First Use of Axially Chiral Thioamides for the Stereocontrol of C–C Bond Formation

Shubhada Dantale,[a] Vincent Reboul,[a] Patrick Metzner,*[a] and Christian Philouze[b]

Abstract: Several *N*-aryl-substituted thioamides with an axis of chirality along the N–C(aryl) bond were prepared in good to excellent yields. NMR spectra revealed preferences for the *E* rotamer (along the N–C(=S) bond). X-ray crystallographic analysis showed that the planes of the aryl and thioamide groups were almost perpendicular (79°). For the first time, these atropisomeric thioamides were used for an asymmetric Claisen rearrangement. LDA deprotonation led selectively to the enethiolates of *Z* stereochemistry, and subsequent reaction with a variety of allyl halides furnished *S*-allyl keteneaminothioacetals. These intermediates were not detected as they rearranged readily to γ-unsaturated thioamides in good to high yields and diastereoselectivities up to 88:12. Chemical correlation allowed the assignment of the (a*R**,2*R**) configuration to the major diastereoisomer. A model was proposed to explain the stereochemical course of the thio-Claisen rearrangement.

Keywords: arenes · asymmetric synthesis · axial chirality · thioamides · thio-Claisen rearrangement

Introduction

Amongst the major advances of asymmetric synthesis is the use of axial chirality. Most examples involve binaphthyl-type auxiliaries.[1, 2] Non-biaryl structures have been investigated only recently.[3] The observation that a number of aromatic compounds, such as benzenecarboxamides or anilides are not flat has been made earlier, but overlooked in terms of synthetic applications. The groups of Fuji,[4, 5] Curran,[6, 7] Clayden,[8, 9] Simpkins[10, 11] and Taguchi[12, 13] have very recently prepared a number of axially chiral amides, bearing the aromatic and amide planes in an almost orthogonal orientation. Introduction of steric hindrance has led to acceptable or significant barriers to rotation along the axis of chirality and opened the way to "atroposelectivity". Reactions that have been stereocontrolled in this fashion include the alkylation and aldol reactions of enolates,[10, 11, 14, 15] nucleophilic addition to carbonyl derivatives[16, 17] and iminium salts,[18] addition of electrophiles to *ortho* or laterally metalated naphthamides,[3, 19–21] Diels–Alder and dipolar cycloadditions,[12, 22] and radical reactions.[6, 23]

[a] Dr P. Metzner, Dr S. Dantale, Dr V. Reboul
Laboratoire de Chimie Moléculaire et Thio-organique (LCMT)
UMR CNRS #6507, ISMRA-Université
6 boulevard du Maréchal Juin, 14050 Caen (France)
Fax: (+33) 231-452-877
E-mail: metzner@ismra.fr

[b] Dr C. Philouze
LEDSS, UMR CNRS #5616
Université Joseph Fourier
BP 53, 38041 Grenoble 9 (France)

We wished to replace the oxygen atom of amides by a sulfur atom, as there seems to be no precedent for the use of atropisomeric thioamides in asymmetric synthesis, and believe that this will present a number of useful characteristics. Two features are necessary: 1) the perpendicularity of the planes of the arene ring and the thioamide moiety and 2) a high barrier to rotation to allow configurational stability. Although, to our knowledge, there is no data available, we assumed by analogy with thiobenzamides that these features would favour thioamides rather than amides.

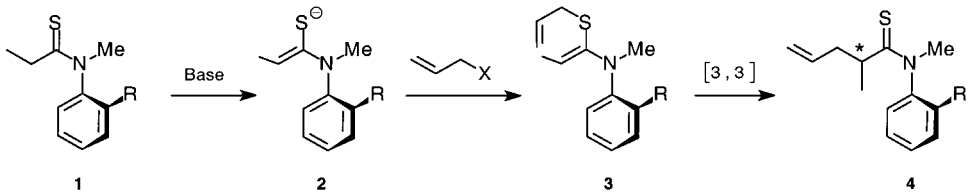
The attractive characteristics of thioamides[24] are their ease of preparation,[25, 26] their stability in air, their crystallinity, the acidity of protons located α to the thiocarbonyl group, the regiospecific S-alkylation of resulting enethiolates, their high nucleophilicity and their facile desulfurization reactions.[27, 28]

Our aim was to prepare a number of thioamides, such as **1**, to examine their structures and explore their stereochemical behaviour in the thio-Claisen rearrangement (Scheme 1).

Deprotonation of thioamides[29] selectively leads to enethiolates **2**. These intermediates exhibit soft character (as compared to enolates) and react with allyl halides by specific S-alkylation.[24, 30] The [3,3]sigmatropic rearrangement of allyl vinyl sulfides[24, 30–33] generally takes place under mild conditions leading to good yields of γ-unsaturated thiocarbonyl compounds. The facile nature of the transformation, as compared to the oxygen series, is mainly of kinetic origin[34] and is explained by the cleavage of the C–S bond being easier relative to the C–O bond.

We report here that this strategy has been successful and that interesting selectivities have been attained.

  0947-6539/02/0803-0632 $ 17.50+.50/0



Scheme 1. [3,3]Sigmatropic rearrangement of *S*-allyl keteneaminothioacetals **3** to γ-unsaturated thioamides **4**.

Results

Synthesis of thioamides: The necessity of configurational stability and unsymmetrical substitution of the arene led us to study amines having a bulky group in the *ortho*-position. We started from commercially available 2-*tert*-butylaniline and 2,5-di-*tert*-butylaniline and transformed them according to the literature[7] into amides **5a–c** (Table 1) by *N*-methylation and acylation (acetyl chloride or propionyl chloride). We also prepared the secondary amide **5d** and two tertiary amides **5e** and **5f** bearing 1-naphthyl and 2-methyl-1-naphthyl groups respectively. Thionation was effected with Lawesson's reagent. Our usual conditions (THF, room temperature) did not cause conversion, revealing the sensitivity of this reaction to steric hindrance. Carrying out the transformation under reflux in toluene afforded good to excellent yields of thioamides **1a–f** (Table 1).

Table 1. Conversion of amides **5** to thioamides **1** with Lawesson's reagent.[a]

Entry	Amide	Time [h]	Thioamide	Yield [%]	*E*/*Z* [%]
1	**5a**	5	**1a**	82	100:0
2	**5b**	5	**1b**	87	100:0
3	**5c**	6	**1c**	90	100:0
4	**5d**	6	**1d**	60	50:50
5	**5e**	6	**1e**	87	60:40
6	**5f**	4	**1f**	90	100:0

[a] In all the above thionation reactions, 0.6 equivalents of Lawesson's reagent was used.

Structure of thioamides: Thioamides **1** may exhibit two types of atropisomerism, along the N–C=(X) bond and along the N–C(aryl) bond (Figure 1). The first type is commonly observed with thioamides,[35, 36] which are known to have higher barriers of rotation relative to the oxygen series,[37] with a difference of 5–7 kcal mol^{-1}, and for increased proportions of the main *E* or *Z* isomer. A rule of thumb, in terms of steric hindrance, is that the more stable configuration has the two largest substituents *trans* to each other along the single bond: usually the chain linked to the thiocarbonyl and the carbon chain on nitrogen.

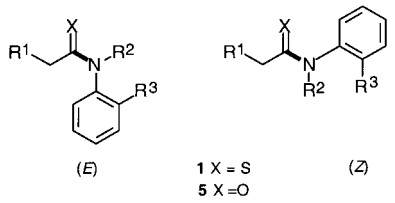


Figure 1. *E* and *Z* rotamers of thioamides **1** and amides **5** along the N–C(=X) bond.

Very few examples of *N*-aryl thioamides have been reported.[38–40] More information is available for the oxygen series. For secondary anilides[7, 41] the main isomer is the *Z* one, which is also the usual configuration observed in peptides. Replacement of the *N*-hydrogen by a methyl group causes a surprising inversion of stereochemistry, studied extensively by Itai[42, 43] and confirmed by Curran[7, 44] for compounds **5a–c**. The major isomer is now the *E* one and the aryl group behaves as a "small group", relative to the methyl, by adopting a perpendicular arrangement. We have examined the structure of thioamides **1** both by NMR spectroscopy in solution and by X-ray diffraction of single crystals.

For the *secondary* thioamide **1d** (R^1 = Me, R^2 = H, R^3 = *t*Bu), the NMR spectrum revealed a 1:1 mixture of rotamers with two triplets for Me at $\delta = 1.27$ and 1.44 and two quartets for CH_2 at $\delta = 2.46$ and 2.90. The *E* configuration was assigned to the upfield shifts by analogy with Curran's data on corresponding amides.[7] Crystallisation of this mixture in dichloromethane/petroleum ether provided single crystals. X-ray diffraction analysis showed a homogeneous arrangement of *Z* configuration. We believe that, in solution, a rapid equilibrium takes place between *E* and *Z* rotamers and that it is the equilibrium ratio that is monitored by NMR spectroscopy. During crystallisation, the *Z* rotamer is isolated, because of lower solubility. The equilibrium proceeds faster than the crystallization, and, thus, the initial mixture is fully converted into the *Z* isomer. We consider this as analogous to "dynamic kinetic resolution".

The X-ray structure of (*Z*)-**1d** (Figure 2) revealed several points. The angle between the phenyl ring and the thioamide planes has a mean value of 68°. The steric bulk of the *tert*-butyl group deviates from the planarity of the thioamide by about 7°.

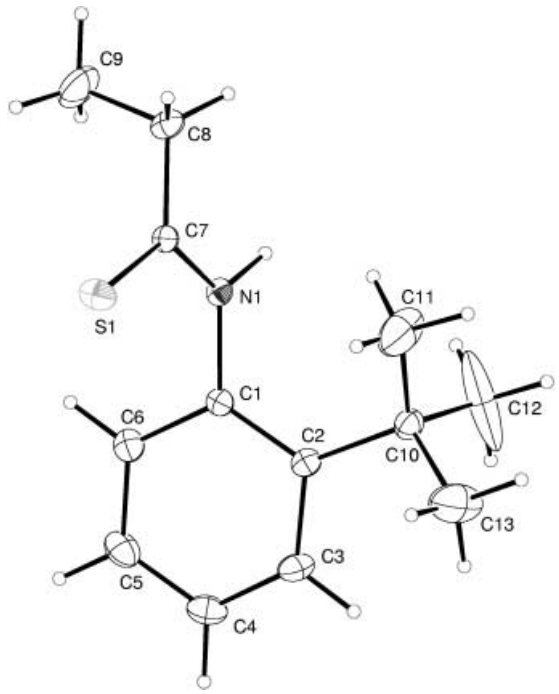


Figure 2. Crystal structure of **1d** (*N*-(2-*tert*-butylphenyl)propanethioamide). Selected interatomic distances (Å), bond angles (°) and torsion angles (°): S1−C7 1.661(3), N1−C7 1.327(4), N1−C1 1.433(4), C2−C10 1.538(5), S1-C7-N1 123.1(2), S1-C7-C8 122.2(2), C1-N1-C7 125.2(3), N1-C1-C2 123.1(3), N1-C1-C6 115.4(3), C1-C2-C10 126.0(3), S1-C7-N1-C1 5.9(5), S1-C7-C8-C9 −84.2(4), N1-C1-C2-C10 6.5(5), N1-C7-C8-C9 94.0(4), C2-C1-N1-C7 −113.0(4), C6-C1-N1-C7 70.8(4).

Tertiary thioamides **1a**–**c** were examined by NMR spectroscopy, and we observed a single isomer in all cases, to which we assigned the *E* configuration (*N*−Me singlet at $\delta = 3.62$). For amides **5a** and **5b** the analogous *E* isomer is favoured, with an *E*:*Z* ratio of 22:1 and 15:1, respectively. A noticeable feature for **1b** and **1c** is that their CH_2 signals were not single quartets but two quartets, providing evidence of diastereotopicity. To estimate the barrier to rotation along the N−C(aryl) bond of **1b**, we heated a sample in [D_6]DMSO up to 140 °C and were not able to observe coalescence of the above signals. This means that the barrier to rotation is rather high and cannot be measured under these conditions. This gave us confidence about the configurational stability necessary for any practical asymmetric induction.

A single crystal of propanethioamide **1c** bearing two *tert*-butyl substituents at the 2- and 5-positions was analyzed by X-ray diffraction (Figure 3). The first observation was the *E* geometry along the N−C(=S) bond in agreement with the NMR spectrum of the compound in solution. Therefore, we have in the sulfur series the same inversion as with the amides: preferred *Z* structure for secondary thioanilides and *E* configuration for tertiary thioanilides. The second important feature is that the planes of the thioamide moiety and the aromatic ring are almost perpendicular with an angle of 79° (C16−C17−N1−C18).

An interesting feature (in the solid state) is the conformation along the C18−C9 propane–thioamide bond. The methyl group and the sulfur atom bonds[45] make an angle of 6°. This is in agreement with the conformations usually observed with

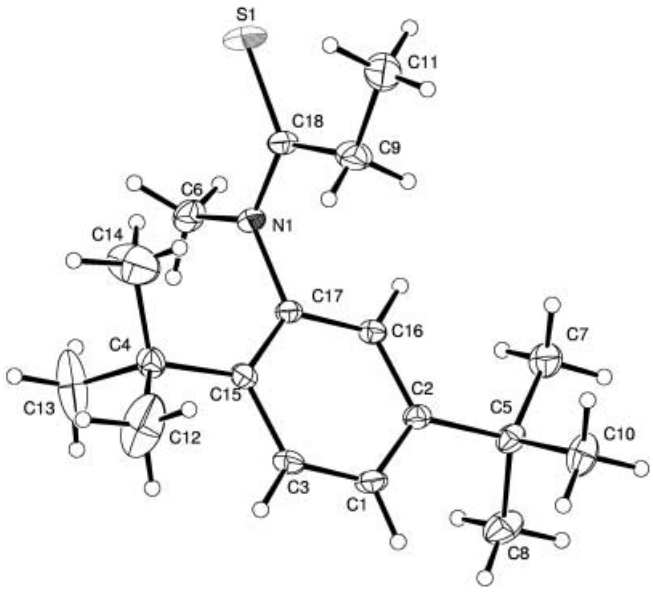
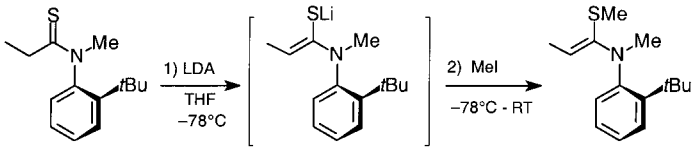


Figure 3. Crystal structure of **1c** (*N*-(2,5-di-*tert*-butylphenyl)-*N*-methylpropanethioamide). Selected interatomic distances (Å), bond angles (°) and torsion angles (°): S1−C18 1.661(2), N1−C17 1.452(2), N1−C18 1.339(2), C9−C18 1.500(3), C6-N1-C17 115.7(1), C6-N1-C18 121.1(2), C17-N1-C18 122.3(2), S1-C18-N1 121.5(2), S1-C18-C9 122.1(1), S1-C18-C9-C11 6.0(3), N1-C18-C9-C11 −173.9(2), C6-N1-C17-C15 −88.1(2), C6-N1-C17-C16 89.9(2), C15-C17-N1-C18 102.7(2), C16-C17-N1-C18 −79.3(2).

Et−C(=O)−X compounds (aldehydes, esters) for which the methyl and oxygen are almost eclipsed.[46]

These structural observations encouraged us and we initiated our synthetic study with racemic thioamides **1**.

Metallation of 1b: Suitable conditions were found by reaction with a variety of bases. Monitoring the formation of the corresponding enethiolate **2b** was achieved by quenching with MeI and NMR spectroscopic detection of *S*-methyl keteneaminothioacetal (**3b**) (Scheme 2).



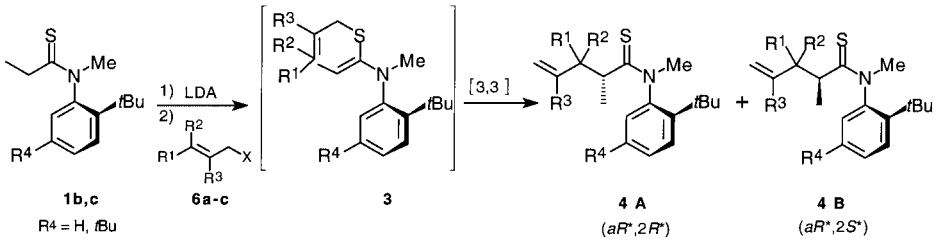
1b **2b** **3b**

Scheme 2. Stereoselective deprotonation and S-alkylation of **1b** to (*Z*)-keteneaminothioacetal **3b**.

n-Butyllithium or *tert*-butyllithium proved ineffective, even at ambient temperature. Sodium 1,1,1,3,3,3-hexamethyldisilazane (NaHMDS) achieved only minor deprotonation (−78 °C to room temperature). Quantitative formation of **3b** was obtained with lithium diisopropylamide (LDA; 2.1 equiv) provided that, after addition at −78 °C, the reaction mixture was brought to ambient temperature. This S-alkylation has the advantage of furnishing important information about the stereochemistry of the carbon–carbon double bond of product **3b**. It has been demonstrated that it reflects the

  0947-6539/02/0803-0634 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 3

configuration of the intermediate enethiolate, as the allylation takes place with retention of configuration.[29, 30, 47, 48] Another characteristic of thiocarbonyl compounds is that their kinetic deprotonation leads to enethiolates with a *cis* structure, with respect to the *S*-lithium and olefinic methyl groups. The ^{1}H NMR of the crude *S*-methyl keteneaminothioacetal (**3b**) showed a single set of signals, including *S*-Me at $\delta = 2.21$, the olefinic methyl at 1.80 and protons at 4.49. Thus, deprotonation occurs in a stereoselective fashion and, by analogy with previous results,[29, 49] we assigned the *Z* configuration to **3b**.



Scheme 3. Asymmetric thio-Claisen rearrangement.

Table 2. Thio-Claisen rearrangement of thioamides **1**.

Entry	Thioamide	Allyl halide[a]	LDA [equiv]	Reflux [h]	Product	Yield [%]	dr[b]
1	**1a**	**6a**	1.5	6	**4aa**	75	–
2	**1a**	**6c**	1.5	8	**4ac**	47	–
3	**1b**	**6a**	1.1	5	**4ba**	82	80:20
4	**1b**	**6b**	1.1	5	**4bb**	80	79:21
5	**1b**	**6c**	1.1	6	**4bc**	78	86:14
6	**1c**	**6a**	1.5	5	**4ca**	84	80:20
7	**1c**	**6b**	1.5	5	**4cb**	85	88:12
8	**1e**	**6a**	1.5	6	**4ea**	65	60:40

[a] Compound **6a**: allyl iodide, **6b**: methallyl iodide, **6c**: prenyl bromide. [b] dr = diastereomer ratio.

Thio-Claisen rearrangement: We allowed racemic thioamides **1a–f** to react with LDA at 0 °C; subsequent addition of allyl halides (allyl and methallyl iodides **6a**, **6b**, respectively, and prenyl bromide **6c**). As the S-allylation was sluggish at ambient temperature, it was necessary to heat under reflux with THF (67 °C). Under these conditions, we observed direct formation of γ-unsaturated thioamides **4**. The intermediate keteneaminothioacetals **3** were not detected. Therefore the S-allylation appears to be the rate-determining step, followed by a fast [3,3]sigmatropic shift (Scheme 3, Table 2).

The first examples (entries 1 and 2) involved rearrangement without any stereochemical concern. For entries 3–8 an asymmetric centre is created in the α-position to the thiocarbonyl group. The presence of two diastereomers was observed in the NMR spectra of thioamides **4ba**, **4bb**, **4bc**, **4ca**, **4cb**, and **4ea**, as anticipated from the two stereochemical elements (axis and centre of chirality). The isomer ratio is around 80:20 for the introduction of allyl and methallyl chains. It increases to 86:14 (entry 5) with prenyl bromide, leading to creation of a C–C bond with a quaternary carbon and greater steric hindrance. The product **4bc** has an inverted allyl chain, thus supporting a mechanism by S-allylation (with retention of allylic configuration) and subsequent rearrangement (with allyl inversion). This example demonstrates that, despite steric hindrance and heating, good yields can be obtained. Using an aromatic moiety with two *tert*-butyl groups (2- and 5-positions) led to the best selectivity, 88:12 (entry 7) with 84% yield.

In all of the above cases we have observed only one rotamer along the N–C(=S) bond, to which we assign the *E* config-

uration by an NMR spectroscopic comparison with the starting thioamides **1a–c**.

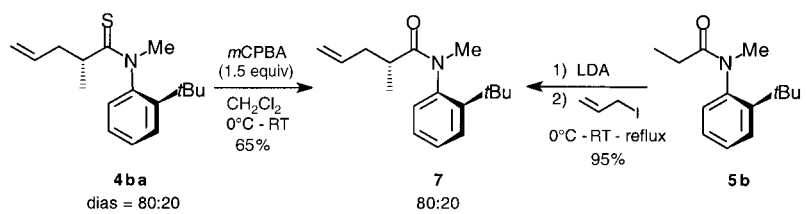
We have not observed a variation of the diastereomer ratio versus time or temperature for a specific example. Even at lower conversion, the ratio had the value reported in Table 2. Therefore, we assume that the product isomers **4** are under kinetic control, though we were not able to provide final evidence. As noted above, we also believe that the barrier to rotation in this series is rather high and prevents thermodynamic equilibration.

Other structures were examined but were less rewarding. Secondary thioamide **1d** led to a bis-allylated product (C and N), but the analysis of the isomer ratio was not successful. *N*-(1-naphthyl)-*N*-phenylpropanethioamide **1e** (entry 8) could be used but the stereoselectivity was poor, 60:40. With *N*-methyl-*N*-(2-methyl-1-naphthyl)propanethioamide (**1f**) the key step could not be conducted to completion and it was unselective, 51:49.

We have also attempted the introduction of a crotyl chain using corresponding bromides or iodides as allylating agents with thioamides **1a** and **1b**. Unfortunately, we were not able to obtain allylated thioamides **4** with an acceptable level of conversion and isolation.

Assignment of stereochemistry: This was carried out by chemical correlation with the corresponding amide **5b**, reported by Simpkins and co-workers.[11] This group has shown that deprotonation and direct allylation of amide **5b** led to unsaturated amide **7** in a 80:20 ratio of diastereomers in favour of an (a*R**,2*R**) configuration. We wished to convert our thioamide **4ba** into Simpkin's amide **7** and correlate the NMR spectra. The thioamide **4ba** was treated with *meta*-chloroperbenzoic acid (1.5 equiv) to obtain the amide **7** in 65% yield as an oil (Scheme 4).[27] NMR spectroscopy showed no change in the diastereoisomer ratio, 80:20. For the main isomer, the methyl doublet was observed at $\delta = 1.06$ (minor at $\delta = 0.99$).

We attempted to allylate the amide **5b**, according to Simpkin's procedure[11] (deprotonation at $-78\,^{\circ}C$ followed by allylation), but we were unsuccessful and had to modify the procedure. The amide was deprotonated at $0\,^{\circ}C$ with LDA and treated with allyl iodide. Warming the reaction mixture up to room temperature and refluxing in THF gave the amide **7** in 95% yield. From NMR spectroscopy we observed a diastereoisomer ratio of 80:20 and the methyl doublet at $\delta =$ 1.06 for the major isomer. These data are the same as those of products from the thio-Claisen rearrangement and thioamide to amide conversions. Thus the major diastereomer of **4ba** has an (a*R**,2*R**) configuration. Homogeneous ^{1}H and ^{13}C NMR shifts, observed for other thioamides **4bb**, **4bc**, **4ca**, and **4cb**, led us to propose assignment of the same stereochemistry.



Scheme 4. Stereochemical assignment for **4ba** (a*R**,2*R**) by chemical correlation with the corresponding amide **7**.

Discussion

We have achieved the first examples of Claisen rearrangements stereocontrolled by an axis of chirality in thioamides, neither is there a precedent available for amides. The closest case of sigmatropic shift in literature is that of imidates reported from binaphthyl derivatives by Metz and his group.[50] The severe steric hindrance of anilides bearing an *ortho-tert*-butyl group obliged us to force somewhat the traditional conditions for deprotonation ($0\,^{\circ}C$ instead of $-78\,^{\circ}C$) and S-allylation (refluxing in THF). On the other hand, the rearrangement step took place readily, stressing once again its relatively facile nature in the sulfur series.[24, 51, 52] Thus, in a number of cases, yields around 80% were obtained for unsaturated thioamides **4**.

The best diastereoselectivity was obtained with thioanilide **1c** (Table 2, entry 7) bearing a *N*-methyl group and two *tert*-butyl groups in the 2- and 5-positions. Examples with only one such latter group (in the 2-position, entries 3–5) were just slightly less selective. Attempts with the naphthalenides **1e** (entry 8) and **1f** showed that the *peri*-interactions are rather weak and provide poor or no selectivity.

Thioamide **4ba** was established as having an (a*R**,2*R**) configuration by chemical correlation. We wish to propose a model to interpret this selectivity. In the acyclic series, the Claisen rearrangement is assumed to involve a pseudo-chair transition state.[53, 54] The double bond of the keteneaminothioacetal has a *Z* configuration. It is probable that the nitrogen atom of the enamino part is mainly planar to allow some orbital overlap with the aromatic ring and with the acyclic double bond, as observed by X-ray analysis of related structures.[55, 56] Such a situation raises the question of orientation of both substituents on the nitrogen atom relative to the groups on the enamino double bond. It might reflect the stereochemistry of the tertiary thioamide **1b**: a stereospecific deprotonation and selective S-allylation would lead to an arrangement with the *N*-methyl and the sulfur atom on the same side of the N–C(=C) bond. We do not know how high the rotation barrier would be for this bond.

Another point concerns the orientation of the aromatic plane with respect to the preceding C=C plane. We assume that it is largely perpendicular, although we were not able to grow single crystals of *S*-methyl keteneaminothioacetal **3b** for X-ray analysis.

We propose the model for the formation of the two isomers (Figure 4). Front approach **B** of the *S*-allyl moiety is largely hindered by the *ortho-tert*-butyl group on the perpendicular arene plane (*Si* face). Back approach **A** now faces the same plane but on the side bearing the *ortho*-hydrogen. It is therefore favoured.

In terms of synthetic interest, the sequence reported here has the advantage of easy availability from commercially available compounds. It nicely complements the direct allylation of amide enolates reported by Simpkins and co-workers.[11]

  0947-6539/02/0803-0636 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 3

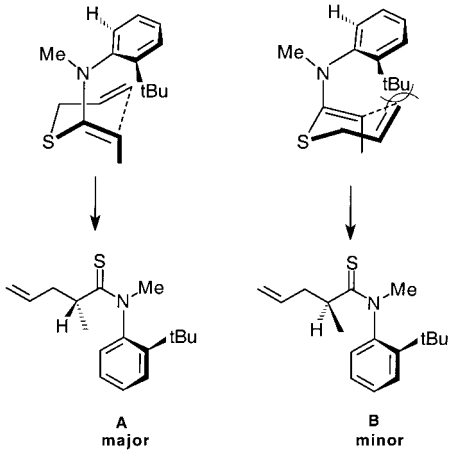


Figure 4. Proposed pseudo-chair transition-state model.

Comparable results have been obtained with the unsubstituted allyl chain. With a substituted chain, such as the prenyl one (entries 2 and 5), we have achieved allyl inversion and creation of a quaternary centre adjacent to the asymmetric carbon, which is usually not possible by direct enolate alkylation.

As noted earlier,[24, 57, 58] thioamides exhibit specific or enhanced reactivity, as compared to amides, and, thus, the unsaturated thioamides, prepared here with relative control of stereochemistry, may be converted to a variety of compounds.

So far our study has involved thioamides in the racemic form. Development of this chemistry will necessitate preparation of enantioenriched thioamides. A number of routes may be envisioned:[12, 22, 59] one approach has been achieved for the synthesis of enantiopure amide **5b** starting from ethyl *S*-lactate,[11] which appears applicable to the further conversion to thioamide **1b**. Another very recent approach involves tartrate ortho-anilides as starting materials.[59]

Conclusion

We have used thioamides with axial chirality for the stereocontrolled formation of C–C bonds. Synthesis of thioanilides with the requisite structure was straightforward. We have achieved the first Claisen rearrangement of atropisomeric (thio)amides. It proceeded in good to high yields and diastereoselectivities of up to 88:12. The structural study of thioanilides bearing an *ortho-tert*-butyl group showed that they have the requisite features. The chemical sequence involved deprotonation with LDA, S-allylation with a variety of allyl halides and facile [3,3]sigmatropic shifts. We were able to assign the (a*R**,2*R**) stereochemistry to the major diastereoisomer by chemical correlation and have proposed a model to explain this stereoselectivity. Our studies on atropisomeric thioamides are continuing.

Experimental Section

Melting points were measured on an Electrothermal 9200 apparatus. NMR spectra were recorded with a Bruker AC DPX spectrometer in $CDCl_3$ with TMS (tetramethyl silane) as an internal standard. The coupling constants are given in Hertz. Mass spectra were recorded on a Nermag Riber R 10 10 H mass spectrometer at 70 eV in the EI mode. Micro-analyses were performed on a CHNS-O (Thermoquest) apparatus. Reactions were monitored by thin-layer chromatography (TLC) on TLC plastic sheets silica gel 60 F_{254}. Silica gel (0.063–0.200 mm, Merck) was used for column chromatography. The petroleum ether used was distilled over P_2O_5 and had a boiling point range of 40–60 °C. THF was freshly distilled over sodium and benzophenone. All reactions were carried out under nitrogen.

N-(2-*tert*-butylphenyl)-*N*-methylacetamide (**5a**), *N*-(2-*tert*-butylphenyl)-*N*-methylpropionamide (**5b**) and *N*-(2,5-di-*tert*-butylphenyl)-*N*-methylpropionamide (**5c**) were prepared by a reported procedure.[7] Similarly, secondary thioamide *N*-(2-*tert*-butylphenyl)propionamide (**5d**) was prepared by using the above procedure. *N*-(1-naphthyl)-*N*-phenylpropionamide (**5e**) was prepared from the commercially available *N*-phenyl-1-naphthylamine and propionyl chloride in the presence of pyridine as a base. *N*-(2-Methyl-1-naphthyl)-*N*-methylpropionamide (**5f**) was prepared from 1-amino-2-methylnaphthalene and propionyl chloride by a similar procedure as amides **5a–c**. 1-Amino-2-methylnaphthalene was prepared from commercially available 2-methylnaphthalene by nitration with conc. HNO_3 and reduction of the nitro compound with iron powder.[60]

Typical procedure to prepare (*E*)-*N*-(2-*tert*-butylphenyl)-*N*-methylacetylthioamide (1a): *N*-(2-*tert*-butylphenyl)-*N*-methylacetamide (0.74 g, 3.6 mmol) was dissolved in toluene (15 mL), and Lawesson's reagent (0.87 g, 2.1 mmol; 0.6 equiv) was added. The reaction mixture was refluxed whilst stirring. Disappearance of the starting amide was monitored by TLC (5 h). Toluene was removed under reduced pressure, and the crude mixture purified by column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (95:5) to give the thioamide **1a** as a solid (0.65 g, 2.94 mmol) in 82% yield. The NMR spectrum showed a single isomer, *N*-Me singlet at $\delta = 3.63$ to which the *E* configuration was assigned. M.p. 101 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.36$ (s, 9H; *t*Bu), 2.34 (s, 3H; Me), 3.63 (s, 3H; *N*-Me), 6.95 (dd, $J = 1.6$, 7.7 Hz, 1H; ArH), 7.23 (dt, $J = 1.6$, 7.2 Hz, 1H; ArH), 7.30 (dt, $J = 1.6$, 7.2 Hz, 1H; ArH), 7.52 (dd, $J = 1.6$, 7.7 Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 32.1$ (Me), 34.7 (Me), 36.2, 47.4 (*N*-Me), 128.1, 129.3, 130.4, 143.9, 144.7, 202.4 (C=S); MS (70 eV, EI): *m*/*z* (%): 221 (25) $[M]^+$, 96 (77), 78 (33), 60 (100), 57 (78); elemental analysis calcd (%) for $C_{13}H_{19}NS$ (221.36): C 70.54, H 8.65, N 6.33, S 14.48; found: C 70.10, H 8.65, N 6.42, S 14.32.

(*E*)-*N*-(2-*tert*-Butylphenyl)-*N*-methylpropanethioamide (1b): This was prepared by the above-mentioned procedure from *N*-(2-*tert*-butylphenyl)-*N*-methylpropionamide (2.0 g, 9.13 mmol) and Lawesson's reagent (2.21 g, 5.47 mmol, 0.6 equiv). Column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (95:5), gave the pure thioamide **1a** as a white solid (1.85 g, 7.8 mmol) in 87% yield. The NMR spectrum showed a single isomer, *N*-Me singlet at $\delta = 3.62$ to which the *E* configuration was assigned. M.p. 78 °C (dichloromethane/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.20$ (t, $J = 7.5$ Hz, 3H; Me), 1.35 (s, 9H; *t*Bu), 2.37 (m, 2H; CH_2), 3.62 (s, 3H; *N*-Me), 6.95 (dd, $J = 1.6$, 7.7 Hz, 1H; ArH), 7.22 (dt, $J = 1.6$, 7.6 Hz, 1H; ArH), 7.30 (dt, $J = 1.6$, 7.6 Hz, 1H; ArH), 7.52 (dd, $J = 1.6$, 7.7 Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 13.7$ (Me), 31.3 (Me), 35.4 (CH_2), 37.0, 46.5 (*N*-Me), 127.1, 127.3, 128.4, 129.4, 142.8, 143.9, 207.6 (C=S); MS (70 eV, EI): *m*/*z* (%): 235 (53) $[M]^+$, 102 (100), 93 (66); elemental analysis calcd (%) for $C_{14}H_{21}NS$ (235.39): C 71.45, H 9.00, N 5.96, S 13.60; found: C 71.31, H 9.16, N 5.74, S 13.39.

(*E*)-*N*-(2,5-Di-*tert*-butylphenyl)-*N*-methylpropanethioamide (1c): This was prepared by the above-mentioned procedure from *N*-(2,5-di-*tert*-butylphenyl)-*N*-methylpropionamide (0.90 g, 3.2 mmol) and Lawesson's reagent (0.79 g, 1.9 mmol, 0.6 equiv). Column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (90:10) gave the pure thioamide **1c** as a white solid (0.87 g, 2.98 mmol) in 90% yield. The NMR spectrum showed a single isomer, *N*-Me singlet at $\delta = 3.63$ to which the *E* configuration was assigned. M.p. 89 °C (dichloromethane/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.20$ (t, $J = 7.5$ Hz, 3H; Me), 1.29 (s, 9H; *t*Bu), 1.32 (s, 9H; *t*Bu), 2.38 (m, 2H; CH_2), 3.63 (s, 3H; *N*-Me), 6.85 (d, $J = 2.2$ Hz, 1H; ArH), 7.36 (dd, $J = 2.2$, 8.5 Hz, 1H; ArH), 7.52 (d, $J = 8.5$ Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 15.8$ (Me), 32.6 (Me), 32.3 (Me), 35.8, 36.9, 39.1, 48.5 (*N*-Me), 126.1, 127.3, 131.0, 142.5, 144.4, 152.4, 209.5 (C=S); MS (70 eV, EI): *m*/*z* (%): 291 $[M]^+$, 234 (100), 218 (26), 91 (22), 73 (43), 70 (40), 57 (47), 45 (28); elemental analysis calcd (%) for

$C_{18}H_{29}NS$ (291.49): C 74.17, H 10.03, N 4.81, S 11.0; found: C 74.45, H 9.90, N 4.92, S 10.84.

***N*-(2-*tert*-butylphenyl)propanethioamide (1d)**: This was prepared by the above-mentioned procedure from *N*-(2-*tert*-butylphenyl)propionamide (0.45 g, 2.19 mmol) and Lawesson's reagent (0.53 g, 1.30 mmol, 0.6 equiv). Column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (80:20) gave the thioamide **1d** as a white solid (0.30 g, 1.35 mmol) in 60% yield. The NMR spectrum showed both *E* and *Z* isomers in an approximately 1:1 ratio, with two sets of triplets for CH_3 at $\delta = 1.27$ and 1.44 and for CH_2 two sets of quartet at $\delta = 2.46$ and 2.90. M.p. 100 °C (dichloromethane/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta =$ 1.27 (t, $J = 7.4$ Hz, 3H of *E* isomer; Me), 1.38 (s, 9H; *t*Bu), 1.44 (t, $J =$ 7.5 Hz, 3H of *Z* isomer; Me), 2.46 (q, $J = 7.4$ Hz, 2H; CH_2), 2.90 (q, $J =$ 7.4 Hz, 2H; CH_2), 7.20 (dd, $J = 1.5$, 7.8 Hz, 1H; ArH), 7.22 (dt, $J = 1.5$, 7.6 Hz, 1H; ArH), 7.50 (dt, $J = 1.5$, 7.6 Hz, 1H; ArH), 7.62 (dd, $J = 1.5$, 7.8 Hz, 1H; ArH), 8.5 (br s, 1H; *N*-H), 9.15 (br s, 1H; *N*-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 13.6$ (Me), 14.0 (Me), 30.9 (Me), 31.2 (Me), 33.8, 35.3 (CH_2), 35.5 (CH_2), 41.2, 127.1, 127.5, 127.6, 127.6, 128, 128.6, 129.3, 129.9, 131.3, 136.7, 137.6, 145.7, 146.1, 207.5 (C=S), 211.0 (C=S); MS (70 eV, EI): *m*/*z* (%): 221 $[M]^+$, 165 (98), 164 (100), 149 (26), 91 (39), 77 (28), 73 (29), 44 (41), 45 (36); elemental analysis calcd (%) for $C_{13}H_{19}NS$ (221.36): C 70.54, H 8.65, N 6.33, S 14.48; found: C 70.83, H 8.93, N 6.22, S 14.77.

***N*-(1-Naphthyl)-*N*-phenylpropanethioamide (1e)**: This was prepared by the above-mentioned procedure from *N*-(1-naphthyl)-*N*-phenylpropionamide (0.45 g, 1.63 mmol) and Lawesson's reagent (0.397 g, 0.97 mmol, 0.6 equiv). Column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (90:10), gave the thioamide **1e** as a yellow sticky oil (0.41 g, 1.40 mmol) in 87% yield. The NMR spectrum showed a mixture of both *E* and *Z* isomers in a 60:40 ratio, with two clear sets of triplets for Me at $\delta = 1.27$ and 1.42 and two sets of quartets for CH_2 at $\delta = 2.46$ and 2.89. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 7.3$ Hz, 3H of *E* isomer; Me), 1.42 (t, $J = 7.3$ Hz, 3H of *Z* isomer; Me), 2.46 (q, $J = 7.3$ Hz, 2H of *E* isomer; CH_2), 2.89 (q, $J = 7.3$ Hz, 2H of *Z* isomer; CH_2), 7.20–8.15 (m, 12H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 15.0$ (Me), 38.0 (CH_2), 123.2, 123.6, 125.7, 126.1; 126.3, 126.7, 127.2, 127.4, 127.9, 128.4, 128.8, 129.7, 130.2, 135.1, 141.5, 147.1, 202.2 (C=S), 212.5 (C=S); MS (70 eV, EI): *m*/*z* (%): 291 (47) $[M]^+$, 85 (34), 78 (68), 50 (100).

(*E*)-*N*-(2-Methyl-1-naphthyl)-*N*-methylpropanethioamide (1f): This was prepared by the above-mentioned procedure from *N*-(2-methyl-1-naphthyl)-*N*-methylpropionamide (0.30 g, 1.32 mmol) and Lawesson's reagent (0.32 g, 0.79 mmol, 0.6 equiv). Column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (95:5), gave the thioamide **1f** as a pale yellow oil (0.29 g, 1.19 mmol) in 90% yield. The NMR spectrum showed a single isomer, *N*-Me singlet at $\delta = 3.74$ to which the *E* configuration was assigned. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta =$ t, $J = 7.4$ Hz, H; Me), 2.67 (m, 2H; CH_2), 2.32 (s, 3H; Me), 3.74 (s, 3H; *N*-Me) 7.38–7.90 (m, 6H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.5$ (Me), 18.1 (Me), 36.2 (CH_2), 44.1 (*N*-Me), 122.3, 126.5, 128.2, 128.7, 129.0, 129.1, 129.3, 131.6, 133.5, 140.0, 209.1 (C=S); MS (70 eV, EI): *m*/*z* (%): 243 (21) $[M]^+$, 70 (100), 42 (28).

Deprotonation of thioamide 1b with LDA to give *S*-methyl keteneaminothioacetal (3b): LDA was freshly prepared by adding 1.6 M *n*-BuLi (0.78 mL, 1.15 mmol, 2.1 equiv) to a solution of diisopropylamine (0.17 mL, 1.15 mmol, 2.1 equiv) in THF (2.5 mL) at −78 °C. To it was added a solution of *N*-(2-*tert*-butylphenyl)-*N*-methylpropanethioamide (0.13 g, 0.55 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, MeI (0.077 mL, 1.15 mmol, 2.1 equiv) was then added, stirring maintained at −78 °C for 20 min, and then the mixture slowly warmed up to room temperature (1 h). TLC showed the thioamide had disappeared. The reaction mixture was quenched with a saturated NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (3×25 mL). The organic layer was washed once with brine (5 mL) and dried over $MgSO_4$. Solvent evaporation gave a crude product (0.100 g, 0.40 mmol) in 73% yield as a viscous liquid that slowly solidified upon cooling in the refrigerator. The NMR spectrum showed the *S*-methylated product **3b** as a single isomer, to which the *Z* configuration was assigned. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.35$ (s, 9H; *t*Bu), 1.80 (d, $J = 6.7$ Hz, 3H; Me), 2.21 (s, 3H; *S*-Me), 3.04 (s, 3H; *N*-Me), 4.49 (q, $J =$ 6.7 Hz, 1H; CH), 7.11 (dd, $J = 1.6$, 7.8 Hz, 1H; ArH), 7.22 (dt, $J = 1.6$, 7.6 Hz, 1H; ArH), 7.30 (dt, $J = 1.6$, 7.6 Hz, 1H; ArH), 7.42 (dd, $J = 1.6$, 7.8 Hz, 1H; ArH).

Typical procedure for the thio-Claisen rearrangement affording (*E*)-*N*-(2-*tert*-butylphenyl)-*N*-methylpent-4-enethioamide (4aa): LDA was freshly prepared by adding 1.6 M *n*-BuLi (0.21 mL, 0.33 mmol, 1.5 equiv) to a solution of diisopropylamine (0.047 mL, 0.33 mmol, 1.5 equiv) in THF (1.5 mL) at 0 °C. To this was added a THF solution of thioamide **1a** (0.050 g, 0.22 mmol) at 0 °C and stirring continued for 30 min. Allyl iodide (0.03 mL, 0.33 mmol, 1.5 equiv) was added, and the mixture stirred for 20 min at 0 °C. It was warmed up to room temperature and refluxed (6 h). The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (3×25 mL). The organic layer was washed once with brine (5 mL) and dried over $MgSO_4$. Solvent evaporation gave the crude mixture, which was purified by column chromatography on silica gel; eluting with petroleum ether/ethyl acetate (95:5) gave the pure **4aa** as an oil (0.044 g, 0.16 mmol) in 75% yield. The NMR spectrum showed the presence of a single isomer having *E* conformation around the N–C(=S) bond. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta =$ s H; *t*Bu), 2.49 (m, 4H), 3.63 (s, 3H; *N*-Me), 4.95 (m, 2H), 5.72 (m, 1H), 6.92 (dd, $J = 1.5$, 8.0 Hz, 1H; ArH), 7.26 (dt, $J = 1.5$, 7.8 Hz, 1H; ArH), 7.36 (dt, $J = 1.5$, 7.8 Hz, 1H; ArH), 7.60 (dd, $J = 1.5$, 8.0 Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 32.2$ (Me), 34.4, 36.2, 40.4, 43.8, 47.3 (*N*-Me), 115.6 (CH_2=), 127.9, 128.3, 129.4, 130.3, 136.8, 137.6, 144.8, 205.9 (C=S); MS (70 eV, EI): *m*/*z* (%): 261 (93) $[M]^+$, 244 (100), 204 (92).

(*E*)-*N*-(2-*tert*-Butylphenyl)-*N*-methyl-3,3-dimethylpent-4-enethioamide (4ac): This was prepared by the above-mentioned procedure from **1a** (0.050 g, 0.22 mmol) and prenyl bromide (0.038 mL, 0.33 mmol, 1.5 equiv) and refluxing for 8 h. Column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (95:5), gave the pure **4ac** as an oil (0.030 g, 0.10 mmol) in 47% yield. The NMR spectrum showed two separate signals for CH_2 at $\delta = 2.34$ and 2.60, diastereotopic protons in relation to the C(aryl)–N axis of chirality. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.05$ (s, 3H; Me), 1.13 (s, 3H; Me), 1.32 (s, 9H; *t*Bu), 2.34 (d, $J = 13.6$ Hz, 1H), 2.60 (d, $J = 13.6$ Hz, 1H), 3.63 (s, 3H; *N*-Me), 4.90 (dt, $J = 1.1$, 10.7 Hz, 2H), 5.91 (q, $J = 10.7$ Hz, 1H), 6.99 (dd, $J = 1.5$, 8.0 Hz, 1H; ArH), 7.23 (dt, $J = 1.5$, 7.4 Hz, 1H; ArH), 7.34 (dt, $J = 1.5$, 7.4 Hz, 1H; ArH), 7.54 (dd, $J = 1.5$, 8.0 Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 28.2$ (Me), 32.3 (Me), 36.2, 38.6, 47.4 (*N*-Me), 55.0 (CH_2), 110.7 (CH_2=), 127.3, 129.1, 129.6, 130.2, 143.7, 145.0, 148.3, 203.5 (C=S); MS (70 eV, EI): *m*/*z* (%): 289 (35) $[M]^+$, 274 (100), 232 (81), 188 (44), 164 (38).

(*E*)-*N*-(2-*tert*-Butylphenyl)-*N*-methyl-2-methylpent-4-enethioamide (4ba): This was prepared by the above-mentioned procedure from **1b** (0.050 g, 0.21 mmol) and allyl iodide (0.025 mL, 0.23 mmol, 1.1 equiv), refluxing for 5 h. Column chromatography on silica gel, eluting with petroleum ether, gave the pure **4ba** as a solid (0.048 g, 0.17 mmol) in 82% yield. The NMR spectrum showed the presence of two isomers A/B: (a*R**,2*S**)/(a*R**,2*R**) in a 80:20 ratio. A single *E* geometry around the N–C(=S) bond was observed. M.p. 65 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta =$ 1.08 (d, $J = 6.0$ Hz, 3H of B; Me), 1.21 (d, $J = 6.0$ Hz, 3H of A; Me), 1.33 (s, 9H; *t*Bu), 2.18 (m, 1H), 2.60 (m, 2H), 3.61 (s, 3H; *N*-Me), 4.91 (m, 2H), 5.41 (m, 1H), 6.97 (dd, $J = 1.6$, 8.0 Hz, 1H; ArH), 7.24 (dt, $J = 1.6$, 7.8 Hz, 1H; ArH), 7.36 (dt, $J = 1.6$, 7.8 Hz, 1H; ArH), 7.57 (dd, $J = 1.6$, 8.0 Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 20.1$ (Me of A), 20.9 (Me of B), 32.4 (Me), 36.3, 41.8 (CH_2), 42.6 (CH_2), 44.1 (CH of A), 44.3 (CH of B), 47.3 (*N*-Me), 47.4 (*N*-Me), 117.1 (CH_2=), 117.3 (CH_2=), 127.5, 128.5, 129.3, 130.5, 136.1, 143.2, 145.1, 211.8 (C=S); MS (70 eV, EI): *m*/*z* (%): 275 $[M]^+$, 115 (56), 103 (25), 91 (100), 77 (56), 57 (23), 45 (76); elemental analysis calcd (%) for $C_{17}H_{25}NS$ (275.45): C 74.13, H 9.15, N 5.08, S 11.64; found: C 74.24, H 9.10, N 5.19, S 11.47.

(*E*)-*N*-(2-*tert*-Butylphenyl)-*N*-methyl-2,4-dimethylpent-4-enethioamide (4bb): This was prepared by the above-mentioned procedure from **1b** (0.050 g, 0.21 mmol) and methallyliodide (0.037 g, 0.23 mmol, 1.1 equiv) under reflux for 5 h. Column chromatography on silica gel, eluting with petroleum ether, gave the pure **4bb** as a solid (0.047 g, 0.16 mmol) in 80% yield. The NMR spectrum showed the presence of two diastereoisomers A/B in a 79:21 ratio. A single *E* geometry around the N–C(=S) bond was observed. M.p. 68 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.04$ (d, $J = 6.3$ Hz, 3H of B; Me), 1.17 (d, $J = 6.3$ Hz, 3H of A; Me), 1.35 (s, 9H; *t*Bu), 2.17 (m, 3H; Me), 2.75 (m, 3H), 3.62 (s, 3H; *N*-Me), 4.61 (d, $J = 5.3$ Hz, 2H), 6.98 (dd, $J = 1.5$, 7.8 Hz, 1H; ArH), 7.28 (dt, $J = 1.5$, 8.0 Hz, 1H; ArH), 7.36 (dt, $J = 1.5$, 8.0 Hz, 1H; ArH), 7.61 (dd, $J = 1.5$, 7.8 Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 19$ (Me of B), 19.9 (Me of A), 21.4 (Me), 30.6 (Me), 34.6, 40.4 (CH_2), 43.3 (CH of B), 44.4 (CH of A), 45.5 (*N*-Me), 111.8

0947-6539/02/0803-0638 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 3

(CH_2=), 126.0, 126.6, 127.6, 128.8, 140.9, 141.4, 143.5, 210.5 (C=S); MS (70 eV, EI): *m*/*z* (%): 289 $[M]^+$, 232 (61), 202 (100), 178 (99), 162 (35), 117 (26), 77 (63), 70 (27), 65 (30), 45 (31); elemental analysis calcd (%) for $C_{18}H_{27}NS$ (289.48): C 74.69, H 9.40, N 4.84, S 11.07; found: C 74.67, H 9.45, N 4.94, S 10.72.

(*E*)-*N*-(2-*tert*-Butylphenyl)-*N*-methyl-2-methyl-3,3-dimethylpent-4-enethioamide (4bc): This was prepared by the above-mentioned procedure from **1b** (0.050 g, 0.21 mmol) and prenyl bromide (0.017 mL, 0.23 mmol, 1.1 equiv) under reflux for 6 h. Column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (98:2), gave the pure **4bc** as a viscous liquid (0.050 g, 0.16 mmol) in 78% yield. The NMR spectrum showed the presence of two isomers A/B in a 86:14 ratio. A single *E* geometry around the N–C(=S) bond was observed. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.02$ (s, 3H; Me), 1.06 (s, 3H; Me), 1.19 (d, $J = 6.0$ Hz, 3H of B; Me), 1.22 (d, $J = 6.0$ Hz, 3H of A; Me), 1.35 (s, 9H; *t*Bu), 2.67 (m, 1H), 3.63 (s, 3H; *N*-Me), 4.89 (dt, $J = 1.2$, 10.8 Hz, 2H), 5.91 (q, $J = 10.8$ Hz,1H), 6.90 (dd, $J = 1.6$, 7.7 Hz, 1H; ArH), 7.25 (dt, $J = 1.6$, 8.0 Hz, 1H; ArH), 7.30 (dt, $J = 1.6$, 8.0 Hz, 1H; ArH), 7.62 (dd, $J = 1.6$, 7.7 Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 17.5$ (Me of B), 18.3 (Me of A), 25.1 (Me), 26 (Me), 32.6 (Me), 36.5, 41.3, 48 (*N*-Me), 49.2 (CH of B), 50.7 (CH of A), 111.6 (CH_2=), 126.8, 128.9, 130.4, 131.1, 142.8, 145.6, 147.6, 211.5 (C=S); MS (70 eV, EI): *m*/*z* (%): 303 (7) $[M]^+$, 70 (99), 58 (100), 42 (62); elemental analysis calcd (%) for $C_{19}H_{29}NS$ (303.50): C 75.19, H 9.63, N 4.61, S 10.56; found: C 75.08, H 9.60, N 4.72, S 10.80.

(*E*)-*N*-(2,5-Di-*tert*-Butylphenyl)-*N*-methyl-2-methylpent-4-enethioamide (4ca): This was prepared by the above-mentioned procedure from **1c** (0.050 g, 0.17 mmol) and allyl iodide (0.023 mL, 0.25 mmol, 1.5 equiv), refluxing for 5 h. Column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (95:5), gave the pure **4ca** as a solid (0.047 g, 0.14 mmol) in 84% yield. The NMR spectrum showed the presence of two isomers A/B in a 80:20 ratio. A single *E* geometry around the N–C(=S) bond was observed. M.p. 70 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.08$ (d, $J = 6.0$ Hz, 3H of B; Me), 1.20 (d, $J = 6.0$ Hz, 3H of A; Me), 1.29 (s, 9H; *t*Bu), 1.32 (s, 9H; *t*Bu), 2.17 (m, 1H), 2.70 (m, 2H), 3.63 (s, 3H; *N*-Me), 4.91 (m, 2H), 5.45 (m, 1H), 6.88 (d, $J = 2.2$ Hz, 1H; ArH), 7.37 (dd, $J = 2.2$, 8.5 Hz, 1H; ArH), 7.48 (d, $J = 8.5$ Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 20.1$ (Me of A), 20.9 (Me of B), 31.4, 32.8, 34.6, 35.8, 42.6, 43.9 (CH of B), 44.3 (CH of A), 47.4 (*N*-Me), 117.1 (CH_2=), 125.0, 126.3, 130.2, 136.0, 141.7, 142.8, 150.9, 211.7 (C=S); MS (70 eV, EI): *m*/*z* (%): 331 $[M]^+$, 261 (64), 219 (45), 115 (23), 91 (65), 79 (25), 57 (100), 55 (70); elemental analysis calcd (%) for $C_{21}H_{33}NS$ (331.56): C 76.07, H 10.03, N 4.22, S 9.67; found: C 75.78, H 10.02, N 4.47, S 9.67.

(*E*)-*N*-(2,5-Di-*tert*-butylphenyl)-*N*-methyl-2,4-dimethylpent-4-enethioamide (4cb): This was prepared by the above-mentioned procedure from **1c** (0.050 g, 0.17 mmol) and methallyl iodide (0.034 g, 0.18 mmol, 1.1 equiv), refluxing for 5 h. Column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (95:5), gave the pure **4cb** as a solid (0.050 g, 0.14 mmol) in 85% yield. The NMR spectrum showed the presence of two diastereoisomers A/B in 88:12 ratio. A single *E* geometry around the N–C(=S) bond was observed. M.p. 73 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.08$ (d, $J = 6.2$ Hz, 3H of B; Me), 1.15 (d, $J = 6.2$ Hz, 3H of A; Me), 1.28 (s, 9H; *t*Bu), 1.32 (s, 9H; *t*Bu), 2.14 (m, 3H; Me), 2.95 (m, 2H), 3.63 (s, 3H; *N*-Me), 4.61 (d, $J = 5.5$ Hz, 2H), 6.88 (d, $J = 2.2$ Hz, 1H; ArH), 7.37 (dd, $J = 2.2$, 8.5 Hz, 1H; ArH), 7.52 (d, $J = 8.5$ Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 19.3$ (Me of A), 20.7 (Me of B), 21.8 (Me), 23.1 (Me), 31.4 (Me), 32.3, 34.6, 35.9, 42.0 (CH_2), 45.1 (CH of B), 45.8 (CH of A), 47.3 (*N*-Me), 113.2 (CH_2=), 124.7, 125.2, 126.5, 130.2, 141.7, 142.4, 150.9, 212.0 (C=S); MS (70 eV, EI): *m*/*z* (%): 345 $[M]^+$, 288 (24), 234 (40), 91 (36), 70 (28), 57 (100); elemental analysis calcd (%) for $C_{22}H_{35}NS$ (345.59): C 76.46, H 10.21, N 4.05, S 9.28; found: C 76.38, H 10.08, N 4.33, S 9.09.

***N*-(1-Naphthyl)-*N*-phenyl-2-methylpent-4-enethioamide (4ea)**: This was prepared by the above-mentioned procedure from **1e** (0.055 g, 0.18 mmol) and allyl iodide (0.026 mL, 0.28 mmol, 1.5 equiv), refluxing for 6 h. Column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (95:5), gave the pure **4ea** as a pale yellow oil (0.040 g, 0.12 mmol) in 65% yield. The NMR spectrum showed four isomers, namely two isomers due to the created asymmetric carbon and another two isomers A and B due to rotation around the N–C(S) bond. Isomer A has the naphthyl group *trans* to the thiocarbonyl and isomer B has the naphthyl group *cis* to the thiocarbonyl. These four isomers (*E*)-A, (*E*)-B, (*Z*)-A and (*Z*)-B represent the two pairs of diastereoisomers of the rotamers A and B, with the doublets at $\delta = 1.18$, 1.23 (major) and $\delta = 1.36$, 1.42 (minor) in the ratio of (60:40). The doublets for Me at $\delta = 1.18$ and 1.23 are for the (*E*)-A and (*E*)-B isomers, respectively, while the allyl group attack is *anti*. The downfield doublets at $\delta = 1.36$ and 1.42 are for (*Z*)-A and (*Z*)-B isomers respectively, while the allyl group attack is *syn*. The isomers (*E*)-A/(*E*)-B/(*Z*)-A/(*Z*)-B ratio is 3:3:2:2: ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.18$ (d, $J = 6.4$ Hz, 2H; Me of A), 1.23 (d, $J = 6.4$ Hz, 2H; Me of A), 1.36 (d, $J = 6.4$ Hz, 2H; Me of B), 1.42 (d, $J = 6.4$ Hz, 2H; Me of B), 2.25–2.60 (m, 3H), 5.10–5.80 (m, 3H), 7.10–8.22 (m, 12H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 22.0$ (Me of A), 22.4 (Me of B), 42.6, 43.3, 44.1 (CH of A), 44.3 (CH of A), 44.9 (CH of B), 45.7 (CH of B), 117.3 (CH_2=), 123.4, 126.0, 126.3, 126.5, 126.8, 127.3, 127.5, 127.9, 128.2, 128.7, 129.0, 129.2, 129.6, 129.7, 130.2, 130.6, 136.2, 136.7, 202.2 (C=S), 216.3 (C=S); MS (70 eV, EI): *m*/*z* (%): 331 $[M^+]$, 219 (28), 180 (26), 172 (22), 84 (25), 49 (100), 51 (57).

(*E*)-*N*-(2-*tert*-Butylphenyl)-*N*-methyl-2-methylpent-4-enamide (7)

From thioamide ***4ba***: A solution of *N*-(2-*tert*-butylphenyl)-*N*-methyl-2-methylpent-4-enethioamide **4ba** (0.11 g; 0.4 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C. Purified 3-chloroperoxybenzoic acid (*m*CPBA) (0.138 g, 0.8 mmol, 2 equiv) was added, and the reaction mixture stirred at 0 °C for 3 h. The reaction mixture was then slowly warmed up to room temperature. After 2 h stirring, TLC showed that the starting thioamide has disappeared. Saturated $NaHCO_3$ solution (2 mL) was added and extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed once with brine (5 mL) and dried over $MgSO_4$. Solvent evaporation gave the crude mixture, which was purified by column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (80:20) to furnish the amide **7** as an oil (0.067 g, 0.259 mmol) in 65% yield. The NMR spectrum showed the presence of two diastereoisomers A/B in a ratio of 80:20.

From amide ***5b***: LDA was freshly prepared by adding 1.6 M *n*-BuLi (0.90 mL, 1.42 mmol, 2.5 equiv) to a solution of diisopropylamine (0.20 mL, 1.42 mmol, 2.5 equiv) in THF (1.5 mL) at 0 °C. To this was added a solution of amide **5b** (0.125 g, 0.57 mmol) in THF (1 mL) at 0 °C and the resulting mixture was stirred for 30 min. Allyl iodide (0.13 mL, 1.42 mmol, 2.5 equiv) was added and stirring was continued for 20 min at 0 °C. The reaction mixture was warmed up to room temperature and refluxed for 8 h. The reaction mixture was cooled to room temperature, quenched with saturated NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (3×25 mL); the organic layer washed once with brine (5 mL) and dried over $MgSO_4$. Solvent evaporation gave the crude mixture, which was purified by column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (80:20) to give pure **7** as a pale yellow oil (0.14 g, 0.40 mmol) in 95% yield. The NMR spectrum showed the presence of two diastereoisomers A/B in a ratio of 80:20. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.99$ (d, $J = 6.1$ Hz, 3H of B; Me), 1.06 (d, $J = 6.1$ Hz, 3H of A; Me), 1.35 (s, 9H; *t*Bu), 1.84 (m, 1H), 2.24 (m, 2H), 3.18 (s, 3H; *N*-Me), 4.94 (m, 2H), 5.65 (m, 1H), 7.05 (dd, $J =$ 1.5, 7.8 Hz, 1H; ArH), 7.22 (dt, $J = 1.5$, 7.4 Hz, 1H; ArH), 7.32 (dt, $J = 1.5$, 7.4 Hz, 1H; ArH), 7.57 (dd, $J = 1.5$, 7.8 Hz, 1H; ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 16.1$ (Me of A), 17.5 (Me of B), 32.4 (Me), 36.4, 37.2 (CH of A), 37.4 (CH of B), 38.9 (CH_2), 39.4 (*N*-Me); 117 (CH_2=), 127.4, 128.8, 130, 130.8, 136.1, 141.9, 146.8, 177.3 (C=O); MS (70 eV, EI): *m*/*z* (%): 259 $[M]^+$, 202 (100), 162 (39), 132 (36), 91 (22); elemental analysis calcd (%) for $C_{17}H_{25}NO$ (259.39): C 78.72, H 9.71, N 5.40; found: C 78.66, H 9.66, N 5.67.

X-ray crystal data of 1c and 1d: Crystallographic data for compounds **1c** and **1d** are given in Table 3. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-166137 and 166138. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

We would like to thank the programme *"Réseau Interrégional de Chimie Organique Fine (RINCOF)"* of the "Contrat de Plan Interrégional du Grand Bassin Parisien" for their generous support for this collaborative project. Discussions and suggestions from our partners at Rouen (IRCOF): Profs Guy Quéguiner, Nelly Plé and Alain Turck are also gratefully acknowleged.

Table 3. Crystal data and refinement for compounds **1c** and **1d**.

	1c	**1d**
formula	$C_{18}H_{22}NS$	$C_{13}H_{19}NS$
M_r	284.44	221.36
crystal system	monoclinic	orthorhombic
space group	$P2_1/a$	$Pbca$
a [Å]	11.27(1)	10.236(5)
b [Å]	9.828(5)	17.168(8)
c [Å]	16.188(8)	15.662(8)
α [°]	90	90
β [°]	95.4(1)	90
γ [°]	90	90
V [Å]	1785(2)	2752(2)
Z	4	8
T [K]	293.2	293.2
ρ_{calcd} [g cm^{-3}]	1.058	1.068
$\mu(Mo_{K\alpha})$ [mm^{-3}]	0.7107	0.7107
R	0.0646	0.0808
wR	0.0994	0.0856

[1] C. Rosini, L. Franzini, A. Raffaelli, P. Salvadori, *Synthesis* **1992**, 503 – 517.
[2] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley-Interscience, New York, **1994**.
[3] J. Clayden, *Angew. Chem.* **1997**, *109*, 986 – 988; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 949 – 951.
[4] T. Kawabata, K. Yahiro, K. Fuji, *J. Am. Chem. Soc.* **1991**, *113*, 9694 – 9696.
[5] K. Fuji, T. Kawabata, *Chem. Eur. J.* **1998**, *4*, 373 – 376.
[6] D. P. Curran, N. C. DeMello, *J. Chem. Soc. Chem. Commun.* **1993**, 1314 – 1317.
[7] D. P. Curran, G. R. Hale, S. J. Geib, A. Balog, Q. B. Cass, A. L. G Degani, M. Z. Hernandes, L. C. G. Freitas, *Tetrahedron: Asymmetry* **1997**, *8*, 3955 – 3975.
[8] J. Clayden, *Synlett* **1998**, 810 – 816.
[9] P. Bowles, J. Clayden, M. Tomkinson, *Tetrahedron Lett.* **1995**, *36*, 9219 – 9222.
[10] A. D. Hughes, D. A. Price, O. Shishkin, N. S. Simpkins, *Tetrahedron Lett.* **1996**, *37*, 7607 – 7610.
[11] A. D. Hughes, D. A. Price, N. S. Simpkins, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1295 – 1304.
[12] O. Kitagawa, H. Izawa, T. Taguchi, M. Shiro, *Tetrahedron Lett.* **1997**, *38*, 4447 – 4450.
[13] O. Kitagawa, S.-i. Momose, Y. Fushimi, T. Taguchi, *Tetrahedron Lett.* **1999**, *40*, 8827 – 8831.
[14] J. Clayden, N. Westlund, M. Helliwell, *Perkin 1* **2000**, 1351 – 1362.
[15] J. Clayden, M. Helliwell, C. McCarthy, N. Westlund, *Perkin 1* **2000**, 3232 – 2349.
[16] J. Clayden, C. McCarthy, N. Westlund, C. S. Frampton, *Perkin 1* **2000**, 1363 – 1378.
[17] J. Clayden, N. Westlund, C. S. Frampton, *Perkin 1* **2000**, 1379 – 1385.
[18] C. R. A. Godfrey, N. S. Simpkins, M. D. Walker, *Synlett* **2000**, 388 – 390.
[19] J. Clayden, N. Westlund, F. X. Wilson, *Tetrahedron Lett.* **1996**, *37*, 5577 – 5580.
[20] J. Clayden, J. H. Pink, *Angew. Chem.* **1998**, *110*, 2040 – 2043; *Angew. Chem. Int. Ed.* **1998**, *37*, 1937 – 1939.
[21] J. Clayden, L. W. Lai, *Angew. Chem.* **1999**, *111*, 2755 – 2757; *Angew. Chem. Int. Ed.* **1999**, *38*, 2556 – 2558.
[22] O. Kitagawa, H. Izawa, K. Sato, A. Dobashi, T. Taguchi, M. Shiro, *J. Org. Chem.* **1998**, *63*, 2634 – 2640.
[23] D. P. Curran, W. Liu, C. H.-T. Chen, *J. Am. Chem. Soc.* **1999**, *121*, 11012 – 11013.
[24] P. Metzner, *Top. Curr. Chem.* **1999**, *204*, 127 – 184.
[25] C. Dell in *Comprehensive Organic Functional Group Transformations*, *Vol. 5* (Eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees, C. J. Moody), Pergamon, Oxford, **1995**, pp. 565 – 628.
[26] E. Schaumann in *Comprehensive Organic Synthesis*, *Vol. 6* (Eds.: B. M. Trost, I. Fleming, E. Winterfeldt, L. A. Paquette), Pergamon, Oxford, **1991**, pp. 419 – 434.
[27] K. S. Kochhar, D. A. Cottrell, H. W. Pinnick, *Tetrahedron Lett.* **1983**, *24*, 1323 – 1326.
[28] H. J. Kim, Y. H. Kim, *Synthesis* **1986**, 970 – 972.
[29] Y. Tamaru, T. Harada, S. Nishi, M. Mizutani, T. Hioki, Z. Yoshida, *J. Am. Chem. Soc.* **1980**, *102*, 7806 – 7808.
[30] P. Metzner, *Synthesis* **1992**, 1185 – 1199.
[31] Y. Tamaru, Y. Furukawa, M. Mizutani, O. Kitao, Z. Yoshida, *J. Org. Chem.* **1983**, *48*, 3631 – 3639.
[32] R. M. Lemieux, A. I. Meyers, *J. Am. Chem. Soc.* **1998**, *120*, 5453 – 5457.
[33] C. Alayrac, C. Fromont, P. Metzner, N. T. Anh, *Angew. Chem.* **1997**, *109*, 418 – 420; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 371 – 374.
[34] S. Yamabe, S. Okumoto, T. Hayashi, *J. Org. Chem.* **1996**, *61*, 6218 – 6226.
[35] W. E. Stewart, T. H. Siddall, *Chem. Rev.* **1970**, *70*, 517 – 551.
[36] H. Kessler, *Angew. Chem.* **1970**, *82*, 237 – 253; *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 219 – 235.
[37] M. Oki, *Top. Stereochem.* **1983**, *14*, 1 – 81.
[38] A. J. Speziale, L. R. Smith, *J. Org. Chem.* **1963**, *28*, 3492 – 3496.
[39] I. D. Rae, *Can. J. Chem.* **1967**, *45*, 1 – 5.
[40] A. R. Katritzky, J.-L. Moutou, Z. Yang, *Synthesis* **1995**, 1497 – 1505.
[41] A. Itai, Y. Toriumi, N. Tomioka, H. Kagechika, I. Azumaya, K. Shudo, *Tetrahedron Lett.* **1989**, *30*, 6177 – 6180.
[42] A. Itai, Y. Toriumi, S. Saito, H. Kagechika, K. Shudo, *J. Am. Chem. Soc.* **1992**, *114*, 10649 – 10650.
[43] S. Saito, Y. Toriumi, N. Tomioka, A. Itai, *J. Org. Chem.* **1995**, *60*, 4715 – 4720.
[44] D. P. Curran, S. J. Geib, N. C. DeMello, *Tetrahedron* **1999**, *55*, 5681 – 5704.
[45] R. Fausto, J. J. C. Teixeira-Dias, P. R. Carey, *J. Mol. Struct.* **1989**, *212*, 61 – 86.
[46] C. E. Wintner, *J. Chem. Educ.* **1987**, *64*, 587 – 590.
[47] P. Beslin, P. Metzner, Y. Vallée, J. Vialle, *Tetrahedron Lett.* **1983**, *24*, 3617 – 3620.
[48] P. Beslin, Y. Vallée, *Tetrahedron* **1985**, *41*, 2691 – 2705.
[49] Y. Tamaru, Y. Amino, Y. Furukawa, M. Kagotani, Z. Yoshida, *J. Am. Chem. Soc.* **1982**, *104*, 4018 – 4019.
[50] P. Metz, B. Hungerhoff, *J. Org. Chem.* **1997**, *62*, 4442 – 4448.
[51] P. Metzner, *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *59*, 1 – 16.
[52] P. Metzner, *Pure Appl. Chem.* **1996**, *68*, 863 – 868.
[53] F. E. Ziegler, *Acc. Chem. Res.* **1977**, *10*, 227 – 232.
[54] P. Wipf in *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, Oxford, **1991**, pp. 827 – 873.
[55] W. Bauer, T. Laube, D. Seebach, *Chem. Ber.* **1985**, *118*, 764 – 773.
[56] K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi, C. Kratky, *Helv. Chim. Acta* **1978**, *61*, 3108 – 3135.
[57] A. I. Meyers, G. P. Brengel, *Chem. Commun.* **1997**, 1 – 8.
[58] C. H. Heathcock, S. K. Davidsen, S. Mills, M. A. Sanner, *J. Am. Chem. Soc.* **1986**, *108*, 5650 – 5651.
[59] D. P. Curran, A. Ates, *J. Am. Chem. Soc.* **2001**, *123*, 5130 – 5131.
[60] E. C. Riesgo, X. Jin, R. P. Thummel, *J. Org. Chem.* **1996**, *61*, 3017 – 3022.

Received: July 2, 2001 [F3385]