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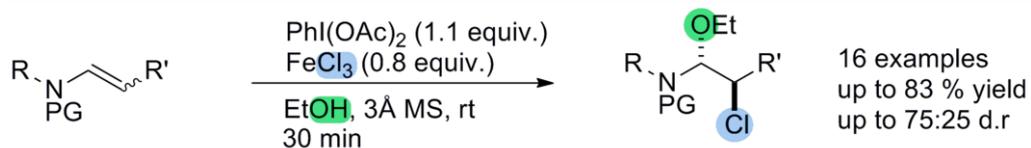
Graphical Abstract

Iodine(III)-mediated ethoxychlorination of enamides with iron(III) chloride

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Iodine(III)-mediated ethoxychlorination of enamides with iron(III) chloride

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ABSTRACT

The combination of PIDA and iron(III) chloride in ethanol allows the efficient regioselective ethoxychlorination of a broad range of enamides. Preliminary studies tend to rule out the involvement of free radical species.

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Keywords:

Hypervalent iodine

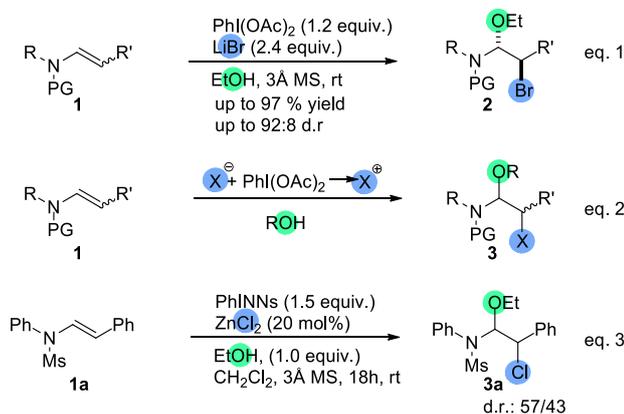
Umpolung

Chlorination

Enamides

1. Introduction

As the need for greener chemical processes increases substantially, hypervalent iodine derivatives have emerged as highly valuable tools to promote a broad range of transformations.¹ Their oxidative nature combined with their particular structure confer them with unique properties, enabling them to be used as surrogates for toxic and/or difficult-to-handle reactants. In this line of thought, I(III)-based compounds such as PIDA (PhenylIodine DiAcetate) have been shown to promote the *umpolung* of halide salts to generate electrophilic halides that can react with carbonyls,² electron-rich arenes,³ olefins⁴ or aliphatic CH bonds.⁵ For our part we have recently demonstrated that the use of PIDA in conjunction with bromide salts triggers the ethoxybromination of a broad range of enamide derivatives (**1**) to yield α -bromo hemiaminals **2** (Scheme 1, eq. 1).



Scheme 1. Initial endeavor

The latter could in turn be used for a variety of transformations.⁶ Consequently, in order to broaden the scope of this strategy, we turned our attention towards the feasibility of an alkoxyhalogenation of the same enamides, using the appropriate source of halides (eq. 2). The first hint towards the application of this strategy to chlorides came during our studies on the copper-catalyzed alkoxyamination of enamides with iminoiodanes.⁷ When enamide **1a** was reacted with an iminoiodane in the presence of zinc(II) chloride instead of a copper catalyst, the main product that was isolated was the ethoxychlorinated adduct **3a** (eq. 3). In this case, it appears that the iminoiodane does not react as a nitrene precursor,⁸ but rather as a chloride-umpolung promoter.⁹ Here, an electrophilic chlorinating agent is generated *in situ* and then reacts with the enamide yielding an iminium, which is trapped by ethanol. The generalization of this process¹⁰ would represent a mild and attractive alternative to the use of chlorine, *t*-butylhypochlorite or *N*-chlorosuccinimide previously employed to promote the oxychlorination of enamide derivatives.¹¹ The α -chloro hemiaminal moiety could grant access to other functionalities through various transformations¹² and is also found in bioactive natural products such as Synoxazolidinones A and C that possess antibacterial and anticancer activities (Figure 1).¹³

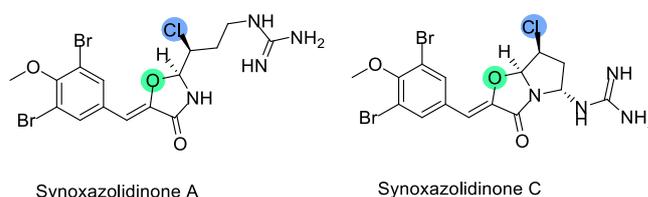
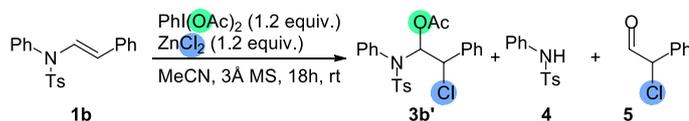


Fig. 1. Synoxazolidinones

2. Results and Discussion

In order to stream down the reaction partners to the essential PIDA and zinc(II) chloride were used as the sole reactants. Our assumption being that an electrophilic chlorinating agent would be generated *in situ* and react with the enamide to yield an iminium, which would then be trapped by the acetate arising from the *umpolung* step. Indeed, under these reaction conditions, enamide **1b** did yield the expected acetoxychlorinated adduct **3b'** along with significant amount of amine **4** and chlorinated aldehyde **5** (Scheme 2).



Scheme 2. Attempt of an acetoxychlorination

Considering that these by-products come from the hydrolysis of the poorly stable acetoxy-hemiaminal we decided to focus on the formation of the more stable ethoxychlorinated adducts. Therefore, based on our previous work on the ethoxybromination,⁶ we chose to conduct the reaction in ethanol and began screening various chloride salts. Furthermore, since the *umpolung* presumably proceeds through ligand exchanges around the hypervalent iodine (*vide infra* for more mechanistic details), we chose to set a Cl:OAc ratio of 1:1 for each reaction condition tested. Thus, enamide **1b** was first reacted with 2.1 equiv. of PIDA and 4.2 equiv. of LiCl in ethanol at rt, which led to the ethoxychlorination product **3b** in 80% yield along with some undesired hydrolysis by-products (Table 1, entry 1). Other alkali chlorides and copper(I) chloride proved less efficient, even at higher temperature, probably because of their lower solubility (entries 2-4). We then switched back to the more Lewis-acidic zinc(II) chloride which efficiently promoted the reaction even when 1.2 equiv. of reactants were used, albeit with a lower d.r. (entries 5,6).

Table 1. Optimisation of the enamide ethoxychlorination^a

entry	MCl _n	Y	X	t (h)	d.r.	yield (%)
1	LiCl	4.2	2.1	3	65/35	80 ^b
2	NaCl	4	2	5	70/30	55 ^c
3	KCl	4	2	5	67/33	n. d. ^{c,d}
4	CuCl	2.4	1.2	96	n. d.	traces
5	ZnCl ₂	2	2	2.5	53/47	98
6	ZnCl ₂	1.2	1.2	2	57/43	n. d. ^d
7	FeCl ₃	0.8	1.1	0.5	75/25	83
8	FeCl ₃	0.8	1.2	1.5	72/28	83 ^c

^a Isolated yields after chromatography on silica gel unless otherwise mentioned; d. r. determined from by analysis of the crude ¹H NMR.

^b Contaminated with aldehyde **5** and amine **4** resulting from the hydrolysis of **3b**.

^c Reaction ran at 40 °C.

^d 80% Conversion, measured by analysis of the crude ¹H NMR.

^e Reaction ran at 0 °C; n.d.: not determined.

Finally the best option was to use 0.8 equiv. of iron(III) chloride to provide a rapid and highly efficient reaction with a slightly increased diastereoselectivity compared to ZnCl₂ (entry 7). Lowering the temperature to 0 °C led to a longer reaction time without any enhancement of the selectivity (entry 8).

The scope of the reaction was then explored using these optimised conditions; results are summarised in Table 2. For styrene-type enamides (**1a-f**) various combinations of sulfonyl protecting groups (mesyl, tosyl, benzenesulfonyl and nosyl) and alkyl and/or aryl groups (phenyl, methyl and allyl) on the nitrogen atom were tolerated to afford the desired ethoxy-chlorinated adduct with good yields and moderate selectivities (53%-83% yield and 55/45 to 75/25 d.r., entries 1-6). Both amides and carbamates were also compatible with the reaction conditions for aniline-derived starting material (**1g,i**, entries 7, 9), and, to a lesser extent, for benzylamine-derived enamides (**1h,j**, entries 8,10). In both cases the carbamate appeared to be more robust than the acetamide and it is noteworthy that the same starting compounds (**1g,j**) mostly led to complex mixtures when submitted to the related ethoxybromination conditions.⁶ The behaviour of amino-acrylates was also studied. The ethoxy-chlorination proceeds smoothly with both *E* and *Z* isomers (**1k-n**, 75%-86% yield, entries 11-14). The d.r. was slightly higher starting from *Z* compounds, which is in contrast to what was observed for the ethoxybromination reaction.⁶ Finally, the corresponding unprotected primary alcohols (**1o-p**) were also tested but reacted poorly (entries 15,16).

Table 2. Substrate scope for the enamide ethoxychlorination

entry	S.M.	R	PG	R'	d.r. ^a	yield (%) ^b
1	1a	Ph	Ms	Ph (<i>E</i>)	64/36	56
2	1b	Ph	Ts	Ph (<i>E</i>)	75/25	83
3	1c	Ph	PhSO ₂	Ph (<i>E</i>)	69/31	60
4	1d	Ph	Ns	Ph (<i>E</i>)	56/44	63
5	1e	Allyl	Ts	Ph (<i>E</i>)	55/45	53
6	1f	Me	PhSO ₂	Ph (<i>E</i>)	57/43	59
7	1g	Ph	Ac	Ph (<i>E</i>)	57/43	55
8	1h	Bn	Ac	Ph (<i>E</i>)	n.d.	c.m.
9	1i	Ph	Boc	Ph (<i>E</i>)	64/36	72
10	1j	Bn	Boc	Ph (<i>E</i>)	70/30	46
11	1k	Bn	Ts	CO ₂ Me (<i>E</i>)	52/48	86
12	1l	Allyl	Ts	CO ₂ Me (<i>E</i>)	58/42	82
13	1m	Bn	Ts	CO ₂ Me (<i>Z</i>)	70/30	75
14	1n	Allyl	Ts	CO ₂ Me (<i>Z</i>)	63/37	75
15	1o	Bn	Ts	CH ₂ OH (<i>E</i>)	70/30	36
16	1p	Allyl	Ts	CH ₂ OH (<i>E</i>)	n.d.	27

^a Determined by analysis of the crude ¹H NMR.

^b Isolated yields; n.d.: not determined; c.m.: complex mixture.

However, isolation and crystallisation of the major diastereoisomer of **3p** was possible and allowed determination of its relative configuration by X-ray analysis (Figure 2).¹⁴

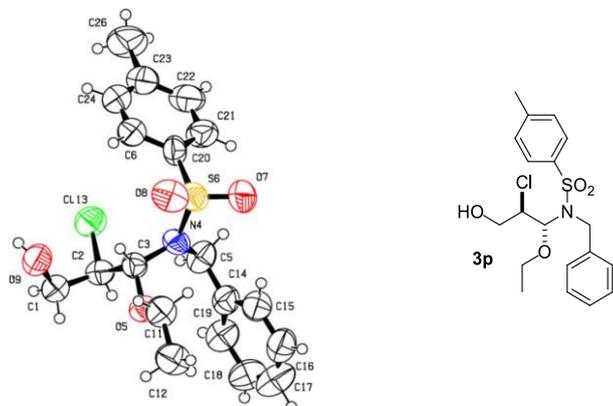
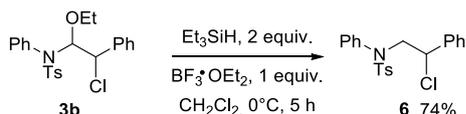


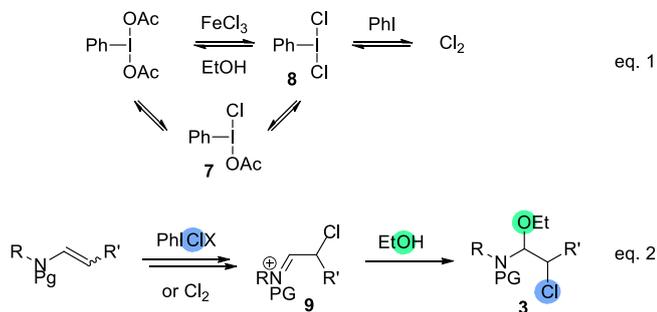
Fig. 2. X-ray structure of the major diastereoisomer of **3p**

Hemiaminals of type **3** are potentially synthetically versatile substrates. Thus, activation of the hemiaminal moiety by a Lewis acid generates the corresponding iminium that can be trapped by a nucleophile. For example, using boron trifluoride etherate and triethylsilane, the corresponding α -chloro amine **6** was obtained with a 74 % yield (Scheme 2).



Scheme 2. Reduction of the hemiaminal

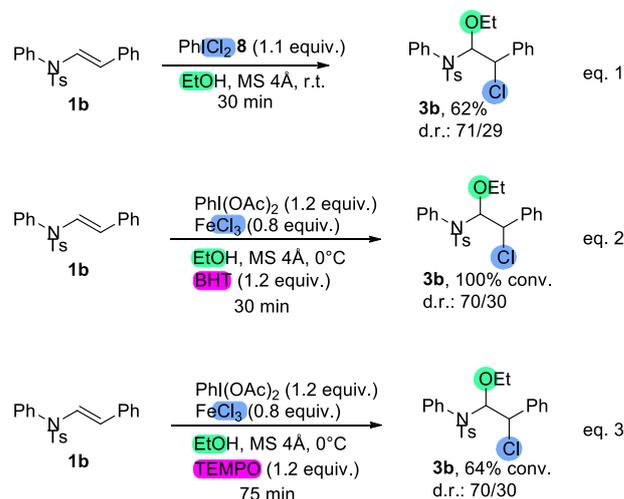
From a mechanistic point of view it can be assumed that PIDA undergoes a series of equilibrated ligand exchanges,¹⁵ eventually leading to dichloride,¹⁶ presumably through the mixed species **7** and dichloriodobenzene **8**, all of which could constitute the actual electrophilic species (Scheme 3, eq. 1). Chlorination of the enamide would then occur to give iminium **9** which would then be trapped by ethanol to afford the ethoxychlorination product **3** (Scheme 3, eq. 2). The intermediacy of this iminium species could account for the exclusive regiochemistry of the reaction as well as for its moderate diastereoselectivity.



Scheme 3. Mechanism proposal

In order to verify these assumptions, a series of control experiments was carried out. First, enamide **1b** was reacted with dichloriodobenzene **7**¹⁷ instead of the PIDA/ FeCl_3 combination in ethanol; ethoxychlorination product **3b** was indeed obtained with similar, albeit slightly lower, yield and diastereoselectivity (Scheme 4, eq. 1).¹⁸ Although this does not prove unequivocally that PhICl_2 is the actual chlorinating agent, it nonetheless shows

that the combination of PIDA and FeCl_3 can act as a suitable surrogate for it. As a free radical manifold has previously been evoked for transformations involving chlorinated hypervalent iodine (III) reagents, the reaction was carried out in the presence of BHT (eq. 2) and TEMPO (eq. 3). In the former case, no change of reactivity was observed and, in the latter case, the reaction was somewhat inhibited (unreacted starting material was observed). This inhibition could be due to the possible reaction between TEMPO and PIDA, consuming the latter.¹⁹ Nevertheless, no adduct arising from the trapping of a free radical intermediate by TEMPO was detected.²⁰ The sum of these observations leads us to conclude that an ionic manifold is at play in this transformation.²¹



Scheme 4. Control experiments

3. Conclusions

In conclusion, we have developed a mild and efficient ethoxychlorination of enamides, mediated by PIDA and iron(III) chloride. Preliminary mechanistic investigations suggest that this reaction proceeds via the intermediacy of a chlorinated hypervalent iodine(III) reagent generated *in situ* and reacting through an ionic manifold. Further studies on the exact nature of the reactive species as well as extension of this process for the selective chlorination of other compounds are currently underway in our laboratory and will be reported in due course.

4. Experimental section

4.1. General considerations

Melting points were measured in capillary tubes on a Büchi B-540 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer. Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on Bruker spectrometers: Avance 300 MHz (QNP - ^{13}C , ^{31}P , ^{19}F - probe or Dual ^{13}C probe) and Avance 500 MHz (BB0 - ATM probe or BBI - ATM probe). Carbon NMR (^{13}C) spectra were recorded at 125 or 75 MHz, using a Broadband decoupled mode with the multiplicities obtained using a DEPT sequence. NMR experiments were carried out in deuteriochloroform (CDCl_3), for which chemical shifts (δ) are reported in parts per million (ppm) with reference to CDCl_3 (^1H : 7.26; ^{13}C : 77.16) and deuterobenzene (C_6D_6), for which chemical shifts (δ) are reported in parts per million (ppm) with reference to C_6D_6 (^1H : 7.15; ^{13}C : 128.62). The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad. Coupling constants (J) are reported in Hertz (Hz). Mass spectra were obtained either with a

LCT (Micromass) instrument using electrospray ionisation (ESI), or from a Time of Flight analyser (ESI-MS) for the high resolution mass spectra (HRMS). Thin-layer chromatography was performed on silica gel 60 F₂₅₄ on aluminium plates (Merck) and visualised under a UVP Mineralight UVLS-28 lamp (254 nm) and with 4-anisaldehyde and phosphomolybdic acid stains in ethanol. Flash chromatography was conducted using Merck silica gel 60 (40-63 µm) at medium pressure (300 mbar). All reagents were obtained from commercial suppliers unless otherwise stated.

Where necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under nitrogen. Starting enamides **1a-p** were prepared according to literature procedures.²²

4.2 General Procedure: Ethoxychlorination Reaction:

To a suspension of enamide (1 equiv.), FeCl₃ (0.8 equiv.) and 3Å molecular sieves in EtOH at rt was added PhI(OAc)₂ (1.1 equiv.). After 30 mins at rt, the reaction mixture was diluted with EtOAc, filtered over alumina (EtOAc) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

4.2.1 *N*-(2-chloro-1-ethoxy-2-phenylethyl)-*N*-phenyl-methanesulfonamide (**3a**)

Analysis of the crude material by ¹H NMR indicated the formation of two diastereoisomers in a 64:36 ratio. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc gradient: 100/0 to 90/10) to afford 35 mg (56%) of the desired product **3a** as a colourless oil; C₁₇H₂₀ClNO₃S; MW 353.86 g.mol⁻¹. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 71(A)/29(B) ratio. ¹H NMR (CDCl₃, 500 MHz): δ(ppm) = 7.56-7.31 (m, 8HA+10HB, Ar), 7.02 (d, *J* = 7.5 Hz, 2H, Ar, A), 5.96 (d, *J* = 9.6 Hz, 1H, NCH, A), 5.66 (d, *J* = 9.5 Hz, 1H, NCH, B), 4.52 (d, *J* = 9.6 Hz, 1H, CHCl, A), 4.37 (d, *J* = 9.5 Hz, 1H, CHCl, B), 4.19-4.11 (m, 1H, CH₂, A), 4.04-3.98 (m, 1H, CH₂, A), 3.81 (dq, *J* = 9.7, 7.0 Hz, 1H, CH₂, B), 3.32 (dq, *J* = 9.7, 7.0 Hz, 1H, CH₂, B), 3.14 (s, 3H, SO₂CH₃, B), 2.51 (s, 3H, SO₂CH₃, A), 1.41 (t, *J* = 7.0 Hz, CH₃, A), 0.89 (t, *J* = 7.0 Hz, CH₃, B); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) = 138.0 (C, B), 137.8 (C, A), 134.5 (C, A), 134.1 (C, B), 132.0, 131.6, 129.7, 129.6, 129.3, 129.2, 129.0, 128.7, 128.5, 128.1, 91.1 (NCH, B), 90.6 (NCH, A), 66.8 (CH₂, A), 65.3 (CH₂, B), 63.0 (CHCl, B), 62.2 (CHCl, A), 40.4 (SO₂-CH₃, B), 39.6 (SO₂-CH₃, A), 15.1 (CH₃, A), 14.5 (CH₃, B); HRMS: *m/z* [M-OEt]⁺ calcd for C₁₅H₁₅³⁵ClNO₂S: 308.0512 found 308.0487; IR: ν = 2977, 1492, 1334, 1154, 695 cm⁻¹.

4.2.2 *N*-(2-chloro-1-ethoxy-2-phenylethyl)-*N*-phenyl-4-toluene-sulfonamide (**3b**)

Analysis of the crude material by ¹H NMR indicated the formation of two diastereoisomers in a 75:25 ratio. The residue was purified by flash chromatography (petroleum ether/EtOAc gradient: 100/0 to 95/05) to afford 87 mg (83%) of the desired product **3b** as a colourless oil; C₂₃H₂₄ClNO₃S; MW 429.96 g.mol⁻¹. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 67(A)/33 (B) ratio. ¹H NMR (CDCl₃, 500 MHz): δ(ppm) = 7.61 (d, *J* = 8.4 Hz, 2H, Ar, B), 7.42-7.28 (m, 20H, Ar), 7.27-7.16 (m, 11H, Ar), 7.08-6.98 (m, 8H, Ar), 6.71 (d, *J* = 7.8 Hz, 2H, Ar, A), 6.04 (d, *J* = 9.4 Hz, 1H, NCH, A), 5.81 (d, *J* = 9.4 Hz, 1H, NCH, B), 4.49 (d, *J* = 9.4 Hz, 1H, CHCl, A), 4.22 (d, *J* = 9.4 Hz, 1H, CHCl, B), 4.10 (dq, *J* = 9.3, 7.0 Hz, 1H, CH₂, A), 3.96 (dq, *J* = 9.3, 7.0 Hz, 1H, CH₂, A), 3.83 (dq, *J* = 9.6, 7.0 Hz, 1H, CH₂, B), 3.35 (dq, *J* = 9.6, 7.0 Hz, 1H, CH₂, B), 2.42 (s, CH₃, B), 2.33 (s, CH₃, A), 1.35 (t, *J* = 7.0 Hz, CH₃, A), 0.87 (t, *J* = 7.0 Hz, CH₃, B); ¹³C

NMR (CDCl₃, 75 MHz): δ(ppm) = 143.7 (C, B), 143.6 (C, A), 138.4 (C, B), 137.9 (C, A), 136.8 (C, B), 136.2 (C, A), 134.4 (C, B), 133.8 (C, A), 133.6 (CH, B), 132.4 (CH, A), 129.3, 129.2, 129.1, 129.0, 128.9, 128.9, 128.6, 128.5, 128.1, 91.0 (CHN, B), 90.2 (CHN, A), 66.7 (CH₂, A), 65.4 (CH₂, B), 63.3 (CHCl, A), 61.6 (CHCl, B), 21.7 (CH₃, B), 21.6 (CH₃, A), 15.0 (CH₃, A), 14.5 (CH₃, B); HRMS: *m/z* [M-OEt]⁺ calcd for C₂₁H₁₉NO₂S³⁵Cl: 384.0825 found 384.0558; IR: 2973, 1597, 1493, 1345, 1164, 696 cm⁻¹.

4.2.3 *N*-(2-chloro-1-ethoxy-2-phenylethyl)-*N*-phenyl-benzene-sulfonamide (**3c**)

Analysis of the crude material by ¹H NMR indicated the formation of two diastereoisomers in a 69:31 ratio. The residue was purified by flash chromatography (petroleum ether/EtOAc gradient: 100/0 to 96/4) to afford 37 mg (60%) of the desired product **3c** as a colourless oil; C₂₂H₂₂ClNO₃S; MW 415.93 g.mol⁻¹. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 70(A)/30(B) ratio. ¹H NMR (CDCl₃, 300 MHz): δ(ppm) = 7.66 (d, *J* = 8.3 Hz, 2H, Ar, B), 7.48 (t, *J* = 7.4 Hz, 1H, Ar, B), 7.38-7.09 (m, 13HA+12HB, Ar), 6.63 (d, *J* = 8.5 Hz, 2H, Ar, A), 5.96 (d, *J* = 9.4 Hz, 1H, NCH, A), 5.74 (d, *J* = 9.5 Hz, 1H, NCH, B), 4.43 (d, *J* = 9.4 Hz, 1H, CHCl, A), 4.15 (d, *J* = 9.5 Hz, 1H, CHCl, B), 3.99 (dq, *J* = 9.3, 7.1 Hz, 1H, CH₂, A), 3.89 (dq, *J* = 9.3, 7.1 Hz, 1H, CH₂, A), 3.75 (dq, *J* = 9.6, 7.1 Hz, 1H, CH₂, B), 3.27 (dq, *J* = 9.6, 7.1 Hz, 1H, CH₂, B), 1.27 (t, *J* = 7.0 Hz, CH₃, A), 0.80 (t, *J* = 7.0 Hz, CH₃, B); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) = 138.0 (C, B), 137.8 (C, A), 134.5 (C, A), 134.1 (C, B), 132.8, 132.7, 132.4, 132.2, 129.2, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 128.5, 128.4, 128.3, 128.0, 127.3, 91.0 (NCH, B), 90.3 (NCH, A), 66.7 (CH₂, A), 65.4 (CH₂, B), 63.2 (CHCl, A), 61.5 (CHCl, B), 14.9 (CH₃, A), 14.4 (CH₃, B); HRMS: *m/z* [M-OEt]⁺ calcd for C₂₀H₁₇³⁵ClNO₂S: 370.0669 found 370.0668; IR: ν = 2977, 1595, 1492, 1448, 1329, 1163, 693 cm⁻¹.

4.2.4 *N*-(2-chloro-1-ethoxy-2-phenylethyl)-*N*-phenyl-4-nitrobenzenesulfonamide (**3d**)

Analysis of the crude material by ¹H NMR indicated the formation of two diastereoisomers in a 56:44 ratio. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc gradient: 100/0 to 96/04) to afford 38 mg (63 %) of the desired product **3d** as a light pink powder; C₂₂H₂₁ClN₂O₅S; MW 460.93 g.mol⁻¹. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 55(A)/45 (B) ratio. ¹H NMR (CDCl₃, 300 MHz): δ(ppm) = 8.21 (d, *J* = 8.9 Hz, Ar, 2H, B), 7.96 (d, *J* = 8.9 Hz, 2H, Ar, A), 7.84 (d, *J* = 8.9 Hz, 2H, Ar, B), 7.39-7.12 (m, 20 H, Ar, 10 HA+10 HB), 7.63 (d, *J* = 8.5 Hz, 2H, Ar, A), 5.93 (d, *J* = 9.5 Hz, 1H, NCH, A), 5.72 (d, *J* = 9.5 Hz, 1H, NCH, B), 4.46 (d, *J* = 9.5 Hz, 1H, CHCl, A), 4.18 (d, *J* = 9.5 Hz, 1H, CHCl, B), 4.09-3.97 (m, 1H, CH₂, A), 3.94-3.86 (m, 1H, CH₂, A), 3.77 (dq, *J* = 9.6, 7.0 Hz, 1H, CH₂, B), 3.29 (dq, *J* = 9.6, 7.0 Hz, 1H, CH₂, B), 1.30 (t, *J* = 7.0 Hz, 3H, CH₃, A), 0.82 (t, *J* = 7.0 Hz, 3H, CH₃, B); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) = 145.2 (C), 144.7 (C), 137.8 (2C), 137.8 (2C), 133.8 (C), 133.0 (C), 132.3, 132.1, 129.9, 129.7, 129.6, 129.4, 129.3, 129.3, 129.1, 128.9, 128.8, 128.6, 128.1, 123.8, 123.6, 91.6 (CHN, A), 91.1 (CHN, B), 67.0 (CH₂, A), 65.6 (CH₂, B), 62.9 (CHCl, A), 61.8 (CHCl, B), 15.0 (CH₃, A), 14.4 (CH₃, B); HRMS: *m/z* [M-OEt]⁺ calcd for C₂₀H₁₆³⁵ClN₂O₄S: 415.0519 found 415.0518; IR: 2979, 1530, 1491, 1348, 1167, 696 cm⁻¹.

4.2.5 *N*-allyl-*N*-(2-chloro-1-ethoxy-2-phenylethyl)-4-toluene-sulfonamide (**3e**)

Analysis of the crude material by ¹H NMR indicated the formation of two diastereoisomers in a 55:45 ratio. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc:

96/04) to afford 33 mg (53 %) of the desired product **3e** as a colourless oil; $C_{20}H_{24}ClNO_3S$; MW 393.93 g.mol⁻¹. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 55(A)/45(B) ratio. ¹H NMR (CDCl₃, 300 MHz): δ(ppm) = 7.84 (d, *J* = 8.3 Hz, Ar, 2H, A), 7.44-7.28 (m, 12H, Ar, 3HA+9HB), 7.11-7.04 (m, 4H, Ar, A), 5.83-5.70 (m, 1H, CH=CH₂, B), 5.59 (d, *J* = 8.4 Hz, 1H, NCH, A), 5.46 (d, *J* = 8.7 Hz, 1H, NCH, B), 5.40-5.27 (m, 1H, CH=CH₂, A), 5.21-4.98 (m, 4H, CH=CH₂, 2HA+2HB), 4.96 (d, *J* = 8.4 Hz, 1H, CHCl, A), 4.81 (d, *J* = 8.7 Hz, 1H, CHCl, B), 3.95-3.73 (m, 4H, CH₂N, 2HA+2HB), 3.71-3.45 (m, 3H, CH₂CH₃, 2HA+1HB), 3.19 (dq, *J* = 9.6, 7.0 Hz, 1H, CH₂CH₃, B), 2.43 (s, 3H, CH₃, B), 2.36 (s, 3H, CH₃, A), 1.25 (t, *J* = 7.0 Hz, 3H, CH₃, A), 0.87 (t, *J* = 7.0 Hz, 3H, CH₃, B); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) = 143.7 (C), 143.6 (C), 138.6 (C), 138.1 (C), 137.5 (C), 136.8 (C), 135.3 (=CH, B), 134.8 (=CH, A), 129.5, 129.4, 129.0, 128.8, 128.6, 128.5, 128.2, 127.9, 118.2 (=CH₂, A), 117.4 (=CH₂, B), 90.3 (NCH, B), 89.4 (NCH, A), 65.3 (OCH₂, A), 64.9 (OCH₂, B), 63.5 (CHCl, A), 61.9 (CHCl, B), 45.8 (NCH₂, B), 45.4 (NCH₂, A), 21.7 (CH₃, A), 21.6 (CH₃, B), 14.7 (CH₂CH₃, B), 14.4 (CH₂CH₃, A); HRMS: *m/z* [M-OEt]⁺ calcd for C₁₈H₁₉³⁵ClNO₂S: 308.0825 found 348.0827; IR: 2978, 1455, 1343, 1157, 663 cm⁻¹.

4.2.6 *N*-(2-chloro-1-ethoxy-2-phenylethyl)-*N*-methyl-benzene-sulfonamide (**3f**)

Analysis of the crude material by ¹H NMR indicated the formation of two diastereoisomers in a 57:43 ratio. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc gradient from 100 to 91/09) to afford 38 mg (59 %) of the desired product **3f** as a colourless oil; C₁₇H₂₀ClNO₃S; MW 353.83 g.mol⁻¹. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 63(A)/37(B) ratio, therefore precise attribution and characterisation of the minor diastereoisomer B is only done when possible. ¹H NMR (CDCl₃, 300 MHz): δ(ppm) = 7.93 (d, *J* = 8.1 Hz, 2H, Ar, B), 7.59-7.15 (m, 18H, Ar, 10HA+8HB), 5.58 (d, *J* = 8.1 Hz, 1H, NCH, A), 5.43 (d, *J* = 8.2 Hz, 1H, NCH, B), 4.80 (d, *J* = 8.1 Hz, 1H, CHCl, A), 4.72 (d, *J* = 8.2 Hz, 1H, CHCl, B), 3.73-3.53 (m, 2H, CH₂, A), 3.45 (dq, *J* = 9.7, 7.0 Hz, 1H, CH₂, B), 3.21 (dq, *J* = 9.7, 7.0 Hz, 1H, CH₂, B), 2.70 (s, 3H, CH₃, B), 2.59 (s, 3H, CH₃, A), 1.26 (t, *J* = 7.0 Hz, 3H, CH₃, A), 0.91 (t, *J* = 7.0 Hz, 3H, CH₃, B); ¹³C NMR (CDCl₃, 75 MHz): δ(ppm) = 139.6 (C), 138.8 (C), 138.9 (C), 138.0 (C), 132.8 (CH, B), 132.6 (CH, A), 129.3, 129.0, 128.9, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 127.4, 89.5 (NCH, B), 88.9 (NCH, A), 65.1 (CH₂, A), 64.9 (CH₂, B), 63.4 (CHCl, A), 61.5 (CHCl, B), 27.8 (CH₃, A), 27.2 (CH₃, B), 14.7 (CH₂CH₃, A), 14.5 (CH₂CH₃, B); HRMS: *m/z* [M-OEt]⁺ calcd for C₁₅H₁₅³⁵ClNO₂S: 308.0508 found 308.0512; IR: 2977, 1586, 1447, 1323, 1163, 1073, 688 cm⁻¹.

4.2.7 *N*-(2-chloro-1-ethoxy-2-phenylethyl)-*N*-phenylacetamide (**3g**)

Analysis of the crude material by ¹H NMR indicated the formation of two diastereoisomers in a 57/43 ratio. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc 95/5) to afford 37 mg (55%) of the desired product **3g** as a colourless oil; C₁₈H₂₀ClNO₂; MW 317.12 g.mol⁻¹. The product decomposed in CDCl₃. ¹H NMR (C₆D₆, 300 MHz): δ(ppm) = 7.22 (d, *J* = 7.2 Hz, 2H, Ar, A), 7.12-6.90 (m, 18H, Ar, 8HA+10HB), 6.75 (d, *J* = 9.8 Hz, 1H, NCH, A), 6.62-6.56 (m, 1H, NCH, B), 4.55 (d, *J* = 9.6 Hz, 1H, CHCl, B), 4.39 (d, *J* = 9.8 Hz, 1H, CHCl, A), 3.86-3.75 (m, 2H, CH₂, B), 3.52 (dq, *J* = 9.8, 7.1 Hz, 1H, CH₂, A), 3.26 (dq, *J* = 9.8, 7.1 Hz, 1H, CH₂, A), 1.78 (m, 3H, CH₃, A), 1.43 (m, 3H, CH₃, B), 1.22 (t, *J* = 7.1 Hz, 3H, CH₂CH₃, A), 0.72 (t, *J* = 7.1 Hz, 3H, CH₂CH₃, B); ¹³C NMR (C₆D₆, 75 MHz): δ(ppm) = 171.7 (C=O), 171.1 (C=O), 139.5 (C), 139.0 (C),

138.9 (C), 131.3 (C), 130.7, 129.9, 129.5, 129.4, 129.1, 129.0, 128.8, 86.1 (NCH), 85.3 (NCH), 66.1 (OCH₂), 65.8 (OCH₂), 64.1 (CHCl), 61.3 (CHCl), 23.8 (CH₃), 23.2 (CH₃), 15.7 (CH₂CH₃), 15.3 (CH₂CH₃); HR/MS: *m/z* [M-OEt-H]⁺ calcd for C₁₆H₁₅³⁵ClNO: 272.0842 found 272.0803; IR: 2977, 1670, 1596, 1369, 1159, 1073, 688 cm⁻¹.

4.2.8 *tert*-Butyl-*N*-(2-chloro-1-ethoxy-2-phenylethyl)-*N*-phenyl-carbamate (**3i**)

Analysis of the crude material by ¹H NMR indicated the formation of two diastereoisomers in a 64/36 ratio. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc 95/5) to afford 70 mg (72%) of the desired product **3i** as a colourless oil; C₂₁H₂₆ClNO₃; MW 375.15 g.mol⁻¹. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 62(A)/38(B) ratio. ¹H NMR (CDCl₃, 300 MHz): δ(ppm) = 7.40-7.17 (m, 12H, Ar, A+B), 7.22-7.15 (m, 6H, Ar, A+B), 6.74-6.66 (m, 2H, Ar, A), 6.27-6.15 (m, 1H, NCH, A), 6.00-5.92 (m, 1H, NCH, B), 4.46 (d, *J* = 9.6 Hz, 1H, CHCl, A), 4.34 (d, *J* = 9.7 Hz, 1H, CHCl, B), 4.01 (dq, *J* = 9.6, 7.0 Hz, 1H, CH₂, A), 4.01 (dq, *J* = 9.6, 7.1 Hz, 1H, CH₂, A), 3.73 (dq, *J* = 9.7, 7.0 Hz, 1H, CH₂, B), 3.40 (dq, *J* = 9.7, 7.0 Hz, 1H, CH₂, B), 1.57-1.23 (m, 21H, 9H, 3CH₃, A + 9H, 3CH₃, B + 3H, CH₂CH₃, A), 0.94 (t, *J* = 7.0 Hz, 3H, CH₂CH₃, B); ¹³C NMR (C₆D₆, 75 MHz): δ(ppm) = 139.8 (C), 139.0 (C), 138.6 (C), 131.0, 130.2, 129.7, 129.5, 129.4 (C), 129.2, 129.1, 129.0, 128.2, 127.6, 89.4 (NCH, B), 88.9 (NCH, A), 81.1 (C(CH₃)₃, A + B), 65.8 (OCH₂, A), 65.5 (OCH₂, B), 64.0 (CHCl, A), 62.5 (CHCl, B), 28.8 (3CH₃, B), 28.6 (3CH₃, A), 15.7 (CH₂CH₃, A), 15.3 (CH₂CH₃, B); HR/MS: *m/z* [M-OEt-Boc-H]⁺ calcd for C₁₄H₁₃³⁵ClN: 230.0737 found 230.0729; IR: 2976, 1701, 1597, 1322, 1162, 1074, 686 cm⁻¹.

4.2.9 *tert*-Butyl-*N*-benzyl-*N*-(2-chloro-1-ethoxy-2-phenylethyl)-carbamate (**3j**)

Analysis of the crude material by ¹H NMR indicated the formation of two diastereoisomers in a 70/30 ratio. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc 99/1) to afford 29 mg (46%) of the desired product **3j** as a colourless oil; C₂₂H₂₈ClNO₃; MW 389.18 g.mol⁻¹. Because of the presence of rotamers, accurate attribution of the NMR signals was only done when possible. ¹H NMR (C₆D₆, 300 MHz): δ(ppm) = 7.57-7.24 (m, 6H, Ar), 7.10-6.97 (m, 14H, Ar), 6.26-6.14 (m, 1H, NCH, A), 5.77-5.75 (m, 1H, NCH, B), 4.91 (d, *J* = 8.8 Hz, 1H, CHCl, A), 4.82 (d, *J* = 9.1 Hz, 1H, CHCl, B), 4.53-4.05 (m, 4H, CH₂, 2HA+2HB), 3.59-2.84 (m, 4H, CH₂, 2HA+2HB), 1.51-1.14 (m, 18H, 9HA + 9HB), 1.03 (t, *J* = 7.1 Hz, 5H, CH₂CH₃, 3HA+2HB), 0.61 (t, *J* = 7.1 Hz, 1H, CH₂CH₃, B); ¹³C NMR (C₆D₆, 75 MHz): δ(ppm) = 139.8 (C), 138.1 (C), 129.2, 128.6, 128.4, 127.7, 127.0, 126.8, 89.8-89.3 (NCH, B), 88.9-88.6 (NCH, A), 80.1-79.9 (C(CH₃)₃, A + B), [65.4 + 65.2 + 64.4 + 64.0] (OCH₂, A + B), 63.3 (CHCl, B), 62.4 (CHCl, A), 45.8-45.6 (NCH₂, A), 45.2-44.9 (NCH₂, B), 28.3-27.8 (3CH₃, A + B), 28.6 (3CH₃, A), 14.7-14.3 (CH₂CH₃, A + B); HR/MS: *m/z* [M-Boc-OEt-H]⁺ calcd for C₁₅H₁₅³⁵ClN: 244.0893 found 244.0826; IR: 2977, 1700, 1455, 1367, 1162, 1091, 699 cm⁻¹.

4.2.10 Methyl-3-(*N*-benzyl-*N*-4-toluenesulfonamido)-2-chloro-3-ethoxypropanoate (**3k/m**)

Starting from (*E*)-isomer **1k**: Analysis of the crude material by ¹H NMR indicated the formation of two diastereoisomers in a 52:48 ratio. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc gradient: 100/0 to 94/06) to afford 53 mg (86%) of the desired product **3k** as a white powder; C₂₀H₂₄ClNO₅S; MW 425.93 g.mol⁻¹. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 52(A)/48(B) ratio. Starting from (*Z*)-isomer **1m**: Analysis of the crude material

by ^1H NMR indicated the formation of two diastereoisomers in a 70:30 ratio. The residue was purified by flash chromatography on alumina gel (Petroleum ether/EtOAc 96/4) to afford 43 mg (70%) of the desired product **3m** as a white powder; $\text{C}_{20}\text{H}_{24}\text{ClNO}_5\text{S}$; MW 425.93 $\text{g}\cdot\text{mol}^{-1}$. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 70(A)/30(B) ratio. ^1H NMR (CDCl_3 , 300 MHz): $\delta(\text{ppm}) = 7.69$ (d, $J = 8.3$ Hz, 2H, Ar, B), 7.62 (d, $J = 8.3$ Hz, 2H, Ar, A), 7.24-7.13 (m, 14H, Ar, 7HA+7HB), 5.57 (d, $J = 9.4$ Hz, 1H, NCH, B), 5.45 (d, $J = 8.6$ Hz, 1H, NCH, A), 4.51-4.31 (m, 4H, NCH₂, 2HA+2HB), 4.20 (d, $J = 8.6$ Hz, 1H, CHCl, A), 3.96 (d, $J = 9.5$ Hz, 1H, CHCl, B), 3.75 (s, 3H, CO_2CH_3 , B), 3.64 (s, 3H, CO_2CH_3 , A), 3.59-3.37 (m, 4H, CH_2CH_3 , 2HA+2HB), 2.41-2.40 (m, 6H, CH_3 , 3HA+3HB), 1.11 (t, 3H, $J = 7.0$ Hz, CH_2CH_3 , A), 1.00 (t, 3H, $J = 7.0$ Hz, CH_2CH_3 , B); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta(\text{ppm}) = 168.0$ (C=O), 167.1 (C=O), 143.9 (C), 143.7 (C), 137.5 (C), 137.4 (C), 136.4 (C), 136.2 (C), 129.5, 129.4, 128.9, 128.5, 128.4, 128.0, 128.0, 127.9, 127.9, 87.9 (CHN), 87.5 (CHN), 66.3 (OCH_2), 65.2 (OCH_2), 58.1 (CHCl), 55.3 (CHCl), 53.0 (CO_2CH_3), 52.9 (CO_2CH_3), 47.6 (NCH_2), 46.9 (NCH_2), 21.7 (CH_3), 14.6 (CH_2CH_3), 14.5 (CH_2CH_3); HRMS: m/z [$\text{M}-\text{OEt}-\text{H}$] $^+$ calcd for $\text{C}_{18}\text{H}_{19}^{35}\text{ClNO}_4\text{S}$: 380.0723 found 380.0732; IR: $\nu = 2979, 1749, 1598, 1437, 1341, 1160, 1093, 656$ cm^{-1} .

4.2.11 Methyl-3-(*N*-allyl-4-methylphenylsulfonamido)-2-chloro-3-ethoxypropanoate (**3l/3n**)

Starting from (*E*)-isomer **1l**: Analysis of the crude material by ^1H NMR indicated the formation of two diastereoisomers in a 58/42 ratio. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc gradient: 100/0 to 96/14) to afford 52 mg (82%) of the desired product **3l** as a colourless oil; $\text{C}_{16}\text{H}_{22}\text{ClNO}_5\text{S}$; MW 375.85 $\text{g}\cdot\text{mol}^{-1}$. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 58(A)/42(B) ratio. Starting from (*Z*)-isomer **1n**: Analysis of the crude material by ^1H NMR indicated the formation of two diastereoisomers in a 63:37 ratio. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc 95/05) to afford 48 mg (75 %) of the desired product **3n** as a colourless oil; $\text{C}_{16}\text{H}_{22}\text{ClNO}_5\text{S}$; MW 420.32 $\text{g}\cdot\text{mol}^{-1}$. The product was obtained as an inseparable mixture of 2 diastereoisomers in a 60(A)/40(B) ratio. ^1H NMR (CDCl_3 , 300 MHz): $\delta(\text{ppm}) = 7.81$ (d, $J = 8.3$ Hz, 2H, Ar, A), 7.74 (d, $J = 8.3$ Hz, 2H, Ar, B), 7.31-7.27 (m, 4H, Ar, 2HA+2HB), 5.75-5.60 (m, =CH-, 2H, HA+HB), 5.55 (d, $J = 9.5$ Hz, 1H, NCH, A), 5.41 (d, $J = 8.4$ Hz, 1H, NCH, B), 5.21-5.03 (m, 4H, =CH₂, 2HA+2HB), 4.49 (d, $J = 8.4$ Hz, 1H, CHCl, B), 4.26 (d, $J = 9.5$ Hz, 1H, CHCl, A), 3.89 (d, $J = 6.5$ Hz, 4H, NCH₂, 2HA+2HB), 3.80 (s, 3H, CO_2CH_3 , A), 3.69 (s, 3H, CO_2CH_3 , B), 3.66-3.41 (m, 4H, OCH_2 , 2HA+2HB), 2.43 (s, 6H, CH_3 , 3HA+3HB), 1.18-1.10 (m, 6H, CH_2CH_3 , 3HA+3HB); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta(\text{ppm}) = 168.0$ (C=O, B), 167.3 (C=O, A), 144.0 (C, A), 143.8 (C, B), 137.4 (C), 137.3 (C), 134.7 (CH=, A), 134.6 (CH=, B), 129.6 (2CH, B), 129.5 (2CH, A), 128.2 (2CH, A), 128.0 (2CH, B), 118.5 (=CH₂, B), 117.8 (=CH₂, A), 87.6 (NCH, A), 87.4 (NCH, B), 65.8 (OCH_2 , B), 64.9 (OCH_2 , A), 58.3 (CHCl, B), 55.2 (CHCl, A), 53.1 (CO_2CH_3 , A+B), 46.6 (NCH_2 , B), 45.2 (NCH_2 , A), 21.7 (CH_3 , A+B), 14.6 (CH_2CH_3 , A+B); HRMS: m/z [$\text{M}-\text{OEt}$] $^+$ calcd for $\text{C}_{14}\text{H}_{17}^{35}\text{ClNO}_4\text{S}$: 330.0874 found 330.0567; IR: 2978, 1750, 1437, 1340, 1162, 656 cm^{-1} .

4.2.12 *N*-benzyl-*N*-(2-chloro-1-ethoxy-3-hydroxypropyl)-4-toluenesulfonamide (**3o**)

Analysis of the crude material by ^1H NMR indicated the formation of two diastereoisomers in a 70:30 ratio. The residue was purified by flash chromatography on silica gel to afford 65 mg of the major diastereoisomer A of **3o** and 25 mg of the minor one B (36 % overall) both as colourless oils; $\text{C}_{19}\text{H}_{24}\text{ClNO}_4\text{S}$; MW 397.92 $\text{g}\cdot\text{mol}^{-1}$. Major diastereoisomer A: ^1H NMR (CDCl_3 , 300 MHz): $\delta(\text{ppm})$

$= 7.73$ (d, $J = 8.4$ Hz, 2H, Ar), 7.40-6.28 (m, 7H, Ar), 6.70 (d, $J = 8.2$ Hz, 2H, Ar), 5.02 (d, $J = 9.1$ Hz, 1H, NCH), 4.67 (d, $J = 14.6$ Hz, 1H, NCH₂), 4.16 (d, $J = 14.6$ Hz, 1H, NCH₂), 3.81 (ddd, $J = 13.0, 5.5, 3.5$ Hz, 1H, CH_2OH), 3.49-3.35 (m, 2H, $\text{CH}_2\text{OH}+\text{CHCl}$), 3.09 (dq, $J = 9.1, 7.0$ Hz, 1H, CH_2CH_3), 2.96 (dq, $J = 9.1, 7.0$ Hz, 1H, CH_2CH_3), 2.77 (dd, $J = 9.4, 5.5$ Hz, 1H, OH), 2.45 (s, 3H, CH_3), 1.05 (t, $J = 7.0$ Hz, 3H, CH_2CH_3); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta(\text{ppm}) = 144.4$ (C), 136.9 (C), 136.6 (C), 130.0 (2CH), 129.6 (2CH), 128.9 (2CH), 128.5 (CH), 127.5 (2CH), 88.2 (NCH), 66.4 (OCH_2CH_3), 64.3 (CH_2OH), 62.5 (CHCl), 46.8 (NCH₂), 21.7 (CH_3), 14.7 (CH_2CH_3); HRMS: m/z [$\text{M}+\text{OEt}$] $^+$ calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_3\text{SNa}^{35}\text{Cl}$: 352.0774 found 352.0738 IR: 3520, 2927, 1598, 1456, 1337, 1096, 1065, 871, 661 cm^{-1} ; mp: 85°C-88°C (crystd from $\text{CH}_2\text{Cl}_2/\text{cyclohexane}$).

Minor diastereoisomer B: ^1H NMR (CDCl_3 , 300 MHz): $\delta(\text{ppm}) = 7.70$ (d, $J = 8.3$ Hz, 2H, Ar), 7.31-7.23 (m, 7H, Ar), 5.44 (d, $J = 8.7$ Hz, 1H, NCH), 4.53-4.23 (m, 2H, NCH₂), 3.89-3.84 (m, 3H, CHCl+ CH_2OH), 3.69-3.49 (m, 2H, CH_2CH_3), 2.45 (s, 3H, CH_3), 1.10 (t, $J = 7.0$ Hz, 3H, CH_2CH_3); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta(\text{ppm}) = 143.6$ (C), 137.5 (C), 136.5 (C), 129.3 (2CH), 129.0 (2CH), 128.4 (2CH), 128.1 (2CH), 127.7 (CH), 88.7 (NCH), 66.9 (CH_2OH), 64.7 (OCH_2CH_3), 61.0 (CHCl), 46.8 (NCH₂), 21.7 (CH_3), 14.6 (CH_2CH_3); HRMS: m/z [$\text{M}+\text{OEt}$] $^+$ calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_3\text{SNa}^{35}\text{Cl}$: 352.0774 found 352.0738; IR: 3531, 2929, 1599, 1456, 1336, 1157, 1069, 880, 661 cm^{-1} .

4.2.13 *N*-benzyl-*N*-(2-chloro-1-ethoxy-3-hydroxypropyl)-4-toluenesulfonamide (**3p**)

Analysis of the crude material by ^1H NMR did not allow determination of the d.r.. The residue was purified by flash chromatography on silica gel to afford 28 mg of only one diastereoisomer of **3p** (27 %) as a colourless oil; $\text{C}_{15}\text{H}_{22}\text{ClNO}_4\text{S}$; MW 347.86 $\text{g}\cdot\text{mol}^{-1}$. The product was unstable and only the ^1H NMR spectrum could be recorded ^1H NMR (CDCl_3 , 500 MHz): $\delta(\text{ppm}) = 7.71$ (d, $J = 8.0$ Hz, 2H, Ar), 7.28 (d, $J = 8.0$ Hz, 2H, Ar), 5.74 (ddt, $J = 17.2, 10.2, 6.4$ Hz, 1H, =CH), 5.61-5.54 (m, 2H), 5.37-5.33 (m, 1H), 5.20 (d, $J = 9.5$ Hz, 1H), 5.13 (d, $J = 17.2$ Hz, 1H, =CH₂), 5.03 (d, $J = 10.2$ Hz, 1H, =CH₂), 3.80 (dd, $J = 16.2, 6.2$ Hz, 1H, NCH₂), 3.69 (dd, $J = 16.2, 6.4$ Hz, 1H, NCH₂), 3.66-3.59 (m, 1H, CH_2CH_3), 3.49-3.43 (m, 1H, CH_2CH_3), 3.50-3.40 (m, 1H, CH_2CH_3), 2.42 (s, 3H, CH_3), 1.16 (t, $J = 7.0$ Hz, 3H, CH_2CH_3).

4.2.14 *N*-(2-chloro-2-phenylethyl-*N*-phenyl)-4-toluenesulfonamide (**6**)

To a solution of **3b** (36 mg, 0.08 mmol, 1 equiv.) in distilled DCM (1 mL) under argon, was added Et_3SiH (27 μL , 0.17 mmol, 2 equiv.). The mixture was cooled to 0 °C and a solution of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (11 μL , 0.08 mmol, 1 equiv.) in distilled DCM (1 mL) was added dropwise at 0 °C. The reaction was stopped after 5 h at 0 °C by addition of a saturated solution of sodium hydrogenocarbonate. The organic layer was then washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc 96/04) to afford 24 mg (74 %) of the reduced product **6** as a colourless oil; $\text{C}_{21}\text{H}_{20}\text{ClNO}_2\text{S}$; MW: 385.91 $\text{g}\cdot\text{mol}^{-1}$. ^1H NMR (300 MHz, CDCl_3): δ (ppm) = 7.42 (d, $J = 8.2$ Hz, 2H), 7.30-7.20 (m, 10H), 6.86-6.83 (m, 2H), 4.95 (t, $J = 7.5$ Hz, 1H, CHCl), 4.12 (dd, $J = 14.1, 7.5$ Hz, 1H, CH_2), 3.97 (dd, $J = 14.1, 7.5$ Hz, 1H, CH_2), 2.41 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 143.8 (C), 139.6 (C), 138.4 (C), 135.1 (C), 129.6, 129.2, 129.1, 128.9, 128.8, 128.2, 127.9, 60.2 (CHBr), 58.3 (CH_2), 21.7 (CH_3); HRMS: m/z [$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{21}\text{H}_{21}^{35}\text{ClNO}_2\text{S}$: 386.0892 found 386.0995; IR (neat): $\nu = 2923, 1596, 1492, 1349, 1162, 696, 656$ cm^{-1} .

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Supplementary Material

Electronic Supplementary Information (ESI) available: copies of ^1H NMR and ^{13}C NMR spectra.