α-Trifluoromethylated tertiary homoallylic amines: diastereoselective synthesis and conversion into β-aminoesters, γ- and δ-aminoalcohols, azetidines and pyrrolidines

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The diastereoselective addition of allyl zinc and allylindium derivatives on α-trifluoromethyl *N-tert*-butanesulfinyl hemiaminals, bench stable precursors of aryl and alkyl trifluoromethyl ketimines allows the synthesis of homoallylic amines containing a tetrasubstituted carbon bearing a trifluoromethyl group with good diastereoselectivities (up to dr > 99:1). This approach was also suitable for accessing chiral homoallylic amines bearing two contiguous stereocenters. The synthetic usefulness of *N-tert*-butanesulfinyl homoallylamines was illustrated by preparing various trifluoromethylated nitrogen containing bifunctional synthons (aminoesters, aminoalcohols) and small azaheterocycles (azetidines, pyrrolidines).

Introduction

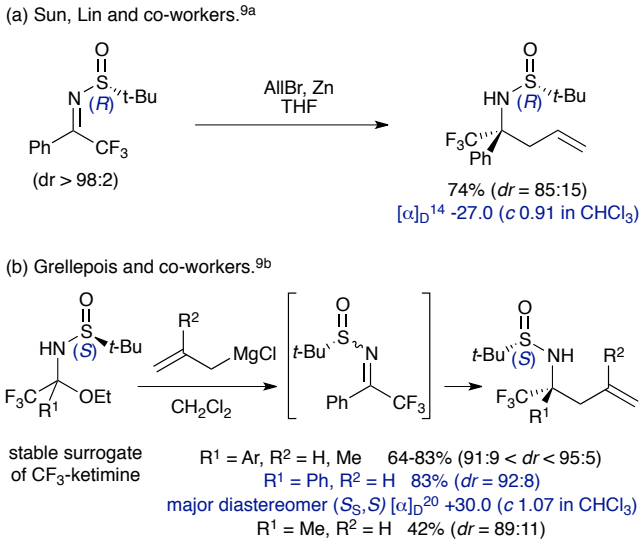
Since the introduction of a fluorine atom and/or a fluorine-containing group may have a range of effects on the lipophilicity, the solubility, the conformation and/or the metabolic stability of bioactive molecules,[1] many pharmaceuticals or agrochemicals include a fluorinated

substituent.[2] For example, the substitution of one or more hydrogen atoms by fluorine close to an amine function not only decreases its basicity but also enhances its metabolic stability.[3] Among the fluorinated substituents, the trifluoromethyl group is one of the most popular.

The enantioenriched homoallylic amines are the key building blocks in the synthesis of many pharmaceuticals and natural products since the double bond of the allylic moiety can be functionalized for accessing numerous polyfunctional synthons (aminoalcohols, aminoacids and aminoepoxides to mention only them) or nitrogen-containing heterocycles (azetidines, pyrrolidines and piperidines for example).[4] The most efficient way to these peculiar amines is certainly the reaction of imines with allyl metal reagents or metalloids, under substrate control, including auxiliaries, or through the use of chiral reagents or catalysts.[4,5] When non-symmetric ketimine derivatives are chosen as substrate, asymmetric allylation reaction leads to the construction of nitrogen-containing tetrasubstituted carbon stereocenter, a still challenging task in synthetic organic chemistry.[4-6]

Racemic aryl and alkyl trifluoromethylated homoallylic tertiary carbinamines (α,α-dibranched amines) have been synthesized by reaction of allylorganomagnesium reagents with trifluoromethyl oxime derivatives[7] or by addition of an allylzinc reagent on a trifluoromethyl *N*-acylhydrazone in the presence of $BF_3.Et_2O$.[8] The asymmetric synthesis of trifluoromethylated homoallylic tertiary carbinamines has only been reported by diastereoselective allylation of trifluoromethyl ketimine derivatives *N*-substituted by the Ellman's chiral auxiliary (Scheme 1).[9,10] Lin, Sun and co-workers[9a] applied the efficient Zn-mediated asymmetric allylation method they developed in non-fluorinated series to the *N*-*tert*-butanesulfinyl ketimine prepared from 2,2,2-trifluoroacetophenone. The corresponding *N*-protected trifluoromethyl homoallylamine was obtained in good yield (74%) and good diastereoselectivity (*dr* = 85:15)

considering the small steric hindrance differences of both sides of this ketimine. Almost at the same time, we disclosed our results concerning the reaction of Grignard reagents with trifluoromethyl *N*-*tert*-butanesulfinyl hemiaminals.[9b] Chiral aryl and alkyl trifluoromethyl *N*-*tert*-butanesulfinyl ketimines being difficult to isolate due to their propensity to hydrolysis,[11] they can be generated *in situ* from their hemiaminals, just before reacting with nucleophiles.[9b,12] Amongst the Grignard reagents used as nucleophiles, allyl and methallylmagnesium chloride reacted successfully with aromatic hemiaminals and led to the corresponding trifluoromethyl homoallylic sulfinamides in good diastereoselectivities (91:9 < *dr* < 95:5) and yields (ranging from 64% to 83%).[9b] Starting from the methyl trifluoromethyl hemiaminal, the allylation led to a more disappointing result, not only in term of yield (42%) but also in term of diastereoselectivity (89:11).[9b] Indeed, even if the examples of addition of nucleophiles on *N*-*tert*-butanesulfinyl trifluoromethyl methyl ketomines are rare, they have occurred with a better stereoselectivity.[11,12a] At first sight, the stereochemical outcomes of these two approaches (addition of Grignard and of zinc reagents) seem to be in sharp contrast,[9] but looking more closely at the reported optical rotations shows rather an inconsistency in the assignment of the absolute configuration of the new created stereocenter (Scheme 1).



Scheme 1: Previous methods reported for the synthesis of enantiopure a-trifluoromethylated -alkyl(aryl) homoallylic sulfinamides.

In this context we think that the allylation of aryl but above all alkyl trifluoromethyl *N*-*tert*-butanesulfinyl hemiaminals deserves to be reexamined. Having shown a few years ago that the *in situ* release of trifluoromethyl ketimines from aryl and alkyl trifluoromethyl *N*-*tert*-butanesulfinyl hemiaminals could be initiated by Reformatsky reaction before the addition of the metal (zinc or copper) enolate,[12a] we reasoned that asymmetric zinc- and indium-mediated allylation starting from aryl and alkyl trifluoromethyl *N*-*tert*-butanesulfinyl hemiaminals could be successfully performed. Besides, the low basicity of allylinzinc and allylindium reagents[4c,9a,13] should avoid the self-condensation of the methyl trifluoromethyl ketimine observed when methyl trifluoromethyl *N*-*tert*-butanesulfinyl hemiaminal reacted with Grignard reagents.[9b] During this study, much efforts have been directed towards the unambiguously elucidation of the absolute configuration of the newly created stereocenters. We describe herein our results in this regard using phenyl and methyl trifluoromethyl *N*-*tert*-butanesulfinyl hemiaminals as model substrates. Having developed an efficient synthesis of a series of enantiomerically pure α-phenyl and α-methyl-α-trifluoromethyl homoallylsulfinamides including β-substituted derivatives bearing two adjacent stereogenic carbon centers, we have

shown the versatile nature of these building blocks by readily transforming them into trifluoromethylated acyclic and cyclic nitrogen-containing small synthons of interest.

Results and Discussion

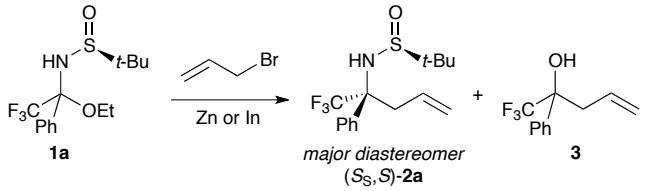
Trifluoromethyl phenyl and methyl (S_S)-hemiaminals **1a-b** have been prepared by treatment of the commercially available 2,2,2-trifluoroacetophenone or 1,1,1-trifluoroacetone with (*S*)-2-methyl-2-propanesulfinamide in the presence of an excess of titanium(IV) ethoxide in hexane.[12a]

We selected the phenyl hemiaminal **1a** and allyl bromide to determine the optimal conditions for the zinc and indium-promoted allylation reaction. The results are summarized in table 1. We initially examined the Zn-mediated allylation reaction using 2.5 equiv of activated zinc powder and 2.5 equiv of allylbromide under Barbier-type conditions (Table 1, entries 1-11). In dry THF at room temperature, the desired *N*-protected tertiary homoallylic amine **2a** was obtained in 77% yield with over 85:15 *dr* after 3 h (Table 1, entry 1). These results are identical to the ones obtained by Lin, Sun and co-workers with phenyl trifluoromethyl ketimine (Scheme 1).[9a] The absolute stereochemistry of the major diastereomer of **2a** was determined unambiguously through X-ray crystallographic analysis of one of its derivative (see *vide infra*). A certain amount (14%) of the known alcohol **3**,[14] was also detected in the ^{19}F NMR spectra of the crude reaction mixture. Alcohol **3** results from the *in situ* hydrolysis of the unstable intermediate ketimine followed by the allylation of the released ketone. Similar amounts of alcohol **3** formed (15%), diastereoselectivity (84:16 ratio) and yield (68%) of the amine **2a** were obtained using the greener solvent 2-Me-THF instead of THF (Table 1, entry 2). The influence of Zn-coordination on the stereochemical outcome of the reaction was then examined. The addition of $Zn(OTf)_2$[15] as Lewis acid had virtually no influences on the diastereoselectivity

despite the presence of extra Zn ions and, unfortunately, increased the reactivity of imine towards hydrolysis (Table 1, entry 3). In THF, decreasing the temperature had a slightly beneficial effect on the diastereoselectivity (89:11 at 0°C instead of 85:15 at room temperature) but without decreasing the amount of the alcohol **3** or increasing the yield (Table 1, entries 4-5). Changing THF for the polar aprotic solvent HMPA led disappointingly to a bigger amount of the alcohol **3** (36%)[16] and decreased the diastereoselectivity of the reaction at room temperature (76:24) without reversal of stereofacial selectivity[17] (Table 1, entry 6). Freshly distilled DMF neither reverse the stereoselectivity of the reaction[9a,17b] but enhanced slightly the diastereoselectivity (from 90:10 at room temperature until 96:4 at -30°C) (Table 1, entries 7-10). The reaction being not complete at -30°C, the best yield (76%) and diastereomeric ratio (96:4) for the sulfinamide **2a** were obtained at -20°C even though alcohol **3** was still detected in the crude reaction mixture (10%) (Table 1, entry 9). As previously observed in THF, addition of $Zn(OTf)_2$ had no beneficial effect (Table 1, entry 11). We then explored the In-mediated allylation reaction using 3 equiv of indium powder and 2 equiv of allylbromide (Table 1, entries 12-19). Indium being compatible with protic solvents, the reaction was first tested in freshly distilled EtOH. Using this solvent, no traces of the *N*-protected amine **2a** were detected in the ^{19}F NMR spectra of the crude reaction mixture when the reaction was conducted at room temperature or at reflux (Table 1, entries 12-13). In dry DMF, allylindium reacted smoothly, the diastereoselectivity was very good at room temperature and at 60°C (respectively 96:4 and 95:5) but a large amount of the undesired hydrolysis product **3** was also formed (49% and 41%) impacting the yield of amine **2a** (40% and 56%, respectively) (Table 1, entries 14-15). The allylation reaction in dry THF at room temperature was not complete and the same moderate amounts of the amine **2a** and of the alcohol **3** were formed (about 40% of each) (Table 1, entries 16). Performing the reaction at reflux enabled to isolate the homoallylic sulfinamide **2a** in good yield (74%) and very good diastereoselectivity (96:4) despite the formation of a non-negligible

amount of the alcohol **3** (24%) (Table 1, entries 17). Adding 4Å molecular sieves only slightly decreased the amount of the alcohol **3** (from 24 to 19%) (table 1, entries 18). The same yield (74%) and diastereoselectivity (96 :4) could be reached performing the reaction in dry Me-THF at 65°C (Table 1, entry 19). Finally, attempt to perform the reaction using only a catalytic amount of In in combination with Al[18] at reflux of THF failed, a complex mixture containing approximately 15% of the amine **2a** was obtained (Table 1, entry 20). Based on this study, zinc in DMF at -20°C and indium in THF at reflux were chosen as the most convenient procedures for the synthesis of the *N*-protected tertiary homoallylic amine **2a**. Under these reaction conditions, the amine **2a** was formed with a slightly better diastereselectivity than the one obtained using allyl Grignard reagent[9b] (96 :4 instead of 92 :8) (Scheme 1 and Table 1, entries 9 and 17).

Table 1: Optimization of the reaction conditions for the Zn- and In-mediated allylation of the (S_S)-phenyl hemiaminal **1a**.[a]



entry	metal / additive	solvent	T°C	Time (h)	ratio[b] **2a**:**3**	*dr* **2a**[b]	yield **2a** (%)
1	Zn	THF	r.t.	3	86:14	85:15	77
2	Zn	Me-THF	r.t.	17	85:15	84:16	68
3	Zn/$Zn(OTf)_2$[c]	THF	r.t.	45	68:32	86:14	57
4	Zn	THF	0	4.5	83:17	89:11	70
5	Zn	THF	-10	7[d]	59:41	89:11	-
6	Zn	HMPA	r.t.	8	64:36	76:24	51
7	Zn	DMF	r.t.	1.5	73:27	90:10	66
8	Zn	DMF	0	1.5	76:24	93:7	68
9	Zn	DMF	-20	18	90:10	96:4	76
10	Zn	DMF	-30	40[e]	90:10	96:4	-
11	Zn/$Zn(OTf)_2$[c]	DMF	-20	45	81:19	95:5	66
12	In	EtOH	r.t.	6	-[f]	-	-
13	In	EtOH	reflux	6.5	-[f]	-	-
14	In	DMF	r.t.	23	51:49	96:4	40
15	In	DMF	60	5	59:41	95:5	56
16	In	THF	r.t.	23	50:50[g]	97:3	-
17	In	THF	reflux	4.5	76:24	96:4	74
18	In/4Å MS	THF	reflux	3	81:19	96:4	65
19	In	Me-THF	65	4	81:19	96:4	74
20	Al/In[h]	THF	reflux	5	-	-	-

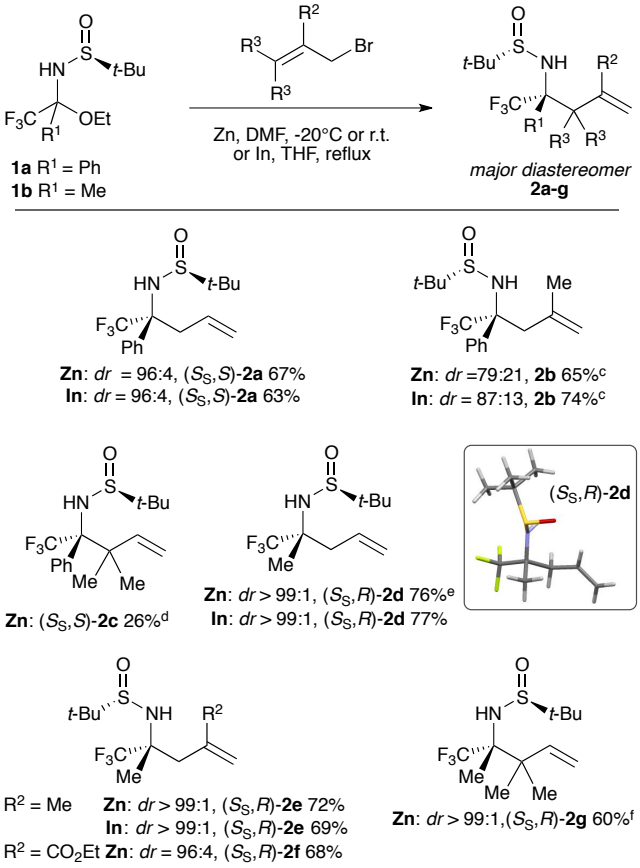
[a] reaction conditions for the Zn-mediated allylation: Zn (2.5 equiv), AllBr (2.5 equiv); reaction conditions for the In-mediated allylation: In (3 equiv), AllBr (2 equiv). [b] ratio **2a**:**3** and diastereomeric ratio (*dr*) of the sulfinamide **2a** determined by ^{19}F NMR spectra of the crude reaction. [c] 1 equiv of $Zn(OTf)_2$. [d] reaction not complete, 38% conversion in sulfinamide **2a** (not separable from the hemiaminal **1a** by chromatography on SiO_2). [e] reaction not complete, only 67% conversion in sulfinamide **2a** (not separable from the hemiaminal **1a** by chromatography on SiO_2). [f] no traces of the sulfinamide **2a** detected by ^{19}F NMR in the crude reaction mixture (90% of hemiaminal **1a** and 10% of alcohol **3** at r.t., 71% of hemiaminal **1a** and 29% of alcohol **3** at reflux). [g] reaction not complete, 38% conversion in sulfinamide **2a** (not separable from hemiaminal **1a** by chromatography on SiO_2). [h] 0.1 equiv of In and 2 equiv of Al were used, very complex mixture formed containing approximately 15% of the sufinamide **2a** (*dr* = 77:23) according to the ^{19}F NMR spectra of the crude reaction – a complex mixture was also formed using the same conditions in absence of In.

With the optimal reaction conditions identified for the Zn- and In-mediated allylation, we turned our attention to the reaction scope.

We first examined the addition of allyl bromide, methallyl bromide, ethyl 2-(bromomethyl)acrylate and prenyl bromide to the (S_S)-phenyl hemiaminal **1a** and the (S_S)-methyl hemiaminal **1b** (Table 2). Starting from (S_S)-phenyl hemiaminal **1a**, both Zn- and In-mediated addition of allyl bromide were performed with a very good diastereoselectivity (96:4) and the major diastereomer (S_S,*S*)-**2a** of the homoallylic sulfinamide was isolated in good yields (67% and 63%, respectively). However, metal-mediated addition of methallyl bromide gave the desired *N*-protected amine **2b** with a much lower diastereoselectivity (79:21 with Zn and 87:13 with In) and the diastereomers of **2b** could not be separated by chromatography on silica gel. As a reminder of the previous work, reaction of methallylmagnesium bromide has led to the sulfinamide derivative **2b** with a 91:9 diastereomeric ratio.[9b] Addition of zinc allyl reagent derived from ethyl 2-(bromomethyl)acrylate gave a very complex mixture regardless of the temperature of the reaction.[19] Addition of prenylzinc bromide at -20°C led almost only to the hydrolysis product (homoallylic alcohol). When the reaction was conducted at room temperature, a complex mixture of products was formed. However, the major diastereomer (S_S,*S*)-**2c** of the *N*-protected amine, bearing two adjacent tetrasubstituted carbons, could be isolated in 26% yield. The corresponding In-mediated allylation led to a complex mixture containing no traces of the desired homoallylic amine **2c**. These relatively disappointing results should be due to the steric hindrance of the electrophilic carbon of the phenyl trifluoromethyl ketimine. We thus turned our attention to the (S_S)-methyl hemiaminal **1b**. Zinc- and indium-mediated addition of allyl bromide and methallyl bromide with the (S_S)-methyl hemiaminal took place with an excellent stereofacial selectivity (*dr* > 99:1). The major diastereomer (S_S,*R*)-**2d** and (S_S,*R*)-**2e** formed for each reaction were isolated in good yields (ranging from 69 to 76%). The absolute configuration of the new stereocenter of the major diastereomer (S_S,*R*)-**2d** of the homoallylic sulfinamide was determined from its X-ray structural analysis. Interestingly, the weaker nucleophilicity of the zinc allyl reagent derived from ethyl 2-(bromomethyl)acrylate

was not a limitation to carry out the addition at -20°C (Table 2, entry 14). *N*-protected γ-aminoester **2f** was obtained with a diastereomeric ratio of 96:4 and the major diastereomer (S_S,*R*)-**2f** was isolated in 68% yield. Addition of more hindered prenylzinc bromide led to a complex mixture at -20°C containing only traces of sulfinamide **2g** as determined by ^{19}F NMR of the crude reaction mixture. However, when performed at room temperature, the reaction was much cleaner, the *N*-protected homoallylic amine **2g** resulting from the γ-addition of the prenyl moiety was formed with an excellent diastereoselectivity (dr > 99:1) and the major diastereomer (S_S,*R*)-**2g** was isolated in 60% yield. The In-mediated allylation with prenyl bromide gave a complex mixture containing no traces of sulfinamide **2g**.

Table 2: Zn- and In-mediated allylation of the hemiaminals **1a-b** with allyl bromide, methallyl bromide, ethyl 2-(bromomethyl)acrylate and prenyl bromide.[a,b]



[a] reaction conditions for the Zn-mediated allylation: Zn (2.5 equiv), AllBr (2.5 equiv), DMF, -20°C (for sulfinamides **2a-b**,**d-f**) or r.t. (for sulfinamides **2c**,**g**), 15-24h; reaction conditions for the In-mediated allylation: In (3 equiv), AllBr (2 equiv), THF, reflux, 4-7h. [b] diastereomeric ratio (*dr*) of sulfinamide **2** determined by ^{19}F NMR spectra of the crude reaction. [c] the 2 diastereomers could not be separated by chromatography on SiO_2. [d] only traces of sulfinamide at -20°C, the reaction was performed at rt - complex mixture in ^{19}F NMR of the crude mixture, the diastereomeric ratio could not be determined. [e] when the reaction is performed in THF at 0°C, (**2d** was obtained in 91% yield (dr > 99:1). [f] only traces of sulfinamide at -20°C, the reaction was performed at rt.

The observed diastereoselectivity for the zinc and indium allylation in THF is consistent with a Zimmerman-Traxler-type transition-state in which the intermediate ketimine adopts an *E*-configuration[11b] and both the sulfinyl oxygen and the imine nitrogen are coordinated to the metal.[4,5,10] In this cyclic chelated model, the trifluoromethyl group prefers to occupy the equatorial position rather than the axial one due to steric hindrance and to the electrostatic repulsion between the trifluoromethyl group and the lone pair of the sulfur group. Thereby,

approach of the organometallic reagent occurs by the *re*-face. In DMF, a polar aprotic solvent having a greater coordinate capacity than THF, the reaction most probably proceeds through an open-chain transition state.[4c] However, as the same diastereoselectivity is observed in THF and DMF, the reaction of the intermediate imine in the s-*cis*-conformation could not be postulated as the *re*-face addition would be blocked by the *tert*-butylsulfinyl group. Accordingly, to account for the observed diastereoselectivity, intermediate imine has to react in less favorable s-*trans*-conformation.[9a]

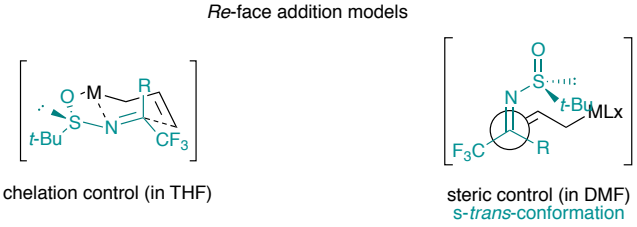
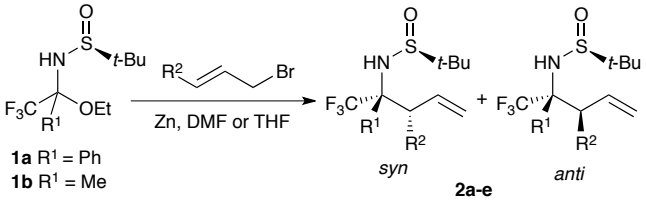


Figure 1: Proposed transition states for the Zn- and In-mediated allylation.

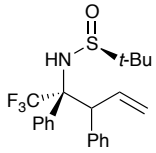
Since the synthesis of optically active *N*-protected *β*-substituted homoallylic amines bearing two adjacent quaternary and tertiary stereocenters in a single step is of interest, the metal-mediated allylation of hemiaminals **1a** and **1b** with *γ*-substituted allyl bromide reagent was also evaluated. Only a few examples of addition of *γ*-substituted allyl metal reagents with chiral *tert*-butanesulfinyl ketimines have been reported to date.[9a,20] The reactions of *γ*-substituted allylindium reagents with trifluoromethylated hemiaminals **1a** and **1b** led in most cases to complex mixtures containing an important amount of homoallylic alcohol, thus only our results with Zn reagents are collected in table 3.[21] Cinnamylation of phenyl hemiaminal **1a** in DMF at 0°C of at lower temperature failed. However, at room temperature, the reaction gave the sulfinamide **2h** as a mixture of three diastereomers with a good *syn*:*anti* diastereoselectivity

although we could not determined which one was formed preferentially. The diastereomers could not be separated but the *N*-protected amine **2h** was isolated in reasonable yield. Cinnamylation of methyl hemiaminal **1b** was performed in DMF at 0°C and gave the sulfinamide **2i** as a mixture of only two diastereomers. Albeit the *syn*:*anti* diastereoselectivity was low (59:41), each of the diastereomers (S_S,*R*,*R*)-**2i** (*syn*-**2i**) and (S_S,*R*,*S*)-**2i** (*anti*-**2i**) were separated by chromatography on silica gel. As a chelated transition state should lead to a better stereocontrol, the reaction was also performed in THF. At room temperature, the reaction led to a mixture of two diastereomers of the *N*-protected amine **2i** with a poor *syn*:*anti* diastereoselectivity (43:57), but reversed compared to the one observed in DMF. The crotylation of the methyl hemiaminal **1b** at -20°C in DMF gave the *N*-protected amine **2j** with a very good *syn:anti* diastereoselectivity (4:96). However, both diastereomers could not be separated by chromatography on silica gel and the *N*-protected amine **2j** was isolated in 60% yield. Some similar results were obtained in THF at room temperature. The Zn-mediated allylation of methyl hemiaminal **1b** with methyl 4-bromocrotonate led to the highly substituted *N*-*tert*-butanesulfinyl $\beta^{2,3,3}$-aminoester **2k** containing a vinyl substituent with a low *syn*:*anti* diastereoselectivity (64:36) but each of the diastereomers (S_S,*R*,*S*)-**2k** (*syn*-**2k**) and (S_S,*R*,*R*)-**2k** (*anti*-**2k**) were separated.[22] A slightly lower and reverse *syn*:*anti* diastereoselectivity (43:57) was observed in THF at room temperature. The addition of γ-substituted allyl zinc reagents on trifluoromethyl methyl ketimines led to the creation of the stereogenic tetrasubstituted carbon with very high face selectivity regardless of the solvent but the second stereogenic centre, trisubstituted, was formed with much lower stereocontrol, especially with bulky phenyl and ester substituents. The absolute stereochemistry of the diastereomers of **2i**-**k** was determined by X-ray crystallographic analysis of their derivatives (see *vide infra*).

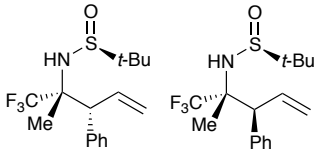
Table 3: Zn-mediated allylation of the hemiaminals **1a-b** with cinnamyl bromide, crotyl bromide and methyl 4-bromocrotonate.[a,b]



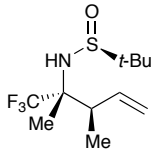
1a R^1 = Ph
1b R^1 = Me



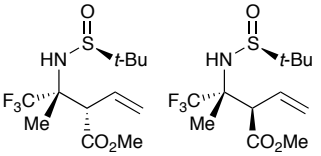
DMF: *dr major:minor* = 88:12
(*dr major* = 100:0)
(*dr minor* = 66:34)
2h 57%



DMF:[c] *dr syn*:*anti* = 59:41
(*dr syn* = *dr anti* = 100:0)
(S_S,*R*,*R*)-**2i** (*syn*-**2i**) 39%
(S_S,*R*,*S*)-**2i** (*anti*-**2i**) 20%
THF: *dr syn*:*anti* = 43:57
(*dr syn* = *dr anti* = 100:0)
2i 65%



DMF: *dr syn*:*anti* = 4:96
(*dr syn* = 75:25)
(*dr anti* = 100:0)
2j 60%
THF: *dr syn*:*anti* = 6:94
(*dr syn* = 75:25)
(*dr anti* = 100:0)
2j 60%



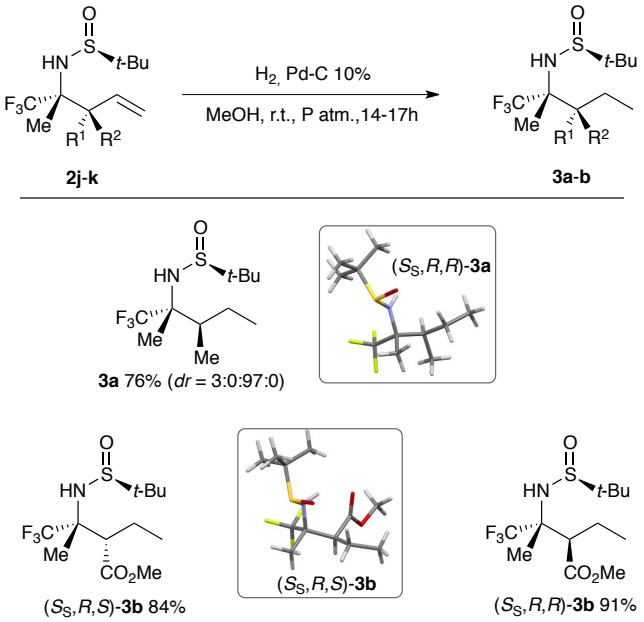
DMF:[d] *dr syn*:*anti* = 36:64
(*dr syn* = *dr anti* = 100:0)
(S_S,*R*,*S*)-**2k** (*syn*-**2k**) 28%
(S_S,*R*,*R*)-**2k** (*anti*-**2k**) 54%
THF: *dr syn*:*anti* = 57:43
(*dr syn* = *dr anti* = 100:0)
2k 78%

[a] reaction conditions: Zn (2.5 equiv), AllBr (2.5 equiv) in DMF at -20°C (for **2j-k**), 0°C (for **2i**) or r.t. (for **2h**) for 15-22h or in THF at r.t. for 4-6h. [b] diastereomeric ratio (*dr*) determined by ^{19}F NMR of the crude reaction mixture; dr *syn*:*anti* determined by ^{19}F NMR after cleavage of the chiral auxiliary except for **2k** – *syn* and *anti* refers to the relative positions of R_2 and the nitrogen-containing substituent with the trifluoromethyl located in the plan. [c] reaction performed on 7.0 mmol scale of hemiaminal **1b**. [d] reaction performed on 5.8 mmol scale of hemiaminal **1b**, diastereomeric relationship determined after treatment of both isolated aminoester under acid conditions at reflux.

Having proposed a convenient methodology towards enantioenriched α-trifluoromethylated tertiary homoallylic amines, we have illustrated their high potential as platform to access a range of useful acyclic[6b] and cyclic[23] nitrogen building blocks using a few simple and efficient reactions.

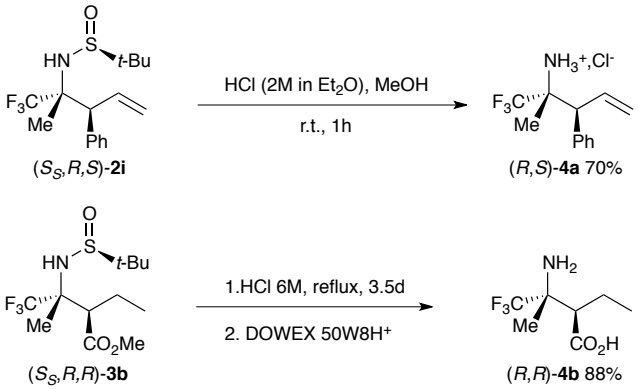
The *N*-protected saturated amine **3a** bearing two contiguous stereocenters was prepared by hydrogenation of sulfinamide **2j** (scheme 2). The sulfinamide **3a** was isolated in

76% yield as a 3:97 *syn*:*anti* mixture of diastereomers. The major (S_S,*R*,*R*)-**3a** diastereomer selectively recrystallized and the absolute configurations of its two stereogenic carbons were determined from its X-ray structural analysis. The hydrogenation of the enantiopure *N*-protected α-vinyl-β-trifluoromethyl-β-methylaminoesters (S_S,*R*,*S*)-**2k** (*syn*-**2k**) and (S_S,*R*,*R*)-**2k** (*anti*-**2k**) led to the corresponding *N*-protected α-ethyl-β-trifluoromethyl-β-methylaminoesters (S_S,*R*,*S*)-**3b** and (S_S,*R*,*R*)-**3b** in 84% and 91% yields, respectively. The absolute configurations of the two stereogenic carbons of (S_S,*R*,*S*)-**3b** were determined through X-ray structural analysis (scheme 2). This approach constitutes a new synthetic routes for preparing enantiomerically pure trifluoromethylated *syn*- and *anti*-$\beta^{2,3,3}$-amino esters derivatives.[22,24]



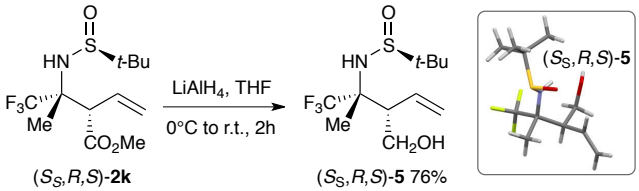
Scheme 2: Preparation of *N*-protected amine **3a** and β-aminoesters **3b** by hydrogenation of homoallylic sulfinamides **2j,k.**

The acidic treatment of the trisubstituted homoallylsulfinamide (S_S,*R*,*S*)-**2i** under classical conditions, using HCl in a mixture of Et_2O and methanol, gave the corresponding *N*-deprotected amine (*R*,*S*)-**4a** in 70% yield (scheme 3). The treatment of the *N*-*tert*-butanesulfinyl aminoester (S_S,*R*,*R*)-**3b** with 6M HCl aqueous solution under reflux for 3.5 days, led directly, after work-up, to the $\beta^{2,3,3}$-*N*-deprotected aminoacid (*R*,*R*)-**4** in 88% yield (scheme 3). [22,24]



Scheme 3: Deprotection of sulfinamides **2i** and **3b** to afford enantiopure aminium chloride **4a** and $\beta^{2,2,3}$-aminoacid **4b**.

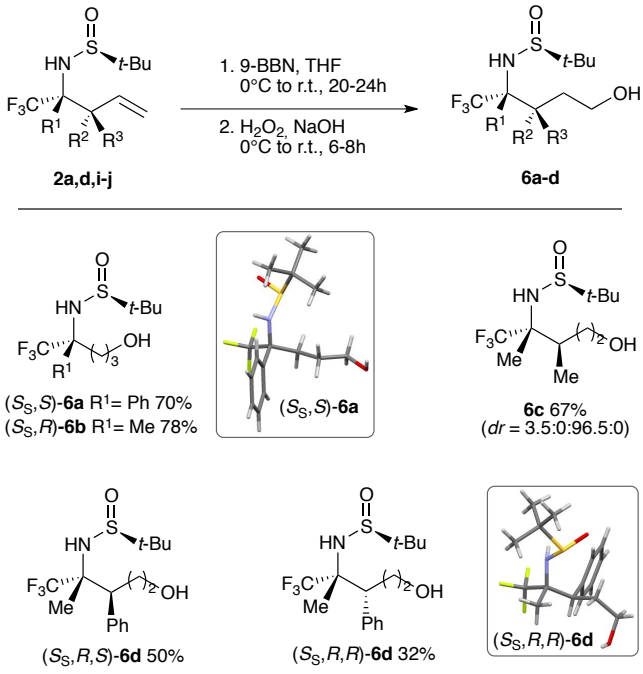
The reduction of the *N*-*tert*-butanesulfinyl aminoester (S_S,*R*,*S*)-**2k** (*syn*-**2k**) with $LiAlH_4$ in THF gave the corresponding *N*-protected γ-aminoalcohol (S_S,*R*,*S*)-**5** in 76% yield.[25] The absolute configurations of the two stereogenic carbons of aminoalcohol (S_S,*R*,*S*)-**5** were confirmed through X-ray structural analysis (scheme 4).



Scheme 4: Preparation of the *N*-*tert*-butanesulfinyl 1,3-aminoalcohol **5** by reduction of *N*-*tert*-butanesulfinyl aminoester **2k**.

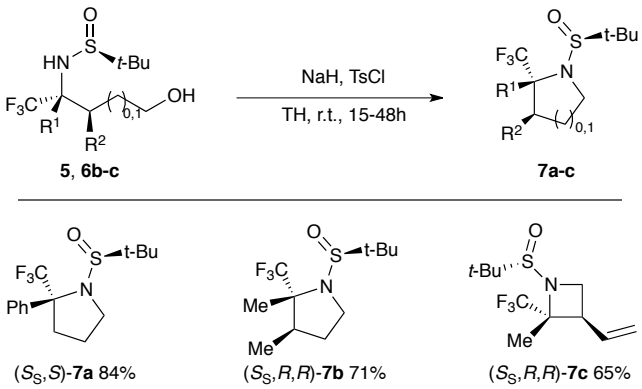
The hydroboration-oxydation of the *N*-protected homoallylic amines (S_S,*S*)-**2a** and (S_S,*R*)-**2d** and of the *N*-protected *β*-substituted homoallylic amines (S_S,*R*,*R*)-**2i**, (S_S,*R*,*S*)-**2i** and **2j** using 9-BBN led to the corresponding *N*-*tert*-butanesulfinyl *δ*-aminoalcohols **6a**-**d** (scheme

5).[26] The *N*-*tert*-butanesulfinyl α,α-disubstituted aminoalcohols **6a-b** and *N*-*tert*-butanesulfinyl α-trifluoromethyl α,β-dimethyl homoallylic aminoalcohol **6c**, prepared respectively from the *N*-protected homoallylic amines (S_S,*S*)-**2a**, (S_S,*R*)-**2d** and **2j**, were obtained in good yields ranging from 67% to 78%. However, hydroboration-oxydation reactions on the more hindered *N*-protected α-trifluoromethyl α-methyl β-phenyl homoallylic amines (S_S,*R*,*R*)-**2i** (*anti*-**2i**) and (S_S,*R*,*S*)-**2i** (*syn*-**2i**) were more sluggish. After 20h of reaction a room temperature, only 79% conversion of *anti*-**2i** and 42% of *syn*-**2i** were observed. The corresponding *N*-protected aminoalcohols (S_S,*R*,*S*)-**6d** and (S_S,*R*,*R*)-**6d** were thus isolated in only 50% and 32% yield, respectively. Replacing 9-BBN with the less bulky $BH_3.Me_2S$ did not improve the yield. Under these last conditions the 1,4-aminoalcohol (S_S,*R*,*R*)-**6d** was isolated in 30% yield. The absolute configurations of the stereogenic carbons of the δ-aminoalcohols (S_S,*S*)-**6a** and (S_S,*R*,*R*)-**6d** were determined by X-ray crystallographic analyses (scheme 5).



Scheme 5: Preparation of the *N*-*tert*-butanesulfinyl 1,4-aminoalcohols **6a-d** by hydroboration-oxidation of the *N*-protected homoallylic amines **2a,d,i-j**.

Pyrrolidines[27] and azetidines,[28] including trifluoromethylated ones,[29,30] are highly versatile small nitrogen-containing rings. The 2-trifluoromethylazetidines and 2-trifluoromethylpyrrolidines bearing the fluorinated substituent on a tetrasubstituted carbon have for most of them been described as trifluoromethylated constrained aminoacids and their derivatives.[31] Other examples of 2-substituted 2-trifluoromethyl 4- and 5-membered aza-heterocycles are less common. To our knowledge, only pyrrolidines belonging to this family of trifluoromethylated building blocks have been reported, and almost exclusively in racemic version,[32] their asymmetric synthesis was described only once to date.[26] The *N*-*tert*-butanesulfinyl pyrrolidines **7a**-**b** were prepared by cyclisation of the 1,4-sulfinamidoalcohols (S_S,*S*)-**6a** and **6c**, while the *N*-*tert*-butanesulfinyl azetidine **7c** was obtained from the 1,3-sulfinamidoalcohol (S_S,*R*,*S*)-**5**. The treatment of the *N*-protected aminoalcohol (S_S,*S*)-**6a** under Mitsunobu conditions (PPh_3, DIAD, Et_3N) led to the desired pyrrolidine (S_S,*S*)-**7a** with only 54% conversion after 32h of reaction at room temperature. The cyclisation was thus achieved by reacting the suitable sulfinamidoalcohol (S_S,*S*)-**6a**, **6c** or (S_S,*R*,*S*)-**5** with NaH and tosyl chloride (scheme 6). Cyclisations of *N*-protected δ-aminoalcohols (S_S,*S*)-**6a** and **6c** were completed within 15h of stirring and the corresponding disubstituted pyrrolidine (S_S,*S*)-**7a** and trisubstituted pyrrolidine (S_S,*R*,*R*)-7**b** were isolated in 84% and 71% yield, respectively, in enantiomerically pure form. The cyclisation of the *N*-protected 1,3-aminoalcohol (S_S,*R*,*S*)-**5** into the trisubstituted *N*-*tert*-butanesulfinyl azetidine (S_S,*R*,*R*)-**7c** was more sluggish but the azetidine (S_S,*R*,*R*)-**7c** was finally isolated in 65% yield. Thanks to the presence of the vinyl substituent, the azetidine (S_S,*R*,*R*)-**7c** could be further functionalized.



Scheme 6: Preparation of the pyrrolidines **7a-b** and the azetidine **7c** by cyclisation of the sulfinamidoalcohols **6a,c** and **5**.

Conclusion

In conclusion, we described the zinc- and indium-mediated asymmetric allylation of *in situ* generated trifluoromethyl *N*-*tert*-butanesulfinyl ketimines to prepare *N*-protected trifluoromethylated homoallylic tertiary carbinamine derivatives. We have shown that variously substituted allylzinc reagents could react even if the yields and the diastereoselectivities highly depend on the steric hindrance of the metal reagent and of the intermediate ketimine. It is interesting to note that this approach gave particularly good results with trifluoromethyl methyl hemiaminal. The scope of the indium-mediated allylation was much narrow. The highly functionalized enantiopure trifluoromethylated homoallylic tertiary carbinamine derivatives containing one or two vicinal stereogenic centers are synthetic building blocks that can be readily transformed into other valuable trifluoromethyl derivatives.

Experimental section

General experimental

Hemiaminals **1a-b** were prepared as previously described.[12a] Zinc was activated by stirring with a 10% (v/v) HCl solution and successive washing with distilled H_2O, 95% EtOH, and Et_2O. Zn

was then dried thoroughly in a vacuum oven at 70°C for at least 24h (activated Zn can be stored under these conditions for 10 days). Indium powder 99.99% was purchased from Strem Chemicals. THF was dried using a Pure Solv solvent drying system over aluminium oxide under an Argon atmosphere. 2-Me-THF (extra-dry, water < 0.005%, on molecular sieves) was purchased from Acros Organics. DMF (extra-dry, water < 0.005%) was purchased from Acros Organics and was freshly distilled on P_2O_5 under reduced pressure. EtOH was freshly distilled on sodium. Thin–layer chromatography using precoated aluminium backed plates (Merck Kieselgel 60F254) were visualized by UV light and/or by phosphomolybdic acid. Homoallylic sulfinamides **2a-i** prepared by Zn-mediated allylation were purified by flash chromatography using silicagel 15-40 μm (Merck) and an Armen flash pump. Otherwise compounds were purified by flash chromatography using silicagel 40-63 μm (Macherey-Nagel GmbH & Co KG). Melting points (mp) were determined on a Stuart apparatus SMP3 and were uncorrected. Optical rotations were measured on a Perkin Elmer precisely model 341 polarimeter at room temperature (*c.a.* 20 °C). NMR spectra were recorded on a Bruker advance 250 or a Bruker Advance III 500. Coupling constants (*J*) are reported in Hz. In the ^{13}C NMR data, reported signal multiplicities are related to C–F coupling. HRMS were recorded on a Micromass ESI-Q–TOF mass spectrometer using an electrospray source in positive mode (ESI^+). X-ray diffraction images were collected on a Bruker D8 Venture diffractometer, using Cu Kα microsource radiation (from a multi-layered focalizing mirrors optics monochromator) and a PHOTON100 CMOS detector. Data were collected using Bruker Apex2 software. Sample temperature was maintained at 100K using Cryostream700 (Oxford Cryosystems). Cell refinement and data reduction were performed by Bruker SAINT. Structure was solved using Sir92 (Giacovazzo et al, 1993) or using SHELXS-97 (Sheldrick, 2008). Structure was refined using SHELXL-97 (Sheldrick, 1997).

General procedure for the Zn-mediated allylation of *N-tert*-butanesulfinyl hemiaminal.

A suspension of trifluoromethylhemiaminal **1a-b**, allylic bromide (2.5 equiv) and activated zinc (2.5 equiv) in freshly distilled DMF was stirred under Ar at -20°C (for amine **2a-b,d-f,j,k**), 0°C (for amine **2i**) or room temperature (for amine **2c,g,h**). After completion (reaction monitored by ^{19}F NMR), the reaction mixture was diluted with AcOEt, filtered on a pad on Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel.

General procedure for the In-mediated allylation of *N-tert*-butanesulfinyl hemiaminal.

To a solution of trifluoromethylhemiaminal **1a-b** in THF was added indium (3 equiv) at room temperature and under Ar. The suspension was heated at reflux and, after 15 minutes of stirring at this temperature, allylic bromide (2 equiv) was added. After completion (reaction monitored by ^{19}F NMR), the reaction mixture was cooled to rt, diluted wit AcOEt and hydrolyzed with an aq. sol. of HCl (1M). The aqueous layer was extracted 3 times with AcOEt. The organic layers were combined, washed with a sat. aq. sol. of Na_2CO_3, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel.

(+)-(*S*)-2-methyl-*N*-((*S*)-1,1,1-trifluoro-2-phenylpent-4-en-2-yl)propane-2-sulfinamide (S_S,*S*)-2a.

Following the general procedure for the Zn-mediated allylation, hemiaminal **1a** (181 mg, 0.56 mmol) reacted with allyl bromide (121 µL, 1.40 mmol, 2.5 equiv) and Zn (92 mg, 1.40 mmol, 2.5 equiv) in DMF (2 mL) at -20°C for 18h. Chromatography of the residue [*dr* (S_S,*S*):(S_S,*R*)=96:4] on silica gel (PE:EtOAc 80 :20) yielded the sulfinamide (S_S,*S*)-**2a**[9b] (120

mg, 67%) as a colorless oil. Following the general procedure for the In-mediated allylation, hemiaminal **1a** (333 mg, 0.56 mmol) reacted with allyl bromide (178 µL, 2.06 mmol, 2 equiv) and In (354 mg, 3.09 mmol, 3 equiv) in THF (12 mL) for 5h. Chromatography of the residue [*dr* (S_S,*S*):(S_S,*R*)=96:4] on silica gel (PE :Et_2O 92:8 to 50 :50) yielded the sulfinamide (S_S,*S*)-**2a**[9b] (206 mg, 63%) as a colorless oil (Found : $[M+Na]^+$, 342.1113. $C_{15}H_{20}F_3NNaOS$ requires 342.1115) ; $[\alpha]_D^{20}$ = +28 (*c* 1.01 in $CHCl_3$) ; δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -73.5 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.25 (9 H, s), 3.06 (1 H, dd, *J* 7.0 and 14.5), 3.14 (1 H, dd, *J* 7.0 and 14.5), 4.12 (1 H, s), 5.20 (1 H, d, *J* 10.0), 5.27 (1 H, dd, *J* 1.5 and 17.0), 5.63 (1 H, m), 7.39 (3 H, m) and 7.59 (2 H, d, *J* 7.5 Hz) ; δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 22.8, 40.0, 57.6, 65.9 (d, *J* 26.0), 121.7, 125.7 (q, *J* 287.0), 128.4, 129.0, 130.8 and 134.9.

(*S*)-2-methyl-*N*-((*S*)-1,1,1-trifluoro-4-methyl-2-phenylpent-4-en-2-yl)propane-2-sulfinamide 2b.

Following the general procedure for the Zn-mediated allylation, hemiaminal **1a** (176 mg, 0.54 mmol) reacted with 3-bromo-2-methylpropene (137 µL, 1.36 mmol, 2.5 equiv) and Zn (89 mg, 1.36 mmol, 2.5 equiv) in DMF (2.5 mL) at -20°C for 16h. Chromatography of the residue [*dr* (S_S,*S*):(S_S,*R*)=79:21] on silica gel (PE:EtOAc 80 :20) yielded the sulfinamide **2b**[9b] (118 mg, *dr*=79 :21, 65%) as a colorless oil. Following the general procedure for the In-mediated allylation, hemiaminal **1a** (326 mg, 1.01 mmol) reacted with 3-bromo-2-methylpropene (204 µL, 2.02 mmol, 2 equiv) and In (346 mg, 3.02 mmol, 3 equiv) in THF (12 mL) for 5h30. Chromatography of the residue [*dr* (S_S,*S*):(S_S,*R*)=87:13] on silica gel (PE:Et_2O 92:8 to 50 :50) yielded the sulfinamide **2b**[9b] (249 mg, *dr*=87:13, 74%) as a colorless oil (Found : $[M+NH]^+$, 334.1457. $C_{16}H_{23}F_3NOS$ requires 334.1452) ; δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -71.4 (s, *minor*) and -72.6 (s, *major*); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.25 and 1.27 (9 H, s, *major* and *minor*), 1.43 and 1.44 (3 H, s, *minor* and *major*), 2.93 and 2.95 (1 H, d, *J* 14.5, *major* and *minor*), 3.04

and 3.09 (1 H, d, *J* 14.5, *major* and *minor*), 4.03 and 4.31 (1 H, s, *minor* and *major*), 4.61 and 4.85 (1 H, s, *minor* and *major*), 4.88 and 4.97 (1 H, t, *J* 1.5, *minor* and *major*), 7.37 (3 H, m, *minor* and *major*), 7.58 and 7.66 (2 H, d, *J* 8.0, *minor* and *major*) ; δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 22.81 and 22.83 (*minor* and *major*), 24.03 and 24.06 (*minor* and *major*), 43.7 and 44.0 (*major* and *minor*), 57.5 and 57.7 (*minor* and *major*), 66.1 and 66.7 (q, *J* 26.0, *major* and *minor*), 117.6 and 118.6 (*minor* and *major*), 125.7 and 125.8 (q, *J* 287.0, *minor* and *major*), 127.8 (q, *J* 2.0, *minor*), 128.4 (*major*), 128.5 (q, *J* 1.5, *major*), 128.6 and 128.7 (*major* and *minor*), 128.9 (*major*), 135.6 and 137.0 (*major* and *minor*), 138.8 and 139.0 (*minor* and *major*).

(-)-(*S*)-2-methyl-*N*-((*S*)-1,1,1-trifluoro-3,3-dimethyl-2-phenylpent-4-en-2-yl)propane-2-sulfinamide (S_S,*S*)-**2c.**

Following the general procedure for the Zn-mediated allylation, hemiaminal **1a** (561 mg, 1.73 mmol) reacted with 3,3-dimethylallylbromide (501 µL, 4.34 mmol, 2.5 equiv) and Zn (284 mg, 4.34 mmol, 2.5 equiv) in DMF (7.5 mL) at room temperature for 15h. Chromatography on silica gel (PE:EtOAc 85 :15) yielded the sulfinamide (S_S,*S*)-**2c**[9b] (178 mg, 26%) as a colorless oil (Found : $[M+Na]^+$, 370.1416. $C_{17}H_{24}F_3NNaOS$ requires 370.1428) ; $[\alpha]_D^{20}$ = -48 (*c* 0.66 in $CHCl_3$) ; δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -60.4 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.00 (3 H, s), 1.20 (3 H, q, *J* 1.5), 1.22 (s, 9 H), 4.42 (1 H, s), 5.22 (1 H, d, *J* 17.5), 5.29 (1 H, d, *J* 11.0), 5.86 (1 H, dd, *J* 11.0 and 17.5), 7.37 (3 H, m) and 7.71 (2 H, d, *J* 7.5) ; δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 22.8, 23.1 (q, *J* 2.5), 24.5 (q, *J* 2.0), 45.2, 58.5, 72.9 (q, *J* 24.0), 116.1, 127.0 (q, *J* 290.0), 127.4, 128.5, 130.1, 133.7 and 143.6 (q, *J* 1.0).

(+)-(*S*)-2-methyl-*N*-((*R*)-1,1,1-trifluoro-2-methylpent-4-en-2-yl)propane-2-sulfinamide (S_S,*R*)-**2d.**

Following the general procedure for the Zn-mediated allylation, hemiaminal **1b** (150 mg,

0.57 mmol) reacted with allyl bromide (124 µL, 1.43 mmol, 2.5 equiv) and Zn (94 mg, 1.43 mmol, 2.5 equiv) in DMF (2.5 mL) at -20°C for 22h. Chromatography of the residue [*dr* (S_S,*R*):(S_S,*S*)>99:1] on silica gel (PE:EtOAc 80 :20) yielded the sulfinamide (S_S,*R*)-**2d**[9b] (111 mg, 76%) as a white solid. Following the general procedure for the In-mediated allylation, hemiaminal **1b** (263 mg, 1.01 mmol) reacted with allyl bromide (173 µL, 2.00 mmol, 2 equiv) and In (345 mg, 3.03 mmol, 3 equiv) in THF (10 mL) for 4h. Chromatography of the residue [*dr*(S_S,*R*):(S_S,*S*)>99:1] on silica gel (PE:Et_2O 50:50) yielded the sulfinamide (S_S,*R*)-**2d**[9b] (200 mg, 77%) as a white solid (Found : $[M+H]^+$, 258.1128. $C_{10}H_{19}F_3NOS$ requires 258.1139) ; mp 94°C (from Et_2O-PE); $[\alpha]_D^{20}$ = +103 (*c* 1.00 in $CHCl_3$) ; δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -80.2 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.18 (9 H, s), 1.53 (3 H, s), 2.42 (1 H, dd, J 8.5 and 14.0), 2.54 (1 H, dd, *J* 6.5 and 14.0), 3.63 (s, 1 H), 5.22 (1 H, dd, *J* 1.5 and 17.0), 5.27 (1 H, d, *J* 10.0) and 5.80 (m, 1 H) ; δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 18.9 (q, *J* 1.5), 22.5, 41.3, 56.6, 59.7 (q, *J* 26.5), 121.9, 126.4 (q, *J* 285.0) and 130.7. An analytical sample of (S_S,*R*)-**2d** was crystallized in CH_2Cl_2-PE. Full crystallographic data for this compound have been deposited with the CCDC, reference number 1577908.

(+)-(*S*)-2-methyl-*N*-((*R*)-1,1,1-trifluoro-2,4-dimethylpent-4-en-2-yl)propane-2-sulfinamide (S_S,*R*)-**2e.**

Following the general procedure for the Zn-mediated allylation, hemiaminal **1b** (155 mg, 0.59 mmol) reacted with 3-methyl-2-methylpropene (150 µL, 1.48 mmol, 2.5 equiv) and Zn (97 mg, 1.48 mmol, 2.5 equiv) in DMF (2.5 mL) at -20°C for 22h. Chromatography of the residue [*dr* (S_S,*R*):(S_S,*S*)>99:1] on silica gel (PE:EtOAc 80 :20) yielded the sulfinamide (S_S,*R*)-**2e** (115 mg, 72%) as a white solid. Following the general procedure for the In-mediated allylation, hemiaminal **1b** (263 mg, 1.01 mmol) reacted with allyl bromide (202

μL, 2.00 mmol, 2 equiv) and In (345 mg, 3.03 mmol, 3 equiv) in THF (12 mL) for 4h. Chromatography of the residue [*dr*(S_S,*R*):(S_S,*S*)>99:1] on silica gel (PE:Et_2O 60:40) yielded the sulfinamide (S_S,*R*)-**2e** (187 mg, 69%) as a white solid (Found : $[M+Na]^+$, 294.1118. $C_{11}H_{20}F_3NNaOS$ requires 294.1115) ; mp 65°C (from Et_2O-PE); $[\alpha]_D^{20}$ = +95 (*c* 1.01 in $CHCl_3$) ; δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -80.3 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.14 (9 H, s), 1.57 (3 H, s), 1.78 (3 H, s), 2.38 (1 H, d, *J* 15.0), 2.41 (1 H, d, *J* 15.0), 3.91 (1 H, s), 4.89 (1 H, s) and 5.02 (1 H, s) ; δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 19.4 (q, *J* 1.5), 22.4, 24.1, 44.4, 56.4, 59.2 (q, *J* 27.0), 118.7, 126.3 (q, *J* 284.5) and 139.4.

(+)-(*R*)-ethyl 4-((*S*)-1,1-dimethylethylsulfinamido)-5,5,5-trifluoro-4-methyl-2-methylenepentanoate (S_S,*R*)-**2f.**

Following the general procedure for the Zn-mediated allylation, hemiaminal **1b** (152 mg, 0.58 mmol) reacted with ethyl (2-bromomethyl)acrylate (201 μL, 1.46 mmol, 2.5 equiv) and Zn (95 mg, 1.46 mmol, 2.5 equiv) in DMF (2.5 mL) at -20°C for 24h. Chromatography of the residue [*dr* (S_S,*R*):(S_S,*S*)=96:4] on silica gel (PE:EtOAc 80 :20) yielded the sulfinamide (S_S,*R*)-**2f** (131 mg, 68%) as a colorless oil (Found : $[M+Na]^+$, 352.1162. $C_{13}H_{22}F_3NNaO_3S$ requires 352.1170) ; $[\alpha]_D^{20}$ = +71 (*c* 1.00 in $CHCl_3$) ; δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -81.4 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.14 (9 H, s), 1.27 (3 H, t, *J* 7.0), 1.52 (3 H, s), 2.38 (1 H, d, *J* 14.0), 2.98 (1 H, d, *J* 14.0), 4.18 (2 H, qd, *J* 1.0 and 7.0), 5.04 (1 H, s), 5.74 (1 H, s) and 6.44 (1 H, s); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 14.1, 17.5, 22.6, 37.2, 56.2, 60.2 (q, *J* 26.5), 61.8, 126.4 (q, *J* 285.0), 131.8, 133.8 and 168.4.

(*S*)-2-methyl-*N*-((*R*)-1,1,1-trifluoro-2,3,3-trimethylpent-4-en-2-yl)propane-2-sulfinamide (S_S,*R*)-**2g.**

Following the general procedure for the Zn-mediated allylation, hemiaminal **1b** (320 mg,

1.22 mmol) reacted with 3,3-dimethylallylbromide (354 μL, 3.06 mmol, 2.5 equiv) and Zn (200 mg, 43.06 mmol, 2.5 equiv) in DMF (5 mL) at room temperature for 16h. Chromatography on silica gel (PE:EtOAc 80:20) yielded the sulfinamide (S_S,*R*)-**2g** (210 mg, 60%) as a colorless oil (Found : $[M+Na]^+$, 308.1265. $C_{12}H_{22}F_3NNaOS$ requires 308.1272) ; $[\alpha]_D^{20}$ = +77 (*c* 0.32 in $CHCl_3$) ; δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -77.3 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.17 (12 H, s), 1.18 (3 H, s), 1.56 (3 H, s), 4.11 (1 H, s), 5.17 (1 H, d, *J* 17.5), 5.27 (1 H, d, *J* 11.0) and 6.02 (1 H, m); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 14.8 (q, *J* 2.0), 22.2 (q, *J* 1.0), 22.8, 23.9 (q, *J* 2.5), 43.2, 56.9, 64.2 (q, *J* 24.5), 116.9, 127.2 (q, *J* 287.5) and 143.8 (q, *J* 1.0).

(*S*)-2-methyl-*N*-(1,1,1-trifluoro-2,3-diphenylpent-4-en-2-yl)propane-2-sulfinamide 2h. Following the general procedure for the Zn-mediated allylation, hemiaminal **1a** (538 mg, 1.66 mmol) reacted with 3-bromo-1-phenyl-1-propene (820 □□, 4.16 mmol, 2.5 equiv) and Zn (272 mg, 4.16 mmol, 2.5 equiv) in DMF (7.5 mL) at room temperature for 15h. Chromatography of the residue (*dr*=4:8:88:0) on silica gel (PE:EtOAc 85:15) yielded the sulfinamide **2h** (372 mg, *dr*=4:8:88:0, 57%) as a pale yellow oil (Found : $[M+H]^+$, 396.1607. $C_{21}H_{25}F_3NOS$ requires 396.1609) ; δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -64.0 (s, 4%), -65.0 (s, 8%) and -66.1 (s, 88%). *major diastereomer* δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.24 (9 H, s), 4.22 (1 H, d, *J* 10.0), 4.52 (1 H, s), 5.31 (2 H, m), 6.35 (1 H, dtd, *J* 1.5, 10.0 and 16.5), 6.97 (2 H, dd, *J* 2.0 and 7.5), 7.22 (3 H, m), 7.40 (3 H, m) and 7.68 (2 H, d, *J* 7.5); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 22.7, 58.2, 58.7, 70.0 (q, *J* 24.0), 120.3, 126.1 (q, *J* 288.5), 127.7, 128.0, 128.1, 128.9, 129.85, 129.93, 134.0, 135.8 and 137.1.

(-)-(*S*)-2-methyl-*N*-((2*R*,3*R*)-1,1,1-trifluoro-2-methyl-3-phenylpent-4-en-2-yl)propane-2-sulfinamide (S_S,*R*,*R*)-**2i** (*syn*-**2i**) and **(+)-(*S*)-2-methyl-*N*-((2*R*,3*S*)-1,1,1-trifluoro-2-**

methyl-3-phenylpent-4-en-2-yl)propane-2-sulfinamide (S_S,*R*,*S*)-**2i** (*anti*-**2i**).

Following the general procedure for the Zn-mediated allylation, hemiaminal **1b** (1.83 g, 7.00 mmol) reacted with 3-bromo-1-phenyl-1-propene (3.45 □, 17.51 mmol, 2.5 equiv) and Zn (1.14 g, 17.51 mmol, 2.5 equiv) in DMF (25 mL) at 0°C for 15h. Chromatography of the residue [*dr*=41:0:59:0, *dr*(S_S,*R*,*R*):(S_S,*R*,*S*)=59:41] on silica gel (PE:EtOAc 90:10) afforded first the sulfinamide (S_S,*R*,*R*)-**2i** (909 mg, 39%) as a colorless oil, and then the sulfinamide (S_S,*R*,*S*)-**2i** (465 mg, 20%) as a colorless oil. (S_S,*R*,*R*)-**2i** (Found : $[M+Na]^+$, 356.1274. $C_{16}H_{22}F_3NaNOS$ requires 356.1272) ; $[\alpha]_D^{20}$ -9 (*c* 0.81 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -75.9 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) □.22 (9 H, s), 1.62 (3 H, s), 3.72 (1H, d, *J* 10.0), 4.15 (1 H, s), 5.23 (1 H, dd, *J* 1.0 and 17.0), 5.29 (1 H, dd, *J* 1.5 and 10.0), 6.52 (1 H, dt, *J* 10.0 and 17.0) and 7.25-7.38 (5 H, m); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 18.4, 22.6, 55.9, 56.8, 62.6 (q, *J* 25.0), 119.3, 126.3 (q, *J* 286.0), 127.6, 128.8, 129.7, 135.8 and 138.6. (S_S,*R*,*S*)-**2i** (Found : $[M+H]^+$, 334.1452. $C_{16}H_{23}F_3NOS$ requires 334.1452) ; $[\alpha]_D^{20}$ +123 (*c* 0.48 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -75.4 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) □.20 (9 H, s), 1.60 (3 H, s), 3.72 (1 H, d, *J* 9.5), 3.95 (1 H, s), 5.20 (1 H, d, *J* 17.0), 5.29 (1 H, d, *J* 10.0), 6.33 (1 H, m) and 7.25-7.37 (5 H, m); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 18.1, 22.6, 56.8, 57.2, 62.7 (q, *J* 25.5), 120.4, 126.4 (q, *J* 286.0), 127.7, 128.6, 130.1, 135.4 and 137.6.

(*S*)-2-methyl-*N*-((2*R*)-1,1,1-trifluoro-2,3-dimethylpent-4-en-2-yl)propane-2-sulfinamide 2j.

Following the general procedure for the Zn-mediated allylation, hemiaminal **1b** (154 mg, 0.59 mmol) reacted with *trans*-crotyl (152 µL, 1.48 mmol, 2.5 equiv) and Zn (96 mg, 0.59 mmol, 2.5 equiv) in DMF (2.5 mL) at -20°C for 22h. Chromatography of the residue (*dr*=96:3:1:0, *dr syn*:*anti* 4:96) on silica gel (PE:EtOAc 80:20) afforded the sulfinamide **2j**

(96 mg, *dr*=96:3:1:0, 60%) as a colorless oil (Found : $[M+Na]^+$, 294.1112. $C_{11}H_{20}F_3NaNOS$ requires 294.1115); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -75.4 (s, 3%), -76.2 (s, 1%) and -76.6 (s, 96%). (S_S,*R*,*R*)-**2j** δ_H (500 MHz ; $CDCl_3$; Me_4Si) □.14 (3 H, d, *J* 7.0), 1.17 (9 H, s), 1.52 (3 H, s), 2.62 (1 H, quint, *J* 7.0), 3.71 (1 H, s), 5.16 (1 H, d, *J* 17.0), 5.22 (1 H, d, *J* 10.5) and 5.87 (1 H, m); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 14.2 (q, *J* 1.5), 16.6 (q, *J* 2.0), 22.6, 42.4, 56.6, 62.1 (q, *J* 25.5), 118.6, 126.6 (q, *J* 286.0) and 137.9.

(+)-(*S*)-methyl 2-((*R*)-2-((*S*)-1,1-dimethylethylsulfinamido)-1,1,1-trifluoropropan-2-yl)but-3-enoate (S_S,*R*,*S*)-**2k** (*syn*-**2k**) and **(+)-(*R*)-methyl 2-((*R*)-2-((*S*)-1,1-dimethylethylsulfinamido)-1,1,1-trifluoropropan-2-yl)but-3-enoate** (S_S,*R*,*R*)-**2k** (*anti*-**2k**).

Following the general procedure for the Zn-mediated allylation, hemiaminal **1b** (1.50 g, 5.76 mmol) reacted with methyl 4-bromocrotonate (2.00 mL, 14.39 mmol, 2.5 equiv) and Zn (940 mg, 14.39 mmol, 2.5 equiv) in DMF (20 mL) at -20°C for 16h. Chromatography of the residue [*dr*=64:0:36:0, *dr*(S_S,*R*,*S*):(S_S,*R*,*R*)=36:64] on silica gel (PE:EtOAc from 80:20 to 60:40) afforded first the *N*-protected aminoester (S_S,*R*,*S*)-**2k** (514 mg, 28%) as a colorless oil, and then the *N*-protected aminoester (S_S,*R*,*R*)-**2k** (989 mg, 54%) as a colorless oil. (S_S,*R*,*S*)-**2k** (Found : $[M+H]^+$, 316.1194. $C_{12}H_{21}F_3NO_3S$ requires 316.1194); $[\alpha]_D^{20}$ +25 (*c* 0.93 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -79.9 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) □.26 (9 H, s), 1.52 (3 H, s), 3.25 (1 H, d, *J* 9.5), 3.71 (1 H, d, *J* 9.5), 3.71 (3 H, s), 5.33 (1 H, d, *J* 17.0), 5.39 (1 H, d, *J* 1.0 and 10.0), 6.01 (1 H, dt, *J* 10.0 and 17.0) and 6.03 (1 H, s); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 17.1 (q, *J* 1.5), 22.8, 52.5, 52.8, 56.6, 61.7 (q, *J* 27.0), 122.5, 126.0 (q, *J* 285.5), 130.4 and 172.8. (S_S,*R*,*R*)-**2k** (Found : $[M+H]^+$, 316.1198. $C_{12}H_{21}F_3NO_3S$ requires 316.1194); $[\alpha]_D^{20}$ +127 (*c* 0.93 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -76.8 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) □.21 (9 H, s), 1.62 (3 H, s), 3.40 (1 H, d,

J 10.0 Hz), 3.71 (3 H, s), 5.10 (1 H, s), 5.22 (1 H, d, *J* 17.0 Hz), 5.30 (1 H, dd, *J* 1.0 and 10.0) and 5.93 (1 H, dtd, *J* 1.0, 10.0 and 17.0); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 18.4 (q, *J* 1.0), 22.6, 52.7, 56.5, 56.7, 61.9 (q, *J* 27.0), 121.9, 125.8 (q, *J* 286.0), 130.4 and 171.2.

General procedure for the hydrogenation reaction.

A suspension of homoallyl amine **2j**,**k** and Pd/C 10% (0.05 equiv) in MeOH was hydrogenated at room temperature and under atmospherique pressure. After 14-17h of stirring, the reaction mixture was filtered on celite®, the filtrate was concentrated under reduced pressure and the residue was purified by chromatography on silica gel.

(*S*)-2-methyl-*N*-((2*R*)-1,1,1-trifluoro-2,3-dimethylpentan-2-yl)propane-2-sulfinamide 3a.

Following the general procedure for the hydrogenation, amine **2j** (145 mg, 0.53 mmol) reacted with H_2 and Pd/C 10% (28 mg, 0.05 equiv) in MeOH (5 mL) for 14h. Chromatography of the residue on silica gel (PE:EtOAc 85:15) yielded the sulfinamide **3a** (111 mg, *dr*=3:0:97:0, 76%) as a white solid (Found : $[M+Na]^+$, 296.1279. $C_{15}H_{22}F_3NaNOS$ requires 296.1272); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -75.4 (s, 3%) and -75.8 (s, 97%). (S_S,*R*,*R*)-**3a** δ_H (500 MHz ; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 7.0), 0.96 (3 H, d, *J* 6.5), 0.99 (1 H, m), 1.15 (9 H, s), 1.38 (3 H, s), 1.56 (1 H, dqd, *J* 2.0, 6.5 and 13.5), 1.74 (1 H, dtd, *J* 5.5, 7.5 and 13.0 Hz) and 3.30 (1 H, s); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 12.6, 13.3 (q, *J* 2.0), 15.0 (q, *J* 2.0), 22.5, 23.4, 41.0, 56.5, 64.0 (q, *J* 25.5), 126.8 (q, *J* 286.0). An analytical sample of (S_S,*R*,*R*)-**3a** was crystallized in Et_2O-hexane. Full crystallographic data for this compound have been deposited with the CCDC, reference number 1577912.

(+)-(2*S*,3*R*)-methyl 3-((*S*)-1,1-dimethylethylsulfinamido)-2-ethyl-4,4,4-trifluoro-3-methylbutanoate (S_S,*R*,*S*)-**3b.**

Following the general procedure for the hydrogenation, *N*-protected aminoester (S_S,*R*,*S*)-**2k** (155 mg, 0.49 mmol) reacted with H_2 and Pd/C 10% (26 mg, 0.05 equiv) in MeOH (5 mL) for 15h. Chromatography of the residue on silica gel (PE:EtOAc 65:35) yielded the *N*-protected aminoester (S_S,*R*,*S*)-**3b** (131 mg, 84%) as a white solid (Found : $[M+Na]^+$, 340.1168. $C_{12}H_{22}F_3NaNO_3S$ requires 340.1170); mp 99-100°C (from Et_2O); $[\alpha]_D^{20}$ +56 (*c* 1.04 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -79.8 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 0.82 (3 H, t, *J* 8.5), 1.18 (9 H, s), 1.59 (3 H, s), 1.67 (1 H, m), 1.76 (1 H, m), 2.52 (1 H, m), 3.66 (3 H, s) and 5.69 (1 H, s); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 11.2, 16.7, 20.5, 22.7, 48.8, 52.1, 56.5, 62.0 (q, *J* 26.5), 126.1 (q, *J* 286.0) and 175.2. An analytical sample of (S_S,*R*,*S*)-**3b** was crystallized in Et_2O-hexane. Full crystallographic data for this compound have been deposited with the CCDC, reference number 1577911.

(+)-(2*R*,3*R*)-ethyl 3-((*S*)-1,1-dimethylethylsulfinamido)-2-ethyl-4,4,4-trifluoro-3-methylbutanoate (S_S,*R*,*R*)-**3b.**

Following the general procedure for the hydrogenation, *N*-protected aminoester (S_S,*R*,*R*)-**2k** (141 mg, 0.45 mmol) reacted with H_2 and Pd-C 10% (24 mg, 0,05 equiv) in MeOH (5 mL) for 17h. Chromatography of the residue on silica gel (PE:EtOAc 65:35) yielded the *N*-protected aminoester (S_S,*R*,*R*)-**3b** (129 mg, 91%) as a white solid (Found : $[M+Na]^+$, 340.1177. $C_{12}H_{22}F_3NaNO_3S$ requires 340.1170); mp 129°C (from Et_2O); $[\alpha]_D^{20}$ +62 (*c* 1.01 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -77.3 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 0.83 (3 H, t, *J* 7.5), 1.16 (9 H, s), 1.56 (3 H, s), 1.69 (1 H, ddq, *J* 7.0, 12.0 and 14.0), 1.81 (1 H, dqd, *J* 3.0, 7.0 and 15.0), 2.54 (1 H, dd, *J* 3.0 and 12.0), 3.66 (3 H, s) and 4.04 (1 H, s); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 12.2, 16.6, 20.3, 22.5, 52.1, 52.8, 56.7, 62.6 (q, *J* 27.0), 125.9

(q, *J* 285.5) and 172.7.

(+)-(2*R*,3*S*)-1,1,1-trifluoro-2-methyl-3-phenylpent-4-en-2-aminium chloride (*R*,*S*)-**4a.**

A solution of (*S*$_S$,*R*,*S*)-**2i** (158 mg, 0.47 mmol) in MeOH (950 μL) reacted with HCl (2M sol. in Et_2O, 950 μL) at room temperature for 1h. The reaction mixture was then concentrated under reduced pressure and the residue was triturated with Et_2O to yield the chlorhydrate (*R*,*S*)-**4a** (88 mg, 70%) as a white solid (Found : $[M+H]^+$, 230.1148. $C_{12}H_{15}F_3N$ requires 230.1157); mp 166°C (from Et_2O); $[\alpha]_D^{20}$ +66 (*c* 0.32 in H_2O); δ_F (235 MHz ; CD_3OD ; $CFCl_3$) -75.5 (s); δ_H (500 MHz ; CD_3OD ; Me_4Si) δ□ □.64 (3 H, s), 3.96 (1 H, d, *J* 10.0), 4.88 (3 H, br s), 5.43 (1 H, d, *J* 10.0), 5.45 (1 H, d, *J* 17.0), 6.41 (1 H, dt, *J* 10.0 and 17.0) and 7.45 (5 H, m); δ_C (125.8 MHz ; CD_3OD ; Me_4Si) 15.9, 54.4, 62.9 (q, *J* 26.5), 112.7, 126.2 (q, *J* 285.0), 129.3, 129.9, 130.3, 134.1 and 137.7.

(+)-(2*R*,3*R*)-3-amino-2-ethyl-4,4,4-trifluoro-3-methylbutanoic acid (*R*,*R*)-**4b.**

A solution of (*S*$_S$,*R*,*S*)-**3b** (285 mg, 0.90 mmol) in an aqueous solution of HCl (6M sol., 10 mL) was heated at reflux for 3.5 days. After cooling to room temperature, the reaction mixture was extracted twice with Et_2O and CH_2Cl_2 and the aqueous layer was concentrated under reduced pressure. The residue was dissolved in H_2O and the product was loaded onto Dowex 50WX8 H^+ ion-exchange resin (20 g). The resin was washed several times with H_2O and the aminoacid was eluted with 12.5% aq. NH_3 and concentrated under reduced pressure to afford the aminoacid (*R*,*R*)-**4b** (159 mg, 88%) as a colorless oil (Found : $[M+H]^+$, 200.0899. $C_7H_{13}F_3NO_2$ requires 200.0898); $[\alpha]_D^{20}$ +5 (*c* 0.70 in EtOH); δ_F (235 MHz ; D_2O ; $CFCl_3$) -75.6 (s); δ_H (500 MHz ; D_2O ; Me_4Si) 0.84 (3 H, t, *J* 7.5), 1.45 (1 H, dq, *J* 6.5 and 14.0), 1.49 (3 H, s), 1.67 (1 H, m) and 2.50 (1 H, dd, *J* 3.5 and 12.0), NH_2 and CO_2H not detected; δ_C (125.8 MHz ; D_2O ; Me_4Si) 11.4, 17.9, 19.7, 51.9, 59.3 (q, *J* 28.0),

124.6 (q, *J* 284.5) and 178.1.

(+)-(*S*)-2-methyl-*N*-((2*R*,3*S*)-1,1,1-trifluoro-3-(hydroxymethyl)-2-methylpent-4-en-2-yl)propane-2-sulfinamide (*S*S,*R*,*S*)-**5.**

To a solution of (*S*S,*R*,*S*)-**2k** (145 mg, 0.46 mmol) in THF (2 mL) was added at 0°C and under Ar a solution of $LiAlH_4$ (1M sol. in THF, 553 µL, 0.55 mmol, 1.2 equiv). The temperature of the reaction was then slowly raised to room temperature. After 2 h of stirring, the reaction mixture was carefully hydrolyzed with ice until no gaz evolved and then filtered on dicalite. The filtrate was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography on silica gel (PE:EtOAc 50:50) yielded the 1,3-aminoalcohol (*S*S,*R*,*S*)-**5** (100 mg, 76%) as a white solid (Found : $[M+Na]^+$, 310.1067. $C_{11}H_{20}F_3NaNO_2S$ requires 310.1065); mp 89-90°C (from CH_2Cl_2-hexane); $[\alpha]_D^{20}$ +72 (*c* 1.01 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -77.5 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.18 (9 H, s), 1.54 (s, 3H), 2.49 (1 H, dd, *J* 6.0 and 7.0), 3.85 (1 H, dd, *J* 5.0 and 11.5), 3.95 (1 H, dd, *J* 2.0 and 11.5), 4.52 (1 H, br s), 5.12 (1 H, dd, *J* 1.0 Hz and 17.0), 5.24 (1 H, dd, *J* 1.0 and 10.0), 5.89 (1 H, s) and 6.03 (1 H, dt, *J* 10.0 and 17.0); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 17.2, 22.7, 49.8, 56.7, 63.4 (q, *J* 25.5), 64.3, 119.5, 126.5 (q, *J* 286.0) and 134.6. An analytical sample of (*S*S,*R*,*S*)-**5** was crystallized in Et_2O-hexane. Full crystallographic data for this compound have been deposited with the CCDC, reference number 1577909.

General procedure for the hydroboration-oxydation reaction.

A solution of sulfinamide **2a**,**d**,**i**,**j** and 9-BBN (0.5 sol. in THF, 2.5 equiv) in THF was stirred at room temperature and under Ar for 20-23 h. NaOAc (20% aq. sol.) and H_2O_2 (35% aq. sol.) were then added to the reaction mixture and the stirring was continued for 6-8.5 h. The reaction mixture was diluted with EtOAc and hydrolyzed with H_2O. The organic layer was

extracted three times with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel.

(+)-(*S*)-2-methyl-*N*-((*S*)-1,1,1-trifluoro-5-hydroxy-2-phenylpentan-2-yl)propane-2-sulfinamide (S_S,*S*)-**6a.**

Following the general procedure for the hydroboration-oxydation reaction, homoallylic sulfinamide (S_S,*S*)-**2a** (104 mg, 0.33 mmol) reacted with 9-BBN (0.5 N sol. in THF, 1.63 mL, 0.82 mmol, 2.5 equiv) in THF (3 mL) for 22 h and then with NaOAc (20% aq. sol., 2.6 mL) and H_2O_2 (35% aq. sol., 0.7 mL) for 6 h. Chromatography of the residue on silica gel (PE:EtOAc from 65:35 to 25:75) yielded the *N*-protected 1,4-aminoalcohol (S_S,*S*)-**6a** (77 mg, 70%) as a white solid (Found : $[M+Na]^+$, 360.1232. $C_{15}H_{22}F_3NaNO_2S$ requires 360.1221); mp 111-112°C (from EtOAc-PE); $[\alpha]_D^{20}$ +43 (*c* 1.01 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -74.6 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) □ □.29 (9 H, s), 1.63 (2 H, m), 2.49 (2 H, m), 2.50 (1 H, br s), 3.62 (2 H, m), 4.18 (1 H, s), 7.39 (3 H, m) and 7.56 (2 H, d, *J* 7.5); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 22.9, 26.4, 31.5, 57.8, 62.1, 66.7 (q, *J* 26.0), 125.9 (q, *J* 287.0), 128.4, 128.5, 129.0 and 135.2. An analytical sample of (S_S,*S*)-**6a** was crystallized in $CHCl_3$-pentane. Full crystallographic data for this compound have been deposited with the CCDC, reference number 1577907.

(+)-(*S*)-2-methyl-*N*-((*R*)-1,1,1-trifluoro-5-hydroxy-2-methylpentan-2-yl)propane-2-sulfinamide (S_S,*R*)-**6b.**

Following the general procedure for the hydroboration-oxydation reaction, homoallylic sulfinamide (S_S,*R*)-**2d** (155 mg, 0.60 mmol) reacted with 9-BBN (0.5 N sol. in THF, 2.41 mL, 1.21 mmol, 2.5 equiv) in THF (7 mL) for 23 h and then with NaOAc (20% aq. sol., 5

mL) and H_2O_2 (35% aq. sol., 1.2 mL) for 8h30. Chromatography of the residue on silica gel (PE:EtOAc from 25:75 to 15:85) yielded the *N*-protected 1,4-aminoalcohol (S_S,*R*)-**6b** (129 mg, 78%) as a white solid (Found : $[M+Na]^+$, 298.1061. $C_{10}H_{20}F_3NaNO_2S$ requires 298.1065); mp 55-56°C (from EtOAc-PE); $[\alpha]_D^{20}$ +59 (*c* 0.77 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -81.3 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) □.18 (9 H, s), 1.48 (3 H, s), 1.67 (2 H, m), 1.81 (2 H, dd, *J* 6.5 and 8.5), 3.14 (1 H, br s), 3.49 (1 H, ddd, *J* 5.5, 7.5 and 10.5), 3.70 (1 H, dt, *J* 5.0 and 10.5) and 4.38 (1 H, s); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 17.5, 22.7, 25.3, 32.0, 56.8, 60.8 (q, *J* 26.5), 61.7 and 126.6 (q, *J* 284.5).

(*S*)-2-methyl-*N*-((2*R*)-1,1,1-trifluoro-5-hydroxy-2,3-dimethylpentan-2-yl)propane-2-sulfinamide 6c.

Following the general procedure for the hydroboration-oxydation reaction, homoallylic sulfinamide **2j** (118 mg, 0.44 mmol) reacted with 9-BBN (0.5 N sol. in THF, 2.18 mL, 1.08 mmol, 2.5 equiv) in THF (4 mL) for 22 h and then with NaOAc (20% aq. sol., 3 mL) and H_2O_2 (35% aq. sol., 0.8 mL) for 6 h. Chromatography of the residue on silica gel (PE:EtOAc from 65:35 to 25:75) yielded the *N*-protected 1,4-aminoalcohol **6c** (85 mg, *dr* = 3.5:0:96.5:0, 67%) as a white solid (Found : $[M+Na]^+$, 312.1220. $C_{11}H_{22}F_3NaNO_2S$ requires 312.1221); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -74.6 (s, 3.5%) and -76.4 (s, 96.5%); (S_S,*R*,*R*)-**6c** δ_H (500 MHz ; $CDCl_3$; Me_4Si) □.02 (3 H, d, *J* 6.0), 1.18 (9 H, s), 1.22 (1 H, m), 1.48 (3 H, s), 1.93 (1 H, m), 1.98 (1 H, m), 3.44 (1 H, td, *J* 3.0 and 10.5), 3.78 (1 H, dt, *J* 4.0 and 10.5) and 4.35 (1 H, s), OH not detected; δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 13.3, 15.6 (d, *J* 2.5), 22.8, 34.6, 35.6, 56.8, 60.1, 63.9 (q, *J* 25.5) and 126.8 (q, *J* 285.5).

(+)-(*S*)-2-methyl-*N*-((2*R*,3*S*)-1,1,1-trifluoro-5-hydroxy-2-methyl-3-phenylpentan-2-yl)propane-2-sulfinamide (S_S,*R*,*S*)-**6d.**

Following the general procedure for the hydroboration-oxydation reaction, homoallylic sulfinamide (S_S,*R*,*S*)-**2i** (96 mg, 0.29 mmol) reacted with 9-BBN (0.5 N sol. in THF, 1.44 mL, 0.72 mmol, 2.5 equiv) in THF (3 mL) for 20 h and then with NaOAc (20% aq. sol., 2 mL) and H_2O_2 (35% aq. sol., 0.4 mL) for 7h30. Chromatography of the residue on silica gel (PE:EtOAc from 75:25 to 25:75) yielded the *N*-protected 1,4-aminoalcohol (S_S,*R*,*S*)-**6d** (50 mg, 50%) as a colorless oil (Found : $[M+Na]^+$, 374.1366. $C_{16}H_{24}F_3NaNO_2S$ requires 374.1378); $[\alpha]_D^{20}$ +61 (*c* 0.36 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -75.7 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) □.22 (9 H, s), 1.63 (3 H, s), 2.00 (1 H, ddt, *J* 3.5, 10.0 and 13.5), 2.33 (1 H, dddd, *J* = 2.5, 5.0, 10.5 and 13.5), 2.80 (1 H, br s), 3.17 (1 H, dd, *J* 2.0 and 10.0), 3.24 (1 H, td, *J* 3.5 and 10.5), 3.66 (1 H, ddd, *J* 3.5, 5.0 and 10.5), 4.31 (1 H, s) and 7.28 (5 H, m); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 15.1, 22.8, 33.7, 48.5, 57.0, 60.3, 64.5 (q, *J* 25.0), 126.4 (q, *J* 286.0), 127.6, 128.5 and 138.7.

(+)-(*S*)-2-methyl-*N*-((2*R*,3*R*)-1,1,1-trifluoro-5-hydroxy-2-methyl-3-phenylpentan-2-yl)propane-2-sulfinamide (S_S,*R*,*R*)-**6d.**

Following the general procedure for the hydroboration-oxydation reaction, homoallylic sulfinamide (S_S,*R*,*R*)-**2i** (117 mg, 0.35 mmol) reacted with 9-BBN (0.5 N sol. in THF, 1.75 mL, 0.82 mmol, 2.5 equiv) in THF (4 mL) for 20 h and then with NaOAc (20% aq. sol., 2.5 mL) and H_2O_2 (35% aq. sol., 0.6 mL) for 7h30. Chromatography of the residue on silica gel (PE:EtOAc from 65:35 to 25:75) yielded the *N*-protected 1,4-aminoalcohol (S_S,*R*,*R*)-**6d** (40 mg, 32%) as a white solid (Found : $[M+Na]^+$, 374.1387. $C_{16}H_{24}F_3NaNO_2S$ requires 374.1378); mp 127-128°C (from EtOAc-PE); $[\alpha]_D^{20}$ +3 (*c* 0.35 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -75.8 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) □.18 (9 H, s), 1.65 (1 H, br s), 1.66 (3 H, s), 2.24 (1 H, m), 3.19 (1 H, ddd, *J* 5.0, 9.5 and 10.5), 3.36 (1 H, dd, *J* 4.0 and 12.0), 3.54 (1 H, ddd, *J* 4.0, 6.0 and 10.), 3.99 (1 H, s), 7.28 (3 H, m) and 7.35 (2 H, m); δ_C

(125.8 MHz ; $CDCl_3$; Me_4Si) 18.0, 22.6, 31.9, 46.7, 56.8, 60.2, 63.7 (q, *J* 24.5), 126.4 (q, *J* 286.5), 127.8, 128.8 and 137.8. An analytical sample of (S_S,*R*,*R*)-**6d** was crystallized by diffusion in $CHCl_3$-pentane. Full crystallographic data for this compound have been deposited with the CCDC, reference number 1577910.

General procedure for the cyclisation reaction.

To a solution of aminoalcohol **5**, **6a,c** in THF was added portionwise at room temperature and under Ar, NaH (60% in oil, 2.03-3.00 equiv) and *p*-toluenesulfonylchloride (1.13-2.00 equiv). The reaction mixture was stirred at room temperature. After 15-48h of stirring, the reaction mixture was hydrolyzed with H_2O. The organic layer was extracted three times with AcOEt. The organic layers were combined, washed with a sat. aq. sol. of $NaHCO_3$, brine, a sat. aq. sol. of NH_4Cl, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel.

(+)-(*S*)-1-((*S*)-*tert*-butylsulfinyl)-2-phenyl-2-(trifluoromethyl)pyrrolidine (S_S,*S*)-**7a.**

Following the general procedure for the cyclisation reaction, 1,4-aminoalcohol (S_S,*S*)-**6a** (93 mg, 0.24 mmol) reacted with NaH (60% in oil, 22 mg, 0.56 mmol, 2.03 equiv) and TsCl (51 mg, 0.27 mmol, 1.13 equiv) in THF (1.5 mL) for 15h. Chromatography of the residue on silica gel (PE:EtOAc 50:50) yielded the pyrrolidine (S_S,*S*)-**7a** (63 mg, 84%) as a colorless oil (Found : $[M+H]^+$, 320.1292. $C_{15}H_{21}F_3NOS$ requires 320.1296); $[\alpha]_D^{20}$ +17 (*c* 0.98 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -71.2 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.18 (9 H, s), 2.05-2.15 (2 H, m), 2.23 (1 H, dt, *J* 6.0 and 13.0), 2.55 (1 H, dt, *J* 8.5 and 13.5), 3.16 (1 H, ddd, *J* 7.0, 8.5 and 10.0), 4.17 (1 H, dt, *J* 4.5 and 10.0), 7.33 (1 H, m), 7.39 (2 H, m) and 7.54 (2 H, dt, *J* 1.5 and 8.5); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 24.3, 24.8, 38.9, 44.0, 59.3, 76.4 (q, *J* 26.5), 127.0 (q, *J* 284.5), 127.6 (q, *J* 2.5), 128.4, 128.6 and 138.3.

(+)-(2*R*,3*R*)-1-((*S*)-*tert*-butylsulfinyl)-2,3-dimethyl-2-(trifluoromethyl)pyrrolidine (S_S,*R*,*R*)-7b.

Following the general procedure for the cyclisation reaction, 1,4-aminoalcohol **6c** (90 mg, 0.31 mmol) reacted with NaH (60% in oil, 25 mg, 0.63 mmol, 2.03 equiv) and TsCl (67 mg, 0.35 mmol, 1.13 equiv) in THF (2.5 mL) for 15h. Chromatography of the residue on silica gel (PE:EtOAc 50:50) yielded the pyrrolidine (S_S,*R*,*R*)-**7b** (60 mg, 71%) as a colorless oil (Found : $[M+Na]^+$, 294.1115. $C_{11}H_{20}F_3NaNOS$ requires 294.1115); $[\alpha]_D^{20}$ +91 (*c* 0.38 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -78.2 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.05 (3 H, d, *J* 7.0), 1.18 (9 H, s), 1.40 (1 H, m), 1.46 (3 H, s), 1.94 (1 H, dt, *J* 6.0 and 12.0), 2.43 (1 H, m), 2.80 (1 H, dt, *J* 6.0 and 10.5) and 3.89 (1 H, t, *J* 9.0); δ_C (125.8 MHz ; $CDCl_3$; Me_4Si) 14.6, 14.9, 24.2, 33.1, 38.5, 41.6, 58.5, 70.6 (q, *J* 26.5) and 127.3 (q, *J* 283.5).

(+)-(2*R*,3*R*)-1-((*S*)-*tert*-butylsulfinyl)-2-methyl-2-(trifluoromethyl)-3-vinylazetidine (S_S,*R*,*R*)-7c.

Following the general procedure for the cyclisation reaction, 1,3-aminoalcohol (S_S,*R*,*S*)-**5** (287 mg, 1.00 mmol) reacted with NaH (60% in oil, 100 mg, 2.50 mmol, 2.5 equiv) and TsCl (286 mg, 1.5 mmol, 1.5 equiv) in THF (10 mL) for 40h. NaH (60% in oil, 20 mg, 0.50 mmol, 0.5 equiv) and TsCl (95 mg, 0.5 mmol, 0.5 equiv) were then added again and the reaction was stirred 8 supplementary hours. Chromatography of the residue on silica gel (pentane:Et_2O 80:20) yielded the azetidine (S_S,*R*,*R*)-**7c** (176 mg, 65%) as a colorless liquid (Found : $[M+Na]^+$, 292.0960. $C_{11}H_{18}F_3NaNOS$ requires 292.0959); $[\alpha]_D^{20}$ +191 (*c* 0.98 in $CHCl_3$); δ_F (235 MHz ; $CDCl_3$; $CFCl_3$) -82.7 (s); δ_H (500 MHz ; $CDCl_3$; Me_4Si) 1.09 (9 H, s), 1.48 (3 H, s), 3.36 (1 H, t, *J* 8.0), 3.49 (1 H, q, *J* 8.0), 4.17 (1 H, td, *J* 2.0 and 8.0), 5.13 (1 H, dd, *J* 1.0 and 17.0), 5.19 (1 H, dd, *J* 1.0 and 10.5) and 5.75 (1 H, m); δ_C (125.8 MHz ;

$CDCl_3$; Me_4Si) 13.1, 23.2, 38.6 (q, *J* 2.5), 44.8, 57.7, 72.0 (q, *J* 30.0), 119.9, 125.5 (q, *J* 281.0) and 132.4.

Acknowledgments

We gratefully thank the Agence Nationale de la Recherche for financial support (TFM4Asym project ANR JCJC: ANR-13-JS07-0011-01), CNRS and the Conseil Regional de Champagne-Ardenne, and the EU-program FEDER for the facilities of the Analytical Platform (PlAneT CPER project). We thank A. Martinez for her technical assistance with NMR, Dr S. Chevreux for X-ray crystallographic structure determinations, S. Lanthony and Dr D. Harakat for HRMS analyses. We also thank the French Fluorine Network (GIS CNRS).

Supporting Information

Electronic supplementary information (ESI) available: Copies of NMR spectra (^{19}F, ^{1}H and ^{13}C) for compounds **2**-**7**.

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