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Highly Enantioselective Reactions of a Lithiated α-Thioallyl Carbanion *via* Thermodynamic Resolution Pathway

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Dedicated to Professor Gerhard Erker on the occasion of his 60th birthday.

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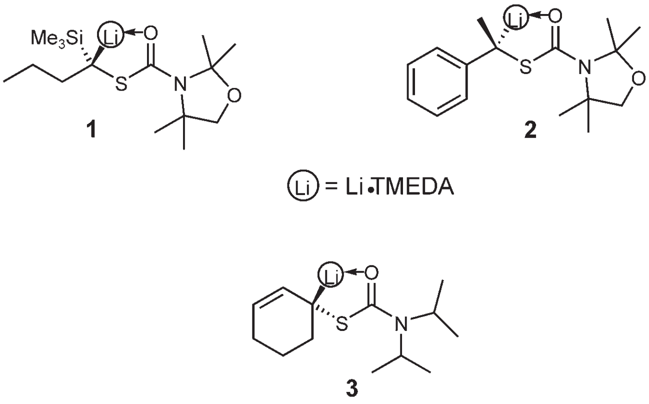
Abstract: *S*-Cinnamyl thiocarbamate **9**, easily accessible from cinnamyl alcohol, undergoes smooth deprotonation with *n*-BuLi in the presence of various chiral ligands to form configurationally unstable organolithium intemediates. With the proper choice of chiral ligand, the diastereomeric equilibrium is almost fully shifted to one side, furnishing highly enantioenriched products after reaction with various electrophiles.

Keywords: chiral ligands; enantioselective synthesis; organolithiums; thermodynamic resolution; thiocarbanion

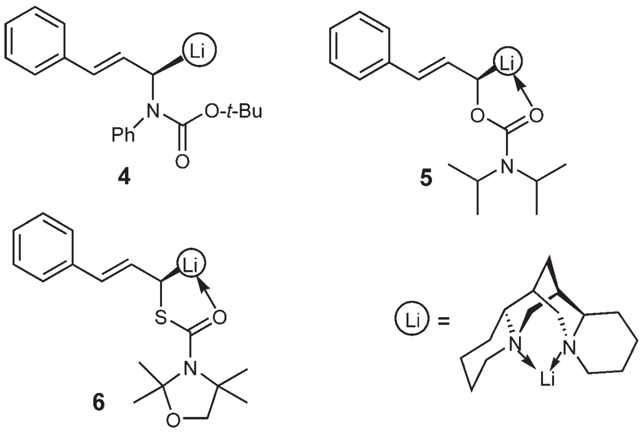
Introduction

Chiral, non-racemic, α-heterosubstituted organolithium compounds have become important tools in enantioselective synthesis.[1] The synthetic utility of these species is dependent upon their stereoselective generation, configurational stability, and the selectivity in the subsequent substitution step with electrophiles. Generally, the last step of this process occurs stereospecifically so the enantioenrichment occurs either in the deprotonation step (kinetic resolution) or in the post-deprotonation steps (dynamic kinetic resolution or thermodynamic resolution).[2] Several dipole-stabilized, α-alkoxy[3] and α-amino[4] organolithium compounds have been designed so as to proceed through the asymmetric deprotonation pathway thereby yielding highly enantioenriched products. An important prerequisite for a successful asymmetric deprotonation process is the configurational stability of the intermediate organolithium derivative. Although this condition is fulfilled by many α-alkoxy[3] and α-amino[4] organolithium compounds, most of their sulfur analogues show notoriously high configurational lability even at −78 °C.[5] This behavior is attributed, among other factors, to a very different mechanism of epimerization of these types of carbanions which indicate that bulky substituents or branching is necessary at the carbanionic center to enhance the configurational stability.[6] Indeed, silylated α-thioalkyllithium **1**,[7a] α-thiobenzyllithium, **2**[7b,c] and α-thioallyllithium **3**[7d,e,f] compounds show considerable configurational stability (Scheme 1).



Scheme 1. Configurationally stable α-thio-organolithium compounds.

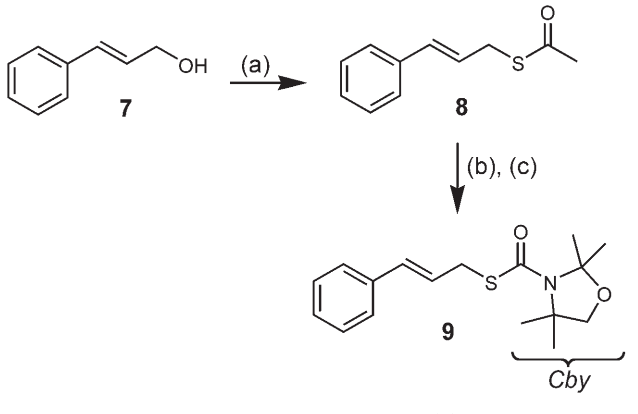
In the absence of branching, the configurational stability of the organolithium derivative decreases to a great extent and, for achieving high selectivity in these cases, one must rely on the post deprotonation processes.[8] It is also well known that mesomerically stabilized organolithium derivatives are more pronounced for configurational lability due to the ease of rapid epimerization.[9] Medium regio- and stereoselectivities upon applying bis(oxazoline) ligands in the lithiation of aryl 2-propenyl sulfides have been reported by Toru and co-workers.[8a] Also, in view of the configurational stability of lithiated cinnamyl amide **4**[10] and configurational lability of α-lithiocinnamyl carbamate **5**[9d] (Scheme 2), we became interested in investigating the corresponding thiocarbanion. Herein we present the detailed investigation of lithiated thiocarbanion **6** with respect to its generation in the presence of various chiral ligands, configurational stability, mechanism of racemization, synthesis of various enantioenriched products, and stereochemical course of electrophilic substitutions.



Scheme 2. Various cinnamyl-derived chiral organolithium compounds.

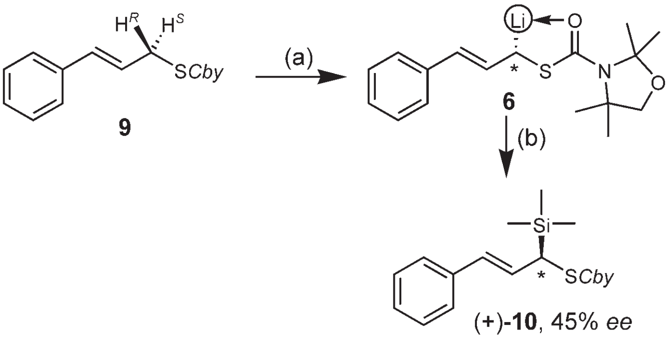
Results and Discussion

Thiocarbamate **9** was synthesized from cinnamyl alcohol **7** in three steps (Scheme 3). Thioesterification of **7** under Mitsunobu reaction conditions[11] yielded the thioester **8** in 90% yield. Reductive cleavage of the ester followed by carbamoylation afforded the desired thiocarbamate **9** in 74% yield over two steps.



Scheme 3. *Reagents and conditions:* (a) Ph_3P, DIAD, CH_3COSH, THF, 0°C, 90%; (b) $LiAlH_4$, Et_2O, room temperature; (c) NaH, *Cby*Cl, THF, room temperature, 74% over 2 steps.

The thiocarbamate **9** underwent smooth deprotonation with 1.2 equivalents of *n*-BuLi in toluene in the presence of various chiral and achiral ligands. The deprotonation was found to be complete within 30 min at −78°C. Thus, when **9** was deprotonated in presence of 1.2 equivalents of (−)-sparteine for 30 min followed by trapping of the intermediate lithium species with trimethylsilyl chloride, the corresponding silane (+)-**10** was obtained with 45% enantiomeric excess and in 97% yield (Scheme 4).



Scheme 4. *Reactions and conditions:* (a) 1.2 equivs. *n*-BuLi, 1.2 equivs. (−)-sparteine, toluene, −78°C, 30 min; (b) 3.0 equivs. TMSCl, 97%.

From this experiment, several questions raised:

(1) Whether (−)-sparteine is able to differentiate efficiently between the enantiotopic protons *pro*-R and *pro*-S?
(2) Is the intermediate lithium derivative formed after deprotonation configurationally stable?
(3) What is the mechanism of enantioenrichment/racemization?
(4) How can synthetically useful enantioenrichment be obtained?

In order to answer the first three questions, several control experiments were done using (−)-sparteine as the ligand. The results obtained from these experiments are outlined in Table 1.

Table 1. Results of the deprotonation-silylation of **9** in the presence of (−)-sparteine.

Entry	Solvent	Temp	Dep. Time	Yield	*er* of **10** (*R*:*S*)
1	Toluene	−78°C	*in situ*	97%	27:73
2	Toluene	−90°C	30 min	90%	30:70
3	Cumene	−78°C	30 min	64%	31:69
4	Pentane	−78°C	30 min	40%	26:74
5	Pentane	−40°C	30 min	42%	66:34
6	Toluene	−78°C	3 h	95%	22:78
7	Toluene	−78°C	6 h	94%	17:83
8	Toluene	−78°C	12 h	0%	-

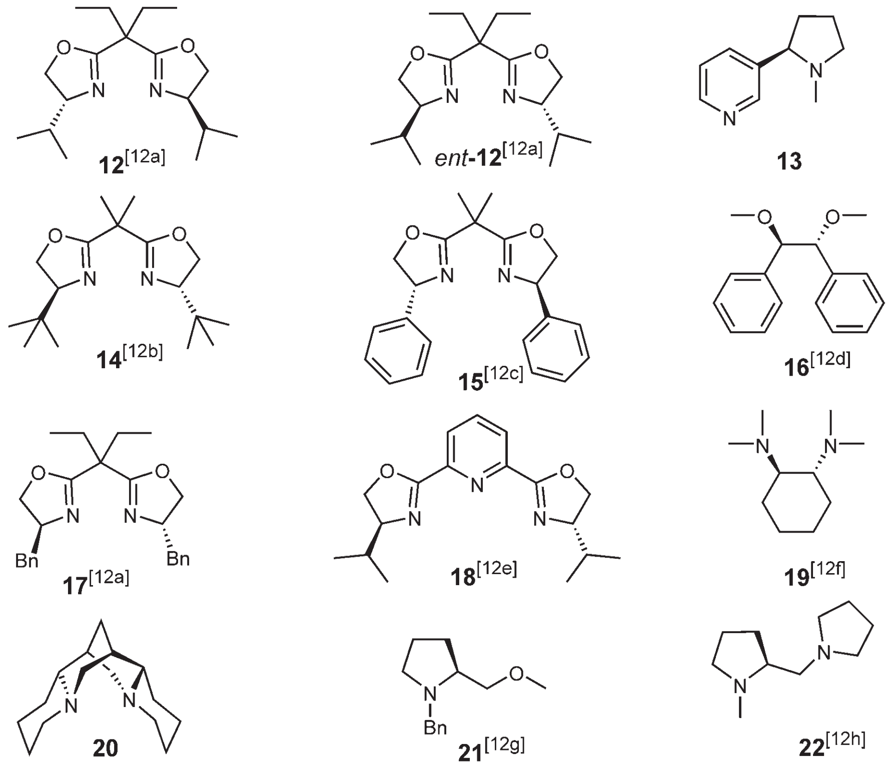
The result of the *in situ* experiment (entry 1) clearly reveals that the enantiotopic differentiation by (−)-sparteine is not sufficient and the epimeric ion-pairs are equilibrating rather slowly as indicated by almost the same enantiomeric ratio as in 30 min deprotonation time (Scheme 4). Changing the solvent from toluene to cumene or pentane did not change the enantioselectivity significantly. In pentane at −78 °C, the enantioselectivity is in the same range as in toluene but the yield is lower due to the low solubility of the starting material. Interestingly, prolonging the deprotonation time showed an increase in enantiomeric excesses of the silylated product (entries 6 and 7). This is an indication of the fact that the lithiated complexes equilibrate and with time, the ratio is shifted to a thermodynamically more stable diastereomeric complex. However, the equilibration time could not be prolonged for more than 6 h because of severe decomposition.

Thus, it can be concluded that (−)-sparteine does differentiate between the enantiotopic protons but not sufficiently and the formed organolithium intermediate is configurationally unstable under the reaction conditions. The only possible way to achieve synthetically useful selectivity in presence of (−)-sparteine might be to induce thermodynamic resolution *via* selective crystallization or by a dynamic kinetic resolution. All the attempts in this direction met with poor success.

As has been shown by Toru and co-workers,[8] the last option for obtaining good selectivites in such cases is *via* thermodynamic resolution. This method relies on choosing a proper ligand-substrate combination in such a way that the two diastereomeric complexes formed after deprotonation differ significantly in their energies, thereby shifting the ratio to one side. Thus, a variety of chiral ligands were synthesized and tested for deprotonation reactions of **9**. The standard conditions for deprotonation were chosen as in Scheme 4. Trimethylsilyl chloride was used as the standard electrophile due to high yield, short reaction time (*ca.* 30 min), and ease of enantiomeric separation on a chiral stationary HPLC phase.

The results of deprotonation of **9** obtained with various chiral ligands (Scheme 5, Table 2) are discussed in the following paragraphs.

Thus, it is very clear from the above results that the bis(oxazoline) ligands **12** and **15** are ideally suited for this substrate, and essentially complete shifting of the diastereomeric ratio takes place yielding a product with > 99 % *ee* (entry 10). Also, the *in situ* experiment (entry 3), wherein the deprotonation is carried out in presence of the electrophile and represents the ratio immediately after deprotonation, reveals that there is no enantiotopic differentiation (4 % *ee*) by these ligands and enantioenrichment takes place after the deprotonation stage. Prolonging the deprotonation time or warming the reaction to higher temperatures (en-



Scheme 5. Various chiral ligands used for the deprotonation-silylation of **9**.

Table 2. Results of deprotonation-silylation of **9** in the presence of various chiral ligands.

Entry	Ligand (Equivs.)	Solvent	Temp.	Dep. Time	Yield of **10**	*er* (HPLC)
1	**20** (1.2)	toluene	−78 °C	30 min	60 %	51:49
2	**12** (1.2)	toluene	−78 °C	30 min	86 %	10:90
3	**12** (1.2)	toluene (*in situ*)	−78 °C	*in situ*	32 %	52:48
4	**12**(1.2)	toluene	−78 °C	12 h	94 %	7:93
5	*ent*-**12**	toluene	−78 °C	12 h	95 %	92:8
6	**17** (1.2)	toluene	−78 °C	30 min	70 %	56:44
7	**14** (1.2)	toluene	−78 °C	30 min	80 %	70:30
8	**15** (1.2)	toluene	−78 °C	14 h	75 %	2:98
9	**15** (1.2)	toluene	warm-cool[a]	1 h	76 %	2:98[b]
10	**15** (1.2)	toluene	−25 °C	30 min	87 %	< 1:99[c]
11	**21** (1.2)	toluene	−78 °C	30 min	78 %	60:40
12	**18** (1.2)	toluene	−78 °C	30 min	0 %	-
13	**19** (1.2)	toluene	−78 °C	30 min	73 %	53:47
14	**13** (1.2)	toluene	−78 °C	30 min	90 %	50:50
15	**16** (1.2)	toluene	−78 °C	30 min	96 %	58:42
16	**22** (1.2)	toluene	−78 °C	30 min	82 %	52:48

[a] Warm-cool procedure: −78 °C (30 min) to −30 °C (10 min) to −78 °C.

[b] $[\alpha]_D^{20}$: +122.3 (*c* 0.94, $CHCl_3$).

[c] $[\alpha]_D^{20}$: +124.0 (*c* 1.0, $CHCl_3$).

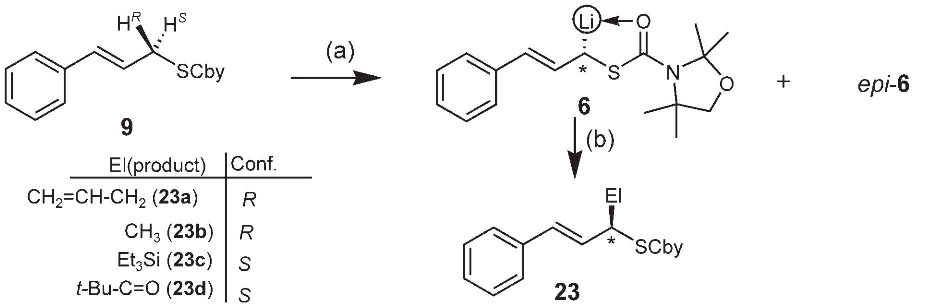
tries 8, 9, 10) further improves the selectivity, proving the thermodynamic factor operating for enantioenrichment.

With this background, we then set out to employ this methodology for other electrophiles and further silylation, alkylation, allylation, and acylation were carried out in good yields and with high selectivities (Scheme 6, Table 3).

A variety of other electrophiles were used successfully for this methodology; however, unfortunately, no suitable method could be found to analytically separate the enantiomers of most of these compounds. Table 4 shows the examples of electrophiles which were successfully used and the resulting racemic products fully characterized.

Assignment of Absolute Configuration and Elucidation of Stereochemical Pathway

Mesomerically stabilized α-thioorganolithium compounds are known to undergo alkylation and silyla-



El(product)	Conf.
CH_2=CH-CH_2 (**23a**)	*R*
CH_3 (**23b**)	*R*
Et_3Si (**23c**)	*S*
t-Bu-C=O (**23d**)	*S*

Scheme 6. *Reaction conditions:* (a) 1.2 equivs. *n*-BuLi, 1.2 equivs. ligand, toluene, 30 min; (b) 3.0 equivs. ElX.

Table 3. Enantioenriched products synthesized by deprotonation-substitution of **9**.

Entry	Lig. (Equivs.)	Electrophile (Product)	Temp	Yield	*er*	$[\alpha]_D^{20}$
1	**15** (1.2)	Allyl bromide (**23a**)	−30 °C	90 %	94:6	−62.6 (*c* 0.72, $CHCl_3$)
2	**15** (1.2)	Methyl triflate (**23b**)	−30 °C	63 %	96:4	+134.5 (*c* 0.72, $CHCl_3$)
3	**15** (1.2)	TESCl (**23c**)	−30 °C	83 %	94:6	+82.8 (*c* 0.99, $CHCl_3$)
4	**12** (1.2)[a]	Pivaloyl chloride (**23d**)	−78 °C	84 %	-[b]	+52.2 (*c* 1.0, $CHCl_3$)

[a] (*S,S*)- and (*R,R*)-bis(oxazoline)s have opposite enantioinductions.

[b] Could not be determined.

Table 4. Various racemic substitution products obtained by the deprotonation of **9**.

Entry	Ligand	Electrophile (Product)	Dep. Time	Yield
1	*rac*-TMCDA	Methyl chloroformate (*rac*-**23e**)	30 min	90%
2	TMEDA	Benzyl bromide (*rac*-**23f**)	30 min	56%
3	TMEDA	CO_2/Ph-NH_2 (*rac*-**23g**)	30 min	77%
4	TMEDA	Benzophenone (*rac*-**23h**)	30 min	53%
5	TMEDA	Benzaldehyde (*rac*-**23i**)	30 min	53%

tion with inversion of configuration[7c,d,f,13]. Fortunately, the methylated product **23b** yielded crystals suitable for measurement by X-ray with anomalous dispersion. The X-ray crystal structure conclusively proved the newly generated stereocenter to be of the (*R*)-configuration (Figure 1).

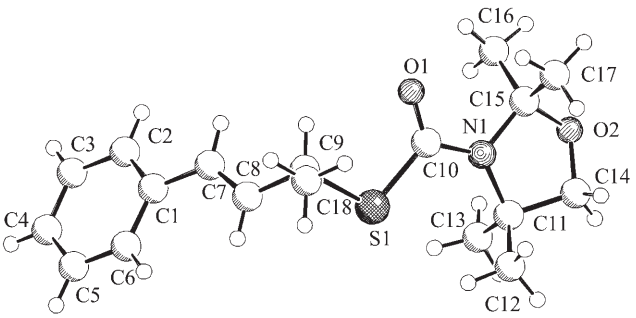


Figure 1. X-ray crystal structure of (*R*)-**23b**.

Unfortunately, the silylated product **10** could only be crystallized in racemic form despite all our attempts to obtain an enantiopure crystal (Figure 2). Nonetheless, the crystal structure (*R*)-**23b** combined with the previous hypotheses regarding mesomerically stabilized thiocarbanions was enough to give evidence for the stereochemical pathway. It can be assumed that silylation of **6**, similar to methylation, proceeds with inversion of configuration, hence (+)-**10** has the (*S*) configuration. Thus, it can be safely concluded that the (*R,R*)-bis(oxazoline) ligands promote deprotonation without enantiotopic differentiation but the diastereomeric equilibrium is shifted towards the (*S*)-configured lithiated intermediate which undergoes alkylation, allylation, and silylation with inversion of configuration. The overall process is summarized in Scheme 7. The (*S,S*)-bis(oxazoline) ligands induce the chirality in a similarly high ratio but with the opposite sense.

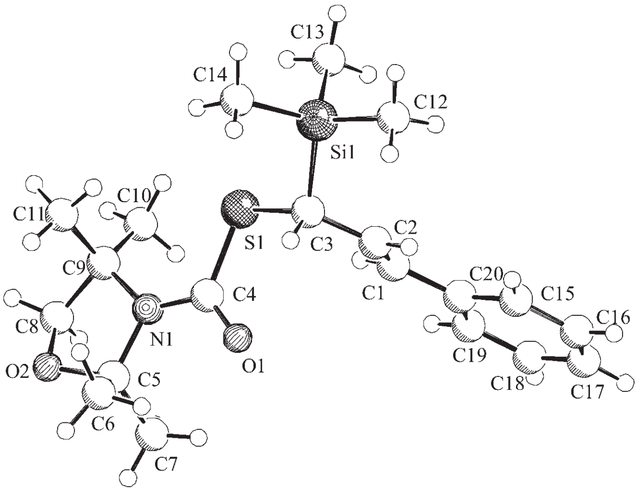
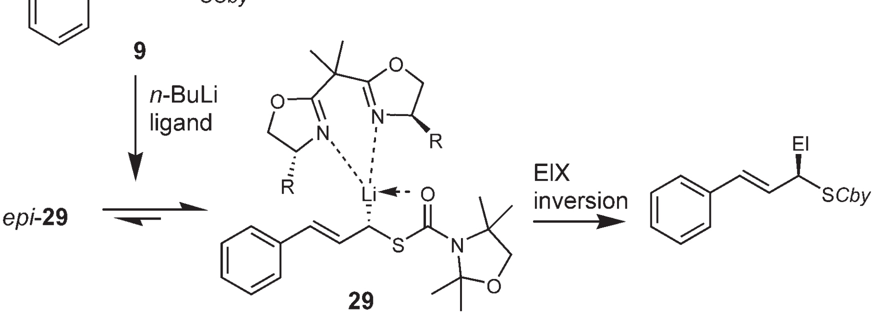


Figure 2. X-ray crystal structure of *rac*-**10**.

Conclusions

This methodology provides an easy access to acyclic, highly enantioenriched allylic thiols. The double bond provides opportunities for further chemical manipulations. Application of this method to other configurationally unstable allylic carbanions is under investigation.



Scheme 7. Stereochemical pathway of the deprotonation-substitution of **9**.

Experimental Section

General Remarks

All solvents were dried and purified prior to use. Unless otherwise specified, materials were obtained from commercial sources and used without purification. All the chiral ligands are known and were synthesized according to the reported procedures except for (−)-sparteine and nicotine, which are commercially available. Diethyl ether and toluene were distilled over sodium benzophenone ketyl, THF over potassium benzophenone ketyl and CH_2Cl_2 was distilled over CaH_2. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA), TMSCl and NEt_3 were distilled from powdered calcium hydride and stored under argon. All reactions were performed under an argon atmosphere in flame-dried glassware using septum and syringe techniques. Flash column chromatography (FCC) was performed on Merck 60 silica gel, 0.040–0.063 mm using an argon pressure of 1.2–1.4 bars, and monitored by thin layer chromatography (TLC) on Merck 60 F_{254} silica gel. Melting points were measured on an SMP3 melting point apparatus from Stuart Scientific, UK (uncorrected values). The optical rotations were measured in a 10 cm cuvette on a polarimeter 241 from Perkin–Elmer, Überlingen. ^1H and ^{13}C NMR data was recorded using Bruker ARX 300, AM 360, AMX 400 or Varian Associated Unity Plus 600 spectrometers; spectra were obtained from solutions in $CDCl_3$ ($\delta_C = 77.0$) and were calibrated relative to residual content of $CHCl_3$ ($\delta_H = 7.24$) or $SiMe_4$ ($\delta_H = 0.0$). Elemental analyses were performed at the Microanalytical Section of the Organisch-Chemisches Institut, WWU Münster, on a Vario El III from Elementar Analysen-Systeme GmbH. Mass spectrometric data was obtained on Finnigan MAT 8230 (EI), Micromass Quattro LCZ (ESI), Micromass MAT 8200 (GC-TOF/HRMS) instruments. Chiral HPLC was performed on a Waters 717 using chiral columns ChiraGrom-1 and ChiraGrom-2, 250×2 mm from GROM ANALYTIK + HPLC GmbH, Herrenberg. The solvent systems used for the measurements were various mixtures of hexane/*i*-PrOH and pentane/*i*-PrOH.

Preparation of Thiocarbamate 9

***S*-Cinnamyl Ethanethioate (8):** To a solution of PPh_3, (26.2 g, 100 mmol, 2.0 equivs.) in 250 mL of THF at 0 °C, diisopropyl azodicarboxylate (DIAD) (20.2 g, 100 mmol, 2.0 equivs.) was added in a dropwise fashion over a period of 30 min and the reaction mixture stirred for 30 min under an argon atmosphere. A white precipitate was formed. A mixture of freshly distilled cinnamyl alcohol (6.7 g, 50 mmol, 1.0 equiv.) and thioacetic acid (7.6 g, 100 mmol, 2.0 equivs.) in 50 mL of THF was added dropwise over a period of 20 min and the mixture was stirred at 0 °C for 1 h and 4 h (until the formation of clear solution) at room temperature. The solvent was evaporated under vacuum and 100 mL of pentane were added to the reaction mixture. The precipitated triphenylphosphine oxide was filtered and the crude product was subjected to column chromatography [diethyl ether:pentane (E/P) = 1:8] to obtain the pure thioester **8** as a light, colorless oil which solidifies in the refrigerator; yield: 8.60 g (44.7 mmol, 90 %).

***S*-Cinnamyl Thiocarbamate 9:** Lithium aluminium hydride (1.30 g, 33.3 mmol, 1.3 equivs.) was suspended in 25 mL of diethyl ether under an argon atmosphere. After stirring for 10 min, the suspension was cooled to 0 °C. Cinnamyl thioester **8**, (4.91 g, 25.6 mmol, 1.0 equiv.) was dissolved in 15 mL of diethyl ether and added slowly to the lithium aluminium hydride suspension over a period of 10 min. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for additional 1 h. Afterwards, the reaction flask was immersed in an ice bath and 2 mL of water were cautiously added into the reaction mixture. After the standard workup, the crude thiol was obtained as a light, colourless, offensively smelling liquid. The crude thiol was used in the subsequent step without further purification.

NaH (60 % in mineral oil, 1.4 g, 35 mmol.) was suspended in 40 mL absolute THF and stirred for 5 min. Then, the stirring was stopped and suspension was allowed to settle down. The supernatant THF was removed by syringe. The procedure was repeated to ensure the complete removal of the mineral oil in NaH. After two of such washings, freshly distilled THF (40 mL) was added and this solution was cooled to 0 °C. In another flask, the crude thiol, obtained as above, was dissolved in 20 mL of dry THF and injected into the NaH solution in a dropwise manner taking care that reaction temperature did not rise. This mixture was stirred for 10 min at 0 °C and a solution of 2,2,4,4-tetramethyl-1,3-oxazolidine-4-carbonyl chloride (*Cby*Cl), (6.70 g, 35 mmol) in 20 mL THF was added to it. The reaction mixture was allowed to warm up to room temperature and stirred at the same temperature for 14 h. Afterwards, the reaction flask was immersed in an ice bath and 25 mL of water were slowly added to get a clear brown solution. To this mixture were added 50 mL of diethyl ether, the phases were separated and the aqueous phase was extracted with diethyl ether (3×20 mL). The collective organic phase was dried over anhydrous $MgSO_4$, filtered through glass wool and the solvent was removed under reduced pressure. The crude thiocarbamate was subjected to column chromatography (E:P = 1:10) to obtain pure thiocarbamate **9** as a light, colorless oil; yield: 5.70 g, (18.9 mmol, 74 % over 2 steps).

General Procedure for Deprotonation of 9 in Presence of Various Chiral Ligands

Cinnamyl thiocarbamate **9** (100 mg, 0.32 mmol, 1.0 equiv.) was dissolved in 5 mL of toluene, the appropriate chiral ligand (0.48 mmol, 1.5 equivs.) was added and the reaction flask was cooled to −78 °C. To this mixture, *n*-BuLi (1.6 M in hexane, 0.24 mL, 0.38 mmol, 1.2 equivs.) was injected in a dropwise manner. The reaction mixture was stirred at −78 °C for 30 min. Then, the appropriate electrophile (0.96 mmol, 3.0 equivs.) was injected and the reaction mixture stirred for 1–12 h until no more of the starting material could be detected by TLC. The reaction was then quenched with 1 mL of methanol followed by 2 mL of water. The layers were separated and the aqueous layer was extracted with diethyl ether (3×10 mL). The collective organic phase was dried over anhydrous $MgSO_4$, filtered through glass wool, and concentrated under reduced pressure to get the crude product. The crude product was subjected to column chromatography (E:P) to obtain the pure enantioenriched product.

X-ray Crystallographic Study

X-ray crystal structure analysis for (*R*)-**23b**: formula $C_{18}H_{25}NO_2S$, $M = 319.45$, colorless crystal $0.35 \times 0.25 \times 0.10$ mm, $a = 6.010(1)$, $b = 7.349(1)$, $c = 39.431(1)$ Å, $V = 1741.6(4)$ Å^3, $\rho_{calc} = 1.218$ g cm^{-3}, $\mu = 1.696$ mm^{-1}, empirical absorption correction ($0.588 \leq T \leq 0.849$), $Z = 4$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 1.54178$ Å, $T = 223$ K, ω and ϕ scans, 5706 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.60$ Å^{-1}, 2856 independent ($R_{int} = 0.032$) and 2816 observed reflections $[I \geq 2\sigma(I)]$, 204 refined parameters, $R = 0.032$, $wR^2 = 0.081$, Flack parameter 0.07(2), max. residual electron density 0.20 (−0.19) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

X-ray crystal structure analysis for *rac*-**10**: formula $C_{20}H_{31}NO_2SSi$, $M = 377.61$, colorless crystal $0.40 \times 0.20 \times 0.20$ mm, $a = 10.063(1)$, $b = 10.716(1)$, $c = 11.783(1)$ Å, $\alpha = 77.20(1)$, $\beta = 67.68(1)$, $\gamma = 66.76(1)$, $V = 1076.2(2)$ Å^3, $\rho_{calc} = 1.165$ g cm^{-3}, $\mu = 1.959$ mm^{-1}, empirical absorption correction ($0.508 \leq T \leq 0.695$), $Z = 2$, triclinic, space group $P\bar{1}$(No. 2), $\lambda = 1.54178$ Å, $T = 223$ K, ω and ϕ scans, 10260 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.60$ Å^{-1}, 3675 independent ($R_{int} = 0.029$) and 3587 observed reflections $[I \geq 2\sigma(I)]$, 233 refined parameters, $R = 0.036$, $wR^2 = 0.097$, max. residual electron density 0.30 (−0.24) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

Data sets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT,[14] data reduction Denzo-SMN,[15] absorption correction Denzo,[16] structure solution SHELXS-97,[17] structure refinement SHELXL-97,[18] graphics SCHAKAL.[19]

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-603269 and CCDC-603270. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

Supporting Information

Complete analytical data for all the synthesized novel compounds are given in the supporting information.

Acknowledgements

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