Synthesis of Citronellal by Rh^I-Catalysed Asymmetric Isomerization of *N*,*N*-Diethyl-Substituted Geranyl- and Nerylamines or Geraniol and Nerol in the Presence of Chiral Diphosphino Ligands, under Homogeneous and Supported Conditions[1])

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For the asymmetric isomerization of geranyl- or neryldiethylamine ((*E*)- or (*Z*)-**1**, resp.) and allyl alcohols geraniol or nerol ((*E*)- or (*Z*)-**2**, resp.) to citronellal (**4**) in the presence of a [Rh^I(ligand)cycloocta-1,5-diene)]$^+$ catalyst, the atropic ligands **5**–**11** are compared under homogeneous and polymer-supported conditions with the non-C_2-symmetrical diphosphino ferrocene ligands **12**–**16**. The ^{t}Bu-josiphos ligand **13** or daniphos ligand **19**, available in both antipodal series, already catalyse the reaction of (*E*)-**1** at 20° (97% e.e.) and favourably compare with the binap ligand **5** (see *Table 1*). Silica-gel- or polymer-supported diphosphino ligands usually afford similar selectivity as compared to the corresponding ligands applied under homogeneous conditions, but are generally less reactive. In this context, a polymer-supported ligand of interest is the polymer-anchored binap (*R*)-**6**, in terms of reactivity, selectivity, and recoverability, with a turnover of more than 14400.

Introduction. – Isomerization of diethylgeranylamine ((*E*)-**1**) for the production of practically optically pure (+)-citronellal ((*R*)-**4**; 98–99% e.e.) in the presence of (−)-(*S*)-binap ((*S*)-**5**)/Rh^I is an exceptional industrial process [1] (binap = [1,1′-binaphthalene]-2,2′-diylbis[diphenylphosphine], leading to key intermediates for the fragrance and flavour industry. The ene cyclization of (*R*)-**4**, affording (−)-isopulegol [2], is certainly the best industrial process [3] for the preparation of (−)-menthol [4], as well as for the synthesis of the insect repellent (+)-*cis*-*p*-menthane-3,8-diol [5]. This methodology has also been successfully extended to the preparation of (+)-7-hydroxy- or (+)-7-methoxycitronellal [6]. The acidic cyclization of the (−)-antipode (*S*)-**4** to (+)-(1*R*,6*S*)-*trans*-dihydrocyclocitral [7][2]) is also fundamental for the synthesis of (+)-norlimbanol [10][3]), as well as of optically pure dihydroionone [7] and dihydrodamascone analogues [12a]. (−)-Citronellal ((*S*)-**4**) has also been used as a potential starting material for the synthesis of (−)-(2*S*,4*R*)-rose oxide [12b,c].

For the Rh^I-catalysed isomerization process (*E*)- or (*Z*)-**1** → **4**, several variants of binap ligands have been tested and patented by *Takasago* [13], *Hoffmann La Roche* [14], and *Bayer* [15], but the technical know-how of the Japanese company, which is reluctant to offer both enantiomers of **4** in bulk quantities, has maintained its monopoly. The efficiency of the binap-containing catalyst was earlier attributed to the

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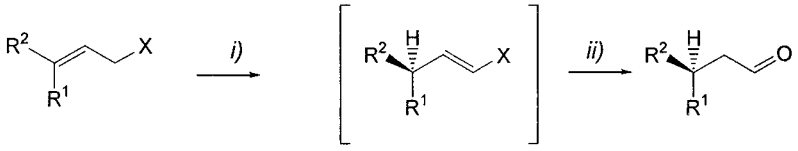
1) Presented at the '13th International Conference on Organic Synthesis', 1-5.07.2000, Warsaw, Poland.

2) For the racemic version, see [8]. See also [9] for a report that ignores the priority of [7][10][11].

3) Norlimbanol is the trivial name for the racemic form of 1-[(1*R*,6*S*)-2,2,6-trimethylcyclohexyl]hexan-3-ol, an extremely strong woody fragrance manufactured by *Firmenich SA* in both racemic and optically active form [10].

high *Lewis* acidity of the central metal atom conferred by the fully aromatic structure of the diphosphino ligand [1d]. Finally, this methodology is also advantageous when compared to the asymmetric hydrogenation of citral, which necessitates a tedious distillative fractionation to obtain the stereoisomerically pure substrates[4]), geranic acid [17][5]) or geraniol [19]. These last substrates require, in addition, a supplementary reductive or oxidative step. We now wish to present the first example of the use of a chiral diphosphino ligand, neither C_2-symmetric nor atropic, which enables the Rh^I-catalysed preparation of **4** in both antipodal forms from (*E*)- or (*Z*)-**1** (or from (*E*)- or (*Z*)-**2**) with similarly high enantioselectivity, under homogeneous or silica-gel- or polymer-supported conditions (*Scheme*).

Scheme



(*E*)-**1** R^1=Me, R^2=$Me_2CCH(CH_2)_2$, X=Et_2N (*S*)-**3** X=Et_2N ((*E*); (+)) ((*S*)-**4** (–))

(*Z*)-**1** R^1=$Me_2CCH(CH_2)_2$, R^2=Me, X=Et_2N (*R*)-**3** X=Et_2N ((*E*); (–)) ((*R*)-**4** (+))

(*E*)-**2** R^1=Me, R^2=$Me_2CCH(CH_2)_2$, X=OH

(*Z*)-**2** R^1=$Me_2CCH(CH_2)_2$, R^2=Me, X=OH

i) [Rh^I (diphosphino ligand) (cod)]CF_3SO_3, THF, 66°. *ii*) AcOH, H_2O, Et_2O.

Results. – First of all, we compared the activity and selectivity of the (+)-(*R*)-binap ligand (*R*)-**5** with its commercially available polymer-supported analogue (*R*)-**6**[6]), using triflate as the counter ion of Rh^+ ([Rh^I(ligand)(cod)]CF_3SO_3; cod = cycloocta-1,5-diene), an anion not mentioned in the Japanese patent [3e,f]. Under these conditions, the ligand (*R*)-**6** exhibited very similar reactivity and selectivity, even at 0.25 mol-% of the catalyst (*i.e.* of the ligand) for both diethylgeranylamine ((*E*)-**1**) [21] and diethylnerylamine ((*Z*)-**1**) [22][7]) when compared to (*R*)-**5** used under homogeneous conditions (see *Table 1*, *Entries 1* and *2*). The ratio (*R*)-**6**/(*E*)-**1** could even be

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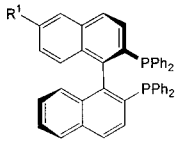
4) By analogy with [16], a 95:5 (*E*)/(*Z*) mixture of geranial was more selectively hydrogenated at 90 atm for 16 h in toluene, in the presence of 1 mol-% of (*R*,*R*)-chiraphos (=(2*R*,3*R*)-(+)-2,3-bis(diphenylphosphino)butane = [(1*R*,2*R*)-1,2-dimethylethane-1,2-diyl]bis[diphenylphosphine]; *Aldrich*) chelated with 0.25 mol-% of [$Rh_4(CO)_{12}$] to afford quantitatively (*S*)-**4** with 83% e.e., while under the same conditions, a 7:93 (*E*)/(*Z*) mixture of neral delivered quantitatively (*R*)-**4** with 84% e.e. The practically similar reactivities of the (*E*)- and (*Z*)-isomers did not allow an efficient dynamic hydrogenation of citral under (*E*)/(*Z*) isomerization conditions.

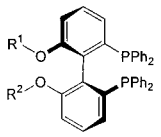
5) For an asymmetric 1,4-reduction of ethyl geranate, see [18].

6) The ligand (*R*)-**6** is not included in the general structure claimed in [3e] and has only been previously reported for asymmetric hydrogenation and aldol or *Mannich* reactions [20].

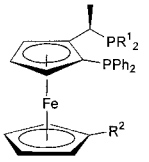
7) For a detailed mechanistic study of this isomerization, see [1d][23].



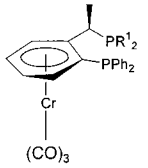
(*R*)-**5** R^1=H
(*R*)-**6** R^1=$(CH_2)_3CO_2CH_2$-Polymer



(*S*)-**7** R^1=R^2=Me
(*S*)-**8** R^1=R^2=H
(*S*)-**9** R^1=R^2=Me_3Si
(*S*)-**10** R^1=H, R^2=$C(O)(CH_2)_2C(O)NH(CH_2)_2$-$(OCH_2CH_2)_{60}$-$OCH_2$-Polymer
(*S*)-**11** R^1=H, R^2=$(CH_2)_2$-$(OCH_2CH_2)_{60}$-OCH_2-Polymer



(*R*,*S*)-**12** R^1=cHex, R^2=H
(*R*,*S*)-**13** R^1=^{t}Bu, R^2=H
(*R*,*S*)-**14** R^1=cHex, R^2=$Si(Me)_2CH_2NHC(O)NH(CH_2)_3Si(OEt)(O_2Si)_n$
(*R*,*S*)-**15** R^1=^{t}Bu, R^2=$Si(Me)_2CH_2NHC(O)NH(CH_2)_3Si(OEt)(O_2Si)_n$
(*R*,*S*)-**16** R^1=cHex, R^2=$CH_2NHC(O)$NH-2,5-Tol-NHC(O)$NHCH_2$-4-Ph-Polymer



(*R*,*S*)-**17** R^1=Ph
(*R*,*S*)-**18** R^1=cHex,
(*R*,*S*)-**19** R^1=^{t}Bu

decreased to 0.1 mol-% without affecting either the conversion or the enantioselectivity[8]). Thus, hydrolysis of the transient enamine (*S*)-**3** and bulb-to-bulb distillation afforded (*S*)-**4** in 98% e.e. and 95% isolated yield. The great advantage of a polymer-supported ligand is its straightforward physical separation from the substrate. Using a 0.25 mol-% ratio, we could thus successfully recycle (*R*)-**6** 37 times by simple decantation/filtration techniques, without any loss of chiral and chemical efficiency.

The isomerization of allyl alcohols was earlier reported [25] to proceed with 37% e.e. for geraniol ((*E*)-**2**) in the presence of $[Rh^I(binap)(cod)]ClO_4$ [23]. We were thus surprised to reach 60% enantioselectivity for the same ligand, but with triflate as counterion. The selectivity decreased to 50% e.e. for nerol ((*Z*)-**2**), accompanied by a lower reactivity (88–90%) as compared to the complete conversion observed for the corresponding amines (*E*)- and (*Z*)-**1** (*Table 1*, *Entries 1* and *2*). The reactivity still decreased in the case of the polymer-supported binap (*R*)-**6**, to 46 and 72% conversion for (*E*)- and (*Z*)-**2**, respectively; however, the selectivity remained identical with that obtained under homogeneous conditions. The fact that traces of (*E*)/(*Z*) isomerization (3–5%) were observed after analysis of the unreacted allyl alcohols **2** partially accounts for the lower selectivity observed with these substrates.

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[8]) The enantioselectivity was determined directly by chiral capillary GC analysis (50% 2,3-di-*O*-acetyl-6-*O*-[(*tert*-butyl)dimethylsilyl]-β-cyclodextrin (*Brechbuehler SA*), 25 m, 0.25 mm) of the enamine (60°, 1.5°/min, 100° for 10 min, 70 KPa iso, 0.92 ml/min, 25.2 cm/s He t_R 32.96 min for (*S*)-**3** and 33.33 min for (*R*)-**3**) or of citronellal (100° for 36 min, 15°/min, 150° for 5 min, 75 KPa for 36 min, 20 KPa/min, 170 KPa for 3 min, 0.8 ml/min, 24.9 cm/s He; t_R 33.1 min for (*S*)-**4** and 34.1 min for (*R*)-**4**) [24]. Standard error ±1%.

Table 1. *Screening of the Substrates Diethylgeranylamine* ((*E*)-**1**), *Diethylnerylamine* ((Z)-**1**), *Geraniol* ((*E*)-**2**, *and Nerol* ((*Z*)-**2**) *in the Presence of Diphosphino Ligands* **5**–**16** (1.0 mol-%) *and* $[Rh^{I}(cod)_2]CF_3SO_3$ (1.0 mol-%) *in Refluxing THF: Conversion [%] to* **4** *after 20 h, Chiroptical Property of* **4** *as well as Its e.e.*

Entry	Ligand	Conversion (sign of α_D of **4**; e.e. of **4**)			
		from (*E*)-**1**	from (*Z*)-**1**	from (*E*)-**2**	from (*Z*)-**2**
1	(*R*)-**5**	99 ((−); 97)[a])	100 ((+); 95)[a])	88 ((−); 60)	90 ((+); 51)
2	(*R*)-**6**	100 ((−); 98)[a])	100 ((+); 98)[a])	46 ((−); 61)	72 ((+); 50)
3	(*S*)-**7**	100 ((+); 97)[a])	100 ((−); 97)[a])	75 ((+); 44)	85 ((−); 32)
4	(*S*)-**8**	95 ((+); 91)	15 ((−); 91)		
5	(*S*)-**9**	95 ((+); 89)	99 ((−); 95)	74 ((+); 51)	78 ((−); 37)
6	(*S*)-**10**	79 ((+); 88)[a])	40 ((−); 95)		
7	(*S*)-**11**	48 ((+); 96)[a])	19 ((−); 96)[a])		
8	(*R*,*S*)-**12**	99 ((−); 78)[a])	100 ((+); 86)[a])	62 ((+); 9)	70 ((−); 16)
9	(*R*,*S*)-**13**	99 ((−); 92)[a])	100 ((+); 97)[a])	85 ((−); 22)	96 ((+); 31)
10	(*R*,*S*)-**14**	81 ((−); 83)	68 ((+); 88)	63 ((−); 21)	54 ((+); 20)
11	(*R*,*S*)-**15**	81 ((−); 96)[a])	99 ((+); 96)	72 ((−); 20)	95 ((+); 21)
12	(*R*,*S*)-**16**	54 ((+); 78)	30 ((−); 81)[a])	62 ((−); 4)	19 ((+); 11)
13	(*R*,*S*)-**17**	44 ((−); 76)			
14	(*R*,*S*)-**18**	99 ((−); 94)[a])			
15	(*R*,*S*)-**19**	99 ((−); 96)[a])			

[a]) In the presence of 0.25 mol-% of catalyst.

We then turned our attention towards the known (*S*)-MeO-biphep ligand (*S*)-**7** [14], since its MeO groups are potential anchors for the attachment to polymeric supports. First of all, (*S*)-**7** was quantitatively deprotected (BBr_3, CH_2Cl_2 (99%) [26]) to afford, without racemization, the new diphosphinobiphenyldiol (*S*)-**8**, prior to refunctionalization, either to the trimethylsilyl(Me_3Si)-protected ether (*S*)-**9** (1-(trimethylsilyl)-1*H*-imidazole and CH_2Cl_2 [27], or Me_3SiCl, Et_3N, and CH_2Cl_2 [28] (99%)), or to the *TentaGel*®-supported [29] ester (*S*)-**10** (*TentaGel*® *S-COOH* dicyclohexylcarbodiimide (DCC), *N*,*N*-dimethylpyridin-4-amine (DMAP), CH_2Cl_2 [30] (77%)) or ether (*S*)-**11** (BuLi, THF, *TentaGel*® *S-Br* (72%)).

The MeO-biphep ligand (*S*)-**7** was as efficient as binap for the isomerization of the allylamines, and slightly less reactive and selective for that of the allyl alcohols (*Table 1*, *Entry 3*), while under homogeneous conditions, the deprotected diphosphinobiphenyldiol (*S*)-**8** and its trimethylsilyl ether (*S*)-**9** gave lower conversions and selectivities (89–95% e.e.; *Entries 4* and *5*). This may be tentatively explained by modification of either the metal bite angle of the chelate and/or the C(2)–C(1)–C(1′)–C(2′) dihedral angle of the diphosphino ligand, the importance of which was earlier demonstrated in the case of asymmetric hydrogenations [31]. With (*E*)-**1**, the *TentaGel*®-supported ester (*S*)-**10** gave a similar selectivity (88% e.e.) as (*S*)-**9**, while its ether analogue (*S*)-**11** was much more selective, yielding 96% e.e., as the MeO-biphep (*S*)-**7** (*Entries 6* and *7*); however, at an identical concentration, (*S*)-**10** and (*S*)-**11** were much less reactive than the analogous ligands (*S*)-**7** and (*S*)-**9** used under homogeneous conditions.

Since the results earlier reported with diphosphinoferrocenes were far from promising (25% e.e. [1a]), we were surprised and gratified to observe that this class of ligands emerged positively from a screening of more than 60 different diphosphino

compounds tested for this isomerization process[9]). The commercially available (*R*,*S*)-josiphos ligand (*R*,*S*)-**12** and its *t*Bu analogue (*R*,*S*)-**13** [32], as well as their known silica-gel- or polymer-supported counterparts (*R*,*S*)-**14** to (*R*,*S*)**16** [33] shall now be presented in more detail[10]). Thus, in the presence of 0.25 mol-% of (*R*,*S*)-josiphos (*R*,*S*)-**12**, complete conversion of (*E*)- or (*Z*)-**1** to **4** was observed after 20 h; a slightly better enantioselectivity was obtained in the case of (*Z*)-**1** (86% e.e.) than in the case of its diastereoisomer (*E*)-**1** (78% e.e.) (*Entry 8*). The same trend was observed with the *t*Bu analogue (*R*,*S*)-**13** (92 and 97% e.e. from (*E*)- and (*Z*)-**1**, resp.; *Entry 9*). This is noteworthy since, in contrast to a C_2-symmetrical ligand, the substrate may now form different diastereoisomeric complexes with the metal. Interestingly, the sense of induction was unexpectedly inverted, in the case of (*R*,*S*)-josiphos (*R*,*S*)-**12**, when the allyl alcohols (*E*)- and (*Z*)-**2** were used as substrates. This may result from a different steric or coordinating behaviour of the free alcohol[11]) or as already observed above, from a more powerful (*E*)/(*Z*)-isomerization activity of this ferrocene derivative[12]). It is noteworthy that, at 0.5 mol-%, the [Rh^I(josiphos)(cod)]PF_6 catalyst could be recycled by simple distillation of the solvent and product **3**, prior to addition of a fresh solution of (*E*)-**1** to the residue. When the josiphos ligand (*R*,*S*)-**12** was attached to a silica gel support (→ (*R*,*S*)-**14**), the selectivity slightly increased from 78 to 83% e.e. for (*E*)-**1** and from 86 to 88% e.e. for (*Z*)-**1** (*Entry 8 vs. Entry 10*). In the case of the analogous silica-gel-supported *t*Bu-josiphos ligand (*R*,*S*)-**15**, compared to the parent (*R*,*S*)-**13**, the enantioselectivity changed from 92 to 96% e.e. and from 97 to 96% e.e., respectively, for the same substrates (*Entry 9 vs. Entry 11*). In these cases, the reactivity was lower under heterogeneous conditions. As for the polymer-supported binap (*R*)-**6**, the ligand (*R*,*S*)-**15** was recycled by simple decantation/filtration techniques to afford (*S*)-**4** in 92% global yield from (*E*)-**1**. Whatever the substrates used, both the selectivity and the reactivity were lower when polymer-supported josiphos (*R*,*S*)-**16** was

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[9]) For example, isomerization of (*E*)-**1** with 1 mol-% of [Rh(diphosphino ligand)(cod)]CF_3SO_3 in refluxing THF for 20 h resulted in the following conversion to and enantioselectivity for (*S*)-**4**: with {(*R*)-1-[(1*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyl}dicyclohexylphosphine (*Fluka*); 81% conversion and 89% e.e.; with {(*R*)-1-[(1*S*)-2-(di-*p*-trifluorotoluylphosphino)ferrocenyl]ethyl}di(*tert*-butyl)phosphine, 100% conversion and 88% e.e.; with {(*R*)-1-[(1*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyl}diphenylphosphine (*Fluka*), 100% conversion and 83% e.e.). In this last case, the selectivity increased to 90% e.e. with PF_6^- as counter ion. Lower conversions were observed with less basic tetraaryldiphosphino josiphos analogues [32] such as {(*R*)-1-[(1*S*)-2-(diphenylphosphino)ferrocenyl]ethyl}diphenylphosphine (71% conversion, 84% e.e.). The fact that alkyl and aryl substituents may be interchanged at the P-atoms of the josiphos analogues without modification of the sense of induction pleads for a pseudo-C_2 symmetry of these ligands.

[10]) For dendrimers containing chiral diphosphinoferrocenes, see [34]; for a (*S*,*S*)-diop-supported Rh^I-catalyst, see [35].

[11]) When the geranyl trimethylsilyl ether [36] was isomerized in the presence of 1.0 mol-% of [Rh{(*R*,*S*)-**12**}(cod)]CF_3SO_3 in refluxing THF, (*S*)-**4** was obtained with 18% e.e.; with ligand (*R*,*S*)-**13**, the (*S*)-**4** produced exhibited 44% e.e. For asymmetric isomerizations of (*tert*-butyl)dimethylsilyl ethers, see [37].

[12]) Since (*E*)- and (*Z*)-**1** have very similar reactivities, the absence of (*E*)/(*Z*) interconversion observed during the isomerization process does not exclude a slow competitive (*E*)/(*Z*) isomerization. The strongly isomerizing properties of diphosphinoferrocenes as compared to binap is demonstrated by the presence of traces (1–3%) of 3,7-dimethyloct-7-enal [38] of similar optical purity. GC Retention times of (−)-(*S*)- and (+)-(*R*)-isocitronellal are t_R 37.8 and 38.1 min, respectively, under the conditions used for the analyses of **4** (see *Footnote 6*). This aldehyde does not influence the subsequent enol acetate acid-mediated cyclization step, since an identical carbocation is generated [7][8][10].

compared to its silica-gel-supported analogue (*R*,*S*)-**14** (*Entry 12 vs. Entry 10*); furthermore, the sense of induction was inverted for the allylamines (*E*)- and (*Z*)-**1**, which hypothetically indicates a steric or coordinating influence of the linker.

We then studied the influence on the isomerization of both the counterion and the diene ligand of the Rh^I catalyst containing the josiphos ligand (*R*,*S*)-**12** or -**13**, *i.e.*, under homogeneous conditions. If the selectivity appeared to be independent of the diene ligand used (cycloocta-1,5-diene (cod) *vs.* norbornadiene (nbd), *Table 2*), the reactivity was much higher in the case of the cyclooctadiene ligand, thus suggesting a much slower displacement of the norbornadiene by the diphosphino ligand[13]). On the other hand, the enantioselectivity seems to be strongly dependent on the counter ion of the Rh^I catalyst, increasing with less-coordinating anions such as PF_6^- (*Table 2*). This prompted us to test the non-coordinating tetrakis[3,5-(trifluoromethyl)phenyl]borate counter ion in the isomerization of (*E*)-**1**, which gave 67% conversion and 89% e.e. after 20 h at reflux in the presence of 1 mol-% of [Rh{(*R*,*S*)-**12**}(cod)]$^+$. This maximum selectivity for (*R*,*S*)-**12** suggests that the transition state is influenced either by the vicinity of the anion or by different aggregation species. The higher reactivity of ClO_4^-, $CF_3SO_3^-$, and PF_6^- presumably results from the higher solubility of their complexes in THF.

Table 2. *Screening of the Counter Ion and Diene Ligand of the Rh^I Catalyst Derived from the josiphos Ligands (*R,S*)-**12** and -**13** (1 mol-%) in the Isomerization of Diethylgeranylamine ((E)-**1**) in Refluxing THF: Conversion [%] to* **4** *after 20 h, and Enantiomeric Excess for* (S)-**4**

	Conversion (ee. of (*S*)-**4**)							
Counterion Diene[a])	ClO_4^- cod	$CF_3SO_3^-$ cod	BF_4^- cod	SbF_6^- cod	PF_6^- cod	ClO_4^- nbd	$CF_3SO_3^-$ nbd	PF_6^- nbd
(*R*,*S*)-**12**	99 (72)	100 (76)	71 (77)	70 (77)	98 (85)	17 (72)	23 (75)	10 (84)
(*R*,*S*)-**13**	98 (89)	99 (92)	43 (90)	39 (90)	99 (92)	42 (93)	69 (92)	73 (92)

[a]) cod = cycloocta-1,5-diene, nbd = norbornadiene = bicyclo[2.2.1]hepta-2,5-diene.

Finally, the kinetics of the isomerization of (*E*)-**1** in the presence of [Rh^I{(*R*,*S*)-**12**}(cod)]CF_3SO_3 or [Rh^I{(*R*,*S*)-**13**}(cod)]CF_3SO_3 were studied at 0.2 mol-% of catalyst in THF (see *Fig. 1*). At this concentration, the catalyst derived from diphosphinoferrocene (*R*,*S*)-**12** required 17 h for complete conversion of (*E*)-**1** to (*S*)-**4** under reflux conditions. The enantioselectivity slightly decreased from 80% at the beginning to 78% e.e. at the end of the reaction. This slow erosion of the e.e. is difficult to explain, but may reflect a non-detected slow (*E*)/(*Z*) isomerization of the reactant, a differential analytical chiral-GC sensitivity, or resolution at low conversion. Under the same

13) For X-ray analyses of [Rh^I(diphosphino ligand)(diene)] complexes, of which one shows a more distorted trigonal bipyramidal chelate in the case of the diene cod *vs.* nbd, see [39]. When the cod ligand in the catalyst was hydrogenated prior to isomerization of (*E*)-**1** to (*S*)-**4**, a reactive but less selective [Rh^I(diphosphino ligand)]CF_3SO_3 species was obtained, resulting in 100% conversion and 67% e.e. for ligand (*R*,*S*)-**12**, and in 100% conversion and 81% e.e. for ligand (*R*,*S*)-**13**. Similar results were obtained with [Rh^I{(*R*,*S*)-**12**}$_2$]CF_3SO_3 or [Rh^I{(*R*,*S*)-**13**}$_2$]CF_3SO_3. Even a chelating monophosphine like (−)-(*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine (*Aldrich*) is active after hydrogenation of the cod ligand in the catalyst: 79% conversion and 88% e.e. Acidic quaternization of (*E*)-**1** ($MeSO_3H$) modified neither the kinetics nor the selectivity.

conditions, complete conversion required only 2 h when the isomerization was catalysed by the Rh^I complex of the *t*-Bu analogue (*R*,*S*)-**13** (97–94% e.e.). This allowed us to decrease the ratio of the ligand (*R*,*S*)-**13** to 0.06 mol-%, to afford (*S*)-**4** with 94% e.e. and 92% yield after 20 h. It is noteworthy that in the presence of 0.2 mol-% of (*R*,*S*)-**13**, (*E*)-**1** was fully isomerized after 72 h at 20°. This unprecedented reactivity allowed us to isolate (*S*)-**4** in 95% yield and 97% e.e. without any traces of isocitronellal[12]), despite an only partial aromatic substitution at the diphosphino moiety. As underlined earlier, the catalytic cycle proceeds by a *Michaelis-Menten*-type mechanism, where the isomerization is markedly retarded by the increasing quantity of the coordinating enamine produced [1d].

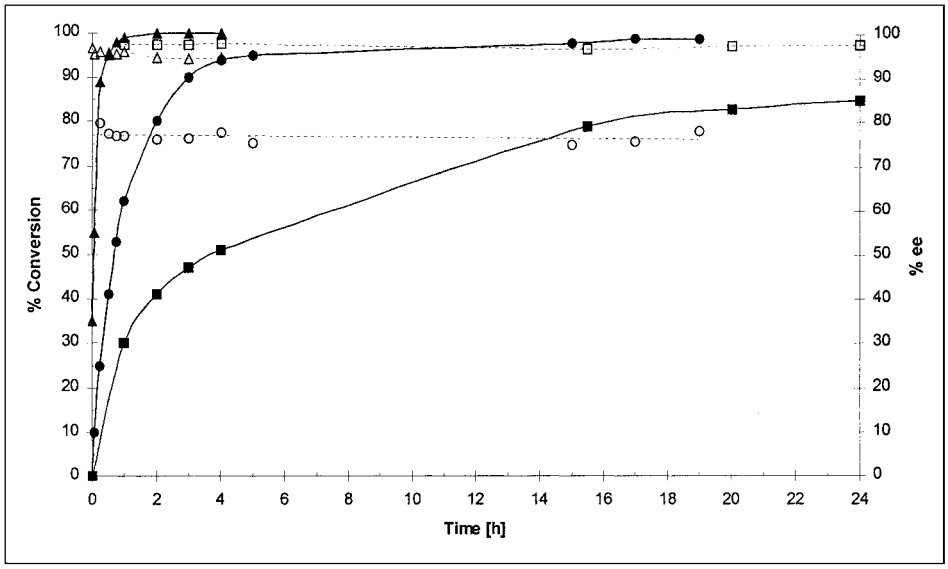

Fig. 1. *Isomerization of* (E)-**1** *performed in the presence of 0.2 mol-% of [Rh(ligand)(cod)]CF_3SO_3 in THF: kinetics* (–●–) *and e.e.* (··○··) *with ligand (*R,S*)-***12** *at 66°; kinetics* (-▲-) *and e.e.* (··△··) *with ligand (*R,S*)-***13** *at 66°; kinetics* (–■–) *and optical purity* (··□··) *with ligand (*R,S*)-***13** *at 20°*

Very recently, *Salzer et al.*, reported the daniphos diphosphino analogues (*R*,*S*)-**17** to (*R*,*S*)-**19** [40a], where the ferrocene subunit of josiphos is replaced by a (η^6-benzene)chromium moiety[14]). When (*E*)-**1** was isomerized in refluxing THF in the presence of 1.0 mol-% of [Rh{(*R*,*S*)-**17**} (cod)]CF_3SO_3, an incomplete conversion of 44% was observed after 20 h, affording, after hydrolysis, (–)-citronellal ((*S*)-**4**) in 76% e.e. This isomerization is slightly less selective than that performed in the presence of the corresponding tetraphenyldiphosphino josiphos analogue[9]). On the other hand, with 0.25 mol-% of ligands (*R*,*S*)-**18** or (*R*,*S*)-**19** under the same conditions, (*E*)-**1** was fully converted to (*S*)-**4** of 94 and 96% e.e., respectively (*Entries 14* and *15*, *Table 1*).

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14) For a (–)-(*S*)-tricarbonyl [(α*R*)-2-(diphenylphosphino)-α,*N*,*N*-trimethylbenzenemethanamine]chromium analogue, see [40b] and ref. cit. therein.

Thus, in this case, the enantioselectivity is slightly higher than in the isomerization catalyzed by the analogous diphosphino ligands (*R*,*S*)-**12** or (*R*,*S*)-**13** (see *Table 1*, *Entries 8* and *9*). Alternatively, in THF at 20° in the presence of 0.20 mol-% of [Rh{(*R*,*S*)-**19**}(cod)]CF_3SO_3, only 70% of conversion was reached (94% e.e.) after 72 h, thus exhibiting slower kinetics as compared to the isomerization catalyzed by its josiphos analogue (*R*,*S*)-**13**[15]).

Based on an *ab initio* model as well as ^{31}P-NMR studies and in full agreement with isotope-labeling experiments [19b], *Noyori* suggested a new N-triggered mechanism *via* a distorted octahedral Rh^{III} hydride [23a] instead of the classical addition/elimination of a metal hydride or a π-allyl mechanism, to explain the overall suprafacial 1,3-H shift producing the (*E*)-configured enamines from the allylamines [1d]. Using *N*,*N*,3-trimethylbut-2-en-1-amine as a model of both geranyl- and neryldiethylamines, and applying the geometrical parameters calculated by *Noyori* [23a], we optimized a simplified molecular seco-model for the possible transition-state precursors derived from (*R*)-**5** and (*R*,*S*)-**13**, where the second allylamine/enamine on the metal is mimicked by a Me_3N molecule. First of all, we confirm that the intermediate **A** (*Fig. 2*) earlier postulated for binap is, among the four possible approaches, the lowest in energy [23a]. The situation of (*R*,*S*)-**13**, with its pseudoequatorial secondary Me group bisecting both ^{t}Bu moieties, is more complicated. Indeed, of all eight stereoisomers, with respect to the Rh center, those whose allylamine is facing the bulky di(*tert*-butyl)phosphino moiety, are much higher in energy than **B**. Similarly, the structures where the Rh–H bond is *syn*-periplanar to the pseudoaxial P–Ph bond are also higher in energy than **B** or **C**. This latter intermediate, 1.2 kcal/mol higher in energy than **B**[16]), is an epimeric cyclometalated allylamine at C(1), generating the (*E*)-enamine of opposite topicity. It is noteworthy that, in contrast to the seven-membered ring chelate of binap, the pseudoaxial/equatorial Rh–Ph bonds are pointing in slightly different directions with respect to those of the distorted six-membered ring of the (*R*,*S*)-**13** complex. This allows, with regard to the remaining skeleton, re-orientation of the aromatic planes of the P-substituents, which become practically orthogonal to each other when both ligands are compared (see **D**). Nevertheless, this does not influence the overall sense of induction[17]).

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[15]) It was already underlined that subtle electronic changes in ligand properties may drastically influence both catalytic activity and stereoselectivity [40c]. Indeed, when the arene ring of the (arene)tricarbonylchromium catalysts (*R*,*S*)-**18** or (*R*,*S*)-**19** was substituted with an additional electron-donating group at C(4), both kinetics and selectivity were slightly diminished (94 → 90% and 96 → 88% e.e., resp., for 0.25 mol-% in refluxing THF) with the increase of the electron-donating properties of the substituent. A higher basicity of the diphosphino ligand should hypothetically shorten the P–Rh bond length, and could thus have a conformational influence on the competitive transition states. Alternatively, substitution at the aromatic ring may also affect the orientation of the $Cr(CO)_3$ moiety. Finally, when the two Ph substituents of the ligand (*R*,*S*)-**18** were replaced by sterically more-demanding aromatic groups, the selectivity remained constant but the reaction rate slowed (44% conversion). We are particularly indebted to Prof. *Salzer* for providing us with these unreported non-commercial diphosphino ligands.

[16]) Due to its simplification, this model is only qualitative, allowing a better evaluation of the acceptable coordination possibilities.

[17]) Calculations suggest that the {(*R*)-1-{(1*S*)-2-[di(*tert*-butyl)phosphino]ferrocenyl}ethyl}di(*tert*-butyl)phosphine and {(*R*)-1-{(1*S*)-2-[di(*tert*-butyl)phosphino]ferrocenyl}ethyl}diphenylphosphine ligands should also be highly enantioselective in favour of (*S*)-**3**.

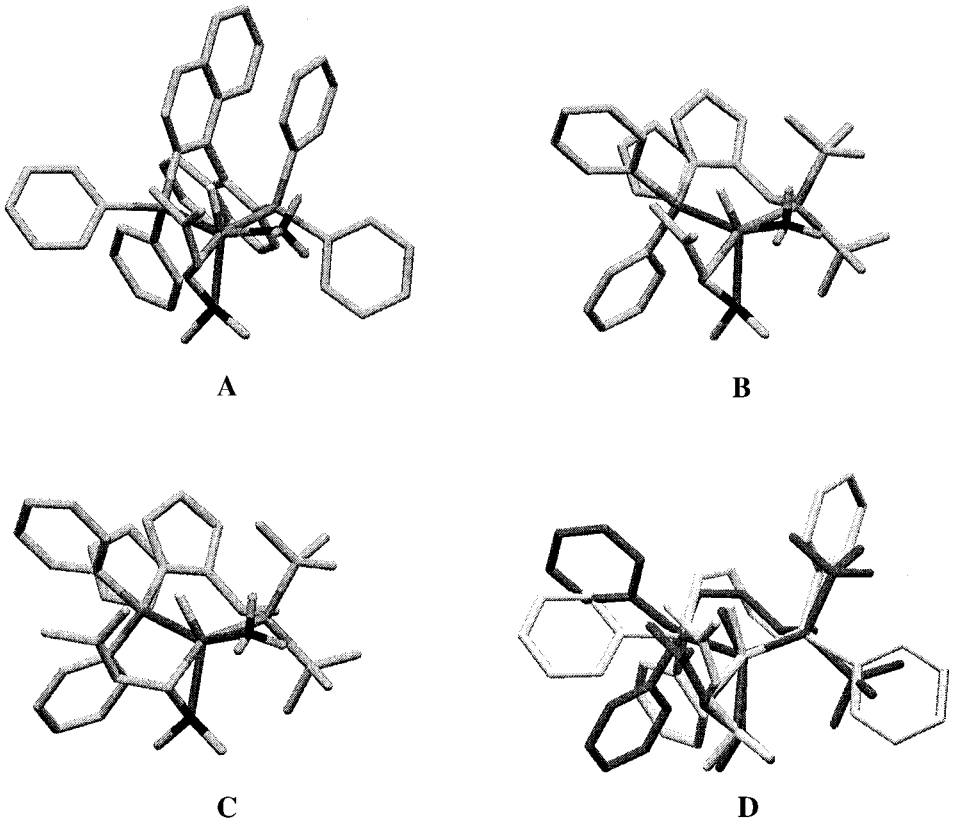

Fig. 2. *Favoured approaches of the allylamine according to the intermediates postulated by* Noyori, *rationalizing the observed absolute configuration of (*S*)-***3*** *from (*E*)-***1***, with ligand (*R*)-***5*** (**A**) or (*R,S*)-***13*** (**B**), and superimposition of their P-substituents with the partial structure of ligand (R,S)-**13** in dark* (**D**). *Intermediate* **C**, *leading to (*R*)-***3***, corresponds to the second more-stable intermediate with ligand (*R,S*)-**13**.*

Conclusion. – The Rh^{I}-catalysed synthesis of optically pure citronellal in the presence of the *t*Bu-josiphos ligand (*R,S*)-**13**, commercially available also as the enantiomer, compares favourably with the use of the binap ligand (*R*)-**5** (similar selectivity of 97% e.e. after complete conversion of (*Z*)- or (*E*)-**1**). For silica-gel- or polymer-supported diphosphino ligands, the selectivity is usually similar to that of their counterparts applied under homogeneous conditions, but the former ligands exhibit a lower reactivity. Moreover, the sense of induction may depend on the support/linker used (silica gel *vs.* polystyrene for (*E*)- or (*Z*)-**1**, *Entry 10 vs. Entry 12*), while, under homogeneous conditions, the sense of induction of the diphosphinoferrocenes may be dependent on the substitution pattern (cyclohexyl *vs. tert*-butyl, *Entry 8 vs. Entry 9*) when the allyl alcohols (*E*)- or (*Z*)-**2** are substrates. The most promising supported ligand is the polymer-anchored binap (*R*)-**6**, in terms of reactivity, selectivity, and recoverability, with a turnover of more than 14400 (see *Exper. Part*).

We are indebted to Drs. *R. Schmid* (*F. Hoffmann-La Roche AG*) for samples of (*R*)- and (*S*)-**7**, to *B. Pugin* (*Novartis AG*) for samples of (*R*,*S*)-**14**, (*R*,*S*)-**15**, and (*R*,*S*)-**16**, as well as to *J. T. Mohr* (*Schering AG*) for samples of steroid-derived binap analogues [41][42]. Dr. *F. Spindler* (*Novartis AG*) is thanked for modified non-commercial josiphos analogues [32][42].

Experimental Part

General. All reagents were stored and prepared in a glove box, and all reactions were performed under N_2 (*Schlenk* line). THF was distilled over $LiAlH_4$. GLC and prep. GLC: *Hewlett-Packard 6890* instrument equipped with a flame-ionization detector (250°) coupled to a *Hewlett-Packard Chemstation 6.03*; capillary columns *Chrompack*, *DB-Wax* (15 m, 0.25 mm), and *DB-1* (15 m, 0.25 mm). Prep. GLC: *Megabore* column *SPB-1* (30 m, 0.53 mm). Bulb-to-bulb distillation: *Büchi GKR-50* oven. Optical rotations: *Perkin-Elmer 241* polarimeter; with pure material, when solvent and concentration not specified. IR Spectra: *Perkin-Elmer 297* spectrometer with *Golden-Gate* reflection device; polymer-anchored ligands in KBr; in cm^{-1}. NMR: *Bruker WH-400* and *Bruker AMX-360* spectrometers; ^1H at 400, ^{13}C at 90, and ^{31}P at 146 MHz in $CDCl_3$ when not specified otherwise; chemical shifts in ppm rel. to $SiMe_4$ or standardized with Ph_3PO (29.64 ppm). MS: *Varian MAT-112* spectrometer (*ca.* 70 eV); *m*/*z* (intensity in % rel. to the base peak (=100%)). Calculations were performed with a *Silicon-Graphics Indigo-2* workstation and the program 'MacroModel', version 5.5 [43].

Starting Materials. Diethylgeranylamine ((*E*)-**1**) [21] free from diethylnerylamine ((*Z*)-**1**) [22] and *vice versa*; geraniol ((*E*)/(*Z*)-**2** 96:4; *Fluka*); nerol ((*E*)/(*Z*)-**2** 0.5:99.5; *Fluka*). $[Rh(cod)Cl]_2$ (*Strem*), $[Rh(nbd)Cl]_2$ (*Strem*), $[Rh(cod)_2]CF_3SO_3$ (*Strem*), $[Rh(cod)_2]BF_4$ (*Fluka*), (*R*)-**5** (*Fluka*), (*R*)-**6** (*Oxford Asymmetry*), (*R*,*S*)-**12** (Fluka), (*R*,*S*)-**13** (*Fluka*), *TentaGel® S-COOH* (*Fluka*), *TentaGel® S-Br* (*Fluka*).

*(−)-(*S*)-6,6′-Bis(diphenylphosphino)[1,1′-biphenyl]-2,2′-diol* (*S*)-**8**. To a soln. of ((−)-(*S*)-MeO-biphep; (*S*)-**7**) [14] (^{31}P-NMR: −15.36; $[\alpha]_D^{20} = -42.5$ ($c = 1.0$, $CHCl_3$)) (300 mg, 0.515 mmol) in CH_2Cl_2 (3 ml), BBr_3 (120 µl, 1.24 mmol) was added dropwise at 0°. After 18 h at 20°, the soln. was cooled, cautiously hydrolysed, diluted with CH_2Cl_2, washed with H_2O, $NaHCO_3$ soln., and H_2O, dried ($MgSO_4$), and concentrated under medium, then high, vacuum: quantitatively (*S*)-**8**. $[\alpha]_{365}^{20} = -109.0$ ($c = 0.8$, $CHCl_3$). M.p. 215–217°. IR: 3533, 3051, 2922, 1567, 1446, 1433, 1279, 1205. ^1H-NMR: 1.6 (br. *s*, 2 H); 6.8 (*m*, 4 H); 7.15 (*m*, 4 H); 7.25 (*m*, 18 H). ^{13}C-NMR: 116.4 (2*d*); 126.9 (2*d*); 128.1 (2*d*); 128.2 (4*d*); 128.5 (4*d*); 128.6 (4*d*); 129.1 (2*d*); 130.6 (2*d*); 133.1 (2*d*); 134.5 (2*d*); 136.7 (2*s*); 137.2 (2*s*); 141.2 (4*s*); 154.3 (2*s*). ^{31}P-NMR: −16.20 at −40°. MS: 554 (5, $M^{+\bullet}$), 491 (13), 369 (100), 262 (50), 183 (65).

*(−)-{(*S*)-6,6′-Bis[(trimethylsilyl)oxy][1,1′-biphenyl]-2,2′-diyl}bis[diphenylphosphine]* (*S*)-**9**. To a soln. of (*S*)-**8** (24 mg, 0.043 mmol) and Et_3N (30.1 µl, 0.216 mmol), Me_3SiCl (19.2 µl, 0.151 mmol) was added dropwise at 0°. After 1 h at 20°, the mixture was diluted with Et_2O, extracted with H_2O, dried ($MgSO_4$), and evaporated under medium then high vacuum.

Alternatively, (*S*)-**8** (50 mg, 0.09 mmol) was treated in CH_2Cl_2 (1 ml) with 1-trimethylsilyl)-1*H*-imidazole (33 µl, 0.225 mmol) at 0°. After 1 h at 20°, the soln. was diluted with CH_2Cl_2, extracted with cold H_2O, dried ($MgSO_4$), and evaporated: (*S*)-**9** (quant.). $[\alpha]_{365}^{20} = -342.0$ ($c = 1.4$, $CHCl_3$). M.p. 55–57°. IR: 3050, 2923, 2853, 1564, 1446, 1277, 1252, 966, 851. ^1H-NMR: −0.05 (*s*, 18 H); 6.65–6.9 (*m*, 4 H); 7.15–7.20 (*m*, 10 H); 7.2–7.4 (*m*, 12 H). ^{13}C-NMR: 0.23 (6*s*); 117.8 (2*d*); 127.1 (2*d*); 127.6 (2*d*); 128.0 (2*d*); 128.1 (2*d*); 128.2 (10*d*); 133.2 (2*d*); 134.2 (2*d*); 136.3 (2*s*); 137.9 (2*s*); 138.9 (2*s*); 139.4 (2*s*); 153.7 (2*s*). ^{31}P-NMR: −15.96; MS: 698 (0, $M^{+\bullet}$), 513 (100), 441 (68), 369 (88), 349 (50), 183 (75).

TentaGel® S-COOH *(*S*)-6,6′-Bis(diphenylphosphino)-2′-hydroxy[1,1′-biphenyl]-2-yl Ester* (*S*)-**10**. (*S*)-**8** (100 mg, 0.18 mmol) was added to a suspension of DCC (40.3 mg, 0.195 mmol), DMAP (1.8 mg, 0.015 mmol), and *TentaGel® S-COOH* (761 mg, 0.19 mmol) in CH_2Cl_2 (5 ml). After 24 h at 20° under orbital stirring (TLC (CH_2Cl_2): no (*S*)-**8** left), the mixture was filtered through a *Büchner* funnel and the solid successively washed with aq. sat. $NaHCO_3$ soln. (2 × 10 ml), H_2O (2 × 10 ml), THF/H_2O 1:1 (2 × 10 ml), THF (10 ml), EtOH (2 × 10 ml), CH_2Cl_2 (2 × 10 ml), and Et_2O (10 ml), and finally dried for 18 h at 50° under high vacuum: (*S*)-**10** (664 mg, 77%). IR: 3600, 3000, 2800, 1800, 1600. ^{31}P-NMR (5 mm diameter NMR tube, under N_2 filled (2 cm) with (*S*)-**10** and enough $CDCl_3$ to wet the beads, without creating two phases; recording as for a homogeneous soln.): −15.27; −15.40. The ^{31}P-NMR analysis was repeated with a known concentration of Ph_3P as internal standard at −6.25 ppm, which allowed the estimation of the ligand loading on the resin to be 0.1 mol/g.

*(*S*)-6,6′-Bis(diphenylphosphino)-2′-[(*TentaGel® S-*yl)oxy] [1,1′-biphenyl]-2′-ol* ((*S*)-**11**). BuLi (117 µl, 0.19 mmol; 1.6M in hexane) was added dropwise to a suspension of (*S*)-**8** (100 mg, 0.18 mmol) in THF (2 ml).

After 1 h, this soln. was added to a suspension of *TentaGel® S-Br* (487 mg, 0.18 mmol) in THF (5 ml). After 48 h of orbital stirring, the mixture was filtered through a *Büchner* funnel and the solid successively washed with H_2O (2×10 ml), THF/H_2O 1:1 (2×10 ml), THF (10 ml), EtOH (2×10 ml), CH_2Cl_2 (2×10 ml), and Et_2O (10 ml), and finally dried for 18 h at 50° under high vacuum: (*S*)-**11** (72%, 412 mg). IR: 3600, 3000, 2900, 2000, 1800, 1600, 1500. ^{31}P-NMR: −14.73.

Isomerization under Homogeneous Conditions: General Procedure. A soln. of $[Rh(cod)_2]CF_3SO_3$ in THF (0.01M; 2.5 ml, 0.025 mmol) was added to (*R*,*S*)-**13** (13.6 mg, 0.025 mmol) (25-ml flask with key stopper). After stirring for 1 h, 1.0M (*E*)-**1** in THF (10 ml, 10 mmol) was added and the key-stopper-closed flask transferred and equipped with a condenser connected to a *Schlenk* line. The condenser was purged with Ar, then the key stopper opened, and the clear soln. refluxed for 20 h. To the soln. cooled to 0°, AcOH/H_2O 1:4 (5 ml) was added, and after 5 min at 0° and then 30 min at 20°, the soln. was extracted with Et_2O, the extract washed with H_2O (10 ml), 15% NaOH soln. (2×10 ml), H_2O to neutral, dried ($MgSO_4$), concentrated, and then bulb-to-bulb distilled (100–110°/10 mbar): pure (*S*)-**4** (92% yield). $[\alpha]_D^{20} = -13.1°$; 92% e.e.

Isomerization under Heterogeneous Conditions: General Procedure. $[Rh(cod)_2]CF_3SO_3$ (0.01M in THF; 3.325 ml, 0.03325 mmol) was added to a suspension of the polymer-anchored binap (*R*)-**6** (78 mg, 0.03325 mmol; 0.426 mmol/g) in THF (6.2 ml) (100-ml flask with key stopper). The mixture was stirred with an orbital stirrer for 1 h, then (*E*)-**1** (3.15 ml, 2.613 g, 12.5 mmol) was added. The suspension was refluxed for 20 h under orbital stirring. The decanted suspension was separated from the supernatant soln., and a fresh amount of (*E*)-**1** was added. The above procedure was repeated 36 times. The 37 portions were hydrolysed and analysed separately to afford, after global bulb-to-bulb distillation, pure (−)-(*S*)-citronellal ((*S*)-**4**) in 95% yield and 97% e.e. $[\alpha]_D^{20} = -13.7°$.

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