), 140 (36, $[M - t\text{-BuO}]^+$), 126 (100). Anal. calc. for $C_{13}H_{27}NO$ (213.37): C 73.18, H 12.76, N 6.56; found: C 73.29, H 12.90, N 6.89.

*(E)-4-(*tert*-Butoxy)*-N,N-*diethyl-2-methylbut-2-enylamine* (**34**): IR: 2798 (N-alkyl); 1676 (C=C); 1387, 1361 (CH_3); 1057 (C–O–C). ^{1}H-NMR (60 MHz): 5.5 (*t* with fine struct., J = 7, H–C(3)); 4.0 (br. *d*, J = 6.5, CH_2(4)); 2.9 (br. *s*, CH_2(1)); 2.45 (*q*, J = 7, $(CH_3CH_2)_2N$); 1.7 (br. *s*, CH_3–C(2)); 1.2 (*s*, *t*-BuO); 1.0 (*t*, J = 7, $(CH_3CH_2)_2N$). MS: 213 (4, M^+), 198 (20, $[M - CH_3]^+$), 140 (18, $[M - t\text{-BuO}]^+$), 126 (15), 86 (100).

1.5. *(E)-*N,N-*Diethyl-3-methyl-4-(trimethylsilyloxy)but-2-enylamine* (**10f**). A mixture of 7.85 g (50 mmol) of **29a**, 16.1 g (100 mmol) of hexamethyldisilazane, and 2 drops of Me_3SiCl was heated under reflux for 5 h. The excess of reagent was removed by distillation at aspirator pressure through a 5-cm *Vigreux* column, and the residue was dissovled in pentane and filtered through a short column of Al_2O_3 (Alox alkaline, act. I). Fractional distillation of the obtained yellow liquid (8.6 g) through a 7-cm *Vigreux* column afforded 2.90 g (25%) of **10f** of 90% GC purity and, as main fraction, 4.60 g (40%) of **10f** of 96% GC purity. B.p. 102–104°/12 mbar. IR: 2807 (N-alkyl); 1677 (C=C); 1383, 1370 (CH_3); 1251, 1069, 877, 841, 749 (Me_3SiO). ^{1}H-NMR (60 MHz): 5.55 (*t* with fine struct., J = 7, H–C(2)); 4.0 (*s*, CH_2(4)); 3.1 (br. *d*, J = 7, CH_2(1)); 2.5 (*q*, J = 7, $(CH_3CH_2)_2N$); 1.65 (br. *s*, CH_3–C(3)); 1.0 (*t*, J = 7, $(CH_3CH_2)_2N$); 0.15 (*s*, Me_3SiO). MS: 229 (15, M^+), 214 (23, $[M - CH_3]^+$), 157 (41, $[M - Et_2N]^+$), 126 (97), 73 (100). Anal. calc. for $C_{12}H_{27}NOSi$ (229.44): C 62.82, H 11.86, N 6.10; found: C 62.76, H 11.84, N 6.38.

1.6. *(E)-*N,N-*Diethyl-4-(methoxymethoxy)-3-methylbut-2-enylamine* (**10g**). Under Ar, 3.25 g (77 mmol) of 55% NaH dispersion in mineral oil were washed with pentane (threefold addition/decantation). Then, 75 ml of THF and 7.85 g (50 mmol) of **29a** were added and stirred at 60° until the H_2 evolution ceased (1 h). At *ca.* 0–5°, 6.26 g (70 mmol) of chloromethyl methyl ether were added, and the mixture was stirred at r.t. for 15 h, then quenched with 10 ml of 2N NaOH. Usual workup with Et_2O followed by bulb-to-bulb distillation at *ca.* 130°/12 mbar afforded 3.60 g (32%) of **10g**. Colourless oil. GC: purity 91%. IR: 2820 (N-alkyl, CH_3O); 1675 (C=C); 1383 (CH_3); 1157, 1102, 1049 (C–O–C). ^{1}H-NMR (60 MHz): 5.6 (*t* with fine struct., J = 7, H–C(2)); 4.65 (*s*, OCH_2O); 4.0 (*s*, CH_2(4)); 3.6 (*s*, CH_3O); 3.15 (br. *d*, J = 7, CH_2(1)); 2.55 (*q*, J = 7, $(CH_3CH_2)_2N$); 1.7 (br. *d*, CH_3–C(3)); 1.05 (*t*, J = 7, $(CH_3CH_2)_2N$). MS: 201 (9, M^+), 186 (14, $[M - CH_3]^+$), 154 (17), 140 (24, $[M - MeOCH_2O]^+$), 126 (35), 124 (16), 86 (21), 73 (16), 72 (21), 58 (55), 45 (100). Anal. calc. for $C_{11}H_{23}NO_2$ (201.31): C 65.63, H 11.52, N 6.96; found: C 64.45, H 11.60, N 7.10, H_2O 1.41.

1.7. *(E)-*N,N-*Diethyl-3-methyl-4-[(prop-2-enyl)oxy]but-2-enylamine* (**10h**). A mixture of 1.31 g (30 mmol) of 55% NaH dispersion in mineral oil, 3.14 g (20 mmol) of **29a** and 30 ml of THF was heated under reflux until the H_2 evolution ceased (1 h). Then, at −20°, 1.68 g (22 mmol) of allyl chloride were added and stirred at r.t. for 120 h. The resulting yellow suspension was treated with ice/H_2O and worked up as usual with Et_2O. Bulb-to-bulb distillation at *ca.* 120°/12 mbar afforded 2.80 g (71%) of **10h**. GC: still *ca.* 4% of **29a**. Further purification by chromatography on Al_2O_3 (Alox alkaline, act. III, hexane/Et_2O) followed by bulb-to-bulb distillation afforded 1.50 g (38%) of **10h**. GC: purity 96.5%. IR: 2810 (N-alkyl); 1677 (C=C); 1647 (CH=CH_2); 1083 (C–O–C); 989, 921 (CH=CH_2). ^{1}H-NMR (60 MHz): 6.3–5.0 (*m*, 4 olef. H); 4.05–3.85 (*m*, CH_2OCH_2); 3.15 (br. *d*, J = 7, CH_2(1)); 2.55 (*q*, J = 7, $(CH_3CH_2)_2N$); 1.7 (br. *s*, CH_3–C(3)); 1.05 (*t*, J = 7, $(CH_3CH_2)_2N$). MS: 197 (6, M^+), 182 (19, $[M - CH_3]^+$), 140 (17, $[M - AllylO]^+$), 126 (10), 86 (29), 72 (20), 71 (26), 67 (28), 58 (100). Anal. calc. for $C_{12}H_{23}NO$ (197.32): C 73.04, H 11.75, N 7.10; found: C 73.22, H 11.68, N 7.40.

1.8. *(E)-*N,N-*Diethyl-4,4-dimethoxy-3-methylbut-2-enylamine* (**10i**). A mixture of 56.4 g (0.30 mol) of *4,4-dimethoxy-3-methylbut-2-enyl acetate* (**35**; (*E*/*Z*) 82:18), 150 ml of Et_2NH, 675 mg (3 mmol, 1 mol-%) of $Pd(OAc)_2$ and 3.9 g (15 mmol, 5 mol-%) of Ph_3P was heated under reflux for 15 h. The mixture was evaporated and the residue treated with Et_2O/pentane and charcoal and filtered through a short pad of *Celite*. The yellow oil obtained after evaporation (60.0 g) was distilled through a 5-cm *Vigreux* column at 40–50°/0.3 mbar: 57.1 g (95%) of **10i** ((*E*/*Z*) 9:1 by GC). Fractionation of this material through a 30-cm distillation column packed with *Fenske* rings (*Normag* distillation head, reflux ratio *ca.* 20:1) afforded a total of 34.8 g (58%) of mixed fractions ((*E*/*Z*) = 86:14) and 14.5 g (24%) of pure **10i** (≥ 99% (*E*) by GC). B.p. 30–32°/0.06 mbar. IR: 2824 (N-alkyl); 1109, 1075, 1058 (C–O–C). ^{1}H-NMR (60 MHz): 5.65 (*t* with fine struct., J = 7, H–C(2)); 4.45 (*s*, H–C(4)); 3.3 (*s*, 2 CH_3O); 3.15 (br. *d*, J = 7, CH_2(1)); 2.5 (*q*, J = 7, $(CH_3CH_2)_2N$); 1.6 (*s* with fine struct., CH_3–C(3)); 1.0 (*t*, J = 7, $(CH_3CH_2)_2N$). MS: 201 (3, M^+), 186 (5, $[M - CH_3]^+$), 169 (74, $[M - CH_3OH]^+$), 154 (100), 126 (43). Anal. calc. for $C_{11}H_{23}NO_2$ (201.31): C 65.63, H 11.52, N 6.96; found: C 64.97, H 11.35, N 6.94.

1.9. *(E)-4-(Diethylamino)-2-methylbut-2-enyl Acetate*. To a soln. of 7.85 g (50 mmol) of **29a** in 6 ml of pyridine were added, at 0°, 6.2 g (60 mmol) of Ac_2O and a few crystals of 4-(dimethylamino)pyridine. After stirring at r.t. for 2 h, the mixture was evaporated, the residue treated with toluene, and the mixture evaporated again. Bulb-to-bulb distillation at *ca.* 95°/0.3 mbar afforded 9.7 g (97%) of the title compound. Yellowish oil. GC: purity 97%. IR: 2809 (N-alkyl); 1740 (br., C=O); 1227 (C–O). ^{1}H-NMR (60 MHz): 5.55 (*t* with fine struct., J = 7, H–C(3′)); 4.45 (*s*, CH_2(1′)); 3.3 (*d* with fine struct., J = 7, CH_2(4′)); 2.7 (*q*, J = 7, $(CH_3CH_2)_2N$); 2.05 (*s*, Ac); 1.65 (br. *s*, CH_3–C(2′)); 1.1 (*t*, J = 7, $(CH_3CH_2)_2N$). MS: 199 (6, M^+), 184 (11, $[M - CH_3]^+$), 140 (11), 127 (17), 86 (14), 73 (13), 60 (37), 43 (100).

1.10. N-*[(E)-4-(*tert-*Butoxy)-3-methylbut-2-enyl]acetamide* (**25**). N-*[(E)-4-(*tert-*Butoxy)-3-methylbut-2-enyl]phthalimide* (**23**) [25] was prepared according to [25a] (*cf.* [23b,c]) starting from the 75:25 mixture **32**/**33** (*cf. 1.4*). After repeated recrystallization from hexane, 40% yield. M.p. 73.5–74° ([25a]: 74–75°). Hydrazinolysis of **23** afforded *(E)-4-(*tert-*butoxy)-3-methylbut-2-enylamine* [25b], yield 81%. Treatment of this material with an excess of Ac_2O at r.t. for 3 h followed by evaporation and bulb-to-bulb distillation at *ca.* 150°/0.1 mbar afforded **25** in 96% yield as an oil which crystallized upon standing at 0°. M.p. 41–43°. IR: 3287 (NH); 1653 (C=O, amide); 1553 (amide II); 1096, 1061 (C–O–C). ^{1}H-NMR (60 MHz); 5.8 (br., CONH); 5.5 (*t* with fine struct., $J = 7$, H–C(2′)); 4.0–3.7 (*m*, CH_2(1′), CH_2(4′)); 1.95 (*s*, Ac); 1.7 (br. *s*, CH_3–C(3′)); 1.2 (*s*, *t*-BuO). MS: 143 (22, $[M - C_4H_8]^+$), 125 (42), 114 (29), 84 (100), 83 (86). Anal. calc. for $C_{11}H_{21}NO_2$ (199.29): C 66.29, H 10.62, N 7.03; found: C 66.15, H 10.80, N 7.28.

2. Isomerizations, Configuration Correlations, and ee Determinations. – 2.1. *General Procedures.* 2.1.1. *Isomerizations.* Small-scale experiments (3–10 mmol) were carried out according to the following procedure: A *Pyrex* tube was charged under N_2 or under Ar with the allylamine isomerization substrate **10** and anh. THF (1–3 ml per mmol of **10**). The soln. was deoxygenated by applying 2 cycles of alternating freeze (liquid N_2)/evacuate/thaw operations. Then the Rh^I-catalyst was introduced by means of a small funnel, and the mixture was again deoxygenated as above. The tube was sealed and heated in an oven at the indicated temp. and for the time specified. In most cases, the Rh-complex dissolved completely and the colour of the soln. changed from yellow-orange to light- or dark-brown. The mixture was evaporated and the residue generally subjected to bulb-to-bulb distillation. The enamine **11** or the product mixture was characterized by GC analysis[11]), IR and NMR spectra, and optical-rotation measurements. Preparative-scale experiments were carried out in 100-ml *Schlenk* tubes equipped with a magnetic stirring bar. The *Schlenk* tube was charged under N_2 with the Rh-catalyst and then stoppered with a rubber septum, and **10** (0.05–0.1 mol) and THF (30–50 ml) were introduced *via* syringes. After replacement of the septum by a ground glass stopper, the mixture was deoxygenated (3 cycles of alternating freeze/evacuate/thaw operations), and the *Schlenk* tube was immersed in an oil bath (temp. 65–70°) for the specified time. The mixture was evaporated, the residue treated with hexane (250 ml) and a little of charcoal, the mixture filtered, and the filtrate evaporated to afford the crude enamine **11** which usually was directly subjected to hydrolysis.

2.1.2. *Enamine Hydrolysis.* Crude or distilled enamine **11** was treated at 0° with a 3–5 fold volume of 10–50% aq. AcOH soln. After stirring the two-phase system at 0° for 10 min, the same volume of hexane or pentane was added, and the mixture was stirred at r.t. for 15 min. Usual workup with hexane and 1N HCl followed by bulb-to-bulb distillation afforded the aldehydes **12** or **13** as colourless liquids.

2.1.3. *ee-Determinations. Ag_2O Oxidation:* To an aq. suspension of Ag_2O (prepared at 0° by addition of 2.2 mmol of $AgNO_3$ in 3 ml of H_2O to a soln. of 4.4 mmol of NaOH in 3 ml of H_2O) was added, at 0°, 1.0 mmol of **12** or **13** and the mixture was stirred at r.t. for 1–2 h. The mixture was filtered through *Celite*, the filtrate washed with Et_2O, then acidified with 2N HCl, and the product extracted with CH_2Cl_2. The extracts were washed with sat. NaCl soln., dried (Na_2SO_4), filtered, and evaporated, and the crude acid obtained was dried *in vacuo* or purified by bulb-to-bulb distillation.

Alternatively, the aldehyde was converted into the acid by a *Jones* oxidation: to a soln. of 1.0 mmol of **12** or **13** in 5–10 ml of acetone was added dropwise, at 0°, *Jones* reagent until a brown colour persisted (consumption *ca.* 0.25 ml of reagent). After stirring for 5–10 min at r.t. a few drops of i-PrOH were added to destroy the excess reagent, and the mixture was diluted with H_2O and worked up as usual with CH_2Cl_2.

The formation of *amide derivatives with (R)-α-methyl-4-nitrobenzylamine* [17] was carried out according to [18]: To a suspension of 61 mg (0.24 mmol) of 2-chloro-1-methylpyridinium iodide in 2 ml of CH_2Cl_2 was added, under Ar, a soln. of 0.20 mmol of the carboxylic acid, 37 mg (0.22 mmol) of (*R*)-α-methyl-4-nitrobenzylamine and 89 mg (0.48 mmol) of Bu_3N in 3 ml of CH_2Cl_2. The mixture was heated under reflux for 0.5–2 h, then worked up as usual with Et_2O to afford the crude amide derivative in virtually quantitative yield. The crude derivative was analyzed by GC (*OV1* capillary column, 50 cm × 0.3 mm, 220–270°, 0.5–1.0°/min, carrier gas H_2) or HPLC (*Lichrosorb SI-60* (5 μ), THF/hexane/(i-Pr)$_2$NH 20:79.9:0.1) for the diastereoisomer composition.

2.2. *Isomerization of Benzyloxy Derivative* **10a**. 2.2.1. *(RS)-4-(Benzyloxy)-3-methylbutanal* ((*RS*)-**12**). Isomerization of **10a** with 1 mol-% of [Rh((*RS*)-**9**)(cod)]BF_4 (90°, 38 h) furnished a yellow oil. GC: 13% of **14**, 14% of (*RS*)-**12**[11]), 67% of (*RS*)-**11a**. Aq. hydrolysis and subsequent purification by chromatography on silica gel (hexane/Et_2O 9:1) and bulb-to-bulb distillation afforded (*RS*)-**12** (*cf.* [7a]) as colourless oil in 46% yield (based on

[11]) The GC analyses of the distilled enamines **11** always indicated the presence of a few % of the corresponding aldehydes, but the amount often varied from injection to injection. It is, therefore, assumed that the hydrolysis to the aldehyde occurred mainly during the sampling procedure.

10a). GC: purity 96%. IR: 2723 (CHO); 1723 (C=O); 1099 (C–O–C); 793, 698 (monosubst. benzene). ^{1}H-NMR (60 MHz): 9.75 (*t*, *J* = 1.8, CHO); 7.35 (br. *s*, 5 arom. H); 4.5 (*s*, PhCH_2); 3.35 (*m*, CH_2(4)); 2.8–2.1 (*m*, CH_2(2), H–C(3)); 1.0 (*m*, CH_3–C(3)). MS: 192 (0.5, $M^{+\cdot}$), 161 (3, $[M - CH_2OH]^+$), 150 (4, $[M - C_2H_2O]^{+\cdot}$), 107 (24), 91 (100). Anal. calc. for $C_{12}H_{16}O_2$ (192.26): C 74.97, H 8.38; found: C 74.91, H 8.75.

A sample of this material was oxidized by Ag_2O to afford *(RS)-4-(benzyloxy)-3-methylbutanoic acid* ((*RS*)-**15**). Colourless oil. Yield 96%. IR: 2722 (br., CO_2H); 1708 (C=O); 1098 (CO_2H); 737, 697 (monosubst. benzene). ^{1}H-NMR (60 MHz): 10.05 (br., CO_2H); 7.35 (br. *s*, 5 arom. H); 4.5 (*s*, PhCH_2); 3.35 (*m*, CH_2(4)); 2.9–2.0 (*m*, CH_2(2), H–C(3)); 1.0 (*m*, CH_3–C(3)). MS: 208 (1, $M^{+\cdot}$), 190 (1, $[M - H_2O]^{+\cdot}$), 107 (38), 91 (100). Anal. calc. for $C_{12}H_{16}O_3$ (208.26): C 69.21, H 7.74; found: C 68.82, H 7.71.

*(3RS)-4-(benzyloxy)-3-methyl-*N*-[(R)-α-methyl-4-nitrobenzyl]butanamide* ((*RS*)-**16**) was obtained in 85% yield as a yellow, viscous oil. Diastereoisomer ratio by GC 50.5: 49.5, by HPLC 48.9:51.1.

2.2.2. *Enantiomer (R)*-**12**. Isomerization of **10a** with 0.5 mol-% of [Rh((*R*)-**9**)(cod)]ClO_4 (75°, 64 h) followed by hydrolysis afforded, after bulb-to-bulb distillation, (*R*)-**12** as colourless oil in 73% yield. GC: purity 98.5%. $[\alpha]_D^{20} = +12.05$ (*c* = 4.4, $CHCl_3$). IR, NMR, MS: identical with corresponding spectra of (*RS*)-**12**. Anal. calc. for $C_{12}H_{16}O_2$ (196.26): C 74.97, H 8.39; found: C 75.50, H 8.47.

A sample of this material was oxidized with Ag_2O to afford (*R*)-**15**. Colourless oil. $[\alpha]_D^{20} = +4.58$ (*c* = 2.1, $CHCl_3$). IR, NMR, MS: identical with corresponding spectra of (*RS*)-**15**. Anal. calc. for $C_{12}H_{16}O_3$ (208.26): C 69.21, H 7.74; found: C 69.26, H 7.92.

Derivative (*R*)-**16** was obtained in 97% crude yield. Off-white solid. Diastereoisomer ratio by GC 99.7:0.3, by HPLC 99.6:0.4. The enantiomeric purity of (*R*)-**12**, therefore, amounted to 99.2–99.4% ee.

In a preparative-scale experiment, 20.0 g (81 mmol) of **10a** in 40 ml of THF were isomerized in the presence of 215 mg (0.25 mmol, 0.31 mol-%) of [Rh((*R*)-**9**)(cod)]ClO_4 at 65° for 137 h. GC (crude mixture): 1% of (*R*)-**12**[11]), 94% of (*R*)-**11a**, and 3% of **10a**. Hydrolysis afforded, after bulb-to-bulb distillation at *ca.* 100–120°/0.1 mbar, 13.4 g (86%) of (*R*)-**12** as colourless oil. GC: purity 99%. A sample of this material was oxidized (Ag_2O) to (*R*)-**15**, which in turn was transformed to (*R*)-**16**. Diastereoisomer ratio by GC 99.7:0.3 and 99.4:0.6 (double determination). The enantiomeric purity of (*R*)-**12**, therefore, amounted to 98.8–99.4% ee.

2.2.3. *Enantiomer (S)*-**12**. Isomerization of **10a** with 1.16 mol-% of [Rh((*S*)-**9**)(cod)]ClO_4 (85°, 41 h), afforded, after bulb-to-bulb distillation at *ca.* 150°/0.2 mbar, a yellowish oil. GC: 11% of **14**, 13% of (*S*)-**12**[11]), and 74% of *(1E,3S)-4-(benzyloxy)-*N,N*-diethyl-3-methylbut-1-enylamine* ((*S*)-**11a**). $[\alpha]_D^{20} = -5.1$ (*c* = 1.1, hexane). IR: 2720 (N-Alkyl); 1725 (C=O, trace of aldehyde); 1650 (C=C, enamine); 1094 (C–O–C); 736, 697 (monosubst. benzene). ^{1}H-NMR (60 MHz): 7.35 (*s*, 5 arom. H); 5.95 (*d*, *J* = 14, H–C(1)); 4.55 (*s*, PhCH_2); 4.05 (*dd*, *J* = 14, 7.5, H–C(2)); 3.5–3.2 (*m*, CH_2(4)); 2.95 (*q*, *J* = 7, (CH_3CH_2)N); 2.7–2.2 (*m*, H–C(3)); 1.0 (*d*, (CH_3CH_2)$_2$N); 1.0 (*d*, *J* = 7, CH_3–C(3)); additional peaks of *ca.* 10% of **14** at 4.50 (*s*, PhCH_2O) and 0.97 (*d*, *J* = 7, CH_3–C(3)).

Usual hydrolysis afforded (*S*)-**12** as colourless oil. Yield 54% (based on **10a**). GC: purity 99%. $[\alpha]_D^{20} = -12.0$ (*c* = 4.1, $CHCl_3$). IR, NMR, MS: identical with corresponding spectra of (*RS*)-**12**. Anal. calc. for $C_{12}H_{16}O_2$ (192.26): C 74.97, H 8.39; found: C 74.71, H 8.35.

A sample of this material was oxidized with Ag_2O to afford (*S*)-**15**; *cf.* [26]. B.p. *ca.* 160°/0.03 mbar. Yield 94%, $[\alpha]_D^{20} = -4.53$ (*c* = 2.1, $CHCl_3$). Anal. calc. for $C_{12}H_{16}O_3$ (208.26): C 69.21, H 7.74; found: C 69.07, H 7.83.

Derivative (*S*)-**16** was obtained in 99% yield. White solid. Diastereoisomer ratio by GC 0.6:99.4, by HPLC 0.85:99.15. The enantiomeric purity of the aldehyde (*S*)-**12**, therefore, amounted to *ca.* 98.3–98.8% ee.

A preparative-scale experiment starting from 20.0 g (81 mmol) of **11a** (0.31 mol-% of [Rh((*S*)-**9**)(cod)]ClO_4, 60 ml of THF, 60°, 93 h, 86% conversion by GC) furnished 12.05 g (77.5% based on **10a**; 90% based on converted material) of (*S*)-**12**. GC: purity 98.7%. Diastereoisomer ratio of (*S*)-**16** by GC 0.5:99.5, by HPLC 0.65:99.35; the enatiomeric purity of (*S*)-**12**, therefore, amounted to *ca.* 98.7–99.0% ee.

2.2.4. *Configuration Correlation.* A soln. of 80 mg (0.415 mmol) (*S*)-**12** in 3 ml of MeOH was treated with 20 mg of $NaBH_4$. After stirring for 15 min at r.t., the mixture was evaporated and the residue partitioned between Et_2O and 1N HCl. Usual work up followed by bulb-to-bulb distillation at *ca.* 140°/0.1 mbar afforded 72 mg (95%) of *(S)-4-(benzyloxy)-3-methylbutan-1-ol* ((*S*)-**17**) as colourless oil. GC: purity 98.5%. $[\alpha]_D^{20} = +2.2$ (*c* = 1.1, EtOH; [5a]: $[\alpha]_D^{20} = -2.8$ (*c* = 1.1, EtOH) for (*R*)-**17**).

2.3. *Isomerization of Benzyloxy Derivatives* **10b–d**. 2.3.1. Isomerization of **10b** with 1.2 mol-% of [Rh((*R*)-**9**)(cod)]ClO_4 (75°, 115 h) afforded, after bulb-to-bulb distillation at *ca.* 180°/0.2 mbar, 93% of a yellow oil. GC: 83% of *(1E,3R)-4-(benzyloxy)-*N,N*-dibutyl-3-methylbut-1-enylamine* ((*R*)-**11b**). $[\alpha]_D^{20} = +6.1$ (*c* = 2.1, hexane). ^{1}H-NMR (60 MHz): 7.3 (*m*, 5 arom. H); 5.95 (*d*, *J* = 14, H–C(1)); 4.5 (*s*, PhCH_2); 3.95 (*dd*, *J* = 14, 7, H–C(2)); 3.45–3.15 (*m*, CH_2(4)); 3.1–2.2 (*m*, $[CH_3(CH_2)_2CH_2]_2$N, H–C(3)); 1.75–0.75 (*m*, $[CH_3(CH)_2CH_2]_2$N); 1.05 (*d*, *J* = 7, CH_3–C(3)). Usual hydrolysis afforded (*R*)-**12**. GC: purity 86%. Yield 48% (based on **10b**). $[\alpha]_D^{20} = +10.2$

(c = 2.7, $CHCl_3$). Enantiomeric purity 98.9–99.0% ee (diastereoisomer ratio of (*R*)-**16**, 99.45:0.55 by GC, 99.5:0.5 by HPLC).

2.3.2. Isomerization of **10c** with 1.0 mol-% of [Rh((*R*)-**9**)(cod)]ClO_4 (75°, 64 h) afforded, after bulb-to-bulb distillation at *ca.* 160°/0.2 mbar, 84% of a yellow oil. GC: 61% of *1-[(1E,3R)-4-(benzyloxy)-3-methylbut-1-enyl)]piperidine* ((*R*)-**11c**) and 26% of **10c**. IR: 1651 (C=C, enamine); 1116, 1095 (C–O–C). ^{1}H-NMR (60 MHz): 7.3 (*s*, 5 arom. H); 5.9 (*d*, J = 14, H–C(1′)); 4.5 (*s*, PhCH_2); 4.25 (*dd*, J = 14, 7, H–C(2′)); 3.45–3.15 (*m*, CH_2(4′)); 3.0–2.2 (*m*, CH_2(2), H–C(3′)); 1.5 (*m*, CH_2(3), CH_2(4), CH_2(5)); 1.05 (*d*, J = 7, CH_3–C(3′)); and additional signals of **10c**. Hydrolysis afforded (*R*)-**12**. GC: purity 95%. Yield 52% (based on **10c**). $[\alpha]_D^{20}$ = +12.14 (c = 3.6, $CHCl_3$). Enantiomeric purity 98.8–99.4% ee (diastereoisomer ratio of (*R*)-**16**, 99.7:0.3 by GC, 99.4:0.4 by HPLC).

2.3.3. Isomerization of **10d** with 1.0 mol-% of [Rh((*R*)-**9**)(cod)]ClO_4 (75°, 64 h) afforded, after bulb-to-bulb distillation at *ca.* 160°/0.2 mbar, 57% of a colourless oil. GC: 85% of *4-[(1E,3R)-4-(benzyloxy)-3-methylbut-1-enyl]morpholine* ((*R*)-**11d**). $[\alpha]_D^{20}$ = +6.9 (c = 2.1, hexane). IR: 1654 (C=C, enamine); 1119, 1097 (C–O–C). ^{1}H-NMR (60 MHz): 7.3 (*s*, 5 arom. H); 5.85 (*d*, J = 14, H–C(1′)); 4.5 (*s*, PhCH_2); 4.35 (*dd*, J = 14, 7, H–C(2′)); 3.8–3.5 (*m*, CH_2(2), CH_2(6)); 3.4–3.15 (*m*, CH_2(4′)); 3.0–2.2 (*m*, CH_2(3), CH_2(5), H–C(3′)); 1.05 (*d*, J = 7, CH_3–C(3′)). Hydrolysis afforded (*R*)-**12**. GC: purity 95%. $[\alpha]_D^{20}$ = +11.4 (c = 3.6, $CHCl_3$). Enantiomeric purity 93.1–93.2% ee (diastereoisomer ratio of (*R*)-**16**, 96.55:3.45 by GC, 96.6:3.4 by HPLC).

2.4. *Isomerization of* tert-*Butoxy Derivative* **10e**. 2.4.1. *(RS)-4-(*tert-*Butoxy)-3-methylbutanal* ((*RS*)-**13e**). Isomerization of **10e** with 1.4 mol-% of [Rh(dppe)(nbd)]PF_6 (110°, 25 h) afforded, after bulb-to-bulb distillation at *ca.* 90°/0.5 mbar, 74% of a colourless oil. GC and GC/MS: 7% of (*RS*)-**13e**[11]), 6% of **18**, 6% of an unknown, 75% of (*RS*)-**11e**, 5% of **10e**. Hydrolysis afforded (*RS*)-**13e** (*cf.* [27]). Colourless, pleasant-smelling liquid. B.p. *ca.* 90°/15 mbar. GC: purity 98%. Yield 55% (based on **10e**). IR: 2725 (CHO); 1726 (C=O); 1082 (C–O–C). ^{1}H-NMR (60 MHz): 9.7 (*t*, J = 2, CHO); 3.5–2.9 (*m*, CH_2(4)); 2.6–1.9 (*m*, CH_2(2), H–C(3)); 1.15 (*s*, *t*-Bu); 0.95 (*d*, J = 7, CH_3–C(3)). MS: 114 (12, $[M - C_2H_4O]^+$), 101 (9, $[M - t\text{-Bu}]^+$), 85 (32, $[M - t\text{-BuO}]^+$), 57 (100, *t*-Bu^+). Anal. calc. for $C_9H_{18}O_2$ (158.24): C 68.31, H 11.47; found: C 68.07, H 11.64.

A sample of (*RS*)-**13e** was converted by *Jones* oxidation to *(RS)-4-(*tert-*butoxy)-3-methylbutanoic acid* ((*RS*)-**19**; *cf.* [28]). Yellow oil. Yield 93.5%.

The *(3RS)-4-(*tert-*butoxy)-3-methyl-*N-*[(R)-α-methyl-4-nitrobenzyl]butanamide* ((*RS*)-**20**) was obtained in virtually quantitative yield as a pale yellow, viscous oil. IR: 3286 (br., NH); 1644 (C=O, amide); 1523 (amide II); 1346 (NO_2); 1081 (C–O–C); 856 (*p*-disubst. benzene). ^{1}H-NMR (270 MHz): 8.18 (*m*, 2 arom. H); 7.48 (*m*, 2 arom. H); 6.72, 6.65 (2*d*, J = 7, NH of 2 diastereoisomers); 5.23–5.1 (*m*, NCH(CH_3)); 3.37–3.28, 3.16–3.07 (2*m*, CH_2(4)); 2.48–2.36 (*m*, H–C(3)); 2.19–2.03 (*m*, CH_2(2)); 1.49 (*d*, J = 7, NCH(CH_3)); 1.17, 1.16 (2*s*, *t*-Bu of 2 diastereoisomers); 0.95, 0.94 (2*d*, J = 7, CH_3–C(3) of 2 diastereoisomers). Diastereoisomer ratio by GC 49.6:50.4, by HPLC *ca.* 1:1 (incomplete base-line separation).

2.4.2. *Enantiomer (R)-*__13e__. Isomerization of **10e** with 0.55 mmol-% of [Rh((*R*)-**9**)(nbd)]BF_4 (110°, 24 h) afforded, after bulb-to-bulb distillation at *ca.* 150°/15 mbar, a yellow oil. GC: 13% of (*R*)-**13e**[11]), 8% of **18**, 68% of (*R*)-**11e**, 6% of **10e**. Hydrolysis furnished the aldehyde (*R*)-**13e** [7a] as colourless, pleasent-smelling liquid. B.p. *ca.* 90°/15 mbar. GC: purity 97.5. Yield 60% (based on **10e**). $[\alpha]_D^{20}$ = +23.0 (c = 5.0, $CHCl_3$). IR, NMR, MS: identical with corresponding spectra of (*RS*)-**10e**. Anal. calc. for $C_9H_{18}O_2$ (158.24): C 68.31, H 11.47; found: C 68.29, H 11.60.

2.4.3. *Configuration Correlation and Optical-Purity Determination. Jones* oxidation of 1.0 g (6.3 mmol) of (*R*)-**13e** furnished 0.92 g of crude (*R*)-**19**; *cf.* [29]. A soln. of this material and 165 mg of TsOH in 50 ml of benzene was heated under reflux for 1.5 h using a *Dean-Stark* trap to remove the H_2O formed. The mixture was diluted with 100 ml of hexane, filtered, and evaporated and the residue distilled at *ca.* 100°/15 mbar: 489 mg (77.5% based on (*R*)-**13e**) of *(R)-3-methyl-λ-butyrolactone* ((*R*)-**1**). Further purification by chromatography on silica gel (hexane/AcOEt 1:1) followed by bulb-to-bulb distillation afforded 367 mg (58%) of (*R*)-**1**. GC: purity 93%. $[\alpha]_D^{20}$ = +23.1 (c = 5.0, $CHCl_3$). Optical purity *ca.* 94% based on chemical purity and an optical rotation of $[\alpha]_D^{20}$ = +26.4 (c = 5.0, $CHCl_3$) for optically pure (*R*)-**1** [30].

2.4.4. *Enantiomer (S)-*__13e__. Isomerization of **10e** with 0.5 mol-% of [Rh((*S*)-**9**)(nbd)]BF_4 (110°, 40 h) afforded, after bulb-to-bulb distillation at *ca.* 110°/0.3 mbar, a yellowish oil. GC: 8.5% of (*S*)-**13e**[11]), 4.5% of **18**, 78.5% of *(1E,3S)-4-(*tert-*butoxy)-*N,N-*diethyl-3-methlybut-1-enylamine* ((*S*)-**11e**), 1% of **10e**. $[\alpha]_D^{20}$ = −4.65 (c = 5.0, $CHCl_3$). IR: 1651 (C=C, enamine); 1094 (C–O–C). ^{1}H-NMR (60 MHz): 5.9 (*d*, J = 14, H–C(1)); 4.1 (*dd*, J = 14, 7, H–C(2)); 3.4–2.0 (*m*, CH_2(4), $(CH_3CH_2)_2$N, H–C(3)); 1.2–0.9 (*m*, $(CH_3CH_2)_2$N, CH_3–C(3), *t*-Bu).

Hydrolysis afforded (*S*)-**13e** as colourless, pleasent smelling liquid. GC: purity 99%. Yield 64% (based on **10e**). $[\alpha]_D^{20}$ = −25.3 (c = 4.9, $CHCl_3$). IR, NMR, MS: identical to corresponding spectra of (*RS*)-**13e**. Enantiomeric purity 92.6% ee (diastereoisomer ratio of (*S*)-**20**, 3.7:96.3 by GC, *ca.* 4:96 by HPLC).

An analogous isomerization experiment of **10e** with 0.5 mol-% of [Rh((*S*)-**9**)(cod)]ClO_4 (90°, 48 h) afforded (*S*)-**13e** in 67% yield. GC: purity 94%. $[\alpha]_D^{20} = -24.8$ ($c = 5.0$, $CHCl_3$). Enantiomeric purity 94.6% ee (diastereoisomer ratio of (*S*)-**20**, 2.7:97.3 by GC, 2.65:97.35 by HPLC).

2.5. *Isomerization of Trimethylsilyloxy Derivative* **10f**. Isomerization of **10f** with 2.1 mol-% of [Rh((*R*)-**9**)(cod)]ClO_4 (80°, 48 h) afforded, after bulb-to-bulb distillation, 82% of a yellow oil. GC: 87% of *(1*E,*3*R*)*-N,N-*diethyl-3-methyl-4-[(trimethylsilyl)oxy]but-1-enylamine* (**11f**). $[\alpha]_D^{20} = -17.1$ ($c = 2.4$, hexane). IR: 1726 (C=O, trace of aldehyde); 1650 (C=C, enamine); 1251, 1073, 878, 840, 747 (Me_3SiO). ^{1}H-NMR (80 MHz): 5.95 (*d*, $J = 14$, H–C(1)); 4.05 (*dd*, $J = 14$, 7, H–C(2)); 3.6–3.1 (*m*, CH_2(4)); 2.95 (*q*, $J = 7$, $(CH_3CH_2)_2N$); 2.5–2.0 (*m*, H–C(3)); 1.5 (*t*, $J = 7$, $(CH_3CH_2)_2N$); 1.0 (*d*, $J = 7$, CH_3–C(3)); 0.1 (*s*, Me_3Si).

To a soln. of 0.53 g of **11f** in 2 ml of AcOH and 5 ml of 0.5N HCl were added, in portions, 100 mg of $NaBH_3CN$ within 1 h. After stirring for an additional 2 h and adjusting the pH to 10 by addition of 4N NaOH, the mixture was saturated with K_2CO_3 and extracted continuously with Et_2O. The residue obtained after evaporation of the extract was purified by chromatography (silica gel, AcOEt) and bulb-to-bulb distillation at *ca.* 100°/0.2 mbar: 148 mg (50.5% based on **10f**) of *(*R*)-2-methylbutane-1,4-diol* ((*R*)-**21**. Colourless oil. GC: purity 99%. $[\alpha]_D^{20} = +14.0$ ($c = 1.9$, MeOH; [1]: $[\alpha]_D^{20} = -14.5$ ($c = 0.6$, MeOH) for (*S*)-**21**); optical purity *ca.* 96%.

2.6. *Isomerization of Methoxymethoxy Derivative* **10g**. Isomerization of **10g** with 1.54 mol-% of [Rh((*R*)-**9**)(cod)]ClO_4 (80°, 48 h) afforded, after bulb-to-bulb distillation at 150°/15 mbar, 67% of a yellowish oil. GC: 15% of **13g**[11]), 13% of an unknown compound, 36% of **10g**, 36% of *(1*E,*3*R*)*-N,N-*diethyl-4-(methoxymethoxy)-3-methylbut-1-enylamine* ((*R*)-**11g**). $[\alpha]_D^{20} = +4.64$ ($c = 2.8$, hexane). IR: 2811 (N-alkyl); 1727 (C=O); 1651 (C=C, enamine); 1150, 1109, 1047 (C–O–C). ^{1}H-NMR (80 MHz): 5.95 (*d*, $J = 14$, H–C(1)); 4.65 (*s*, OCH_2O); 4.05 (*dd*, $J = 14$, 7.5, H–C(2)); 3.4 (*m*, CH_2(4), CH_3O); 2.95 (*q*, $J = 7$, $(CH_3CH_2)_2N$); 2.5–2.0 (*m*, H–C(3)); 1.05 (*m*, CH_3–C(3), $(CH_3CH_2)_2N$); additional signals of **10g**.

To a soln. of 430 mg of the mixture in 7 ml of 30% AcOH soln. were added, in portions, 100 mg of $NaBH_3CN$, and the mixture was stirred overnight. Usual workup with Et_2O afforded a yellow oil (90 mg) which was dissolved in 1.5 ml of THF and treated with 0.5 ml of 2N HCl at 60° for 15 min. After adjusting the pH to *ca.* 10 by addition of 1N NaOH, the mixture was saturated with K_2CO_3 and extracted continuously with Et_2O. Evaporation of the extract and bulb-to-bulb distillation at *ca.* 100°/0.2 mbar gave 63 mg (19% based on **10g**) of (*R*)-**21**. Colourless oil. $[\alpha]_D^{20} = +13.6$ ($c = 1.0$, MeOH); optical purity *ca.* 94% (*cf. 2.5*).

2.7. *Isomerization of Allyloxy Derivative* **10h**. 2.7.1. *(*RS*)-3-Methyl-4-{[(*E/Z*)-prop-1-enyl]oxy}butanal* ((*RS*)-**13h**). Isomerization of **10h** with 0.66 mol-% of [Rh((*RS*)-**9**)(cod)]ClO_4 (75°, 64 h) afforded, after bulb-to-bulb distillation at *ca.* 90°/0.03 mbar, 78% of a yellowish oil. GC: 6% of (*RS*)-**13h**[11]) ((*Z*/*E*) 1:4), 85% of *(1*E,*3*RS*)*-N,N-*diethyl-3-methyl-4-{[(*E/Z*)-prop-1-enyl]oxy}but-1-enylamine* ((*RS*)-**11h**; (*Z*/*E*) *ca.* 1:4 for enol ether. IR: 1728 (C=O, trace of aldehyde); 1652 (C=C, enamine, enol ether); 1098 (C–O–C); 982 (CH=CH, *trans*). ^{1}H-NMR (80 MHz): 6.3 (*dq*, $J = 13$, 1.5, OC*H*=CH, *trans*); 6.0 (*m*, OC*H* = CH, *cis*); 5.98 (*d*, $J = 14$, H–C(1)); 4.8 (*dq*, $J = 13$, 7, OCH=C*H*, *trans*); 4.4 (*m*, OCH=C*H*, *cis*); 4.05 (*dd*, $J = 14$, 7, H–C(2)); 3.7–3.25 (*m*, CH_2(4)); 3.15–2.2 (*m*, $(CH_3CH_2)_2N$, H–C(3)); 1.6 (*dd*, $J = 6.5$, 2, OCH=CHCH_3, *cis*); 1.55 (*dd*, $J = 7$, 1.5, OCH=CHCH_3, *trans*); 1.25–0.8 (*m*, $(CH_3CH_2)_2N$, CH_3–C(3)).

Hydrolysis of this material afforded (*RS*)-**13h**. Colourless liquid. B.p. *ca.* 90°/0.03 mbar. GC: purity 98%, (*Z*/*E*) 20:80. Yield 61% (based on **10h**). IR: 2724 (CHO); 1725 (C=O); 1658 (C=C, enol ether); 1183 (C–O–C). ^{1}H-NMR (80 MHz): 9.85 (*t*, $J = 1.5$, CHO); 6.25 (*dq*, $J = 13$, 1.5, OC*H*=CH, *trans*); 5.95 (*dq*, $J = 6.5$, 2, OC*H*=CH, *cis*); 4.8 (*dd*, $J = 13$, 7, OCH=C*H*, *trans*); 4.4 (*m*, OCH=C*H*, *cis*); 3.55 (*m*, CH_2(4)); 2.75–2.05 (*m*, CH_2(2), H–C(3)); 1.6 (*dd*, $J = 6.5$, 2, OCH=CHCH_3, *cis*); 1.55 (*dd*, $J = 7$, 1.5, OCH=CHCH_3, *trans*); 1.0 (*d*, $J = 7$, CH_3–C(3)). MS: 142 (1, M^+), 85 (91), 57 (87), 41 (100). Anal. calc. for $C_8H_{14}O_2$ (142.20): C 67.57, H 9.92; found: C 67.81, H 10.03.

2.7.2. *Enantiomer (*R*)-***13h***.* Isomerization of **10h** with 1.0 mol-% of [Rh((*R*)-**9**)(cod)]ClO_4 (75°, 87 h) afforded 81% of a colourless oil. GC: 9% of (*R*)-**13**[11]) ((*Z*/*E*) 1:4), 82% of (*R*)-**11h** ((*Z*/*E*) *ca.* 1:4 for enol ether). $[\alpha]_D^{20} = +17.3$ ($c = 1.8$, hexane). NMR: virtually identical to NMR of (*RS*)-**11h**. Hydrolysis yielded (*R*)-**13h**. B.p. *ca.* 110°/15 mbar. GC: purity 94%, (*Z*/*E*) 25:75. Yield 30% (based on **10h**). $[\alpha]_D^{20} = -2.0$ ($c = 1.3$, hexane). NMR: identical to NMR of (*RS*)-**10h**.

2.7.3. *Configuration Correlation. Jones* oxidation of (*R*)-**13h** afforded, after bulb-to-bulb distillation at *ca.* 115°/15 mbar, 29% of (*R*)-**1**. GC: purity 88%. $[\alpha]_D^{20} = +16.4$ ($c = 1.14$, $CHCl_3$); optical purity *ca.* 70% (*cf.* 2.4.3).

2.8. *Isomerization of Acetal Derivative* **10i**. 2.8.1. *(*RS*)-4,4-Dimethoxy-3-methylbutanal* ((*RS*)-**13i**). Treatment of 10.1 g (50 mmol) of **10i** ((*Z*/*E*) 14:86) with 0.5 mol-% of [Rh(dppe)(nbd)]PF_6 (100°, 16 h) afforded 9.7 g of an oil. B.p. *ca.* 80°/0.2 mbar. GC: 65% of **10i** ((*Z*/*E*) 1:64) and 30% of *(1*E,*3*R*)*-N,N-*diethyl-4,4-dimethoxy-3-methylbut-1-enylamine* ((*R*)-**11i**). This material was added to a stirred suspension of 13 g of silica gel and 1.3 ml of H_2O in 26 ml of CH_2Cl_2. The mixture was stirred for 5 min, then filtered, the silica gel washed with CH_2Cl_2, and the

filtrate evaporated. Chromatography (silica gel, hexane/AcOEt 9:1, then AcOEt/MeOH 1:1) and subsequent bulb-to-bulb distillation afforded 1.60 g of (*RS*)-**13i** (*cf.* [31]) as colourless, pleasant-smelling liquid, b.p. *ca.* 80°/0.05 mbar, and 5.60 (56% recovery) of **10i** ((*Z*/*E*) 1.5:98.5). Yield of (*RS*)-**13i**: 23% (based on **10i**), 52% (based on converted material). IR: 2832 (CH_3O); 2725 (CHO); 1725 (C=O); 1104, 1096 (C–O–C). ^{1}H-NMR (60 MHz): 9.7 (*t*, *J* = 2, CHO); 4.1 (*m*, H–C(4)); 3.35 (*s*, 2 CH_3O); 2.75–2.0 (*m*, CH_2(2), H–C(3)); 1.0 (*d*, *J* = 7, CH_3–C(3)). ^{1}H-NMR (80 MHz; equal weight of [Eu(hfc)$_3$] (= tris[3-(heptafluoropropylhydroxymethylidene)-*d*-camphorato]europium(III)): 3 lines for CH_3O, intensity ratio 1:1:2. MS: 145 (1, $[M-H]^+$), 115 (13, $[M-CH_3O]^+$), 114 (9), 85 (24), 83 (17), 75 (100).

2.8.2. *Enantiomer (*S*)-***13i***. Isomerization of **10i** (≥ 99% (*E*)) with 1 mol-% of [Rh((*S*)-**9**)(nbd)]BF_4 (90°, 40 h) afforded 85% of a pale yellow oil. GC and GC/MS: 3% of (*S*)-**13i**[11]), 2% of **22**, 21% of **10i**, 70% of (*S*)-**11i**. $[\alpha]_D^{20} = -12.9$ (*c* = 4.1, hexane). IR: 2827 (CH_3O); 1727 (C=O, trace of aldehyde); 1653 (C=C, enamine); 1074 (C–O–C). ^{1}H-NMR (80 MHz): 5.9 (*d*, *J* = 14, H–C(1)); 4.1 (*dd*, *J* = 14, 7, H–C(2)); 4.0 (*d*, *J* = 6, H–C(4)); 3.4 (*s*, 2 CH_3O); 2.95 (*q*, *J* = 7, $(CH_3CH_2)_2N$); 2.6–2.1 (*m*, H–C(3)); 1.2–0.85 (*m*, CH_3–C(3), $(CH_3CH_2)_2N$); additional signals of **10i**.

Hydrolysis of this mixture with wet silica gel as described above afforded (*S*)-**13i** as colourless, pleasant smelling liquid. B.p. *ca.* 100°/15 mbar. GC: purity 96%. Yield 34% (based on **10i**), 43% (based on converted material). $[\alpha]_D^{20} = -23.2$ (*c* = 4.7, hexane). IR, NMR: identical to corresponding spectra of (*RS*)-**13i**. NMR (presence of Eu(hfc)$_3$): 2 lines for CH_3O, intensity ratio 1:1; no indication for second enantiomer at an estimated limit of detection of 5%. The enantiomeric purity of (*S*)-**13i**, therefore, amounts to ≥ 90% ee.

2.8.3. *Configuration Correlation.* A soln. of 143 mg (0.98 mmol) of (*S*)-**13i** in 3 ml of MeOH was treated at 0° with 33 mg of $NaBH_4$. After stirring for 15 min, the mixture was evaporated and the residue filtered through a short pad of silica gel: 140 mg of *(*S*)-4,4-dimethoxy-3-methylbutan-1-ol* as a colourless liquid. This material was dissolved at 0° in 1 ml of 85% HCOOH soln. After stirring for 15 min, the soln. was diluted with 1 ml of H_2O and the pH adjusted to 4.0 with 50% NaOH soln. Then, 50 mg of $NaBH_3CN$ were added and the mixture stirred at r.t. for 60 h. Then, the mixture was made alkaline by addition of 4N NaOH, saturated with K_2CO_3, and extracted continuously with Et_2O. Bulb-to-bulb distillation at *ca.* 80°/0.1 mbar afforded 74 mg (72%) of (*S*)-**21**. GC: purity 98%. $[\alpha]_D^{20} = -11.9$ (*c* = 2.1, MeOH); optical yield *ca.* 84% *(cf. 2.5)*. The decrease of optical purity with respect to (*S*)-**13i** has to be attributed to partial racemization at the aldehyde stage.

2.9. *Isomerization of Phthalimide* **23**. Treatment of 1.44 g (5.0 mmol) of **23** with 19 mg (0.023 mmol, 0.46 mol-%) of [Rh((*RS*)-**9**)(nbd)]BF_4 (110°, 25 h) afforded a brown solid which was treated with charcoal in hexane to yield 1.35 g (94%) of **24** ((*E*/*Z*) 85:15, GC, NMR). Recrystallization from hexane afforded 0.86 g (60%) of pure *N-[(*E*)-4-(*tert*-butoxy)-3-methylbut-3-enyl]phthalimide* ((*E*)-**24**). White needles. M.p. 81.5–83°. IR (KBr): 1772, 1708 (C=O); 1673, 1164 (enol ether); 719 (*o*-disubst. benzene). ^{1}H-NMR (80 MHz): 7.9–7.6 (*m*, 4 arom. H); 5.95 (*s* with fine struct., H–C(4′)); 3.75 (*t*, *J* = 7, CH_2(1′)); 2.25 (*t*, *J* = 7, CH_2(2′)); 1.65 (*d*, *J* = 1.2, CH_3–C(3′)); 1.05 (*s*, *t*-Bu); assignment of (*E*)- (and (*Z*)-) configuration by NOE. MS: 287 (1, $M^{+\cdot}$), 272 (1, $[M-CH_3]^+$), 231 (24, $[M-C_4H_8]^+$), 161 (53), 160 (30), 148 (44), 84 (100). Anal. calc. for $C_{17}H_{21}NO_3$ (287.36): C 71.06, H 7.37, N 4.87; found: C 71.37, H 7.56, N 4.99.

2.10. *Isomerization of Acetamide* **25**. Treatment of 1.0 g (5.0 mmol) of **25** with 44 mg (0.051 mmol, 1 mol-%) of [Rh((*RS*)-**9**)(cod)]ClO_4 (90°, 38 h) afforded, after bulb-to-bulb distillation at *ca.* 100°/0.2 mbar, 510 mg (81.5%) of *1-(2,3-dihydro-4-methyl-1*H*-pyrrol-1-yl)ethanone* (**26**) as a colourless oil which solidified on standing. GC: purity 94%. A sample was crystallized from hexane/Et_2O at −15°. M.p. 45–47.5°. IR (KBr): 1636 (C=O); 1444. ^{1}H-NMR (60 MHz): 6.65, 6.15 (2 *sext.*, *J* = 1.5, H–C(5′) of *'cisoid'*- and *'transoid'*-rotamer; ratio 1:2); 4.05–3.65 (*m*, CH_2(2′)); 2.85–2.25 (*m*, CH_2(3′)); 2.08, 2.02 (2*s*, Ac of *'transoid'*- and *'cisoid'*-rotamer); 1.75 (*q*, *J* = 1.5, CH_3–C(4′)). MS: 125 (39, $M^{+\cdot}$), 83 (58, $[M-CH_2CO]^+$), 82 (100), 68 (48). Anal. calc. for $C_7H_{11}NO$ (125.17): C 67.17, H 8.86, N 11.19; found: C 66.97, H 9.12, N 11.17.

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