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An umpolung sulfoxide reagent for use as a functionalized benzyl carbanion equivalent☆

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ABSTRACT

N-Methyl *ortho*-carbamoylaryl benzyl sulfoxides can be used as synthetic equivalents for α-hydroxy, α-chloro, and α-acetammido benzyl carbanions by means of a two-step sequence involving highly diastereoselective α-C-alkylation with alkyl halides followed by displacement of the sulfinyl residue (which can be recovered and recycled) by a hydroxyl, a chlorine or an acetamido, respectively, under non-oxidative Pummerer conditions. The scope and limits of the method, including a stereoselective version of the reaction, as well as the mechanism of the process are discussed in detail.

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1. Introduction

The methods for achieving umpolung reactivity of the natural reactivity of functional groups, developed over the last four decades has proved to be a significant enrichment in synthetic organic chemistry.[1] The problem owes the start of its vigorous research to Corey and Seebach in the mid 1960s[2] when they defined umpolung as 'any process by which donor and acceptor reactivity of an atom are interchanged'.[3] In their pioneering work, they reversed the electrophilic character of an acyl carbon by creating a nucleophilic acylating reagent by protecting the carbonyl group of an aldehyde as dithioacetal. Since then, the concept of polarity inversion of functional groups has considerably expanded the portfolio of useful chemical transformations and has been consequently well used in organic synthesis. Not only have many other different nucleophilic acylating reagents been developed, such as unprotected acyl or acyl-analogous derivatives, vinyl-ether type protected acyl anions, and aldeydes hydrazones,[4] but the concept has been applied to reverse the polarity of atoms other than carbon, such as hydrogen and its isotopes (D^- and T^-), by using a hexacoordinated dihydrophosphate as a key species,[5] halogens by using halide sources (X^-) in combination with readily available oxidizing agents, thereby affecting the in situ generation of X^+ equivalents,[6] and nitrogen in the addition to imine double bond in which the nitrogen acts as the electrophilic center.[7] Moreover, the umpolung concept has routinely been used in organometallic chemistry,[8] and very recently, has also been applied to aromatic chemistry by converting an electron-rich aromatic ring (nucleophile) to the relatively highly electrophilic quinone species,[9] and to peptide chemistry by performing the synthesis of amides using α-halo nitroalkanes as acyl donors for a variety of common amines.[10]

Sulfoxides constitute a family of organic compounds, which has gained importance during the past decades. The intrinsic stereogenicity of the sulfinyl sulfur, as well as its configurational stability, makes possible the synthesis of optically pure sulfoxides, which are of importance in medicinal and pharmaceutical chemistry, and have contributed to enhance the synthetic importance of sulfoxides in the field of asymmetric synthesis.[11] In this context, α-sulfinyl carbanions are useful chiral intermediates, which have been used extensively to achieve stereoselective C–C bond-forming reactions by alkylation with suitable electrophiles, Michael addition to α,β-unsaturated systems, addition to C=O bonds of aldehydes and ketones and addition to C=N bonds of imines.[12] In this context, we recently demonstrated that enantiomerically pure α-Li sulfoxides

☆ In memory of Prof. Carlo Rosini.

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can be used as chiral α-hydroxy and α-chloro carbanion equivalents with alkyl and aryl imines,[13] by means of a two-step procedure based on: (1) C–C bond-forming reaction leading to β-sulfinyl amines, and (2) 'non-oxidative' Pummerer reaction (NOPR)[14] or chloro-Pummerer reaction (NOCPR),[15] which allow for replacing the sulfinyl auxiliary by an OH or a Cl atom, respectively, with an S_N2-like pathway (stereoinversion at carbon). This strategy was exploited by us and others for the stereoselective synthesis of biologically important β-amino-alcohols, such as statine,[15] and its trifluoromethyl (Tfm) analog,[16] Tfm-analogs of ephedra alkaloids,[17] several phenyl-glycinols,[18] β-chloro-amines and aziridines.[15] As an extension of this synthetic concept, we commenced a project aimed at developing sulfoxide reagents to be used as functionalized carbanion equivalents of broader scope. For this purpose, we recently demonstrated the usefulness of an arylsulfoxide reagent bearing an *ortho*-*N*-methylformamide function, as umpolung α-hydroxy and α-chloro benzyl carbanion equivalents[19] as well as precursor for the synthesis of both aryl-tetralin and benzopyran structural frameworks.[20] In this paper, we provide a full account on the scope and limits of this methodology as well as a discussion of the mechanism. Of particular interest are (1) a new application of such reagent as α-acetamido benzyl carbanion equivalent and (2) the use of an optically enriched version of this sulfoxide reagent for the synthesis of non-racemic products (Fig. 1).

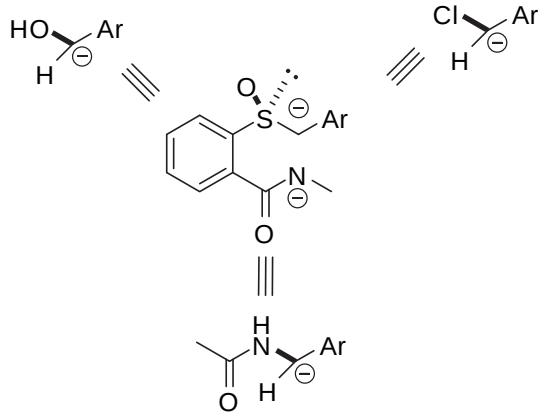


Fig. 1. The new chiral umpolung synthon.

2. Results

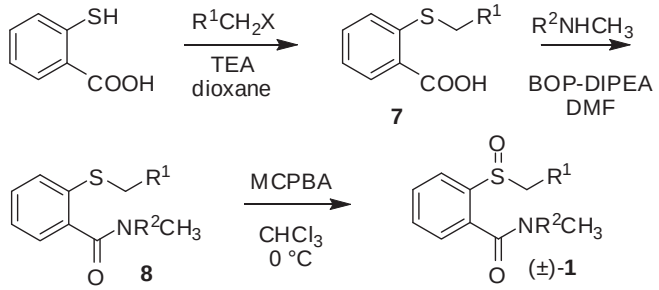
In our strategy C-alkylation of racemic *ortho*-[(*N*-alkyl)carbamoyl]phenyl sulfoxide **1** with an alkyl halide was planned to give the α-alkylsulfoxide **2**. Next we expected that treatment of **2** under Pummerer or chloro-Pummerer conditions, i.e., trifluoroacetic anhydride (TFAA) or oxalyl chloride, respectively, in the presence of 1 equiv of *sym*-collidine (TMP) in DCM, could give rise to NOPR- or NOCPR-like outcomes, namely the formation of the corresponding alcohol **3** and chloride **4**. Using Tf_2O as a promoter of the Pummerer reaction in some cases we observed the formation of products, which very likely came from the intermediate formation of a benzylic carbocation.[20] Since Tf_2O reacts with the sulfinyl oxygen producing TfO^-, which is an extremely poor nucleophile, we argued that the same reaction in the presence of a nucleophilic solvent, such as acetonitrile could be used to form the corresponding acetamides **5**.

The process portrayed in Scheme 1 leads to the formation of benzisothiazolone **6** as the co-product. However, **6** could be easily recycled by a three-step synthetic sequence, namely regioselective reduction of the N–S bond, alkylation of the corresponding thiophenol, and oxidation of the sulfide into sulfoxide **1**. The possibility to reconvert the co-product **6** into the starting sulfoxide **1** was conceived as an advantage in terms of atom economy.

Since it has been demonstrated that NOPR and NOCPR performed on β-sulfinyl amines are stereoselective processes leading to the formation of optically pure α-amino alcohols and -chlorides, respectively, through an S_N2-like pathway,[14,15] we decided to prepare enantiomerically enriched sulfoxides **1** in order to (1) investigate whether the reaction is stereoselective or rather takes place through the formation of a carbocation intermediate and (2) obtain non-racemic alcohols **3**, chlorides **4**, and acetamides **5**.

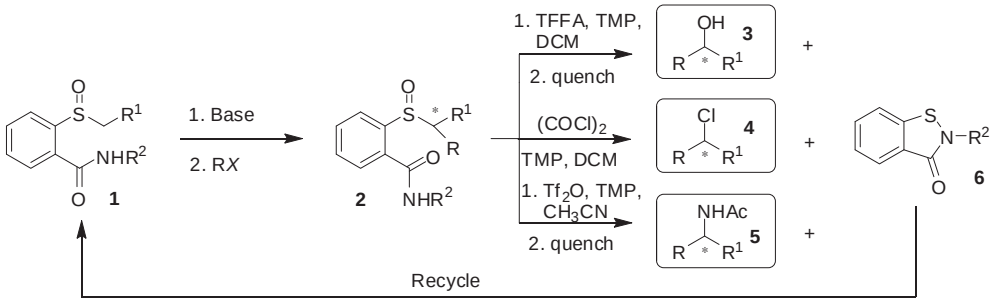
2.1. Synthesis of sulfoxides 1

The preparation of racemic sulfoxides (±)-**1** started with *S*-alkylation of commercially available thiosalicylic acid with alkyl halides affording the *ortho*-carboxy sulfides **7**, which were transformed into amides **8** by coupling with CH_3NH_2 and $(CH_3)_2NH$, and oxidized with MCPBA to (±)-**1a**–**g** in good overall yields (Scheme 2, Table 1).



Scheme 2. Preparation of sulfoxides (±)-**1**.

Similarly, enantiomerically pure sulfoxides (+)-**1a** and (−)-**1a** were prepared by *S*-alkylation of thiosalicilic acid with benzyl bromide and treatment of the resulting sulfide with enantiomerically pure (+)-2-β-naphthyl-ethylamine (Scheme 3). The following

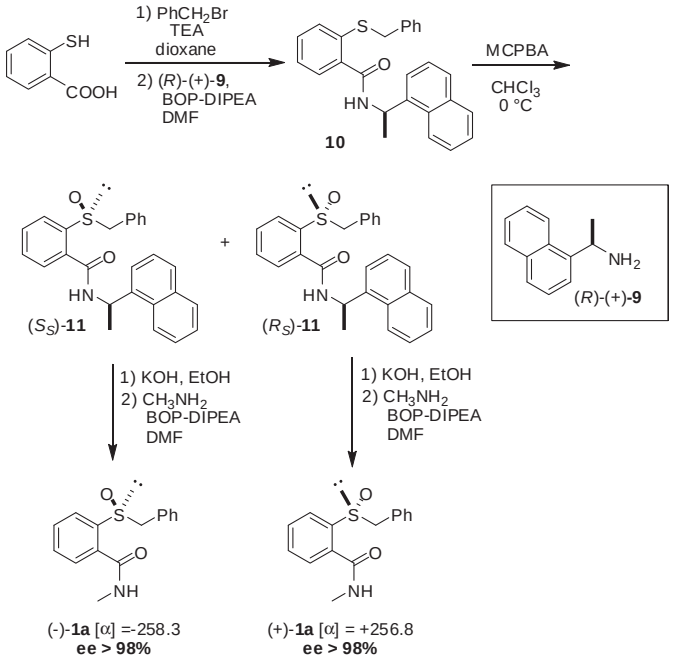


Scheme 1. Planned synthetic strategy.

Table 1
Preparation of sulfoxides (±)-**1**

Entry	Prod.	X	R^1	R^2	Yield[a] (%)
1	**1a**	Br	C_6H_5	H	82
2	**1b**	Br	4-MeO–C_6H_4	H	78
3	**1c**	Br	4CF_3–C_6H_4	H	68
4	**1d**	Br	4NO_2–C_6H_4	H	75
5	**1e**	Br	Et	H	81
6	**1f**	I	H	H	77
7	**1g**	Br	Ph	Me	84

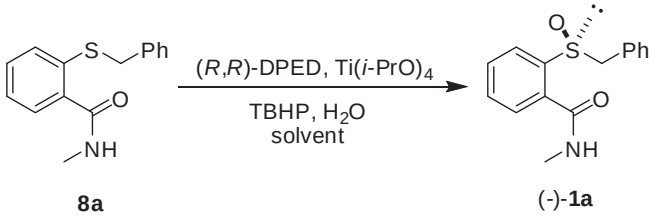
[a] Overall isolated yield from thiosalicylic acid.



Scheme 3. Preparation of enantiomerically pure sulfoxides (+)- and (−)-**1a**.

oxidation with MCPBA afforded an equimolar mixture of the two diastereoisomers (S_S)- and (R_S)-**11**, which were easily separated by flash-chromatography. After basic hydrolysis with KOH in refluxing ethanol, followed by coupling of the resulting acid with CH_3NH_2 in the same conditions described above we obtained the formation of (+)-**1a** and (−)-**1a** with ee >98%.

The preparation of enantiomerically enriched sulfoxide (−)-**1a** was also attempted by Ti-catalyzed enantioselective oxidation of sulfide **8a**. Oxidation of **8a** was then performed with *tert*-butyl hydroperoxide (TBHP) in the presence of catalytic amounts of the Ti alcoholate of enantiopure 1,2-diphenylethane-1,2-diol (DPED), following a procedure, which proved to be highly efficient and enantioselective in the oxidation of aryl benzyl sulfides (Scheme 4).[21]



Scheme 4. Enantioselective oxidation of sulfide **8a**.

At first, oxidation of **8a** was carried out using (*R*,*R*)-DPED as chiral ligand and following the best standard conditions set up in previous work.[21a,b] The reaction was then carried out at a temperature of 0 °C in CCl_4, under N_2 atmosphere, employing a reagent ratio sulfide/DPED/Ti/H_2O=1.0:0.1:0.05:1.0 and 2 equiv of TBHP (70% in water) as oxidant. Usually, these optimized conditions are the best compromise in order to limit sulfone formation (<10%), to have a satisfactory conversion, and good to high ees. However, under these conditions the reaction of **8a** was very slow and sulfoxide (−)-**1a** was obtained in modest 46% ee and low 28% yield after 4 h. This result can be ascribed to the very low solubility of **8a** in CCl_4. The long reaction time can also explain the low ee obtained, because it has been demonstrated that the Ti-DPED alcoholate, i.e., the chiral catalyst, spontaneously decomposes after some hours.[21a] We then performed the oxidation at 0 °C and with the same reagents ratio but in CH_2Cl_2, where **8a** is completely soluble. Also in these conditions, however, a modest 46% ee was obtained, enriched to 60% ee by a single recrystallization from hexane. Also the reaction performed in CH_2Cl_2 at rt, with the aim to speed up the reaction, provided (−)-**1a** in the same ee. Finally, the reaction was performed in CCl_4 at rt. In these conditions sulfide **8a** slowly dissolves, giving rise to a homogeneous solution after 5 h. The reaction was stopped after 20 h, recovering sulfoxide (−)-**1a** in excellent 94% yield and satisfactory 70% ee. After a single recrystallization from hexane sulfoxide (−)-**1a** was recovered in 80% ee and 85% overall yield.

In previous studies the use of (*R*,*R*)-DPED as chiral ligand for sulfide oxidation always provided aryl benzyl sulfoxides of (*S*) absolute configuration,[21] therefore we could expect also in this case the same stereochemical outcome. In order to obtain a reliable assignment of the absolute configuration of (−)-**1a** analysis of its circular dichroism (CD) spectrum (Fig. 2) was undertaken. An empirical correlation between CD spectra and absolute configuration of aryl alkyl sulfoxides was established by Mislow and co-workers

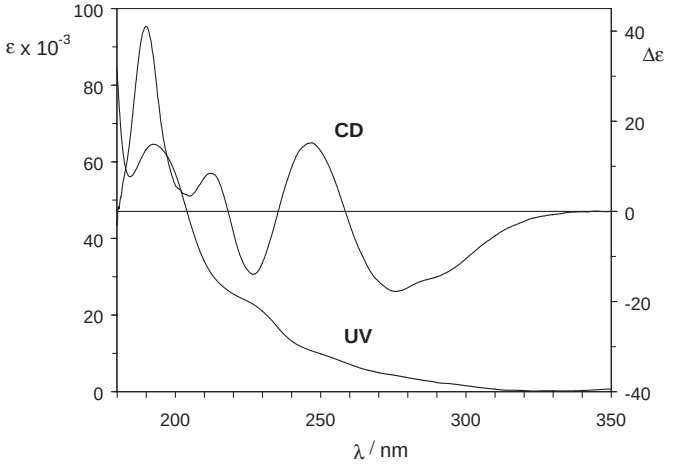


Fig. 2. UV and CD spectra (CH_3CN) of sulfoxide (−)-**1a**.

more than forty years ago,[22] but only more recent nonempirical analyses of their CD spectra provided suitable methods for a reliable absolute configuration assignment of these compounds.[23] In these recent studies it has been shown that in phenyl alkyl and phenyl benzyl sulfoxides two main absorption bands appear at 220 and 250 nm allied, respectively, to the ^1L_a benzene transition and the S=O transition. In correspondence to these two absorptions oppositely signed Cotton effects (CEs) appear in the CD spectrum, the longer wavelength one being negative for a (*S*) configured sulfoxide. The presence of substituents on both the phenyl moieties does not affect the main spectral features and only in the presence of strong electron withdrawing substituents, like the nitro one, a red shift was observed in both the UV and CD spectra. Very recently, the CD spectra of aryl benzyl sulfoxides have also been interpreted by means of computational methods, providing further support to the previous qualitative approaches.[24] The experimental UV spectrum of (−)-**1a** in acetonitrile shows the main absorption bands at 192 nm, followed by two shoulders at 228 and 250 nm. In the CD spectrum five intense CEs are clearly visible: at 190 nm ($\Delta\varepsilon$ 41.0), 212 nm ($\Delta\varepsilon$ 8.4), 227 nm ($\Delta\varepsilon$ −13.9), 247 nm ($\Delta\varepsilon$ 15.2), and 275 nm ($\Delta\varepsilon$ −17.7). Both the spectra then appear red shifted of about 30 nm with respect to those of unsubstituted benzyl phenyl sulfoxide,[23,24] an effect that can be attributed to the presence of the electron withdrawing carboxy amide group. In particular, in the CD spectrum of (−)-**1a** CE allied to the S]O transition at 275 nm is negative and, following previously established correlation,[23] a (*S*) absolute configuration shall be assigned to this enantiomer. Interestingly, the CD spectrum of (−)-**1a** appears in an almost mirror image relationship with the one of the (*R*)-2-carboxyethyl benzyl sulfoxide[24] in which a very similar chromophoric system is present. This qualitative comparison also provides further support to the previous configurational assignment.

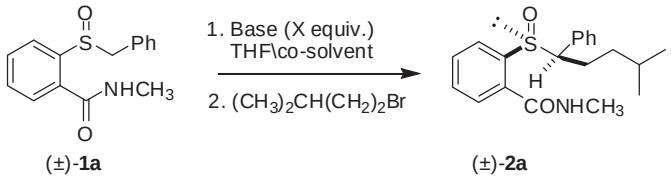
2.2. Alkylation of sulfoxides 1

In order to optimize yield and diastereoselectivity for the alkylation of sulfoxides **1**, we selected sulfoxide (±)-**1a** and 1-Br-3-methylbutane as model reaction partners (Table 2), then different reaction parameters, such as base, co-solvents and their equivalents were systematically modified (Scheme 5).[25]

Table 2
Alkylation of (±)-**1a** with 1-Br-3-methylbutane

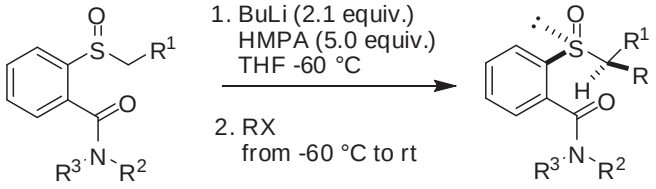
Entry	Base (equiv)	co-solvent (equiv)	de[a] (%)	Yield[b] (%)
1	LDA (2.1)	None	—	n.r.[c]
2	LDA (1.05) BuLi (1.05)	None	<5	11
3	BuLi (2.1)	None	<5	32
4	BuLi (2.1)	HMPA (2.4)	94	19[d]
5	BuLi (2.1)	HMPA (2.4)	94	55[e]
6	BuLi (2.1)	TMEDA (2.4)	—	n.r.[c,e]
7	BuLi (2.1)	HMPA (5)	94	92[e]

[a] Measured by HPLC/^{1}H NMR.
[b] Overall isolated yield.
[c] No reaction occurred and the starting sulfoxide was almost completely recovered.
[d] HMPA was added after deprotonation with BuLi.
[e] Co-solvent was added before BuLi.



Scheme 5. Alkylation of (±)-**1a** with 1-Br-3-methylbutane.

Since, in general, lithium amides (such as LDA) and alkyl lithium reagents are the most used bases to remove the α-proton of a sulfoxide (although alkyl lithium compounds are less used because they can cleave the C–S bond by nucleophilic attack) we first treated benzyl sulfoxide (±)-**1a** with 2.1 equiv of freshly prepared LDA (the first equiv is quenched by the amidic hydrogen) before adding the electrophile. However, in these conditions we recovered almost quantitatively the unreacted starting sulfoxide (entry 1, Table 2), whereas by using 1.05 equiv of LDA followed by 1.05 equiv of less sterically hindered BuLi we obtained the formation of a small amount of the products (11% yield) as an almost equimolar ratio of the two diastereoisomers (entry 2, Table 2). These results demonstrated that our system is very sensitive to the steric hindrance of the base. In fact, by treating sulfoxide (±)-**1a** with 2.1 equiv of *n*-BuLi[26] we obtained the formation of the desired products (±)-**2a**, again in an almost diastereoisomeric equimolar ratio, but with higher yield (32%), even if still too low to have practical uses (entry 3, Table 2). Importantly, we did not detect any product arising from the cleavage of the C–S bond, thus implying that *n*-BuLi could be a suitable base. In order to improve the yield and, possibly, also the diastereoselectivity, we tried the reaction in the presence of HMPA, which is known to sequestrate the lithium cations from the solution thus rendering the *C,N*-bis-anion more reactive. Accordingly, we were able to raise all at once the yields (55%) and the diastereoselectivity (de 94%) by using 2.4 equiv of HMPA (entry 5, Table 2). However, the co-solvent HMPA had to be added before *n*-BuLi otherwise the yields dropped down to 19% while preserving the de (entry 4, Table 2). Finally, by increasing the quantity of HMPA to 5 equiv we obtained the formation of (±)-**2a** in very high yields (92%) and diastereoselectivity (94%, entry 7, Table 2). We then turned our attention to studying the scope and limitations of the reaction by applying the optimized conditions to the reaction of *ortho*-[(*N*-alkyl)carbamoyl]phenyl sulfoxides with different alkyl halides (Scheme 6). The results are summarized in Table 3.



Scheme 6. Alkylation of *ortho*-[(*N*-alkyl)carbamoyl]phenyl sulfoxide.

Highly reactive benzyl bromide and crotyl bromide reacted smoothly with sulfoxide (±)-**1a** leading to the formation of the desired products (±)-**2b**,**c**, respectively, with high yield and lower, although still good, diastereoselectivities (entries 1 and 2, Table 3). Due to the high reactivity and the low steric hindrance of the electrophile, the reaction with methyl iodide afforded the desired sulfoxide (±)-**2d** with low diastereocontrol together with the corresponding *C,N*-dimethylated product (34%, entry 3, Table 3). However, this was the only case where N-alkylation was observed. Less reactive bromides, such as 1-Br-3-Ph-propane, 1-Br-4-pentene, and 1-Br-pentane produced alkylated sulfoxides (±)-**2e**–**g**, respectively, with high yields and high diastereoselectivities (entries 4–6, Table 3). The stereochemistry of the main diastereoisomer (±)-**2g** was assessed by single crystal X-ray diffraction (Fig. 3), and the configurations of the other main diastereoisomers were assigned on the basis of spectroscopic and analytic analogies with (±)-**2g**.

Interestingly, the two phenyl rings are nearly coplanar, the dihedral angle between them being of 8.1(2)°. Furthermore the amidic carbonyl and the S–O bond are linearly arranged, with an angle of 175.7(6)°. Finally, the amide group plane and the phenyl ring show an interplanar angle of 11.1(2)°.

Table 3
Alkylation of *ortho*-[(*N*-alkyl)carbamoyl]phenyl sulfoxide

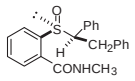
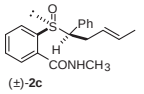
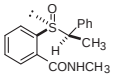
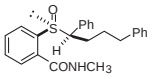
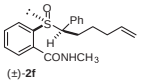
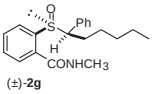
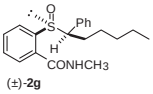
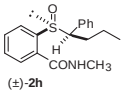
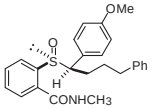
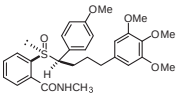
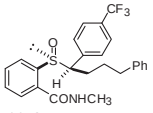
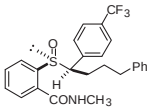
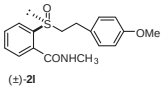
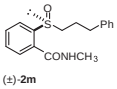
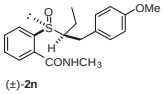
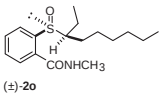
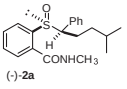
Entry	Substrate	R^1	R^2	R^3	Alkyl halide	Product	de[a]	Yield[b] %
1	(±)-**1a**	Ph	Me	H	$PhCH_2Br$	 (±)-**2b**	58	96
2	(±)-**1a**	Ph	Me	H	(*E*)-$CH_3CH]CHCH_2Br$	 (±)-**2c**	66	79
3	(±)-**1a**	Ph	Me	H	CH_3I	 (±)-**2d**	50	48[c]
4	(±)-**1a**	Ph	Me	H	$Ph(CH_2)_3Br$	 (±)-**2e**	94	74
5	(±)-**1a**	Ph	Me	H	$CH_27{=}CH(CH_2)_3Br$	 (±)-**2f**	92	95
6	(±)-**1a**	Ph	Me	H	$CH_3(CH_2)_4Br$	 (±)-**2g**	88	69
7	(±)-**1a**	Ph	Me	H	$CH_3(CH_2)_4I$	 (±)-**2g**	86	65
8	(±)-**1a**	Ph	Me	H	$CH_3(CH_2)_2I$	 (±)-**2h**	92	74
9	(±)-**1b**	4-MeO–C_6H_4	Me	H	$Ph(CH_2)_3Br$	 (±)-**2i**	86	78
10	(±)-**1b**	4-MeO–C_6H_4	Me	H	(3,4,5-TriMeO–C_6H_2)–C_6H_2)–$(CH_2)_3Br$	 (±)-**2j**	96	88
11	(±)-**1c**	4-CF_3–C_6H_4	Me	H	$Ph(CH_2)_3Br$	 (±)-**2k**	78	51
12	(±)-**1c**	4CF_3–C_6H_4	Me	H	$Ph(CH_2)_3Br$	 (±)-**2k**	42[g]	65[d]
13	(±)-**1d**	4NO_2–C_6H_4	Me	H	$Ph(CH_2)_3Br$	—	—	n.r.[e]
14	(±)-**1f**	H	Me	H	(4-MeO–C_6H_4)CH_2Cl	 (±)-**2l**	—	62
15	(±)-**1f**	H	Me	H	$Ph(CH_2)_3Br$	 (±)-**2m**	—	85
16	(±)-**1e**	Et	Me	H	(4-MeO–C_6H_4)CH_2Cl	 (±)-**2n**	32	70

Table 3 (*continued*)

Entry	Substrate	R^1	R^2	R^3	Alkyl halide	Product	de[a]	Yield[b] %
17	(±)-**1e**	Et	Me	H	$CH_3(CH_2)_5Br$	 (±)-**2o**	<5	60
18	(±)-**1g**	Ph	Me	Me	$PhCH_2Br$	—	—	n.r.[e]
19	(+)-**11**	Ph	(*S*)-(1-$C_{10}H_7$)CH(CH_3)	H	$PhCH_2Br$	—	—	n.r.[e]
20	(*S*)(−)-**1a**	Ph	Me	H	$(CH_3)_2CH(CH_2)_2Br$	 (-)-**2a**	94	92[f]

[a] Measured by HPLC/^{1}H NMR.
[b] Overall isolated yield.
[c] A 34% of the corresponding *C*,*N*-dimethylated product was recovered.
[d] Reaction stopped after 330 min (−70 °C→rt).
[e] No reaction occurred.
[f] No epimerization at sulfur occurred.
[g] Reversal of diastereoselectivity was obtained.

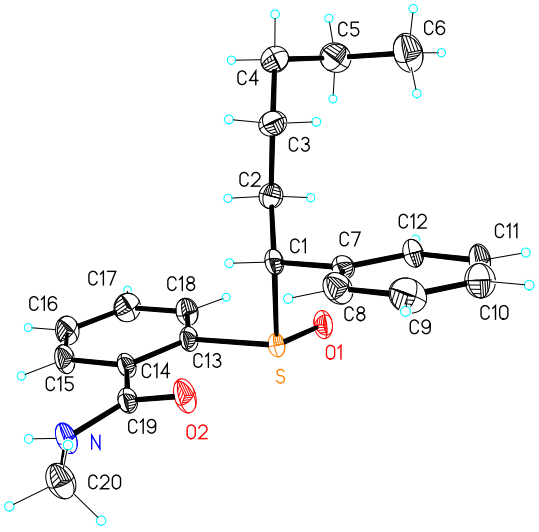


Fig. 3. X-ray structure of **2g**.

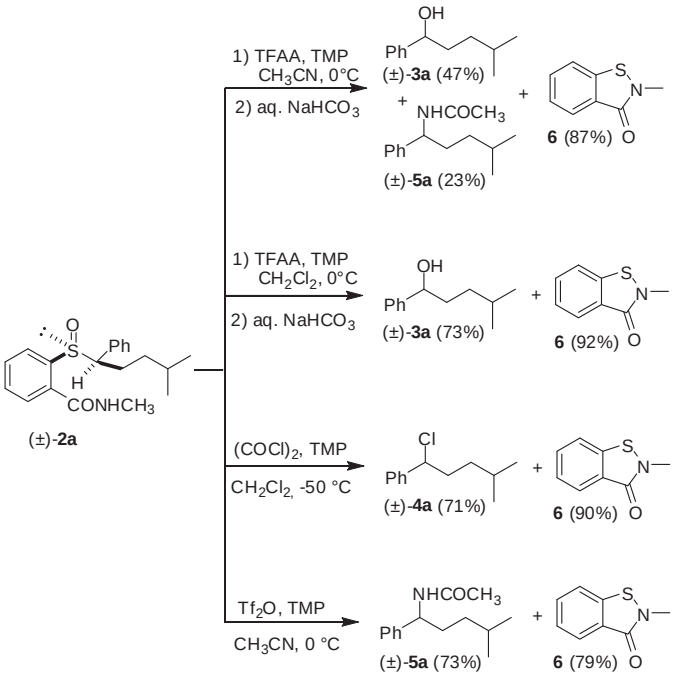
The reactivity of alkyl iodides was very similar to that of the corresponding bromides. Accordingly, 1-I-pentane reacted smoothly with sulfoxide (±)-**1a** leading to the formation of the corresponding sulfoxide (±)-**2g** with very similar yield and diastereoselection as compared to 1-Br-pentane (entry 7, Table 3), while with 1-I-propane we obtained the sulfoxide (±)-**2h** with even higher de (entry 8, Table 3). Excellent results, both in terms of yields and diastereoselectivities, were obtained with the electron rich, and therefore highly nucleophilic, α-lithiated *p*-MeO—Bn sulfoxide (±)-**1b**. In fact, with 1-Br-3-C_6H_4-propane we observed the formation of (±)-**2i** with a 94% de (entry 9, Table 2), the same result obtained with the unsubstituted benzyl sulfoxide (±)-**1a**. Similar results were observed by using 1-Br-3-(3,4,5-triMeO)C_6H_2-propane as electrophile (entry 10, Table 3). The reactivity of the less nucleophilic α-lithiated *p*-CF_3—Bn sulfoxide (±)-**1c** proved to be quite different. In fact, the reaction with 1-Br-3-Ph-propane at −60 °C gave the formation of the desired alkylated product (±)-**2k** with high, albeit lower diastereocontrol, but in modest yield, independently of the reaction time (entry 11, Table 3). Quite surprisingly, attempts of increasing the yield by warming the reaction temperature to rt, produced an inversion of diastereoselectivity (entry 12, Table 3).[27] Finally, the even less nucleophilic *p*-NO_2—Bn sulfoxide (±)-**1d** did not react at all with 1-Br-3-Ph-propane leading to the formation of a complex mixture of products when the temperature was allowed to reach rt (entry 13, Table 3).

Then, we investigated the reactivity of alkyl sulfoxides, such as methyl sulfoxide (±)-**1f** and propyl sulfoxide (±)-**1e**. Compound (±)-**1f** reacted smoothly with both highly reactive *p*-MeO—benzyl chloride and less reactive 1-Br-3-Ph-propane giving rise to the formation of sulfoxides (±)-**2l**,**m**, respectively, in high yields (entries 14 and 15, Table 3). Also α-lithiated propyl sulfoxide (±)-**1e** reacted with *p*-MeO—benzyl chloride affording derivative (±)-**2n** in good yields but low diastereoselectivity (entry 16, Table 3). Moreover, with less reactive 1-Br-pentane we observed the formation of an almost equimolar ratio of the two diastereoisomers (±)-**2o** (entry 17, Table 3). These latter results suggest that the high diastereoselection obtained with those sulfoxides having a benzyl substituent likely arise from an interaction between the aromatic rings in the reaction transition state, possibly a π-staking interaction between the electron poor phenyl ring, bearing the sulfoxide and the carbamoyl substituents, and the aromatic ring of the sulfoxide benzyl substituent.[28] This hypothesis is corroborated by (1) the higher stereocontrol obtained with electron-rich or -neutral benzyl substituents, such as *p*-MeO—benzyl in (±)-**1b** and benzyl in (±)-**1a**, as compared with the electron poor *p*-CF_3—benzyl substituent in (±)-**1c**, (2) by the fact that the reaction is highly dependent on steric factors,[29] and (3) the tendency of the phenyl rings to adopt a planar conformation in the solid state, as evidenced by the X-ray of (±)-**2g** (see above). Moreover, no reaction was observed with the *N*,*N*-dimethylamide (±)-**1f** even with highly reactive benzyl bromide (entry 18, Table 3), suggesting that the *ortho*-lithiated amide function might play an important role in this reaction. Further support for this hypothesis came from the observation that benzyl *p*-tolylsulfoxide was unreactive with 1-Br-hexane under the same conditions (*n*-BuLi, HMPA), whereas using LDA as base and HMPA as co-solvent afforded in modest yield and no stereoselection both diastereoisomers of 1-phenyl-1-(*p*-tolylsulfinyl)heptane.

Finally, reaction of enantiomerically pure sulfoxide (+)-**11** with benzyl bromide did not afford the desired product probably owing to steric factors (entry 19, Table 3), while using enantiomerically pure (+)-**1a** with 1-Br-3-methylbutane we observed the formation of the corresponding product (+)-**2a** without loss of ee (entry 20, Table 3). This result is very important because, in perspective, the high stereoselectivity of the C-alkylation of enantiomerically pure sulfoxide reagents, along with the preservation of the ee, may represent a key factor for the development of an asymmetric version of the planned methodology, whose success will also rely on the preparation of alcohols, chloride, and acetamides in high enantiomeric purity.

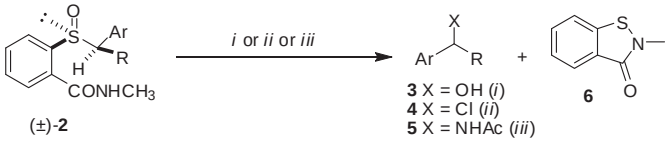
2.3. Use of umpolung sulfoxide reagents 2

The first evidence that sulfoxide reagents **2** could undergo Pummerer reactions under non-oxidative pathways was obtained when we observed that benzylated sulfoxide (±)-**2b** spontaneously decompose to (*E*)-stilbene and benzisothiazolone **6** after prolonged storing at rt. Several authors reported that *N*-monosubstituted *ortho*-carbamoyl–arylsulfoxides undergo an 'interrupted' Pummerer reaction[30] upon treatment with certain electrophiles, providing the corresponding benzisothiazolones and esters (with Ac_2O/H_2SO_4 or trichloroacetic anhydride) or chlorides (with $SOCl_2$, diphosgene or AcCl) as co-products.[31] Thus, we submitted derivative (±)-**2a** to the classical conditions for the NOPR, namely TFAA, TMP in CH_3CN at 0 °C followed by treatment in situ with aqueous $NaHCO_3$, and we obtained the formation of the desired alcohol (±)-**3a** and benzisothiazolone **6** along with the acetamide (±)-**5a** (23%, Scheme 7).



Scheme 7. NOPR on sulfoxide (±)-**2a**.

By performing the reaction in DCM instead of acetonitrile, we observed the exclusive formation of the alcohol (±)-**3a** along with the benzisothiazolone co-product **6** in very good yield. These preliminary experiments were very important because they provided clear evidence that *N*-methyl *ortho*-carbamoylaryl sulfoxides are not only synthetic equivalents of α-hydroxy carbanions, but can also be used as synthetic equivalents of an α-acetamido carbanion. We reasoned that the formation of the acetamide (±)-**5a** probably arose from a benzylic carbocationic intermediate originated by the action of TFAA on the sulfinyl moiety of (±)-**2a**. The latter is trapped by the nucleophilic solvent (CH_3CN) leading to the formation of the corresponding acetamide by hydrolysis occurring during the reaction quenching. To render this mechanism useful for the synthesis of acetamide (±)-**5a** we sought to identify reaction conditions, which suppressed the formation of the corresponding alcohol (±)-**3a**. We reasoned that replacing TFAA as a promoter of the Pummerer reaction with Tf_2O, which is known to react with the sulfinyl oxygen producing TfO^-, which is an extremely poor nucleophile, could maximize the formation of the target acetamide. Rewardingly, by treating sulfoxide (±)-**2a** with Tf_2O in CH_3CN at 0 °C we obtained the formation of the acetamide (±)-**5a** in good yield as the only product of the NOPR along with the heterocycle **6**. Concerning the NOCPR, racemic (±)-**1a** was already known to give very good yields of benzyl chloride upon treatment with $SOCl_2$.[31] As expected, we found that also the NOCPR conditions (oxalyl chloride, TMP, DCM, −50 °C) worked well on substrate (±)-**2a** affording the benzylic secondary chloride (±)-**4a**, together with **6**, in very good yield. In order to expand the scope of the reaction, we applied the same conditions to the different racemic sulfoxides (±)-**2** synthesized as described before (Scheme 8). The results are listed in Table 4.



i. TFAA, TMP, DCM, 0 °C, then aq. $NaHCO_3$; *ii*. $(COCl)_2$, TMP,DCM -50 °C; *iii*. Tf_2O, TMP, CH_3CN 0 °C

Scheme 8. Synthesis of alcohols **3**, chlorides **4**, and acetamides **5**.

Table 4
Synthesis of alcohols **3**, chlorides **4**, and acetamide **5**

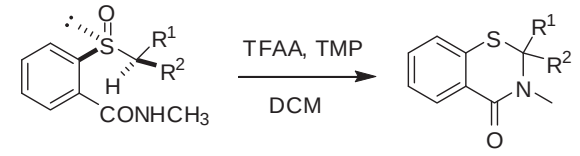
Subs.	Ar	R	Prod	X	Yield[a] (%)
(±)-**2e**	Ph	$Ph(CH_2)_3$	(±)-**3e**	OH	86
(±)-**2f**	Ph	$CH_2{=}CH(CH_2)_3$	(±)-**3f**	OH	72
(±)-**2i**	4-MeO–Ph	$Ph(CH_2)_3$	(±)-**3i**	OH	67
(±)-**2k**	4-CF_3–Ph	$Ph(CH_2)_3$	(±)-**3k**	OH	77
(±)-**2e**	Ph	$Ph(CH_2)_3$	(±)-**4e**	Cl	90
(±)-**2f**	Ph	$CH_2{=}CH(CH_2)_3$	(±)-**4f**	Cl	60
(±)-**2i**	4-MeO–Ph	$Ph(CH_2)_3$	(±)-**4i**	Cl	63
(±)-**2k**	4-CF_3–Ph	$Ph(CH_2)_3$	(±)-**4k**	Cl	78
(±)-**2g**	Ph	$CH_3(CH_2)_5$	(±)-**5g**	NHAc	62
(±)-**2h**	Ph	$CH_3(CH_2)_2$	(±)-**5h**	NHAc	67
(±)-**2j**	4-MeO–Ph	3,4,5-TriMeO–Ph–$(CH_2)_3$	(±)-**5j**	NHAc	48[b]
(±)-**2k**	4-CF_3–Ph	$Ph(CH_2)_3$	(±)-**5k**	NHAc	57[b]

[a] Overall isolated yield.
[b] Formation of the corresponding tetralines as by-products was observed (see Ref. 20).

The NOPR resulted to be quite general, working well with neutral benzyl sulfoxides (±)-**2e**,**f** producing the corresponding alcohols (±)-**3e**,**f** in good yields, with electron-rich benzyl sulfoxide (±)-**2i** as well as with the electron poor benzyl alcohol (±)-**2k**, which afforded the corresponding alcohols (±)-**3i**,**k**, respectively, in good yields. Analogous results were achieved by performing the NOCPR on the same starting sulfoxides, which afforded the chlorides (±)-**4e**,**f**,**i**,**k** always in good yields.[32]

Finally, when the R substituent did not contain an aromatic ring, such as in sulfoxides (±)-**2g**,**h** the reaction worked well also with Tf_2O producing acetamides (±)-**5g**,**h** in good yield, while with sulfoxides (±)-**2j**,**k** we obtained the corresponding acetamides (±)-**5j**,**k** in lower yield due to the concomitant formation of the tetraline derivatives as by-products.[20]

Unfortunately, non-benzylic sulfoxides failed to provide the corresponding alcohols under NOPR conditions. In fact, using the TFAA/TMP protocol unsubstituted (R^2=H) sulfoxide (±)-**2l** and dialkyl sulfoxide (±)-**2n** gave moderate yields of two main products, which were tentatively identified as the benzo[1,3]thiazin-4-ones **12a**,**b** resulting from a normal Pummerer mechanism (Scheme 9).

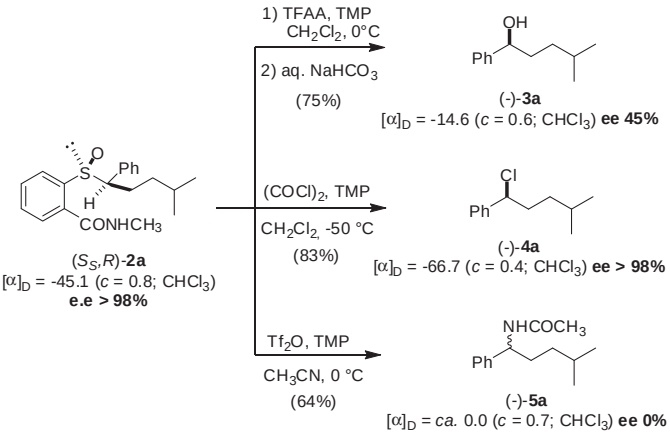


(±)-**2l** (R^1 = 4-MeO-Ph-CH_2; R^2 = H)
(±)-**2n** (R^1 = 4-MeO-Ph-CH_2; R^2 = Et)

Scheme 9. Reaction of non-benzylic sulfoxide under NOPR conditions.

Concerning the NOCPR with non-benzylic sulfoxides, the process worked well with the homobenzylic sulfoxide (±)-**2l** producing the corresponding 1-*p*-methoxyphenyl-3-Cl-propane in 80% yield, while it did not work at all with (±)-**2l** leading also in this case to benzo[1,3]thiazin-4-one **12b**.

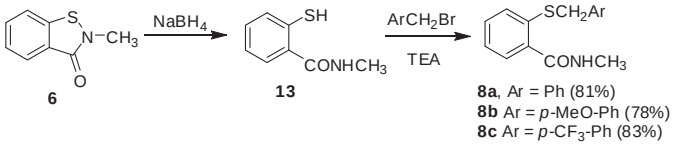
Thus, with the aim of (1) synthesizing enantiomerically enriched alcohols, chlorides, and acetamides and (2) having more information about the mechanism of this intriguing process, we performed the NOPR starting from the enantiomerically pure sulfoxide (−)-**2a** using the same conditions described above (Scheme 10).



Scheme 10. Pummerer reactions on enantiomerically pure (*S*S,*R*)-**2a**.

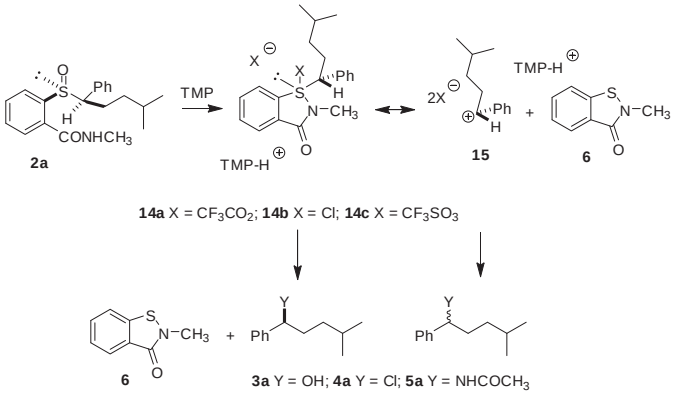
As expected, the NOPR afforded the alcohol (−)-**3a** with inversion of configuration at the benzylic stereocenter.[33] However, we observed partial loss of enantiomeric purity (ee 45% starting from sulfoxide (*S*S,*R*)-**2a** with ee >98%), which evidenced that the reaction did not occur exclusively through a S_N2 mechanism as in the case of β-sulfinyl-amines.[14] To enhance the enantioselectivity of the reaction we explored the use of trichloroacetic anhydride (TCAA), which produces the more nucleophilic CCl_3COO^- anion under Pummerer conditions. Gratifyingly, we obtained the formation of the corresponding alcohol with better enantioselectivity ([α]D −19.7, ee 61%). Even more satisfactorily, NOCPR on (*S*S,*R*)-**2a** provided the corresponding chloride (−)-**4a** without any loss of ee as evidenced by chiral HPLC. Finally, reaction with Tf_2O in CH_3CN afforded the racemic acetamide **5a** confirming that this reaction probably takes place through the intermediate formation of a carbocation.

In line with our synthetic plan, the co-product **6** was reduced with an excess of $NaBH_4$ to the thiol **13**, which was reconverted to the starting benzyl sulfides **8** by S-benzylation in ca. 80% overall yields in all cases (Scheme 11).



Scheme 11. Recycle of the co-product **6**.

In agreement with Uchida and Oae,[31a] and by considering our experimental results, we suggest that benzyl sulfoxides **2** might react according to the sequence shown in Scheme 12 for the model substrate **2a**.



Scheme 12. Proposed mechanism for the Pummerer reactions.

Acylation of the sulfinyl oxygen by TFAA, $(COCl)_2$[34] or Tf_2O, followed by capture of the transient sulfur cation by the *ortho*-carbamoyl nitrogen provides the intermediate **14a**–**c**. The latter, when the nucleophile X^- is sufficiently strong, such as in the case of Cl^-, undergoes fragmentation (S–X and C–S bonds breaking leading to **6**) and recombination (formation of a new Cl–C bond) through an S_N2-like mechanism to afford benzyl chloride **4a** with complete inversion of configuration.[35] When X^- is a poor nucleophile, such as in the case of TfO^-, this internal rearrangement cannot occur and the fragmentation produces the intermediate carbocation **15**, which can be trapped by a sufficiently nucleophilic solvent, i.e., CH_3CN, to afford, after hydrolysis, the acetamide **5a** with complete epimerization. Probably, with TFAA the two mechanistic pathways are competitive and the alcohol **3a** is formed with partial loss of ee because the S_N2-like mechanism is not exclusive. This hypothesis is supported by the fact that better ee was obtained when the reaction was promoted by TCAA, which generates a stronger nucleophile (CCl_3COO^- vs CF_3COO^-). It is noteworthy that the S_N2-like mechanism proposed here is very similar to the mechanism we propose previously for the NOPR and NOCPR involving β-sulfinyl amines as substrates,[14,15] with the notable difference that in the latter cases the sulfurane intermediate **14**-like is a highly reactive four membered ring that is exceptionally prone to undergo ring opening even with poor nucleophile like CF_3COO^-. That is probably the driving force of the stereospecificity featured by NOPR and NOCPR, whereas in the process discussed here the sulfurane moiety in **14a**–**c** belongs to a very stable, condensed five member ring and the nucleophilic attack to the electrophilic carbon must take place in *exo*-cyclic manner, which is less favorable.

3. Conclusions

In conclusion we have developed a family of new umpolung sulfoxide reagents for the synthesis of α-benzyl alcohols, chlorides, and acetamides. The synthesis of such reagents is very easy, highly modular and allowed for the preparation of different reagents in high yields and grams quantity. Such reagents could be considered as synthetic equivalents of functionalized benzyl carbanions. In fact, they can be easily converted to the corresponding α-benzyl alcohols, chlorides, and acetamides through a two-step procedure, namely a highly stereoselective alkylation of the sulfoxides followed by 'non-oxidative' Pummerer reactions, which allow for the replacement of the sulfinyl auxiliary by an hydroxy, a chloride, and an acetamido group, respectively, in a very efficient manner both in terms of yield and atom economy. The preparation of optically pure or enantiomerically enriched sulfoxides, respectively, through diastereoisomeric synthesis and enantioselective oxidation of the corresponding sulfides, led us to a proper understanding of the mechanism of the non-oxidative Pummerer process, which could arise (1) from a stereospecific S_N2-like mechanism when the nucleophile X^-, which is formed after the reaction of the sulfoxide with the electrophile, is sufficiently strong, such as in the case of Cl^-, leading to the synthesis of enantiomerically pure benzyl chlorides, (2) through the formation of a benzylic carbocation, which is trapped by the solvent, i.e., CH_3CN, producing the corresponding acetamides as racemates, when the nucleophile is very poor, such as TfO^-, and (3) through both the mechanisms above when the formed anion has an intermediate nucleophilic strength, such as CF_3COO^- leading to the final formation of enantiomerically enriched benzylic alcohols. We are currently investigating the application of such umpolung sulfoxide reagents to the synthesis of more complex, biologically important structures.

4. Experimental section

4.1. General method

Commercially available reagent-grade solvents were employed without purification unless otherwise stated. Dry THF was distilled from sodium while dry DCM was distilled from calcium hydride. Melting points (mp) were obtained on a capillary apparatus. TLC were run on silica gel 60 F_{254} Merck. Flash chromatographies (FC) were performed with silica gel 60 (60–200 μm, Merck). ^{1}H NMR spectra were run on spectrometers 250, 400 or 500 MHz. Chemical shifts are expressed in parts per million (δ), using tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C nuclei (δ_H and δ_C=0.00). Absorption and CD spectra of compound (−)-**1a** were recorded on a JASCO J815 spectropolarimeter at rt, in acetonitrile, using 0.1 mm cells and concentrations of about 1×10^{-3} M. During the measurement, the instrument was thoroughly purged with nitrogen. High-resolution MS spectra were recorded with an FT-ICR (Fourier Transform Ion Ciclotorn Resonance) instrument, equipped with an ESI source, or a standard MS instrument, equipped with an EI source.

4.2. General procedure for the synthesis of compounds 7

To a cooled solution of thiosalicylic acid (1 equiv) and TEA (2.1 equiv) in dioxane (0.1 M) benzyl bromide (1.1 equiv) was added drop-wise at 0 °C. After 10 min the organic solvent was evaporated, the residue diluted in 1 N HCl aqueous solution and extracted with AcOEt. The collected organic layers were dried on anhydrous Na_2SO_4, filtered and the solvent evaporated in vacuo.

*4.2.1. 2-(Benzylthio)benzoic acid (**7a**).* White solid, R_f=0.47 (hexane/AcOEt 50:50); mp 180–182 °C (MeOH); FTIR (film) 3440, 1639, 1255 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J=7.8 Hz, 1H), 7.49 (m, 2H), 7.42 (m, 2H), 7.33 (m, 2H), 7.26 (m, 1H), 7.20 (m, 1H), 4.20 (s, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 167.6, 141.5, 136.8, 132.6, 131.1, 129.4, 128.7, 127.8, 127.4, 125.9, 124.2, 35.9; MS (70 eV): e/z (%): 244 (12) [M^++1], 91 (100); HRMS calcd for [$C_{15}H_{14}O_3S$] 274.0664, found 244.0667.

*4.2.2. 2-(4-Methoxybenzylthio)benzoic acid (**7b**).* White solid, R_f=0.57 ($CHCl_3$/MeOH=95:5); mp 213–215 °C (H_2O); FTIR (microscope) ν 3459, 1674 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, J=7.6 Hz, 1H), 7.44 (m, 2H), 7.33 (d, J=8.6 Hz, 2H), 7.17 (m, 1H), 6.88 (d, J=8.6 Hz, 2H), 4.12 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 167.7, 158.3, 140.7, 131.5, 130.5, 130.2, 128.3, 125.6, 123.7, 113.8, 55.0, 35.2; EIMS (m/z) 274 [M^+, (18)], 121 (100); HRMS calcd for [$C_{14}H_{12}O_2S$] 244.0558, found 244.0554.

*4.2.3. 2-(4-(Trifluoromethyl)benzylthio)benzoic acid (**7c**).* White solid, R_f=0.49 ($CHCl_3$/MeOH=95:5); FTIR (microscope) ν 2941, 1690 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J=7.6 Hz, 1H), 7.67 (m, 4H), 7.46 (m, 2H), 7.21 (m, 1H), 4.31 (s, 2H); ^{19}F NMR (235.4 MHz, DMSO-d_6) δ −61.0 (s, 3F); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 167.6, 142.1, 140.5, 132.5, 131.1, 128.1, 127.6, 125.8, 125.4 (q, J=3.7 Hz), 124.4 (q, J=271.9 Hz), 124.3, 122.2, 35.0; EIMS (m/z) 312 [M^++1, (26)], 159 (100), 153 (59); HRMS calcd for [$C_{15}H_{11}F_3O_2S$] 312.0432, found 312.0435.

*4.2.4. 2-(4-Nitrobenzylthio)benzoic acid (**7d**).* White solid, R_f=0.59 ($CHCl_3$/MeOH=95:5); mp 205–206 °C (MeOH); FTIR (microscope) ν 3460, 1682 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J=8.6 Hz, 2H), 7.87 (d, J=7.6 Hz, 1H), 7.71 (d, J=8.6 Hz, 2H), 7.46 (m, 2H), 7.22 (m, 1H), 4.37 (s, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 167.3, 146.5, 145.3, 139.7, 132.2, 130.8, 130.2, 128.3, 126.0, 124.3, 123.5, 34.9; EIMS (m/z) 289 [M^+, (100)], 153 (81), 89 (77); HRMS calcd for [$C_{14}H_{11}NO_4S$] 289.0409, found 289.0411.

*4.2.5. 2-(Propylthio)benzoic acid (**7e**).* White solid, R_f=0.55 (hexane/AcOEt 50:50); FTIR (film) 1734, 1681, 1252 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.88 (d, J=7.5 Hz, 1H), 7.40 (m, 2H), 7.15 (m,1H), 2.89 (t, J=7.2 Hz, 2H), 1.69 (sextet, J=7.2 Hz, 2H), 1.06 (t, J=7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 170.5, 142.3, 132.9, 132.0, 130.9, 127.3, 124.9, 35.0, 22.9, 13.9; MS (70 eV): e/z (%): 197 (34) [M^++1], 153 (100); HRMS calcd for [$C_{10}H_{12}O_2S$] 196.0558, found 196.0555.

4.3. General procedure for the synthesis of compounds 8

To a solution of crude **7** (17.9 mmol, 4.38 g) in DMF (0.1 M) were added, respectively, solid BOP (1 equiv), the amine (1.1 equiv), and DIPEA (2 equiv). The solution was stirred at rt over-night. The organic solvent was evaporated and the residue purified by flash-chromatography.

*4.3.1. 2-(Benzylthio)-N-methylbenzamide (**8a**).* White solid, R_f=0.39 (hexane/AcOEt 50:50); mp 134–136 °C (AcOEt); FTIR (film) 3250, 1630, 1405 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, J=7.3 and 1.8 Hz, 1H), 7.40 (m, 1H), 7.30 (dt, J=7.3 and 1.8 Hz, 1H), 7.28–7.21 (m, 5H), 7.16 (m, 2H), 4.06 (s, 2H), 2.90 (d, J=4.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.7, 138.2, 137.2, 133.0, 132.5, 130.4, 128.8, 128.5, 127.3, 127.2, 40.3, 26.7; MS (70 eV): e/z (%): 257 (4) [M^++1], 166 (75), 91 (100); HRMS calcd for [$C_{15}H_{15}NOS$] 257.0874, found 257.0875.

*4.3.2. 2-(4-Methoxybenzylthio)-N-methylbenzamide (**8b**).* White solid, R_f=0.57 (hexane/AcOEt=80:20); FTIR (microscope) ν 3430, 1638, 1510 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (d, J=7.7 Hz, 1H), 7.33 (m, 2H), 7.21 (m, 1H), 7.17 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.6 Hz, 2H), 4.06 (s, 2H), 3.73 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 171.9, 160.2, 139.0, 136.0, 131.7, 131.2, 131.1,

130.4, 128.6, 127.1, 114.8, 55.7, 39.3, 26.7; EIMS (*m*/*z*) 287 [M^+, (100)]; HRMS calcd for [$C_{16}H_{17}NO_2S$] 287.0980, found 287.0984.

*4.3.3. N-Methyl-2-(4-(trifluoromethyl)benzylthio)benzamide (**8c**).* Yellowish oil, R_f=0.49 (hexane/AcOEt=50:50); FTIR (microscope) ν 3435, 1643, 1435 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.53 (d, *J*=8.2 Hz, 2H), 7.46 (d, *J*=8.2 Hz, 2H), 7.37 (m, 2H), 7.30 (m, 1H), 7.23 (m, 1H), 4.20 (s, 2H), 2.87 (s, 3H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 171.9, 143.6, 139.7, 135.1, 132.1, 131.2, 130.6, 130.1, 128.8, 127.6, 126.2 (q, *J*=3.6 Hz), 125.6 (q, *J*=271.4 Hz), 39.2, 26.7; EIMS (*m*/*z*) 325 [M^+, (100)]; HRMS calcd for [$C_{16}H_{14}F_3NOS$] 325.0748, found 325.0750.

*4.3.4. N-Methyl-2-(4-nitrobenzylthio)benzamide (**8d**).* Yellowish oil; FTIR (microscope) ν 3427, 1636, 1518 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.08 (d, *J*=8.6 Hz, 2H), 7.48 (d, *J*=8.6 Hz, 2H), 7.36 (m, 2H), 7.31 (m, 1H), 7.24 (m, 1H), 4.22 (s, 2H), 2.88 (s, 3H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 171.8, 148.3, 147.0, 139.9, 134.5, 132.5, 131.3, 131.0, 128.8, 127.9, 124.4, 39.1, 26.7; EIMS (*m*/*z*) 302 [M^+, (15)], 166 (100); HRMS calcd for [$C_{15}H_{14}N_2O_3S$] 302.0725, found 302.0722.

*4.3.5. N-Methyl-2-(propylthio)benzamide (**8e**).* Yellowish oil, R_f=0.42 (hexane/AcOEt 50:50); FTIR (film) 3340, 1638, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J*=7.8 and 1.4 Hz, 1H), 7.33 (m, 1H), 7.28 (m, 1H), 7.12 (dt, *J*=7.8 and 1.4 Hz, 1H), 7.04 (br s, 1H), 2.90 (d, *J*=4.9 Hz, 3H), 2.82 (t, *J*=7.3 Hz, 2H), 1.61 (sextet, *J*=7.3 Hz, 2H), 0.98 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.6, 136.3, 134.7, 129.9, 129.4, 128.4, 125.4, 35.8, 26.2, 21.9, 13.4; MS (70 eV): *e*/*z* (%): 210 (30) [M^++1], 152 (100); HRMS calcd for [$C_{11}H_{15}NOS$] 209.0874, found 209.0877.

*4.3.6. 2-(Benzylthio)-N,N-dimethylbenzamide (**8g**).* White solid, R_f=0.49 (hexane/AcOEt 50:50); FTIR (film) 3420, 1652, 947 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.16 (m, 9H), 4.10 (s, 2H), 3.09 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.8, 139.5, 137.2, 132.1, 131.6, 128.8, 128.2, 127.0, 126.9, 126.4, 39.1, 38.0, 34.4; MS (70 eV): *e*/*z* (%): 272 (24) [M^++1], 91 (100); HRMS calcd for [$C_{16}H_{17}NOS$] 271.1031, found 271.1030.

4.4. General procedure for the synthesis of compounds 1

To a cooled solution of **8** (1 equiv) in $CHCl_3$ (0.1 M) was added drop-wise a 50% in weight solution of MCPA (1 equiv) in $CHCl_3$ (0.1 M) at 0 °C. After the addition was complete (ca. 30 min) the solution was stirred for additional 20 min, quenched with a saturated aqueous solution of $NaHCO_3$, and the temperature was raised to rt. The mixture was extracted with $CHCl_3$, the collected organic layers dried on anhydrous Na_2SO_4, filtered and the solvent evaporated in vacuo. The residue was purified by flash-chromatography.

*4.4.1. (S)-2-(Benzylsulfinyl)-N-methylbenzamide ((S)-(−)-**1a**).* White solid, R_f=0.38 ($CHCl_3$/MeOH=95:05); mp 167–169 °C (AcOEt/MeOH); $[\alpha]_D^{20}$ −258.3 (*c* 1.1, $CHCl_3$); FTIR (film) 3478, 1633, 1027 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.38 (m, 3H), 7.21 (m, 3H), 7.10 (m, 2H), 4.48 (d, *J*=12.4 Hz, 1H), 4.03 (d, *J*=12.4 Hz, 1H), 2.89 (d, *J*=4.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.9, 144.4, 132.1, 131.3, 130.7, 130.5, 130.4, 128.2, 128.0, 126.6, 125.7, 62.5, 26.9; MS (70 eV): *e*/*z* (%): 274 (41) [M^++1], 182 (83), 91 (100); HRMS calcd for [$C_{15}H_{15}NO_2S$] 273.0823, found 273.0821.

*4.4.2. 2-(4-Methoxybenzylsulfinyl)-N-methylbenzamide (**1b**).* White solid, R_f=0.20 (AcOEt/hexane=80:20); mp 154–156 °C (AcOEt/MeOH=1:1); FTIR (microscope) ν 3296, 1646, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.43 (m,1H), 7.37 (m, 1H), 7.10 (br s, 1H), 7.03 (d, *J*=7.7 Hz, 2H), 6.74 (d, *J*=7.7 Hz, 2H), 4.43 (d, *J*=12.4 Hz, 1H), 3.99 (d, *J*=12.4 Hz, 1H), 3.74 (s, 3H), 2.92 (d, *J*=3.5 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.0, 159.5, 144.8, 132.1, 131.8, 131.1, 130.2, 126.6, 125.5, 122.7, 113.6, 62.2, 55.2, 26.8; EIMS (*m*/*z*) 303 (100) [M^++1]; HRMS calcd for [$C_{16}H_{17}NO_3S$] 303.0929, found 303.0932.

*4.4.3. N-Methyl-2-(4-(trifluoromethyl)benzylsulfinyl)benzamide (**1c**).* White solid, R_f=0.30 (AcOEt/hexane=70:30); mp 204–205 °C (AcOEt/MeOH=1:1); FTIR (microscope) ν 3282, 1646, 1322 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.48 (d, *J*=7.7 Hz, 2H), 7.43 (m, 2H), 7.24 (d, *J*=7.7 Hz, 2H), 6.76 (br s, 1H), 4.52 (d, *J*=12.4 Hz, 1H), 4.16 (d, *J*=12.4 Hz, 1H), 2.98 (d, *J*=4.6 Hz, 3H); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −63.6 (s, 3F); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.9, 144.7, 134.9, 132.0, 131.4, 130.9, 130.6, 126.4, 125.6, 124.9 (q, *J*=3.6 Hz), 124.2 (q, *J*=271.8 Hz), 62.2, 26.9; EIMS (*m*/*z*) 342 [M^++1, (39)], 182 (100), 159 (96); HRMS calcd for [$C_{16}H_{14}F_3NO_2S$] 341.0697, found 341.0700.

*4.4.4. N-Methyl-2-(4-nitrobenzylsulfinyl)benzamide (**1d**).* White solid, R_f=0.52 (AcOEt); mp 177–179 °C (AcOEt/MeOH=1:1); FTIR (microscope) ν 3296, 1646, 1519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J*=8.5 Hz, 2H), 7.59 (m, 2H), 7.46 (m, 2H), 7.27 (d, *J*=8.5 Hz, 2H), 6.66 (br s, 1H), 4.56 (d, *J*=12.4 Hz, 1H), 4.28 (d, *J*=12.4 Hz, 1H), 3.02 (d, *J*=4.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.8, 147.7, 144.5, 138.3, 131.9, 131.6, 131.4, 130.7, 126.3, 125.6, 123.1, 61.9, 26.9; EIMS (*m*/*z*) 319 [M^++1, (10)], 182 (100); HRMS calcd for [$C_{15}H_{14}N_2O_4S$] 318.0674, found 318.0677.

*4.4.5. N-Methyl-2-(propylsulfinyl)benzamide (**1e**).* Yellowish oil, R_f=0.24 (AcOEt); FTIR (film) 3419, 1644, 998 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J*=7.8 Hz, 1H), 7.87 (br s, 1H), 7.75 (d, *J*=7.8 Hz, 1H), 7.62 (t, *J*=7.8 Hz, 1H), 7.44 (t, *J*=7.8 Hz, 1H), 3.26 (ddd, *J*=17.4, 12.8, and 6.4 Hz, 1H), 2.93 (d, *J*=4.6 Hz, 3H), 2.71 (ddd, *J*=17.4, 12.8, and 5.0 Hz, 1H), 1.92 (m, 1H), 1.72 (m, 1H), 1.02 (t, *J*=7.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.7, 145.7, 131.8, 131.4, 130.0, 127.0, 124.4, 59.5, 26.6, 16.5, 12.9; MS (70 eV): *e*/*z* (%): 226 (25) [M^++1], 182 (46), 152 (100); HRMS calcd for [$C_{11}H_{15}NO_2S$] 225.0823, found 225.0827.

*4.4.6. N-Methyl-2-(propylsulfinyl)benzamide (**1f**). see* Ref. [36]

*4.4.7. 2-(Benzylsulfinyl)-N,N-dimethylbenzamide (**1g**).* White solid, R_f=0.41 (AcOEt); mp 90–91 °C (AcOEt); FTIR (film) 1626, 1397, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J*=7.8 Hz, 1H), 7.45 (t, *J*=7.8 Hz, 1H), 7.38 (t, *J*=7.8 Hz, 1H), 7.31 (d, *J*=7.8 Hz, 1H), 7.23 (m, 3H), 7.12 (m, 2H), 4.42 (d, *J*=12.8 Hz, 1H), 4.08 (d, *J*=12.8 Hz, 1H), 3.13 (s, 3H), 2.89 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.0, 141.1, 133.2, 130.4, 130.3, 129.8, 129.4, 127.9, 127.8, 126.2, 125.4, 61.9, 38.9, 34.8; MS (70 eV): *e*/*z* (%): 287 (33) [M^+], 196 (64), 91 (100); HRMS calcd for [$C_{16}H_{17}NO_2S$] 287.0980, found 287.0982.

4.5. General procedure for the synthesis of compounds 2

To a cooled solution of **1** (1.83 mmol, 500 mg) and dry HMPA (5 equiv) in dry THF (0.05 M) was added drop-wise, at −70 °C and under Ar atmosphere, a 2.5 M hexane solution of BuLi (1.2 equiv). After 10 min, at −78 °C 3-methyl-1-bromo-butane (1.2 equiv) was added. After the reaction was complete (TLC monitoring), saturated aqueous NH_4Cl was added, the temperature raised to rt and the solution extracted with AcOEt. The collected organic layers were dried on anhydrous Na_2SO_4, filtered and the solvent evaporated in vacuo. The residue was purified by flash-chromatography.

*4.5.1. N-Methyl-2-(4-methyl-1-phenylpentylsulfinyl)benzamide ((S,R)-**2a**).* White solid, R_f=0.50 (AcOEt); $[\alpha]^D_{23}$ −45.1 (*c* 0.8, $CHCl_3$, ee 98%); mp 108–109 °C (AcOEt); FTIR (film) 3383, 1653, 1000 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J*=7.5 Hz, 1H), 7.62 (d, *J*=7.5 Hz, 1H), 7.54 (t, *J*=7.5 Hz, 1H), 7.44 (t, *J*=7.5 Hz, 1H),

7.37–7.22 (m, 5H), 6.82 (br s, 1H), 4.25 (dd, *J*=11.3 and 3.8 Hz, 1H), 2.90 (d, *J*=4.2 Hz, 3H), 2.05 (m, 1H), 1.80 (m, 1H), 1.39 (m, 1H), 0.89 (m, 2H), 0.70 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.9, 143.1, 136.5, 133.5, 130.8, 130.6, 129.1, 128.6, 128.0, 127.8, 126.8, 68.8, 35.5, 27.8, 26.8, 22.7, 21.8; MS (70 eV): *e*/*z* (%): 344 (2) [M^++1], 183 (91), 117 (100), 91 (100); HRMS calcd for [$C_{20}H_{25}NO_2S$] 343.1606, found 343.1610.

*4.5.2. 2-(1,2-Diphenylethylsulfinyl)-N-methylbenzamide (**2b**). Major diast.*: Yellowish oil, R_f=0.51 (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J*=7.8 Hz, 1H), 7.83–7.76 (m, 3H), 7.60–7.07 (m, 9H), 6.91 (m, 2H), 4.67 (dd, *J*=11.4 and 3.9 Hz, 1H), 3.44 (dd, *J*=14.2 and 11.4 Hz, 1H), 3.24 (dd, *J*=14.2 and 3.9 Hz, 1H), 3.04 (d, *J*=3.9 Hz, 3H); MS (70 eV): *e*/*z* (%), mixture of both diastereoisomers: 364 (12) [M^++1], 91 (100); HRMS calcd for [$C_{22}H_{21}NO_2S$] 363.1293, found 363.1294. *Minor diast.*: R_f=0.51 (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J*=7.8 Hz, 1H), 7.83–7.76 (m, 3H), 7.60–7.07 (m, 9H), 6.96 (m, 2H), 4.84 (dd, *J*=9.6 and 6.2 Hz, 1H), 3.87 (dd, *J*=14.2 and 6.2 Hz, 1H), 3.65 (dd, *J*=14.2 and 9.6 Hz, 1H), 3.04 (d, *J*=3.9 Hz, 3H).

*4.5.3. (E)-N-Methyl-2-(1-phenylpent-3-enylsulfinyl)benzamide (**2c**). Major diast.*: Yellowish oil, R_f=0.60 (AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J*=7.7 Hz, 1H), 7.64–6.75 (m, 9H), 5.28 (m, 1H), 5.01 (m, 1H), 4.36 (dd, *J*=11.5 and 4.4 Hz, 1H), 2.92 (d, *J*=4.9 Hz, 3H), 2.78 (m, 1H), 2.43 (m, 1H), 1.42 (d, *J*=6.6 Hz, 3H); MS (70 eV): *e*/*z* (%), mixture of both diastereoisomers: 327 (15) [M^+], 91 (100). *Minor diast.*: R_f=0.60 (AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J*=8.2 Hz, 1H), 7.64–6.75 (m, 9H), 5.63 (m, 1H), 5.44 (m, 1H), 4.53 (dd, *J*=8.8 and 7.1 Hz, 1H), 3.08 (m, 1H), 2.98 (d, *J*=4.4 Hz, 3H), 2.91 (m, 1H), 1.60 (d, *J*=6.6 Hz, 3H).

*4.5.4. 2,2-(1,4-Diphenylbutylsulfinyl)-N-methylbenzamide (**2e**). Major diast.*: White solid, R_f=0.59 (AcOEt); mp 130–131 °C (AcOEt); FTIR (film) 3451, 1661, 1019 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J*=7.9 Hz, 1H), 7.61 (d, *J*=7.9 Hz, 1H), 7.53 (t, *J*=7.9 Hz, 1H), 7.42 (t, *J*=7.9 Hz, 1H), 7.40–7.24 (m, 5H), 7.11 (m, 3H), 6.91 (m, 2H), 6.85 (br s, 1H), 4.35 (dd, *J*=11.7 and 4.1 Hz, 1H), 2.89 (d, *J*=4.1 Hz, 3H), 2.42 (m, 2H), 2.12 (m, 1H), 1.74 (m, 1H), 1.44 (m, 1H), 1.29 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.9, 143.2, 141.7, 136.4, 133.3, 130.9, 130.5, 129.2, 128.7, 128.2, 128.1, 128.0, 127.6, 126.8, 125.6, 68.3, 35.3, 28.1, 26.8, 24.1; MS (70 eV): *e*/*z* (%): 392 (2) [M^++1], 332 (87), 165 (78), 117 (100); HRMS calcd for [$C_{24}H_{25}NO_2S$] 391.1606, found 391.1608.

*4.5.5. 2N-Methyl-2-(1-phenylhex-5-enylsulfinyl)benzamide (**2f**). Major diast.*: Yellowish oil, R_f=0.52 (AcOEt); FTIR (film) 3279, 1639, 996 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J*=8.0 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.56 (t, *J*=8.0 Hz, 1H), 7.45 (t, *J*=8.0 Hz, 1H), 7.39–7.25 (m, 5H), 6.78 (br s, 1H), 5.57 (m, 1H), 4.81 (m, 2H), 4.31 (dd, *J*=11.5 and 3.5 Hz, 1H), 2.93 (d, *J*=3.5 Hz, 3H), 2.09 (m, 1H), 1.90 (m, 2H), 1.79 (m, 1H), 1.22 (m, 1H), 1.09 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.0, 140.2, 137.0, 134.1, 131.7, 130.7, 129.3, 128.7, 126.7, 126.1, 125.5, 120.3, 114.8, 69.0, 33.6, 33.3, 32.4, 26.0; MS (70 eV): *e*/*z* (%): 342 (31) [M^++1], 166 (90), 117 (100); HRMS calcd for [$C_{20}H_{23}NO_2S$] 341.1449, found 341.1451.

*4.5.6. N-Methyl-2-(1-phenylhexylsulfinyl)benzamide (**2g**). Major diast.*: White solid, R_f=0.56 (AcOEt); FTIR (film) 3290, 1643, 1554, 996 cm^{-1}; mp 110–111 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J*=7.7 Hz, 1H), 7.62 (d, *J*=7.7 Hz, 1H), 7.50 (dt, *J*=7.7 and 1.3 Hz, 1H), 7.47 (dt, *J*=7.7 and 1.3 Hz, 1H), 7.35–7.24 (m, 5H), 6.64 (br s, 1H), 4.28 (dd, *J*=11.6 and 4.1 Hz, 1H), 2.95 (d, *J*=4.9 Hz, 3H), 2.08 (m, 1H), 1.82 (m, 1H), 1.35 (m, 6H), 0.74 (m, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.0, 143.0, 136.3, 133.8, 130.9, 130.7, 129.2, 128.6, 128.0, 127.3, 68.9, 31.4, 26.9, 26.3, 25.3, 22.2, 13.9; MS (70 eV): *e*/*z* (%): 344 (2) [M^++1], 136 (84), 117 (75), 91 (100); HRMS calcd for [$C_{20}H_{25}NO_2S$] 343.1606, found 343.1608.

*4.5.7. N-Methyl-2-(1-phenylbutylsulfinyl)benzamide (**2h**). Major diast.*: White solid, R_f=0.25 (AcOEt); FTIR (film) 3285, 1653, 1016 cm^{-1}; mp 123–125 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J*=7.6 Hz, 1H), 7.62 (d, *J*=7.6 Hz, 1H), 7.56 (dt, *J*=7.6 and 1.2 Hz, 1H), 7.48 (dt, *J*=7.6 and 1.2 Hz, 1H), 7.33–7.26 (m, 5H), 6.55 (br s, 1H), 4.30 (dd, *J*=11.4 and 3.8 Hz, 1H), 2.95 (d, *J*=5.0 Hz, 3H), 2.09 (m, 1H), 1.79 (m, 1H), 1.18 (m, 1H), 1.02 (m, 1H), 0.76 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.0, 136.2, 134.0, 131.7, 131.0, 129.2, 128.6, 128.1, 127.4, 126.7, 125.5, 68.7, 27.6, 26.9, 19.9, 13.7; MS (70 eV): *e*/*z* (%): 316 (34) [M^++1], 165 (88), 117 (77), 91 (100); HRMS calcd for [$C_{18}H_{21}NO_2S$] 315.1293, found 315.1296.

*4.5.8. 2-(1-(4-Methoxyphenyl)-4-phenylbutylsulfinyl)-N-methylbenzamide (**2i**). Major diast.*: Yellowish oil, R_f=0.53 (AcOEt); FTIR (microscope) ν 3291, 1646, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J*=7.7 Hz, 1H), 7.60 (d, *J*=7.5 Hz, 1H), 7.52 (m, 1H), 7.41 (m, 1H), 7.28 (m, 2H), 7.12 (m, 3H), 6.93 (d, *J*=8.5 Hz, 2H), 6.89 (br s, 1H), 6.85 (d, *J*=8.5 Hz, 2H), 4.34 (dd, *J*=11.4 and 3.6 Hz, 1H), 3.78 (s, 3H), 2.90 (d, *J*=4.9 Hz, 3H), 2.43 (m, 2H), 2.07 (m, 1H), 1.71 (m, 1H), 1.46 (m, 1H), 1.27 (8m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.9, 159.5, 143.1, 141.7, 133.3, 130.9, 130.6, 130.3, 128.4, 128.2, 128.1, 127.6, 126.7, 125.6, 114.1, 67.5, 55.2, 35.3, 28.1, 26.8, 24.1; ESI (*m*/*z*) 441 (M^++Na); HRMS calcd for [$C_{25}H_{27}NO_3S$] 421.1712, found 421.1709.

*4.5.9. 2-(1-(4-Methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)butylsulfinyl)-N-methylbenzamide (**2j**). Major diast.*: Yellowish oil, R_f=0.22 (AcOEt); FTIR (microscope) ν 3316, 1663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J*=7.7 Hz, 1H), 7.61 (m, 1H), 7.54 (m, 1H), 7.45 (m, 1H), 7.27 (m, 3H), 6.85 (d, *J*=8.3 Hz, 2H), 6.69 (br d, *J*=3.6 Hz, 1H), 6.17 (s, 2H), 4.32 (dd, *J*=11.6 and 3.9 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.75 (s, 6H), 2.94 (d, *J*=3.6 Hz, 3H), 2.41 (m, 2H), 2.10 (m, 1H),1.75 (m, 1H), 1.48 (m, 1H), 1.31 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.0, 159.6, 153.0, 131.8, 130.8, 130.6, 130.5, 130.4, 129.0, 128.2, 128.0, 127.6, 127.0, 114.1, 105.4, 67.8, 60.8, 56.0, 55.3, 35.7, 28.0, 26.9, 24.3; ESI (*m*/*z*) 550 (M^++K), 534 (M^++Na); HRMS calcd for [$C_{28}H_{33}NO_6S$] 511.2029, found 511.2031.

*4.5.10. N-Methyl-2-(4-phenyl-1-(4-(trifluoromethyl)phenyl)butylsulfinyl)benzamide (**2k**). Major diast.*: Yellowish oil, R_f=0.50 (AcOEt/hexane=70:30); FTIR (microscope) ν 3322, 1649 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J*=8.0 Hz, 1H), 7.67–7.05 (m, 5H), 6.90 (d, *J*=7.2 Hz, 2H), 6.81 (br s, 1H), 4.48 (dd, *J*=11.6 and 3.6 Hz, 1H), 2.94 (d, *J*=3.6 Hz, 3H), 2.43 (m, 2H), 2.14 (m, 1H), 1.68 (m, 1H), 1.41 (m, 1H), 1.26 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.6, 143.1, 141.3, 141.1, 132.5, 131.3, 130.7, 129.6, 128.4, 128.3, 128.2, 127.2, 126.6, 125.8, 125.6 (q, *J*=3.6 Hz), 67.6, 35.2, 27.9, 26.9, 23.4, CF_3 signal is obscured due to its low intensity; EIMS (*m*/*z*) 460 [M^++1, (2)], 276 (43), 165 (73), 104 (72), 91 (100); HRMS calcd for [$C_{25}H_{24}F_3NO_2S$] 459.1480, found 459.1481.

*4.5.11. 2-(4-Methoxyphenethylsulfinyl)-N-methylbenzamide (**2l**).* Yellowish oil, R_f=0.43 (AcOEt/hexane=70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (m, 1H), 7.65 (m, 2H), 7.50 (m, 1H), 7.12 (d, *J*=8.2 Hz, 2H), 6.90 (br s, 1H), 6.78 (d, *J*=8.2 Hz, 2H), 3.75 (s, 3H), 3.20–2.95 (m, 4H), 2.98 (d, *J*=4.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.8, 157.8, 143.0, 134.1, 133.2, 131.7, 131.2, 129.8, 128.4, 123.7, 114.2, 56.1, 55.8, 33.0, 26.7; HRMS calcd for [$C_{17}H_{19}NO_3S$] 317.1086, found 317.1089.

*4.5.12. N-Methyl-2-(4-phenylbutylsulfinyl)benzamide (**2m**).* Yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J*=8.1 Hz, 1H), 7.60 (m, 2H), 7.45 (m, 1H), 7.23 (m, 2H), 7.13 (m, 3H), 6.97 (br s, 1H), 3.31 (m,1H), 2.93 (d, *J*=4.6 Hz, 3H), 2.77 (m, 1H), 2.61 (m, 2H),

1.96 (m, 1H), 1.75 (m, 3H); MS (70 eV): *e*/*z* (%): 316 (4) [M^++1], 152 (75), 91 (100); HRMS calcd for [$C_{17}H_{19}NO_2S$] 301.1136, found 301.1139.

*4.5.13. 2-(1-(4-Methoxyphenyl)butan-2-ylsulfinyl)-N-methylbenzamide (**2n**).* Yellowish oil, inseparable mixture of diastereoisomers, R_f=0.63 (AcOEt/hexane=70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (m, 2H), 7.64 (m, 4H), 7.51 (m, 2H), 7.10 (m, 4H), 6.91 (br s, 2H), 6.80 (m, 4H), 3.77 (s, 3H), 3.72 (s, 3H), 3.22–2.98 (m, 6H), 2.96 (m, 6H), 1.63 (m, 4H), 0.98 (t, *J*=7.5 Hz, 3H), 0.92 (t, *J*=7.5 Hz, 3H); MS (70 eV): *e*/*z* (%): 346 (19) [M^++1], 84 (100).

*4.5.14. N-Methyl-2-(nonan-3-ylsulfinyl)benzamide (**2o**). One dist.*: Yellowish oil, R_f=0.41 (AcOEt); FTIR (film) 3298, 1651, 1550, 1000 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J*=7.5 Hz, 1H), 7.63 (m, 2H), 7.47 (m, 1H), 6.99 (br s, 1H), 3.00 (m, 1H), 2.96 (d, *J*=6.6 Hz, 3H), 1.78 (m, 2H), 1.47 (m, 2H), 1.31 (m, 11H), 0.71 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.8, 142.8, 131.1, 130.3, 128.6, 127.6, 126.9, 64.4, 31.7, 29.6, 29.4, 26.8, 26.6, 22.6, 17.9, 14.0, 11.4; MS (70 eV): *e*/*z* (%): 310 (17) [M^+], 183 (25), 84 (100). *Other diast.*: R_f=0.33 (AcOEt); FTIR (film) 3298, 1651, 1550, 1000 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J*=7.5 Hz, 1H), 7.63 (m, 2H), 7.48 (m, 1H), 6.81 (br s, 1H), 3.01 (m, 1H), 2.97 (d, *J*=4.9 Hz, 3H), 1.85 (m, 2H), 1.44 (m, 2H), 1.17 (t, *J*=7.5 Hz, 3H), 1.14 (m, 4H), 1.06 (m, 4H), 0.79 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.9, 143.4, 132.7, 131.0, 130.2, 127.3, 126.6, 64.2, 31.4, 29.0, 26.9, 23.9, 23.4, 22.4, 14.0, 11.3; MS (70 eV): *e*/*z* (%): 310 (17) [M^+], 183 (25), 84 (100); HRMS calcd for [$C_{17}H_{27}NO_2S$] 309.1762, found 309.1764.

4.6. General procedure for the synthesis of compounds 3

To a cooled solution of **2** (1 equiv) and TMP (3 equiv) in dry DCM (0.1 M) was added neat TFAA (5 equiv) at 0 °C and under Ar atmosphere. The temperature was left to reach rt and the reaction was stirred until complete disappearance of the starting material was monitored (TLC). The organic solvent was evaporated, the residue diluted with MeOH and water and an excess of solid K_2CO_3 was added until basic pH was reached. The mixture was extracted with AcOEt, the collected organic layers dried on anhydrous Na_2SO_4, filtered and the solvent evaporated in vacuo. The residue was purified by flash-chromatography.

*4.6.1. 4-Methyl-1-phenylpentan-1-ol ((−)-**3a**).* Yellowish oil, R_f=0.66 (AcOEt/hexane=70:30); $[\alpha]^{p23}$ −14.6 (*c* 0.6, $CHCl_3$, ee 45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 4.62 (t, *J*=6.8 Hz, 1H), 1.83–1.68 (m, 2H), 1.60–1.50 (m, 1H), 1.37–1.26 (m, 2H), 1.18–1.09 (m, 1H), 0.87 (d, *J*=3.0 Hz, 3H), 0.86 (d, *J*=3.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.9, 128.4, 127.5, 125.9, 75.0, 37.0, 34.9, 28.0, 22.6, 22.5; EIMS (*m*/*z*) 178 [M^++1, (100)].

*4.6.2. 1,4-Diphenylbutan-1-ol (**3e**).* Yellowish oil, R_f=0.60 (AcOEt/hexane=70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.03 (m, 10H), 4.45 (t, *J*=5.0 Hz, 1H), 2.75 (s, 1H), 2.51 (t, *J*=7.0 Hz, 2H), 1.75–1.44 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.5, 141.9, 128.1, 128.03, 127.97, 127.1, 125.6, 125.4, 74.0, 38.4, 35.6, 27.4; EIMS (*m*/*z*) 227 [M^++1, (100)]; HRMS calcd for [$C_{16}H_{18}O$] 226.1358, found 226.1360.

*4.6.3. 1-Phenylhex-5-en-1-ol (**3f**).* Yellowish oil, R_f=0.70 (AcOEt/hexane=60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H), 5.75 (m, 1H), 5.00–4.90 (m, 2H), 4.58 (m, 1H), 2.55 (br s, 1H), 1.32–2.07 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.9, 128.5, 128.4, 127.6, 114.6, 74.7, 65.3, 38.4, 33.5; EIMS (*m*/*z*) 176 [M^++1, (100)]; HRMS calcd for [$C_{12}H_{16}O$] 176.1201, found 176.1199.

*4.6.4. 1-(4-Methoxyphenyl)-4-phenylbutan-1-ol (**3i**).* Yellowish oil, R_f=0.64 (AcOEt/hexane=60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.13 (m, 7H), 6.87 (d, *J*=8.6 Hz, 2H), 4.63 (t, *J*=5.3 Hz, 1H), 3.80 (s, 3H), 2.62 (t, *J*=7.1 Hz, 2H), 1.90–1.57 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.5, 142.0, 136.8, 128.1, 127.9, 126.8, 125.4, 113.4, 73.4, 54.8, 38.2, 35.4, 27.3; EIMS (*m*/*z*) 257 [M^++1, (100)]; HRMS calcd for [$C_{17}H_{20}O_2$] 256.1463, found 256.1466.

*4.6.5. 4-Phenyl-1-(4-(trifluoromethyl)phenyl)butan-1-ol (**3k**).* Yellowish oil, R_f=0.68 (AcOEt/hexane=60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=8.0 Hz, 2H), 7.50–7.11 (m, 5H), 4.66 (br s, 1H), 2.60 (t, *J*=6.8 Hz, 2H), 2.31 (br s, 1H), 1.81–1.52 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.5, 141.9, 129.5 (q, *J*=32.3 Hz), 128.3, 126.0, 125.8, 125.2 (q, *J*=3.6 Hz), 125.1, 124.2 (q, *J*=272.2 Hz), 73.6, 38.5, 35.5, 27.2; EIMS (*m*/*z*) 294 [M^++1, (100)]; HRMS calcd for [$C_{17}H_{17}F_3O$] 294.1231, found 294.1234.

4.7. General procedure for the synthesis of compounds 4

To a cooled solution of **2** (1 equiv) and TMP (3 equiv) in dry DCM (0.1 M) was added neat oxalyl chloride (1.2 equiv) at −50 °C and under Ar atmosphere. After complete disappearance of the starting material (TLC), the reaction was quenched with 1 N HCl, the temperature raised to rt and the mixture extracted with DCM. The collected organic layers were dried on anhydrous Na_2SO_4, filtered and the solvent evaporated in vacuo. The residue was purified by flash-chromatography.

*4.7.1. (1-Chloro-4-methylpentyl)benzene ((−)-**4a**).* Yellowish oil; $[\alpha]^{p23}$ −66.7 (*c* 0.4, $CHCl_3$, ee >98%); FTIR (film) 1651, 1456, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.27 (m, 5H), 4.83 (dd, *J*=8.0 and 6.2 Hz, 1H), 2.10 (m, 2H), 1.59 (m, 1H), 1.40 (m, 1H), 1.20 (m, 1H), 0.90 (d, *J*=7.1 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.1, 128.6, 128.2, 126.9, 64.2, 38.0, 36.2, 27.7, 22.5, 22.4; MS (70 eV): *e*/*z* (%): 198 (7) [M^++2], 196 (21) [M^+], 125 (100), 91 (55); HRMS calcd for [$C_{12}H_{17}Cl$] 196.1019, found 196.1017.

*4.7.2. (1-Chloro-4-methylpentyl)benzene (**4e**).* Yellowish oil, R_f=0.67 (AcOEt/hexane=90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.11 (m, 10H), 4.84 (dd, *J*=8.0 and 6.5 Hz, 1H), 2.63 (t, *J*=7.7 Hz, 2H), 2.14 (m, 1H), 2.06 (m, 1H), 1.83 (m, 1H), 1.66 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.7, 128.6, 128.4, 128.2, 126.9, 125.9, 63.6, 39.4, 35.2, 28.7; HRMS calcd for [$C_{16}H_{17}Cl$] 244.1019, found 244.1018.

*4.7.3. (1-Chloro-4-methylpentyl)benzene (**4f**).* Yellowish oil, R_f=0.70 (AcOEt/hexane=90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.05 (m, 5H), 5.75 (m, 1H), 4.93 (m, 2H), 4.81 (br s, 1H), 2.03 (m, 4H), 1.59–1.41 (m 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.9, 138.1, 128.6, 128.3, 126.9, 115.1, 63.7, 39.4, 33.1, 29.7, 26.3; HRMS calcd for [$C_{12}H_{15}Cl$] 194.0862, found 194.0863.

4.8. General procedure for the synthesis of compounds 5

To a cooled solution of **2** (1 equiv) and TMP (3 equiv) in dry CH_3CN (0.1 M) was added neat Tf_2O (5 equiv) at −50 °C and under Ar atmosphere. After complete disappearance of the starting material (TLC), the reaction was quenched with 1 N HCl, the temperature raised to rt and the mixture extracted with AcOEt. The collected organic layers were dried on anhydrous Na_2SO_4, filtered and the solvent evaporated in vacuo. The residue was purified by flash-chromatography.

*4.8.1. N-(4-Methyl-1-phenylpentyl)acetamide (**5a**).* Yellowish oil, R_f=0.34 (AcOEt/hexane=60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 5H), 5.63 (br s, 1H), 4.91 (br s, 1H), 2.03 (s, 3H),1.78 (m, 2H), 1.54 (m, 1H), 1.98 (m, 1H), 1.06 (m, 1H), 0.80 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.5, 128.7, 127.3, 126.6, 53.8, 35.3, 34.0, 27.9,

23.5, 22.5, 22.4; MS (70 eV): *e*/*z* (%): 220 (21) [M^+], 106 (100); HRMS calcd for [$C_{14}H_{21}NO$] 219.1623, found 219.1621.

*4.8.2. N-(1-Phenylheptyl)acetamide (**5g**).* White solid, R_f=0.42 (AcOEt/hexane=50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.12 (m, 5H), 5.81 (br d, *J*=7.8 Hz, 1H), 4.87 (dd, *J*=8.0 Hz, both, 1H), 1.88 (s, 3H), 1.70 (m, 2H), 1.19 (m, 8H), 0.78 (t, *J*=8.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.1, 142.6, 128.6, 127.2, 126.6, 53.5, 36.2, 31.6, 29.0, 26.1, 23.3, 22.5, 13.9; MS (70 eV): *e*/*z* (%): 256 (100) [M^++Na]; HRMS calcd for [$C_{15}H_{23}NO$] 233.1780, found 233.1783.

*4.8.3. 1-N-(1-Phenylbutyl)acetamide (**5h**).* White solid, R_f=0.29 (AcOEt/hexane=50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.18 (m, 5H), 5.80 (br s, 1H), 4.97 (dd, *J*=8.0 Hz, both, 1H), 1.98 (s, 3H), 1.83–1.68 (m, 2H), 1.34 (m, 2H), 0.92 (t, *J*=8.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.7, 142.4, 128.8, 127.5, 126.7, 38.4, 29.8, 23.5, 19.6, 13.9; MS (70 eV): *e*/*z* (%): 214 (100) [M^++Na]; HRMS calcd for [$C_{12}H_{17}NO$] 191.1310, found 191.1313.

4.9. Enantioselective oxidation of sulfide 8a

To a suspension of (*R*,*R*)-DPED (8 mg, 0.038 mmol) in CCl_4 or CH_2Cl_2 (1.2 mL) were drop-wise added in sequence Ti(*i*-PrO)$_4$ (5 μL, 0.018 mmol) and H_2O (7 μL, 0.39 mmol). To the resulting homogeneous solution was added **8a** (100 mg, 0.38 mmol), stirring at rt for 15 min. The solution was then cooled at 0 °C and TBHP (70% in water, 100 μL, 0.77 mmol) added. The mixture was left stirring at the chosen temperature, then diluted with CH_2Cl_2, and dried over Na_2SO_4 for a few minutes. After filtration and evaporation of solvent the residue was immediately purified by column chromatography (EtOAc) isolating sulfoxide (−)-**1a**.

Enantiomeric purity of **1a** was determined by HPLC on chiral stationary phase Chiralcel OD (hexane/isopropanol 90:10; flow=1.0 mL/min; λ=254 nm).

4.10. X-ray crystallographic study

A colorless block shaped single crystal, of 0.2×0.3×0.6 mm, was obtained by crystallization from hexane/AcOEt. Crystal data are as follows: $C_{20}H_{25}NO_2S$, M_r=343.5; orthorhombic, space group *Pna2*(1), *a*=15.403(1), *b*=9.818(1), *c*=12.172(1), *V*=1840.7(3) 3, *Z*=4, D_c=1.239 g cm^{-3}, *F*(000)=736, μ (Cu Kα)=1.644 mm^{-1}. Diffraction data were collected on a Siemens P4 diffractometer with graphite monochromated (Cu Kα) radiation (λ=1.54179), using $\theta/2\theta$ scan technique. Unit cell parameters were determined using 44 reflections in the range 11.6≤θ≤47.4°. A total of 2074 reflections (1517unique, R_{int}=0.039) were collected at rt in the range 2.88°<θ<60° (completeness to theta of 95.8%). Three standard reflections, monitored every 97 reflections, showed no intensity decay during the data collection. The structure was solved by direct methods (SIR97) and refined by full-matrix least-squares on F^2 (SHELXL97) with anisotropic temperature factors for non-H atoms, for 226 parameters. The H-atoms, with the exception of H1N, which was freely refined, were placed geometrically and treated as riding with isotropic temperature factors (1.2 or 1.5 times the temperature factors of the attached atom). The final stage converged to *R*=0.0476 for 1398 observed reflections, with $I\geq 2\sigma(I)$, and *R*=0.0520 for all unique reflections after merging. Goodness of fit=1.059. The final difference map showed a maximum and a minimum residual peaks of 0.488 and −0.327 e^{-3}, respectively. CCDC deposition number: 245649.

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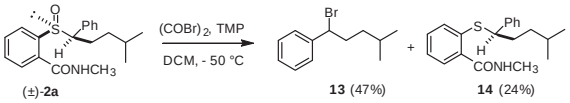

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