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Studies on the diastereoselective allylation of aldehydes with enantiopure 2-sulfinylallyl building blocks

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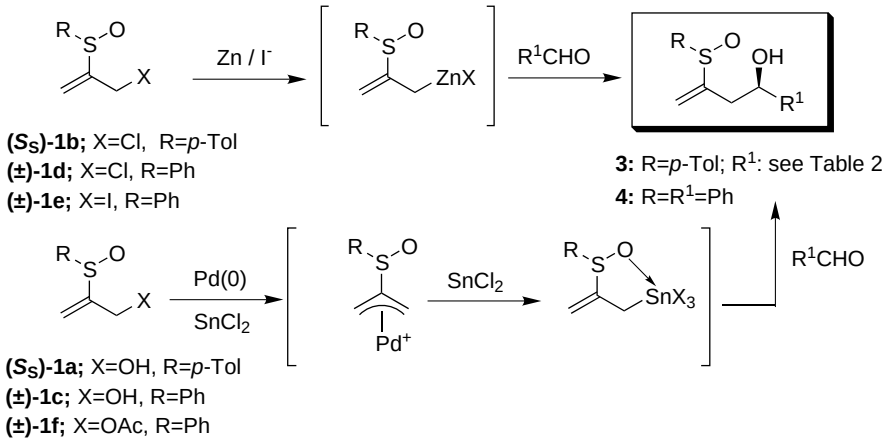
Abstract—A comparative study on the allylation of aldehydes with enantiopure (S_S)-2-(*p*-tolylsulfonyl)-prop-2-en-1-ol (S_S)-**1a** and the corresponding chloride (S_S)-**1b** under two different reaction systems is reported. In general, better yields were obtained from chloride (S_S)-**1b**, whereas higher diastereoinduction was observed from alcohol (S_S)-**1a**. The sense of diastereoinduction is the same in both systems and the stereochemistry of the major diastereomer has been determined. Moreover, the configurational stability of the sulfoxide group on the resulting sulfinyl homoallylic alcohols **3** has been proven in each reaction system, which demonstrates the efficiency of the sulfoxide group as chiral auxiliary in these allylation processes. Finally, as an example of the synthetic potential of the resulting adducts, a total synthesis of natural enantioenriched (*S*)-nicotine from sulfinylalcohol **3h** is reported.

1. Introduction

The formation of C–C bonds by reaction of carbonyl derivatives with allyl organometallic reagents is a well established synthetic methodology.[1] In recent years, efficient asymmetric versions of this process have emerged in which the chiral information resides on the carbonyl derivative[2,3] the allylmetal moiety[4–6] or the Lewis acid catalyst.[7–9] In the course of our current research aimed at the development of new building blocks based on the use of sulfoxides as chiral auxiliaries,[10] we recently reported our preliminary results on the diastereoselective allylation of aldehydes with enantioenriched (S_S)-3-chloro-2-(*p*-tolylsulfinyl)-1-propene (S_S)-**1b** under environmentally friendly Zn-promoted Barbier conditions to give the synthetically versatile homoallylic alcohols **3**.[11](Scheme 1).



Scheme 1.

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Although this method is compatible with water and takes place at low temperatures, the induced diastereoselectivity was moderate in all of the examples studied. In the search for alternative procedures to improve the diastereoselectivity, we examined the palladium-catalyzed carbonyl allylation by allylic alcohols with $SnCl_2$.[12] This method is attractive due to the higher stability of the allylic alcohol starting material in comparison with the corresponding halides used in the Barbier protocol. Moreover, carbonyl allylation under these conditions does not require the use of anhydrous solvents (a small amount of water is even beneficial) and the commonly used palladium catalysts are also stable to air, which makes the experimental procedure very simple.

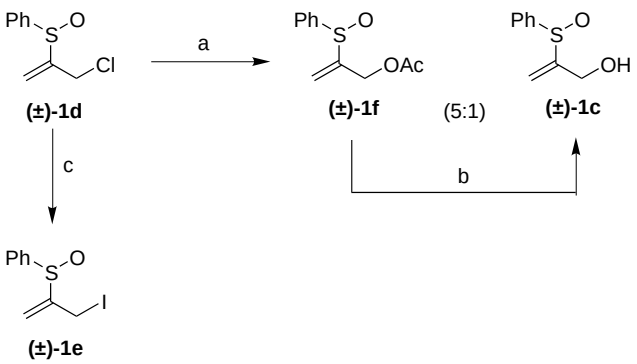
Herein, we wish to present a full account and a comparative study of our carbonyl allylation protocols with sulfinyl allyl derivatives (S_S)-**1a** and (S_S)-**1b** (Scheme 1). Special emphasis was placed on: (a) optimization of the reaction protocol in order to increase the diastereoselectivity of the processes; (b) assessment of the stereochemical integrity of the sulfoxide in the course of the allylation process; and (c) determination of the absolute configuration of the new stereogenic center of the major diastereomer **3** in each system.

In addition, as an example of the synthetic versatility of the resulting homoallylic alcohols **3**, a total synthesis of enantioenriched (*S*)-(−)-nicotine from **3h** is reported.

2. Results and discussion

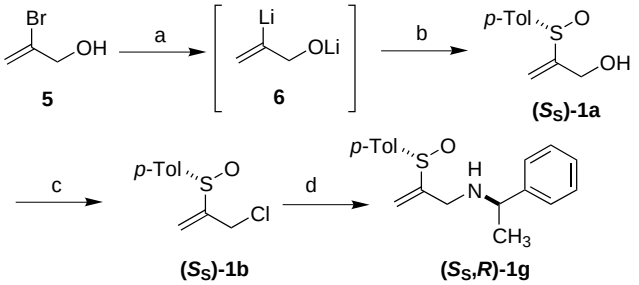
2.1. Synthesis of the allylating agents

For the preliminary studies, model sulfinyl allylic derivatives (±)-**1c**–**f** were required. Sulfinyl allylic chloride (±)-**1d** was prepared following a reported procedure,[13] whereas alcohol (±)-**1c**, iodide (±)-**1e**, and acetate (±)-**1f** were readily obtained from (±)-**1d** as depicted in Scheme 2.



Scheme 2. *Reagents and conditions*: (a) NaOAc, THF/H_2O, 80°C (91%); (b) $NaHCO_3$, THF/H_2O, 80°C (90%); (c) KI, acetone, reflux (72%).

Alcohol (S_S)-**1a**[14] was obtained from bromoalcohol **5** by a modification of a described procedure,[15] as indicated in Scheme 3. Synthesis of (S_S)-**1b** was carried out by treatment of (S_S)-**1a** with mesyl chloride in DMF followed by reaction of the intermediate mesylate (S_S)-**1f** with LiCl in DMF (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) *t*-BuLi, phenanthroline; (b) (S_S)-menthyl *p*-toluenesulfinate (50%); (c) (1) MsCl, DMF, Et_3N, (2) LiCl, DMF (70% overall); (d) (*R*)-1-phenylethylamine, CH_2Cl_2, rt (quantitative).

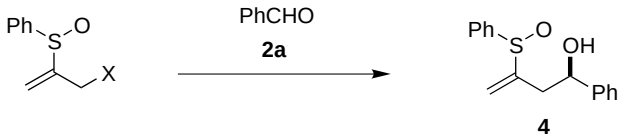
The enantiomeric excess (e.e.) of (S_S)-**1a** was determined by Mosher ester analysis, whereas that of (S_S)-**1b** was determined after reaction with (*R*)-1-phenylethylamine to give (S_S,*R*)-**1g** (Scheme 3) and comparison of selected ^1H NMR signals with those observed by reaction with (*RS*)-1-phenylethylamine (see Section 4). The e.e. of (S_S)-**1b** was comparable to that of its precursor (S_S)-**1a**, thus indicating that sulfoxide epimerization does not takes place during the transformation.

2.2. Allylation studies

Exploratory experiments were carried out with benzaldehyde and the racemic allylic derivatives (±)-**1c**–**f**. Our previous allylation studies under zinc-promoted Barbier conditions[11] revealed the importance of iodide as counterion for optimal diastereoinduction. Thus, iodide (±)-**1e** proved superior to chloride (±)-**1d** under identical conditions although the reaction occurred in lower yield[16] (Table 1, entries 1 and 2). However, it is worth noting that the diastereoselectivity from chloride (±)-**1d** could be increased upon addition of an external iodide source (entry 3).

Tin-promoted palladium-catalyzed carbonyl allylation[12] with (±)-**1c** was considered as a suitable alternative to the above Barbier-type process. Optimization experiments with (±)-**1c** in the presence of $SnCl_2$ (3 equiv.) and catalytic $Pd(PhCN)_2Cl_2$[17] under a variety of reaction conditions are collected in Table 1 (entries 5–13). The system THF/H_2O (6:1) in the presence of 10 mmol% catalyst (entry 6) afforded homoallylic alcohol **3** in better yield and diastereoselectivity than any other solvent system able to dissolve $SnCl_2$, such as DMI (entry 8), ethylene glycol (entry 9) or dioxane (entry 5). In comparison with our previously described Barbier conditions,[11] the allylations were sluggish and diastereoselectivities were higher (between 6:1 and 12:1) although at the expense of the overall yield.[18] Interestingly, the corresponding allylic acetate (±)-**1f** also afforded **3** although in lower yield (entries 7 and 10).

Table 1. Metal-promoted 2-sulfinylallylation of benzaldehyde



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Entry	Allyl	X	Metal	Catalyst (mmol%)	System[a]	Time (h)	D.r.[b]	Yield (%)[c]
1	(±)-**1d**	Cl	Zn	–	A	4	4:1	89
2	(±)-**1e**	I	Zn	–	A	1	6:1	40
3	(±)-**1d**	Cl	Zn	–	B	18	5:1	82
4	(±)-**1e**	I	Zn	–	C[d]	3	2:1	81
5	(±)-**1c**	OH	Sn/Pd	10	D	45	4:1	26
6	(±)-**1c**	OH	Sn/Pd	10	E	72	9:1	65
7	(±)-**1c**	OH	Sn/Pd	5	E	192	9:1	45
8	(±)-**1c**	OH	Sn/Pd	5	F	79	7:1	50
9	(±)-**1c**	OH	Sn/Pd	20	G	96	6:1	21
10	(±)-**1f**	OAc	Sn/Pd	5	E	48	9:1	32
11	(±)-**1c**	OH	Sn/Pd	10	E[d]	48	7:1	31
12	(±)-**1c**	OH	Sn/Pd	10	H	48	1:1	12
13	(±)-**1c**	OH	Sn/Pd	10	E[e]	50	9:1	26

[a] System A: satd aqueous NH_4Cl/THF (6:1), rt; B: NaI (3 equiv.), 1.6N aqueous NH_4I/THF (6:1), rt; C: satd aqueous NH_4Cl/THF (1:5), rt; D: dioxane/H_2O (6:1), 100°C; E: THF/H_2O (6:1), 70°C; F: DMI/H_2O (6:1), 50°C; G: ethylene glycol/H_2O (3:1), 65°C; H: 35 mM SDS/H_2O (see Ref. 20).

[b] Diastereomeric ratio calculated by ^1H NMR.

[c] Isolated yield.

[d] $Yb(OTf)_3$, 1 equiv.

[e] Sonication (see Ref. 21).

Attempts to improve these allylation processes led us to explore the use of a lanthanide as an external Lewis acid.[19] However, in our case, the use of $Yb(OTf)_3$ was detrimental in terms of diastereoselectivity in both reaction systems (comparing entries 2 with 4 and 6 with 11), although the reaction yield from (±)-**1e** was substantially improved under Barbier conditions (entry 2 versus entry 4). Finally, tin-promoted allylation in a micellar system (entry 12)[20] or under sonication (entry 13)[21] proved equally ineffective.

The best reaction conditions for each process (entries 3 and 6, Table 1) were applied to the allylation of different aldehydes with enantioenriched (S_S)-**1a** and (S_S)-**1b** (Table 2). However, initial experiments with (S_S)-**1b** and benzaldehyde under Barbier-type conditions gave rise to a somewhat lower diastereoselectivity than those observed from chloride (±)-**1d**. This drawback could be easily overcome by running the reaction at 0°C (Table 2, entry 2). This temperature was routinely used for further allylation experiments of (S_S)-**1b** with different aldehydes under Barbier conditions.

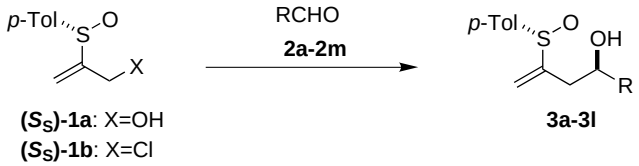
As can be seen in Table 2, both reaction systems were compatible with a range of aliphatic, cycloaliphatic and aromatic aldehydes. However, electron-rich arylcarbaldehydes such as **2f**, **2g**, and **2l** (entries 10, 12 and 19, respectively) were incompatible with the Sn/Pd allylation system.[22] Interestingly, this system allowed the allylation of dimethylacetal **2m** (entry 20) without noticeable differences from the reaction of the free aldehyde (entry 1).

In general, Barbier-type Zn-promoted allylations afforded sulfinyl allyl alcohols **3** in higher yields at lower temperatures and with shorter reaction times than the Sn/Pd system. However, the Sn/Pd methodology proved superior in terms of diastereoselectivity. The sense of diastereoinduction was identical in both allylation systems, as evidenced by comparison of crude allylation mixtures arising from condensation of (S_S)-**1a** and (S_S)-**1b** with **2a–c**, **2e**, and **2h**.

The configuration of the new stereogenic center in the major diastereomers of sulfinyl homoallylic alcohols **3** was assigned as (*R*) after ozonolysis of **3a** and **3b** to the corresponding enantioenriched β-hydroxy acids and comparison with reported data for the (*S*) enantiomers (Scheme 4).[11] Based on these results, an identical stereoinduction for the remaining homoallyl alcohols **3** was inferred.

Taking into account the generally accepted 'cyclic' and 'open-chain' transition-state models for carbonyl allylations,[23] the observed stereochemical outcome suggests the operation, in both systems, of an open antiperiplanar transition state **O1**[24] in preference to the alternative and presumably more energetic cyclic transition state **C2**.[25] On the other hand, formation of the minor diastereomers could be better explained from the cyclic transition state **C1** in preference to the open transition state **O2** (Scheme 5). The diastereoinduction achieved from each allylating system might be indicative of the contribution of each transition state (**O1** and **C1**) as a result of the different coordination properties of the

Table 2. Barbier-type and Sn-promoted/Pd-catalyzed 2-sulfinylallylation of aldehydes

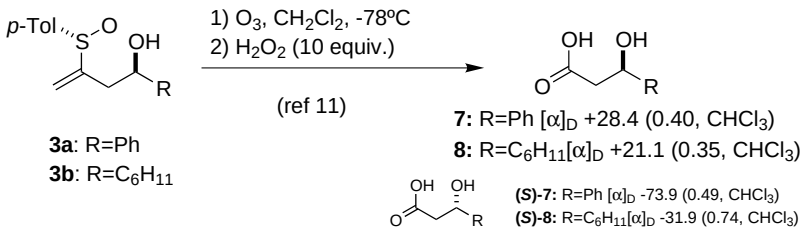


(S_S)-1a: X=OH
(S_S)-1b: X=Cl

3a-3l

Entry	Allyl	Aldehyde	R	Cond.[a]	Product	D.r.[b]	Yield (%)[c]
1	(S_S)-**1a**	**2a**	Ph	A	**3a**	9:1	55
2	(S_S)-**1b**	**2a**	Ph	B	**3a**	6:1	80
3	(S_S)-**1a**	**2b**	Cyclohexyl	A	**3b**	6:1	45
4	(S_S)-**1b**	**2b**	Cyclohexyl	B	**3b**	5:1	60
5	(S_S)-**1a**	**2c**	*n*-Bu	A	**3c**	6:1	47
6	(S_S)-**1b**	**2c**	*n*-Bu	B	**3c**	3:1	67
7	(S_S)-**1a**	**2d**	*i*-Pr	A	**3d**	9:1	48
8	(S_S)-**1a**	**2e**	*tert*-Bu	A	**3e**	12:1	30
9	(S_S)-**1b**	**2e**	*tert*-Bu	B	**3e**	5:1	60
10	(S_S)-**1a**	**2f**	*p*-(OCH_3)Ph	A	**3f**	–	–
11	(S_S)-**1b**	**2f**	*p*-(OCH_3)Ph	B	**3f**	5:1	70
12	(S_S)-**1a**	**2g**	2-Furyl	A	**3g**	–	–
13	(S_S)-**1b**	**2g**	2-Furyl	B	**3g**	4:1	60
14	(S_S)-**1a**	**2h**	3-Pyr (HCl)	A	**3h**	6:1	50
15	(S_S)-**1b**	**2h**	3-Pyr (HCl)	B	**3h**	3:1	55
16	(S_S)-**1b**	**2i**	$BnOCH_2$	B	**3i**	2:1	75
17	(S_S)-**1a**	**2j**	*p*-(F)Ph	A	**3j**	9:1	72
18	(S_S)-**1a**	**2k**	*p*-(CF_3)Ph	A	**3k**	9:1	50
19	(S_S)-**1a**	**2l**	2-Thienyl	A	**3l**	–	–
20	(S_S)-**1a**	**2m**	[d]	A	**3a**	10:1	49

[a] Conditions A: $SnCl_2$ (3 equiv.), $Pd(PhCN)_2Cl_2$ (10 mmol%), THF/H_2O (6:1), 70°C; B: Zn dust, NaI (3 equiv.), 1.6N NH_4I/THF (6:1), 0°C.
[b] Diastereomeric ratio calculated by ^1H NMR.
[c] Isolated.
[d] Benzaldehyde dimethylacetal.



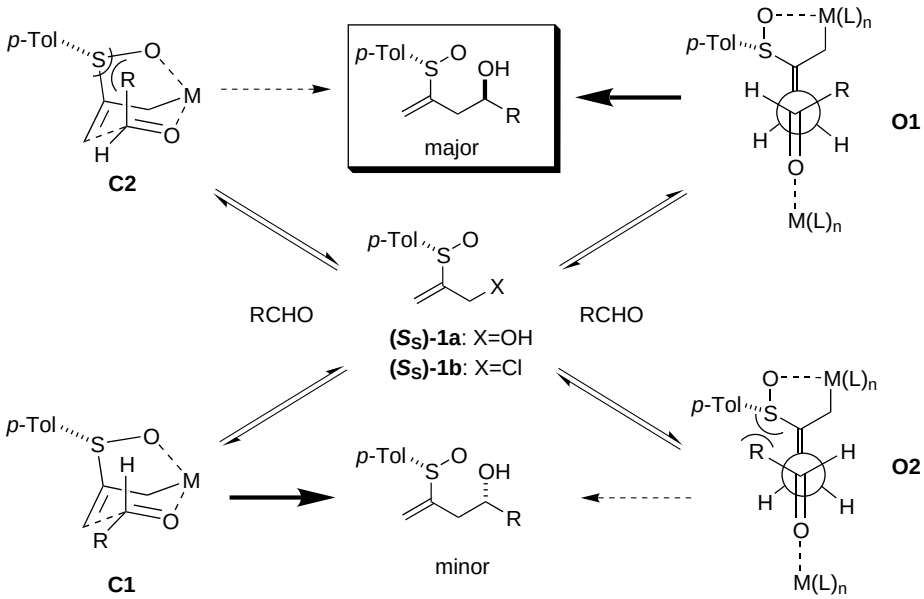
Scheme 4.

metal in each system. Thus, while a single metal–sulfoxide coordination takes place in the open transition states, a double metal–oxygen chelation can be postulated for the cyclic ones. It is thus conceivable that the lower coordination ability of Sn versus Zn is responsible for the higher contribution of **O1** versus **C1** in the Sn/Pd system in comparison with the Zn system. Moreover, the beneficial effect of iodide ions on Zn-promoted allylations is also consistent with the decrease in the Lewis acidity of Zn by coordination with iodide,[26] which would disfavor transition state **C1**.

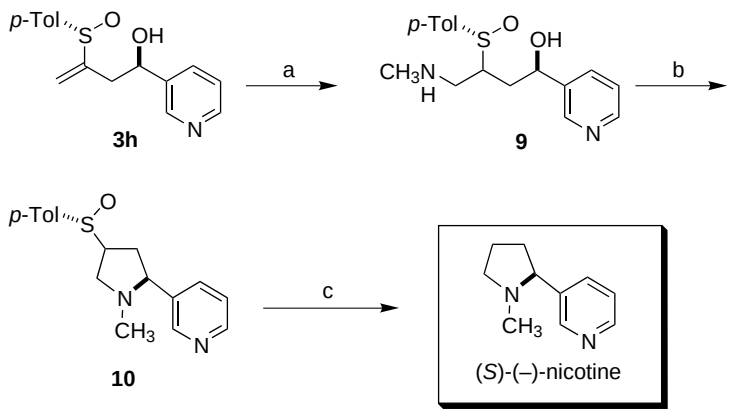
Assesment of the stereochemical integrity of the sulfoxide moiety in the allylation adducts becomes crucial to prove its efficiency as a chiral auxiliary in these processes. This was confirmed by ^1H NMR Mosher ester analysis of **3a** and **3h** (as mixture of diastereomers) with (*R*)-MTPA and comparison with the corresponding (*RS*)-MTPA esters. The observed e.e. was similar in each case to that of the starting allylic alcohol (S_S)-**1a** or allylic chloride (S_S)-**1b**, thus indicating that no significant epimerization takes place under our reaction conditions.

2.3. Synthetic applications of sulfinyl homoallylic alcohols 3

As an example of the versatility of the sulfinyl homoallylic alcohols **3**, a total synthesis of enantioenriched (*S*)-(−)-nicotine from sulfinyl alcohol **3h** was devised (Scheme 6).



Scheme 5.



Scheme 6. *Reagents and conditions*: (a) 40% aq. CH_3NH_2 (20 equiv./mol)/MeOH (90%); (b) DIAD (2 equiv./mol), Ph_3P (2 equiv./mol), $Et_3NH{\cdot}HCl$ (1 equiv./mol), CH_2Cl_2, 0°C (85%); (c) Raney-Ni, EtOH, 80°C (67%).

Starting from a 6:1 mixture of **3h** (entry 14, Table 2), Michael addition of methylamine to the vinylsulfinyl moiety afforded a diastereomeric mixture of sulfinyl aminoalcohols **9** which were submitted to intramolecular Mitsunobu reaction[27] without further purification.

Examples of intramolecular cyclization of aminoalcohols under classical Mitsunobu conditions to give the corresponding azaheterocycles are scarce in the literature.[28] According to the well accepted mechanism for this transformation, the monoanion of the intermediate hydrazide, formed as a result of the activation of the hydroxyl group, can compete favorably as a nucleophile with the amine when intramolecular attack is slow. In fact, preliminary experiments from **9** under standard conditions afforded complex reaction mixtures where *iso*-propyl esters were apparent. To circumvent this problem, it is accepted that either the nucleophilicity of the amine has to be increased, by generation of the corresponding anion, or the nucleophilicity of the hydrazide anion has to be decreased by protonation.[29] In our case, addition of $Et_3N{\cdot}HCl$ (1 mol equiv.) as an external proton source precluded the formation of undesired by-products arising from hydrazide attack and the desired pyrrolidines **10** were obtained as a mixture of diastereomers in 85% combined yield.[30] Reduction of the sulfinyl group with freshly prepared Raney-Ni[31] afforded enantioenriched (*S*)-(−)-nicotine, whose spectroscopic data and sign of optical rotation were in agreement with those reported in the literature.[32,33] This result confirms the stereochemistry of the major isomer of **3h** and is consistent with the expected inversion of configuration that operates in the Mitsunobu reaction.

3. Conclusion

In summary, a simple and diastereoselective allylation of aldehydes with enantiopure building blocks (S_S)-**1a** and (S_S)-**1b** is described. Studies addressed at exploiting the synthetic potential of the homoallylic alcohols **3** are

currently underway in our group and will be reported in due course.

4. Experimental

FT-IR spectra are reported in cm^{-1}. NMR spectra were registered at 300 MHz (^1H) and 75.4 MHz (^{13}C) unless otherwise indicated. Solvents were distilled prior to use and dried by standard methods. Usual reaction work-up consists of extraction of the aqueous phase with an organic solvent, washings with brine, drying of the extracts over Na_2SO_4, filtration, and evaporation to dryness. EIHRMS were carried out at SCSIE, University of Valencia.

4.1. (S_S)-(+)-2-(*p*-Tolylsulfinyl)prop-2-en-1-ol (S_S)-1a

In a 250 mL flame-dried three-necked flask under Ar, bromoalcohol **5**[14] (1.37 g, 10 mmol) and a single crystal of phenanthroline was dissolved in Et_2O (50 mL). The solution was cooled to −78°C and *tert*-BuLi (approximately 1.7N solution in pentane) was added dropwise until the development of an intense dark red color. The solution was treated with additional *tert*-BuLi (twice the volume used to turn the starting solution dark red) keeping the temperature below −50°C and stirred at −78°C for an additional 45 min. A solution of (S_S) menthyl *p*-toluenesulfinate (2.35 g, 8 mmol) in anhydrous THF (20 mL) was quickly added to the above solution and allowed to react for 3 min. The reaction mixture was quenched with satd NH_4Cl (3 mL) and the temperature was allowed to raise to rt. The mixture was treated with H_2O (5 mL) and extracted with CH_2Cl_2/Et_2O 1:2 (3×30 mL). Work-up afforded an oil which was purified by flash chromatography (CH_2Cl_2/MeOH 98:2) to give (S_S)-**1a** (790 mg, 50%); $[\alpha]_D = +170$ (*c* 0.55, EtOH); e.e.: 91%; lit.[14] $[\alpha]_D = +103$ (*c* 0.55, EtOH); IR (film): 3361, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.36 (3H), 3.63 (1H), 3.87–3.92 (1H), 4.17–4.23 (1H), 5.83 (1H), 5.99 (1H), 7.24 (2H), 7.46 (2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): 21.3, 59.2, 118.2, 125.0, 130.0, 138.3, 141.9, 153.3. The e.e. was determined by ^{19}F NMR, Mosher ester analysis with (*R*)-(+)-MTPA[34] and comparison with the corresponding Mosher ester from (±)-**1a**, showing diagnostic singlets at −59.79 and −59.87 ppm (relative to TFA).

4.2. (±)-2-(*p*-Tolylsulfinyl)prop-2-en-1-ol (±)-1a

(±)-**1a** was obtained in 41% yield from bromoalcohol **4** and *iso*-propyl *p*-toluenesulfinate[35] following the above procedure for (S_S)-**1a**.

4.3. (S_S)-(+)-3-Chloro-2-(*p*-tolylsulfinyl)prop-2-ene (S_S)-1b

A solution of methanesulfonyl chloride (0.44 mL, 5.6 mmol) in anhydrous DMF (2 mL) was added dropwise to an ice cooled solution of (S_S)-**1a** (1.1 g, 5.6 mmol) and Et_3N (1.2 mL, 8.4 mmol) in anhydrous DMF (20 mL) under Ar. When no starting material was detected by TLC (CH_2Cl_2/MeOH 19:1), the mixture was treated with LiCl (0.71 g, 16.8 mmol) in anhydrous DMF (10 mL) and allowed to warm to rt. The reaction was monitored by TLC (hexanes/EtOAc 70:30) and evaporated to dryness after consumption of the intermediate mesylate. The residue was washed with Et_2O/CH_2Cl_2 (2:1) (3×30 mL) and filtered. The filtrates are evaporated to dryness and the resulting oil was purified by flash chromatography (hexanes/EtOAc 4:1) to give (S_S)-**1b** (840 mg, 70%); $[\alpha]_D = +128$ (*c* 0.68, MeOH); 90% e.e; IR (film): 2950, 2923, 1595, 1492, 1082, 1053, 933, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.38 (3H), 3.76–3.82 (1H), 4.09–4.15 (1H), 5.99 (1H), 6.21 (1H), 7.29 (2H), 7.49 (2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): 21.4, 39.0, 120.4, 125.1, 130.1, 138.3, 142.3, 150.7. The e.e. was determined by condensation with (*R*)-1-phenylethylamine, as described below, and comparison of selected ^1H NMR signals with those arising from condensation with (*RS*)-1-phenylethylamine.

4.4. 2-(Phenylsulfinyl)prop-2-en-1-ol ((±)-1c) and acetate (±)-1f

A solution of (±)-**1d**[13] (2.0 g, 10 mmol) in a mixture of THF (15 mL) and H_2O (25 mL) was treated with NaOAc (4.1 g, 50 mmol) of and stirred at 80°C until no starting material was detected by TLC (CH_2Cl_2/MeOH 98:2). The aqueous phase was extracted with Et_2O (3×35 mL) and the combined organic extracts were worked up in the usual way to give an oil (2.1 g). Flash chromatography on CH_2Cl_2/MeOH (98:2) afforded acetate (±)-**1f** (1.7 g, 76%) and alcohol (±)-**1c** (0.28 g, 15%). Alcohol (±)-**1c** was also obtained by treatment of (±)-**1f** (0.7 g, 3.1 mmol) with $NaHCO_3$ (0.78 g, 9.3 mmol) in a 1:1 mixture of THF–H_2O (8 mL) at 80°C until the starting acetate was completely consumed. Extraction of the reaction mixture with EtOAc (3×10 mL), followed by usual work-up and flash chromatography on CH_2Cl_2/MeOH (98:2) afforded (±)-**1c** (0.51 g, 90%).

Alcohol (±)-**1c**. IR (film): 3361, 3055, 2858, 1444, 1031 cm^{-1}; ^1H NMR: δ 3.64, 3.89–3.94 (1H), 4.21–4.26 (1H), 5.86 (1H), 6.03 (1H), 7.44–7.49 (3H), 7.56–7.61 (2H); ^{13}C NMR: δ 59.1, 118.7, 124.8, 129.3, 131.3, 141.7, 153.3.

Acetate (±)-**1f**. IR (film): 3058, 2943, 1745, 1444, 1371, 1226, 1082, 1047 cm^{-1}; ^1H NMR: δ 1.86 (3H), 4.46–4.51 (1H), 4.60–4.65 (1H), 5.93 (1H), 6.24 (1H), 7.46–7.49 (3H), 7.60–7.64 (2H); ^{13}C NMR: δ 20.3, 59.4, 121.0, 125.1, 129.3, 131.4, 142.0, 149.3, 170.0.

4.5. 3-Iodo-2-(phenylsulfinyl)prop-1-ene (±)-1e

Solid KI (10 mmol) was added portionwise to a solution of the chloride (±)-**1d**[13] (850 mg, 4.25 mmol) of in acetone (30 mL). The resulting mixture was heated under reflux and evaporated to dryness when no starting material was detected by ^1H NMR analysis. The resulting residue was taken up in H_2O (10 mL) and worked-up with CH_2Cl_2 (3×10 mL) in the usual way to give (±)-**1e** (890 mg, 72%); IR (film): 3055, 1475, 1442, 1157, 1083, 1049 (SO st) cm^{-1}; ^1H NMR (200 MHz,

$CDCl_3$): δ 3.50–3.57 (1H), 3.82–3.89 (1H), 5.96–6.04 (1H), 6.21 (1H), 7.46–7.66 (5H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ −5.5, 121.2, 125.2, 129.4, 131.7, 141.8, 151.5.

4.6. (S_S,*R*)- and (S_S,*RS*)-*N*-[(2-*p*-Tolylsulfinyl)-2-propenyl]-*N*-(1-phenylethyl)amine 1g

A solution of (*R*)- or (*RS*)-1-phenylethylamine (36 mg, 0.3 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added to an ice-cooled solution of (S_S)-**1a** (21 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (1 mL). The reaction mixture was allowed to warm to rt and monitored by TLC (hexanes/EtOAc 7:3). When the starting halide was completely consumed CH_2Cl_2 (5 mL) was added and the mixture was worked up in the usual way to give the allylic amine (30 mg, quantitative). Selected ^1H NMR signals used for % e.e. determination (300 MHz, C_6D_6): (a) from (S_S,*R*): 1.33 (3H), 5.41 (1H), 6.09 (1H); (b) from (S_S,*S*): 1.04 (3H), 5.44 (1H), 6.13 (1H).

4.7. General allylation methods

4.7.1. Method A: Tin-promoted Pd-catalyzed allylation. The appropriate aldehyde **2a**–**m** (2 mmol) was added to a solution of sulfinyl allylic alcohol (S_S)-**1a** (1 mmol) in THF (6 mL) under argon. The resulting mixture was sequentially treated with water (1 mL), $SnCl_2$ (3 mmol), and $Pd(PhCN)_2Cl_2$ (0.1 mmol) and heated to 70°C. The reaction was monitored by TLC (CH_2Cl_2/MeOH 49/1) and judged to be complete when no starting allylic alcohol was observed (usually after 60–96 h). The reaction mixture was then poured into aqueous HCl (1N, 5 mL) and extracted with a mixture of CH_2Cl_2/Et_2O (1:2, 3×20 mL). The organic extracts were sequentially washed with satd $NaHCO_3$ (5 mL) and brine (5 mL), dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The crude mixture thus obtained was purified by flash chromatography (hexane/EtOAc 7:3) to afford **3a**–**k** (see Table 2).

4.7.2. Method B: Barbier-type allylation. A solution of (S_S)-**1b** (1 mmol) in THF (1.0 mL) was treated with NaI (450 mg, 3 mmol) and stirred at 0°C. After 5 min, aqueous NH_4I (1.6N, 9 mL) was added dropwise, followed by a solution of the aldehyde **2a**–**i** (1 mmol) in THF (0.5 mL). The mixture was cooled to 0°C (ice bath) and Zn dust (130 mg, 2 mmol) was added portionwise. The reaction mixture was stirred at 0°C until consumption of the starting halide (TLC monitoring) and diluted with EtOAc. The organic extracts are separated, dried ($MgSO_4$), and concentrated to give **3a**–**i** as a mixture of diastereomers, which, in some instances, could be separated by careful flash chromatography on hexanes–EtOAc (8:2 or 7:3).

Compound **3a** (major (R,R_S) diastereomer): ^1H NMR: δ 2.43 (3H), 2.47–2.55 (1H), 2.57–2.64 (1H), 4.20 (1H), 4.88 (1H), 5.28 (1H), 5.94 (1H), 7.20–7.35 (7H), 7.48–7.52 (2H); ^{13}C NMR: δ 21.4, 38.9, 71.0, 124.0, 124.9, 125.7, 127.1, 128.1, 129.9, 137.9, 141.7, 143.1, 150.0.

Compound **3a** (minor (S,R_S) diastereomer): ^1H NMR: δ 2.39 (3H), 2.43–2.47 (2H), 4.88 (1H), 5.81 (1H), 6.12 (1H), 7.20–7.35 (7H), 7.47–7.49 (2H); ^{13}C NMR: δ 21.4, 40.3, 73.3, 123.3, 124.7, 125.6, 127.4, 128.3, 129.9, 137.8, 141.7, 143.7, 151.2; EIHRMS (mixture of diastereomers) calcd for $C_{17}H_{16}OS$ (M^+−18): 268.092188; found: 268.092255.

Compound **3b** (major (R,R_S) diastereomer): ^1H NMR: δ 0.4–1.3 (6H), 1.5–1.8 (5H), 2.12–2.21 (1H), 2.25–2.32 (1H), 2.34 (3H), 2.8 (1H), 3.34 (1H), 5.73 (1H), 6.08 (1H), 7.27 (2H), 7.46 (2H); ^{13}C NMR: δ 21.4, 25.9, 26.0, 26.3, 28.1, 29.2, 34.3, 42.9, 73.4, 127.7, 125.1, 129.9, 138.4, 141.6, 152.2; IR (film): 3402, 2923, 2852, 1492, 1450, 1037, 1014 cm^{-1}; $[\alpha]_D$ = +89.2 (*c* 0.8, acetone); mp 79–81°C.

Compound **3b** (minor (S,R_S) diastereomer): ^1H NMR: δ 0.8–1.4 (6H), 1.6–1.8 (5H), 2.03–2.11 (1H), 2.27–2.33 (1H), 2.41 (3H), 3.31 (1H), 3.44 (1H), 5.73 (1H), 6.07 (1H), 7.31 (2H), 7.47 (2H); ^{13}C NMR: δ 21.4, 26.1, 26.2, 26.5, 28.0, 29.0, 34.9, 43.8, 75.1, 122.5, 124.8, 129.9, 138.2, 141.6, 153.5; IR (film): 3400, 2925, 2852, 1492, 1450, 1082, 1039, 1014 cm^{-1}; $[\alpha]_D$ +6.0 (*c* 0.40, acetone).

Compound **3c** (major (R,R_S) diastereomer): ^1H NMR: δ 0.83 (3H), 1.17–1.37 (6H), 2.12–2.19 (1H), 2.26–2.32 (1H), 2.37 (3H), 3.26 (1H), 3.62 (1H), 5.70 (1H), 6.04 (1H), 6.09 (1H), 7.25–7.28 (2H), 7.42–7.47 (2H); ^{13}C NMR: δ 14.0, 21.3, 22.5, 27.9, 36.2, 37.3, 68.7, 122.6, 125.0, 129.9, 138.1, 141.3, 151.4.

Compound **3c** (minor (S,R_S) diastereomer): ^1H NMR (selected signals from the mixture of diastereomers): 0.83 (3H), 1.17–1.37 (6H), 1.99–2.20 (2H), 2.37 (3H), 3.49 (1H), 3.98 (1H); ^{13}C NMR: δ 14.0, 21.3, 22.6, 27.9, 37.0, 38.1, 70.8, 122.6, 124.8, 129.9, 138.0, 141.3, 151.4; IR (film, mixture of diastereomers): 3400, 2956, 2929, 2871, 2860, 1596, 1492, 1082, 1035, 1014 cm^{-1}; EIHRMS (mixture of diastereomers) calcd for $C_{15}H_{20}OS$ [M^+−18]: 248.123827; found: 248.123488.

Compound **3d** (major (R,R_S) diastereomer): ^1H NMR: δ 0.80 (3H), 0.85 (3H), 1.55 (1H), 2.11–2.19 (1H), 2.24–2.31 (1H), 2.37 (3H), 2.87 (1H), 3.35 (1H), 5.74 (1H), 6.08 (1H), 7.27 (2H), 7.47 (2H); ^{13}C NMR: δ 17.8, 18.8, 21.4, 33.2, 34.3, 74.2, 121.6, 125.1, 129.9, 138.4, 141.6, 152.1; IR (film, mixture of diastereomers): 3406, 2958, 2929, 2873, 2860, 1596, 1492, 1082, 1041, 1014 cm^{-1}; EIHRMS (mixture of diastereomers) calcd for $C_{14}H_{18}OS$ [M^+−18]: 234.107852; found: 234.107838.

Compound **3e** (major (R,R_S) diastereomer): ^1H NMR: δ 0.79 (9H), 1.93–2.01 (1H), 2.19 (1H), 2.31 (1H), 2.38 (3H), 3.33 (1H), 5.75 (1H), 6.04 (1H), 7.27 (2H), 7.49 (2H); ^{13}C NMR: δ 21.4, 25.5, 31.7, 35.0, 77.6, 120.0, 125.4, 129.8, 138.9, 142.1, 152.7; IR (film): 3402, 2956, 2869, 1596, 1492, 1479, 1363, 1082, 1039, 1014 cm^{-1}; EIHRMS calcd for $C_{15}H_{20}OS$ [M^+−18]: 248.123488; found: 248.123567; $[\alpha]_D$ = +135.2 (*c* 0.75, acetone); mp 108–109°C.

Compound **3e** (minor (S,R_S) diastereomer): ^1H NMR: δ 0.86 (9H), 1.94–2.02 (1H), 2.31 (1H), 2.39 (3H), 3.15

(1H), 3.90 (1H), 5.71 (1H), 6.04 (1H), 7.28 (2H), 7.45 (2H); ^{13}C NMR: δ 21.4, 25.7, 32.4, 35.0, 78.8, 122.4, 124.7, 129.9, 138.2, 141.5, 153.7; IR (film): 3402, 2954, 2869, 1596, 1492, 1479, 1363, 1081, 1031, 1014 cm^{-1}; $[\alpha]_D = -19.75$ (c 0.80, acetone); mp 70–72°C.

Compound **3f** (major (R,R_S) diastereomer): ^{1}H NMR: δ 2.38 (3H), 2.38–2.45 (1H), 2.48–2.55 (1H), 3.75 (3H), 4.05 (1H), 4.77 (1H), 5.32 (1H), 5.93 (1H), 6.80 (2H), 7.12 (2H), 7.26 (2H), 7.45 (2H); ^{13}C NMR: δ 21.5, 38.4, 55.2, 71.9, 113.7, 125.9, 126.8, 127.1, 130.3, 133.3, 133.9, 143.0, 145.9, 159.0; IR (film): 3459, 3033, 2956, 2234, 1612, 1514, 1492, 1249, 1178, 1033 cm^{-1}.

Compound **3f** (minor (S,R_S) diastereomer): ^{1}H NMR: δ 2.32–2.36 (2H), 2.37 (3H), 3.74 (3H), 4.57 (1H), 5.75 (1H), 6.08 (1H), 7.2 (2H); ^{13}C NMR: δ 21.5, 37.1, 55.2, 72.9, 113.9, 125.7, 126.8, 127.5, 130.3, 133.2, 133.8, 143.1, 146.3, 159.2; EIHRMS (mixture of diastereomers) calcd for $C_{18}H_{18}O_2S$ (M^+–18): 298.102752; found: 298.102758.

Compound **3g** (major (R,R_S) diastereomer): ^{1}H NMR: δ 2.39 (3H), 2.55 (1H), 2.70 (1H), 4.47 (1H), 4.82 (1H), 5.42 (1H), 5.96 (1H), 6.22 (1H), 6.27 (1H), 7.29 (3H), 7.46 (2H); ^{13}C NMR: δ 21.3, 36.2, 65.7, 106.5, 110.2, 124.6, 124.8, 130.0, 137.7, 141.4, 141.7, 150.0, 155.8.

Compound **3g** (minor (S,R_S) diastereomer): ^{1}H NMR: δ 2.37 (3H), 2.44–2.62 (2H), 4.47 (1H), 4.64 (1H), 5.77 (1H), 5.09 (1H), 6.20 (1H), 7.29 (3H), 7.46 (2H); ^{13}C NMR: δ 21.3, 36.7, 67.3, 105.9, 110.1, 123.5, 124.8, 130.0, 137.7, 141.4, 141.7, 151.6, 155.6; EIHRMS (mixture of diastereomers) calcd for $C_{15}H_{15}O_2S$ [(M+1)$^+$–18]: 259.079277; found: 259.079223.

Compound **3h** (major (R,R_S) diastereomer): ^{1}H NMR: δ 2.38 (3H), 2.45–2.52 (1H), 2.48–2.55 (1H), 4.89 (1H), 5.27 (1H), 5.92 (1H), 7.18–7.21 (1H), 7.28 (2H), 7.44 (2H), 7.62 (1H), 8.4 (2H); ^{13}C NMR: δ 21.4, 39.0, 68.7, 123.2, 124.7, 125.1, 130.0, 133.9, 137.5, 138.9, 141.8, 147.3, 148.2, 149.7.

Compound **3h** (minor (S,R_S) diastereomer): ^{1}H NMR: δ 2.31–2.41 (2H), 2.36 (3H), 4.65 (1H), 5.81 (1H), 6.11 (1H), 7.18–7.21 (1H), 7.28 (2H), 7.44 (2H), 7.62 (1H), 8.4 (2H); ^{13}C NMR: δ 21.4, 40.5, 71.1, 123.4, 124.6, 125.1, 130.1, 133.7, 137.5, 139.5, 141.8, 147.4, 148.5, 151.6; EIHRMS (mixture of diastereomers) calcd for $C_{16}H_{16}ONS$ (M^+–17): 270.095262; found: 270.095283.

Compound **3i** (major (R,R_S) diastereomer): ^{1}H NMR: δ 2.24–2.31 (1H), 2.32–2.38 (1H), 2.38 (3H), 3.30–3.35 (1H), 3.34–3.39 (1H), 3.65 (1H), 3.88 (1H), 4.47 (2H), 5.73 (1H), 6.09 (1H), 7.26–7.32 (7H), 7.45 (2H); ^{13}C NMR: δ 21.3, 33.0, 67.3, 72.5, 73.2, 122.9, 124.9, 127.6, 127.7, 128.4, 129.9, 137.8, 138.1, 141.6, 150.7.

Compound **3i** (minor (S,R_S) diastereomer): ^{1}H NMR: δ 2.06–2.14 (1H), 2.38 (3H), 2.38–2.45 (1H), 3.29–3.34 (1H), 3.43–3.48 (1H), 3.72 (1H), 4.07 (1H), 4.49 (2H), 5.75 (1H), 6.06 (1H), 7.26–7.32 (7H), 7.45 (2H); ^{13}C NMR: δ 21.3, 34.3, 69.6, 73.3, 74.5, 122.5, 124.8, 127.7, 128.3, 129.9, 137.9, 138.0, 141.6, 152.1; EIHRMS (mixture of diastereomers) calcd for $C_{19}H_{23}O_3S$ [M^++1]: 331.136792; found: 331.136779.

Compound **3j** (major (R,R_S) diastereomer): ^{1}H NMR: δ 2.39 (3H), 2.40–2.50 (1H), 2.51–2.58 (1H), 4.53 (1H), 4.84 (1H), 5.33 (1H), 5.91 (1H), 6.91–6.99 (2H), 7.14–7.20 (2H), 7.28 (2H), 7.45 (2H); ^{13}C NMR: δ 21.4, 39.1, 70.3, 114.8, 124.6, 124.8, 127.3, 130.0, 133.7, 138.9, 141.7, 149.8, 161.8;

Compound **3j** (minor (S,R_S) diastereomer): ^{1}H NMR: δ 2.37 (3H), 4.53 (1H), 4.58–4.63 (1H), 5.77 (1H), 6.09 (1H), 6.91–6.99 (2H), 7.14–7.20 (2H), 7.28 (2H), 7.48 (2H); ^{13}C NMR: δ 21.4, 40.6, 72.8, 114.8, 124.7, 125.3, 129.7, 133.6, 141.7; EIHRMS (mixture of diastereomers) calcd for $C_{17}H_{15}FOS$ [M^+–18]: 286.082766; found: 286.082711.

3k (major (R,R_S) diastereomer): ^{1}H NMR: δ 2.39 (3H), 2.46–2.52 (1H), 2.51–2.58 (1H), 4.93 (2H), 5.27 (1H), 5.89 (1H), 7.27–7.30 (2H), 7.32–7.35 (2H), 7.42–7.45 (2H), 7.51–7.53 (2H); ^{13}C NMR: δ 21.3, 39.0, 70.3, 124.7, 125.0, 125.3, 126.1, 129.6, 130.0, 137.4, 141.8, 147.3, 149.6.

Compound **3k** (minor (S,R_S) diastereomer): ^{1}H NMR: δ 2.37 (3H), 4.67 (1H), 5.1 (1H), 5.81 (1H), 6.11 (1H); ^{13}C NMR: δ 21.3, 40.5, 72.9, 124.6, 125.2, 125.3, 126.0, 130.0, 137.5, 149.7.

Compound **4** (major diastereomer): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.2–2.6 (2H), 4.77 (1H), 5.3 (1H), 5.89 (1H), 7.05–7.6 (10H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 38.8, 71.1, 124.1, 124.9, 125.6, 127.1, 128.1, 129.2, 131.1, 141.4, 143.1, 150.0.

Compound **4** (minor diastereomer): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.2–2.6 (2H), 4.51–4.59 (1H), 5.71 (1H), 6.02 (1H), 7.05–7.60 (10H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 40.1, 71.1, 123.5, 124.7, 125.6, 127.4, 128.3, 143.8, 151.8. Elemental analysis (mixture of diastereomers) calcd for $C_{16}H_{16}O_2S$: C, 70.59%; H, 5.88%; S, 11.76%; found: C, 70.31%; H, 6.01%; S, 11.56%.

4.8. Addition of methylamine to 3h

A solution of **3h** (6:1 mixture of diastereomers, 0.40 g, 1.45 mmol) in MeOH (4 mL) was treated with 40% aqueous methylamine (3.5 mL) and the resulting mixture stirred at rt for 12 h. The reaction mixture was then evaporated to dryness and the residue was taken up in CH_2Cl_2 and dried over anhydrous $MgSO_4$ to afford **3h** as a mixture of diastereomers (0.40 g, 90%). Spectroscopic data for the major diastereomer.

IR (film): 3299, 2937, 2862, 1594, 1577, 1492, 1474, 1425, 1083, 1027, 1014 cm^{-1}; ^{1}H NMR: δ 2.02–2.23 (2H), 2.37–4.45 (6H), 2.48–2.60 (1H), 2.71 (1H), 3.18 (1H), 4.96 (1H), 7.09–7.33 (5H), 7.38–7.69 (2H), 8.40–

8.51 (2H); ^{13}C NMR: δ 21.4, 34.6, 35.9, 51.0, 58.4, 67.8, 123.1, 124.5, 129.9, 133.1, 137.2, 139.2, 141.8, 147.4, 148.0.

4.9. Cyclization of 9 under Mitsunobu conditions

A solution of DIAD (404 mg, 2 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise to an ice-cooled solution of **9** (318 mg, 1 mmol, mixture of isomers) containing $Et_3N{\cdot}HCl$ (138 mg, 1 mmol) and Ph_3P (524 mg, 2 mmol) in anhydrous CH_2Cl_2 (20 mL) under argon. The reaction was monitored by TLC (CH_2Cl_2/MeOH 85:15) until starting material was totally consumed (around 4 h). When the reaction was complete, the volatiles were removed by evaporation and the residue was taken up in CH_2Cl_2/Et_2O (1:2, 10 mL) and treated with an excess of a satd solution of hydrogen chloride in Et_2O (5 mL) and H_2O (20 mL). The aqueous phase was washed with 1:2 CH_2Cl_2/Et_2O (3×10 mL), made alkaline with 1N NaOH and extracted with CH_2Cl_2 (3×15 mL). Standard work-up of the combined organic phases afforded an oil (360 mg) which afforded a mixture of stereoisomers **10** in 85% overall yield after flash chromatography (CH_2Cl_2/MeOH 97:3); EIHRMS (mixture of diastereomers) calcd for $C_{17}H_{19}N_2S$ (M^+–17): 283.126896; found: 283.126896. Major diastereomer (relative stereochemistry not determined): ^{1}H NMR: δ 2.06 (3H), 2.21–2.38 (2H), 2.37 (3H), 2.58 (1H), 3.18 (1H), 2.23–3.29 (1H), 3.35 (1H), 7.24–7.29 (3H), 7.53 (2H), 7.80 (1H), 8.45 (1H), 8.49 (1H); ^{13}C NMR: δ 21.4, 34.2, 39.7, 57.6, 61.7, 68.4, 123.9, 124.7, 129.8, 135.2, 136.9, 140.2, 141.8, 149.3, 149.5; $[\alpha]_D = +78.9$ (*c* 0.55, $CHCl_3$).

4.10. (*S*)-(−)-Nicotine

To neat **10** (0.10 g, 0.33 mmol) was added a suspension of Raney-Ni (Ref. 20) in EtOH (2 mL) under argon. After stirring the mixture for 10 min, no starting material was detected by TLC (CH_2Cl_2/MeOH 95:5). The reaction mixture was filtered through a pad of Celite® and the solids are washed with additional CH_2Cl_2. The filtrates are evaporated to give (*S*)-(−)-nicotine (0.03 g, 65%) whose purity was estimated to be higher than 95% by ^{1}H NMR analysis.[32] ^{1}H NMR: δ 1.64–2.0 (3H), 2.12–2.22 (1H), 2.14 (3H), 2.24–2.33 (1H), 3.06 (1H), 3.18–3.25 (1H), 7.23 (1H), 7.67 (1H), 8.48 (2H); ^{13}C NMR: δ 22.6, 35.1, 40.4, 57.0, 68.9, 123.6, 134.9, 138.7, 148.6, 149.5; $[\alpha]_D$ −97 (*c* 0.75, acetone); lit.[33] $[\alpha]_D = -169$ (neat).

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16. This moderate yield can be attributed, in part, to the instability of the starting iodide under the reaction conditions.
17. This catalyst proved superior to other Pd catalysts, its use is well precedented (see Ref. 12 and references cited therein). Based on these results, no further attempts to improve the reaction outcome by using a different catalyst system were made.
18. It is known (Ref. 12) that electron-deficient allylic alcohols require longer reaction times and afford lower yields under this tin-promoted palladium-catalyzed system. In our case, by-products arising from dimerization or reduction of the putative π-allylpalladium intermediate (see Scheme 1) have been observed. This might account for the lower yields on sulfinyl alcohols **3** in comparison with our previously reported Barbier-type allylation process (Ref. 11).
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