Cyclic Sulfonimidates by Dynamic Diastereomer-Differentiating Cyclisation: Large-Scale Synthesis and Mechanistic Studies

Michael Reggelin* and Bernd Junker[a]

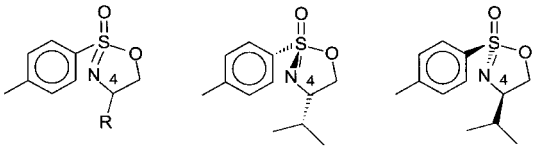
Dedicated to Professor Horst Kunz on the occasion of his 60th birthday

Abstract: A dynamic diastereomer differentiating cyclisation is the key step in a new large-scale synthesis of both enantiomers of the cyclic sulfonimidates **1** (Aldrich no. 54099-4) and *ent*-**1** (Aldrich no. 54412-4). These are valuable starting materials in the asymmetric synthesis of chiral oxa- and azaheterocyclic compounds. NMR spectroscopic studies on the reacting system reveal N-chloro sulfinamides to be reactive intermediates in the oxidative chlorination of sulfinamides with *tert*-butyl hypochlorite and allow for the inspection of the configurational behaviour of the involved sulfonimidoyl chlorides and sulfonimidoyl bromides.

Keywords: asymmetric synthesis · chiral resolution · diastereomer differentiation · NMR spectroscopy · sulfonimidates

Introduction

Chiral, non-racemic sulfoximines are valuable intermediates in asymmetric synthesis.[1] In particular, allylic sulfoximines have gained much attention in this area. Amongst the successful applications of these compounds are asymmetric S_N2'-reactions with organo cuprates[2, 3] and allyl transfer reactions.[4–6] The primarily formed vinyl sulfoximines of the latter reaction can be transformed to isomerically pure highly substituted tetrahydrofurans,[7] oxabicyclic systems,[8] and pyrrolidines.[9, 10] Cyclic sulfonimidates of type **1** have shown to be excellent precursors for the synthesis of these powerful solutions for asymmetric d^3-synthons.[11, 12]



1: R = *i*Pr
1a: R = Me
1b: R = *i*Bu
1c: R = Ph

1 *ent*-**1**

They are easily converted to a broad range of enantiomerically pure sulfoximines including allylic sulfoximines by nucleophilic ring opening with inversion of the configuration at sulfur.[4, 11] 2-Cycloalkenylmethyl sulfoximines are accessible through an addition–elimination isomerization sequence starting from cyclic ketones.[3, 5] The most prominent member of this family of cyclic sulfonimidates, the isopropyl derivative **1** and its enantiomer *ent*-**1**, are available on an intermediate scale by oxidative cyclization of the sulfinamides *epi*-**2** and **2**, respectively, involving two stereoselective transformations (Scheme 1, black arrows).[12]

Diastereomerically pure, crystalline **2** was obtained from the crystallization of the 1:1 mixture of **2** and *epi*-**2** formed during the sulfinamide synthesis employing racemic *para*-toluene sulfinylchloride. In the mother liquor of this crystallization *epi*-**2** is enriched to approximately 4:1–5:1 and the oxidative cyclization of this mixture via *epi*-**3** (Scheme 1, black arrows) yields the heterocycles **1**:*epi*-**1** in the same ratio. Fortunately **1** has a much higher bias to crystallization than *epi*-**1** and therefore they can be separated satisfactorily. Although this procedure works quite well even on an intermediate scale (up to 0.4 mol of sulfinamides) it has some severe drawbacks:

1) From our work with allylic sulfoximines derived from **1** and *S-epi*-**1** we learned that the *lk*-relative configuration in **1** (S_S, S_C) or *ent*-**1** (R_S, R_C) is favourable to achieve maximum asymmetric inductions.[5, 8] Therefore it is desirable to find an efficient procedure for the synthesis of this diastereomer.
2) Unfortunately the cyclization of the mother liquors being enriched in *epi*-**2** delivers only a mixture of sulfonimidates, which means the product must be recrystallised. Thus for the preparation of **1** at least two crystallisations are necessary.

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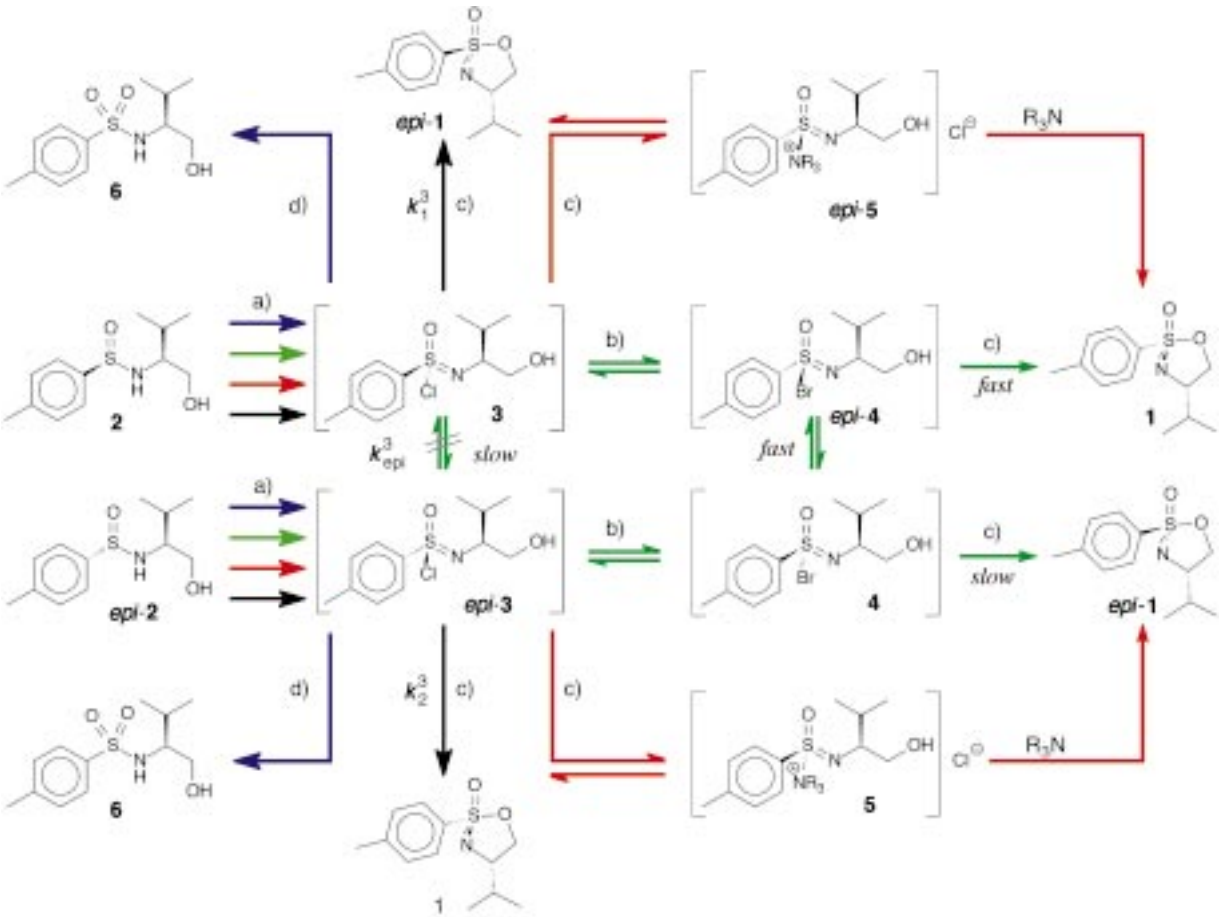

Scheme 1. Oxidative chlorination of sulfinamides and cyclisation of the generated sulfonimidoyl chlorides to the target sulfonimidates **1** and *epi*-**1**. a) *t*BuOCl, THF. b) KBr, 2–5 mol% [18]crown-6. c) Various amine bases; the most successful were DBU and Me_2NEt. d) H_2O.

3) Only about 35% of the crystalline sulfinamide **2** can be transformed to *epi*-**1** and only 30–35% of the preferred heterocycle **1** is available from the oily sulfinamide *epi*-**2**.

This analysis led us to the conclusion that instead of using the current strategy which is based on the preservation of the isomeric purity of the sulfinamides **2** and *epi*-**2** in a series of stereocontrolled reaction steps, it may be better to synthesise **1** or *ent*-**1** through a diastereomer differentiating cyclisation of a configurationally labile precursor.

Results and Discussion

Large-scale preparation of cyclic sulfonimidates: The early work of Cram[13] and Johnson[14] concerning the configurational behaviour of sulfonimidoyl chlorides encouraged us to work with the diastereomeric sulfonimidoyl chlorides **3** and *epi*-**3** as potentially labile intermediates (Scheme 1, Table 1).

Various mixtures of the configurationally stable epimeric sulfinamides **2** and *epi*-**2** were oxidatively chlorinated at various temperatures in THF using *tert*-butyl hypochlorite as the reagent.[15] The resulting mixture of sulfonimidoyl chlorides **3** and *epi*-**3** was transformed to the target sulfonimidates **1** and *epi*-**1** by addition of a number of different nitrogen bases without prior isolation of the former compounds. From the results of these experiments we derived the scenario depicted in Scheme 1 (the bromine containing compounds **4** and *epi*-**4** will be discussed later). After the oxidative chlorination yielding **3** and *epi*-**3** the system may follow different reaction pathways encoded by different colours.

Table 1. Base-induced cyclisations of sulfonimidoyl chlorides **3** and *epi*-**3** derived from sulfinamides **2** and *epi*-**2**.[a]

Entry	base	T [°C][b]	**2**:*epi*-**2**	**1**:*epi*-**1**	Main reaction path[c]
1	DBU	–78	22.6:1.0	1.0:18	black (*oinv*)
2	DBU	–40	22.6:1.0	1.9:1.0	black/red
3	$(iPr)_2NEt$	–40	18.6:1.0	5.7:1.0	black/red
4	$(Me)_2NEt$	–40	18.6:1.0	16.4:1.0	red (*oret*)
5	$(Me)_2NEt$	–40	11.8:1.0	13.7:1.0	red (*oret*)
6	$(Me)_2NEt$	–40	22.6:1.0	23.3:1.0	red (*oret*)
7	$(Me)_2NEt$	–30	11.8:1.0	10.8:1.0	red (*oret*)
8	$(Me)_2NEt$	–40	1.0:1.0	2.8:1.0	black/red
9	$(Me)_2NEt$	–40	2.7:1.0	1.0:1.3	black/red
10	$(Me)_2NEt$	–20	18.6:1.0	7.8 :1.0	black/red
11	$(Me)_2NEt$	–10	18.6:1.0	4.7:1.0	black/red
12	$(Me)_2NEt$	0	18.6:1.0	2.9:1.0	black/red
13	$(Me)_2NEt$	–50	11.8:1.0	8.3:1.0	(black)/red
14	$(Me)_2NEt$	–72	22.6:1.0	9.0:1.0	black/red
15	2,6-lutidine	0	18.6:1.0	-	blue
16	pyridine	0	18.6:1.0	–	blue
17	pyridine	–20	18.6:1.0	–	blue

[a] All cyclisations proceeded in quantitative yields. [b] Internal temperature. [c] *oinv*: overall inversion, *oret*: overall retention.

1) The "blue pathway": If the base is too weak as with pyridine or 2,6-lutidine, no cyclisation takes place and only the hydrolysis product **6** is isolated after aqueous workup (entries 15-17, Table 1).
2) The "black pathway": If the base is sufficiently strong to transform the OH group in **3** and *epi*-**3** into an oxygen nucleophile which intramolecularly attacks the sulfur atom with inversion of its configuration, the cyclised products *epi*-**1** and **1** are formed. If the oxidative chlorination of the sulfinamides **2** and *epi*-**2** occurs with retention of the sulfur configuration, as Cram and Johnson have found, then the overall process proceeds with *inversion*. This pathway should be preferred for strong, non-nucleophilic bases (see below).
3) The "red pathway": If the base is a small molecule and a reasonable nucleophile, displacement of the chloride ion may successfully compete with oxygen-deprotonation. As a consequence the sulfonimide ammonium salts **5** and *epi*-**5** are produced with inversion of the sulfur configuration. These intermediates can now undergo a base induced cyclisation reaction regenerating the base and delivering the target heterocycles **1** and *epi*-**1**, again with inversion of the sulfur configuration. The overall process now proceeds with *retention* and the base plays a double role: it is a catalyst for the first inversion occurring during the chloride ion displacement reaction and a stoichiometric reagent for the cyclisation.
4) The "green pathway" [excluding the transhalogenation reaction b)]: If, as hoped, the sulfonimidoyl chlorides **3** and *epi*-**3** are configurationally labile on the timescale of any other reaction with the base ($k^3_{epi} \gg k^3_1, k^3_2$) and if $k^3_1 \neq k^3_2$ then a major precondition for a dynamic epimer differentiation would be fulfilled. The sulfonimidates **1** and *epi*-**1** should be produced in unequal amounts in a constant ratio independent from both the initial **3**:*epi*-**3** (and therefore also **2**:*epi*-**2**) ratio and the reaction progress.[16–18] With the **2**:*epi*-**2** ratio being close to one (which is their usual ratio[11, 12]) then the achievable diastereomeric excess of **1** or *epi*-**1** is controlled by the ratio of the reaction rates of the concurring cyclisation reactions (k^3_2/k^3_1).

The analysis of the data in Table 1 clearly shows that the latter scenario, two diastereoselective cyclisations coupled to a rapid preequilibrium between two configurationally labile precursors, obviously doesn't occur. The observed diastereomeric composition of the sulfonimidates (**1** and *epi*-**1**) is strongly dependent on temperature, base and the initial ratio of the diastereomeric sulfinamides **2** and *epi*-**2**. Nevertheless there is not only bad news from these experiments. Of special importance from a synthetic point of view are those entries describing a conservation of a given diastereomeric composition (entries 1, 4–7). The low-temperature cyclisation with DBU (first entry) refers to our previously published protocol.[12] A given sulfinamide composition, here 22.6:1, in favour of **2** is "translated" to a corresponding sulfonimidate ratio (here 1:18 in favour of *epi*-**1**) with overall inversion of the sulfur configuration (Scheme 1, black pathway). When DBU is replaced by dimethyl ethyl amine (Me_2NEt) and the temperature is raised to $-40\,^{\circ}C$, then the same 22.6:1 ratio of sulfinamides **2** and *epi*-**2** is converted through the red pathway (Scheme 1) to a 23.3:1 ratio of sulfonimidates but this time favouring the overall retention of product **1** (Table 1, entry 6, base premixed with sulfinamide). As described above we believe this to be a consequence of a series of three stereoselective steps: oxidative chlorination (retention), nucleophilic displacement of Cl^- by the small base (inversion) and finally a base-induced cyclisation (inversion). This interpretation is corroborated by entries 4–7 in Table 1. Within experimental error every **2**:*epi*-**2** ratio can be "translated" into the corresponding **1**:*epi*-**1** ratio. As expected, every increase in the steric bulk of the amine hampers the nucleophilic displacement step from **3**/*epi*-**3** to **5**/*epi*-**5** (Scheme 1, red pathway). This entails the black, direct pathway to become more and more competitive which in turn leads to a product mixture reflecting the relative weight of these two concurring reaction alternatives (Table 1, entries 2 and 3). Furthermore it is interesting to note that the optimum reaction temperature is -30– $-40\,^{\circ}C$. Both higher (entries 10–12) as well as lower (entries 13 and 14) temperatures increase the importance of the direct cyclisation (black pathway) and lower the stereoselectivity of the reaction. Finally from entries 8 and 9 it can be deduced that this direct cyclisation always plays some role even at the optimum temperature for the red pathway. With the **2**:*epi*-**2** ratio approaching 1:1 significant deviations from the expected product ratios occurs. With **2**:*epi*-**2** = 1:1, a slight excess of epimer **1** (**1**:*epi*-**1** = 2.8:1) is observed rather than the expected 1:1 product ratio. This may be due to either an enhanced reactivity of **3** in the red pathway or a faster reaction of *epi*-**3** in the direct cyclisation (black) pathway. Assuming the first alternative to be true, then a slight excess of **2** in the starting material should "translate" to a pronounced excess of **1** in the resulting product mixture. In fact, the opposite is true, when **2**:*epi*-**2** = 2.7:1 a final product mixture of **1**:*epi*-**1** = 1.0:1.3 is obtained (Table 1, entry 9). This strongly suggests that the slight deviations of the product compositions from the expected 1:1 relation between the **2**:*epi*-**2** ratio and the **1**:*epi*-**1** ratio can be traced back to a slightly enhanced reactivity of the sulfonimidoyl chloride *epi*-**3** in the direct cyclisation pathway.

These results show that there is a certain reactivity difference between the cyclisation precursors **3** and *epi*-**3** and that it is possible to synthesize *both* epimers of **1** as pure diastereomers starting from only *one* precursor sulfinamide **2** or *epi*-**2**. Although this is a nice feature of the system, especially due to the fact that it is much easier to isolate the crystalline **2** diastereomerically pure, it is still necessary to separate the former compound by fractionated crystallization or column chromatography. Faced with this situation we started thinking about the possibility of lowering the barrier of epimerisation of the cyclisation precursor by a transhalogenation reaction.

Assuming a dehalogenation–rehalogenation reaction to be the key step in the epimerisation process of a sulfonimidoyl halogenide, a change of the halogen from chlorine to bromine should lower the barrier of sulfur inversion. We therefore tried to convert the mixture of **3** and *epi*-**3** obtained after the oxidative chlorination into the corresponding sulfonimidoyl bromide mixture of **4** and *epi*-**4** (Scheme 1, green pathway) by addition of an equimolar amount of potassium bromide prior

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to the reaction with *tert*-butyl hypochlorite. Indeed at −30 °C and even better at −20 °C a 3:1 (**2**:*epi*-**2**) mixture of sulfinamides was converted to a 6.0:1.0 and a 6.7:1.0 mixture of the target sulfonimidates **1** and *epi*-**1**, respectively (Table 2, entries 1 and 2).

Table 2. Oxidative cyclisation of the sulfinamides **2** and *epi*-**2** with sulfonimidoyl bromide involvement.[a]

Entry	Bromine source	T [°C]	**2**:*epi*-**2**	**1**:*epi*-**1**
1	KBr	−30	3.0:1.0	6.0:1.0
2	KBr	−20	3.0:1.0	6.7:1.0
3	KBr	0	3.0:1.0	4.5:1.0
4	KBr	−20	12.0:1.0	9.0:1.0
5	KBr/0.5% 18C6	−20	1.0:1.0	4.6:1.0
6	KBr/5% 18C6	−20	1.0:1.0	9.0:1.0
7	KBr/5% 18C6	−20	18.0:1.0	9.0:1.0
8	KBr/5% 18C6	−20	1.0:5.0	9.5:1.0
9	KBr/2% 18C6	−20	22.0:1.0	11.0:1.0
10	KBr/2% 18C6	−10	1.0:1.0	6.5:1.0
11	Br_2[b]	−20	3.0:1.0	1.0:1.6
12	Br_2[b]	−20	12.0:1.0	1.0:1.0
13	TBAB[c]	−20	1.0:1.0	3.0:1.0

[a] All experiments were carried out using Me_2NEt as the base. [b] 3 mL toluene per mmol substrate, 2.3 equiv Me_2NEt premixed prior to hypochlorite addition. [c] TBAB: tetrabutylammonium bromide.

A comparison with the experimental results achieved under similar conditions with the chlorides **3** and *epi*-**3** alone (Table 1, entry 9) shows that the addition of KBr is accompanied by a disproportionate increase in the amount of **1** produced in the cyclisation. This can be interpreted as the result of a rapid cyclisation via *epi*-**4**, disfavouring the slower alternative involving the epimer **4**. Although we cannot exclude the other pathways involving the chlorides to interfere with the desired green pathway (Scheme 1), the experimental result clearly shows a significant effect of the KBr addition and therefore gives a strong indication that the bromides **4** and *epi*-**4** participate in the reaction sequence (see also the NMR studies described below). Unfortunately, even at the optimum temperature (−20 °C) the product composition was still not independent from the initial sulfinamide composition (Table 2, entry 4). At least two reasons for this behaviour are plausible:

1) The epimerisation preequilibrium interconverting **4** and *epi*-**4** is still not fast enough to decouple the diastereoselectivity of the cyclisation from the reaction progress.
2) The concentration of the bromides is too low and therefore, although the bromides are expected to be more reactive, a significant fraction of the product is still formed via the configurationally stable chlorides.

To accelerate the sulfonimidoyl bromide formation we added [18]crown-6 (18C6) (5 mol%) to the heterogenous reaction mixture containing the substrate (**2**/*epi*-**2**, 3 mL THF per mmol) and KBr at −20 °C. To our delight a 1.0:1.0 mixture, a 18.0:1.0 mixture and a 1.0:5.0 mixture of the sulfinamides **2** and *epi*-**2** was converted to an about 9:1 mixture of sulfonimidates **1** and *epi*-**1**, respectively (Table 2, entries 6–8). A reduction of the 18C6 content to 2% was tolerable (Table 2, entry 9), whereas a further reduction of its concentration to 0.5% eroded the stereoselectivity considerably (Table 2, entry 5). Obviously under these optimized conditions (−20 °C, 1.2 equiv KBr, 2–5% 18C6, slow amine addition after oxidative chlorination) the superposition of a halide differentiation (the bromides react faster than the chlorides) and a dynamic epimer differentiation (*epi*-**4** reacts ca. 9–10 times faster than **4**) leads to a quantitative conversion of any given sulfinamide composition to a sulfonimidate mixture being highly enriched (9.0:1.0–11.0:1.0) in the desired heterocycle **1**. This reaction can easily be scaled up and has been performed on a 300 g scale (see Experimental Section).

For the sake of completeness it must be noted that the obvious variant, the use of bromine as oxidation agent and source of bromide ion failed (Table 2, entries 11 and 12). To our surprise this was also true in the experiment employing tetrabutyl ammonium bromide (TBAB) as bromide source (Table 2, entry 13). The low stationary concentration of **4** and *epi*-**4** maintained by the 18C6 assisted transhalogenation step is suspected to hide an answer to this question. To gain further insight into the complex reaction processes and to corroborate our interpretations from the chemical experiments we studied the reaction by NMR spectroscopy.

NMR Studies: First we prepared three samples (**A**, **B**, **C**; all in 0.4 mL [D_8]THF; Table 3) defining three different starting conditions.

Table 3. NMR samples studied.[a]

Sample	**2**/*epi*-**2** [μmol]	**2**:*epi*-**2**	*t*BuOCl [μmol]	KBr [μmol]	18C6 [μmol]
A	149	1.00:1.48	–	–	–
A-Cl	149	1.00:1.48	160	–	–
B	145	1.00:1.48	–	174	5.8[b]
B-Cl	145	1.00:1.48	160	174	5.8[b]
C	128	29.22:1.00	–	156	5.2[c]
C-Cl	128	29.22:1.00	143	156	5.2[c]

[a] All experiments were carried out in 0.4 mL [D_8]THF. [b] 4.0 mol% with respect to **2**/*epi*-**2**. [c] 4.1 mol% with respect to **2**/*epi*-**2**.

Sample **A** contained a mixture of **2** and *epi*-**2** in a molar ratio of 1:1.48, sample **B** was a mixture of **2** and *epi*-**2** (1:1.48), KBr and [18]crown-6 (18C6) and sample **C** was composed like **B** but this time almost pure **2** (**2**:*epi*-**2** = 29.2:1.0) was used. Parts of the 400 MHz proton spectrum of **A** at −20 °C are depicted in Figure 1 (black trace, methyl group region in Figure 1A, aromatic region in Figure 1B).

After the addition of 160 μmol *t*BuOCl to this mixture at −20 °C (generating sample **A**-Cl, Table 3) a quantitative conversion of the sulfinamide mixture to the corresponding mixture of the epimeric sulfonimidoyl chlorides **3** and *epi*-**3** was observed (Figure 1, red traces). A closer inspection of these spectra led us to the following conclusions:

1) The oxidative chlorination is a fast (seconds time scale) and clean reaction even at −20 °C.
2) The diastereomeric ratio of the sulfinamides (**2**:*epi*-**2** = 1:1.48) is perfectly conserved in the product sulfonimidoyl chlorides **3**:*epi*-**3**. This ratio changes only very slowly

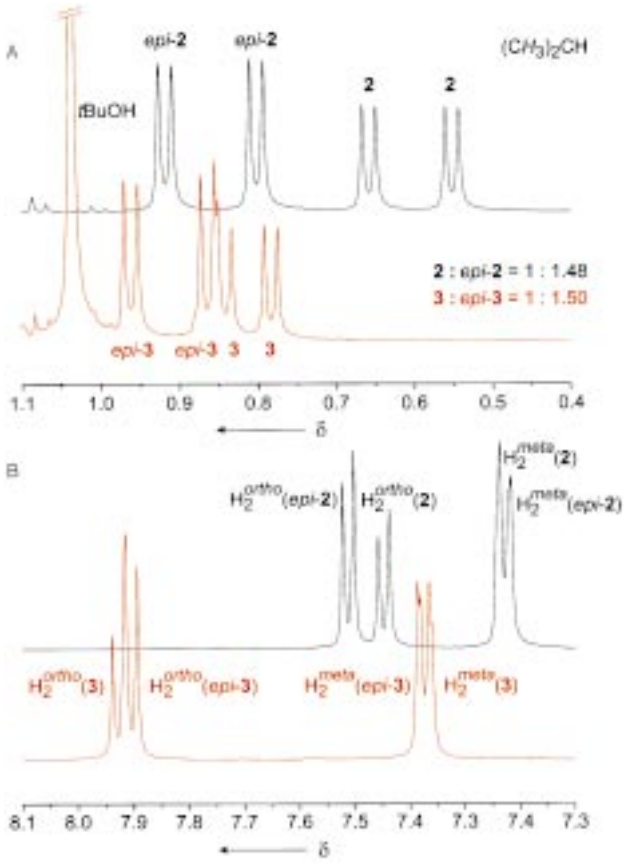

Figure 1. A) Methyl group resonances in the ^{1}H NMR spectrum of a 1.00:1.48 mixture of **2** and *epi*-**2** (in black) and the resulting mixture of sulfonimidoyl chlorides **3** and *epi*-**3** (in red) after oxidative chlorination. B) Aromatic region of the same spectra. The chemical shift difference between the *ortho* and *meta* protons is indicative of the oxidation state of the sulfur compounds under consideration; $\Delta\delta_{o,m}$(**2**) = 0.22, $\Delta\delta_{o,m}$(*epi*-**2**) = 0.29, $\Delta\delta_{o,m}$(*epi*-**3**) = 0.53, $\Delta\delta_{o,m}$(**3**) = 0.56.

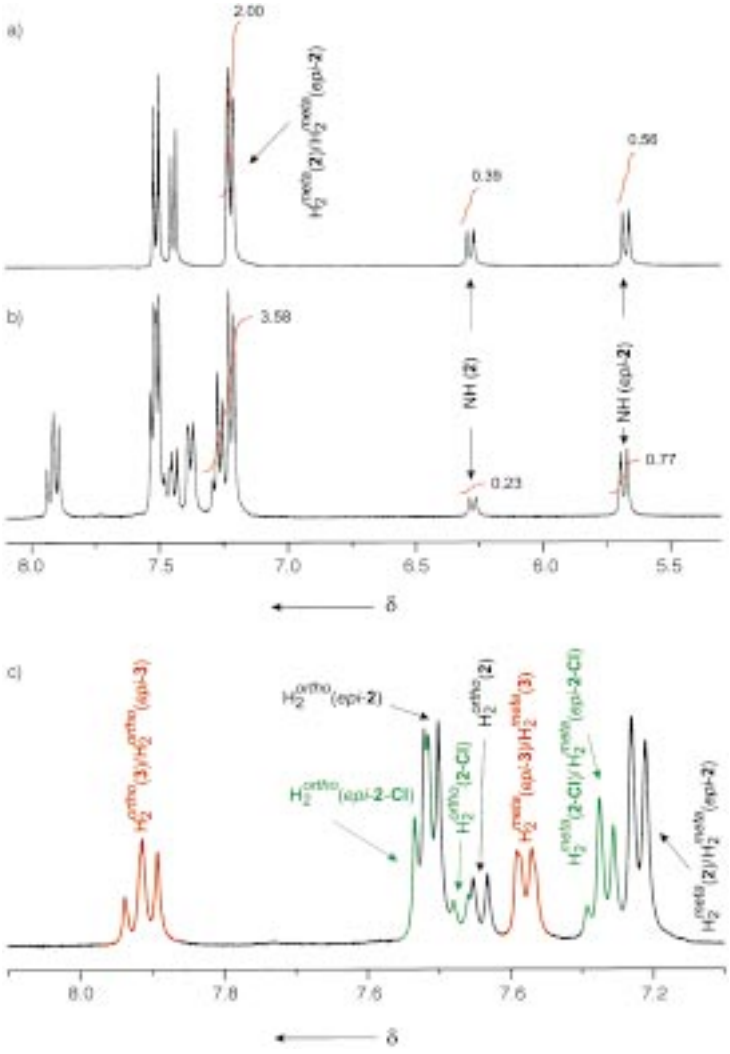

Figure 2. a) Aromatic region and NH signals of the 1.00:1.48 mixture of the sulfinamides **2** and *epi*-**2**. The integrated intensity of the NH's equals half of the intensitiy of the *meta*-protons as expected. b) Immediately after the addition of *tert*-butyl hypochlorite a number of new signals in the highfield aromatic portion of the ^{1}H NMR spectrum appear. The integrated intensity of the sulfur(IV)-related *meta*-signals exceeds the expected 1:2 ratio. c) Expansion of the aromatic region of the spectrum shown in b). The black signals correspond to the *ortho*- and *meta*-protons of the starting sulfinamides (**2** and *epi*-**2**), the red signals belong to the oxidation product (**3** and *epi*-**3**) and the green signals are due to the N-chlorinated sulfinamides **2**-Cl and *epi*-**2**-Cl.

within hours at that temperature, accounting for a considerable configurational stability of these chlorides under the measuring conditions (see also Figure 4 and the related discussion below).

3) The aromatic part of these spectra (Figure 1B) displays the expected differences in the chemical shifts of the *ortho* and *meta* protons for the sulfur(IV) and sulfur(VI) species. From our experience we know that a chemical shift difference of approximately 0.25 for the *ortho* and *meta* protons ($\Delta\delta_{o,m}$) of a *para*-toluene-substituted sulfur compound is characteristic for the oxidation state IV, whereas a $\Delta\delta_{o,m}$ of about 0.5 is indicative of sulfur(VI) species. In accordance with these correlations, $\Delta\delta_{o,m}$ = 0.22 and 0.29 for **2** and *epi*-**2**, respectively. For the oxidised **3** and *epi*-**3** mixture, $\Delta\delta_{o,m}$ = 0.56 and 0.53, respectively.

To learn more about the oxidative chlorination process and the influence of the added KBr and 18C6 we studied sample **B** (Table 3). Again a ^{1}H NMR spectrum was recorded at $-20\,^\circ$C in [D$_8$]THF (Figure 2a).

As expected the integrated intensity of the overlapping *meta*-protons of both epimers is twice as high as the integrated intensity of the corresponding NH signals. As with sample **A**, *tert*-butyl hypochlorite was added to initiate the oxidative chlorination but this time this was done at $-78\,^\circ$C. The cold sample was then placed into the probehead at $-20\,^\circ$C and immediately after receiving a lock signal (some seconds later) a single scan ^{1}H NMR spectrum was recorded (Figure 2b). As we had hoped the reaction was not complete this time (56 % of the starting sulfinamides **2** and *epi*-**2** had been consumed). From the relative intensity of the residual NH signals it can be deduced that sulfinamide **2** reacts slightly faster than *epi*-**2**. What was very interesting was the analysis of the ratio between the combined NH intensity and the sulfur(IV)-related *meta*-protons. The integral of these latter protons considerably exceeded the expected factor of two (3.58:1 instead of 2:1). An obvious explanation for this observation is that the new sulfur(IV)-compounds generated lack NH protons. We

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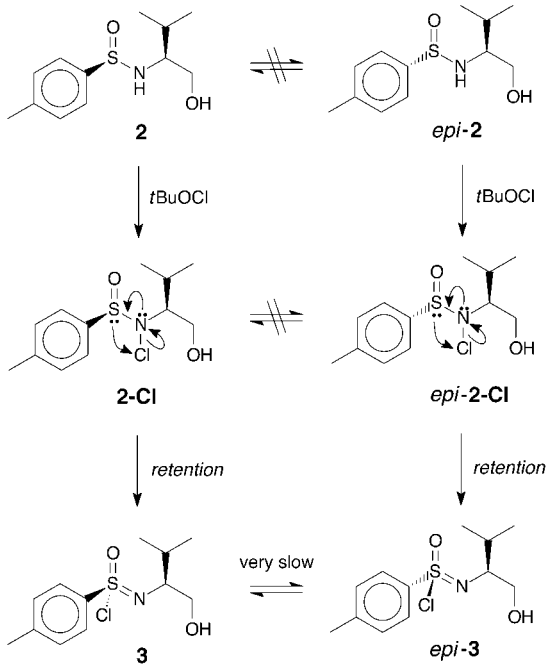
believe these compounds to be the N-chlorinated sulfinamides **2**-Cl and *epi*-**2**-Cl (($\Delta\delta_{o,m} = 0.18$ for **2**-Cl and $\Delta\delta_{o,m} = 0.26$ for *epi*-**2**-Cl, Figure 2c and Scheme 2).



Scheme 2. The oxidative chlorination of sulfinamides with *tert*-butyl hypochlorite occurs through N-chlorination.

Therefore, to our surprise, the initial step in the oxidative chlorination of sulfinamides with *tert*-butyl hypochlorite is *not* an electrophilic attack of the reagent at sulfur but a N-chlorination. The sulfonimidoyl chlorides **3** and *epi*-**3** then are generated by a rearrangement process with retention of the configuration at the sulfur. By comparison with authentic samples it was possible to assign the signals in the aromatic region of the ^{1}H NMR spectrum (Figure 2c) and by careful integration we were able to determine the concentration of all contributing species in this sample (**2** and *epi*-**2** (black): 44.2%; **3** and *epi*-**3** (red): 24.8%; **2**-Cl and *epi*-**2**-Cl (green): 31.0%). In accordance with our interpretation that the N-chlorinated species is a reactive intermediate we observed a clean convergence of all associated ^{1}H NMR signals to a final signal set representing the epimeric mixture of the sulfonimidoyl chlorides **3** and *epi*-**3** (Figure 3).

The zero point of the time course of the reaction was defined as the first spectrum we were able to obtain after mixing of the components as described above.

The final molar ratio of these sulfonimidoyl chlorides (**3**:*epi*-**3** = 1.00:0.97, determined using sample **C**, Figure 4, trace h) is different from the molar ratio of the epimeric sulfinamides (**2**:*epi*-**2** = 1:1.48 in sample **B** or 29.22:1.00 in sample **C**, Table 3) used as starting materials.

Given the configurational stability of the chlorides **3** and *epi*-**3** and their stereospecific formation (retention) from the sulfinamides we have to conclude that there must be configurationally labile, albeit invisible, intermediates. We believe these to be the already mentioned sulfonimidoyl bromides **4** and *epi*-**4** (Scheme 1, green equilibrium arrows). A small

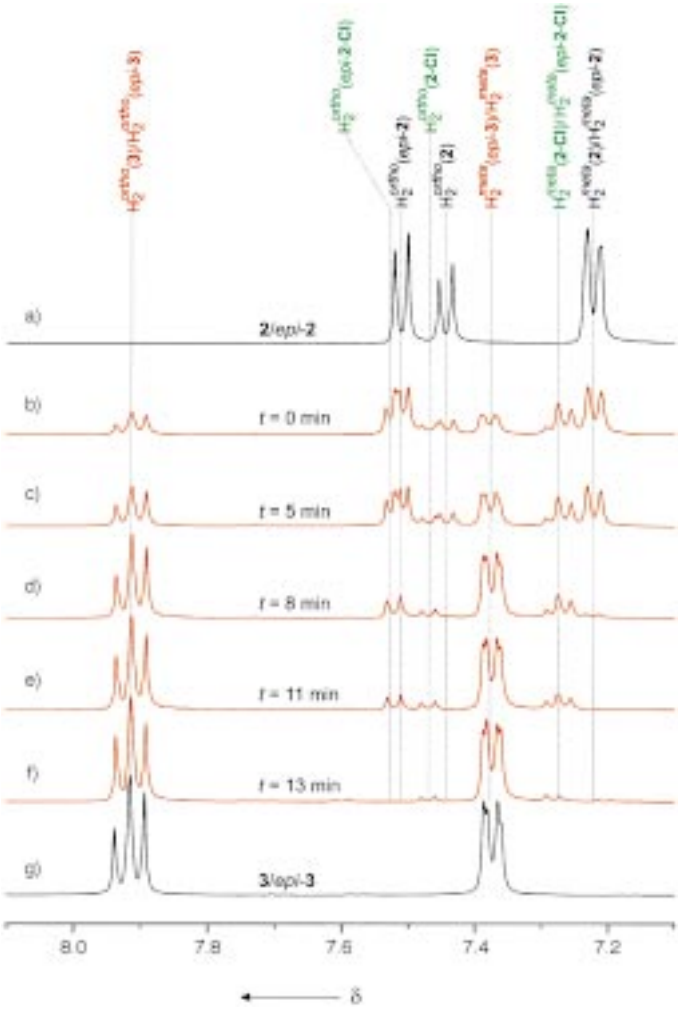


Figure 3. b)–f) Time evolution of the signals in the aromatic region observed during the oxidative chlorination of a 1.00:1.48 **2**:*epi*-**2** [shown in trace a)] mixture with *tert*-butyl hypochlorite in the presence of [18]crown-6 (4 mol%) and KBr (1.2 equiv) in [D_8]THF at $-20\,^\circ$C. g) The same spectral region of an independently prepared mixture of **3** and *epi*-**3** (1:1.50).

fraction ($\leq 5\%$) of **3**/*epi*-**3** is converted to **4**/*epi*-**4** through nucleophilic displacement of Cl^- by KBr/18C6. The generated sulfonimidoyl bromides are configurationally labile at $-20\,^\circ$C and start to epimerise. At the same time we have to assume that the KCl produced during the transhalogenation reaction takes part in the back reaction regenerating the starting chlorides **3** and *epi*-**3**. The overall effect is a sulfonimidoyl bromide induced epimerisation of the precursor sulfonimidoyl chlorides. Within this mechanistic picture the final **3**:*epi*-**3** ratio reflects the equilibrium composition of the "invisible" bromides **4** and *epi*-**4**. As already mentioned, this ratio was found to be 1.00:0.97 and therefore is not only different from the sulfinamide composition but also clearly different from the **1**:*epi*-**1** ratio (9:1) observed in the cyclization experiments described above (Scheme 1). Under the reasonable assumption that this cyclization is a stereospecific (stereoselective by reaction mechanism) nucleophilic displacement reaction, this discrepancy in the molar ratio is a strong indication that the stereochemical outcome of the reaction sequence yielding the target sulfonimidates **1** and *epi*-**1** via the sulfonimidoyl bromides **4** and *epi*-**4** is not a conservation of their equilibrium

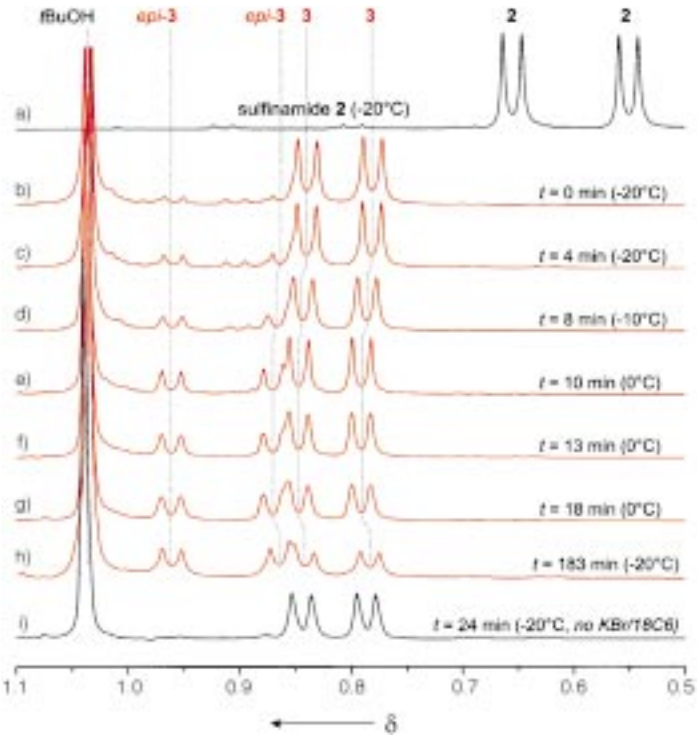


Figure 4. Time evolution of an oxidative chlorination reaction of almost pure sulfinamide **2** (29.2:1) in the presence of KBr (1.2 equiv) and [18]crown-6 (4 mol%) and proof of the configurational stability of the sulfonimidoyl chlorides **3** and *epi*-**3** under the reaction conditions. a) Proton resonances of the diastereotopic methyl groups of isomer **2** at $-20\,^{\circ}C$ in [D_8]THF solution. b)–g) Same spectral region after addition of *tert*-butyl hypochlorite. The temperature was raised to $0\,^{\circ}C$ during the experiment which explains the chemical shift deviation of the signals of interest from the reference resonances. h) Composition of the mixture after equilibration (**3**:*epi*-**3** = 1.00:0.97). i) KBr/[18]crown-6-free sample of almost pure sulfonimidoyl chloride **3** (24.3:1.0) prepared by oxidation of **2** (29.3:1.0) shows only little epimerisation after 24 min at $-20\,^{\circ}C$.

concentrations but indeed a kinetic dynamic epimer differentiating cyclisation. This interpretation is corroborated by the already mentioned NMR experiment using almost pure sulfinamide **2** (Sample **C**, Table 3, Figure 4). After the addition of *tert*-butyl hypochlorite the time evolution of this sample was studied at $-20\,^{\circ}C$ to $0\,^{\circ}C$ (Figure 4). Again the zero point of the reaction was defined as the first ^1H NMR spectrum recorded after the addition of the reagent (Figure 4b). The highfield portion of this spectrum is clearly dominated by the methyl signals of **3**. As time passes by the intensity of the upcoming signals of the epimer, *epi*-**3**, increase, thus clearly demonstrating the sulfonimidoyl bromide mediated epimerisation discussed above. After 18 min the **3**:*epi*-**3** ratio is close to 2:1 (Figure 4g) and after about 3 h at $-20\,^{\circ}C$, equilibrium (**3**:*epi*-**3** = 1.00:0.97) is established (Figure 4h). Finally from Figure 4i) it can be derived that the initial **3**:*epi*-**3** ratio of 1.00:29.2 (which should be identical with the ratio of the sulfinamide precursors **2**:*epi*-**2** (Figure 4a) if the oxidation proceeds with clean retention of the configuration at sulfur) is only slightly changed to 1.00:24.34 indicating a significantly slower epimerization rate of the chlorides compared to the bromides. From these results it is obvious that the bromides are involved in the reaction sequence and are responsible for the **3**/*epi*-**3** epimerisation.

Conclusions

A highly efficient entry to the enantiomerically pure sulfonimidate **1**, being a valuable starting material for a number of asymmetric transformations[1, 4, 5, 7–9] has been developed. A key feature of this preparation is a dynamic kinetic differentiation of the configurationally labile sulfonimidoyl bromides **4** and *epi*-**4** generated in substoichiometric amounts prior to the final cyclisation event. The target sulfonimidate **1** can be obtained on a large scale (checked up to 300 g) usually[19] in quantitative yield as a 9:1 mixture (**1**:*epi*-**1**) irrespective of the diastereomeric ratio of the starting sulfinamides **2** and *epi*-**2**.

^1H NMR studies on the reacting system revealed that the initial step in the oxidative chlorination of sulfinamides with *tert*-butyl hypochlorite is not S- but N-chlorination generating N-chlorinated sulfinamides. These constitutionally labile (seconds to some minutes time scale at $-20\,^{\circ}C$) intermediates rearrange with retention of the configuration at sulfur to the corresponding sulfonimidoyl chlorides which are configurationally fairly stable at $-20\,^{\circ}C$ at least on the time scale of the subsequent reactions. Transhalogenation with KBr and 18C6 yields the configurationally labile sulfonimidoyl bromides that are responsible for a slow interconversion of the chlorides through the back reaction (chlorination of the sulfonimidoyl bromides). The epimerisation of the bromides is fast enough to decouple the diastereoselectivity of the subsequent epimer differentiating cyclisation from both the reaction progress and the diastereomeric composition of the starting material.

This new synthetic protocol allows for the large-scale preparation of the valuable chiral auxiliary **1** (and, of course, *ent*-**1** starting from D-valine) and replaces less efficient procedures published earlier.[11, 12] We think that all obstacles hampering a broad application of this powerful tool for the asymmetric synthesis of highly substituted hetero(poly)cyclic compounds have now been overcome. Finally we would like to mention that **1** and *ent*-**1** will soon be commercially available (**1**: Aldrich no. 54099-4, *ent*-**1**: Aldrich no. 54412-4).

Experimental Section

Large-scale preparation of (2*S*,4*S*)-4-isopropyl-2-*para*-toluene-4,5-dihydro-[1,2λ^6,3]oxathiazole-2-oxide (1): A 6 L three-necked flask equipped with a mechanical stirrer, a 250 mL dropping funnel and a thermometer ($-80\,^{\circ}C$ to $30\,^{\circ}C$) was charged with a crude mixture (ca. 75% purity from ^1H NMR) of the epimeric sulfinamides **2** and *epi*-**2** (300.0 g, 1.243 mol) (the usual molar ratio from their preparation[11] is around 1:1, but every other ratio is tolerable as well) dissolved in THF (3.73 L, 3 mL per mmol). Finely ground, dry KBr (177.51 g, 1.492 mol, 1.2 equiv) and [18]crown-6 (9.86 g, 37.3 mmol, 3.0 mol%) was added at RT with stirring. After stirring for an additional 30 min at ambient temperature, the mixture was cooled to about $-30\,^{\circ}C$ and freshly prepared *t*BuOCl (148.45 g, 1.367 mol, 1.1 equiv) was added slowly, ensuring that the internal temperature did not exceed $-20\,^{\circ}C$ (the application of an efficient cryostat is highly recommended, although at this stage of the preparation temperature control is not as critical as in the following step). After the addition was complete stirring was continued for 30 min during which the internal temperature was carefully adjusted to $-22\,^{\circ}C$. Ethyl dimethyl amine (269.37 g, 2.486 mol, 2.0 equiv) (DO NOT use triethylamine or any other base!) was added with *careful control* of the internal temperature ($-22\,^{\circ}C \le T \le -19\,^{\circ}C$). The resulting suspension was again stirred for an additional 30 min at $-20\,^{\circ}C$ and then poured into a

0947-6539/01/0706-1238 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 6

rapidly stirred mixture of sat. NH_4Cl solution (2 L) and diethyl ether (ca. 500 mL). Water was added until all solids dissolved and the resulting clear phases were separated. The aqueous layer was extracted three times with ether (ca. 200 mL) and the combined organic extracts dried over Na_2SO_4 and the solvents were removed under reduced pressure yielding a crude, semicrystalline product (ca. 300 g) containing a 8.6:1.0 mixture of the epimeric sulfonimidates **1** and *epi*-**1**. Recrystallisation of the material from *tert*-butyl methyl ether and hexanes/petroleum ether (b.p. 40–70 °C) yielded **1** as a white crystalline solid (142.4 g, 0.596 mol, 64 %). The yield is corrected for the real sulfinamide content of the starting material. Usually the yield of this cyclisation is considerably higher, but the low quality of the sulfinamide mixture reduces not only the theoretical yield but also hampers crystallisation. M.p. 81 °C; $R_f = 0.43$ (diethyl ether/hexanes 1:1); $[\alpha]_D^{20} = -93.8$ ($c = 1.0$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): $\delta = 7.86$ ("d", 2H; *o*-H_2), 7.31 ("d", 2H; *m*-H_2), 4.66 (dd, 1H; 5′-H), 4.02 (ddd, 1H; 4-H), 3.83 (dd, 1H; 5-H), 2.44 (s, 3H; *p*-CH_3), 1.79 (dqq, 1H; 4-C*H*$(CH_3)_2$), 1.17, 0.95 (2 × d, 2 × 3H; 4-CH(CH_3)$_2$); $J_{5,5'} = 7.6$ Hz, $J_{5,4} = 9.0$ Hz, $J_{5',4} = 6.0$ Hz, $J_{4,4\text{-}CH(CH_3)_2} = 8.3$ Hz, $J_{4\text{-}CH(CH_3)_2,4\text{-}CH(CH_3)_2} = 6.7$ Hz; ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): $\delta = 144.81$ (*p*-C), 135.02 (*ipso*-C), 129.67 (*m*-C), 129.10 (*o*-C), 75.45 (5-C), 70.88 (4-C), 34.09 (4-*C*H$(CH_3)_2$), 21.53 (*p*-CH_3), 20.31 (4-CH(*C*H_3)$_2$), 18.43.

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[19] The rather low yield given in the experimental part of this paper is due to the low quality of the sulfinamide mixture which has been provided as a gift.

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