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Enantiomerically pure tetrahydroisoquinolines by enzyme catalysis and gold-catalyzed phenol synthesis

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ABSTRACT

Five different furfural derivatives were converted to chiral cyanohydrins by enzyme catalysis in good enantiomeric excess. After a sequence of silyl protection, nitrile reduction, tosylation and propargylation, substrates for the gold(I) catalyzed cycloisomerization of δ-alkynyl furans delivered good yields of enantiomerically pure dihydroxytetrahydroisoquinoline building blocks. Neither racemization nor elimination to quinolines was observed.

1. Introduction

Over the past eight years, gold catalysis has become a highly useful tool for organic synthesis.[1] One of the new reactions developed, is the gold-catalyzed phenol synthesis, which has a very broad synthetic scope, especially for the synthesis of benzo-anellated heterocycles.[2] Such heterocycles are often found as substructures in natural products, but then in most cases possess stereocenters, for example, in the benzylic position of the heterocycle. These stereocenters cannot be set in the gold-catalyzed cyclization of **1** to **2**, thus for enantiomerically pure building blocks these stereocenters have to be implemented during the synthesis of [1] (Scheme 1).

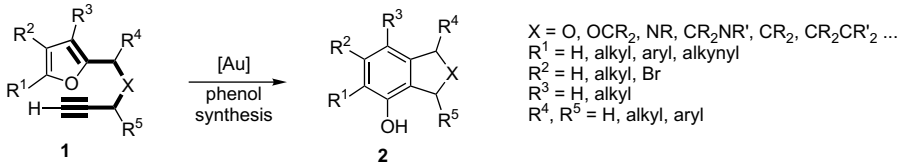
For setting a furylic stereocenter in **1**, we were inspired by the work of Effenberger, who developed a beautiful and simple enzyme-catalyzed asymmetric formation of cyanohydrins from aldehydes (Scheme 2).[3]

Different enzymes, the hydroxynitrile lyases (HNL), are available for the selective synthesis of each of the enantiomeric form of the product cyanohydrin **4** (for example: from almonds, *Prunus amygdalus*, (*R*)-PaHNL; from manihot, *Manihot esculenta*, (*S*)-MeHNL).[4] The aim of this investigation was to extend the use of these enzymes to different furylic substrates and to explore the scope and limitations in the subsequent functional group modifications and the gold-catalyzed synthesis of tetrahydroisoquinoline building blocks with benzylic stereocenters bearing a hydroxy group. Regarding the gold-catalyzed step, the presence of this benzylic stereocenters will be of interest, since it would be important to avoid an elimination or an even elimination/aromatization processes, what is, in principle, possible in gold catalysis.[5]

We report herein our findings with regard of this synthesis of enantiomerically pure dihydroxytetrahydroisoquinolines.

2. Results and discussion

For the investigation of the first, enzyme-catalyzed step, we chose a series of furfural derivatives **5a**–**e** possessing a various substitution patterns (Scheme 3). For analytical purposes, in



1 **2**

Scheme 1. The gold-catalyzed phenol synthesis.

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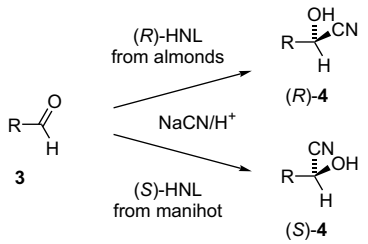


Scheme 2. Enzymes for both enantiomers of the cyanohydrin are available.

addition to the enzyme-catalyzed enantioselective conversions, an uncatalyzed cyanohydrin formation was also investigated for each case. This synthetic sequence delivered racemic samples as reference material for the determination of the enantiomeric excess of the product obtained from enzyme catalysis and gold catalysis. In one case, namely **5d**, both the non-racemic and the racemic materials were carried through the whole sequence, in order to proof that—as expected—the stereocenter does neither racemize in any of the subsequent functional group manipulations nor in the gold-catalyzed step. It is important to note, that due to the CIP nomenclature system, for the same steric arrangement of the four substituents at the chiral centre, the opposite stereodiscriptor is obtained (the furan oxygen atom has a higher priority than the nitrile nitrogen atom), thus the (*R*)-HNL in the case of furyl-substituents delivers the (*S*)- and not the (*R*)-product.

The results are summarized in Table 1. Since the stability of the unprotected cyanohydrin **6** is limited and especially an enantiomer analysis is difficult for this substrate, the crude material was directly engaged in the silylation step to furnish the silyl-protected derivative **7**, which is completely stable and easy to handle. Since the yields in the silylation step usually are excellent and the stereocenter in **6** is not changed during the protection, the ee values and yields of **7** are good indicators for the efficiency of the step from **5** to **6**. For the unsubstituted furfural **5a** as well as for the methyl substituted **5b**, the ethyl substituted **5d** and the dimethyl derivative **5e**, excellent ee values were obtained (entries 1, 3, 7 and 9). The reaction conditions for the catalyzed and uncatalyzed reaction are quite different: in the case of enzyme catalysis the undesired, uncatalyzed cyanohydrin formation must be suppressed. Thus in the case of the sterically more demanding phenyl group in **5c** and **5e** with a methyl group in 4-position of the furan ring, much lower yields were obtained in enzyme catalysis (entries 5 and 9); in the case of **5a**, **5b** and **5d**, the enzyme-catalyzed and the uncatalyzed cyanohydrin formation provide similar yields. This clearly indicates that for these two substrates there is a steric problem in the active centre of the enzyme, which significantly reduces the rate of reaction. For *rac*-**7c** a crystal structure analysis was obtained (Fig. 1).[6] The structure shows a typical dihedral angle for O–C–C–O.

Table 1
Synthesis of furfural-derived and protected cyanohydrins **7**

Entry	Furfural	Method[a]	Product[b] (yield)	Enantiomeric excess of **7** (ee)
1	**5a**: R^1, R^2=H	A	(*S*)-**7a** (81%)	98%
2	**5a**: R^1, R^2=H	B	*rac*-**7a** (93%)	—
3	**5b**: R^1=Me, R^2=H	A	(*S*)-**7b** (64%)	98%
4	**5b**: R^1=Me, R^2=H	B	*rac*-**7b** (82%)	—
5	**5c**: R^1=Ph, R^2=H	A	(*S*)-**7c** (15%)	95%
6	**5c**: R^1=Ph, R^2=H	B	*rac*-**7c** (76%)	—
7	**5d**: R^1=Et, R^2=H	A	(*S*)-**7d** (93%)	99%
8	**5d**: R^1=Et, R^2=H	B	*rac*-**7d** (93%)	—
9	**5e**: R^1=Me, R^2=Me	A	(*S*)-**7e** (32%)	99%
10	**5e**: R^1=Me, R^2=Me	B	*rac*-**7e** (83%)	—

[a] Method A: *Pa*-HNL/KCN/H_2O/DIPE; Method B: KCN/HOAc.
[b] Due to the sensitivity of the unprotected cyanohydrin, **6** is not purified; the crude product **6** is directly silylated to **7**, which is stable and allows the determination of the ee value.

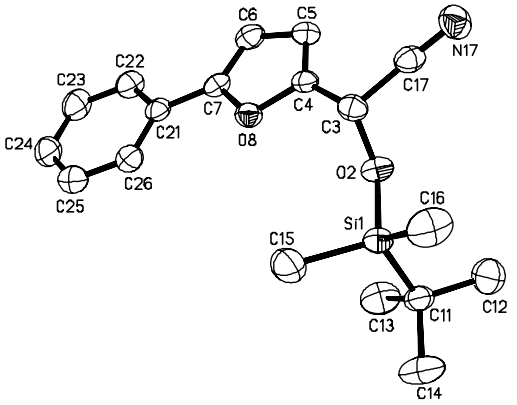
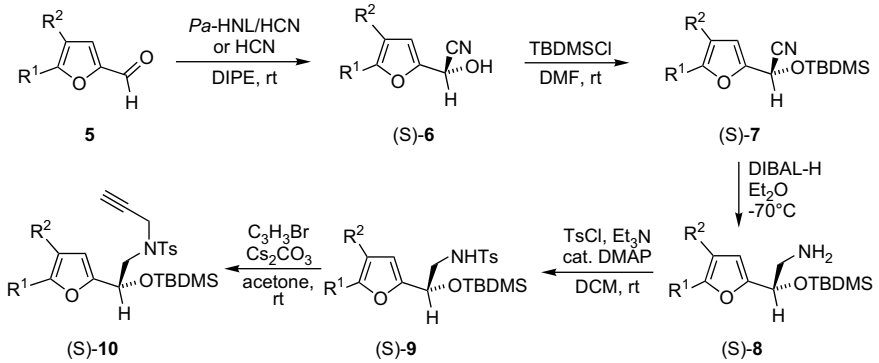


Figure 1. Solid state structure of *rac*-**7c**.

A subsequent reduction of the nitrile to amine **8**, followed by a tosylation to sulfonamide **9** and a propargylation to alkyne **10** provided the substrates for the gold catalysis. From previous work[2a,7] it was known that a purification of **8** does not deliver good yields, it was preferable to use the crude material for the subsequent tosylation, the purification of **9** did not cause any difficulty. In the case of **7d**, the racemic sample was also converted to *rac*-**10d**; the comparison of (*S*)-**10d** and *rac*-**10d** proofed that, as one would expect for these steps, the stereocenter was not harmed—by HPLC still the 99% ee were detected for (*S*)-**10d**. Figure 2 shows the results of a crystal structure analysis of (*S*)-**10a**. The conformation of the tether between the furan ring and the alkyne is oriented in a way



Scheme 3. Enzyme-catalyzed asymmetric cyanohydrin formation and conversion to protected *N*-propargyl tosylamides **10**.

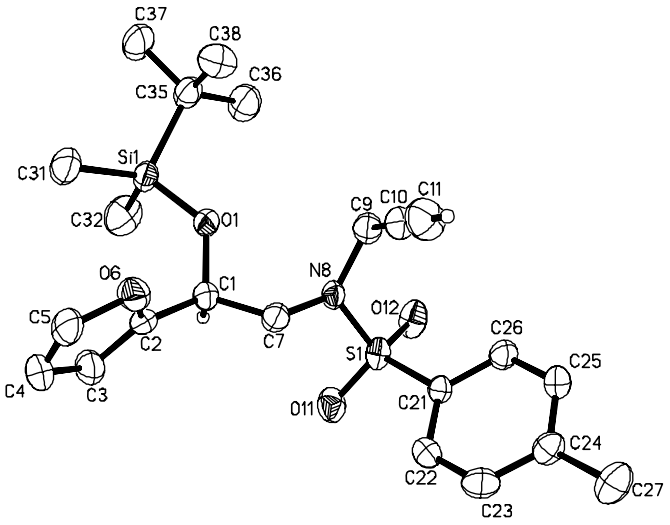


Figure 2. Solid state structure of (*S*)-**10a**.

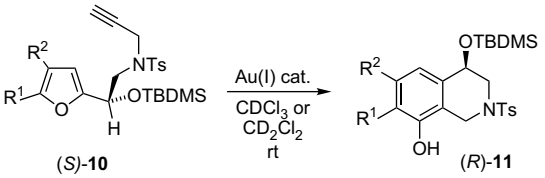
Table 2
Further conversion of chiral **7** to substrate **10**

Entry	**7**	**9** (Yield, ee)[a]	**10** (Yield, ee)
1	(*S*)-**7a**: R^1, R^2=H	(*S*)-**9a** (23%)	(*S*)-**10a** (80%)
2	(*S*)-**7b**: R^1=Me, R^2=H	(*S*)-**9b** (47%)	(*S*)-**10b** (99%)
3	(*S*)-**7c**: R^1=Ph, R^2=H	(*S*)-**9c** (32%)	(*S*)-**10c** (79%)
4	(*S*)-**7d**: R^1=Et, R^2=H	(*S*)-**9d** (93%)	(*S*)-**10d** (80%, 99%)
5	*rac*-**7d**: R^1=Et, R^2=H	*rac*-**9d** (93%)	*rac*-**10d** (80%)
6	(*S*)-**7e**: R^1=Me, R^2=Me	(*S*)-**9e** (54%)	(*S*)-**10e** (92%)

[a] Compound **8** is not purified and directly engaged in the tosylation step to obtain **9** as a stable, easy to handle material.

suitable for a cyclization reaction, similar conformers have been discussed previously (Table 2).[7]

The gold-catalyzed cycloisomerization to hydroxytetrahydroisoquinolines **11**. The stereodescriptor switches again, since the oxygen atom from the furan is more remote now, without a change of the steric arrangement of the substituents, the (*R*)-configuration is now obtained in product **11**. For this investigation the biaryl phosphane-based gold(I) precatalysts **13** was used.[8] With substrate (*S*)-**10a** two constitutional isomers, namely (*R*)-**11a** and (*R*)-**12a** (Fig. 3), were obtained (Table 3, entry 1), which is in agreement with our previous observations for reactions of furans without substituents in the 5-position.[2a] The other four substrates (*S*)-**10b–e** gave good yields of (*R*)-**11b–e**, as one would expect for furans with a substituent in the 5-position (entries 2–6). Most important is the observation that no elimination to the isoquinoline was observed. Based on recent findings in the synthesis of benzofurans by a gold-catalyzed cyclization/elimination reaction,[5] one could have surmised that such an elimination might occur. Again, comparison of the racemic sample of **11d** with (*R*)-**11d** proved that, as one could expect on the basis of previous conversion of substrates with stereocenters in the tether,[9] the ee-value remained unchanged in the gold-catalyzed step. For **10b** we also tested an other successful precatalysts, with 5 mol % of $[(Ph_3PAu)_2Cl]BF_4$ only 90% of (*R*)-**11b** were obtained (Scheme 4).



(*R*)-**12a**

Figure 3. (*R*)-**12a** as an expected second product in the conversion of (*S*)-**10a**.

Table 3
Results of the gold-catalyzed conversions of **10**[a]

Entry	Substrate **10**	Product **11** (yield, ee)
1	(*S*)-**10a**: R^1, R^2=H	(*R*)-**11a** (45%)+12a (20%)
2	(*S*)-**10b**: R^1=Me, R^2=H	(*R*)-**11b** (99%)
3	(*S*)-**10c**: R^1=Ph, R^2=H	(*R*)-**11c** (82%)
4	(*S*)-**10d**: R^1=Et, R^2=H	(*R*)-**11d** (85%, 99%)
4	*rac*-**10d**: R^1=Et, R^2=H	*rac*-**11d** (85%)
4	(*S*)-**10e**: R^1=Me, R^2=Me	(*R*)-**11e** (81%)

[a] Catalyst loadings: 7 mol % for **10a**, 5 mol % for **10b–e**.

(*S*)-**10** (*R*)-**11**

Scheme 4. Gold-catalyzed conversion of **10**.

3. Conclusion

A sequence including the enzyme-catalyzed asymmetric addition of HCN to furfurals and a gold-catalyzed cycloisomerization delivers chiral derivatives of 4,8-dihydroxytetrahydroisoquinolines. The stereocenter formed by enzyme catalysis suffers no racemization in this sequence.

An advantage of this sequence is the availability of enzymes for both series of enantiomers, a limitation is a low conversion in the enzyme-catalyzed step for furfurals with substituents in the 4-position of the furan ring or bulky substituents in the 5-position. In the gold-catalyzed step no undesired elimination is observed.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at room temperature on the following spectrometers: Bruker ARX 250, Bruker AC 300 or Bruker Avance DRX-300, Bruker Avance DRX-500. ^{13}C NMR spectra were recorded at room temperature on the following spectrometers: Bruker AC 300 (75.5 MHz), Bruker Avance DRX-300 (75.5 MHz), Bruker Avance DRX-500 (125.6 MHz). The multiplicity of signals refers to the DEPT 135- and DEPT 90-spectra. IR spectra (IR) were measured on a Bruker Vector 22 FT-IR. The substances were employed as film or KBr pressed disk. Flash column chromatography was accomplished using silica gel (0.032–0.062 mm) purchased from Macherey–Nagel as stationary phase. Mass spectra (MS) and high-resolution mass spectra (HRMS) were determined on the following instruments: Vakuum Generators ZAB-2F, Finnigan MAT TSQ 700, JEOL JMS-700. Elemental analyses were carried out on an Elementar Vario EL.

All ee determinations were carried out on an Agilent 1100 Series instrument with a Daicel Chiralpak AS-H (250×4 mm) column.

In all cases the mobile phase was 99% *n*-hexane and 1% isopropanol, an UV-detector was used, flow rate of 0.5 ml/min, temperature 25 °C.

4.2. Synthesis of (*S*)-furan-2-yl-hydroxyacetonitrile ((*S*)-6a, FA-334)

Citric acid (23.8 g) was dissolved in 32 ml water and 130 ml DIPE was added. A solution of 5.42 g (104 mmol) KCN in 13 ml water was added slowly. After 30 min the aqueous layer was separated and added to a mixture of 25.8 g of powdered almonds with 130 ml buffer, 32 ml DIPE and 5.00 g (52.0 mmol) of the furfural was added. After 30 min the organic layer was quickly filtered from the powdered almonds, dried over $MgSO_4$, filtered and the solvent removed in vacuo. Thus 2.78 g of (*S*)-**6a** as a yellow liquid was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=4.25 (br s, 1H), 5.53 (s, 1H), 6.41 (d, *J*=1.8 Hz, *J*=3.4 Hz 1H), 6.58 (d, *J*=3.4 Hz, 1H), 7.47 (d, *J*=1.9 Hz, 1H).

4.3. Synthesis of *rac*-furan-2-yl-hydroxyacetonitrile (*rac*-6a, FA-107)

Furfural (5.08 g, 52.0 mmol) was dissolved in 26 ml glacial acetic acid and cooled to 0 °C. Then a solution of 8.14 mg (156 mmol) KCN in 16 ml H_2O was added dropwise and the mixture was stirred over night at room temperature. Then 26 ml H_2O was added, the product was extracted with Et_2O (3×20 ml) and dried over $MgSO_4$. After filtration and addition of toluene, the solvent was removed. Crude *rac*-**6a** (6.94 g) was obtained and directly used in the next step without further purification. ^{1}H NMR data identical to (*S*)-**6a**.

4.4. Synthesis of (*S*)-(*tert*-butyldimethylsilanyloxy)furan-2-yl-acetonitrile ((*S*)-7a, FA-335)

Crude *rac*-**6a** (2.78 g, 22.6 mmol) was dissolved in 14 ml DMF, 6.80 g (45.1 mmol) imidazole and 3.84 g (56.4 mmol) TBDMSCl were added and the mixture was stirred over night at room temperature. After column chromatography (silica; PE/EE, 20:1) 4.40 g (81% over two steps) of the yellow liquid (*S*)-**7a** was obtained. R_f (PE/EE, 20:1)=0.28. IR (film): ν=2956, 2931, 2888, 2859, 1500, 1472, 1391, 1363, 1304, 1255, 1147, 1071 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=0.14 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 5.55 (s, 1H), 6.40 (d, *J*=3.2 Hz, 1H), 6.53 (d, *J*=3.2 Hz, 1H), 7.44 (d, *J*=3.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−5.21 (q), 18.19 (s), 25.48 (q), 58.10 (d), 109.46 (d), 110.79 (d), 117.27 (s), 143.80 (s), 148.54 (s). MS (ESI (+), 70 eV): *m*/*z* (%): 260 (100) [M+Na]$^+$. $C_{12}H_{19}NO_2Si$ (237.37): calcd C 60.72, H 8.07, N 5.90; found C 60.93, H 8.06, N 5.92. HRMS (ESI (+), 70 eV): $C_{12}H_{19}NO_2Si$: calcd 237.1075; found 237.1072. $[\alpha]^{578}$ 17.8; $[\alpha]^{546}$ 20.4; $[\alpha]^{436}$ 37.1.

4.5. Synthesis of (*S*)-2-(*tert*-butyldimethylsilanyloxy)-2-furan-2-ylethylamine ((*S*)-8a, FA-109)

Compound (*S*)-**7a** (3.50 g, 14.7 mmol) was dissolved in 100 ml Et_2O and cooled to −70 °C. Then 29.4 ml DIBAL-H (1.0 M solution in hexane) was added dropwise and the solution was warmed to −20 °C. After cooling to −70 °C again, 45 ml MeOH and 1.11 g (29.4 mmol) $NaBH_4$ were added and the solution was allowed to warm to room temperature over night. Et_2O (50 ml) was added and the organic layer was washed with 50 ml 2 N NaOH, 50 ml H_2O, 50 ml brine and then dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, 4.01 g (*S*)-**8a** was obtained as a yellow oil, which was used in the next step directly. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.01 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.77 (m, 1H), 3.01 (m, 2H), 4.74 (dd, *J*=4.7, 6.1 Hz, 1H), 6.24 (d, *J*=3.3 Hz, 1H), 6.32 (dd, *J*=1.9, 3.3 Hz, 1H), 7.36 (d, *J*=1.8 Hz, 1H).

4.6. Synthesis of (*S*)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-furan-2-ylethyl]-4-methylphenylsulfonamide ((*S*)-9a, FA-110)

Crude (*S*)-**8a** (1.35 g, 5.56 mmol) was dissolved in 50 ml DCM, 1.16 ml (8.34 mmol) NEt_3, 68.0 mg (556 μmol) DMAP and finally 1.06 g (5.56 mmol) tosyl chloride were added slowly at room temperature. After stirring over night, 20 ml H_2O was added, the aqueous phase was extracted with 3×20 ml DCM. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed in vacuo. After column chromatography (silica gel; PE/EE, 20:1) 1.35 g (23% over two steps) of (*S*)-**9a** was obtained as a yellow oil. R_f (PE/EE, 20:1)=0.30. IR (film): ν=3287, 2953, 2929, 2886, 2856, 1599, 1463, 1406, 1329, 1252, 1159, 1085 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=−0.14 (s, 3H), 0.00 (s, 3H), 0.82 (s, 9H), 2.42 (s, 3H), 3.22 (t, *J*=6.2 Hz, 2H), 4.64 (t, *J*=6.1 Hz, 1H), 4.73 (t, *J*=6.1 Hz, 1H), 6.20 (d, *J*=3.2 Hz, 1H), 6.29 (d, *J*=3.2 Hz, 1H), 6.30 (d, *J*=3.2 Hz, 1H), 7.30 (d, *J*=8.1 Hz, 2H), 7.72 (d, *J*=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−5.09 (q), 18.10 (s), 21.53 (q), 25.72 (q), 47.92 (t), 67.15 (d), 107.63 (d), 110.25 (d), 127.11 (d), 129.76 (d), 136.96 (s), 142.17 (d), 143.48 (s), 153.49 (s). MS (EI, 70 eV): *m*/*z* (%): 395 (6) [M$^+$], 340 (8), 339 (14), 338 (62), 212 (18), 211 (100), 155 (12), 91 (17), 75 (17), 73 (36), 28 (22). $C_{19}H_{29}NO_4SSi$ (395.59): calcd C 57.69, H 7.39, N 3.54; found C 58.12, H 7.42, N 3.53. HRMS (70 eV): $C_{19}H_{29}NO_4SSi$: calcd 395.1587; found 395.1605.

4.7. Synthesis of (*S*)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-furan-2-ylethyl]-4-methyl-*N*-prop-2-ynylphenylsulfonamide ((*S*)-10a, FA-111)

Compound (*S*)-**9a** (1.18 g, 2.99 mmol) was dissolved in 20 ml acetone; 2.92 g (8.96 mmol) Cs_2CO_3 and 1.00 ml (8.96 mmol) propargyl bromide (80 wt % in toluene) were added. After stirring over night, the solvent was removed in vacuo and the residue was taken up in 20 ml H_2O. After three extractions with 20 ml DCM each the organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo. After column chromatography (silica gel; PE/EE, 20:1) 1.04 g (*S*)-**10a** (80%) was obtained as a yellow solid. Mp: 59 °C. R_f (PE/EE, 20:1)=0.40. IR (film): ν=3297, 2929, 2857, 2363, 2214, 2118, 2023, 1737, 1598, 1472, 1161, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=−0.06 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.99 (t, *J*=2.5 Hz, 1H), 2.41 (s, 3H), 3.44 (d, *J*=6.6 Hz, 2H), 4.01 (dd, *J*=2.4, 18.4 Hz, 1H), 4.20 (dd, *J*=2.5, 18.5 Hz, 1H), 5.01 (t, *J*=6.5 Hz, 1H), 6.28 (d, *J*=3.2 Hz, 1H), 6.32 (d, *J*=1.9 Hz, 1H), 7.28 (d, *J*=8.3 Hz, 2H), 7.37 (d, *J*=1.9 Hz, 1H), 7.73 (d, *J*=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−5.09 (q), 14.18 (s), 18.08 (d), 21.52 (q), 25.72 (q), 38.76 (t), 51.33 (t), 68.73 (d), 73.44 (s), 107.57 (d), 110.26 (d), 127.78 (d), 129.40 (d), 136.08 (s), 142.01 (d), 143.47 (s), 153.14 (s). MS (EI, 70 eV): *m*/*z* (%): 433 (7) [M$^+$], 377 (10), 376 (36), 222 (9), 212 (18), 211 (100), 155 (10), 91 (17), 73 (36), 28 (16). $C_{22}H_{31}NO_4SSi$ (433.6374): calcd C 60.93, H 7.21, N 3.23; found C 61.61, H 7.23, N 3.16. HRMS (70 eV): $C_{22}H_{31}NO_4SSi$: calcd 433.1743; found 433.1750. $[\alpha]^{578}$ −47.2; $[\alpha]^{546}$ −54.1; $[\alpha]^{436}$ −98.6.

4.8. Synthesis of (*R*)-4-(*tert*-butyldimethylsilanyloxy)-7-phenyl-2-(toluol-4-sulfonyl)-1,2,3,4-tetrahydroisoquinoline-8-ol ((*R*)-11a, FA-347)

Compound (*R*)-**10a** (100 mg, 230 μmol) was dissolved in an NMR tube in 500 μl CD_2Cl_2, then 8.20 mg (16.3 μmol, 7 mol %) of di-*tert*-butyl-{3,4,5,6-tetramethyl-2-[2,4,6-(triisopropyl)phenyl]phenyl}-phosphingold chloride (**13**) the gold complex and 5.00 mg (16.3 μmol) $Ag[SbF_6]$ in CD_2Cl_2 were added. The reaction was monitored by ^{1}H NMR spectroscopy. When complete, the solvent was removed in vacuo and the residue purified by column chromatography (silica gel; PE/EE, 3:1), delivering 45 mg (45%) of (*R*)-**11a** and 20 mg (20%) of (*R*)-**12a**, both as colourless solids. In the

crude material the ratio of (*R*)-**11a**/(*R*)-**12a** was determined to be 71:29 by ^{1}H NMR spectroscopy.

Compound **11a**: Mp: 142 °C. R_f (PE/EE, 3:1)=0.19. IR (film): ν=3485, 2956, 2929, 1597, 1470 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.00 (s, 6H), 0.753 (s, 9H), 2.59 (dd, *J*=5.2, 11.4 Hz, 1H), 3.63 (dd, *J*=6.3, 11.4 Hz, 1H), 3.69 (d, *J*=15.9 Hz, 1H), 4.35 (d, *J*=15.8 Hz, 1H), 4.64 (dd, *J*=5.2, 8.2 Hz, 1H), 4.77 (br s, 1H), 6.43 (t, *J*=7.8 Hz, 1H), 6.80 (d, *J*=7.8 Hz, 1H), 6.91 (t, *J*=7.8, Hz, 1H), 7.13 (d, *J*=7.9 Hz, 2H), 7.55 (d, *J*=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 76 MHz): δ=−4.75 (q), −4.30 (q), 21.51 (q), 25.82 (q), 43.37 (t), 49.61 (t), 67.08 (d), 113.55 (d), 118.70 (d), 127.43 (d), 127.83 (d), 129.80 (d), 133.72 (s), 139.03 (s), 143.73 (s), 151.56 (s). MS (ESI, eV): *m*/*z* (%): 456 (100) [M+Na$^+$]. HRESI (eV): $C_{22}H_{31}NNaO_4SSi$: calcd 456.1633 [M+Na]$^+$; found 456.1638 [M+Na]$^+$. $[\alpha]^{578}$ 33.3; $[\alpha]^{546}$ 35.3; $[\alpha]^{436}$ 45.5.

Compound **12a**: Mp: 142 °C. R_f (PE/EE, 3:1)=0.15. IR (film): ν=3485, 2956, 2929, 1597, 1470 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.00 (s, 6H), 0.75 (s, 9H), 2.23 (s, 3H), 2.59 (dd, *J*=5.2, 11.4 Hz, 1H), 3.62 (dd, *J*=5.3, 8.2 Hz, 1H), 3.72 (d, *J*=15.9 Hz, 1H), 4.35 (d, *J*=15.8 Hz, 1H), 4.63 (dd, *J*=5.2, 11.4 Hz, 1H), 5.53 (br s, 1H), 6.43 (d, *J*=7.8 Hz, 1H), 6.80 (d, *J*=7.8 Hz, 1H), 7.08 (s, 1H), 7.13 (d, *J*=7.9 Hz, 2H), 7.55 (d, *J*=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 76 MHz): δ=−4.75 (q), −4.30 (q), 21.07 (q), 25.64 (q), 43.37 (t), 49.61 (t), 67.08 (d), 113.49 (d), 118.66 (d), 127.38 (d), 127.60 (d), 129.80 (d), 133.72 (s), 138.99 (s), 143.73 (s), 151.56 (s). MS (ESI, eV): *m*/*z* (%): 456 (100) [M+Na$^+$]. HRESI (eV): $C_{22}H_{31}NNaO_4SSi$: calcd 456.1633 [M+Na]$^+$; found 456.1638 [M+Na]$^+$.

4.9. Synthesis of (*S*)-5-methylfuran-2-yl-hydroxyacetonitrile ((*S*)-6b)

Citric acid (23.8 g) was dissolved in 32 ml water and 50 ml DIPE was added. A solution of 5.42 g (104 mmol) KCN in 13 ml water was added slowly. After 30 min the aqueous layer was separated and added to a mixture of 25.8 g of powdered almonds with 130 ml buffer, 32 ml DIPE and 1.10 g (10.0 mmol) of **5b** was added. After 30 min the organic layer was quickly filtered from the powdered almonds, dried over $MgSO_4$, filtered and the solvent removed in vacuo. Thus 1.38 g of (*S*)-**6b** was obtained as a yellow liquid.

4.10. Synthesis of *rac*-5-methylfuran-2-yl-hydroxyacetonitrile (*rac*-6b)

Compound **5b** (1.10 g, 10.0 mmol) was dissolved in 15 ml glacial acetic acid and cooled to 0 °C. Then a solution of 4.07 g (78.0 mmol) KCN in 16 ml H_2O was added dropwise and the mixture was stirred over night at room temperature. Then 20 ml H_2O was added, the product was extracted with Et_2O (3×20 ml) and dried over $MgSO_4$. After filtration and addition of toluene, the solvent was removed. Crude *rac*-**6b** (940 mg) was obtained.

4.11. (*S*)-(−)-(*tert*-Butyldimethylsilyloxy)-(5-methylfuran-2-yl)acetonitrile ((*S*)-7b, PH-300A)

Crude cyanohydrin (*S*)-**6b** (1.38 g, 10.0 mmol) was dissolved in 6 ml DMF and at room temperature 1.70 g (25.0 mmol) imidazole and 3.01 g (20.0 mmol) TBDMSCl were added and the mixture was stirred over night. After the usual work up and purification by column chromatography (SiO_2, PE/EE=10:1) 1.62 g (64%) (*S*)-**7b** was obtained as a colourless solid. Mp 36–38 °C. R_f (PE/EE, 5:1)=0.54. IR (neat): ν=2932, 2891, 2857, 1465, 1360, 1322, 1251, 1086, 1013, 963, 925, 837, 775 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=0.13 (s, 3H), 0.15 (s, 3H), 0.91 (s, 9H), 2.31 (s, 3H), 5.49 (s, 1H), 5.97 (d, *J*=3.1 Hz, 1H), 6.38 (s, *J*=3.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=−5.21 (q), −5.12 (q), 13.54 (q), 18.17 (s), 25.48 (q, 3C), 58.10 (d), 106.69 (d), 110.38 (d), 117.43 (s), 146.60 (s), 153.90 (s). MS (EI (+), 70 eV): *m*/*z* (%): 251 (1) [M$^+$], 194 (97), 75 (100). Elemental analysis: $C_{13}H_{21}NO_2Si$ (251.40): calcd C 62.11, H 8.42, N 5.57; found C 62.15, H 8.38, N 5.53. $[\alpha]_D^{20}$ −24.4 (*c* 0.52 g/100 ml, $CHCl_3$).

4.12. (*S*)-(*tert*-Butyldimethylsilyloxy)-2-(5-methylfuran-2-yl)-ethylamine ((*S*)-8b, PH-310)

Compound (*S*)-**7b** (1.10 g, 4.38 mmol) was dissolved in 40 ml Et_2O and cooled to −70 °C; 5.26 ml DIBALH (1.0 M in hexane) added slowly, then the mixture is allowed to warm to −20 °C. After cooling to −70 °C, 14 ml MeOH and then 331 mg (8.76 mmol) $NaBH_4$ was added and the solution was slowly warmed to room temperature. Et_2O (20 ml) was added, the organic layer is washed with 75 ml 2 N NaOH, 75 ml H_2O, and 75 ml brine and then dried over $MgSO_4$. Removal of the solvent in vacuo delivered 975 mg of amine (*S*)-**8b** as a colourless oil, which is directly used in the next step.

4.13. *N*-[(*S*)-(*tert*-Butyldimethylsilyloxy)-2-(5-methylfuran-2-yl)ethyl]-4-methyl-benzenesulfonamide ((*S*)-9b, PH-311A)

Compound (*S*)-**8b** (975 mg) was dissolved in 20 ml DCM and 916 µl (665 mg, 6.57 mmol) NEt_3, 53.8 mg (440 µmol) DMAP and 919 mg (4.82 mmol) tosyl chloride were added at room temperature. After complete conversion of the substrate, 20 ml H_2O was added, the organic layer was extracted with 20 ml DCM. The organic layer was dried over Na_2SO_4, filtered, the solvent removed in vacuo. After column chromatography (SiO_2, PE/EE=10:1) 842 mg (2.06 mmol, 47% over two steps) of (*S*)-**9b** was obtained as a pale yellow oil. R_f (PE/EE, 5:1)=0.34. IR (neat): ν=2931, 2891, 2857, 1461, 1405, 1331, 1253, 1160, 1087, 1017, 965, 837, 781 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=−0.13 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 2.21 (d, *J*=1.0 Hz, 3H), 2.42 (s, 3H), 3.18–3.26 (m, 2H), 4.62–4.67 (m, 2H), 5.86 (dq, *J*=3.1, 1.0 Hz, 1H), 6.04 (d, *J*=3.1 Hz, 1H), 7.30 (d, *J*=8.2 Hz, 2H), 7.72 (d, *J*=8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=−5.19 (q), −5.00 (q), 13.50 (q), 18.13 (s), 21.54 (q), 25.77 (q, 3C), 47.88 (t), 67.18 (d), 106.13 (d), 108.51 (d), 127.13 (d, 2C), 129.74 (d, 2C), 137.05 (s), 143.43 (s), 151.52 (s), 151.98 (s). MS (EI (+), 70 eV): *m*/*z* (%): 409 (1) [M$^+$], 394 (1), 352 (20), 225 (100). EA: $C_{20}H_{31}NO_4SSi$ (409.61): calcd C 58.64, H 7.63, N 3.42; found C 58.92, H 7.71, N 3.44. $[\alpha]_D^{20}$ +110.2 (*c* 0.48 g/100 ml, $CHCl_3$).

4.14. *N*-[(*S*)-(*tert*-Butyldimethylsilyloxy)-2-(5-methylfuran-2-yl)ethyl]-4-methyl-*N*-prop-2-ynylbenzenesulfonamide ((*S*)-10b, PH-312A)

Compound (*S*)-**9b** (778 mg, 1.90 mmol) was dissolved in 10 ml of acetone; 1.86 g (5.70 mmol) Cs_2CO_3 and 633 µl (678 mg, 5.70 mmol) propargyl bromide (80 wt % in toluene) were added. After stirring over night, the solvent was removed in vacuo and the residue was taken up in 10 ml H_2O. After three extractions with 10 ml DCM each the organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo. After column chromatography (silica gel; PE/EE, 10:1) 848 mg (1.89 mmol, 99%) of (*S*)-**10b** was obtained as a colourless solid. Mp 58–60 °C. R_f (PE/EE, 5:1)=0.29. IR (neat): ν=3279, 2936, 2891, 2855, 1598, 1558, 1437, 1343, 1253, 1188, 1154, 1086, 1006, 937, 832, 786, 716, 652, 591 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=−0.06 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 1.99 (t, *J*=2.4 Hz, 1H), 2.26 (d, *J*=1.0 Hz, 3H), 2.41 (s, 3H), 3.43 (d, *J*=6.6 Hz, 2H), 4.02 (dd, *J*=18.4, 2.4 Hz, 1H), 4.21 (dd, *J*=18.4, 2.4 Hz, 1H), 4.92 (sichtbares t, *J*=6.6 Hz, 1H), 5.89 (dq, *J*=3.0, 1.0 Hz, 1H), 6.12 (d, *J*=3.0 Hz, 1H), 7.27 (d, *J*=8.3 Hz, 2H), 7.74 (d, *J*=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=−5.07 (q), −4.99 (q), 13.56 (q), 18.14 (s), 21.55 (q), 25.80 (q, 3C), 38.70 (t), 51.29 (t), 68.78 (d), 73.41 (d), 77.31 (s), 106.12 (d), 108.45 (d), 127.81 (d, 2C), 129.41 (d, 2C), 136.27 (s), 143.44 (s), 151.80 (s), 152.26 (s). MS (EI (+), 70 eV): *m*/*z* (%): 447 (2) [M$^+$], 432 (1), 390 (16), 225 (100). EA: $C_{23}H_{33}NO_4SSi$ (447.66): calcd

C 61.71, H 7.43, N 3.13; found C 61.59, H 7.41, 3.10. $[\alpha]_D^{20}$ +265.0 (*c* 0.50 g/100 ml, $CHCl_3$).

4.15. (*R*)-(*tert*-Butyldimethylsilyloxy)-7-methyl-2-(toluol-4-sulfonyl)-1,2,3,4-tetrahydroisoquinolin-8-ol ((*R*)-11b, PH-314A)

From 58.7 mg (131 μmol) (*S*)-**10b** was dissolved in an NMR tube in 600 μL CD_2Cl_2 and 8.48 mg (6.56 μmol, 5 mol %) **13** and 2.25 mg (6.56 mmol) Ag[SbF_6] in CD_2Cl_2 were added. The reaction was monitored by ^{1}H NMR spectroscopy, when complete the solvent was removed in vacuo and the residue purified by column chromatography (silica gel; PE/EE, 10:1), delivered 20.1 mg (44.9 μmol, 34%) of (*R*)-**11b** as a colourless solid (NMR-yield 90%). Mp 159–161 °C. R_f (PE/EE, 10:1)=0.20. IR (neat): ν=3496, 2932, 2856, 1593, 1462, 1336, 1244, 1158, 1081, 954, 897, 818, 780, 652 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=0.17 (s, 6H), 0.93 (s 9H), 2.20 (s, 3H), 2.42 (s, 3H), 2.78 (dd, *J*=11.4, 8.4 Hz, 1H), 3.79 (ddd, *J*=11.4, 5.1, 1.0 Hz, 1H), 3.93 (d, *J*=15.8 Hz, 1H), 4.56 (d, *J*=15.8 Hz, 1H), 4.83 (dd, *J*=8.4, 5.1 Hz, 1H), 4.87 (br s, 1H), 6.90 (d, *J*=7.9 Hz, 1H), 7.00 (d, *J*=7.9 Hz, 1H), 7.32 (d, *J*=8.3 Hz, 2H), 7.75 (d, *J*=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=−4.76 (q), −4.31 (q), 15.33 (q), 18.11 (s), 21.50 (q), 25.81 (q, 3C), 43.51 (t), 49.60 (t), 66.94 (d), 118.52 (d), 118.78 (s), 120.79 (s), 127.62 (d, 2C), 128.83 (d), 129.73 (d, 2C), 133.84 (s), 136.83 (s), 143.62 (s), 149.59 (s). MS (CI (+), 70 eV): *m*/*z* (%): 446 (5) $[M-H]^+$, 432 (9), 390 (100), 316 (70). HRMS (CI (+)): $C_{23}H_{33}NO_4SSi$: $[M-H]^+$ calcd 446.1821; found 446.1825. $[\alpha]_D^{20}$ =−24.5 (*c* 0.82 g/100 ml, $CHCl_3$).

4.16. Synthesis of (*S*)-hydroxy(5-phenylfuran-2-yl)acetonitrile ((*S*)-6c, FA-ER-26)

Citric acid (21.1 g) was dissolved in 30 ml water and 30 ml DIPE were added. A solution of 4.81 g (92.3 mmol) in 12 ml water was added slowly. After 30 min the aqueous layer was separated and added to a mixture of 22.9 g of powdered almonds with 110 ml buffer, 115 ml DIPE and 7.94 g (46.1 mmol) of 5-phenylfurfural was added. After 30 min the organic layer was quickly filtered from the powdered almonds, dried over $MgSO_4$, filtered and the solvent removed in vacuo. Thus 4.93 g of crude (*S*)-**6c** was obtained as a greenish liquid.

4.17. Synthesis of *rac*-hydroxy(5-phenylfuran-2-yl)acetonitrile (*rac*-6c, FA-217)

5-Phenylfurfural (500 mg, 2.90 mmol) was dissolved in 3.5 ml glacial acetic acid and cooled to 0 °C. Then a solution of 457 mg (8.71 mmol) KCN in 3.5 ml H_2O was added dropwise and the mixture was stirred over night at room temperature. Then 3.5 ml H_2O was added, the product was extracted with Et_2O (3×10 ml) and dried over $MgSO_4$. After filtration and addition of toluene, the solvent was removed. Crude *rac*-**6c** (560 mg) was obtained and directly used in the next step without further purification.

4.18. Synthesis of (*S*)-(*tert*-butyldimethylsilanyloxy)-(5-phenylfuran-2-yl)acetonitrile ((*S*)-7c, FA-219)

Crude (*S*)-**6c** (560 mg, 2.83 mmol) was dissolved in 10 ml DMF, 385 mg (5.66 mmol) imidazole and 639 mg (168 mmol) TBDMSCl were added and the mixture was stirred over night at room temperature. After column chromatography (silica; PE/EE, 10:1) 677 mg (76% over two steps) of the yellow solid (*S*)-**7c** was obtained. Mp: 54 °C. R_f (PE/EE, 3:1)=0.27. IR (film): ν=2958, 2949, 2931, 2858, 1470, 1335, 1264, 1256, 1215, 1074 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=9.64 (s, 1H), 7.85 (d, *J*=8.1 Hz, 1H), 7.70 (d, *J*=7.2 Hz, 1H), 7.39 (m, 3H), 6.86 (d, *J*=3.7 Hz, 1H), 6.68 (d, *J*=3.4 Hz, 1H), 5.6 (s, 1H), 0.90 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 76 MHz): δ=−5.16 (q), 18.16 (q), 25.44 (q), 58.20 (d), 105.73 (d), 114.44 (d), 117.19 (s), 123.94 (d), 128.05 (d), 128.74 (d), 129.55 (s), 147.73 (s), 155.23 (s). MS (EI, 70 eV): *m*/*z* (%): 313 (8) $[M^+]$, 298 (5), 256 (100), 251 (3), 201 (4), 182 (89), 151 (9), 113 (8). $C_{18}H_{23}NO_2Si$ (313.15): calcd C 68.97, H 7.40, N 4.47; found C 69.08, H 7.45, N 4.47. HRMS (70 eV): $C_{18}H_{23}NO_2Si$: calcd 313.1498; found 313.1495. $[\alpha]^{578}$ 3.6; $[\alpha]^{546}$ 4.0; $[\alpha]^{436}$ 7.4.

4.19. Synthesis of (*S*)-2-(*tert*-butyldimethylsilanyloxy)-2-(4,5-dimethylfuran-2-yl)ethylamine ((*S*)-8c, FA-278)

Compound (*S*)-**7c** (1.88 g, 10.9 mmol) was dissolved in 30 ml Et_2O and cooled to −70 °C. Then 21.9 ml DIBAL-H (1.0 M solution in hexane) was added dropwise and the solution was warmed to −20 °C. After cooling to −70 °C again, 8 ml MeOH and 825 mg (21.9 mmol) $NaBH_4$ were added and the solution was allowed to warm to room temperature over night. Et_2O (30 ml) was added and the organic layer was washed with 30 ml 2 N NaOH, 30 ml H_2O and 30 ml brine, then dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, 1.86 g (*S*)-**8c** was obtained as a yellow oil, which was used in the next step directly.

4.20. Synthesis of (*S*)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-(5-phenylfuran-2-yl)-ethyl]-4-methylphenylulfonamide ((*S*)-9c, FA-281)

Crude (*S*)-**8c** (620 mg, 1.19 mmol) was dissolved in 10 ml DCM, 160 μl (1.19 mmol) NEt_3, 14.5 mg (119 μmol) DMAP and finally 227 g (119 mmol) tosyl chloride were added slowly at room temperature. After stirring over night, 20 ml H_2O was added, the aqueous phase was extracted with 3×10 ml DCM. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed in vacuo. After column chromatography (silica gel; PE/EE, 10:1) 1.69 g (32% over three steps) of (*S*)-**9c** was obtained as a yellow oil. R_f (PE/EE, 10:1)=0.14. IR (film): ν=2954, 2930, 2857, 1486, 1470, 1448, 1406, 1361, 1332, 1254 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=−0.03 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 2.33 (s, 3H), 3.33–3.21 (m, 3H), 4.71 (t, *J*=5.8 Hz, 1H), 4.79 (dd, *J*=5.0, 6.5 Hz, 1H), 6.34 (d, *J*=3.3 Hz, 1H), 6.58 (d, *J*=3.3 Hz, 1H), 7.39–7.33 (m, 3H), 7.59 (d, *J*=10.0 Hz, 2H), 7.61 (d, *J*=8.5 Hz, 2H), 7.68 (d, *J*=10.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 76 MHz): δ=−5.20 (q), −5.00 (q), 25.6 (q), 53.20 (t), 105.50 (d), 110.10 (d), 123.60 (d), 123.80 (d), 127.00 (d), 127.80 (d), 128.60 (d), 128.70 (d), 136.80 (s), 143.40 (s), 152.00 (s), 153.00 (s). MS (FAB^+): *m*/*z* (%): 471 (9) $[M^+]$, 470 (12), 456 (23), 414 (57), 387 (14), 340 (100). HRMS ($HRFAB^+$): $C_{25}H_{33}NO_4SSi$: calcd 471.1967; found 471.1967.

4.21. Synthesis of (*S*)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-furan-2-ylethyl]-4-methyl-*N*-prop-2-ynylphenylsulfonamide ((*S*)-10c, FA-283)

Compound (*S*)-**9c** (561 mg, 1.19 mmol) was dissolved in 20 ml acetone; 1.16 g (3.57 mmol) Cs_2CO_3 and 3.57 ml (3.57 mmol) propargyl bromide (80 wt % in toluene) were added. After stirring over night, the solvent was removed in vacuo and the residue was taken up in 10 ml H_2O. After three extractions with 10 ml DCM each the organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo. After column chromatography (silica gel; PE/EE, 5:1) 478 g (79%) (*S*)-**10c** was obtained as a yellow solid. R_f (PE/EE, 5:1)=0.30. IR (film): ν=3297, 2929, 2857, 2363, 2214, 2118, 2023, 1737, 1598, 1472, 1161, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.20 (d, *J*=3.0 Hz, 3H), 0.94 (s, 9H), 2.41 (s, 3H), 2.77 (dd, *J*=3.0, 6.0 Hz, 1H), 3.90 (d, *J*=18.0 Hz, 1H), 4.60 (d, *J*=15.0 Hz, 1H), 4.89 (dd, *J*=6.0, 9.0 Hz, 1H), 5.28 (s, 1H), 7.03 (d, *J*=6.0 Hz, 1H), 7.12 (d, *J*=9.0 Hz, 1H), 7.30–7.73 (m, 7H), 7.75 (d, *J*=6.0 Hz, 2H). ^{13}C NMR

($CDCl_3$, 125 MHz): δ=18.11 (q), 21.51 (q), 25.77 (q), 38.78 (t), 51.44 (t), 68.82 (d), 73.53 (s), 105.65 (d), 109.59 (d), 123.74 (d), 127.38 (d), 127.79 (d), 129.44 (d), 130.71 (s), 136.12 (s), 143.50 (s), 153.42 (s), 153.86 (s). MS (EI, 70 eV): *m*/*z* (%): 509 (38) [M^+], 508 (22), 452 (100), 404 (9). HRMS (70 eV): $C_{28}H_{35}NO_4SSi$: calcd 509.2056; found 509.2018.

4.22. Synthesis of (*R*)-4-(*tert*-butyldimethylsilanyloxy)-7-phenyl-2-(toluol-4-sulfonyl)-1,2,3,4-tetrahydroisoquinoline-8-ol ((*R*)-11c, FA-ER-35)

Compound (*S*)-**10c** (181 mg, 355 μmol) was dissolved in an NMR tube in 500 μl CD_2Cl_2, then 12.7 mg (17.7 μmol, 5 mol %) **13** and 7.71 mg (17.7 μmol) $Ag[SbF_6]$ in CD_2Cl_2 were added. The reaction was monitored by ^1H NMR spectroscopy, when complete the solvent was removed in vacuo and the residue purified by column chromatography (silica gel; PE/EE, 10:1), delivering 149 mg (82%) of (*R*)-**11c** as colourless oil, which solidifies in the freezer but melts at room temperature. R_f (PE/EE, 8:1)=0.10. IR (film): ν=3500, 2954, 2929, 1344, 1255, 1233, 1167, 1127, 1091, 1074, 991 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.20 (d, *J*=3.0 Hz, 3H), 0.94 (s, 9H), 2.41 (s, 3H), 2.77 (dd, *J*=3.0, 6.0 Hz, 1H), 3.90 (d, *J*=18.0 Hz, 1H), 4.60 (d, *J*=15.0 Hz, 1H), 4.89 (dd, *J*=6.0, 9.0 Hz, 1H), 5.28 (s, 1H), 7.03 (d, *J*=6.0 Hz, 1H), 7.12 (d, *J*=9.0 Hz, 1H), 7.30–7.73 (m, 7H), 7.75 (d, *J*=6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−4.74 (q), −4.26 (q), 21.54 (q), 25.85 (q), 43.67 (t), 49.53 (t), 67.04 (d), 118.49 (d), 119.18 (s), 127.66 (d), 128.17 (d), 128.22 (d), 128.96 (d), 129.66 (d), 129.76 (d), 127.80 (s), 133.91 (s), 136.37 (s), 138.69 (s), 143.63 (s), 148.06 (s). MS (ESI, eV): *m*/*z* (%): 508 (31) [$M]^+$, 494 (11), 452 (58), 436 (9), 434 (7), 378 (100), 352 (22). HRESI (eV): $C_{28}H_{35}NO_4SSi$: calcd 508.2056 [$M]^+$; found 508.1972 [$M]^+$. $[\alpha]^{578}$ 17.1; $[\alpha]^{546}$ 18.7; $[\alpha]^{436}$ 31.0.

4.23. Synthesis of (*S*)-5-ethylfuran-2-yl-hydroxyacetonitrile ((*S*)-6d, FA-307)

Citric acid (3.68 g) was dissolved in 20 ml water and 75 ml DIPE was added. A solution of 3.20 g (61.2 mmol) KCN in 13 ml water was added slowly. After 30 min the aqueous layer was separated and added to a mixture of 15.2 g of powdered almonds with 76 ml buffer, 30 ml DIPE and 3.80 g (30.6 mmol) of **5d** was added. After 30 min the organic layer was quickly filtered from the powdered almonds, dried over $MgSO_4$, filtered and the solvent removed in vacuo. Thus 2.72 g of crude (*S*)-**6d** was obtained as a yellow liquid. ^1H NMR ($CDCl_3$, 250 MHz): δ=1.29 (t, *J*=7.6 Hz, 3H), 2.71 (q, *J*=7.6 Hz, 2H), 3.42 (br s, 1H), 5.48 (s, 1H), 6.04 (d, *J*=3.1 Hz, 1H), 6.52 (d, *J*=3.3 Hz, 1H).

4.24. Synthesis of *rac*-(5-ethylfuran-2-yl)hydroxyacetonitrile (*rac*-6d, FA-288)

Compound **5d** (2.00 g, 16.1 mmol) was dissolved in 8 ml glacial acetic acid and cooled to 0 °C. Then a solution of 2.52 mg (48.3 mmol) KCN in 16 ml H_2O was added dropwise and the mixture was stirred over night at room temperature. Then 8 ml H_2O was added, the product was extracted with Et_2O (3×10 ml) and dried over $MgSO_4$. After filtration and addition of toluene, the solvent was removed. Crude *rac*-**6d** (2.70 g) was obtained and directly used in the next step without further purification.

4.25. Synthesis of (*S*)-(*tert*-butyldimethylsilanyloxy)(5-ethylfuran-2-yl)acetonitrile ((*S*)-7d, FA-315)

Crude (*S*)-**6d** (1.36 g, 9.06 mmol) was dissolved in 5 ml DMF, 1.54 g (22.7 mmol) imidazole and 2.73 g (18.1 mmol) TBDMSCl were added and the mixture was stirred over night at room temperature. After column chromatography (silica; PE/EE, 20:1) 2.23 g (93% over two steps) of liquid (*S*)-**7d** was obtained. R_f (PE/EE, 20:1)=0.37. IR (film): ν=2930, 2886, 2858, 1556, 1464, 1363, 1255, 1204, 1086, 1015, 911, 839 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ=0.01 (s, 6H), 0.78 (s, 9H), 1.10 (t, *J*=7.6 Hz, 3H), 2.52 (q, *J*=7.6 Hz, 2H), 5.37 (s, 1H), 5.85 (d, *J*=3.2 Hz, 1H), 6.28 (d, *J*=3.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−5.28 (q), 12.02 (q), 18.17 (s), 21.37 (t), 25.46 (q), 58.13 (d), 105.15 (d), 110.19 (d), 117.44 (s), 146.43 (s), 159.50 (s). MS (EI, 70 eV): *m*/*z* (%): 265 (12) [M^+], 250 (74), 239 (11), 209 (16), 208 (100), 194 (4), 181 (5), 134 (11), 119 (4), 75 (47). $C_{14}H_{23}NO_2Si$ (265.42): calcd C 63.35, H 8.73, N 5.28; found C 63.43, H 8.98, N 5.07. $[\alpha]^{578}$ 4.8; $[\alpha]^{546}$ 5.5; $[\alpha]^{436}$ 9.8.

4.26. Synthesis of (*S*)-2-(*tert*-butyldimethylsilanyloxy)-2-(5-ethylfuran-2-yl)ethylamine ((*S*)-8d, FA-292)

Compound (*S*)-**7d** (4.44 g, 16.7 mmol) was dissolved in 50 ml Et_2O and cooled to −70 °C. Then 33.4 ml DIBAL-H (1.0 M solution in hexane) was added dropwise and the solution was warmed to −20 °C. After cooling to −70 °C again, 20 ml MeOH and 1.26 g (33.4 mmol) $NaBH_4$ were added and the solution was allowed to warm to room temperature over night. Et_2O (50 ml) was added and the organic layer was washed with 50 ml 2 N NaOH, 50 ml H_2O and 50 ml brine, then dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, 4.09 g (*S*)-**8d** was obtained as a yellow oil, which was used in the next step directly. ^1H NMR ($CDCl_3$, MHz): δ=−0.07 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 1.18 (t, *J*=6.0 Hz, 2H), 1.44 (br s, 2H), 2.59 (q, *J*=6.0 Hz, 1H), 2.99–2.82 (m, 2H), 4.57 (t, *J*=6.0 Hz, 1H), 5.87 (d, *J*=3.0 Hz, 1H), 6.05 (d, *J*=3.0 Hz, 1H).

4.27. Synthesis of (*S*)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-(5-ethylfuran-2-yl)ethyl]-4-methylphenylsulfonamide ((*S*)-9d, FA-294)

Crude (*S*)-**8d** (2.00 g, 5.08 mmol) was dissolved in 20 ml DCM, 700 μl (5.08 mmol) NEt_3, 62.0 mg (508 μmol) DMAP and finally 968 mg (5.08 mmol) tosyl chloride were added slowly at room temperature. After stirring over night, 20 ml H_2O was added, the aqueous phase was extracted with 3×10 ml DCM. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed in vacuo. After column chromatography (silica gel; PE/EE, 10:1) 2.30 g (93% over two steps) of (*S*)-**9d** was obtained as a yellow oil. R_f (PE/EE, 10:1)=0.30. IR (film): ν=3055, 2955, 2931, 2858, 1462, 1421, 1334, 1265, 1162, 1091 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=−0.16 (s, 3H), −0.02 (s, 3H), 0.80 (s, 9H), 0.88 (d, *J*=7.5 Hz, 3H), 2.41 (s, 3H), 2.54 (q, *J*=7.6 Hz, 2H), 3.21 (t, *J*=6.2 Hz, 3H), 4.62 (q, *J*=6.2 Hz, 2H), 5.84 (d, *J*=3.1 Hz, 1H), 6.03 (d, *J*=3.1 Hz, 1H), 7.25 (d, *J*=8.1 Hz, 2H), 7.70 (d, *J*=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 76 MHz): δ=−5.23 (q), −5.06 (q), 12.20 (q), 21.36 (q), 25.66 (q), 47.82 (t), 67.12 (d), 104.35 (d), 108.23 (d), 127.10 (d), 129.72 (d), 137.03 (s), 143.41 (s), 151.32 (s), 157.68 (s). MS (FAB^+): *m*/*z* (%): 423 (2) [M^+], 408 (11), 390 (6), 366 (46), 316 (8), 292 (66), 258 (4), 239 (100). $C_{21}H_{23}NO_4Si$ (423.64): calcd C 59.54, H 7.85, N 3.31; found C 59.67, H 8.36, N 3.25. HRMS ($HRFAB^+$): $C_{21}H_{33}NO_4SSiNa$: calcd 423.1900; found 446.1783.

4.28. Synthesis of (*S*)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-(5-ethylfuran-2-ylethyl)ethyl]-4-methyl-*N*-prop-2-ynylphenylsulfonamide ((*S*)-10d, FA-295)

Compound (*S*)-**9d** (2.15 g, 5.09 mmol) was dissolved in 10 ml acetone; 5.00 g (15.3 mmol) Cs_2CO_3 and 1.40 ml (15.3 mmol) propargyl bromide (80 wt % in toluene) were added. After stirring over night, the solvent was removed in vacuo and the residue was taken up in 10 ml H_2O. After three extractions with 10 ml DCM each the organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo. After column chromatography (silica gel; PE/EE, 50:1) 1.46 g (80%) (*S*)-**10d** was obtained as a colourless oil, which

solidifies in the fridge. R_f (PE/EE, 50:1)=0.10. IR (film): ν=2995, 2931, 2856, 1461, 1350, 1255, 1185, 1161, 1092, 1011 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ=−0.08 (s, 3H), 0.06 (s, 3H), 0.84 (s, 9H), 1.19 (t, J=7.5 Hz, 3H), 2.39 (s, 3H), 2.59 (q, J=7.6 Hz, 2H), 3.41 (d, J=6.7 Hz, 2H), 3.95 (dd, J=2.4, 18.5 Hz, 1H), 4.18 (dd, J=2.5, 18.5 Hz, 1H), 4.90 (t, J=6.6 Hz, 1H), 5.87 (d, J=3.1 Hz, 1H), 6.12 (d, J=3.1 Hz, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.71 (d, J=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−5.11 (q), 12.28 (s), 21.36 (t), 21.52 (q), 25.78 (q), 38.62 (t), 51.19 (t), 68.73 (d), 73.38 (s), 104.55 (d), 108.23 (d), 127.78 (d), 129.39 (d), 136.28 (s), 143.41 (s), 152.08 (s), 157.52 (s). MS (FAB^+, eV): m/z (%): 461 (11) [M^+], 466 (9), 404 (36), 330 (100), 305 (4). $C_{24}H_{35}NO_4SSi$ (461.6905): calcd C 62.44, H 7.64, N 3.03; found C 62.14, H 7.79, N 2.92. HR FAB^+ (eV): $C_{22}H_{31}NO_4SSi$: calcd 461.2056; found 461.2065. $[\alpha]^{578}$ −50.5; $[\alpha]^{546}$ −57.9.

4.29. Synthesis of (*R*)-4-(*tert*-butyldimethylsilanyloxy)-7-ethyl-2-(toluol-4-sulfonyl)-1,2,3,4-tetrahydroisoquinoline-8-ol ((*R*)-11d, FA-350)

Compound (*S*)-**10d** (143 mg, 310 μmol) was dissolved in an NMR tube in 500 μl CD_2Cl_2, then 11.0 mg (15.3 μmol, 5 mol %) **13** and 6.70 mg (15.3 μmol) Ag[SbF_6] in CD_2Cl_2 were added. The reaction was monitored by ^1H NMR spectroscopy, when complete the solvent was removed in vacuo and the residue purified by column chromatography (silica gel; PE/EE, 20:1), delivering 95 mg (85%) of (*R*)-**11d** as colourless solid. Mp: 113 °C. R_f (PE/EE, 20:1)=0.15. IR (film): ν=2954, 2928, 2857, 1494, 1447, 1341, 1254, 1223, 1163, 1163, 1126, 1090 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ=0.61 (s, 6H), 0.91 (s, 9H), 1.19 (t, J=9.0 Hz, 2H), 2.40 (s, 3H), 2.53 (q, J=9.0 Hz, 2H), 2.47 (dd, J=9.0, 12.0 Hz, 1H), 3.79 (dd, J=6.0, 12.0 Hz, 1H), 3.87 (d, J=15.0 Hz, 1H), 4.54 (d, J=18.0 Hz, 1H), 4.83 (dd, J=6.0, 9.0 Hz, 1H), 6.93 (d, J=9.0 Hz, 1H), 7.01 (d, J=6.0 Hz, 1H), 7.31 (d, J=9.0 Hz, 2H), 7.73 (d, J=9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−4.77 (q), −4.30 (q), 8.30 (q), 13.78 (q), 21.52 (q), 22.42 (t), 25.83 (q), 43.54 (t), 49.58 (t), 66.97 (d), 118.75 (d), 118.93 (s), 127.05 (d), 127.64 (d), 129.73 (d), 133.90 (s), 136.80 (s), 143.60 (s), 149.00 (s). MS (FAB^+, eV): m/z (%): 461 (37) [M^+], 460 (100), 459 (13), 404 (49), 393 (7), 362 (2), 330 (83), 307 (14), 304 (13), 289 (18). HR FAB^+ (eV): $C_{24}H_{35}NO_4SSi$: calcd 462.2136 $[M+H]^+$; found 426.2068 $[M+H]^+$. $[\alpha]^{578}$ −8,2; $[\alpha]^{546}$ −10.5; $[\alpha]^{436}$ −12.5.

4.30. Synthesis of (*S*)-(4,5-dimethylfuran-2-yl)hydroxy-acetonitrile ((*S*)-6e, FA-336)

Citric acid (18.4 g) was dissolved in 25 ml water and 100 ml DIPE was added. A solution of 4.20 g (80.6 mmol) in 10 ml water was added slowly. After 30 min the aqueous layer was separated and added to a mixture of 20.0 g of powdered almonds with 100 ml buffer, 25 ml DIPE and 5.00 g (40.7 mmol) of **5e** was added. After 30 min the organic layer was quickly filtered from the powdered almonds, dried over $MgSO_4$, filtered and the solvent removed in vacuo. Thus 4.42 g of crude (*S*)-**6e** was obtained as a yellow liquid. ^1H NMR ($CDCl_3$, 500 MHz): δ=−0.19 (s, 3H), 0.00 (s, 3H), 0.76 (s, 9H), 1.77 (s, 3H), 2.05 (s, 3H), 5.29 (s, 1H), 6.12 (s, 1H).

4.31. Synthesis of *rac*-(4,5-dimethylfuran-2-yl)hydroxy-acetonitrile (*rac*-6e, FA-231)

Compound **5e** (3.00 g, 24.2 mmol) was dissolved in 24 ml glacial acetic acid and cooled to 0 °C. Then a solution of 3.78 mg (72.5 mmol) KCN in 24 ml H_2O was added dropwise and the mixture was stirred over night at room temperature. Then 24 ml H_2O was added, the product was extracted with Et_2O (3×10 ml) and dried over $MgSO_4$. After filtration and addition of toluene, the solvent was removed. Crude *rac*-**6e** (3.34 g) was obtained and directly used in the next step without further purification.

4.32. Synthesis of (*S*)-(*tert*-butyldimethylsilanyloxy)-(4,5-dimethylfuran-2-yl)acetonitrile ((*S*)-7e, FA-232)

Crude (*S*)-**6e** (1.50 g, 9.92 mmol) was dissolved in 20 ml DMF, 1.35 g (19.8 mmol) imidazole and 2.24 g (14.9 mmol) TBDMSCl were added and the mixture was stirred over night at room temperature. After column chromatography (silica; PE/EE, 10:1) 2.18 g (83% over two steps) of the yellow solid (*S*)-**7e** was obtained. Mp: 30 °C. R_f (PE/EE, 10:1)=0.43. IR (film): ν=2960, 2929, 2887, 2859, 1636, 1570, 1472, 1464, 1362, 1292 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=6.26 (s, 1H), 5.42 (s, 1H), 2.18 (s, 3H), 1.91 (s, 3H), 0.90 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 76 MHz): δ=−5.14 (q), 9.72 (q), 11.36 (q), 25.49 (q), 58.09 (d), 112.63 (d), 115.15 (s), 117.53 (s), 145.34 (s), 149.14 (s). MS (EI, 70 eV): m/z (%): 265 (3) [M^+], 250 (6), 210 (6), 208 (100), 181 (4), 134 (20), 75 (40). $C_{14}H_{23}NO_2Si$ (265.15): calcd C 63.35, H 8.73, N 5.28; found C 62.98, H 8.72, N 5.20. HRMS (70 eV): $C_{14}H_{23}NO_2Si$: calcd 265.1498; found 265.1467. $[\alpha]^{578}$ 19.6; $[\alpha]^{546}$ 22.5; $[\alpha]^{436}$ 40.8.

4.33. Synthesis of (*S*)-2-(*tert*-butyldimethylsilanyloxy)-2-(4,5-dimethylfuran-2-yl)ethylamine ((*S*)-8e, FA-236)

Compound (*S*)-**7e** (200 mg, 753 mmol) was dissolved in 10 ml Et_2O and cooled to −70 °C. Then 1.51 ml DIBAL-H (1.0 M solution in hexane) was added dropwise and the solution was warmed to −20 °C. After cooling to −70 °C again, 2 ml MeOH and 57.0 g (1.51 mmol) $NaBH_4$ were added and the solution was allowed to warm to room temperature over night. Et_2O (10 ml) was added and the organic layer was washed with 5 ml 2 N NaOH, 5 ml H_2O and 5 ml brine, then dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, 166 mg (*S*)-**8e** was obtained as a yellow oil, which was used in the next step directly. ^1H NMR ($CDCl_3$, 300 MHz): 6.29 (s, 1H), 4.79 (t, 2H), 3.26 (s, 3H), 2.43 (s, 3H), 2.53 (br s, 2H).

4.34. Synthesis of (*S*)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-(4,5-dimethylfuran-2-yl)ethyl]-4-methylbenzenesulfonamide ((*S*)-9e, FA-238)

Crude (*S*)-**8e** (500 g, 1.86 mmol) was dissolved in 10 ml DCM, 260 μl (1.86 mmol) NEt_3, 22.7 mg (168 μmol) DMAP and finally 345 mg (1.86 mmol) tosyl chloride were added slowly at room temperature. After stirring over night, 20 ml H_2O was added, the aqueous phase was extracted with 3×10 ml DCM. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed in vacuo. After column chromatography (silica gel; PE/EE, 10:1) 230 mg (54% over two steps) of (*S*)-**9e** was obtained as a yellow oil. R_f (PE/EE, 10:1)=0.21. IR (film): ν=2956, 2928, 2906, 2886, 2857, 2241, 1730, 1671, 1601, 1330 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=7.68 (d, J=8.3 Hz, 2H), 7.26 (d, J=8.3 Hz, 2H), 5.95 (s, 1H), 4.70 (t, J=5.9 Hz, 1H), 2.94 (d, J=7.2 Hz, 1H), 2.85 (d, J=6.8 Hz, 1H), 2.15 (s, 3H), 1.89 (s, 3H), 0.84 (s, 9H), 0.02 (s, 3H), −0.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 76 MHz): δ=−5.28 (q), −5.03 (q), 9.72 (q), 11.19 (q), 18.04 (s), 21.43 (q), 25.77 (q), 47.76 (t), 67.03 (d), 110.76 (d), 114.37 (s), 127.03 (d), 129.56 (d), 136.97 (s), 143.29 (s), 147.02 (s), 150.10 (s). MS (FAB^+): m/z (%): 423 (11) [M^+], 408 (25), 406 (9), 366 (74), 365 (5), 292 (100), 290 (11). HRMS ($HRFAB^+$): $C_{21}H_{33}NO_4SSi$: calcd 423.1900; found423.1868.

4.35. Synthesis of (*S*)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-(4,5-dimethylfuran-2-yl)ethyl]-4-methyl-*N*-prop-2-ynylbenzenesulfonamide ((*S*)-10e, FA-239)

Compound (*S*)-**9e** (100 mg, 236 μmol) was dissolved in 10 ml acetone; 231 mg (708 μmol) Cs_2CO_3 and 660 μl (708 μmol) propargyl bromide (80 wt % in toluene) were added. After stirring over

night, the solvent was removed in vacuo and the residue was taken up in 10 ml H_2O. After three extractions with 10 ml DCM each the organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo. After column chromatography (silica gel; PE/EE, 10:1) 39 mg (92%) (*S*)-**10e** was obtained as a yellow solid. Mp: 32 °C. R_f (PE/EE, 10:1)=0.28. IR (film): ν=3307, 2957, 2929, 2885, 2857, 1601, 1482, 1347, 1257, 1223 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=7.73 (d, *J*=8.6 Hz, 2H), 7.27 (d, *J*=8.6 Hz, 2H), 6.01 (s, 1H), 4.88 (t, *J*=6.6 Hz, 1H), 4.20 (dd, *J*=18.6, 2.6 Hz, 1H), 4.00 (dd, *J*=18.6, 2.4 Hz, 1H), 3.40 (d, *J*=6.8 Hz, 2H), 2.41 (s, 3H), 2.16 (s, 3H), 1.98 (t, *J*=2.2 Hz, 1H), 1.90 (s, 3H), 0.86 (s, 9H), 0.08 (s, 3H), −0.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 76 MHz): δ=−5.01 (q), 9.84 (q), 11.29 (q), 21.51 (q), 25.80 (q), 38.65 (t), 51.23 (t), 68.69 (s), 73.32 (d), 110.82 (d), 127.79 (d), 129.36 (d), 136.28 (s), 143.36 (s), 146.91 (s), 150.89 (s). MS (FAB$^+$, eV): *m*/*z* (%): 461 (56) [M$^+$], 460 (68), 446 (34), 405 (36), 404 (100), 366 (11), 330 (100). HRMS (HRFAB$^+$): $C_{24}H_{35}NO_4SSi$: calcd 461.2056; found 461.2075. $[\alpha]^{578}$ −64.6; $[\alpha]^{546}$ −74.0; $[\alpha]^{436}$ −134.6.

4.36. Synthesis of (*R*)-4-(*tert*-butyldimethylsilanyloxy)-6,7-dimethyl-2-(toluol-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline-8-ol ((*R*)-11e, FA-351)

Compound (*S*)-**10e** (344 mg, 745 μmol) was dissolved in an NMR tube in 500 μl CD_2Cl_2, then 26.6 mg (37.3 μmol, 5 mol%) **13** and 16.2 mg (37.7 μmol) Ag[SbF_6] in CD_2Cl_2 were added. The reaction was monitored by ^1H NMR spectroscopy, when complete the solvent was removed in vacuo and the residue purified by column chromatography (silica gel; PE/EE, 10:1), delivering 280 mg (81%) of (*R*)-**11e** as colourless solid. Mp: 58 °C. R_f (PE/EE, 10:1)=0.27. IR (film): ν=3500, 2955, 2930, 2857, 1461, 1341, 1253, 1202, 1166, 1090 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ=0.15 (s, 3H), 0.16 (s, 3H), 0.93 (s, 9H), 2.08 (s, 3H), 2.40 (s, 3H), 2.74 (dd, *J*=9.0, 12.0 Hz, 1H), 3.77 (dd, *J*=9.0, 12.0 Hz, 1H), 3.85 (d, *J*=15.0 Hz, 1H), 4.49 (d, *J*=18.0 Hz, 1H), 4.79 (d, *J*=18.0 Hz, 1H), 4.79 (dd, *J*=6.0, 9.0 Hz, 1H), 6.79 (s, 1H), 7.30 (d, *J*=9.0 Hz, 2H), 7.73 (d, *J*=9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−4.72 (q), −4.27 (q), 11.29 (q), 20.39 (q), 21.50 (q), 25.84 (t), 43.53 (t), 49.67 (t), 66.91 (d), 116.45 (s), 119.59 (s), 120.12 (d), 127.62 (d), 129.71 (d), 134.02 (s), 135.66 (s), 143.55 (s), 149.34 (s). MS (ESI, eV): *m*/*z* (%): 484 (100) [M+Na$^+$], 351 (5), 297 (10), 216 (7). HRESI (eV): $C_{24}H_{35}NNaO_4SSi$: calcd 484.1954 [M+H]$^+$; found 484.19483 [M+H]$^+$. $[\alpha]^{578}$ 36.3; $[\alpha]^{546}$ 39.8; $[\alpha]^{436}$ 67.6.

References and notes

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6. CCDC 706502 (**7c**) and 706503 (**10a**) contain the supplementary crystallographic data for this paper. These data can be obtained online free of charge (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).
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