Diastereoselective reduction of enantiopure N-p-toluenesulfinyl ketimines derived from pyridyl ketones

Diastereoselective reduction of enantiopure *N*-*p*-toluenesulfinyl ketimines derived from pyridyl ketones

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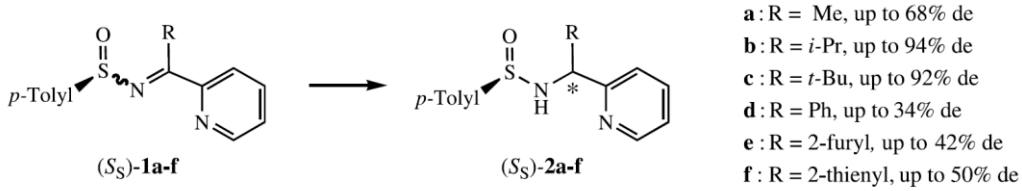
Abstract. DIBAL reduction of enantiopure *N*-*p*-toluenesulfinyl ketimines derived from 2-pyridyl ketones bearing an additional substituent on the 6-position of the pyridine ring afforded the related *N*-*p*-toluenesulfinyl amines with high yields and diastereoselectivities. The results of a number experiments exploring the conversion of a optically active 1-substituted *N*-toluenesulfinyl 1-(6-bromopyridin-2-yl)methylamine in a number of more complex pyridine derivatives with maintenance of the toluenesulfinyl group *N*-protecting group is also reported.

1. Introduction

Optically active 1-substituted-1-(pyridyl)methylamines have attracted much academic and commercial interest,[1] primarily due to their existence in naturally occurring compounds such as tobacco alkaloids (nicotine, nornicotine, anabatine, etc.)[2] or as key fragments within potential drug candidates.[3] Moreover, they have proven utility as ligands in metal complexes for asymmetric catalysis.[4] Notwithstanding the many routes an asymmetric syntheses of these compounds that have been developed,[1] new opportunities are yet to be explored. Accordingly, we have recently investigated the diastereoselective reduction of enantiopure N-p-toluenesulfinyl pyridyl ketimines with a variety of hydride transfer reagents obtaining 1-substituted- 1-(pyridin-2-yl)methylamines with diastereomeric excesses up to 94% (Scheme 1).[5]



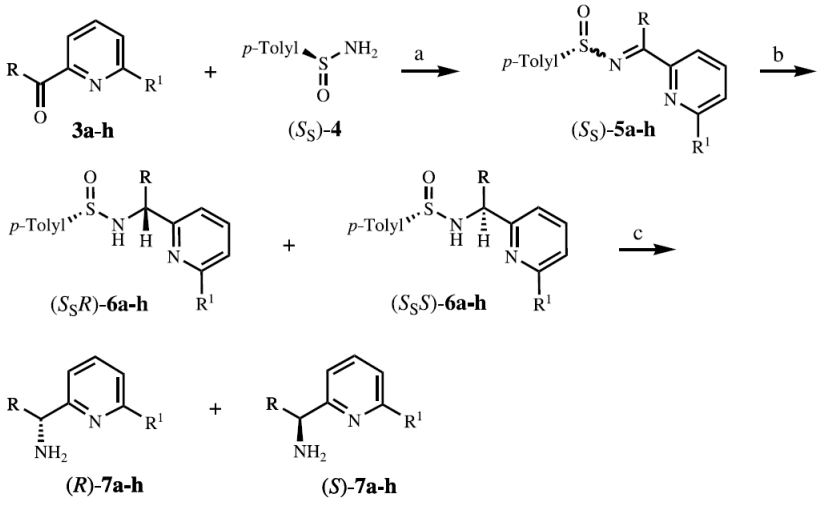
Scheme 1.

In this paper, as part of our ongoing work in this area, we report the results obtained in the reduction of a number of chiral N-p-toluenesulfinyl ketimines 5 derived from 2-pyridyl ketones 3 bearing an additional substituent on the 6-position of the pyridine ring (Scheme 2). The results of some experiments exploring the conversion of one optically active 1-substituted N-toluenesulfinyl 1-(6-bromopyridin- 2-yl)methylamine in a number of pyridylmethylamine derivatives with maintenance of the toluenesulfinyl group N-protecting group are also reported (Scheme 3).

2. Results and discussion

It has been reported that the diastereoselectivity of addition reactions involving functionalised pyridines depends on the position of the functional group with respect to the pyridine nitrogen. For instance, the Michael addition of chiral non-racemic lithium amides to tert-butyl 3-(pyridin-3-yl)- and 3-(pyridin-4-yl)prop-2-enoates afforded the addition product in good yields and diastereoselectivities (84%), whereas the application of this methodology to the analogous b-2-pyridyl system afforded very low levels of stereoselectivity (6% de) unless the pyridine ring was also substituted at the 6-position.[6] In order to probe the influence on the diastereoselectivity of an additional substituent on the 6-position of the pyridine ring in our system, the 4-methyl-N-[1-(6-methylpyridin- 2-yl)ethylidene]benzenesulfinamide (Ss)-5a was prepared from 1-(6-methylpyridin-2-yl)ethanone (3a) (Scheme 2). Reduction of 5a at -78 °C with DIBAL, which was on average the best performing hydride transfer reagent among those evaluated in the reduction of 2a–f, afforded a 2:98 mixture of diastereomers (Ss,R)-6a:(Ss,S)-6a with an improved facial selectivity with

respect to the unsubstituted system 2a ((Ss,R):(Ss,S)=16:84). Encouraged by this result, we investigated the diastereoselective reduction of a set of related pyridyl systems (Ss)-5a–h with varying steric and electronic demand about the pyridine and imine moieties (Scheme 2).



a: R = Me, R^1 = Me; **b**: R =Me, R^1 = Br; **c**: R = Me, R^1 = Ph; **d**: R = *t*-Bu, R^1 = Br;
e: R = *t*-Bu, R^1 = Ph; **f**: R = Ph, R^1 = Me; **g**: R = Ph, R^1 = Br; **h**: R = Ph, R^1 = Ph

a: $Ti(OEt)_4$, THF, 70 °C, 24-36 h, 34-75%; b: DIBAL, THF, -78 °C, 3-6 h;
c: CF_3COOH, MeOH, r.t., 12 h, >90%.

Scheme 2.

N-p-Toluenesulfinyl ketimines 5a–h were obtained by condensation[7] of commercially available (S)-(C)-Np- toluenesulfinamide 4 (1 equivalent) with a series of 2-pyridyl ketones 3a–h (1.1 equiv) with different steric and/or electronic demands on the carbonyl and the pyridine ring. The reactions were performed employing $Ti(OEt)_4$
(2 equivalents) in CH_2Cl_2 at 40 °C for 2a (47%), 2b (75%) and 2c (78%) or THF at 70 °C for 2d (41%), 2e (49%), 2f (75%), 2g (86%) and 2h (85%). All imines were obtained as a single stereoisomer as determined by the ^1H NMR spectra (for the related configurations vide infra). Sulfinyl imines (Ss)-5a–h were reduced with DIBAL at -78 °Cto give the corresponding sulfinylamines (Ss,R)-6a–h and (Ss,S)-6a–h. The obtained results are reported in Table 1.

The extent of the asymmetric induction was determined directly by ^1H NMR spectroscopy of the crude reaction mixture of the diastereoisomeric sulfinyl amines. In order to confirm unambiguously these results, all reductions were also carried out using $NaBH_4$ that afforded sulfinyl amines in high yields and low selectivities, except in the case of sulfinyl amines (Ss)-6d and (Ss)-6e (R=tert-Bu) that were obtained with moderate diastereoselectivities (83:17 dr).

Table 1. Reduction of (S_S)-**5a–h** with DIBAL (Scheme 2)

Compound	Substituents		Ratio[a] (S_S,*R*)-**6**: (S_S,*S*)-**6**	Yield[b] (%)
	R	R^1		
5a	Me	Me	2:98	82
5b	Me	Br	<2:>98	92
5c	Me	Ph	28:72	87
5d	*t*-Bu	Br	98:2	95
5e	*t*-Bu	Ph	>99:1	95
5f	Ph	Me	92:8	85
5g	Ph	Br	88:12	76
5h	Ph	Ph	93:7	86

[a] Ratio of the crude reaction mixture determined by ^1H NMR spectroscopy.
[b] Isolated yields.

The substitution of the 2-pyridyl system resulted in a significant increase of diastereoselectivity upon reduction compared with the related 6-unsubstituted pyridine (Scheme 1). The only exception was the sulfinyl imine (Ss)-5c (R=Me, R1=Ph) that afforded a lower diastereoselectivity in comparisonwith its unsubstituted counterpart 2a.

The configuration of the new stereocentre in the reduction products was tentatively assigned by comparison of 1HNMR chemical shifts of the benzylic protons of 6 with those of the related known unsubstituted pyridines 2.[5] Moreover, this assignment was corroborated by converting the bromopyridine 6d both into the sulfinyl amines 6e and 2c[5] (vide infra).

It should be noted that independently from the 6-substituent on the pyridine the reduction of the sulfenyl imines 6a–c (R=Me) gave the opposite prevailing diastereomer with respect to the other imines 6d–h (R=t-Bu or Ph). Moreover, the very high diastereoselectivity of the imine reduction process achieved with DIBAL compared to the much lower selectivity with $NaBH_4$ suggests that the coordination with the imines 6 is essential. According to models proposed for related systems,[8] the reduction would take place through the chelated species illustrated in Figure 1.

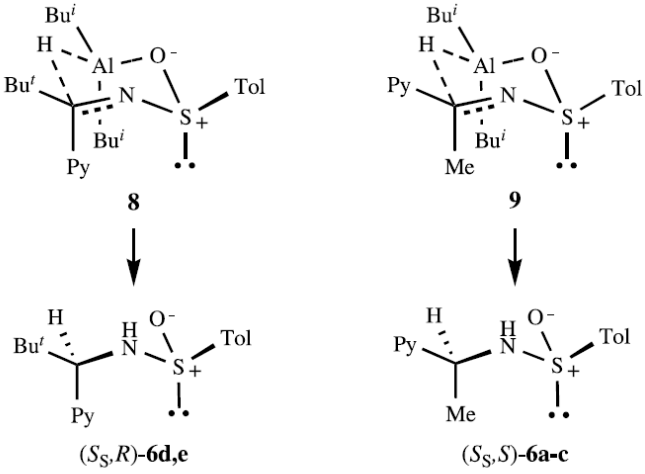
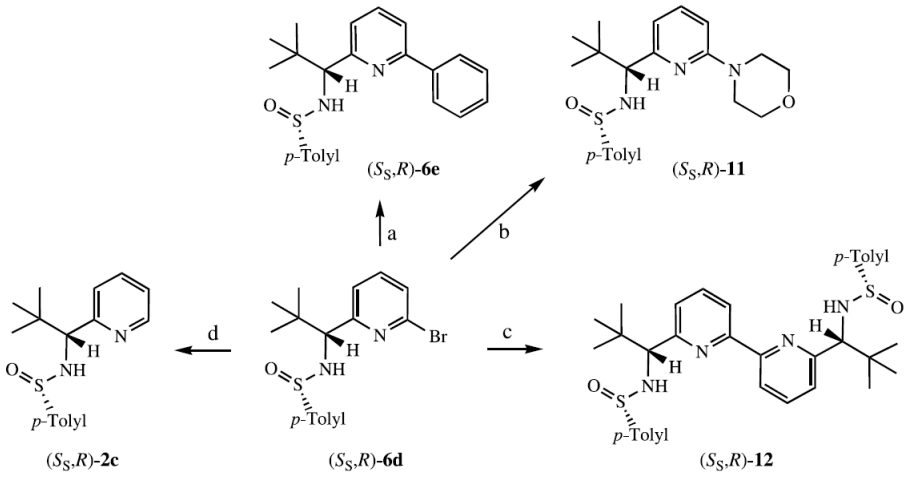


Figure 1.

The coordination of the aluminium with the sulfoxide oxygen would be expected to form a chelation controlled chair-like transition state [for instance 8 (R=t-Bu) and 9 (R=Me)] in which the groups on the sulfur atom and the large group on the imine are in pseudo-equatorial positions (Fig. 1). It has been assumed that the imine exists in the configuration in which the sulfoxide moiety is trans to the larger group on the imine moiety. According to this model, the reduction of imines 5d and 5e (R=t-Bu) affords the predominant diastereomers (Ss,R)-6d and (Ss,R)-6e through the transition states 8 (R=t-Bu) whereas the reduction of imines 6a–c (R=Me) gives (Ss,S)-6a–c through the transition states 9 (R=Me). In the case of the reduction of imines 6f–h (R=Ph) the situation appears less clear and to explain the stereochemical result using this model it must be supposed that in these imines the phenyl group assumes a configuration trans to the sulfoxide moiety rather than the pyridyl group. Accordingly, also in the reduction of the analogous unsubstituted pyridyl imine 1d the prevailing diastereomer 2d has the same (Ss,R)-configuration, although the diastereoselectivty was much lower.

The increase in facial selectivity observed upon reduction relative to the unsubstituted system 2a, appears to indicate that the group at the 6-position of the pyridine ring serves to sterically impede the competing coordination of the pyridyl nitrogen to the aluminium. This reduced coordination to the pyridyl nitrogen would then minimize the disruption of the normal chelation-controlled transition state,[8] thus disfavouring the competing nonstereoselective pathway for the reduction.

The finding that 1-substituted N-toluenesulfinyl 1-(6-bromopyridin-2-yl)methylamines such as 5b and 5d can be obtained with high diastereoselectivity and the consideration that the N-toluenesulfinyl group can be considered as a N-protecting group,[9] should allow for further elaboration of the 6-bromo substituent in order to build up more complex pyridine derivatives. With the aim of demonstrating this opportunity a number of reactions have been carried out using (Ss,R)-6d as a model substrate (Scheme 3).



a: $Pd(PPh_3)_4$, $PhB(OH)_2$, MeOH, aqueous Na_2CO_3, toluene, 80-85 °C, 14 h, 85%;
b: $Pd_2(dba)_3$, dppp, $NaOBu^t$, toluene , 70 °C, 9 h, 93%;
c: $NiCl_2$-$6H_2O$, Zn, PPh_3, DMF, 60 °C, 1 h then **6d**, 70°C, 8 h, 33%;
d: $Pd(OAc)_2$, PPh_3, $NaBH_4$, TMEDA, THF, r.t., 3 h, 95%.

Scheme 3.

Since the Suzuki cross-coupling reaction between a pyridyl halide or triflate with boronic acids or esters offers the opportunity to introduce a variety of substituents on a pyridine ring,[10] the coupling reaction of the bromopyridine (Ss,R)-6d (96% d.e.) with the phenylboronic acid was initially examined. Under standard Suzuki-type conditions ($Pd(PPh_3)_4$, $PhB(OH)_2$ in MeOH, aqueous Na_2CO_3, toluene, 80–85 °C, 14 h) the phenylpyridine (Ss,R)-6e was obtained in 85% yield and as a 98:2 mixture of diastereomers, demonstrating the compatibility of the starting point with the conditions of the Suzuki cross-coupling reaction (Scheme 3).

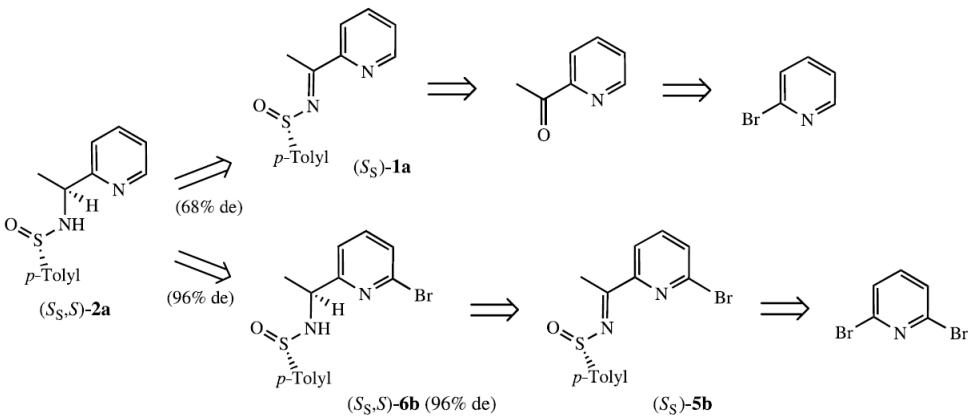
The metal-catalysed amination reaction has proved to be a valuable strategy for the selective introduction of an amino group on a pyridine ring. As a prototype of amination reaction, the Pd-catalysed reaction of (Ss,R)-6d with morpholine ($Pd_2(dba)_3$, dppp, $NaOBu^t$, toluene, 70 °C, 9 h) was checked.[11] The reaction proceeded smoothly affording the reaction product (Ss,R)-11 in high yield (93%) and with the same diastereomeric purity of the starting material (Scheme 3).

The preparation of the C_2-symmetric 2,2′-bipyridine 12 was pursued by nickel-catalysed homo-coupling reaction of bromopyridine (Ss,R)-6d (Scheme 4). The bipyridine 12 was obtained in 33% yield according to Tiecco's procedure[12] that entails the in situ formation of a Ni(0)-catalyst ($NiCl_2$–$6H_2O$, Zn, PPh_3, DMF, 60 °C, 1 h) followed by addition of 6d (70 °C, 8 h). Interestingly, we noted no difference in the yield when the reaction was performed mixing all components at once and then heating the mixture for 8 h at 70°C. Hoping to increase the yield, a preformed Ni(0)-catalyst was also employed ($Ni(CO)_2(PPh_3)_2$, DMF, 70 °C, 10 h),[13] but all attempts failed.

Finally, substitution of the bromine with hydrogen was obtained. Initial attempts of carrying out the hydrodehalogenation by hydrogenolysis catalysed by palladium metal on carbon or palladium hydroxide (H_2, MeOH, NaOAc, rt, 48 h) at atmospheric pressure failed, whereas when the pressure was increased to 3 atm (Parr apparatus) only the amine (R)-1-(6-bromopyridin-2-yl)-2,2-dimethylpropan-1-amine derived from hydrogenolysis of the N–S bond was obtained in very low yield. To overcome this drawback the metal-catalysed reductive debromination was examined. Taking into account the successfully palladiumcatalysed reductive hydrodebromination of highly brominated benzenes, we sough to adapt this procedure to our specific needs.[14] Gratifyingly, stirring at room temperature (Ss,R)-6d with $NaBH_4$ in the presence of a Pd-catalyst ($Pd(OAc)_2$, PPh_3, TMEDA, THF, 3 h) the pyridine 2c was obtained in excellent yield (O90%). The diastereomeric excess of the obtained 2a was estimated to be 96% indicating no racemization occurred during the reaction.

Interestingly, the high diastereoselectivity obtained in the reduction of 1-substituted N-toluenesulfinyl 1-(6-bromopyridin-2-yl)methylamines and the possibility to remove the bromine with high yield and maintenance of the integrity of the stereocentres can make up a strategy to obtain monosubstituted pyridyl amines with high diastereomeric excess. This opportunity is exemplified

in the Scheme 4 where the methyl derivative (Ss,S)-2a can be obtained in 68% de through reduction of imine (Ss,S)-1a, prepared from 2-bromopyridine, or in 96% de by hydrodebromination of the amine (Ss,S)-6a obtained in the usual way from the 2,6-dibromopyridine.



Scheme 4.

In conclusion, we have demonstrated that the DIBAL reduction of enantiopure N-p-toluenesulfinyl ketimines derived from 2-pyridyl ketones bearing a substituted on the 6-position of the pyridine ring affords the related N-p-toluenesulfinyl amines with a significant increase of the diastereoselectivity compared to the unsubstituted counterparts. This approach can also be pursued to obtain monosubstituted pyridyl amines with high diastereomeric excess. Finally, we presented a variety of examples in which a 1-substituted N-toluenesulfinyl 1-(6-bromopyridin- 2-yl)methylamine is converted in more complex pyridine derivatives with maintenance of the toluenesulfinyl group N-protecting group. Further studies on this subject are currently in progress.

3. Experimental

3.1 General methods

Melting points were determined on a Bu¨chi 510 capillary apparatus and are uncorrected. The NMR spectra were obtained with a Varian VXR-300 spectrometer at 300 for ^{1}H and 75.4 MHz for ^{13}C. Chemical shifts are reported in ppm downfield from internal Me_4Si in $CDCl_3$. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin-Elmer 240 B analyser. Ethyl acetate and petroleum ether were distilled before use. THF was distilled from sodium-benzophenone ketyl and CH_2Cl_2 from P_2O_5. Both solvents were degassed thoroughly with dry nitrogen directly before use. (S)-(C)-N-p-Toluenesulfinamide was purchased from Aldrich. 1-(6-Bromopyridin-2-yl)ethanone (3b),[15] 1-(6-phenylpyridin-2-yl)ethanone (3c),[16] 1-(6-bromopyridin-2-yl)-2,2-dimethylpropan-1-one (3d),[15] 1-(6-phenylpyridin-2-yl)-2,2-dimethylpropan-1-one (3e),[15] (6-phenylpyridin-2-yl)phenylmethanone (3h)[17] were prepared according to reported procedures. 1-(6-Methylpyridin-2-yl)ethanone (3a) and (6-methylpyridin-2-yl)phenylmethanone (3f) were obtained by addition of the Grignard reagent prepared from bromobenzene and methyliodide, respectively to 2-cyano-6-methylpyridine following the procedure reported by Case et al.[16] (6-Bromopyridin-2-yl)phenylmethanone (3g) was prepared by addition of the 2-lithio-6-bromopyridine to benzonitrile according to Bolm et al.[15]

3.2 General procedure for the preparation of N-p-toluenesulfinyl ketimines 5a–h

A solution of 2-pyridyl ketone 3 (0.55 mmol), (S)-(C)-Np-toluenesulfinamide (78.0 mg, 0.5 mmol) and $Ti(OEt)_4$ (0.228 g, 1.0 mmol) in anhydrous CH_2Cl_2 or THF (2 mL) was heated at 40 or 70 °C, respectively, for the proper time. After cooling the solvent was removed under vacuum and the residue was taken up in ethyl acetate (10 mL). This solution was vigorously stirred while a saturated solution of brine (2 mL) was slowly added. After 15 min the mixture was filtered through a plug of Celite that was washed

with ethyl acetate. The organic phase was separated and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by flash chromatography.

3.2.1. (Ss)-N-(1-(6-Methylpyridin-2-yl)ethylidene)-4-methylbenzenesulfinamide (5a). Reaction solvent: CH_2Cl_2; reaction time: 60 h; chromatographic eluent: petroleum ether/ethyl acetate=1/1; 0.062 g (47%); yellow oil; $[a]_D^{25}$C84.5 (c 0.21, $CHCl_3$). ^{1}HNMR: d 7.98 (d, 1H, J= 7.8 Hz), 7.73 (d, 2H, J=8.4 Hz), 7.59 (t, 1H, J=7.8 Hz), 7.31 (d, 2H, J=8.4 Hz), 7.19 (d, 1H, J=7.8 Hz), 2.84 (s, 3H), 2.54 (s, 3H), 2.38 (s, 3H). ^{13}CNMR: d 175.2, 157.4, 153.9, 142.9, 141.8, 136.4, 129.6, 125.2, 124.9, 119.1, 24.2, 21.2, 19.0. Anal. Calcd for $C_{15}H_{16}N_2OS$: C, 66.15; H, 5.92; N, 10.29. Found: C, 66.36; H, 5.90; N, 10.31.

3.2.2. (Ss)-N-(1-(6-Bromopyridin-2-yl)ethylidene)-4-methylbenzenesulfinamide (5b). Reaction solvent: CH_2Cl_2; reaction time 12 h; chromatographic eluent: petroleum ether/ethyl acetate =7/3; 0.126 g (75%); yellow solid; mp 54–55 °C; $[a]_D^{25}$+35.2 (c 0.55, $CHCl_3$); ^{1}HNMR: d 8.13 (d, 1H, J=7.5 Hz), 7.72 (d, 2H, J=8.1 Hz), 6.63–7.53 (m, 2H), 7.33 (d, 2H, J=8.1 Hz), 2.82 (s, 3H), 2.41 (s, 3H). ^{13}C-NMR: d 173.1, 155.5, 142.7, 142.2, 141.0, 138.7, 130.3, 129.9, 125.0, 121.0, 21.4, 19.0. Anal. Calcd for $C_{14}H_{13}BrN_2OS$: C, 49.86; H, 3.89; N, 8.31. Found: C, 49.66; H, 3.67; N, 8.12.

3.2.3. (Ss)-N-(1-(6-Phenylpyridin-2-yl)ethylidene)-4-methylbenzenesulfinamide (5c). Reaction solvent: CH_2Cl_2; reaction time: 48 h; chromatographic eluent: petroleum ether/ethyl acetate=1/1; 0.130 g (78%); yellow oil: $[a]_D^{25}$ -32.8 (c 0.66, $CHCl_3$); ^{1}H NMR: d 8.13 (d, 1H, J=6.0 Hz), 8.04 (d, 2H, J=8.1 Hz), 7.84–7.67 (m, 4H), 7.47–7.40 (m, 3H), 7.32 (d, 2H, J=8.1 Hz), 2.96 (s, 3H), 2.40 (s, 3H). ^{13}C-NMR: d 175.1, 156.0, 154.3, 143.0, 142.0, 138.4, 137.3, 129.8, 129.3, 128.7, 126.7, 125.1, 122.1, 120.5, 21.4, 19.1. Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.98; H, 5.44; N, 8.39.

3.2.4. (Ss)-N-(1-(6-Bromopyridin-2-yl)-2,2-dimethylpropylidene)-4-methylbenzenesulfinamide (5d). Reaction solvent: THF; reaction time: 36 h; chromatographic eluent: petroleum ether/ethyl acetateZ8/2 then 1/1; 0.077 g (41%); yellow solid; mp 111–112 °C, $[a]_D^{25}$ -73.0 (c 0.19, $CHCl_3$). ^{1}H NMR: 7.67–7.59 (m, 3H), 7.52 (d, 1H, J=9.0 Hz), 7.31 (d, 2H, J=8.1 Hz), 7.18 (d, 1H, J=7.5 Hz), 2.41 (s, 3H), 1.22 (s, 9H). ^{13}C-NMR: d 183.7, 156.1, 142.6, 141.9, 141.5, 138.1, 129.7, 128.1, 125.3, 120.9, 41.7, 27.9, 21.5. Anal. Calcd for $C_{17}H_{19}BrN_2OS$: C, 53.83; H, 5.05; N, 7.39. Found: C, 53.85; H, 5.03; N, 7.41.

3.2.5. (Ss)-N-(1-(6-phenylpyridin-2-yl)-2,2-dimethylpropylidene)-4-methylbenzenesulfinamide (5e). Reaction solvent: THF; reaction time 48 h; chromatographic eluent: petroleum ether/ethyl acetateZ1/1; 92.1 mg (49%); yellow solid; mp 110–111 °C; $[a]_D^{25}$ -78.5 (c 0.11, $CHCl_3$). ^{1}H NMR: d 7.99 (dd, 2H, JZ6.9, 1.5 Hz), 7.88–7.76 (m, 2H), 7.57 (d, 2H, J=8.4 Hz), 7.52–7.42 (m, 3H), 7.21 (d, 2H, J=8.4 Hz), 7.13 (dd, 1H, J=6.9, 1.5 Hz), 2.37 (s, 3H), 1.27 (s, 9H). ^{13}C-NMR: d 148.4, 125.2, 124.5, 115.2, 114.2, 111.5, 110.4, 104.9, 104.3, 102.8, 102.5, 101.7, 97.7, 97.4, 37.9, 27.5, 22.5. Anal. Calcd for $C_{23}H_{24}N_2OS$: C, 73.37; H, 6.42; N, 7.44. Found: C, 73.54; H, 6.45; N, 7.43.

3.2.6. (Ss)-N-((6-Methylpyridin-2-yl)phenylmethylene)-4-methylbenzenesulfinamide (5f). Reaction solvent: THF; reaction time: 48 h; chromatographic eluent: petroleum ether/ethyl acetate=1/1; 0.125 g (75%); oil; $[a]_D^{25}$ +25.6 (c 0.66, $CHCl_3$); ^{1}H NMR: d 7.92 (d, 2H, J=6.6 Hz), 7.76–7.62 (m, 3H), 7.44 (t, 1H, J=8.1 Hz), 7.38–7.21 (m, 5H), 7.12 (d, 1H, J=6.6 Hz), 2.60 (s, 3H), 2.34 (s, 3H). ^{13}C-NMR: d 172.6, 158.0, 152.3, 142.1, 141.2, 136.2, 136.0, 131.8, 129.6, 129.1, 127.9, 125.3, 124.2, 121.2, 23.9, 21.0. Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.62; H, 5.45; N, 8.36.

3.2.7. (Ss)-N-((6-Bromopyridin-2-yl)phenylmethylene)-4-methylbenzenesulfinamide (5g). Reaction solvent: THF; reaction time: 48 h; chromatographic eluent: petroleum ether: ethyl acetate=7/3; 0.172 g (86%); yellow solid mp 44–45 °C; $[a]_D^{25}$ +37.0 (c 0.71,

$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): d 7.94 (s broad, 2H), 7.70–7.52 (m, 4H), 7.46 (t, 1H, J=7.5 Hz), 7.45–7.26 (m, 5H), 7.35 (s, 3H). ^{13}C NMR: d 169.83, 153.77, 142.74, 141.75, 141.31, 138.52, 135.51, 132.15, 129.39, 129.31, 128.13, 125.46, 123.09, 60.01, 21.21. Anal. Calcd for $C_{19}H_{15}BrN_2OS$: C, 57.15; H, 3.79; N, 7.02. Found: C, 57.35; H, 3.81; N, 7.04.

3.2.8. (S_S)-N-((6-Phenylpyridin-2-yl)phenylmethylene)-4-methylbenzenesulfinamide (5h). Reaction solvent: THF; reaction time: 48 h; chromatographic eluent: petroleum ether/ethyl acetate=1/1; 0.168 g (85%); yellow solid; mp 102–104 °C; $[a]_{D\ 25}$ +43.1 (c 0.60, $CHCl_3$); ^{1}H NMR: d 7.98–7.52 (m, 8H), 7.51 (t, 1H, J=7.5 Hz), 7.48–7.36 (m, 5H), 7.29–7.21 (m, 3H), 2.38 (s, 3H). ^{13}C-NMR: d 173.0, 157.2, 153.6, 143.2, 141.6, 138.0, 137.1, 136.3, 132.2, 129.9, 129.5, 129.4, 128.6, 128.2, 127.1, 125.7, 122.4, 121.4, 21.3. Anal. Calcd for $C_{25}H_{20}N_2OS$: C, 75.73; H, 5.08; N, 7.07. Found: C, 75.55; H, 5.10; N, 7.06.

3.3. General procedure for the reduction of imines 5a–h

Diisobutylaluminium hydride (0.45 mL of a 1.0 M solution in THF, 0.45 mmol) was added to a solution of 5 (0.20 mmol) in THF (2 mL) at -78 °C. After 6 h MeOH (1 mL) was added at -78 °C to the mixture, which was then warmed at room temperature and evaporated under reduced pressure. Aqueous 2 M NaOH (2 mL) was added to the residue and the crude mixture was extracted with ethyl acetate. The organic phase was separated, dried (Na_2SO_4), the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether/ethyl acetate=7/3 to ethyl acetate)

3.3.1. (S_S,R)- and (S_S,S)-N-(1-(6-Methylpyridin-2-yl)-ethyl)-4-methylbenzenesulfinamide (6a). This compound was obtained as a mixture of diastereomers ((S_S,R)-6a:(S_S,S)-6a=2:98); 43.6 mg (82%); oil; ^{1}H NMR: d 7.55 (d, 2H, J=8.1 Hz), 7.44 (t, 1H, J=7.5 Hz), 7.23 (d, 2H, J=8.1 Hz), 6.96 (d, 1H, J=7.5 Hz), 6.83 (d, 1H, J=7.5 Hz), 5.79 (d, 1H, J=6.3 Hz, minor isomer), 5.41 (d, 1H, J=6.6 Hz), 4.55 (q, 1H, J=6.6 Hz), 2.48 (s, 3H), 2.38 (s, 3H), 1.58 (d, 3H, J=6.6 Hz). ^{13}C-NMR: d 161.0, 157.8, 141.6, 140.9, 136.7, 129.3, 125.9, 121.6, 117.5, 60.3, 53.3, 24.3, 24.2. Anal. Calcd for $C_{15}H_{18}N_2OS$: C, 65.66; H, 6.61; N, 10.21. Found: C, 65.52; H, 6.63; N, 10.25.

3.3.2. (S_S,R)- and (S_S,S)-N-(1-(6-Bromopyridin-2-yl)-ethyl)-4-methylbenzenesulfinamide (6b). This compound was obtained as a mixture of diastereomers ((S_S,R)-6b:(S_S,S)-6b=98:2; 62.4 mg (92%); oil; ^{1}H NMR: d 7.63 (d, 2H, J=8.1 Hz, minor isomer), 7.51 (d, 2H, J=8.1 Hz, major isomer), 7.50 (t, 1H, J=7.8 Hz, minor isomer), 7.38 (t, 1H, J=7.5 Hz, major isomer), 7.34 (t, 2H, J=8.7 Hz, minor isomer), 7.29 (d, 1H, J= 7.5 Hz, major isomer), 7.21 (d, 2H, J=8.1 Hz, minor isomer), 7.21 (d, 2H, J=8.1 Hz, major isomer), 7.22 (d, 1H, J=7.8 Hz, minor isomer), 6.94 (d, 1H, J=7.5 Hz, major isomer), 5.29 (d, 1H, J=7.2 Hz, minor isomer), 4.97 (d, 1H, J=7.2 Hz, major isomer), 4.54 (q, 1H, J= 7.2 Hz, major isomer), 4.49 (q, 1H, J=7.2 Hz, minor isomer), 2.37 (s, 3H, major isomer), 2.43 (s, 3H, minor isomer), 1.57 (d, 3H, J=7.2 Hz, major isomer), 1.31 (d, 3H, J=7.2 Hz, minor isomer). ^{13}C-NMR: d 163.7, 141.6, 141.2, 141.2, 138.8, 129.3, 126.4, 125.8, 119.8, 52.6, 24.1, 21.3. Anal. Calcd for $C_{14}H_{15}BrN_2OS$: C, 49.57; H, 4.46; N, 8.26. Found: C, 49.68; H, 4.44; N, 8.24.

3.3.3. (S_S,R)- and (S_S,S)-N-(1-(6-Phenylpyridin-2-yl)-ethyl)-4-methylbenzenesulfinamide (6c). This compound was obtained as a mixture of diastereomers ((S_S,R)-6c:(S_S,S)-6c=28:72); 58.5 mg (87%); oil; ^{1}H NMR: d 7.96 (d, 2H, J=8.1 Hz, major isomer), 7.92 (d, 2H, J= 8.1 Hz, minor isomer), 7.66–7.50 (m, 4H, major isomer), 7.50–7.35 (m, 3H, major isomer), 7.22 (d, 2H, J=8.1 Hz, major isomer), 7.02 (d, 2H, J=8.1 Hz, minor isomer), 6.97 (d, 1H, J=7.5 Hz, major isomer), 6.92 (d, 1H, J=7.5 Hz, minor isomer), 6.36 (d, 1H, J=7.8 Hz, minor isomer), 5.38 (d, 1H, J=6.6 Hz, major isomer), 4.61 (q, 1H, J=6.6 Hz, major isomer), 4.54 (q, 1H, J=6.6 Hz, minor isomer), 2.36 (s, 3H, major isomer), 2.24 (s, 3H, minor isomer), 1.49 (d, 3H, J=6.6 Hz, minor isomer), 1.66 (d, 3H, J=6.6 Hz, major isomer). Anal. Calcd for $C_{20}H_{20}N_2OS$: C, 71.40; H, 5.99; N, 8.33. Found: C, 71.61; H, 5.98; N, 8.31.

3.3.4. (S_S,R)-N-(1-(6-Bromopyridin-2-yl)-2,2-dimethylpropyl)-4-methylbenzenesulfinamide (6d). This compound was obtained as a mixture of diastereomers ((S_S,R)-6d:(S_S,S)-6d=98:2); 72.4 mg (95%); mp 91–92 °C; $[a]_{D\ 25}$+258.0 (c 0.14, $CHCl_3$); ^{1}H NMR: d 7.56 (d, 2H, J= 8.1 Hz), 7.46 (t, 1H, J=7.5 Hz), 7.32 (t, 3H, J=9.9 Hz), 7.08 (d, 1H, J=7.5 Hz), 5.64 (d, 1H, J=9.6 Hz), 3.84 (d, 1H, J=9.6 Hz), 2.42 (s, 3H), 0.70 (s, 3H). ^{13}C-NMR: d 162.3, 141.2, 141.2, 141.0, 138.1, 129.3, 126.3, 126.0, 122.1, 62.9, 34.9, 26.6, 21.4. Anal. Calcd for $C_{17}H_{21}BrN_2$-OS: C, 53.54; H, 5.55; N, 7.35. Found: C, 53.64; H, 5.54; N, 7.37.

3.3.5. (S_S,R)-N-(2,2-Dimethyl-1-(6-phenylpyridin-2-yl)-propyl)-4-methylbenzenesulfinamide (6e). This compound was obtained as a sole diastereomer; 71.8 mg (95%); oil; $[a]_{D\ 25}$ +223.7 (c 0.77, $CHCl_3$). ^{1}H NMR: d 7.99 (d, 2H, J=8.1 Hz), 7.70–7.52 (m, 3H), 7.50–7.38 (m, 4H), 7.25 (d, 2H, J=8.1 Hz), 7.07 (d, 1H, J=7.5 H Hz), 6.01 (d, 1H, J=9.3 Hz), 4.00 (d, 1H, J=9.3 Hz), 2.38 (s, 3H), 0.75 (s, 9H). ^{13}C-NMR: d 159.8, 155.2, 141.6, 140.7, 138.9, 136.2, 128.9, 128.5, 128.3, 126.5, 125.6, 121.5, 118.1, 63.3, 34.6, 26.5, 21.0. Anal. Calcd for $C_{23}H_{26}N_2$OS: C, 72.98; H, 6.92; N, 7.40. Found: C, 72.76; H, 6.94; N, 7.38.

3.3.6. (S_S,R)- and (S_S,S)-N-((6-Methylpyridin-2-yl)-(phenyl)methyl)-4-methylbenzenesulfinamide (6f). This compound was obtained as a mixture of diastereomers ((S_S,R)-6f:(S_S,S)-6f=92:8); 57.1 mg (85%); oil; ^{1}H NMR (300 MHz, $CDCl_3$): d 7.60 (d, 1H, J=8.1 Hz, minor isomer), 7.46–7.36 (m, 3H, major isomer), 7.50–7.00 (m, 6H, major isomer), 6.60 (d, 1H, J=7.5 Hz, major isomer), 6.93–6.86 (m, 2H, major isomer), 6.82 (d, 1H, J= 7.5 Hz, major isomer), 6.17 (d, 1H, J=3.6 Hz, minor isomer), 5.67 (d, 1H, J=3.6 Hz, minor isomer), 5.51 (d, 1H, J=4.8 Hz, major isomer), 2.57 (s, 3H, major isomer), 2.46 (s, 3H, minor isomer), 2.39 (s, 3H, minor isomer), 2.30 (s, 3H, major isomer). ^{13}C-NMR: d 158.8, 157.1, 142.8, 140.6, 140.5, 136.9, 128.9, 127.9, 127.6, 126.6, 126.2, 121.5, 119.3, 55.6, 24.4, 21.1. Anal. Calcd for $C_{20}H_{20}N_2$OS: C, 71.40; H, 5.99; N, 8.33. Found: C, 71.61; H, 5.98; N, 8.32.

3.3.7. (S_S,R)- and (S_S,S)-N-((6-Bromopyridin-2-yl)-(phenyl)methyl)-4-methylbenzenesulfinamide (6g). This compound was obtained as a mixture of diastereomers ((S_S,R)-6g:(S_S,S)-6g=88:12); 60.9 mg (76%); oil; ^{1}HNMR: d 7.54 (d, 2H, J=8.1 Hz, minor isomer), 7.45 (d, 2H, J=8.1 Hz, major isomer), 7.42–7.18 (m, 4H), 7.12–7.05 (m, 4H), 6. 99 (d, 1H, J=7.5 Hz, minor isomer), 6.96–6.91 (m, 2H), 6.42 (d, 1H, J=5.4 Hz, major isomer), 5.67 (d, 1H, J=4.8 Hz, minor isomer) 5.63 (d, 1H, J=4.8 Hz, minor isomer), 5.50 (d, 1H, J=5.4 Hz, major isomer), 2.38 (s, 3H, minor isomer), 2.33 (s, 3H, major isomer). Anal. Calcd for $C_{19}H_{17}BrN_2$OS: C, 56.86; H, 4.27; N, 6.98. Found: C, 56.68; H, 4.13; N, 6.77.

3.3.8. (S_S,R)- and (S_S,S)-N-(Phenyl(6-phenylpyridin-2-yl)-methyl)-4-methylbenzenesulfinamide (6h). This compound was obtained as a mixture of diastereomers ((S_S,R)-6h:(S_S,S)-6h=93:7); 68.5 mg (86%); oil; ^{1}H NMR: d 7.97 (d, 2H, J=8.1 Hz, major isomer), 7.90 (d, 2H, J=8.1 Hz, minor isomer), 7.62–7.40 (m, 7H), 7.26–6.84 (m, 8H), 6.18 (d, 1H, J=4.2 Hz, minor isomer), 5.75 (d, 1H, J=4.2 Hz, minor isomer), 5.62 (d, 1H, J=4.2 Hz, major isomer), 2.35 (s, 3H, minor isomer), 2.31 (s, 3H, major isomer). ^{13}C-NMR: d 159.3, 155.8, 142.6, 140.7, 140.4, 138.8, 137.5, 129.1, 128.9, 128.6, 128.0, 127.6, 126.9, 126.7, 126.2, 120.9, 118.8, 56.0, 21.1. Anal. Calcd for $C_{25}H_{22}N_2$OS: C, 75.35; H, 5.56; N, 7.03. Found: C, 75.55; H, 5.59; N, 7.04.

3.3.9. (S_S,R)-N-(2,2-Dimethyl-1-(pyridin-2-yl)propyl)-methylbenzenesulfinamide (2c). Bromopyridine (S_S,R)-6d (126.0 mg, 0.33 mmol, 96% de), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), PPh_3 (35.4 mg, 0.135 mmol), $NaBH_4$ (40.2 mg, 3.96 mmol), TMEDA (0.576 g, 4.96 mmol) and anhydrous THF (30 mL) were introduced in a oven-dried Schenk flask that was purged with argon. The mixture was stirred at room temperature under argon for 3 h and then the solvent was evaporated under vacuum. The residue was taken up in H_2O and extracted with ethyl acetate. The organic phase was separated, dried (Na_2SO_4), the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether/ethyl acetate=1/1) to give compound 2c as a mixture of diastereomers ((S_S,R)-2c:(S_S,S)-2c=97:3): 87.0 mg (95%); oil; $[a]_{D\ 25}$ +226.1 (c 0.57, $CHCl_3$); ^{1}H NMR: d 8.55 (d, 1H, J= 4,5 Hz, major isomer), 8.46 (d, 1H, J=4,8 Hz, major isomer), 7.63–7.48 (m, 1H), 7.56 (d, 2H, J=10, 5 Hz), 7.29 (d, 1H, J=8,1 Hz), 7.23–

7.01 (m, 3H), 5.85 (d, 1H, J= 9,3 Hz major isomer), 5.68 (d, 1H, J=8,4 Hz, minor isomer), 4.17 (d, 1H, J=8,4 Hz, major isomer), 3.92 (d, 1H, J=9,3 Hz, minor isomer), 2.41 (s, 3H, major isomer), 2.38 (s, 3H, minor isomer), 0.96 (s, 9H minor isomer), 0.71 (s, 9H, major isomer). ^{13}C-NMR: 160.4, 148.3, 141.5, 141.0, 135.5, 129.2, 125.9, 123.3, 121.9, 63.6, 34.9, 26.7, 21.3. Anal. Calcd for $C_{18}H_{25}N_2OS$: C, 68.10; H, 7.94; N, 8.82. Found: C, 68.36; H, 7.91; N, 8.81.

3.3.10. (S_S,R)-N-(2,2-Dimethyl-1-(6-phenylpyridin-2-yl)propyl)-4-methylbenzenesulfinamide (6e). A solution of the bromopyridine (S_S,R)-6d (0.183 g, 0.48 mmol, 96% de) and tetrakis(triphenylphosphane)palladium(0) (16.0 mg, 0.014 mmol) in toluene (0.96 ml) was treated with a solution of Na_2CO_3 (0.10 g, 0.95 mmol) in H_2O (0.48 ml) followed by a solution of phenylboronic acid (0.07 g, 0.57 mmol) in methanol (0.24 ml). The mixture was heated at 80–85 °C under argon for 14 h. After cooling at room temperature, a solution of concentrated aqueous NH_3 (0.24 ml) in saturated aqueous Na_2CO_3 (2.4 ml) was added and the mixture was extracted with CH_2Cl_2 (3x 10 ml). The combined organic layers were washed with brine (5 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue with was purified by flash chromatography (petroleum ether: ethyl acetate=6:4) to give compound 6e as a mixture of diastereomers ((S_S,R)-6e:(S_S,S)-6e=98:2): 96.4 mg (85%). Spectroscopic data of this compound were identical to all respect with the above.

3.3.11. (S_S,R)-N-[2,2-Dimethyl-1-(6-morpholinopyridin-2-yl)propyl]-4-methylbenzenesulfinamide (11). Bromopyridine (S_S,R)-6d (114.3 mg, 0.30 mmol, 96% de), morpholine (31.3 mg, 3.6 mmol), $Pd_2(dba)_3$ (6.0 mg, 0.012 mmol), 1,3-bis(diphenylphosphino)propane (4.8 mg, 0.012 mmol), NaO-t-Bu (40.2 mg, 0.42 mmol) and toluene (2.7 mL) were introduced in a oven-dried Schenk flask that was purged with argon. The mixture was heated at 70 °C under argon for 9 h. After cooling, the mixture was taken up in diethyl ether and washed three times with saturated brine. The organic phase was separated and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by flash chromatography (diethyl ether/petroleum ether=1/1) to give the starting material (S_S,R)-6d (63.0 mg) and compound 11 as a mixture of diastereomers ((S_S,R)-11: (S_S,S)-11=98:2): 48.4 mg (93% based on the converted starting material); foam solid; $[a]_{D\ 25}$ +173.1 (c 0.19, $CHCl_3$); ^{1}H NMR: d 7.52 (d, 2H, J=8.1 Hz), 7.43 (dd, 1H, J=8.7, 7.5 Hz), 7.26 (d, 2H, J=8.1 Hz), 7,51 (dd, 2H, J=8.7, 7.5 Hz), 5.65 (d, 1H, J=9.0 Hz), 3.86 (d, 1H, J= 9.0 Hz), 3.84–3.56 (m, 4H), 3.48–3.40 (m, 4H), 2.41 (s, 3H), 0.73 (s, 9H). ^{13}C-NMR: d 158.3, 158.3, 142.1, 141.0, 137.3, 129.2, 125.8, 113.4, 105.1, 66.7, 64.1, 45.2, 34.9, 29.7, 26.8. Anal. Calcd for $C_{21}H_{29}N_3O_2S$: C, 65.08; H, 7.54; N, 10.84. Found: C, 65.16; H, 7.51; N, 10.87.

3.3.12. 6,6-Bis{[(S_S,R)-2,2-dimethyl-1-(methylbenzenesulfinyl) propyl)]}-2,2'-bipyridine (12). Zinc powered (44.0 mg, 0.7 mmol) was added at 60 °C to a stirred mixture of nickel(II) chloride hexahydrate (0.159 g, 0.7 mmol) and triphenylphosphine (0.64 g, 2.4 mmol) in carefully degassed (by three freeze-pump-thaw cycles) DMF (5 ml). After 1 h, a solution the bromopyridine (S_S,R)-6d (0.229 g, 0.6 mmol, 96% de) in DMF (3 ml) was added. The mixture was stirred at 70 °C for 7 h and then taken up with ethyl acetate. The organic phase was washed with dilute ammonia solution (12 ml), with H_2O (10 ml) and then dried (Na_2SO_4). The solvent was evaporated and the residue was purified by flash chromatography (CH_2Cl_2/methanol= /1) to give 12: 63.2 mg (35%); mp 62–64 °C; $[a]_{D\ 25}$ -34.2 (c 0.43, $CHCl_3$); ^{1}H NMR: 7.47 (d, 2H, J=8.1 Hz), 7.34 (t, 1H, J=7.8 Hz), 7.21 (d, 2H, J=8.1 Hz), 6.84 (d, 1H, J=7.8 Hz), 6.73 (d, 1H, J=7.8 Hz), 3.57 (s, 1H), 2.39 (s, 3H), 0.86 (s, 9H). ^{13}C-NMR: d 162.3, 160.1, 139.1, 135.8, 135.4, 130.0, 127.2, 119.2, 118.7, 65.3, 35.1, 26.5, 21.2. Anal. Calcd for $C_{34}H_{42}N_4O_2S_2$: C, 67.74; H, 7.02; N, 9.29. Found: C, 68.01; H, 7.04; N, 9.25.

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