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Synthesis of new mono-*N*-tosylated diamine ligands based on (*R*)-(+)-limonene and their application in asymmetric transfer hydrogenation of ketones and imines

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ABSTRACT

A synthetic procedure leading to the preparation of a new family of enantiopure mono-*N*-tosylated-1,2-diamines derived from (*R*)-(+)-limonene is described. (+)-Limonene was transformed into the appropriate *N*-tosyl derivative using *N*-tosylaziridination based on chloramine-T trihydrate. Subsequent ring opening by sodium azide afforded the corresponding isomeric azides. Finally, reduction of the azide function gave enantiomerically pure mono-*N*-tosylated-1,2-diamines. The ligands obtained proved to be effective in the asymmetric transfer hydrogenation protocol on aromatic ketones and imines.

1. Introduction

Naturally occurring monoterpenes, such as (+)-3-carene, (−)-α-pinene, (−)-β-pinene and (+)-limonene, are readily available chiral substrates used widely in organic synthesis. They have served as inexpensive starting materials from renewable sources for the construction of complex chiral molecules.[1] The monoterpenes have also been incorporated in the structure of chiral adjuvants and auxiliaries used as ligands in a variety of stereoselective catalytic transformations.[2] Limonene itself (both enantiomers and dipentene) as well as its oxygenated derivatives are valuable components in food additives, cosmetics, pharmaceuticals and agrochemicals.[3] From a chemical point of view, limonene enantiomers are very attractive and simple starting materials. However, despite the relatively simple chemical structure, limonene has quite a complex chemistry and a fully selective functionalization of this molecule creates a considerable challenge. For example, due to the presence of two olefinic bonds, both enantiomers of limonene form eight epoxides that are difficult to isolate in a pure form.[4] Other addition reactions usually also give a mixture of products.[5] Recently, several effective and selective procedures for limonene functionalization have been proposed. Basing on the commercially available 47:53 mixture of *cis*- and *trans*-epoxides (limonene epoxides), Palmieri et al. developed a convenient synthesis of new diamines, aminoalcohols and aminophosphines.[6] A tandem hydroformylation/reductive amination procedure proposed by Rosa et al. allowed a one-pot preparation of secondary and tertiary amines from (*R*)-(+)-limonene.[7] Limonene oxides were also starting materials for the preparation of diastereomeric aziridines.[8] The selective addition of nitrosyl chloride to limonene afforded the formation of the corresponding dimeric nitrosochloride, which was then trapped by a reactive diamine to afford chiral ligands for binuclear complexes with $PdCl_2$.[2f] The highly selective formation of limonene aziridines[9] allowed their further transformation into bifunctionalized limonenes as reported by Voronkov et al.[10]

Considering that chiral vicinal diamines are valuable synthetic auxiliaries, such as their application as chiral ligands for various catalytic asymmetric transformations,[2e,11,12] we recently reported a simple method for the transformation of limonene into *trans*-1,2-diamine derivatives.[13] In particular, the appropriate mono-*N*-tosylated compounds were applied as ligands in asymmetric hydrogen transfer reaction.

Herein we report our studies on the synthesis of mono-*N*-tosylated-1,2-diamines from limonene and on the evaluation of their catalytic utility in the asymmetric transfer hydrogenation of aromatic ketones and imines.

2. Results and discussion

The application of direct *N*-tosylaziridination reactions on limonene is very attractive starting point for the synthesis of blabblaba chiral diamine derivatives.[14] Thus, the reaction of (*R*)-(+)-limonene **1** with Chloramine-T trihydrate in the presence of phenyltrimethylammonium tribromide (PTAB) gave a mixture

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of (1*S*,4*R*,6*R*)- and (1*R*,4*R*,6*S*)-aziridinolimonene in 62% yield, in which the main product was the diastereoizomer **2a** (Scheme 1). Aziridines **2a**,**b** were isolated by column chromatography on silica gel using hexane/ethyl acetate as the eluent (from 0% to 5% of ethyl acetate). The ratio of both isomers formed was approximately 75–25%, based on the ^{1}H NMR spectrum of the crude reaction mixture. The generation of aziridine (1*S*,4*R*,6*R*)-**2a** as the predominant product can be explained by considering the analogous mechanism of aziridination of Δ^3-carene.[14] The first step of this Sharpless procedure was the formation of the bromonium ion, which occurs selectively in a *trans*-fashion due to the steric interaction caused by the substituents at the cyclohexene moiety. Subsequent opening of the bromonium ion by Chloramine-T proceeds from the α-face of the molecule and the whole process ends up with the formation of an aziridine with a *cis*-disposition of the heterocyclic ring versus the isopropylidene moiety of carene. In the case of (*R*)-(+)-limonene, an analogous mechanism seems to operate, giving rise to the predominant formation of aziridine **2a**. The formation of **2b** is thus less likely due to the energetically unfavorable structure of the *trans*-bromonium ion. The nucleophilic ring opening of *N*-tosylaziridines **2b** by the azide anion is regio- and diastereoselective, as was described for analogous epoxides.[6,10] Therefore, the reaction of (1*R*,4*R*,6*S*)-**2b** with NaN_3 occurs at the more sterically hindered tertiary carbon atom, forming the azido amine **5** (27% yield) with the inversion of configuration at this stereogenic centre. Instead, nucleophilic attack on (1*S*,4*R*,6*R*)-**2a** is diastereoselective but not regioselective. The main product, amino azide **3** (51% yield), was formed by the nucleophilic attack of NaN_3 on aziridine **2a** at the less sterically hindered secondary carbon atom. However, in the case of the second isomer **4** (isolated in 12% yield), nucleophilic attack of the azide anion on derivative **2a** occurred at the more sterically hindered C-1 position giving isomer **4** with an inversion of configuration at the C-1 position. Isomers **3–5** were isolated from the reaction mixture by gradient elution column chromatography on silica gel using hexane/ethyl acetate, 0–10% of ethyl acetate, as the eluent system. When DMF (rt, 12 h) was used as the solvent in the aziridination reaction, isomer **4** was formed with only 5% yield while the yield of regioisomer **3** was increased to 57%.

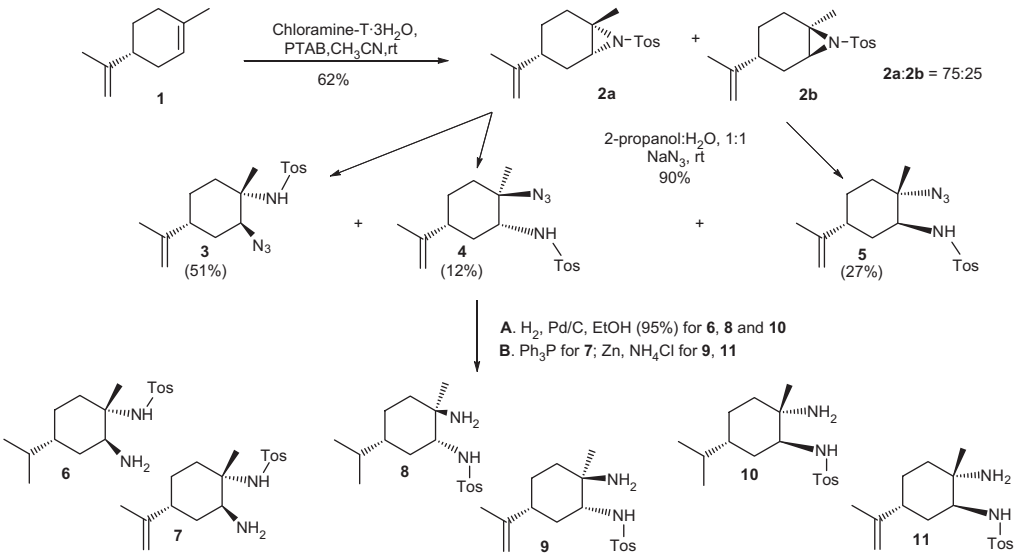
In our preliminary study we reported on the presence of five isomers formed in the reaction of **2** with the azide ion. Further studies showed that the two unidentified peaks on the HPLC chromatogram corresponded to the regioisomers in which the azide substituent is present in the isopropylidene part of the limonene molecule.

Finally, regioisomers **3–5** were transformed into the corresponding diamines by the reduction of azide function. Thus compounds **3–5** were individually hydrogenated over 10% Pd/C to afford the desired monotosylated diamines **6**, **8** and **10** almost quantitatively. Alternatively, only the azide substituent was reduced in derivatives **3–5**. Diamine **7** was obtained from **3** in 51% yield under typical Staudinger reduction conditions.[15] However, the reduction of azides **4** and **5** under the same conditions failed and only the presence of a cyclic aziridine such as **2** was detected by MS analysis. For the reduction of compounds **4** and **5**, a simple procedure presented by Lin was applied.[16] In the reaction of azides **4** and **5** with zinc and ammonium chloride as the reducing agent, diamines **9** and **11** were obtained in 56% and 64% yield, respectively.

The absolute configurations of compounds **6–10** were determined on the basis of an X-ray analysis, as shown in Figures 1–5. The detailed stereo structures of these amines can be helpful in the better understanding of the activity of catalysts **12–18** which were formed in the reaction with ruthenium–arene complexes.

In order to evaluate amines **6–11** as potential ligands, we chose to use the Ru-catalysed asymmetric hydrogen transfer (ATH) protocol on a series of ketones. The catalysts were prepared in situ by mixing $[RuCl_2(benzene)]_2$ or $[RuCl_2(p\text{-cymene})]_2$ with monotosylated diamines **6–11** and triethylamine (Ru/Amine/Et_3N molar ratio = 1:2.5:2) in acetonitrile (Fig. 6). After 20 min of stirring at room temperature, the solution of the catalyst and the formic acid/triethylamine azeotrope was added to a ketone. The reduction of aromatic ketones (Scheme 2) was carried out at room temperature and the reaction progress was monitored by TLC. The products were isolated by a short-path column chromatography on SiO_2 and the enantiomeric excess was determined by GC analysis on a chiral stationary phase. Recently, we presented our preliminary data for the asymmetric reduction of aromatic ketones using catalysts **12**, **14** and **16**.[13] Tables 1 and 2 summarize the results for complexes **13**, **15**, **17** and **18**.

As shown in Tables 1 and 2, the rate and enantioselectivity of the reaction are highly influenced by the structure of the ligands **6–11** and the η^6–arene part of the complex. The catalytic activity of complex **12**[13] and **13** exhibited low activity and low asymmetric induction. In both cases, the reaction was carried out at room temperature and was not completed even after 20 days, still giving



Scheme 1. Synthetic pathway for monotosylated diamines **6–11**.

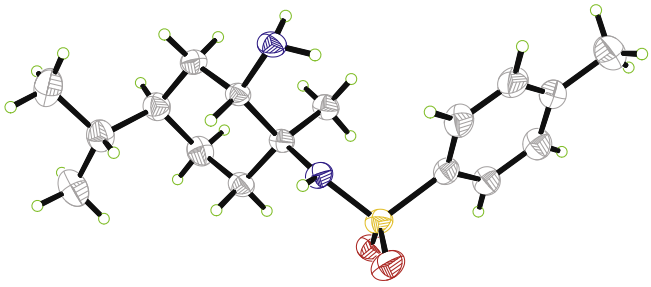


Figure 1. The ORTEP diagram for the X-ray analysis of compound **6**.

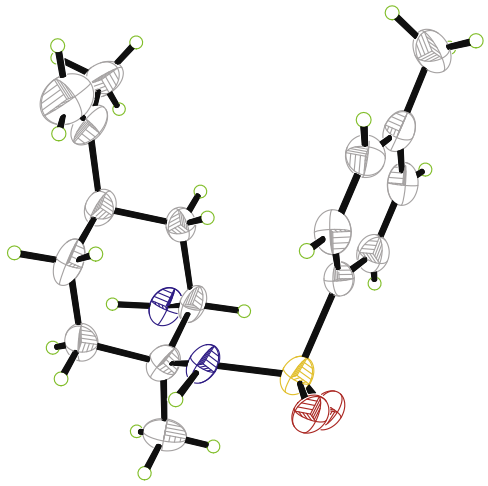


Figure 2. The ORTEP diagram for the X-ray analysis of compound **7**. Only one molecule from the independent part is shown for clarity.

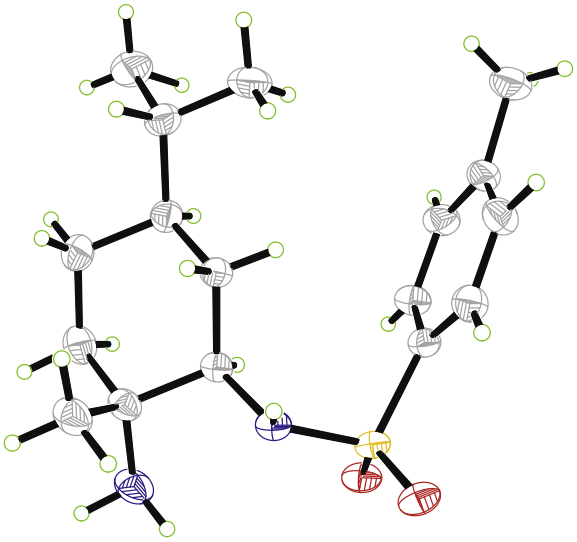


Figure 3. The ORTEP diagram for the X-ray analysis of compound **8**.

unsatisfactory ee values (1–36%) of the products. The presence of the C=C double bond in the structure of catalyst **13** gave a significant increase in the enantioselectivity of ketone reduction (Table 1). Generally, the reduction of aromatic ketones using catalysts **14**[13] and **15** possessing a tertiary amine group gave products with high chemical yield and good enantiomeric excess. The introduction of a *p*-cymene ligand in the structure of catalyst **16**[13] gave 1-phenylethanol with a lower yield and with lower

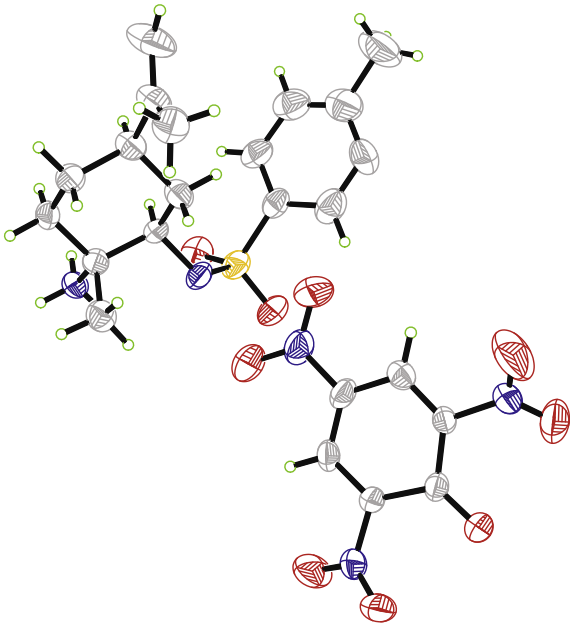


Figure 4. The ORTEP diagram for the X-ray analysis of compound **9** picrate. For the sake of clarity, the second molecule of compound and picrate anion, as well as the solvent molecules are omitted.

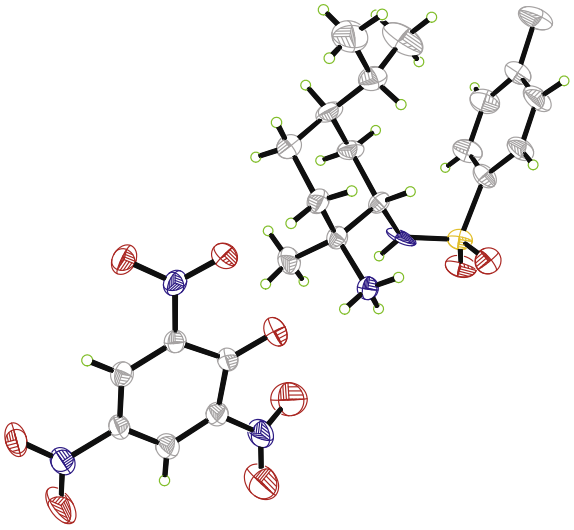


Figure 5. The ORTEP diagram for the X-ray analysis of compound **10** picrate. Only one molecule of compound and one picrate anion are shown.

enantioselectivity in comparison to catalysts **14**–**15**. In this case, catalyst **15** which contained a C=C bond, afforded alcohols with the same or slightly better enantioselectivity. The exception was the reduction of the *ortho*-substituted acetophenones where probably due to unfavorable steric interactions, significant decrease in stereoselectivity was observed (Table 2).

Complexes **17** and **18** unexpectedly showed lower values for the asymmetric induction than catalysts **14**–**15** (Table 2). The change in efficacy of complexes **17**–**18** was connected with the reversed configuration at the carbon atoms bearing amine functions from (*R*,*R*) in **14**–**15** to (*S*,*S*) in **17**–**18**.

On the basis of these promising results in the enantioselective reduction of various aromatic ketones, complexes **12**–**18** were then applied to the asymmetric hydrogenation of endocyclic imines. Ini-

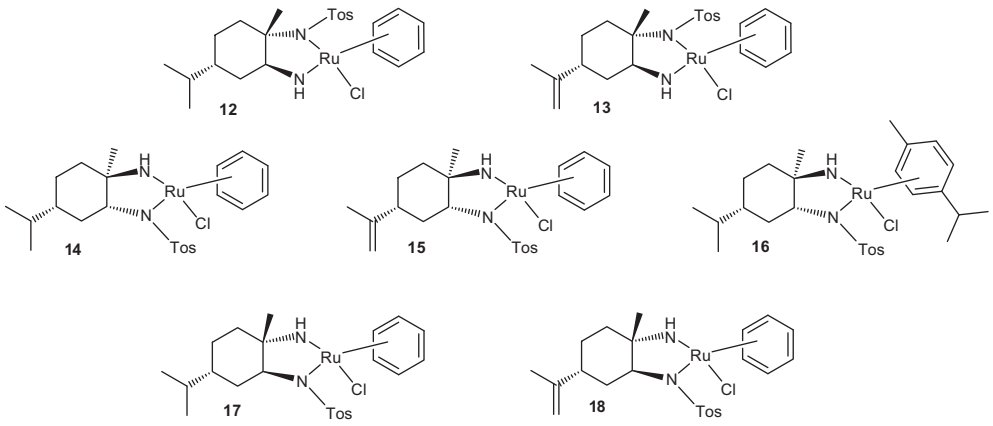
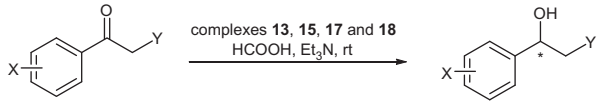


Figure 6. The structure of catalysts **12**–**18**.



Scheme 2. Asymmetric transfer hydrogenation of aromatic ketones with catalysts **13**, **15**, **17** and **18**.

Table 1
The ATH reduction of ketones with catalyst **13**[a]

Entry	Cat.	X	Y	Time (days)	Conv. (%)	ee (%)[b,c]	$[\alpha]_D^{23}$[d]
1	**13**	H	H	20	44	17 (*R*)	+9.2
2	**13**	H	CH_3	20	15	36 (*R*)	+19.3
3	**13**	*o*-Br	H	20	63	15 (*R*)	+7.6
4	**13**	*m*-Br	H	20	45	15 (*R*)	+4.9
5	**13**	*p*-Br	H	20	36	8 (*R*)	+3.2

[a] The reaction was carried out at room temperature using a ketone (2.40 mmol) in CH_3CN (1 mL) and a formic acid–triethylamine mixture (5:2, 1 mL) with *S*/*C* = 100.
[b] Determined by GC analysis using a Supelco cyclodextrin-DEX 120 capillary column (20 m × 0.25 mm I.D. and 0.25 μm film thickness).
[c] Determined by the sign of specific rotation of the isolated product.
[d] *c* 1, $CHCl_3$.

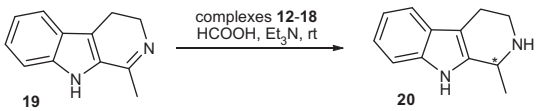
tially, the ATH process was applied to the reduction of 1-methyl-3,4-dihydro-β-carboline (Scheme 3). As might be expected, the best results were obtained using catalysts **14**–**15**. Complex **15**, which possessed a C=C bond gave amine **7** with excellent results, 100% yield and 98% ee (Table 3). A similar decrease in activity of compounds **17**–**18** versus **14**–**15** was observed as in the case of ketones. The change of configuration caused unfavorable steric interactions, which led to a significant loss of asymmetric induction. Additionally, the change of configuration from (1*R*,2*R*) in catalysts **14**–**15** to (1*S*,2*S*) in complexes **17**–**18** led to a change of course of the imine reduction and gave amine **20** with opposite configuration. Complexes **12**–**13** gave amine **7** with an enantioselectivity comparable to derivatives **17**–**18**.

The results obtained for 1-methyl-3,4-dihydro-β-carboline **19** prompted us to apply our catalytic platform to a variety of imines and iminium salts (Fig. 7). The asymmetric reduction of imine **21**, possessing a less accessible C=N double bond using complexes **14**–**15** gave the appropriate amine with a slightly lower enantioselectivity than the Noyori-type catalyst (Ru-TsCYDN).[17] The more sterically demanding complex **16** was not able to effectively reduce the iminium double bond and gave a racemic product. We observed a lack of activity for derivatives **17**–**18**. In the case of imine **22**, the results of the asymmetric hydrogenation for all complexes

Table 2
The ATH reduction of ketones with catalysts **15**, **17** and **18**[a]

Entry	Cat.	X	Y	Time (h)	Conv. (%)	ee (%)[b,c]	$[\alpha]_D^{23}$[d]
1	**15**	H	H	42	100	93 (*R*)	+50.7
2	**17**	H	H	96	10	60 (*S*)	−33.0
3	**18**	H	H	96	21	37 (*S*)	−20.5
4	**15**	H	CH_3	72	66	90 (*R*)	+48.0
5	**17**	H	CH_3	96	12	52 (*S*)	−27.5
6	**18**	H	CH_3	96	36	34 (*S*)	−18.0
7	**15**	*o*-Br	H	18	100	14 (*R*)	+7.1
8	**17**	*o*-Br	H	96	41	32 (*S*)	−16.7
9	**18**	*o*-Br	H	96	37	31 (*S*)	−15.9
10	**15**	*m*-Br	H	18	100	82 (*R*)	+26.3
11	**17**	*m*-Br	H	96	52	56 (*S*)	−18.0
12	**18**	*m*-Br	H	96	34	50 (*S*)	−16.1
13	**15**	*p*- Br	H	18	100	81 (*R*)	+30.3
14	**17**	*p*- Br	H	96	82	74 (*S*)	−28.0
15	**18**	*p*- Br	H	96	67	52 (*S*)	−19.3
16	**15**	*o*-CH_3	H	52	83	26 (*R*)	+22.2
17	**15**	*m*-CH_3	H	52	100	86 (*R*)	+49.2
18	**17**	*m*-CH_3	H	96	24	62 (*S*)	−35.3
19	**18**	*m*-CH_3	H	96	41	51 (*S*)	−29.4
20	**15**	*p*-CH_3	H	52	92	91 (*R*)	+53.4
21	**15**	*o*-Cl	H	18	100	16 (*R*)	+11.0
22	**17**	*o*-Cl	H	96	81	15 (*S*)	−10.2
23	**18**	*o*-Cl	H	96	62	20 (*S*)	−14.2
24	**15**	*m*-Cl	H	18	95	82 (*R*)	+32.9
25	**17**	*m*-Cl	H	96	60	81 (*S*)	−32.8
26	**18**	*m*-Cl	H	96	96	62 (*S*)	−25.0
27	**15**	*p*-Cl	H	18	100	87 (*R*)	+41.2[e]
28	**17**	*p*-Cl	H	96	83	67 (*S*)	−32.3[e]
29	**18**	*p*-Cl	H	96	70	47 (*S*)	−22.4[e]
30	**15**	*p*-OCH_3	H	72	82	88 (*R*)	+44.5
31	**17**	*p*-OCH_3	H	96	16	7 (*S*)	−3.5
32	**18**	*p*-OCH_3	H	96	8	13 (*S*)	−6.5

[a] The reaction was carried out at room temperature using a ketone (2.40 mmol) in CH_3CN (1 mL) and a formic acid–triethylamine mixture (5:2, 1 mL) with *S*/*C* = 100.
[b] Determined by GC analysis using a Supelco cyclodextrin-DEX 120 capillary column (20 m × 0.25 mm I.D. and 0.25 μm film thickness).
[c] Determined by the sign of specific rotation of the isolated product.
[d] *c* 1, $CHCl_3$.
[e] *c* 1, Et_2O.



Scheme 3. Asymmetric transfer hydrogenation of imine **19** with catalysts **12**–**18**.

12–**18** were comparable and provided the product with low enantiomeric purity (24–34% ee). The reduction of iminium chloride **23**

Table 3
The ATH reduction of imines/iminium salts with catalysts **12**–**18**

Entry	Cat.	Imine	Time (h)	Conv. (%)	ee (%)[a,b]	$[\alpha]_D^{23}$[d]
1	**12**	**19**	20	100	59 (*S*)[c]	−36.6[e]
2	**13**	**19**	20	100	50 (*S*)[c]	−31.3[e]
3	**14**	**19**	20	100	95 (*S*)[c]	−60.6[e]
4	**15**	**19**	20	100	98 (*S*)[c]	−61.3[e]
5	**17**	**19**	20	100	54 (*R*)[c]	+33.6[e]
6	**18**	**19**	20	100	48 (*R*)[c]	+30.2[e]
7	**12**	**21**	19	14	19 (*S*)	−8.1
8	**13**	**21**	19	17	22 (*S*)	−9.4
9	**14**	**21**	19	55	47 (*R*)	+19.8
10	**15**	**21**	19	70	48 (*R*)	+20.1
11	**16**	**21**	19	0	*rac*	0
12	**17**	**21**	19	32	*rac*	0
13	**18**	**21**	19	47	*rac*	0
14	**12**	**22**	4	100	27 (*R*)	+23.0
15	**13**	**22**	4	100	24 (*R*)	+20.2
16	**14**	**22**	1.5	100	33 (*R*)	+28.1
17	**15**	**22**	1.5	100	25 (*R*)	+21.0
18	**16**	**22**	5	0	rac	0
19	**17**	**22**	4	100	34 (*S*)	−28.6
20	**18**	**22**	4	100	33 (*S*)	−27.8
21	**12**	**23**	16	77	*rac*	0
22	**13**	**23**	16	76	*rac*	0
23	**14**	**23**	5	72	84 (*S*)	−84.0
24	**15**	**23**	5	74	53 (*S*)	−53.4
25	**16**	**23**	16	70	1 (*S*)	−1.0
26	**17**	**23**	8	72	16 (*S*)	−16.2
27	**18**	**23**	8	81	10 (*S*)	−10.2
28	**12**	**24**	16	94	6 (*S*)	−6.9
29	**13**	**24**	16	90	*rac*	0
30	**14**	**24**	5	90	48 (*S*)	−52.1
31	**15**	**24**	5	89	56 (*S*)	−60.5
32	**16**	**24**	16	87	3 (*S*)	−3.0
33	**17**	**24**	8	89	31 (*S*)	−34.0
34	**18**	**24**	8	90	35 (*S*)	−38.6

[a] Determined by the sign and value of the specific rotation of the isolated product.
[b] Determined by the sign and value of the specific rotation of the isolated product.
[c] Determined by HPLC analysis using Daicel OD-H column.
[d] *c* 1, $CHCl_3$.
[e] *c* 1, EtOH.

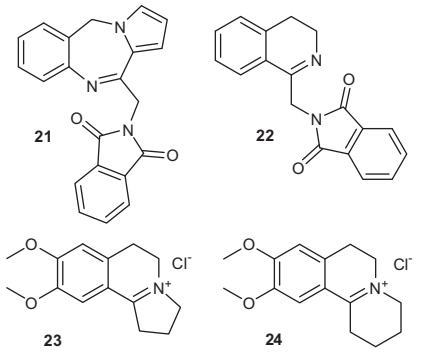


Figure 7. The structure of imines/iminium salts for ATH.

using complex **14** gave (*S*)-crispine A with good enantiomeric purity (84% ee). Lower asymmetric induction (53% ee) was obtained when catalyst **15** was used. Catalysts **12**–**13** gave racemic crispine A, and for **17**–**18** a very low level of asymmetric induction was observed.

Similar results were collected for the hydrogenation of iminium salt **24**, but the enantiomeric excess of obtained product did not exceed 56% for complex **15**. Obviously the enantioselectivity of the reduction strongly depends both on the structure of the catalyst and the structure of the substrate.

3. Conclusion

In conclusion, we have presented a simple synthesis of a new class of monotosylated diamine **6–11** starting from an inexpensive enantiomerically pure natural product (*R*)-(+)-limonene. The *N*-tosylaziridination procedure followed by sodium azide treatment and reduction afforded compounds **3** in 51%, **4** in 12% and **5** in 27% yield. The asymmetric hydrogen transfer protocol using **6–11** as ligands gave good to excellent results for the reduction of aromatic ketones as well as for selected endocyclic imines.

4. Experimental

4.1. General

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz for ^1H NMR and at 125 MHz for ^{13}C NMR. The spectra were measured in $CDCl_3$ and are given as δ values (in ppm) relative to TMS. Mass spectra were collected on Quatro LC Micromass and LCT Micromass TOF HiRes apparatuses. Optical rotations were measured on a Perkin–Elmer 247 MC polarimeter. TLC analyses were performed on silica gel plates (Merck Kiesegel GF_{254}) and visualized using UV light or iodine vapour. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (230–400 mesh, Merck) using mixtures of chloroform/methanol and hexane/ethyl acetate as eluents. The enantiomeric purity was determined by HPLC analysis using Chiralcel OD-H column or by GC analysis using a β-DEX 120 capillary column. Melting points were determined on a Boetius hot-plate microscope and are uncorrected. All solvents used in the reactions were anhydrous. The single crystal X-ray measurements were carried out on an Oxford Diffraction Excalibur R CCD κ-axis diffractometer using monochromatic CuKα radiation. After initial corrections and data reduction, intensities of reflections were used to solve and consecutively refine structures using SHELXS97 and SHELXL97 programs.[18]

4.2. (1*S*,2*S*,5*R*)-*N*-(2-Azido-5-isopropenyl-2-methyl-cyclohexyl)-4-methyl-benzenesulfonamide 5

To a stirred solution of aziridines **2a**,**b** mixture (15.40 g, 50.42 mmol) in isopropanol (80 mL), distilled water (80 ml) and sodium azide (12.50 g, 201.70 mmol) were added. The resulting suspension was stirred at room temperature for 72 h. After evaporation of the solvents to the residue, diethyl ether (250 mL) and water (125 mL) were added. The layers were separated and the water layer was extracted twice with diethyl ether (200 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent was evaporated in vacuo. Compound **5** was isolated by column chromatography on silica gel using hexane/ethyl acetate (3–6% of ethyl acetate) as eluent system to afford 4.74 g (27%) of compound **5** as a colourless oil; $[\alpha]_D^{23} = +3.9(c1.0, CHCl_3)$. The enantiomeric purity was determined by HPLC [Chiracel OD-H, hexane/*i*-PrOH (90:10), 1 mL/min]; the (1*S*,2*S*,4*R*)-isomer eluted at 7.6 min. ^1H NMR ($CDCl_3$, 500 MHz): δ 1.19–1.24 (m, 1H), 1.27 (s, 3H), 1.43–1.55 (m, 3H), 1.57 (s, 3H), 1.66–1.72 (m, 2H), 1.86–1.90 (m, 1H), 2.43 (s, 3H), 3.23–3.26 (m, 1H), 4.60 (s, 1H), 4.67 (t, 1H, J = 1.5 Hz), 5.08 (d, 1H, J = 10.0 Hz), 7.31 (d, 2H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.8, 21.6, 23.1, 25.7, 31.6, 31.8, 37.6, 55.7, 62.8, 109.7, 127.1, 129.8, 137.6, 143.8, 147.8. HRMS: *m*/*z* calcd for $C_{17}H_{24}N_4O_2NaS$ $[M+Na]^+$: 371.1518; found: 371.1524.

4.2.1. (1*S*,2*S*,4*R*)-*N*-(2-Amino-4-isopropyl-1-methyl-cyclohexyl)-4-methyl-benzenesulfonamide 6

Amine **6** was synthesized from azide **3** according to the literature.[13] Monocrystals of **6** suitable for crystallographic measurements were obtained from a diethyl ether solution by slow evaporation. The absolute structure of the studied crystal, and hence the absolute configuration of the compound was determined based on the value of the Flack parameter.[19] Since its value for the structure shown in Figure 1 was approximately 0, the molecular structure has the depicted configuration. The data were deposited with Cambridge Crystallographic Data Centre under the number CCDC 923755.

4.2.2. (1*S*,2*S*,4*R*)-*N*-(2-Amino-4-isopropenyl-1-methyl-cyclohexyl)-4-methyl-benzenesulfonamide 7

To a stirred solution of azide **3** (1.0 g, 2.87 mmol) in THF (50 mL), triphenylphosphine (829 mg, 3.16 mmol) and distilled water (5 mL) were added and the resulting mixture was stirred at room temperature for 1 h and then at 60 °C for 3 h. The solvents were evaporated in vacuo, and to the residue 50 mL of CH_2Cl_2 and 15 mL of water were added and the mixture was basified with solid K_2CO_3. The layers were separated and the water layer was extracted twice with CH_2Cl_2 (25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residual oil was purified by column chromatography on silica gel using chloroform/methanol, 0–3% of methanol as eluent system to afford 0.48 g (51%) of compound **7** as a colourless solid; $[\alpha]_D^{23} = +10.1(c1.0, CHCl_3)$; mp = 141–142 °C. The enantiomeric purity was determined by HPLC [Chiracel OD-H, hexane/*i*-PrOH (90:10), 1 mL/min]; the (1*S*,2*S*,4*R*)-isomer eluted at 19.2 min. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.61 (s, 3H), 1.41–1.50 (m, 3H), 1.65 (s, 3H), 1.66–1.81 (m, 3H), 2.18–2.22 (m, 1H), 2.41 (s, 3H), 3.06 (t, 1H, J = 3.0 Hz), 4.63 (s, 1H), 4.72 (s, 1H), 4.94 (bs, 1H), 7.27 (d, 2H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.3, 21.5, 22.1, 25.5, 32.3, 34.1, 37.2, 53.2, 59.8, 109.6, 126.9, 129.5, 140.7, 142.8, 148.1. HRMS: m/z calcd for $C_{17}H_{26}N_2O_2SNa$ $[M+Na]^+$: 345.1613; found: 345.1608.

Monocrystals of **7** suitable for crystallographic measurements were obtained from a diethyl ether solution by slow evaporation. Compound crystallizes in non-centrosymmetric monoclinic space group $P2_1$ with two independent molecules of the same enantiomer in the asymmetric part of the unit cell. The absolute structure of the studied crystal, and hence the absolute configuration of the compound was determined based on the value of the Flack parameter.[19] Since its value for the structure shown in Figure 2 was approximately 0, the molecular structure has the depicted configuration. The data were deposited with Cambridge Crystallographic Data Centre under the number CCDC 923757.

4.2.3. (1*R*,2*R*,5*R*)-*N*-(2-Amino-5-isopropyl-2-methyl-cyclohexyl)-4-methyl-benzenesulfonamide 8

Amine **8** was synthesized from azide **4** according to the literature.[13] Monocrystals of **8** suitable for crystallographic measurements were obtained from a diethyl ether solution by slow evaporation. Compound crystallizes in non-centrosymmetric monoclinic space group $P2_1$ with one molecule in the asymmetric part of the unit cell. The absolute structure of the studied crystal, and hence the absolute configuration of the compound was determined based on the value of the Flack parameter.[19] Since its value for the structure shown in Fig. 3 was approximately 0, the molecular structure has the depicted configuration. The data were deposited with Cambridge Crystallographic Data Centre under the number CCDC 923756.

4.2.4. *N*-(1*R*,2*R*,5*R*)-*N*-(2-Amino-5-isopropenyl-2-methyl-cyclohexyl)-4-methyl-benzenesulfonamide 9

To a stirred suspension of azide **4** (0.5 g, 1.44 mmol) in a mixture of ethanol (10 mL) and distilled water (3 mL) were added ammonium chloride (175 mg, 3.30 mmol) and then zinc powder (122 mg, 1.86 mmol) and the resulting mixture was stirred vigorously at 70 °C for 2 h. After completion of the reaction, ethyl acetate (50 mL), concentrated aqueous ammonia (2 mL) and distilled water (5 mL) were added. The layers were separated and the organic layer was extracted with water (10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The oily residue was purified by column chromatography on silica gel using chloroform/methanol, 0–8% of methanol as eluent system to afford 0.26 g (56%) of compound **9** as a colourless oil; $[\alpha]_D^{23} = -40.0(c1.0, CHCl_3)$. The enantiomeric purity was determined by HPLC [Chiracel OD-H, hexane/*i*-PrOH (90:10), 1 mL/min]; the (1*R*,2*R*,4*R*)-isomer eluted at 16.5 min. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.99 (s, 3H), 1.13 (q, 1H, J = 12.5 Hz),1.21–1.34 (m, 2H), 1.56–1.64 (m, 5H), 1.72–1.76 (m, 1H), 1.81–1.86 (m, 1H), 2.42 (s, 3H), 2.89 (dd, 1H, J = 12.0, 4.0 Hz), 4.58 (s, 1H), 4.64 (t, 1H, J = 1.5 Hz), 7.31 (d, 2H, J = 8.0 Hz), 7.78 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.8, 20.9, 21.5, 27.7, 35.0, 40.6, 44.3, 52.0, 62.7, 109.1, 127.1, 129.7, 137.6, 143.5, 148.1. HRMS: m/z calcd for $C_{17}H_{26}N_2O_2SNa$ $[M+Na]^+$: 345.1613; found: 345.1620.

Monocrystals of **9** picrate suitable for crystallographic measurements were obtained from an ethanol solution by slow evaporation. Compound crystallizes in non-centrosymmetric orthorhombic space group $P2_12_12_1$ with two independent molecules of the same enantiomer, two picrate anions and solvent molecules in the asymmetric part of the unit cell. The absolute structure of the studied crystal, and hence the absolute configuration of the compound was determined based on the value of the Flack parameter.[19] Since its value for the structure shown in Figure 4 was approximately 0, the molecular structure has the depicted configuration. The data were deposited with Cambridge Crystallographic Data Centre under the number CCDC 923758.

4.2.5. (1*S*,2*S*,5*R*)-*N*-(2-Amino-5-isopropyl-2-methyl-cyclohexyl)-4-methyl-benzenesulfonamide 10

To a stirred solution of azide **5** (0.55 g, 1.58 mmol) in anhydrous ethanol (20 mL) was added palladium on carbon-10% (90 mg) and the resulting suspension was stirred at room temperature in an atmosphere of hydrogen at room temperature for 17 h. The ethanolic solution was filtered and the solvent was evaporated in vacuo. The oily residue was purified by column chromatography on silica gel using chloroform/methanol, 0–7% of methanol as an eluent system to afford 0.42 g (82%) of compound **10** as a colourless oil; $[\alpha]_D^{23} = +1.1(c1.0, CHCl_3)$. The enantiomeric purity was determined by HPLC [Chiracel OD-H, hexane/*i*-PrOH (90:10), 1 mL/min]; the (1*R*,2*R*,4*R*)-isomer eluted at 14.6 min. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.62 (d, 3H, J = 7.0 Hz), 0.76 (d, 3H, J = 7.5 Hz), 1.02 (s, 3H), 1.03–1.09 (m, 1H), 1.19–1.50 (m, 7H), 2.41 (s, 3H), 3.03 (bs, 1H), 4.70 (bs, 1H), 7.29 (d, 2H, J = 7.5 Hz), 7.76 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.0, 20.2, 21.5, 24.1, 30.5, 35.3, 38.3, 51.3, 58.9, 127.2, 129.7, 137.9, 143.3. HRMS: m/z calcd for $C_{17}H_{29}N_2O_2S$ $[M+H]^+$: 325.1950; found: 325.1957.

Monocrystals of **10** picrate suitable for crystallographic measurements were obtained from an ethanol solution by slow evaporation. Compound crystallizes in non-centrosymmetric monoclinic space group C2 with two independent molecules of the same enantiomer and two picrate anions in the asymmetric part of the unit cell. The absolute structure of the studied crystal, and hence the

absolute configuration of the compound was determined based on the value of the Flack parameter.[19] Since its value for the structure shown in Figure 5 was approximately 0, the molecular structure has the depicted configuration. The data were deposited with Cambridge Crystallographic Data Centre under the number CCDC 923759.

4.2.6. *N*-(1*S*,2*S*,5*R*)-*N*-(2-Amino-5-isopropenyl-2-methyl-cyclohexyl)-4-methyl-benzenesulfonamide 11

To a stirred suspension of azide **5** (0.45 g, 1.29 mmol) in ethanol (10 mL) and distilled water (3 mL) were added ammonium chloride (157 mg, 2.97 mmol) and then zinc powder (110 mg, 1.68 mmol) and the resulting mixture was stirred vigorously at 70 °C for 3 h. After completion of the reaction, ethyl acetate (50 mL), concentrated aqueous ammonia (2 mL) and distilled water (5 mL) were added. The layers were separated and the organic layer was extracted with water (10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The oily residue was purified by column chromatography on silica gel using chloroform/methanol, 0–5% of methanol as eluent system to afford 0.26 g (64%) of compound **11** as a colourless oil; $[\alpha]_D^{23} = +12.5(c1.0, CHCl_3)$. The enantiomeric purity was determined by HPLC [Chiracel OD-H, hexane/*i*-PrOH (90:10), 1 mL/min]; the (1*R*,2*R*,4*R*)-isomer eluted at 17.2 min. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.01 (s, 3H), 1.37–1.48 (m, 3H), 1.53–1.56 (m, 5H), 1.71–1.77 (m, 1H), 2.02 (bs, 1H), 2.42 (s, 3H), 3.07 (br s, 1H), 4.57 (s, 1H), 4.70 (d, 1H, J = 1.0 Hz), 4.94 (br s, 1H), 7.31 (d, 2H, J = 8.0 Hz), 7.78 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.4, 21.5, 25.3, 31.7, 35.5, 38.2, 51.3, 58.8, 109.9, 127.2, 129.7, 137.8, 143.4, 147.3. HRMS: *m*/*z* calcd for $C_{17}H_{26}N_2O_2SNa$ $[M+Na]^+$: 345.1613; found: 345.11603.

4.3. General procedure for the synthesis of catalysts 12–18

A mixture of $[RuCl_2(C_6H_6)]_2$ (6 mg, 12 μmol) or $[RuCl_2(p\text{-cymene})]_2$ (7.3 mg, 12 μmol, ligands **6–11** (9.7 mg, 30 μmol) and Et_3N (24 μmol) in 1 mL of CH_3CN was stirred at room temperature for 30 min. After this time, the resulting pale brown solution of catalyst was used immediately for the reduction of the ketones or imines/iminium salts.

4.4. General procedure for ketone reduction using catalysts 12–18

To a ketone (2.4 mmol) placed in a vial, 1 mL of CH_3CN solution of preformed ruthenium catalyst (24 μmol) and formic acid/triethylamine azeotropic mixture (1 mL) were added. The mixture was then stirred at room temperature and the progress of the reaction was monitored by TLC until the specified conversion was achieved. After evaporation of the solvents, 4 mL of CH_2Cl_2 and 1.5 mL of 10% aqueous HCl solution were added to the residue. The layers were separated and the water layer was extracted twice with 2 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The oily residue was purified by column chromatography on silica gel using chloroform (dried over $CaCl_2$) as eluent to afford the appropriate ketone. The enantiomeric excess was determined by GC analysis using a Supelco cyclodextrin β-DEX 120 capillary column (20 m × 0.25 mm I.D. and 0.25 μm film thickness). The results of the reduction are summarized in Tables 1 and 2.

4.5. General procedure for imines/iminium salts reduction using catalysts 12–18

To a suspension of imine/iminium salt (0.3 mmol) in 1 mL of CH_3CN placed in a vial, a solution of preformed ruthenium catalyst (6 μmol in 0.5 mL of CH_3CN) and formic acid/triethylamine azeotropic mixture (1.2 mL) were added. The mixture was then stirred at room temperature and the progress of the reaction was monitored by TLC until the specified conversion was achieved. After evaporation of the solvents, 4 mL of CH_2Cl_2 and 2 mL of water were added and the mixture was basified with solid K_2CO_3. The layers were separated and the water layer was extracted twice with 3 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The crude product **20** was purified by column chromatography on aluminium oxide using chloroform/methanol, (0–5% of methanol) as the eluent system. The enantiomeric excess of compound **20** was determined by HPLC analysis using a Chiracel OD-H column, hexane/*i*-PrOH/diethylamine (90:10:0.1), 1 mL/min. The products of the reduction of imines **21** and **22** were purified by column chromatography on silica gel using chloroform. The products of the reduction of imines **23** and **24** were purified by column chromatography on aluminium oxide using chloroform. The enantiomeric excess and the configuration of the products of the reduction of compound **21–24** were determined by comparison of the values and sign of specific rotation. The results of the reduction are summarized in Table 3.

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