Enantioselective Carbometalation of Cinnamyl Derivatives: New Access to Chiral Disubstituted Cyclopropanes—Configurational Stability of Benzylic Organozinc Halides

Stephanie Norsikian,[b] Ilan Marek,*[a] Sophie Klein,[b] Jean F. Poisson,[b] and Jean F. Normant*[b]

Abstract: A stoichiometric or catalytic amount of (−)-sparteine can serve as a promoter for the enantioselective carbolithiation of cinnamyl derivatives by primary and secondary organolithium compounds. The enantiofacial choice of the addition reaction is dependent on the stereochemistry of the initial double bond. The resulting benzylic organolithium compounds can be derivatized to a linear phenylated chain that bears two contiguous stereogenic centers with given configurations. The use of the dimethyl acetal of the (*E*)-cinnamyl alcohol allows the highest enantioselective carbolithiation and by simply warming the reaction mixture to room temperature, the resulting benzylic organolithium intermediate undergoes a 1,3-elimination to give the chiral disubstituted cyclopropane in high enantiomeric excess (90–95% *ee*). Another significant finding is the observation that the Li–Zn transmetalation in a benzylic species occurs with inversion of configuration, and the corresponding acyclic benzylic zinc halides have observable configurational stability at −30 °C.

Keywords: asymmetric catalysis · carbolithiation · cyclopropane · organolithium compounds · (−)-sparteine

Introduction

The formation of carbon–carbon bonds by means of organometallic reagents, which began after discoveries made by Barbier and Grignard, has commonly been achieved by their reactions with polar carbon electrophiles. In the search for new types of selective formation of carbon–carbon bonds by the use of organometallic reagents, and following the pioneering Ziegler addition of some anionic initiators to nonpolarized carbon–carbon bonds,[1] the controlled carbometalation reaction has emerged as a new tool. Carbometalation reactions are reactions which result in the addition of the carbon–metal bond of an organometallic reagent across a carbon–carbon double bond to produce a new organometallic compound in which the newly formed carbon–metal bond can be used for further synthetic transformations. An outstanding number of organometallic additions to C=C bonds have already been reported and reviewed.[2, 3]

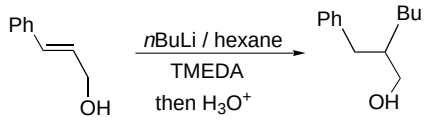
[a] Dr I. Marek
Department of Chemistry, Technion-Israel Institute of Technology
Technion City, Haifa 32000 (Israel)
Fax: (+972) 4-823-37-35
E-mail: chilanm@tx.technion.ac.il

[b] Prof. J. F. Normant, S. Norsikian, S. Klein, J. F. Poisson
Laboratoire de Chimie des Organoéléments, associé au CNRS
Tour 44–45, Université P. et M. Curie
4 Place Jussieu, F-75252 Paris Cedex 05 (France)
Fax: (+33) 1-44-27-71-50
E-mail: normant@ccr.jussieu.fr

If an efficient method was available to render such a process asymmetric, it would acquire a tremendous utility as a method to create asymmetric vicinal carbon atoms, particularly if acyclic substrates are employed. However, until now, reports of such enantioselective carbometalation reactions are scarce,[4] in spite of the increasing worldwide interest. This is because of the difficulties associated with the enantiofacial differentiation of an unactivated alkene. The most important results in this field come from the asymmetric ethylmagnesiation reactions[5] developed mainly by Hoveyda et al. and by the asymmetric carboalumination reaction developed by Negishi et al.[6] In both cases, the enantioselectivities arise from chiral zirconium derivatives.[6, 7] Moreover, the enantioselective allylmetalation of a cyclopropene ketal with a chiral bisoxazoline ligand was also reported by Nakamura et al.[8] Some years ago, we were interested in the carbometalation of unstrained and unactivated olefins by the synthesis of geminate organobimetallic derivatives.[9] Our attention was attracted to a report by Kuwajima et al.[10] on the diastereoselective carbolithiation reaction of cinnamyl alcohol. Indeed, one very interesting result arose from this work: the carbolithiation of these substrates proceeded in hexane only *in the presence of TMEDA* to give the carbometalated product (Scheme 1).[11] .

This observation led us to consider the enantioselective carbolithiation reaction of cinnamyl derivatives since it would only be necessary to switch from an achiral diamine (TMEDA) to a chiral one. But what kind of chiral diamine

  0947-6539/99/0507-2055 $ 17.50+.50/0



Scheme 1. Carbolithiation of cinnamyl alcohol.

should be the most appropriate as a chiral ligand for alkyllithium?. Fortunately, Hoppe et al. have shown that the complexation of one equivalent of *s*BuLi with one equivalent of (−)-sparteine leads to a chiral organometallic which induces enantioselective deprotonation of achiral alkyl carbamates.[12] The lupine alkaloid (−)-sparteine is readily available and is obtained through the extraction of certain papilionaceous plants.[13] This diamine is also admirably suited for the enantioselective deprotonation of *N*-Boc pyrrolidines[14] and can also be utilized in the thermodynamically controlled equilibration of configurationally labile epimeric organolithium derivatives.[12, 14] Therefore, we decided to study the effect of the complexation of alkyllithium with (−)-sparteine in carbometalation reactions, rather than in the metalation reactions previously described.

Abstract in Hebrew: .

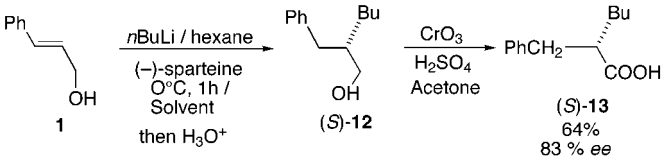
ניתן להשתמש בכמויות סטוכיומטריות או קטליטיות של (-) ספרטאין לקרבוליתיאציה אננטיוסלקטיבית של נגזרות צינמיליות באמצעות תרכובות אורגנוליתיום ראשוניות ושניוניות. ההעדפה האננטיוסלקטיבית של תגובת הסיפות תלויה בסטריאוכימיה של הקשר הכפול במגיב. מתוצר בנזיל הליתיום המתקבל ניתן לקבל את השרשרת הלינארית המתאימה הכוללת שני מרכזים סטריאוגנים סמוכים בעלי קופיגורציה ידועה. שימוש בדימתיל אצטל של (E) - צינמיל אלכוהול נותן את דרגת האננטיוסלקטיבית הגבוהה ביותר בתגובת הקרבוליתיאציה, ובחימום של תערובת התגובה לטמפרטורת החדר, חומר הביניים (הבנזיל ליתיום) המתקבל עובר תגובת אלמינציה מסוג 1,3 כדי לתת את הציקלופרופן הדי-מותמר הכירלי בניצולת ee גבוהה (95%-90%).

ממצא מעניין אחר הוא שתגובת הטרנס-מתלציה של תרכובות בנזיל ליתיום בה מוחלף ליתיום באבץ, מתרחשת תוך היפוך של קונפיגורציה, והתוצר המכיל אבץ יציב קונפיגורציונית ב- 30^0C-.

Abstract in French: *Une quantité stoechiométrique, ou catalytique, de (−)-spartéine permet d'effectuer la carbolithiation énantiosélective de dérivés cinnamiques par les organolithiens primaires et secondaires. Le choix facial dépend de la stéréochimie ((E),(Z)) de la double liaison. Les organolithiens benzyliques ainsi formés peuvent être utilisés en synthèse pour accéder à des chaînes linéaires phénylées portant 2 centres stéréogènes contigus, de configuration bien définie. L'emploi d'un acétal dérivé de l'alcool cinnamique (E) permet d'atteindre la meilleure énantiosélection, et par réchauffement du milieu réactionnel à température ambiante, le lithien intermédiaire provoque une élimination 1,3 pour engendrer un cyclopropane disubstitué avec un ee élevé (90–95%). Un autre aspect important de ce travail concerne la transmétallation de ces lithiens benzyliques en zinciques correspondants avec inversion de configuration. Ces zinciques benzyliques ont une bonne stabilité configurationnelle à −30°C*

Results and Discussion

The addition of (*E*)-cinnamyl alcohol (**1**) to a solution of *n*BuLi in various solvents in the presence of (−)-sparteine (1 equiv) led to a red solution which was then hydrolyzed to give the corresponding alcohol (Scheme 2) in the yields and *ee* values shown in Table 1.



Scheme 2. Enantioselective carbolithiation of cinnamyl alcohol.

Table 1. Effect of the solvent on the enantioselectivity.

Entry	Solvent	Yield [%][a]	*ee* [%][b]
1	THF	61	0
2	Et_2O	67	20
3	hexane	81	78
4	cumene	82	83

[a] Based on pure isolated material. [b] Determined by ^{31}P NMR spectroscopy, see ref. [16].

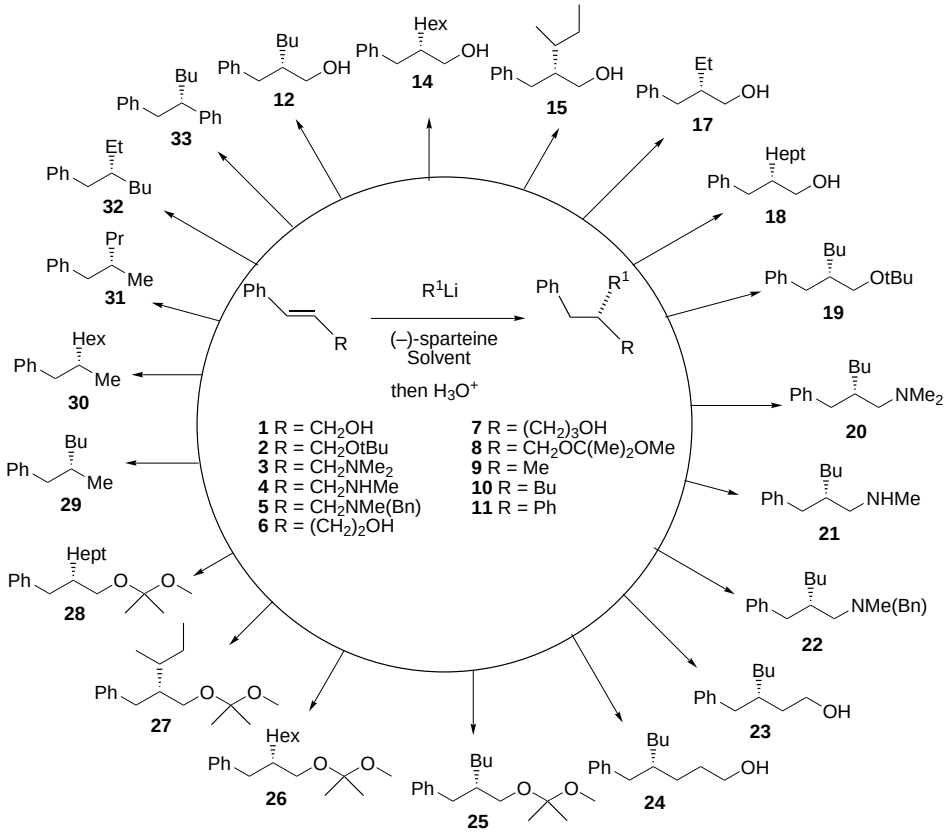
As expected, (−)-sparteine has a most pronounced effect in the absence of donor solvents, such as diethyl ether or THF (Table 1, entries 1 and 2). Indeed, in hexane (entry 3) or even better in cumene (entry 4),[15] higher *ee* values are obtained for the carbolithiation reaction. The purity of the chiral alcohol **12** was determined by the ^{31}P NMR analysis of derived diastereomeric phosphorus products.[16] The absolute configuration of the *chiral* center was determined to be *S*, through comparison with data[17] reported for the corresponding acid (Scheme 2).

Thus, this simple method (carbolithiation of cinnamyl substrates by complexation of one equivalent of (−)-sparteine with alkyllithium) produced the first enantioselective introduction of an *n*-butyl group across a double bond by means of a simple alkyllithium compound.[18]

In order to examine the scope of this reaction, we decided to extend this carbolithiation reaction to other alkyllithium compounds and to other cinnamyl substrates (Scheme 3, Table 2).

Commercially available (in hydrocarbon solvent) primary alkyllithium compounds (Table 2, entries 1 and 2) as well as a secondary alkyllithium compound (Table 2, entry 3) led to good *ee* values, whereas the addition of a tertiary alkyllithium compound (Table 2, entry 4) gave the racemic compound in a low yield. These results correlated well with the extent of the complexation of the alkyllithium compounds with (−)-sparteine: the complexation is strongest with the sterically less demanding organolithium derivatives and weakest with sterically congested environments, such as *t*BuLi.[19] However, when the same reaction was applied to *n*BuLi in the presence of LiBr, and *independent of the nature of the solvent* (hexane, cumene, diethyl ether, or THF), no carbolithiation reaction

0947-6539/99/0507-2056 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 7



Scheme 3. Enantioselective carbolithiation of cinnamyl derivatives.

Table 2. Generalization of the carbolithiation reaction.

Entry	Substrate	RLi	Product	Solvent	Yield [%][a]	*ee* [%][b]
1	**1**	*n*BuLi	**12**	cumene	85	83
2	**1**	*n*HexLi	**14**	cumene	76	87
3	**1**	*s*BuLi	**15**	cumene	65	72
4	**1**	*t*BuLi	**16**	cumene	40	0
5	**1**	*n*BuLi/LiBr[c]	**12**	cumene	60	56
6	**1**	*n*BuLi/LiBr[d]	**12**	cumene	65	66
7	**1**	EtLi/LiBr[d]	**17**	cumene	68	85
8	**1**	HeptLi/LiBr[d]	**18**	cumene	50	63
9	**1**	MeLi	–	–[g]	–	–
10	**1**	PhLi	–	–[g]	–	–
11	**2**	*n*BuLi	**19**	hexane	82	80
12	**3**	*n*BuLi	**20**	hexane	71	82[f]
13	**4**	*n*BuLi	**21**	Et_2O	62	66
14	**5**	*n*BuLi	**22**	hexane	64	84
15	**6**	*n*BuLi	**23**	cumene	72	70
16	**7**	*n*BuLi	**24**	cumene	75	70
17	**8**	*n*BuLi	**25**	cumene	77[e]	95
18	**8**	nHexLi	**26**	cumene	70[e]	94
19	**8**	*s*BuLi	**27**	cumene	80[e]	90
20	**8**	HeptLi/LiBr[d]	**28**	cumene	50[e]	90
21	**9**	*n*BuLi	**29**	hexane	83	85
22	**9**	*n*HexLi	**30**	hexane	86	84
23	**9**	*n*PrLi/LiCl[d]	**31**	hexane	92	76
24	**10**	EtLi/LiCl[d]	**32**	hexane	73	86
25	**11**	*n*BuLi	**33**	cumene	81	70

[a] Based on pure isolated product. [b] Determined by ^{31}P NMR spectroscopy, see ref. [16]. [c] This reaction was carried out in the presence of four equivalents of (−)-sparteine. [d] The organolithium compound was prepared in Et_2O and the addition was carried out in cumene, see text. [e] After deprotection of the acetal (yield of the deprotection >95%). [f] The enantioselectivity was determined by chiral HPLC on Chirasel OD. [g] THF, Et_2O, cumene, and hexane were tested without success.

was observed! This result implicates a mixed aggregate of lithium halide and sparteine which deactivates the carbolithiation reaction.[20] It was then necessary to add sufficient sparteine to combine with all the lithium salts present in solution. Indeed, the carbolithiation reaction of cinnamyl alcohol with three equivalents of *n*BuLi and then three equivalents of LiBr occurred in the presence of four equivalents of (−)-sparteine (one equivalent of diamine for each lithium bromide and one equivalent for the alkyllithium). This mixture gave the carbometalated product with 56% *ee* (Table 2, entry 5). Several other attempts were made to try to selectively complex the lithium salt with a nonchiral diamine, whereby the alkyllithium would be complexed by the (−)-sparteine; however, it did not succeed.[21] Finally, in order to minimize the amount of chiral ligand required for the alkyllithium, which was prepared in diethyl ether from BuBr and Li, we took advantage of the insolubility of the lithium salt in cumene. After the formation of the alkyllithium compound in Et_2O, dry cumene was added to the reaction mixture and Et_2O was removed under vacuum. Under these conditions, the carbometalation reaction required only one equivalent of (−)-sparteine to give the alkylated product in a moderate yield and with good enantioselectivity (Table 2, entry 6). Accordingly, EtLi/LiBr (from EtBr + Li) as well as heptyllithium/LiBr (from bromo-1-heptane + two equivalents of *t*BuLi) were added to the olefin to produce the products with good enantioselectivity (Table 2, entries 7 and 8, respectively). In contrast, whatever the experimental conditions used, the introduction of MeLi or PhLi groups failed in this reaction (Table 2, entries 9 and 10). Therefore, from these results we can deduce that the enantioselective carbometalation with a primary or a secondary alkyllithium compound occurs with good enantioselectivity, whereas the introduction of a tertiary group led to a racemic product; Me and Ph groups failed to react.

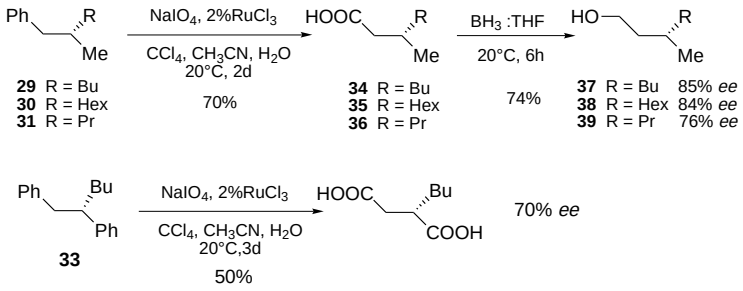
This reaction is not restricted to the cinnamyl alcohol as the substrate and several other cinnamyl derivatives were also carbometalated with good enantioselectivity. The presence of a free alcohol is not compulsory for the reaction to proceed and similar enantioselectivity (80% *ee*) was obtained with the *tert*-butyl ether derivative **2** (Table 2, entry 1 versus entry 11). The absolute configuration (*S*) was determined after deprotection of the *tert*-butyl ether to the alcohol **12**,[22] and comparison with an authentic sample. Cinnamyldimethylamine (**3**) also led to the carbometalated product with

82% *ee*[23] (Table 2, entry 12), whereas the enantioselective carbolithiation of the secondary amine **4** afforded a lower *ee* (66%)[24] (Table 2, entry 13). In this case, the reaction did not occur in the nonpolar solvent, as previously described; Et_2O was necessary to achieve this carbolithiation, and, as we have already seen (Table 1, entry 2), the carbolithiation in diethyl ether occurred with low enantioselectivity. This major drawback can be circumvented by the use of benzylmethylcinnamylamine (**5**) (Table 2, entry 14), followed by hydrogenolysis of the benzyl moiety of the addition product. The secondary amine was now obtained in 84% *ee*. The absolute configuration was determined by chemical correlation with an authentic sample prepared by tosylation of the alcohol **12** and displacement with dimethylamine.

Carbolithiation of 4-phenyl-3-buten-1-ol (**6**, homoallylic cinnamyl alcohol, Table 2 entry 15) and of 5-phenyl-4-penten-1-ol (**7**, Table 2, entry 16) also led to the carbometalated products with 70% *ee*.[25]

In the constant search to increase the enantioselectivity, we found that the dimethyl acetal **8** of the (*E*)-cinnamyl alcohol was the best substrate. Indeed, addition of *n*BuLi to this substrate, in the presence of one equivalent of (−)-sparteine, led, after hydrolysis and deprotection of the acetal moiety, to the alkylated product in 95% *ee*! (Table 2, entry 17).[26] The use of this acetal allows the reaction to be performed at −50 °C instead of 0 °C, as described for the carbolithiation of the cinnamyl alcohol (Table 2, entry 1). The same trend was observed for the carbolithiation with HexLi (94% *ee*), *s*BuLi (90% *ee*), or an alkyllithium in the presence of lithium salts, such as HeptLi/LiBr (90% *ee*) as shown in Table 2 (entries 18–20, respectively).

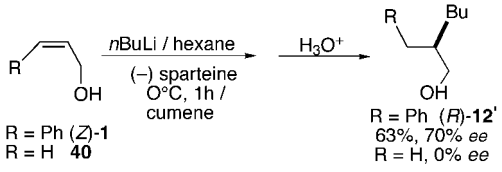
During this study, we realized that the presence of an allylic heteroatom, even in the β- or γ-position from the C=C unsaturation, was not very crucial for impeding a polymerization process, and we became aware of a report that styrene undergoes efficient addition reactions with a range of organolithium reagents without polymerization.[27] As we have been able to perform such a reaction on the 5-phenyl-4-penten-1-ol (**7**, Table 2, entry 16) without a trace of polymerization (whereas a nonfavorable seven-membered metalacycle between the alcoholate and the benzylic organolithium compound should be formed before hydrolysis), we investigated the enantioselective carbolithiation of β-substituted, nonfunctionalized styrenes.[28] Addition of *n*BuLi to β-methylstyrene (**9**) in the presence of one equivalent of sparteine, led in 4 h at −15 °C, to the corresponding carbometalated product in 85% *ee* (Table 2, entry 21) and without polymerization. Additions of *n*HexLi (Table 2, entry 22) and *n*PrLi/LiCl (Table 2, entry 23) also gave the products with good enantioselectivities (84 and 76% *ee*, respectively[29]). Optical purities as well as the absolute configurations of **29** and **30** were determined by comparison with authentic samples.[30] Moreover, these three carbometalated products (Table 2, entries 21–23) were also derivatized into the corresponding known acids[31] and then into the alcohols[32] (Scheme 4) in order to corroborate their optical purities by means of NMR spectroscopy.[16]



Scheme 4. Correlation of the carbometalated products.

Several other substrates were also carbometalated, such as β-butylstyrene (**10**) with EtLi/LiCl (entry 24) or, more interestingly, the *trans*-stilbene (**11**) with *n*BuLi (entry 25) with good enantioselectivities. In the latter example, we were able to perform a desymmetrization of the starting material into a chiral adduct (we were not able to prepare this product by the carbolithiation of **10** with PhLi since the latter failed to react (Table 2, entry 10). The corresponding optical purities as well as the absolute configurations were deduced by chemical correlation after oxidation[33] of the two phenyl rings into the corresponding acids[34] (Scheme 4). An elegant *intramolecular* carbometalation of cinnamyl substrates mediated by (−)-sparteine was published recently;[12, 35] this increases the scope of the reaction.

The stereochemistry of the olefin is crucial to the enantioselectivity of the carbolithiation. While the asymmetric carbolithiation of (*E*)-cinnamyl alcohol gave the (*S*)-alkylated product (Scheme 2), the reaction of the (*Z*)-**1** isomer, under the same experimental conditions, led to **12′**, the enantiomer of **12** (with a (*R*) configuration), with 70% *ee* (Scheme 5). Moreover, when the allylic alcohol is not substituted, as in the case of 2-propen-1-ol (**40**), the carbolithiation reaction led to the racemic alcohol (Scheme 5).

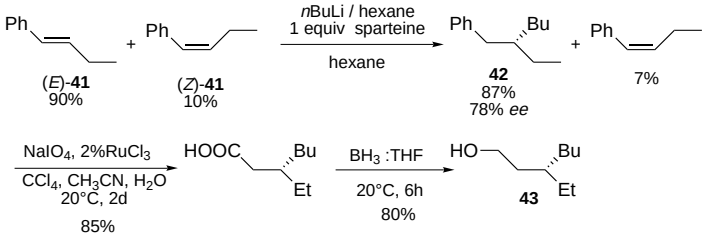


Scheme 5. Enantioselective carbolithiation of the (*Z*)-cinnamyl alcohol.

Thus, in order to obtain an enantioselective carbometalation reaction on a cinnamyl substrate, it is necessary to start with an ethylenic C=C bond of given geometry. The stereochemical selectivity is of tremendous utility since sparteine is commercially available in only one enantiomeric form; however, two enantiomeric carbometalated products are available, at will, according to the stereochemistry of the starting material.[36] Additionally, because the carbolithiation

0947-6539/99/0507-2058 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 7

of the (*Z*)-*β*-alkylstyrenes is slower than that of their (*E*) isomers,[37] we carried out a study of the kinetic resolution during the carbolithiation of *β*-ethylstyrene (**41**). Indeed, the addition of *n*BuLi to this substrate with an (*E*)/(*Z*) ratio of 90:10, gave the carbometalated derivative **42** in 87% yield and 78% *ee*; and the (*Z*)-**41** was still present in the crude reaction mixture (7%) (Scheme 6). The absolute configuration, (*S*), as well as the *ee* of **42** were determined after derivatization into the known alcohol **43**.



Scheme 6. Kinetic resolution in the carbometalation of *β*-ethylstyrene.

The enantioselective and straightforward synthesis of **42** and **43** is an interesting entry to the elaboration of the West fragment of a potent tripeptide immunomodulator.[38]

Since these cinnamyl derivatives were shown to be unreactive towards the addition of alkyllithium in hydrocarbon solvents without an external diamine, the potential for catalysis was obvious. The results, summarized in Table 3, show that addition of these derivatives to alkyllithium compounds and catalytic amounts of (−)-sparteine also leads to good enantiomeric excesses (70–92% *ee*). Even with 1% of chiral diamine, the chiral adduct is obtained in 85% *ee* (entry 4). Moreover, the product itself is not an enantioselective catalyst[39] since the hydrolysis of the reaction mixture after only 30% conversion led to the same *ee* value.

In the first part of this work, we hydrolyzed the newly formed benzylic organolithium compounds formed in these reactions in order to study the enantioselectivity of the carbolithiation step. However, since we had synthesized these benzylic organolithium compounds, we decided to study the stereochemical outcome of their reactions with several electrophiles and to create two chiral centers in a one-pot operation and in an acyclic system. Kuwajima et al.[10] have recently reported the reactivity of such benzylic organolithium compounds, in a racemic substrate, with electrophiles. When applied to our enantioselective approach on cinnamyl alcohol, the reactions proceeded in a highly diastereoselective manner (Scheme 7).

All compounds had the same ^{1}H and ^{13}C NMR spectra as the products prepared with TMEDA[10] instead of (−)-sparteine;

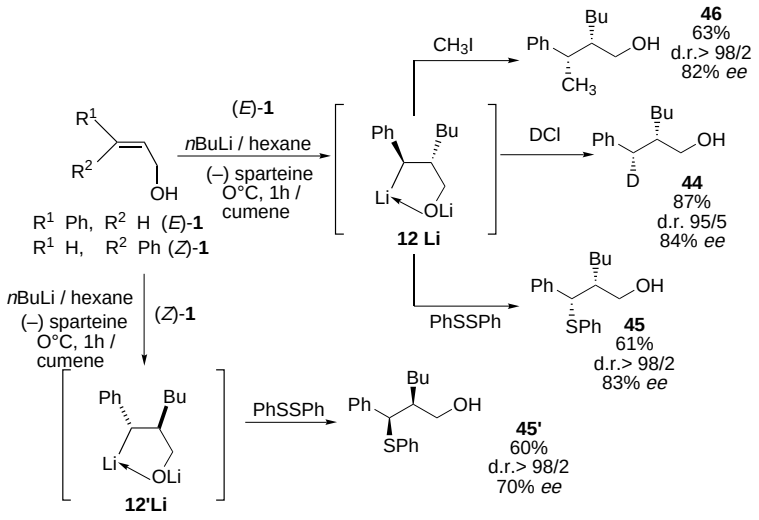
Table 3. Catalytic enantioselective carbolithiation reaction.

Entry	Substrate	RLi	Product	Sparteine (equiv)	Yield [%][a]	*ee* [%][b]
1	**1**	*n*BuLi	**12**	0.05	55	84
2	**3**	*n*BuLi	**20**	0.05	70	82
3	**8**	*n*BuLi	**25**	0.1	67[c]	92
4	**8**	*n*BuLi	**25**	0.01	50[c]	85
5	**8**	*n*HexLi	**26**	0.1	65[c]	92
6	**8**	*s*BuLi	**27**	0.1	77[c]	92
7	**9**	*n*BuLi	**29**	0.1	50	70

[a] Based on pure isolated product. [b] Determined by ^{31}P NMR spectroscopy, see ref. [16]. [c] After deprotection of the acetal (yield of the deprotection > 95%).

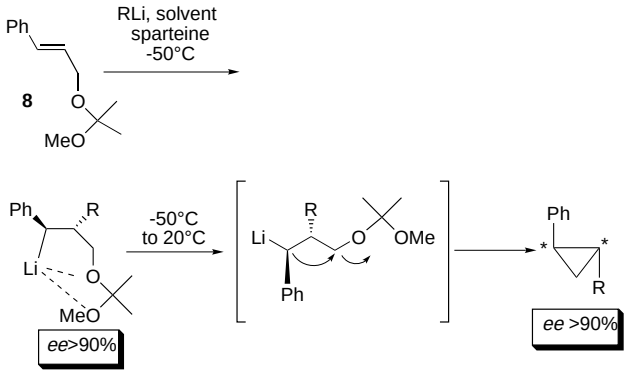
therefore, the reaction affords the *syn* product. The lithium alkoxide functionality in **12 Li**, obtained after the carbolithiation step, is able to fix the configuration at the benzyl position;[40] the *anti* intermediate is expected to be more stable (thermodynamic equilibration[41]) as a result of the steric hindrance of the phenyl and alkyl groups. The reaction of the benzylic organolithium thus formed with different electrophiles was determined to occur with *inversion* of configuration.[10, 42] In all cases examined, the products were obtained in a diastereomeric ratio (*dr*) of > 98:2 prior to purification and with the enantioselectivity of the carbolithiation step. When the starting material was the (*Z*)-**1** cinnamyl alcohol (see Scheme 5), the carbolithiation step led to the benzylic organolithium **12′ Li**, the opposite enantiomer of **12 Li** (Scheme 7). After reaction with diphenyl disulfide, the enantiomeric adduct **45′** was obtained with a diastereoselectivity of > 98/2 and an enantioselectivity of 70%. Thus, two chiral centers were created in a one-pot operation in a diastereospecific and enantioselective manner on an acyclic system.

We then studied the reaction of the benzylic organolithium with an intramolecular electrophile, namely the acetal moiety **8** described in Table 2. When the chelating moiety was a *dimethyl* methoxy methyl ether, the benzylic organolithium species formed was not stabilized, and it became thermally labile.[43] Indeed, when the reaction mixture was simply



Scheme 7. Creation of two chiral centers.

warmed to room temperature the benzylic organolithium intermediate led to the pure chiral *trans*-disubstituted cyclopropane,[44] by means of an internal nucleophilic substitution (Scheme 8 and Table 4).



Scheme 8. Enantioselective cyclopropanation.

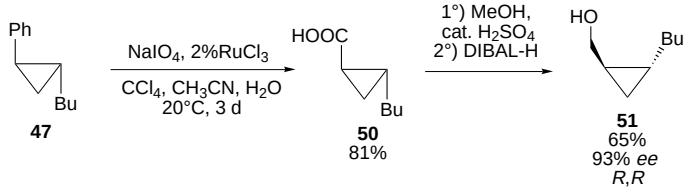
Table 4. Enantioselective cyclopropanation.

Entry[a]	RLi	Cyclopropane	(−)-Sparteine [equiv][b]	Solvent	Yield [%][c]	*ee* [%]
1	*n*BuLi	**47**	1	cumene	60	95
2	*n*BuLi	**47**	0.1	hexane	61	93
3	*s*BuLi[d]	**48**	0.1	hexane	66	92
4	HexLi	**49**	0.1	hexane	59	92

[a] After the carbometalation reaction, the mixture was rapidly warmed to room temperature. [b] Based on the cinnamyl substrate. [c] Based on pure isolated product and calculated from the cinnamyl substrate. [d] As a mixture of two diastereomers as a result of the use of *s*BuLi.

The alkyl and phenyl groups in these cyclopropanes are *anti* to each other and may result from a W-shaped transition state.[45] In this transformation, the initially formed stereogenic center C–R is invariant, when established during the carbolithiation reaction step, whereas the benzylic carbon atom is free to epimerize[10] and to promote the formation of the thermodynamically more stable *trans*-cyclopropane. According to this, the optical purities of the *trans*-cyclopropanes thus obtained[46] are considered to be the same as those of the linear acetals described in Table 2.

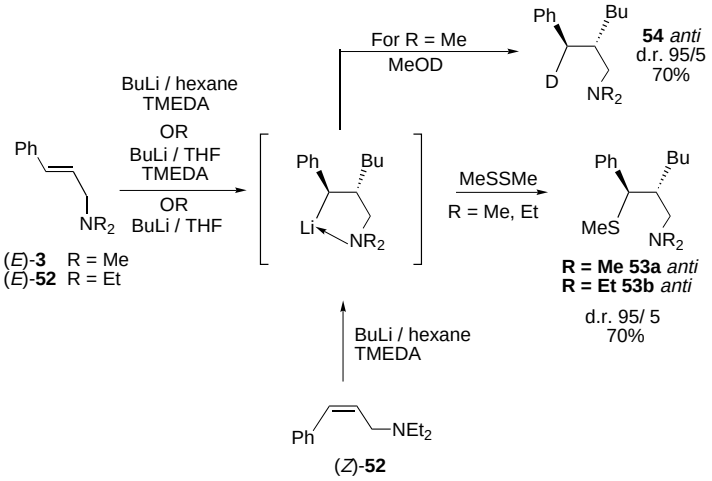
In order to prove this enantioselection and the absolute configuration, the cyclopropane **47** was derivatized into a known alcohol (Scheme 9).



Scheme 9. Correlation of the disubstituted cyclopropane.

The (1*R*)-phenyl-(2*R*)-butyl cyclopropane (**47**) was first oxidized[33] into the corresponding acid **50** in 81% yield. The esterification followed by the reduction of the resulting ester led to the known (2*R*)-butyl-(1*R*)-cyclopropyl methanol (**51**),[47] and the purity of the chiral disubstituted cyclopropanol (93% *ee*) was determined by NMR spectroscopy by the use of chiral derivatizing agents.[16] The same sequence was performed on the cyclopropane **47**, generated in the presence of a catalytic amount of (−)-sparteine, and the same enantiomeric excess was obtained for **51**. Then, by the use of the same strategy as previously described on the dimethyl cinnamyl acetal **8**, several chiral purely *trans*-disubstituted cyclopropanes were readily obtained in a one-pot operation mediated by a catalytic amount of (−)-sparteine.

Stereochemical outcome of the benzylic organolithium compound formed by the carbolithiation of cinnamyl amines 3 and 52: During the course of our study on the reactivity of benzylic organolithium compounds with electrophiles (we performed these experiments with TMEDA instead of (−)-sparteine in hexane, since we were only interested in the diastereoselectivity of the reaction), we found that the stereochemical outcome was unexpectedly *dependent* on the nature of the heteroatom. When (*E*)-cinnamyl dimethylamine (**3**) was treated with 1.5 equivalents of butyllithium at 0 °C in hexane in the presence of 1.5 equivalent of TMEDA, we obtained the corresponding benzylic organolithium which was then trapped by several electrophiles (Scheme 10). The same stereochemical outcome was obtained when the carbolithiation reaction was performed in other solvent systems (Scheme 10). Thus, the stereochemical outcome of the reaction of a benzylic organolithium is totally different when the chelating group is a lithium alcoholate (Scheme 3) or an amino group (Scheme 10).



Scheme 10. Stereochemical outcome of the benzylic organolithium compound in the cinnamyl dialkylamine series.

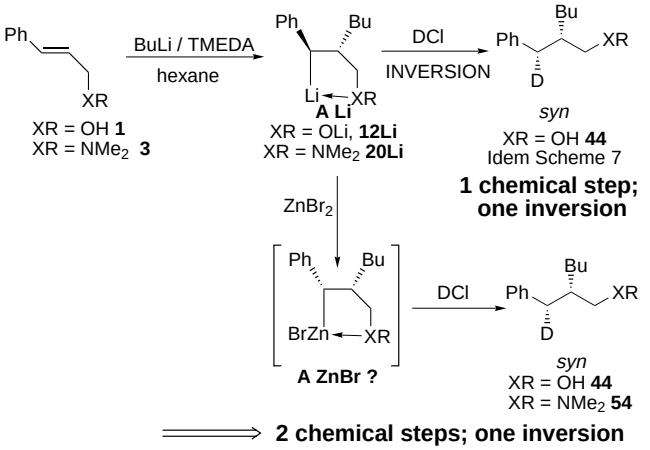
Evidence for the stereochemical assignments of the products **53** and **54** was obtained by comparison with authentic samples, prepared independently.[48] In the case of **54**, the two benzylic protons are well distinguished by ^{1}H NMR spectroscopy (ABX system) so that the diastereoselectivity can be easily determined. The high diastereoselectivity observed in this reaction may again be accounted for by a thermodynamic control of the organolithium intermediate, as shown by the formation of the same product starting from the (*Z*)-cinnamyl

0947-6539/99/0507-2060 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 7

amine (*Z*)-**52**. Thus, a tertiary amino group (NEt_2 or NMe_2) at the appropriate position blocks the configuration of the benzyllithium, after thermodynamic equilibration,[41] through coordination which allows a diastereoselective introduction of electrophiles with *retention of configuration*. The same trend was recently reported on a secondary amine, and PM3 semiempirical calculations as well as ^{1}H NMR measurements explained the different stereoselectivities between the lithium reagents derived from the cinnamyl alcohol and cinnamyl amines in their reactions with electrophiles.[42]

Configurational stability of benzylic organozinc halides:

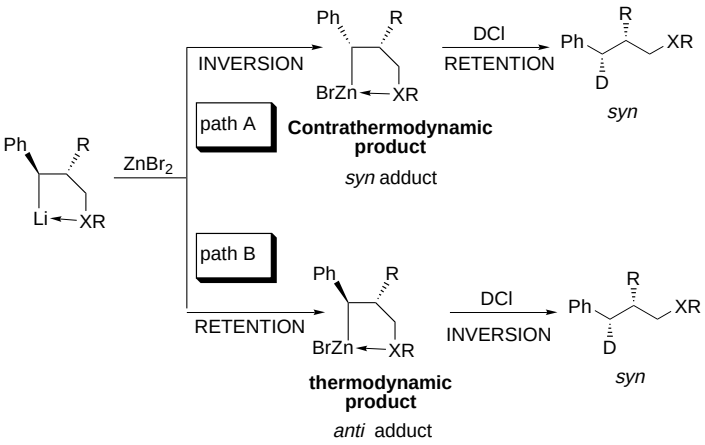
We have previously seen that the reaction of several electrophiles with the benzylic organolithium **12Li** (which contains an alcoholate moiety, see Scheme 7) gave the alkylated product with an *inversion* of the configuration and with very good diastereoselectivity (98:2). Taking this observation into account, we were interested to study a new electrophile in this reaction which would provide the means to investigate the configurational stability of benzylic organometallic compounds. Indeed, if we consider that a zinc salt can be an electrophile in this reaction, the thermodynamic benzylic organolithium **ALi** (Scheme 11) should also react



Scheme 11. Stereochemical outcome of the transmetalation of a benzylic organolithium to the corresponding organozinc halide.

with ZnX_2 with *inversion* of the configuration to give a new benzylic organozinc halide **AZnBr**; however, this entity would be a contrathermodynamic moiety (phenyl *syn* to alkyl, see Scheme 11). Knowing the high covalent character of organozinc halides,[49] and their configurational stability,[50] we thus had an opportunity to study such configurational stability in the benzylic series.[53]

The transmetalation of the benzylic organolithium intermediate **ALi** (**12Li** or **20Li**, Scheme 11) with a solution of zinc bromide in Et_2O at $-60\,^\circ C$, followed by slow warming to $-30\,^\circ C$, and quenching the resulting benzylic organozinc bromide with DCl or MeOD led to the *syn* adducts. In both cases the overall process occurred with an overall complete inversion of the stereochemistry[51] for the two chemical steps (transmetalation and reaction with the electrophile). How can we explained these results? There are two possible hypotheses (Scheme 12).



Scheme 12. Configurational stability of the benzylic organic halide.

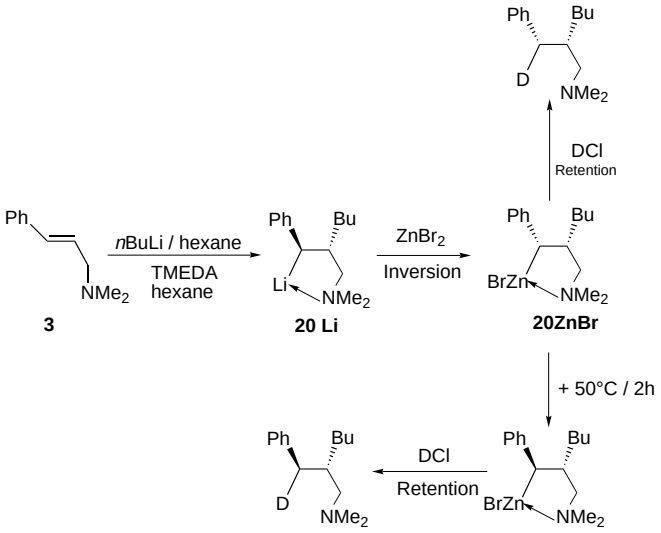
The first hypothesis is that the transmetalation occurred with *inversion* of the configuration so that quenching with DCl with *retention* would lead to the *syn* product (Scheme 12, path A). The second hypothesis is the opposite process: transmetalation with *retention* of configuration and reaction with DCl with *inversion* which would lead to the same *syn* product (Scheme 12, path B). In order to discriminate between these two hypotheses, we investigated the configurational stability of the intermediate benzylic organozinc halide at various time intervals: according to path A, the *syn* adduct should be sensitive to the experimental conditions (such as solvents, temperature, nature of the Zn–X derivatives), whereas the *anti* adduct from path B is the thermodynamic product, and should be insensitive to these experimental parameters. The results are summarized in Table 5, and in Schemes 13 and 14.

Starting from the tertiary amine **3**,the transmetalation from Li to ZnX occurred with *inversion* of configuration to lead to the less stable *syn* isomer **20ZnX** (compare entry 1 with entries 2 and 3 in Table 5) and the configurational stability of this organozinc bromide derivative was dependent on the temperature (compare entries 2 and 3 with entries 4 and 5). Therefore, the benzylic organozinc bromide slowly epimer-

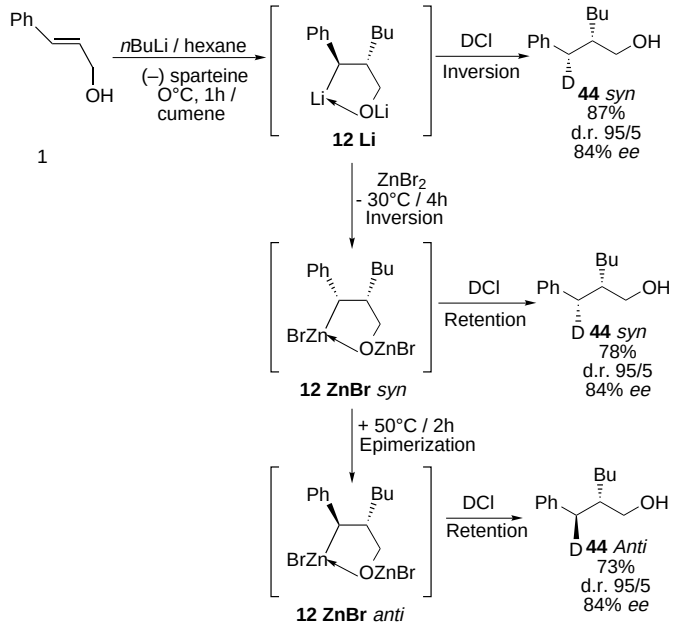
Table 5. Configurational stability of the benzylic organozinc halide after various time intervals.

Entry	Substrate	Zinc additive[a]	T [°C]	Time before quenching with DCl[b]	Product	*syn*:*anti*[c]
1	**3**	none	20	30 min	**54**	8:92
2	**3**	$ZnBr_2$	–30	30 min	**54**	98:2
3	**3**	$ZnBr_2$	–30	4 h	**54**	98:2
4	**3**	$ZnBr_2$	–30 to 0	15 min	**54**	70:30
5	**3**	$ZnBr_2$	0	1 h	**54**	50:50
6	**3**	$ZnBr_2$	50	2 h	**54**	2:98
7	**3**	$ZnCl_2$	–30 to 0	15 min	**54**	70:30
8	**3**	BuZnBr	–30 to 0	30 min	**54**	30:70
9	**3**	Et_2Zn	0	1 h	**54**	20:80
10	**3**	Et_2Zn	–50	30 min	**54**	20:80
11	**1**	$ZnBr_2$	–30	4 h	**44**	98:2
12	**1**	$ZnBr_2$	50	1 h	**44**	2:98

[a] The zinc derivative was slowly introduced at $-60\,^\circ C$ in Et_2O. [b] DCl was added at $-60\,^\circ C$. [c] A value of 98/2 indicates that only one stereoisomer was detected by ^{1}H NMR spectroscopy (400 MHz) with ≈80–95% deuteration.



Scheme 13. Synthesis of both diasteroisomers starting from a common substrate.



Scheme 14. Enantioselective carbometalation of cinnamyl alcohol and reactivity of the corresponding zinc derivatives.

ized to produce the more stable *anti* diastereoisomer. This epimerization is *remarkably slow* so that the varying ratios of products can be observed as a function of time. When the reaction mixture was heated at 50 °C for 2 h (entry 6), the thermodynamic product was obtained quantitatively. Therefore, because both diastereoisomers are available on warming the reaction mixture, path A of Scheme 12 is operative; the transmetalation occurred with *inversion* of configuration to give a benzylic organozinc halide configurationally stable up to a temperature of $-30\,^{\circ}C$,[52] and the latter reacts with DCl with *retention* of configuration (Scheme 13).

Although the electronegativity of the chlorine atom in $ZnCl_2$ should allow a more tight cyclic transition state in favor of the *syn* isomer, the diastereomeric ratio was unchanged (entry 4 versus entry 7). Meanwhile, if the lithium atom is replaced by an alkylzinc moiety (entry 8) or a zincate (entries 9 and 10), the diastereomeric ratio was in favor of the thermodynamic product. This points to the great difference between an organozinc halide and a bisorganozinc[50b] or zincate reagent as regards their configurational stability.

When the chelating group was an alcoholate moiety (alcoholate **12 Li**), the same stereochemical outcome was observed: the transmetalation into the benzylic organozinc halide occurred with *inversion* of the configuration to lead to the contrathermodynamic product (*syn* adduct) at low temperatures and the electrophile reacts with *retention* of configuration to give **44** with d.r. > 98/2 (entry 11). However, if this benzylic organozinc bromide intermediate is heated at 50 °C for 2 h, a complete epimerization occurred to give the *trans* organometallic derivative, and, after reaction with the same electrophile, the opposite diastereomer was obtained (entry 12).[53]

In the latter case (see Scheme 14), the reaction was performed in the presence of (−)-sparteine, instead of TMEDA (as in Scheme 13) and both diastereomers of **44** were obtained by means of this strategy; however, both with 84 % *ee*.

Conclusions

The carbolithiation reaction of styryl derivatives by various primary and secondary alkyllithium compounds with a stoichiometric or catalytic amount of (−)-sparteine led to the alkylated product with very good enantioselectivities (≥ 95 % *ee*). The addition is dependent on the stereochemistry of the initial double bond, and the resulting benzylic organolithium compounds can be derivatized to the linear phenylated chain which bears two contiguous stereogenic centers with given configurations (d.r. ≤ 98:2). When the starting material is the dimethyl acetal, a new access to several disubstituted pure *trans*-cyclopropanes is available with very good enantioselectivities (≤ 95 % *ee*) in the presence of a catalytic amount of (−)-sparteine. Finally, the observation that the Li–Zn transmetalation in a benzylic species occurs with *inversion* of configuration led us to study the configurational stability of benzylic organozinc halides; we were able to demonstrate that they have a remarkable configurational stability up to $-30\,^{\circ}C$.

Experimental Section

General: Experiments involving organometallic compounds were carried out under a positive pressure of dry nitrogen. All glassware was oven-dried at 150 °C overnight and assembled quickly while still hot under a stream of nitrogen. Liquid nitrogen was used as a cryogenic fluid at all given temperatures, unless otherwise stated, referred to internal ones. Diethyl ether and THF were distilled from sodium benzophenone ketyl. $ZnBr_2$ was melted under a stream of nitrogen and handled as a 1 M solution in diethyl ether. (−)-Sparteine was purchased from Aldrich and used as received. Organolithium reagents were titrated with 2-butanol (1 M in toluene) with 1,10-phenantroline as the indicator. NMR spectra were recorded on either a Brucker AC400 or a AC200 spectrometer in $CDCl_3$. Chemical shifts are reported in part per million (ppm) relative to tetramethylsilane (TMS) as the internal standard (0.1 %) in the ^1H NMR spectra. If a trimethylsilyl

0947-6539/99/0507-2062 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 7

moiety was present within the molecule, then $CHCl_3$ was used as the reference. In ^{13}C NMR spectra, $CDCl_3$ ($\delta = 77.2$) was used as the reference.

Procedure for the derivatization of alcohols for the determination of the enantiomeric excesses:[16] Into a dried NMR tube were introduced the chiral diamine ((1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine (0.15 mmol, 38.4 mg) or (1*S*,2*S*)-(−)-*N*,*N*′-dimethyl-1,2-bis[3-(trifluoromethyl)phenyl]-1,2-ethanediamine (0.15 mmol, 59.6 mg) or (1*R*,2*R*)-(−)-*N*,*N*′-dimethylcyclohexane diamine (0.15 mmol, 22.7 mg)) and $CDCl_3$ (1 mL). The tube was shaken until completed dissolution. *N*,*N*-Diethylaniline (0.75 mmol, 130 μL) was added with a microsyringe, followed by slow addition of PCl_3 (0.15 mmol, 12.8 μL) also with a microsyringe. The NMR tube was shaken and an exothermic reaction took place. The alcohol to be analyzed (0.15 mmol) was then added into the NMR tube. For the special cases of (*S*)-2-benzyl-hexyl-methylamine (**21**) and (*S*)-3-benzyl-1-heptanol (**23**) and 4-benzyloctan-1-ol (**24**), selenium or sulfur were added, respectively. The NMR tube was shaken and the ^{31}P spectrum was recorded.

General procedure for the carbolithiation with RLi in hexane and in the presence of a stoichiometric amount of (−)-sparteine:

Carbolithiation of cinnamyl alcohol, homologues, and cinnamyl amines: General procedure A: A solution of the cinnamyl derivative (x mmol) in dry solvent (see Table 2) ($x+1$ mL) was added dropwise over a period of 0.5 h at −10 °C to a solution of RLi (3x mmol) in hexane in the presence of (−)-sparteine (x mmol) in dry solvent (see Table 2) ($x+2$ mL). The red reaction mixture was stirred at 0 °C for 1 h. After cooling to 0°, the reaction mixture was poured into 1N HCl (for the alcohols) or NH_3/NH_4Cl (for the amines). The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated and the residue was then chromatographed on silica gel.

Carbolithiation of cinnamyl acetal: General procedure B: To a solution of RLi/hexane (2.2 equiv) in dry solvent (5 mL) was added (−)-sparteine (0.46 mL, 2 mmol) at −78 °C. The mixture was allowed to warm to 0 °C for a few minutes. The solution was then cooled to −50 °C and a solution of **8** (0.41 g, 2 mmol) in dry solvent (3 mL) was added dropwise over a period of 0.5 h. The orange reaction mixture was stirred at −50 °C for 5–6 h, quenched with MeOH (1 mL) at −80 °C, and then with HCl (1N, 5 mL) at 0 °C. The aqueous layer was extracted with diethyl ether (3 × 15 mL), the combined organic phases were washed with saturated solution of $NaHCO_3$, and then dried over K_2CO_3. The solvents were removed under reduced pressure and the product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate: 95/5) to afford the carbometalated product.

Carbolithiation of β-alkylated styrenes: General procedure C: To a solution of RLi/hexane (2.2 equiv) in dry hexane (5 mL) was added (−)-sparteine (0.46 mL, 2 mmol) at −50 °C. The mixture was allowed to warm to 0 °C for a few minutes and then cooled to −20 °C. A solution of β-alkylated styrene (2 mmol) in dry hexane (3 mL) was added dropwise over a period of 0.5 h. The orange reaction mixture was stirred at −20 °C for 4 h. The mixture was quenched with HCl (1N, 5 mL) at −20 °C. The aqueous layer was extracted with diethyl ether (3 × 15 mL), the combined organic phases were washed with brine, and then dried over $MgSO_4$. The solvents were removed under reduced pressure and the product was purified by column chromatography (silica gel, pentane) to afford the carbometalated product.

Carbolithiation of *trans*-stilbene (11): General procedure D: A solution of *n*BuLi (1.6M/hexane, 2.2 equiv) was added at −10 °C to a solution of *trans*-stilbene (**11**, 0.45 g, 2.5 mmol) and (−)-sparteine (0.57 mL, 2.5 mmol) in dry cumene. The orange reaction mixture was then stirred at 0 °C for 8 h. The mixture was quenched with HCl (1N, 5 mL) at −20 °C. The aqueous layer was extracted with diethyl ether (3 × 15 mL), the combined organic phases were washed with brine, and then dried over $MgSO_4$. The solvents were removed under reduced pressure and the product was purified by column chromatography (silica gel, cyclohexane) to afford the carbometalated product in 81% yield.

Carbolithiation with RLi in Et_2O and in the presence of a stoichiometric amount of (−)-sparteine: General Procedure E:

Carbolithiation of cinnamyl alcohol: General procedure: RLi (9 mmol) was prepared in Et_2O, then Et_2O was removed under vacuum and dry cumene was added. After the addition of (−)-sparteine (3 mmol), a solution of cinnamyl derivatives (3 mmol) in dry cumene (5 mL) was added dropwise over a period of 0.5 h at 0 °C. The remainder of the procedure is analogous to that of procedure A.

Carbolithiation of cinnamyl acetal 8: General procedure: RLi (6 mmol) was prepared in Et_2O, then Et_2O was removed under vacuum and dry cumene (5 mL) was added. (−)-Sparteine (0.46 mL, 2 mmol) was added at −78 °C and the mixture was allowed to warm to 0 °C for a few minutes. The solution was then cooled to −50 °C and a solution of **8** (2 mmol, 0.41 g) in dry cumene (3 mL) was added dropwise over a period of 0.5 h. The remainder of the procedure is analogous to that of procedure B.

Carbolithiation of β-alkylated styrene: General procedure: RLi (6.6 mmol) was prepared in Et_2O, then Et_2O was removed under vacuum and dry hexane (5 mL) was added. (−)-Sparteine (0.46 mL, 2 mmol) was added at −50 °C and the mixture was allowed to warm to 0 °C for a few minutes. The solution was then cooled to −20 °C and a solution of β-alkylated styrene (2 mmol) in dry hexane (3 mL) was added dropwise over a period of 0.5 h. The remainder of the procedure is analogous to that of procedure C.

Carbolithiation reaction with a catalytic amount of (−)-sparteine: General procedure:

Carbolithiation of cinnamyl alcohol: A solution of cinnamyl alcohol (2 mmol) in dry cumene (3 mL) was added dropwise over a period of 0.5 h at −10 °C to a solution of RLi/hexane (6 mmol) in the presence of (−)-sparteine (0.046 mL) in dry cumene (5 mL). The red reaction mixture was stirred at 0 °C for 1 h. The remainder of the procedure is analogous to that of procedure A.

Carbolithiation of cinnamyl acetal 8: To a solution of RLi/hexane (3 equiv) in dry hexane (10 mL) was added (−)-sparteine (0.1 mL when the reaction was performed with 10% mol and 10 μL when the reaction was performed with 1% mol) at −78 °C. The mixture was allowed to warm to 0 °C for a few minutes and then cooled to −50 °C. A solution of **8** (0.93 g, 4.5 mmol) in dry hexane (5 mL) was added dropwise over a period of 1 h. The orange reaction mixture was stirred at −50 °C for 7–8 h. The mixture was quenched with MeOH (1 mL) at −80 °C and then with HCl (1N, 10 mL) at 0 °C. The aqueous layer was extracted with diethyl ether (3 × 20 mL), the combined organic phases were washed with a saturated solution of $NaHCO_3$, and then dried over K_2CO_3. The solvents were removed under reduced pressure and the product was purified by column chromatography (silica gel, cyclohexane/AcOEt 95:5) to afford the carbometalated product.

Carbolithiation of β-methylstyrene (9): (−)-Sparteine (0.46 mL, 2 mmol) was added to a solution of *n*BuLi (2.8 mL, 1.6N/hexane, 2.2 equiv) in dry hexane (5 mL) at −50 °C. The mixture was allowed to warm to 0 °C for a few minutes and then cooled to −20 °C. A solution of β-methylstyrene (2 mmol) in dry hexane (3 mL) was added dropwise over a period of 0.5 h. The orange reaction mixture was stirred at 0 °C for 8 h then for 12 h at room temperature. The mixture was quenched with HCl (1N, 5 mL) at −20 °C. The aqueous layer was extracted with diethyl ether (3 × 15 mL), the combined organic phases were washed with brine, and then dried over $MgSO_4$. The solvents were removed under reduced pressure and the product was purified by column chromatography (silica gel, pentane) to afford the carbometalated product.

(2*S*)- and (2*R*)-2-Benzyl-1-hexanol (12): The reaction was performed on **1** (0.523 g, 4 mmol) according to Procedure A (eluent: cyclohexane/ethyl-acetate: 80/20).

(S)-**12**: Yield: 85% (0.632 g); $[\alpha]_D^{25} = -4.1$ ($c = 0.02$, CH_2Cl_2); ^{31}P NMR (90 MHz, $CDCl_3$): $\delta = 136.83$ (s, 91.5%), 137.50 (s, 8.5%), 83% *ee*.

(R)-**12**: Yield: 63% (0.484 g); $[\alpha]_D^{20} = 3.5$ ($c = 0.01$, CH_2Cl_2); ^{31}P NMR (36.22 MHz, $CDCl_3$): $\delta = 139.25$ (s, 85%), 139.86 (s, 15%), *ee* = 70%; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 7.1$ Hz), 1.15–1.40 (m, 6H), 1.70 (m, 1H), 2.65 (d, $J = 7.1$ Hz, 2H), 3.50 (d, $J = 5.1$ Hz, 2H), 7.10–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.92, 22.83, 28.98, 30.15, 37.35, 41.33, 64.34, 125.57, 128.02, 129.03, 140.73$.

(2*S*)-2-Benzyl-1-octanol (14): The reaction was performed on **1** (0.201 g, 1.5 mmol) according to Procedure A (eluent: cyclohexane/ethyl acetate: 80/20). Yield: 76% (0.25 g); $[\alpha]_D^{25} = -5.29$ ($c = 0.02$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.7$ Hz, 3H), 1.2–1.4 (m, 8H), 1.8 (m, 1H), 2.63 (d, $J = 7.1$ Hz, 2H), 3.52 (d, $J = 4.7$ Hz, 2H), 7.1–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.09, 15.28, 22.66, 29.60, 30.84, 31.84, 37.71, 41.61, 65.87, 125.86, 128.3, 129.18$; ^{31}P NMR (162 MHz, (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine, $CDCl_3$): $\delta = 137.81$ (s,

93.5%), 138.58 (s, 6.5%); 87% *ee*; anal. calcd for $C_{15}H_{24}O$: C 81.76, H 10.98; found C 81.70, H 10.99.

(2*S*,3*RS*)-2-Benzyl-3-methyl-1-pentanol (15): The reaction was performed on **1** (0.523 g, 4 mmol) according to Procedure A (eluent: cyclohexane/ethyl acetate 80:20). Yield: 65% (0.5 g); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.98 (m, 6H), 1.25 (s, 1H), 1.28 (m, 2H), 1.55 (m, 2H), 1.8 (m, 1H), 2.42 (dd, $J = 9.7$, 13.7 Hz, 1H), 2.66 (d, $J = 8$ Hz, 2H), 2.7 (dd, $J = 13.7$ Hz, 1H), 3.5 (m, 2H), 7.2–7.3 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.18$, 12.32, 15.80, 15.39, 26.98, 26.81, 33.70, 34.64, 34.97, 35.38, 47.40, 63.01, 63.58, 125.92, 128.47, 129.13, 139; ^{31}P NMR (160 MHz, $CDCl_3$): $\delta =$ *diastereoisomer 1*: 138.97 (s, 14%), 137.55 (s, 86%); 72% *ee*; *diastereoisomer 2*: 138.47 (s, 14%), 136.98 (s, 86%); 70% *ee*.

(2*S*)-2-Benzyl-3,3-dimethyl-1-butanol (16): The reaction was performed on **1** (0.523 g, 4 mmol) according to Procedure A (eluent: cyclohexane/ethyl acetate 80:20). Yield: 40% (0.3 g); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.05$ (s, 9H), 1.55 (m, 1H), 2.5 (dd, $J = 10.7$, 13.7 Hz, 1H), 2.9 (dd, $J = 3.4$, 13.7 Hz), 3.64 (m, 2H), 7.10–7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.42$, 38, 34, 53, 62.60, 125.47, 127, 128.42, 129, 142.28. ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 136.76$ (s, 50%), 135.48 (s, 50%); 0% *ee*.

(2*S*)-2-Benzyl-1-butanol (17): The reaction was performed on **1** (0.4 g, 3 mmol) according to procedure E (eluent: cyclohexane/ethyl acetate 70:30). Yield: 68% (0.335 g); $[\alpha]_D^{25} = 4$ ($c = 0.08$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (t, $J = 7.5$ Hz, 3H), 1,37 (m, 2H), 1.7 (m, 1H), 1.85 (m, 1H), 2.62 (m, 2H), 3.50 (d, $J = 5.4$ Hz, 2H), 7.2–7.3 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.73$, 23.69, 37.68, 44.53, 64.79, 126.25, 128.70, 129.61, 141.32; ^{31}P NMR (36.22 MHz, $CDCl_3$): $\delta = 136.96$ (s, 92%), 137.84 (s, 7%); 85% *ee*; anal. calcd for $C_{11}H_{16}O$: C 80.43, H 9.83; found C 80.57, H 9.67.

(2*S*)-2-Benzyl-1-nonanol (18): The reaction was performed on **1** (0.4 g, 3 mmol) according to procedure E (eluent: cyclohexane/ethyl acetate 70:30). Yield: 50% (0.351 g); $[\alpha]_D^{25} = -3.2$ ($c = 0.01$, CH_2Cl_2).^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.83$ (t, $J = 6.1$ Hz, 3H), 1.1–1.35 (m, 12H), 1.75 (m, 1H), 2.6 (d, $J = 7.1$ Hz, 2H) 3.5 (d, $J = 5.1$ Hz, 2H), 7.1–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.11$, 22.67, 26.95, 29.28, 29.88, 30.73, 31.86, 37.64, 42.55, 64.83, 125.82, 129.16, 129.55, 140.83; ^{31}P NMR (162 MHz, (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine, $CDCl_3$): $\delta = 137.52$ (s, 81.5%), 138.32 (s, 18.5%); 63% *ee*.

(2*S*)-2-Benzyl-1-*tert*-butoxyhexane (19): The reaction was performed on **2** (0.125 g, 1.1 mmol) according to Procedure A (eluent: cyclohexane/ethyl acetate 98:2). Yield: 82% (0.185 g); $[\alpha]_D^{25} = -0.4$ ($c = 0.01$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.7$% (t, $J = 6.9$ Hz, 3H), 1.07 (s, 9H), 1.18–1.24 (m, 6H), 1.70 (m, 1H), 2.44 (dd, $J = 6.8$, 13.5 Hz, 1H), 2.63 (dd, $J = 6.8$, 13.5 Hz, 2H), 3.09 (m, 2H), 7.07–7.18 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$), 14,53, 23.44, 28.01, 29.62, 31.17, 38.33, 41.19, 63.71, 125.94, 128.42, 129.75, 141,85; anal. calcd for $C_{17}H_{28}O$: C 82.19H, 11.37; found C 82.68H, 11.65.

***N*,*N*-Dimethyl-(2*S*)-2-benzyl-1-hexanamine (20)**: The reaction was performed on **3** (0.322 g, 2 mmol) according to Procedure A (eluent: cyclohexane/diethyl ether 1:1 containing a few drops of 32% aqueous NH_3). Yield: 71% (0.306 g); $[\alpha]_D^{25} = -11.96$ ($c = 0.02$, CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (m, 3H), 1.28 (m, 6H), 1.81 (m,1H), 2.10 (dd, $J = 7.6$, 12.9 Hz, 2H), 2.20 (s, 6H), 2.50 (dd, $J = 7.5$, 13.6 Hz, 1H), 2.70 (dd, $J = 5.9$, 13.6 Hz, 1H), 7.20–7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.38$, 23.30, 29.16, 31.73, 38.13, 38.79, 46.15, 64.28, 125.80, 128.26, 129.60, 141.41; anal. calcd for $C_{15}H_{25}N$: C 82.13, H 11.49; N, 6.38; found C 81.93, H 11.36; N, 6.25; HPLC analysis (UV monitoring ($\nu = 254$ nm), Chiracel OD column; flow rate: 0.1 mL min^{-1}; eluent: hexane; 82% *ee*.

(2*S*)-*N*-Methyl-2-benzyl-hexanamine (21): The reaction was performed on **4** (0.294 g, 2 mmol) according to Procedure A (eluent: CH_2Cl_2/methanol 90:10 containing a few drops of 32% aqueous NH_3). Yield: 66% (0.258 g); $[\alpha]_D^{25} = -4.38$ ($c = 0.01$, CH_2Cl_2).^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.87$ (m, 3H), 1.30 (m, 6H), 1.50 (m,1H), 1.8 (m, 1H), 2.39 (s, 3H), 2.47 (d, $J =$ 6.0 Hz, 2H), 2.60 (d, $J = 6.0$ Hz, 2H), 7.10–7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.99$, 22.89, 26.87, 31.57, 36.48, 38.90, 39.88, 55.17, 125.64, 128.43, 129.05, 1409.8; ^{31}P NMR (36.22 MHz, $CDCl_3$): $\delta = 83.32$ (s, 83%), 83.53 (s, 17%); 66% *ee*; anal. calcd for $C_{14}H_{23}N$: C 81.88, H 11.30; N, 6.82; found C 81.24, H 11.65; N, 6.78.

***N*-Benzyl-*N*-methyl-(2*S*)-2-benzyl-1-hexanamine (22)**: The reaction was performed on **5** (0.5 g, 2.1 mmol) according to Procedure A (eluent: cyclohexane/diethyl ether 1:1 containing a few drops of 32% NH_3). Yield: 64% (0.62 g); $[\alpha]_D^{25} = -6.2$ ($c = 0.01$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (m, 3H), 1.2–1.27 (m, 6H) 1.9 (m, 1H), 2.16 (s, 3H), 2.24 (m, 2H), 2.5 (dd, $J = 7.2$, 13.5 Hz,1H), 2.78 (dd, $J = 5.6$, 13.6 Hz, 1H), 3.46 (m, 2H), 7.16–7.34 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.08$, 23.02, 28.72, 31.36, 37.86, 38.53, 42.59, 61.63, 62.66, 125.45, 126.69, 127.96, 128.04, 128.84, 129.27, 139.63, 141.29; anal. calcd for $C_{21}H_{29}N$: C 85.36, H 9.9; N,4.74; found: C 85.72, H 10.15, N 5.03

3-Butyl-4-phenyl-1-butanol (23): The reaction was performed on 4-phenyl-3-butene-1-ol (**6**, 0.592 g 4 mmol) according to Procedure A (eluent: cyclohexane/ethylacetate 80:20). Yield: 72% (0.6 g); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.89$ (m, 3H), 1.3 (m, 6H), 1.5 (q, $J = 6.8$ Hz, 2H), 1.6 (m, 1H), 1.75 (m, 1H),.2.48 (dd, $J = 7.2$, 13.5 Hz, 1H) 2.58 (dd, $J = 6.8$, 13.5 Hz, 1H), 3.6 (m, 2H), 7.1–7.3 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.11$, 22.98, 26.91, 28.7, 33.13, 36.42, 40.65, 60.95, 125.72, 128.17, 129.17, 141.25; ^{31}P NMR (36.22 MHz, $CDCl_3$, (1*R*,2*R*)-(−)-*N*,*N*′-dimethylcyclohexane diamine, S_8): $\delta = 88.33$ (s, 15%), 83.35 (s, 85%); 70% *ee*.

4-Butyl-5-phenyl-1-pentanol (24): The reaction was performed on 5-phenyl-4-en-1-pentanol (**7**, 0.65 g 4 mmol) according to Procedure A (eluent: cyclohexane/ethyl acetate 80:20). Yield: 75% (0.6 g); $[\alpha]_D^{25} = 2.5$ ($c = 0.01$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 6.7$, 3H), 1.25–1.45 (m, 6H), 1.5–1.7 (m, 4H), 2.55 (dd, $J = 7.2$, 13.5 Hz, 1H), 2.61 (dd, $J = 6.9$, 13.5, 1H), 3.6 (t, $J = 6.6$ Hz, 2H), 7.15–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.25$, 23.14, 28.87, 29.13, 29.90, 32.94, 39.58, 40.61, 63.42, 125.75, 128.25, 129.28, 141.64; ^{31}P NMR (162 MHz, $CDCl_3$, (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine, Se): $\delta = 83.38$ (s, 15%), 83.40 (s, 85%); 70% *ee*.

(2*S*)-[2-Benzyl-1-(1-methoxy-1-methylethoxy)]hexane (25): The reaction was performed on **8** (0.41 g 2 mmol) according to Procedure B. Yield: 77% (0.4 g); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.3$ Hz, 3H), 1.4–1.2 (m, 12H), 1.86 (m, 1H), 2.56 (dd, $J = 7.1$, 13.5 Hz, 1H), 2.74 (dd, $J = 7.1$, 13.6 Hz, 1H), 3.2 (s, 3H), 7.3–7.5 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.08$, 22.97, 24.46, 29.17, 30.81, 38.01, 40.44, 48.42, 62.60, 99.25, 125.61, 128.06, 129.23, 141.19; anal. calcd for $C_{17}H_{28}O_2$: C 77.22, H 10.67; found C 77.15, H 10.78.

(2*S*)-[2-Benzyl-1-(1-methoxy-1-methylethoxy)]octane (26): The reaction was performed on **8** (0.41 g, 2 mmol) according to Procedure B. Yield: 70% (0.41 g); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.3$ Hz, 3H), 1.4–1.2 (m, 12H), 1.86 (m, 1H), 2.56 (dd, $J = 7.1$, 13.5 Hz, 1H), 2.74 (dd, $J = 7.1$, 13.6 Hz, 1H), 3.2 (s, 3H), 7.3–7.5 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.08$, 22.97, 24.46, 29.17, 30.81, 38.01, 40.44, 48.42, 62.60, 99.25, 125.61, 128.06, 129.23, 141.19; anal. calcd for $C_{17}H_{28}O_2$: C 77.22, H 10.67; found C 77.15, H 10.78.

(2*S*)-[2-Benzyl-1-(1-methoxy-1-methylethoxy)-3-methyl]pentane (27): The reaction was performed on **8** (0.41 g, 2 mmol) according to Procedure B. Yield: 80% (0.422 g); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.8–0.95$ (m, 6H), 1.0–1.6 (m, 9H), 1.85 (m, 1H), 2.4–2.8 (m, 2H), 3.1 (s, 3H), 3.14 (s, 3H), 3.2–3.5 (m, 2H), 7.1–7.35 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 13.09, 13.23, 16.34, 25.37, 27.59, 27.72, 34.82, 35.53, 36.44, 45.67, 46.08, 61.35, 61.76, 100.75, 126.49, 129.06, 130.03; anal. calcd for $C_{17}H_{28}O_2$: C 77.22, H 10.67; found C 77.09, H 10.76.

(2*S*)-[2-Benzyl-1-(1-methoxy-1-methylethoxy)]nonane (28): The reaction was performed on **8** (0.41 g, 2 mmol) according to procedure E (eluent: cyclohexane/ethyl acetate 95:5). Yield: 50% (0.306 g); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.9$ (t, $J = 6.9$ Hz, 3H), 1.2–1.4 (m, 18H), 1.86 (m, 1H), 2.56 (dd, $J = 7$, 13.4 Hz, 1H), 2.74 (dd, $J = 7.0$, 13.5 Hz, 1H), 3.2 (s, 3H), 3.29 (m, 2H), 7.15–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.24$, 22.79, 24.59, 29.41, 29.83, 30.01, 31.25, 31.98, 38.16, 40.58, 48.54, 62.71, 99.84, 125.74, 128.16, 139.36, 141.31; anal. calcd for $C_{20}H_{34}O_2$: C 78.38, H 11.18; found C 78.21, H 11.26.

(2*S*)-2-Benzylhexane (29): The reaction was performed on **9** (0.26 mL, 2 mmol) according to Procedure C. Yield: 83% (0.292 g); $[\alpha]_D^{25} = -7.72$ ($c = 0.05$, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (d, $J = 6.6$ Hz, 3H), 0.96 (t, $J = 6.64$ Hz, 3H), 1.2–1.5 (m, 6H), 1.78 (m, 1H), 2.42 (dd, $J = 8.24$, 13.32 Hz, 1H), 2.71 (dd, $J = 6$, 13.32 Hz, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.67$, 17.92, 21.48, 27.89, 33.53, 34.98, 42.25, 124.06, 126.56, 127.69, 140.18.

(2*S*)-2-Benzyloctane (30): The reaction was performed on **9** (0.26 mL, 2 mmol) according to Procedure C. Yield: 86% (0.351 g); $[\alpha]_D^{25} = -10.08$ ($c = 0.05$, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.75$ (d, $J = 6.6$ Hz, 3H), 0.8 (t, $J = 6.6$ Hz, 3H), 1.05–1.35 (m, 10H), 1.65 (m, 1H), 2.26 (dd, $J = 8.2$,

0947-6539/99/0507-2064 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 7

13.3 Hz, 1H), 2.52 (dd, $J = 6,0$, 13.3 Hz, 1H), 7.05–7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.57$, 19.84, 23.14, 27.54, 30.03, 32.38, 35.47, 37.21, 44.17, 125.98, 128.47, 129.62, 142.12.

(2*S*)-2-Benzylpentane (31): The reaction was performed on **9** (0.26 mL, 2 mmol) according to procedure E. Yield: 92% (0.298 g); $[\alpha]_D^{25} = -4.96$ (0.05, Et_2O); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.9$ (m, 6H), 1.1–1.4 (m, 4H), 1.75 (m, 1H), 2.35 (dd, $J = 8.1$, 13.3 Hz, 1H), 2.65 (dd, $J = 6.0$, 13.3 Hz, 1H), 7.1–7.4 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.45$, 19.51, 20.37, 34.93, 39.22, 43.91, 125.71, 128.19, 129.31, 141.77.

(3*R*)-3-Benzylheptane (32): The reaction was performed on **10** (0.32 g, 2 mmol) according to procedure E. Yield:73% (0.277 g); $[\alpha]_D^{25} = +7.09$ ($c = 0.05$, Et_2O).

(2*S*)-2-Benzyl-1-nonanol (18): The reaction was performed on **1** (0.4 g, 3 mmol) according to procedure E (eluent: cyclohexane/ethyl acetate 70:30). Yield: 50% (0.351 g); $[\alpha]_D^{25} = -3.2$ ($c = 0.01$, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.83$ (t, $J = 6.1$ Hz, 3H), 1.1–1.35 (m, 12H), 1.75 (m, 1H), 2.6 (d, $J = 7.1$ Hz, 2H), 3.5 (d, $J = 5.1$ Hz, 2H), 7.1–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.11$, 22.67, 26.95, 29.28, 29.88, 30.73, 31.86, 37.64, 42.55, 64.83, 125.82, 129.16, 129.55, 140.83; ^{31}P NMR (162 MHz, (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine, $CDCl_3$): $\delta = 137.52$ (s, 81.5%), 138.32 (s, 18.5%); 63% *ee*.

(2*S*)-1,2-Biphenylhexane (33): The reaction was performed on **11** (0.45 g, 2.5 mmol) according to procedure D. Yield: 81% (0.482 g); $[\alpha]_D^{25} = +35.7$ ($c = 0.03$, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.8$ (t, $J = 7.4$ Hz, 3H), 1.05–1.5 (m, 4H), 1.65 (m, 2H), 2.8 (m, 1H), 2.85 (dd, $J = 2.8$, 8.1 Hz, 2H), 7.0–7.3 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.42$, 23.14, 30.17, 35.68, 44.30, 48.45, 126.10, 128.17, 128.41, 128.57, 129.56, 141.27, 145.74; anal. calcd for $C_{12}H_{22}$: C 90.70, H 9.30; found C 90.70, H 9.33.

(2*S*)-3-Benzylheptane (42): The reaction was performed on **41** (0.264 mg, 2 mmol) ((*E*)/(*Z*) 90/10) according to procedure C. Yield: 87% (0.33 g); $[\alpha]_D^{25} = -6.39$ ($c = 0.05$, Et_2O); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.9$ (m, 6H), 1.15–1.3 (m, 8H), 1.59 (m, 1H), 2.55 (d, $J = 7$ Hz, 1H), 7.1–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.97$, 14.34, 23.27, 25.61, 29.07, 32.55, 40.35, 41.31, 125.70, 128.25, 129.38, 142.03.

2-Methyl-1-hexanol: A solution of 2-propen-1-ol (**40**, 0.230 g, 4 mmol) in dry cumene (3 mL) was added dropwise over a period of 0.5 h at $-10\,^\circ$C to a solution of *n*BuLi/hexane (7.5 mL, 12 mmol) in the presence of (−)-sparteine (0.92 mL, 4 mmol) in dry cumene (5 mL). The reaction mixture was stirred at 0 °C for 1 h. After cooling, the reaction mixture was poured into a solution of HCl (1N). The aqueous layer was extracted with diethyl ether (2×10 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent the residue was chromatographed (silica gel, pentane/ethyl acetate 80:20). Yield: 64% (0.300 g); 0% *ee*; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.88$ (m,6H); 1.38 (m, 7H); 3.33 (m, 2H); 5.14 (s, 1H).

Deprotection of dimethylacetal: General procedure F: Dimethylacetal (**25–28**) was dissolved in MeOH (5 mL) and aqueous HCl solution (4N, 0.5 mL) was added. The resulting mixture was refluxed for 1 h, cooled to room temperature, and then quenched by the addition of a saturated $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether. The combined organic phases were dried over K_2CO_3 and evaporated under reduced pressure. Purification by flash chromatography (SiO_2, cyclohexane/AcOEt 75/25) afforded the alcohol as a colorless oil (>95% yield).

(2*S*)-2-Benzylhexanoic acid ((*S*)-13): Chromium(VI) oxide (1.11 g, 11.1 mmol) in sulfuric acid (6.75 mL, 4M) was added to a solution of (*S*)-**2** (0.576 g, 3 mmol) in acetone (5 mL) in an ice cooled bath. After 1 h of stirring, sodium sulfite was added, and the product was extracted with diethyl ether. The extract was dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified on silica gel (eluent: cyclohexane/ethyl acetate 60:40). Yield: 64% (0.433 g); $[\alpha]_D^{25} = 18.2$ ($c =$ 0.07, benzene); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$ (m, 3H), 1.20–1.70 (m, 6H), 2.60 (m, 1H), 2.75 (dd, $J = 9.50$, 14 Hz,1H), 2.95 (dd, $J = 9.5$, 14 Hz, 1H), 7.10–7.25 (m, 5H), 9.5 (s, 1H); ^{13}C (50 MHz, $CDCl_3$): $\delta =$ 13.02, 22.69, 22.50, 31.61, 38.25, 47.55, 126.57, 128.56, 129.03, 139.32, 181.94.

Derivatization of *n*-benzylalkanes into acids: General procedure: To a solution of *n*-benzylalkane (*x* mmol) in CCl_4 (4*x* mL), CH_3CN (4*x* mL), and H_2O (8.2*x* mL) was added sodium metaperiodate (14.5*x* equiv). To this biphasic solution was added ruthenium trichloride hydrate (2.2% mol) and the mixture was stirred vigorously for three days at room temperature. The resulting mixture was then diluted with CH_2Cl_2 (20 mL). The precipitate was filtered through a hyflo plug and washed with CH_2Cl_2. The aqueous phase was then extracted with CH_2Cl_2 (2×10 mL) and the combined organic phases were washed with a saturated solution of $NaHCO_3$ (3×10 mL).The aqueous extracts were combined, and a solution of HCl (35%) was added until the pH reached 1. The mixture was extracted with CH_2Cl_2 (3×20 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude acid which was filtered over SiO_2 with Et_2O as the eluent.

(3*S*)-3-Methylheptanoic acid (34): The reaction was performed on **29** (0.27 g, 1.5 mmol). Yield: 71% (0.154 g); $[\alpha]_D^{25} = -2.34$ ($c = 0.10$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.3$ Hz, 3H), 0.94 (d, $J =$ 6.5 Hz, 3H), 1.1–1.4 (m, 6H), 1.9 (m, 1H), 2.1 (dd, $J = 8.03$, 14.82 Hz, 1H), 2.33 (dd, $J = 5.9$, 14.81 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 13.99, 19.63, 22.72, 29.05, 30.07, 36.30, 41.63, 180.17.

(3*S*)-3-Methylnonanoic acid (35): The reaction was performed on **30** (0.39 g, 1.9 mmol). Yield: 60% (0.196 g); $[\alpha]_D^{25} = -2.83$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.6$ Hz, 3H), 0.96 (d, $J =$ 6.6 Hz, 3H), 1.1–1.4 (m, 10H), 1.95 (m, 1H), 2.16 (dd, $J = 8$, 14.74 Hz, 1H), 2.33 (dd, $J = 5.84$, 14.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 13.99, 19.60, 22.56, 26.77, 29.30, 30.07, 31.76, 36.59, 41.58, 180.00.

(3*S*)-3-Methylhexanoic acid (36): The reaction was performed on **31** (0.284 g, 1.75 mmol). Yield: 80% (0.182 g); $[\alpha]_D^{25} = -1.73$ ($c = 0.02$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H), 1.1–1.4 (m, 4H), 1.9 (m, 1H), 2.05 (dd, $J = 8.1$, 14.7 Hz, 1H), 2.3 (dd, $J = 5.8$, 14.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.08$, 19.61, 19.97, 29.87, 38.89, 41.64, 179.99.

(3*S*)-3-Ethylheptanoic acid: The reaction was performed on **42** (0.264 g, 1.4 mmol). Yield: 90% (0.277 g); $[\alpha]_D^{25} = -1.15$ ($c = 0.02$, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (m, 6H), 1.2–1.45 (m, 8H), 1.8 (m, 1H), 2.29 (dd, $J = 1.4$, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.81$, 14.14, 22.97, 26.29, 28.82, 33.05, 36.30, 38.73, 180.51.

Butylsuccinic acid: To a solution of (*S*)-1,2-diphenylhexane (**33**, 0.35 g, 1.47 mmol) in CCl_4 (12 mL), CH_3CN (12 mL), and H_2O (25 mL) was added sodium metaperiodate (9.12 g, 29 equiv). To this biphasic solution was added ruthenium trichloride hydrate (15 mg, 4.5%) and the mixture was stirred vigorously for three days at room temperature. The resulting mixture was then diluted with CH_2Cl_2 (20 mL). The precipitate was filtered through a hyflo plug and washed with CH_2Cl_2. The aqueous phase was then extracted with CH_2Cl_2 (2×10 mL) and the combined organic phases were washed with a saturated solution of $NaHCO_3$ (3×10 mL). The aqueous extracts were combined, a HCl (35%) solution was added until the pH reached 1, and the mixture was extracted with CH_2Cl_2 (3×20 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude acid which was recrystallized in water. Yield: 50% (0.128 g); $[\alpha]_D^{25} = -17.22$ ($c = 0.01$, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.73$ (t, $J = 6.8$ Hz, 3H), 1.17 (m, 4H), 1.46 (m, 2H), 2.5 (m, 2H), 2.7 (m 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.39$, 22.11, 28.60, 31.26, 35.97, 41.56, 176.92, 180.47; ^{31}P NMR (162 MHz, (1*S*,2*S*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine, $CDCl_3$): $\delta = 136.54$ (s, 85%), 137.09 (s, 85%), 137.25 (s, 15%), 137.51 (s, 15%); 70% *ee*.

General procedure for the reduction of the acid with $BH_3 \cdot THF$: To a solution of acid (*x* mmol) in THF (5*x* mL) was added a solution of $BH_3 \cdot$ THF (1M, THF, 1 equiv) at 0 °C and the mixture was allowed to warm to room temperature and stirred for 6 h. The mixture was then quenched with an aqueous solution of HCl (1N) at 0 °C. The aqueous layer was extracted with diethyl ether (3×10 mL), the organic extracts were washed with a saturated solution of $NaHCO_3$ (5 mL), dried over K_2CO_3, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, pentane/diethyl ether 80:20) to afford the expected alcohol as a colorless oil.

(3*S*)-3-Methylheptan-1-ol (37): The reaction was performed on **34** (0.15 g, 1.04 mmol). Yield: 70% (0.095 g); $[\alpha]_D^{25} = -1.82$ ($c = 0.06$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.9$ (m, 6H), 1.1–1.65 (m, 9H), 3.7 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.05$, 19.61, 22.93, 29.16, 29.49, 36.79, 39.38, 61.15; ^{31}P NMR (162 MHz, (1*S*,2*S*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine, $CDCl_3$): $\delta = 139.29$ (s, 7.5%), 139.51 (s, 92.5%); 85% *ee*.

(3*S*)-3-Methylnonan-1-ol (38): The reaction was performed on **35** (0.166 g, 0.96 mmol). Yield: 74% (0.113 g); $[\alpha]_D^{25} = -3.02$ ($c = 0.05$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.9$ (m, 6H), 1.1–1.65 (m, 13H), 3.7 (m,

2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.29, 19.81, 22.87, 27.11, 29.67, 29.80, 32.11, 37.34, 40.13, 61.34$; ^{31}P NMR (162 MHz, (1*S*,2*S*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine, $CDCl_3$): $\delta = 139.11$ (s, 8%), 139.32 (s, 92%); 84% *ee*.

(3*S*)-3-Methylhexan-1-ol (39): The reaction was performed on **36** (0.15 g, 1.2 mmol). Yield: 70% (0.098 g); $[\alpha]_D^{25} = -1.1$ ($c = 0.04$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.80$ (m, 6H), 1.05–1.6 (m, 7H), 2.0 (m, 1H), 3.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.68, 19.93, 20.39, 29.59, 39.80, 40.27, 61.44$; ^{31}P NMR (162 MHz, (1*S*,2*S*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine, $CDCl_3$): $\delta = 139.07$ (s, 12%), 139.32 (s, 88%); 76% *ee*.

(3*S*)-3-Ethylheptan-1-ol (43): The reaction was performed on (*S*)-3-ethylheptanoic acid (0.19 g, 1.2 mmol). Yield: 70% (0.122 g); $[\alpha]_D^{25} = -0.32$ ($c = 0.05$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (m, 6H), 1.2–1.6 (m, 11H), 2.25 (m, 1H), 3.64 (t, $J = 14$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 10.89, 14.32, 23.30, 26.17, 29.03, 33.09, 35.81, 36.64, 61.31$.

Enantioselective cyclopropanation: General procedure: To a solution of RLi/hexane (3.3 equiv) in dry solvent (10 mL) was added (−)-sparteine (0.7 mL when the reaction was performed with one equivalent and 70 μL when the reaction was performed with 10% mol) at −78 °C and the mixture was allowed to warm to 0 °C for a few minutes. The solution was then cooled to −50 °C and a solution of **8** (0.62 g, 3 mmol) in dry solvent (5 mL) was added dropwise over a period of 0.5 h. After 7 h at −50 °C, the orange reaction mixture was rapidly warmed to room temperature and stirred for 12 h. The mixture was then poured into an aqueous HCl (2N) solution and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvents were removed under reduce pressure and the product was purified by column chromatography (silica gel, cyclohexane) to afford the expected cyclopropane as a colorless oil.

(1*R*,2*R*)-1-Butyl-2-phenylcyclopropane (47): Yield: 60% (0.313 g) when the reaction was performed with a stoichiometric amount of (−)-sparteine in cumene and 61% (0.32 g) when the reaction was performed with a catalytic amount of (−)-sparteine in hexane; $[\alpha]_D^{25} = -85.5$ ($c = 0.03$, $CHCl_3$) with *ee* = 93%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.8$ (m, 1H), 0.9 (m, 4H), 1.1 (m, 1H), 1.4 (m, 6H), 1.6 (m, 1H), 7.0–7.3 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2, 16.3, 22.6, 23.3, 24.0, 31.7, 34.1, 125.2, 125.7, 128.3, 144.3$; anal. calcd for $C_{13}H_{18}$: C 89.59, H 10.41; found C 89.12, H 10.58.

(1*R*,2*R*)-1-(1-Methylpropyl)-2-phenylcyclopropane (48): Yield: 66% (0.345 g); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.8$ (m, 1H), 0.85–0.95 (m, 7H), 0.97–1.0 (m, 6H), 1.05 (m, 6H), 1.43 (m, 2H), 1.58 (m, 2H), 1.68 (m, 1H), 1.72 (m, 1H), 7.05–7.3 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.71, 11.97, 19.28, 19.37, 21.77, 23.26, 29.65, 30.04, 30.44, 40.23, 40.37, 125.08, 125.56, 125.72, 128.19, 144.08, 144.23$; anal. calcd for $C_{13}H_{18}$: C 89.59, H 10.41; found C 89.42, H 10.48.

(1*R*,2*R*)-1-Hexyl-2-phenylcyclopropane (49): Yield: 59% (0.34 g); $[\alpha]_D^{25} = -71.1$ ($c = 0.03$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.77$ (m, 1H), 0.93 (m, 4H), 1.05 (m, 1H), 1.2–1.5 (m, 10H), 1.6 (m, 1H), 7.05–7.3 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.12, 16.20, 22.67, 23.24, 23.92, 29.16, 29.89, 31.89, 34.46, 125.08, 125.55, 128.19, 144.15$; anal. calcd for $C_{15}H_{22}$: C 89.04, H 10.96; found C 88.88, H 11.01.

[(1*R*,2*R*)-1-(2-Butylcyclopropyl)]methanoic acid (50): To a solution of the cyclopropane **47** (1.8 mmol, 0.225 g) in CCl_4 (7 mL), CH_3CN (7 mL), and H_2O (14.5 mL) was added sodium metaperiodate (5.6 g, 14.5 equiv). To this biphasic solution was added ruthenium trichloride hydrate (8 mg, 2.2% mol). The mixture was stirred vigorously for three days at room temperature and then diluted with CH_2Cl_2 (20 mL). The precipitate was filtered through a hyflo plug and washed with CH_2Cl_2. The aqueous phase was then extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic phases were washed with a saturated solution of $NaHCO_3$ (3 × 10 mL). The aqueous extracts were combined and a HCl (35%) solution was added until the pH reached 1. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude acid which was filtered over SiO_2 with Et_2O as the eluent. Yield: 81% (0.168 g); $[\alpha]_D^{25} = -76.7$ ($c = 0.04$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.8$ (m, 1H), 0.9 (m, 4H), 1.1–1.5 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.2, 16.43, 20.16, 22.38, 24.1, 31.27, 32.76, 161.36$; 93% *ee*; anal. calcd for $C_8H_{14}O_2$: C 67.57, H 9.92; found C 67.65, H 10.01.

Methyl (1*R*,2*R*)-2-butylcyclopropanecarboxylate: To a solution of cyclopropane **50** (1.1 mmol) in methanol (10 mL) was added a few drops of a H_2SO_4 (95%) solution. The mixture was stirred for two days at room temperature. A saturated solution of $NaHCO_3$ was then added and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The organic extracts were dried over K_2CO_3, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, pentane/diethyl ether 95:5). Yield: 73% (0.134 g); $[\alpha]_D^{25} = -70$ ($c = 0.08$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.71$ (m, 1H), 0.9 (m, 4H), 0.9 (t, $J = 7$ Hz, 3H), 1.15 (m, 1H), 1.25–1.5 (m, 8H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.05, 15.61, 20.02, 22.41, 23.05, 31.33, 32.80, 51.60, 175.07$; 93% *ee*; anal. calcd for $C_9H_{16}O_2$: C 69.19, H 10.32; found C 69.05, H 10.36.

(1*R*,2*R*)-2-butylcyclopropanemethanol (51): To a solution of methyl [(1*R*,2*R*)-1-(2-butylcyclopropyl)]methanoate (0.85 mmol) in dry diethyl ether (10 mL) was added at 0 °C a solution of DiBAlH (1M in hexane, 2.2 equiv) and the mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was then quenched with MeOH (1 mL) at 0 °C and an aqueous HCl (1N) solution. The aqueous layer was extracted with diethyl ether (2 × 10 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, pentane/diethyl ether 70:30). Yield: 89% (0.097 g); $[\alpha]_D^{25} = -26.1$ ($c = 0.02$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.5–0.3$ (m, 2H), 0.6 (m, 1H), 0.8–1.0 (m, 4H), 1.2–1.5 (m, 6H), 2.8 (m, 1H), 3.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.82, 14.02, 17.07, 21.07, 22.38, 31.73, 33.18, 67.13$; ^{31}P NMR (162 MHz, (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine, $CDCl_3$): $\delta = 139.98$ (s, 96.5%), 140.41 (s, 3.5%); 93% *ee*; anal. calcd for $C_8H_{16}O$: C 74.94, H 12.58; found C 74.88, H 12.65.

Reaction of 12Li and 12′Li with electrophiles:

Synthesis of (2*R*,3*S*)-2-butyl-3-phenyl-3-phenylthio-1-propanol (45) and (2*S*,3*R*)-2-butyl-3-phenyl-3-phenylthio-1-propanol (45′): A solution of (*E*)-**1** or (*Z*)-**1** (0.523 g, 4 mmol) in dry cumene (3 mL) was added dropwise over a period of 0.5 h at 0 °C to a solution of *n*BuLi/hexane (7.5 mL, 12 mmol) in the presence of (−)-sparteine (0.92 mL, 4 mmol) in dry cumene (5 mL). The red reaction mixture was stirred at 0 °C for another 0.5 h, allowed to warm to room temperature, and then stirred for 1 h. After cooling to −60 °C, dry tetrahydrofuran (15 mL) was added, followed by diphenyl disulfide (5.23 g, 24 mmol). The reaction was completed by stirring for 1 h at room temperature. The reaction mixture was poured into a saturated solution of $NaHCO_3$. The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic phases were washed with HCl (1N) and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (silica gel, CH_2Cl_2).

45 *(2R,3S)*: Yield: 61% (0.732 g); $[\alpha]_D^{25} = -156.4$ ($c = 0.100$, CH_2Cl_2); ^{31}P NMR (36.22 MHz, $CDCl_3$): $\delta = 136.36$ (s, 88%), 136.83 (s, 12%); 76% *ee*, (the enantiomeric purity of the chiral diamine was 92%, thus $ee_{corr} = 83\%$).

45′ *(2S,3R)*: Yield: 60% (0.720 g); $[\alpha]_D^{25} = 131$ ($c = 0.11$), CH_2Cl_2); ^{31}P NMR (90 MHz, $CDCl_3$): $\delta = 136.49$ (s, 17.5%), 136.96 (s, 82.5%); 65% *ee* (the enantiomeric purity of the chiral diamine was 92%, thus $ee_{corr} = 70\%$); ^{1}H NMR (200 MHz $CDCl_3$) 0.87 (t, $J = 6.6$ Hz, 3H), 1.10–1.55 (m, 6H), 1.70 (m, 1H), 2.03 (m, 1H), 3.53 (dd, $J = 4.2$, 11.1 Hz, 1H), 3.73 (dd, $J = 6.0$, 10.9 Hz, 1H), 4.40 (d, $J = 6.7$ Hz, 1H), 7.12–7.37 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.98, 22.81, 27.71, 29.45, 46.64, 55.83, 62.90, 126.51, 126.92, 128.24, 128.36, 128.62, 131.21, 135.61, 141.25$; anal. calcd for $C_{18}H_{24}OS$: C 75.95, H 8.05; found C 75.20, H 7.89.

(2*R*,3*S*)-2-Butyl-3-phenyl-1-butanol (46): A solution of (*E*)-**1** (0.523 g, 4 mmol) in dry cumene (3 mL) was added dropwise over a period of 0.5 h at 0 °C to a solution of *n*BuLi/hexane (7.5 mL, 12 mmol) in the presence of (−)-sparteine (0.92 mL, 4 mmol) in dry cumene (5 mL). The red reaction mixture was stirred at 0 °C for another 0.5 h, was allowed to warm to room temperature, and then stirred for 1 h. After cooling to −60 °C, dry tetrahydrofuran (15 mL) was added, followed by methyl iodide (1.5 mL, 24 mmol). The reaction was completed by stirring for 1 h at room temperature. The reaction mixture was poured into HCl (1N). The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (silica gel, CH_2Cl_2). Yield: 63% (0.520 g); $[\alpha]_D^{25} = 8.7$ ($c = 0.01$, CH_2Cl_2); ^{31}P NMR (36.22 MHz, $CDCl_3$): $\delta = 137.73$ (s, 91%), 136.79 (s, 9%); 82% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$):

0947-6539/99/0507-2066 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 7

$\delta = 0.91$ (t, $J = 6.9$ Hz, 3H), 1.22–1.67 (m, 6H), 1.30 (d, $J = 7.1$ Hz, 3H), 1.67 (m, 1H), 2.85 (q, $J = 7.3$ Hz, 1H), 3.41 (dd, $J = 4.9$, 11.0 Hz, 1H), 3.52 (dd, $J = 5.2$, 11.0, 1H), 7.20–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 14.05, 18.52, 23.10, 27.65, 29.30, 40.35, 47.03, 63.45, 126.04, 127.54, 128.37, 146.38.

(2*R*)-2-[(*S*)-phenyl(deuterio)methyl]-1-hexanol (44): A solution of (*E*)-**1** (0.523 g, 4 mmol) in dry cumene (3 mL) was added dropwise over a period of 0.5 h at 0 °C to a solution of *n*BuLi/hexane (7.5 mL, 12 mmol) in the presence of (−)-sparteine (0.92 mL, 4 mmol) in dry cumene (5 mL). The red reaction mixture was stirred at 0 °C for another 0.5 h, was warmed to room temperature, and then stirred for 1 h. After cooling to −60 °C, DCl (prepared from D_2O (0.48 mL, 24 mmol) and acetyl chloride (1.7 mL, 24 mmol) in dry diethyl ether (20 mL)) was added dropwise at −60 °C, the mixture was allowed to warm to room temperature. The reaction was completed by stirring for 1 h at room temperature. After cooling, the reaction mixture was poured into HCl (1N). The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvents, the residue was chromatographed (silica gel, cyclohexane/ethyl acetate 80:20). Yield: 87% (0.675 g); $[\alpha]_D^{25} = -4.13$ ($c = 0.12$ CH_2Cl_2); d.r. = 95:5; ^{31}P NMR (36.22 MHz, $CDCl_3$, (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine): $\delta = 136.81$ (s, 92%), 137.48 (s, 8%); 84% *ee*; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 7.1$ Hz), 1.15–1.40 (m, 6H), 1.70 (m, 1H), 2.65 (m, 1H), 3.50 (d, $J = 5.1$ Hz, 2H), 7.10–7.35 (m, 5H).

***N*,*N*′-Dimethyl-(2*S**)-[(*S**)-(methylthio)benzyl]-1-hexanamine (53a); *N*,*N*′-diethyl-(2*S**)-[(*S**)-(methylthio)benzyl]-1-hexanamine (53b)**: To a solution of (*E*)-**3** or (*E*)-**52** (0.378 g, 2 mmol, R = Et) or (0.322 g, 2 mmol, R = Me) in dry hexane (20 mL) was added *n*BuLi (1.82 mL, 1.65M in hexane, 3 mmol) followed by dry TMEDA (0.45 mL, 3 mmol) at −70 °C. The cooling bath was removed and the resultant red reaction mixture was stirred at 0 °C for 3 h. MeSSMe (0.54 mL, 6 mmol) in hexane (10 mL) was added dropwise at −60 °C and the reaction completed by stirring for 1 h at room temperature. After cooling, the reaction mixture was poured into aqueous NH_3 (3 mL, 20%). The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic phases were dried over K_2CO_3. After evaporation of the solvent, the residue was chromatographed (silica gel, cyclohexane/diethyl ether 1:1 containing a few drops of 32% NH_3). Yield: 73% (0.427 g, R = Et); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.0$ Hz, 3H), 0.9 (t, $J = 7$ Hz, 6H), 1.25 (m, 6H), 1.85 (s 3H), 2 (m, 1H), 2.25 (m, 2H), 2.47 (q, $J = 7$ Hz, 4H) 4.09 (d, $J = 5.1$ Hz, 1H), 7.15–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 11.27$, 13.84, 14.76, 22.78, 28.95, 29.30, 41.88, 46.70, 53.69, 54.92, 126.44, 127.60, 129.15, 140.25. Yield: 68% (0.360 g, R = Me); ^{1}H NMR (200 MHz, $CDCl_3$ major isomer) 0.85 (m, 3H), 1.25 (m, 6H), 1.65 (m, 1H), 1.90 (s, 3H), 2.10 (m, 2H), 2.25 (s, 6H), 4.13 (d, $J = 4.4$ Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.96$, 14.91, 22.80, 26.60, 29.41, 41.62, 45.66, 53.50, 61.26, 126.60, 128.01, 129.26, 139.86; anal. calcd for $C_{16}H_{27}NS$: C 72.39, H 10.25; found C 72.98, H 10.78.

***N*,*N*′-Dimethyl-(2*R**)-[(*S**)-deuterobenzyl]-1-hexanamine**: To a solution of (*E*)-**3** (0.322 g, 2 mmol) in dry hexane (20 mL) was added *n*BuLi (1.82 mL, 1.65M in hexane, 3 mmol) followed by dry TMEDA (0.45 mL, 3 mmol) at −70 °C. The cooling bath was removed and the resultant red reaction mixture was stirred at 0 °C for 3 h. MeOD (0.3 mL, 6 mmol) in hexane (3 mL) was added dropwise at −60 °C and the reaction completed by stirring for 1 h at room temperature. After cooling, the reaction mixture was poured into NH_3 (20%) in water (3 mL). The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic phases were dried over K_2CO_3. After evaporation of the solvent the residue was chromatographed (silica gel, cyclohexane/diethyl ether 1:1 containing a few drops of 32% NH_3). Yield: 70% (0.308 g); ^{1}H NMR (400 MHz, $CDCl_3$ major isomer): $\delta = 0.88$ (m, 3H), 1.28 (m, 6H), 1.81 (m,1H), 2.10 (dd, $J =$ 7.6, 12.9 Hz, 2H), 2.20 (s, 6H), 2.51 (d, $J = 7.7$ Hz, 1H), 7.20–7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.09$, 23.05, 26.98, 31.56, 37.69, 38.27, 38.65, 45.91, 64.09, 125.72, 126.03, 129.37, 141.20; anal. calcd for $C_{15}H_{24}DN$: C 81.75, H 11.89; found C 82.10, H 11.50.

***N*,*N*′-Dimethyl-(2*R**)-[(*R**)-deuterobenzyl]-1-hexanamine**: To a solution of (*E*)-**3** (0.322 g, 2 mmol) in dry hexane (20 mL) was added *n*BuLi (1.82 mL, 1.65M in hexane, 3 mmol) followed by dry TMEDA (0.45 mL, 3 mmol) at −70 °C. The cooling bath was removed and the resultant red reaction mixture was stirred at 0 °C for 3 h. $ZnBr_2$ (4 mL, 1N in diethyl ether, 4 mmol) was added dropwise and the reaction mixture was stirred at the required temperature (see Table 1). DCl [prepared from D_2O (0.4 mL, 10 mmol) and acetyl chloride (0.7 mL, 10 mmol) in dry diethyl ether (10 mL)] was added dropwise at −60 °C and the reaction completed by stirring overnight at room temperature. After cooling, the reaction mixture was poured into NH_3 (20%) in water (3 mL).The aqueous layer was extracted with diethyl ether (2 × 10 mL).The organic layer was treated overnight with an aqueous solution of Na_2S, washed with Na_2CO_3 (10 mL), and dried over K_2CO_3. After evaporation of the solvent the residue was chromatographed (silica gel, cyclohexane/diethyl ether 1:1 which contained a few drops of 32% NH_3). Yield: 69% (0.305 g); ^{1}H NMR (400 MHz, $CDCl_3$ major isomer): $\delta = 0.88$ (m, 3H), 1.28 (m, 6H), 1.81 (m,1H), 2.10 (dd, $J = 7.6$, 12.9 Hz, 2H), 2.20 (s, 6H), 2.66 (d, $J = 5.7$ Hz, 1H), 7.20–7.30 (m, 5H).

[1] K. Ziegler, K. Bähr, *Chem. Ber.* **1928**, *61*, 253.

[2] P. Knochel, *Comprehensive Organic Synthesis* (Eds.: B Trost, I. Fleming), Pergamon, New York, **1991**, *4*, 865.

[3] I. Marek, J. F. Normant, Carbometalation Reactions in *Cross Coupling Reactions* (Eds.: P. J. Stang, F. Diederich,), Wiley-VCH **1998**, 271.

[4] The authors wish to point out the large difference between the enantioselective carbometalation with a chiral ligand on the organometallic derivative (chiral complexation) with the diastereoselective carbometalation generated by a chiral substrate (even if the chiral moiety can be cleaved in a second step). In this bibliographic section, only the former case is described. For the references concerning the second alternative, see ref. [3].

[5] a) A. H. Hoveyda, J. P. Morken, *J. Org. Chem.* **1993**, *58*, 4237; b) J. P. Morken, M. T. Didiuk, A. H. Hoveyda, *J. Am. Chem. Soc.* **1993**, *115*, 6997; c) M. S. Visser, N. M. Heron, M. T. Didiuk, J. F. Sagal, A. H. Hoveyda, *J. Am. Chem. Soc.* **1996**, *118*, 4291; d) A. H. Hoveyda, J. P. Morken, *Angew. Chem.* **1996**, *108*, 1378; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1262; e) A. F. Houri, Z. Xu, D. A. Cogan, A. H. Hoveyda, *J. Am. Chem. Soc.* **1995**, *117*, 2943; f) Z. Xu, C. W. Johannes, A. F. Houri, D. S. La, D. A. Cogan, G. E. Hofinela, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 10302; g) J. P. Morken, M. T. Didiuk, M. S. Visser, A. H. Hoveyda, *J. Am. Chem. Soc.* **1994**, *116*, 3123; h) M. S. Visser, A. H. Hoveyda, *Tetrahedron* **1995**, *51*, 4383; i) S. M. Visser, J. P. A. Harrity, A. H. Hoveyda, *J. Am. Chem. Soc.* **1996**, *118*, 3779; j) L. Bell, R. J. Whitby, R. J. Jones, M. C. H. Standen, *Tetrahedron Lett.* **1996**, *37*, 7139.

[6] a) D. Y. Kondakov, E. I. Negishi, *J. Am. Chem. Soc.* **1995**, *117*, 10771; b) D. Y. Kondakov, E. I. Negishi, *J. Am. Chem. Soc.* **1996**, *118*, 1577; c) G. Dawson, C. A. Durrant, G. G. Kirk, R. J. Whitby, R. V. H. Jones, M. C. H. Standen, *Tetrahedron Lett.* **1997**, *38*, 2335.

[7] a) F. R. W. P. Wild, H. Wasiucionek, G. Huttner, H. Brintzinger, *J. Organomet. Chem.* **1985**, *288*, 63; b) B. Chin, S. L. Buckwald, *J. Org. Chem.* **1997**, *62*, 2267.

[8] a) M. Nakamura, M. Arai, E. Nakamura, *J. Am. Chem. Soc.* **1995**, *117*, 1179; b) E Nakamura, *Pure Appl. Chem.* **1996**, *68*, 123.

[9] I. Marek, J. F. Normant, *Chem. Rev.* **1996**, *96*, 3241.

[10] a) T. Kato, S. Marumoto, I. Sato, I. Kuwajima, *Synlett* **1991**, 671; b) S. Marumoto, I. Kuwajima, *Chem. Lett.* **1992**, 1421.

[11] a) H. Felkin, A. Swierczewski, A Tambute. *Tetrahedron Lett.* **1969**, 707; b) J. K. Crandall, A. C. Clark, *J. Org. Chem.* **1972**, *37*, 4236.

[12] D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282, and references therein.

[13] D. Hoppe, *Encyclopedia of reagents for the Organic Synthesis*, *Vol 7* (Ed.: L. A. Paquette), 1st ed., Wiley, Chichester **1995**, 4662.

[14] P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552, and references therein.

[15] As a result of the low solubility of the starting material in hexane, cumene was preferred for the carbolithiation of cinnamyl alcohol.

[16] a) A. Alexakis, J. C. Frutos, S. Mutti, P. Mangeney, *J. Org. Chem.* **1994**, *59*, 3326; b) A. Alexakis, S. Mutti, P. Mangeney, *J. Org. Chem.* **1992**, *57*, 1224.

[17] K. Soai, H. Hayashi, A. Shinozaki, H. Umebayashi, Y. Yamada, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3450.

[18] S. Klein, I. Marek, J. F. Poisson, J. F. Normant, *J. Am. Chem. Soc.* **1995**, *117*, 8853.

[19] D. J. Gallagher, H. Du, S. A. Long, P. Beak, *J. Am. Chem. Soc.* **1996**, *118*, 11391.
[20] This puzzling outcome is still unexplained; however it has been already been reported: see, ref. [11a].
[21] M. Imai, A. Hagihara, H. Kawasaki, K. Manabe, K. Koga *J. Am. Chem. Soc.* **1994**, *116*, 8829.
[22] The *ee* value was determined after deprotection of the *tert*-butyl diethyl ether into the corresponding alcohol; see, A. Alexakis, M. Gardette, S. Colin *Tetrahedron Lett*. **1988**, *29*, 2954.
[23] The enantioselection of the carbolithiation of the *N*,*N*′-dimethyl-(2*S*)-benzyl-1-hexanamine was determined by chiral HPLC on Chiracel OD.
[24] The *ee* value was also determined by ^{31}P NMR spectroscopic analysis of the diastereomeric phosphorus product. See ref. [16].
[25] The absolute configurations were not determined; however, by analogy with all the other examples, we consider them to be (*S*).
[26] S. Norsikian, I. Marek, J. F. Poisson, J. F. Normant *J. Org. Chem*. **1997**, *62*, 4898.
[27] a) X. Wei, R. J. K. Taylor, *Tetrahedron Assymetry* **1997**, *8*, 665; b) X. Wei, R. J. K. Taylor, *Tetrahedron Lett*. **1996**, *37*, 4209; c) X. Wei, R. J. K. Taylor, *J. Chem. Soc. Chem. Commun.* **1996**, 187; d) K. G. Richey, Jr., A. S. Heyn, W. F. Erickson, *J. Org. Chem*. **1983**, 48, 3821.
[28] S. Norsikian, I. Marek, J. F. Normant, *Tetrahedron Lett*. **1997**, *38*, 7523.
[29] In the case of the addition of *n*PrLi, the *ee* value is lower (76% instead of 85%) since the preparation of this reagent required Et_2O as the solvent. See discussion in the text.
[30] a) M. B. Watson, G. W. Youngson, *J. Chem. Soc*. **1968**, 258; b) R. L. Letsinger, *J. Am. Chem. Soc*. **1948**, *70*, 406.
[31] a) A. I. Meyers, K. Kamata, *J. Org. Chem.* **1974**, *39*, 1603; b) K. Mori, T. Sugai, *Synthesis* **1982**, 752.
[32] a) M. Bergdahl, M. Nilsson, T. Olsson, K. Stern, *Tetrahedron* **1991**, *47*, 9691; b) T. Tsunoda, M. Nagaku, C. Nagino, Y. Kawamura, F. Ozaki, H. Hioki, S. Ito, *Tetrahedron Lett.* **1995**, *36*, 2531; c) S. Senda, K. Mori, *Agric. Biol. Chem*. **1983**, *47*, 795; d) R. Breitenbach, C. K. F. Chiu, S. S. Masset, M. Maltz, C. W. Murtiashaw, S. L. Pezzullo, T. Staigers, *Tetrahedron Asymmetry*, **1996**, *7*, 435.
[33] H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless *J. Org. Chem*. **1981**, *46*, 3936.
[34] $[\alpha]_D = 26.5$ ($c = 0.1$; EtOH) according to K.Petterson, *Arkiv för Kemi* **1953**,*7*, 39.
[35] a) M. J. Woltering, R. Fröhlich, D. Hoppe, *Angew. Chem.* **1997**, *109*, 1804; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 1764; b) M. Oestreich, R. Fröhlich, D. Hoppe, *Tetrahedron Lett*. **1998**, *39*, 1745; c) M. J. Woltering, R. Fröhlich, B. Wibbeling, D. Hoppe, *Synlett* **1998**, 797. For some references on the carbocyclization of chiral organolithium, see: I. Coldham, R. Hufton, D. J. Snowden *J. Am. Chem. Soc.* **1996**, *118*, 5322; K. Tomooka, N. Komone, T. Nakai, *Tetrahedron Lett.* **1997**, *38*, 8939.
[36] However, when the same reaction was applied to the dimethyl acetal (or the cinnamyl diethylamine) of (*Z*) sterochemistry, (*Z*)-**8**, the opposite enantiomer is effectively obtained; however, the enantioselectivity dropped to only 30%.
[37] The carbolithiation of (*Z*)-**9** occurred in 8 h at 0 °C to yield only 50% of carbometalated product with 28% *ee*.
[38] a) C.K-F. Chiu, *Tetrahedron Asymmetry* **1995**, *6*, 881; b) J. P. Rizzi, *US Patent*, 4, 767,743, **1988**.
[39] For a highlight, see: C. Bolm, F. Bienewald, A. Seger, *Angew. Chem.* **1996**, *108*, 1767; *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 1657, and references therein.
[40] When an electrophile (such as MeOD) is added to the benzylic organolithium compound, generated by carbolithiation on β-methylstyrene (no intramolecular chelation), the diastereoselectivity is poor (d.r. = 60:40).
[41] For epimerization of carbanionic centers into the thermodynamic product, see: a) P. G. Mc Dougal, B. D. Condon, M. D. Lafosse, Jr., A. M. Lauro, D. Vanderveer, *Tetrahedron Lett.* **1988**, *29*, 2547; b) R. Hoffmann, M. Bewersdorf, *Tetrahedron Lett*. **1990**, *31*, 67; c) D. R. Williams, J. G. Philipps, J. C. Huffman, *J. Org. Chem.* **1981**, *46*, 4101; d) A. Krief, M. Hobe, *Tetrahedron Lett* **1992**, *33*, 6527; e) A. Krief, M. Hobe, *Tetrahedron Lett*. **1992**, *33*, 6529; f) P. Beak, J. E. Hunter, Y. M. Jun, A. P. Wallin, *J. Am. Chem. Soc* **1987**, *109*, 5403; g) W. H. Miles, S. L. Riviera, J. D. Rosario, *Tetrahedron Lett*. **1992**, *33*, 305; h) A. I. Meyers, J. Guiles, J. S. Warmus, M. A. Gonzales, *Tetrahedron Lett*. **1991**, *32*, 5505; i) W. H. Pearson, A. C. Lindbeck, *J. Am. Chem. Soc*. **1991**, *113*, 8546; j) W. H. Pearson, A. C. Lindbeck, J. W. Kampf, *J. Am. Chem. Soc*. **1993**, *115*, 2622.
[42] For a more complete discussion, see: C. Mück-Lichtenfeld, H. Ahlbrecht, *Tetrahedron* **1996**, *52*, 10025.
[43] The formation of cyclopropane by 1,3-elimination between an organogembismetallic and a methoxymethyl ether has already been described: a) I. Marek, D. Beruben, J. F. Normant, *Tetrahedron Lett*. **1995**, *36*, 3695; b) D. Beruben, I. Marek, J. F. Normant, N. Platzer, *J. Org. Chem*. **1995**, *60*, 2488; c) D. Beruben, I. Marek, J. F. Normant, N. Platzer, *Tetrahedron Lett.* **1993**, *34*, 7575.
[44] For some representative formations of chiral cyclopropanes, see: a) A. B. Charette, J.F Marcoux, *Synlett* **1995**, 1197, and references therein; b) J. Salaün, *Chem. Rev*. **1989**, *89*, 1247; c) D. Romo, A. I. Meyers, *J. Org. Chem*. **1992**, *57*, 6265; d) H. M. L. Davies, N. J. S. Huby, W. R. Cantrell, Jr., J. L. Olive, *J. Am. Chem. Soc*. **1993**, *115*, 9468; e) M. P. Doyle in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**; Chapt. 3; f) A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339; g) D. A. Evans, K. A. Woerpel, M. J. Scott, *Angew. Chem.* **1992**, *104*, 439; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 430; h) S. E. Denmark, S. P. O'Connor, *J. Org. Chem*. **1997**, *62*, 584.
[45] A. Krief, M. Hobe, *Tetrahedron Lett.* **1992**, *33*, 6529.
[46] For a previous report on the synthesis of chiral cyclopropane mediated by a stoichiometric amount of (−)-sparteine, see: M. Paetow, M. Kotthaus, M. Grehl, R. Fröhlich, D. Hoppe, *Synlett* **1994**, 1034.
[47] T. Imai, H. Mineta, S. Nishida, *J. Org. Chem.* **1991**, *55*, 4986.
[48] The correlation was made from the alcohols **30** and **31** by tosylation and displacement with dimethylamine.
[49] P. Knochel, R. D. Singer *Chem. Rev.* **1993**, *93*, 2117.
[50] a) F. Wang, T. Tang, L. Labaudiniere, I. Marek, J. F. Normant, *Synlett* **1995**, 723; b) C. Darcel, F. Flachsmann, P. Knochel, *Chem. Commun*. **1998**, 205; c) R. Duddu, M. Eckhardt, M. Furlong, P. Knoess, S. Berger, P. Knochel, *Tetrahedron* **1994**, *50*, 2415; d) F. Lhermitte, P. Knochel, *Angew. Chem.* **1998**, *110*, 2598; *Angew. Chem. Int. Ed.* **1998**, *37*, 2460; e) L Micouin, M. Oestreich, P. Knochel, *Angew. Chem.* **1997**, *109*, 274; *Angew. Chem. Int. Ed. Engl*. **1997**, 36, 245; f) Sakami, T. Houkawa, M. Asaoka, H. Takei, *J. Chem. Soc. Perkin Trans. 1*, **1995**, 285; g) T. Houkawa, T. Ueda, S. Sakami, M. Asaoka, H. Takei, *Tetrahedron Lett*. **1996**, *37*, 1045.
[51] Cases where some organometallic compounds react with inversion of configuration are: the [2,3] Wittig rearrangement: a) K. Tomooka, T. Igarashi, M. Watanabe, T. Nakai, *Tetrahedron Lett*. **1992**, *33*, 5795; b) R. Hoffmann, R. Brückner, *Angew. Chem.* **1992**, *104*, 646; *Angew. Chem. Int. Ed. Engl*. **1992**, *31*, 647; c) K. Brickmann, R. Brückner, *Chem. Ber*. **1993**, *126*, 1227; d) E. J. Verneer, T. Cohen, *J. Am. Chem. Soc*. **1992**, *114*, 375. For the [1,2] Wittig rearrangement, see: e) R. Hoffmann, T. Bückert, R. Brückner, *Tetrahedron Lett*. **1993**, *34*, 297; f) E. J. Verneer, T. Cohen, *J. Org. Chem*. **1992**, *57*, 1072. For the transmetalation of metalated allyl carbamates with $[Ti(OiPr)_4]$, see: g) D. Hoppe, O. Zschage, *Angew. Chem.* **1989**, *101*, 67; *Angew. Chem. Int. Ed. Engl*. **1989**, *28*, 69; h) D. Hoppe, T. Krämer, *Tetrahedron Lett*. **1987**, *28*, 5149; i) B. Peschke, J. Lüßmann, M. Dyrbusch, D. Hoppe, *Chem. Ber*. **1992**, *125*, 1421. For lithiated benzylic carbamates, see: j) D. Hoppe, A. Carstens, T. Kramer, *Angew. Chem.* **1990**, *102*, 1455; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1424. For the benzylic lithium derivatives, see: ref. [10].
[52] The benzylic organolithium compound epimerizes very rapidly, even at −78 °C, see: ref. [10].
[53] S. Klein, I. Marek, J. F. Normant, *J. Org. Chem*. **1994**, *59*, 2925.

Received: December 2, 1998 [F 1473]

  0947-6539/99/0507-2068 $ 17.50+.50/0