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Organic Chemistry

Arkivoc **2017**, part ii, 162-172

Chiral pyrrolidine thioethers and 2-azanorbornane derivatives bearing additional nitrogen functions. Enantiopure ligands for palladium-catalyzed Tsuji-Trost reaction

Elżbieta Wojaczyńska,[a]* Karolina Kamińska,[a] Jacek Wojaczyński,[b] and Jacek Skarżewski[a]

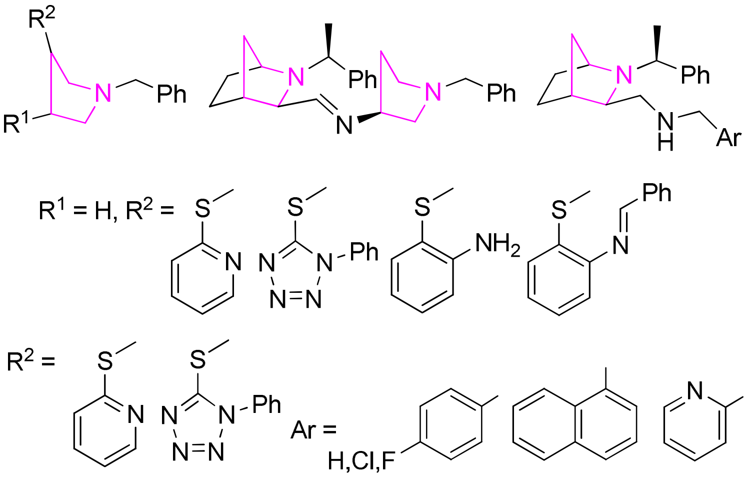
[a] *Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Science and Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland*
[b] *Faculty of Chemistry, University of Wrocław, 14 F. Joliot-Curie St., 50-383 Wrocław, Poland*
E-mail: elzbieta.wojaczynska@pwr.edu.pl

Dedicated to Prof. Jacek Młochowski on the occasion of his 80th birthday

Received 07-10-2016 **Accepted** 08-11-2016 **Published on line** 08-31-2016

Abstract

An efficient procedure for the synthesis of new enantiopure pyrrolidine-based sulfides bearing additional nitrogen donors and secondary amines based on a bicyclic 2-azanorbornane skeleton was developed. Their application as ligands in palladium-catalyzed Tsuji-Trost reactions led to high yields and up to 82% *ee*.



Keywords: Amines, 2-azanorbornane, pyrrolidine, stereoselectivity, thioethers, Tsuji-Trost reaction

Introduction

The pyrrolidine ring can be found in various biologically important compounds, including the amino acids proline **1** and hydroxyproline **2**, and numerous alkaloids (nicotine **3**, hygrine **4**, cuscohygrine **5**, and others, Figure 1). Pyrrolidine derivatives (*e.g.* procyclidine, bepridil, pramanicin, rolipram, piracetam, epolactaene, and kainic acid), in many cases chiral, are used as drugs or have been tested as drug candidates, to fight numerous disorders such as cancer, Alzheimer's disease, epilepsy, and cardiovascular diseases.[1]

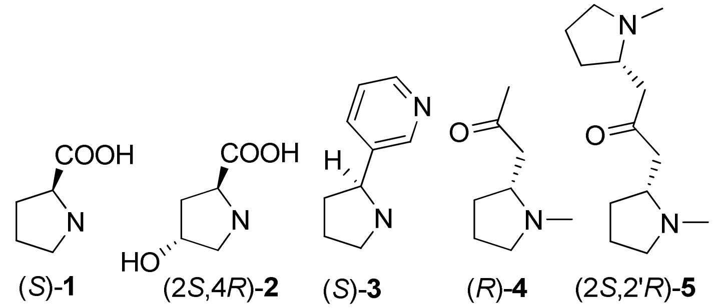
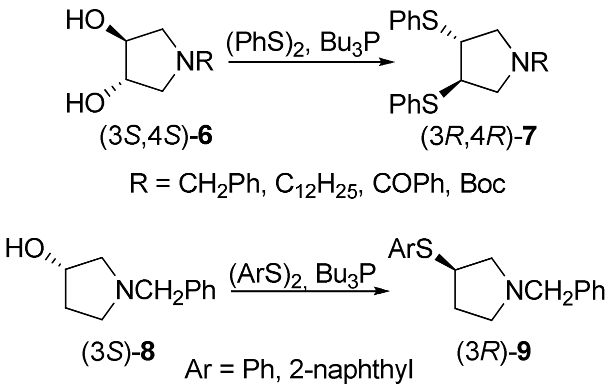


Figure 1. Naturally occurring pyrrolidine derivatives.

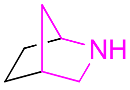
The appropriately substituted five-membered nitrogen-containing ring has also served as a skeleton of useful chiral building blocks for asymmetric synthesis. The resulting structures, often available in both enantiomeric forms, have found wide application as catalysts or ligands in various stereoselective transformations as well as chiral resolving agents.[2]

In our laboratory, we have prepared a number of pyrrolidine derivatives which were found to be effective as bidendate ligands for asymmetric catalysis.[3,4] The *trans*-diol **6** was used as a convenient starting material, which was subjected to nucleophilic substitution (Hata reaction[5]), leading to the corresponding bis-sulfides **7** (Scheme 1) with complete inversion of configuration. Similarly, the *N*-substituted 3-hydroxypyrrolidine **8** was converted into the corresponding monosulfides **9**. We tested the obtained chiral ligands containing a sulfur donor in the palladium-catalyzed Tsuji-Trost reaction (asymmetric allylic alkylation, AAA).[6] The best results (with enantiomeric excesses up to 90% accompanied with an 80% yield) were noted for derivatives **9**, acting as N,S-donor ligands.[7]



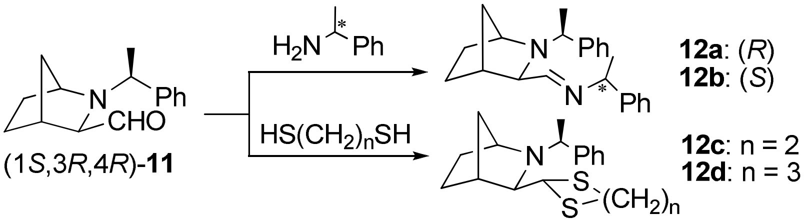
Scheme 1. Synthesis of chiral S-donating pyrrolidine derivatives.

2-Azanorbornane (2-azabicyclo[2.2.1]heptane) **10** can be regarded as an intrinsically chiral bridged pyrrolidine derivative (Figure 2). This bicyclic system is easily available in a highly stereoselective aza-Diels-Alder reaction and can be used as a convenient platform for the synthesis of ligands and catalysts with wide application in asymmetric synthesis.[8] 2-Azanorbornane-derived ligands were also assessed in a palladium-catalyzed Tsuji-Trost reaction. The oxazolidine derivative prepared by Okayama *et al.* showed a poorer performance than its pyrrolidine analog.[9] In our studies, we converted aldehyde **11** into Schiff bases **12a**, **12b** and thioacetals **12c**, **12d**; using these derivatives, we obtained the product of the AAA reaction in 86-95% yield and 48-95% *ee*.[10]



(1*S*,4*R*)-**10**

Figure 2. 2-Azanorbornane as a bridged pyrrolidine analogue.



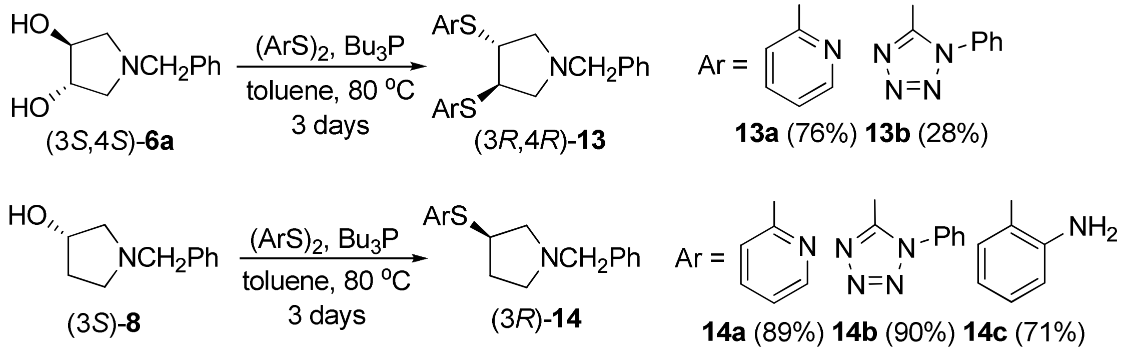
Scheme 2. Preparation of 2-azanorbornane derivatives active in Tsuji-Trost reaction.[10]

These results prompted us to explore further the use of pyrrolidine and 2-azanorbornane skeletons as a convenient platform for the synthesis of enantiopure derivatives bearing additional sulfur and nitrogen functions for their possible use in Tsuji-Trost and other metal-catalyzed or organocatalytic asymmetric transformations.

Results and Discussion

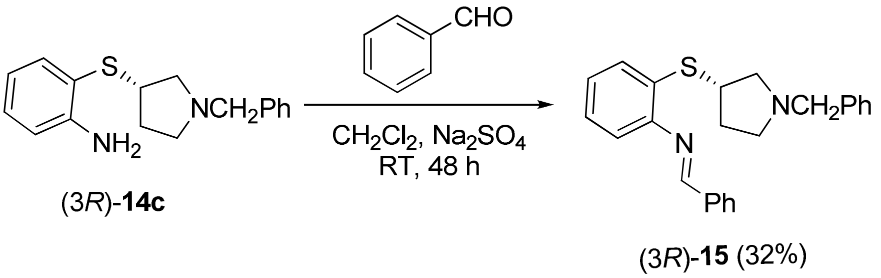
Our earlier investigations proved the utility of Hata reactions for the stereoselective preparation of mono- and bis-sulfides based on a five-membered pyrrolidine and cyclopentane ring.[3,4] We decided to test the protocol using disulfides bearing additional nitrogen donors in their structure. The substitution of hydroxyl groups in the *trans*-diol (3*S*,4*S*)-**6a** proceeded according to a S_N2 mechanism with a complete inversion of configuration of both stereocenters in 76% (**13a**) and 28% yield (**13b**, Scheme 3). The difficulties in the synthesis of bis-tetrazole derivative can be explained by a steric hindrance introduced by the phenyl-substituted heterocyclic rings. Both ^1H NMR and ^{13}C NMR spectra revealed the presence of a single diastereomer of **13a** and **13b**. In the latter case, however, the hindered rotation of tetrazole substituents creates two non-equivalent sides in the molecule, which results in the increased number of signals in the NMR spectra.

Substitution of the hydroxyl group in the pyrrolidine-derived alcohol (3*S*)-**8** was also performed, leading to monosulfides **14a-14c** in 71-90% yields. A complete inversion of configuration resulted in (*R*)-products in agreement with the S_N2 mechanism (Scheme 3). This observation was further confirmed by a small-scale synthesis in which alcohol (3*R*)-**8** was used: enantiomers of compounds **14a-14c** were obtained with the opposite values of specific rotation.



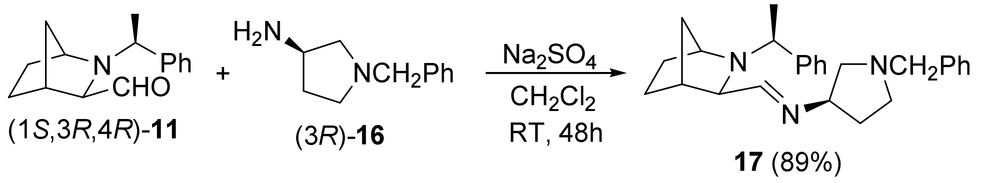
Scheme 3. Synthesis of bis- and monosulfides.

The presence of an amine group in derivative **14c** opens the possibility of modification of this arylthiopyrrolidine. To verify this, we converted this compound into the Schiff base derivative **15** (32% yield; Scheme 4).



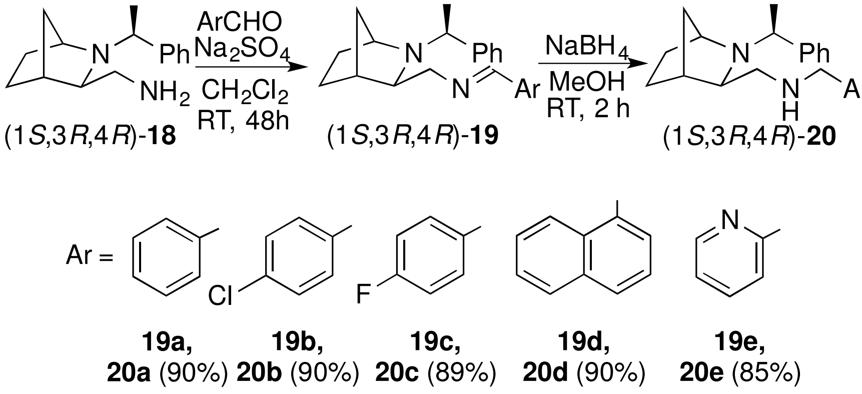
Scheme 4. Preparation of imine **15**.

For comparison, we synthesized another imine with a nitrogen donor directly attached to the pyrrolidine fragment. To this end, (3*R*)-3-amino-*N*-benzylpyrrolidine **16** was reacted with an enantiopure aldehyde **11** derived from bicyclic 2-azanorbornane.[10-12] Imine **17** was formed as a single stereoisomer in 89% yield (Scheme 5). This way, an enantiopure ligand was obtained combining two structural motifs – pyrrolidine and 2-azanorbornane. This compound can be regarded as an analogue of the previously described bicyclic derivative **12a** bearing an additional nitrogen donor.



Scheme 5. Preparation of Schiff base **17**

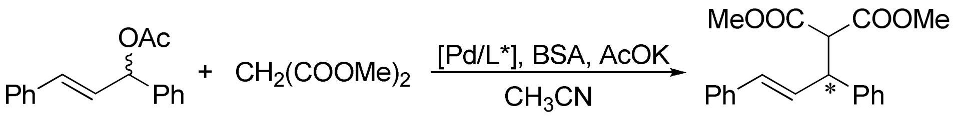
Aldehyde **11** was recognized as a useful synthetic precursor of chiral 2-azabicyclo[2.2.1]heptanes which have found various applications in asymmetric synthesis.[10-12] In our laboratory, it was utilized in the preparation of ligands bearing additional donor atoms (N, S, P, O) and polyamine derivatives exhibiting interesting antiproliferative activity.[10,13,14] In particular, amine **18** based on a 2-azanorbornyl skeleton was obtained from **11** *via* its conversion into an oxime followed by reduction.[14] In the present work, we decided to extend the family of N,N-donating ligands containing four stereogenic centers by reacting amine **18** with aryl aldehydes leading to the series of imines **19a-19e** (Scheme 6). Since these imines were too unstable to be isolated, they were reduced *in situ* to the corresponding secondary amines with various aryl substituents **20a-20e** (85-90% overall yields). All new compounds were characterized by HRMS, IR, ^{1}H and ^{13}C NMR spectroscopy, and their structures were further confirmed by 2D NMR spectra. This allowed a full assignment of NMR resonances which is given in Table S1 (Supplementary Material).



Scheme 6. Synthesis of secondary amines **20a-20e.**

We tested the newly obtained chiral derivatives as ligands in a palladium-catalyzed Tsuji-Trost (AAA) reaction between dimethyl malonate and a racemic 1,3-diphenyl-2-propenyl acetate. The results are collected in Table 1.

Table 1. Results of palladium-catalyzed AAA reaction with chiral ligands [a]



Ligand L*	Yield	*R:S*
14a	30%	84:16
17	90%	16:84
18	90%	22:78
20a	>99%	9:91
20b	>99%	18:82
20b[b]	80%	17:83
20c	>99%	13:87
20d	95%	19:81
20e	90%	60:40

[a] The reaction was conducted over 3 days at room temperature with 10% of chiral ligand L*.
[b] The reaction was performed at 5 °C.

On the basis of our previous experiments with sulfides **9**,[7] we could expect a good performance of compounds **14a-14c**. However, a racemic product was obtained (in *ca*. 30% yield) when sulfide **14b** was applied as a source of chirality, and the use of **14a** resulted in a similar yield and a modest enantiomeric excess (68%). Still, this result is encouraging when compared with the lack of asymmetric induction observed for alcohol **8** in this reaction.

In the series of bicyclic ligands, the (*S*) enantiomer of the product was preferentially formed in all cases, except for **20e**. Molecular models of the transition state indicate that formation of η^3-1,3-diphenylallyl M-shaped complex should be restricted due to the spatial proximity of the substituent of the coordinating N(2) atom of the norbornyl system and one of the phenyl groups of substrate (Figure 3). Predominant formation of a W-shaped complex, together with the preference of the nucleophile for *trans* attack with respect to the secondary nitrogen donor is responsible for the observed stereochemical outcome of catalytic reaction with **17**, **18**, and **20a-20d**. An interesting reversal of stereochemical preference observed for the 2-pyridyl derivative **20e** can be accounted for by the presence of an additional donor in the molecule, which apparently is engaged in palladium coordination. As a consequence, a different transition state structure can be expected, leading to the preferred formation of the (*R*) product (albeit with rather low *ee*).

An example with ligand **20b** shows the influence of temperature on the outcome of the catalytic reaction. When the AAA process was conducted at 5 °C, the stereoselectivity remained practically unchanged, while the yield was significantly lower as compared to the original conditions.

Imine **17** (90% yield, 68% *ee*) performed better than its analogue **12a** described previously (86% yield, 50% *ee*),[10] but the results were significantly inferior to those obtained for **12b** (epimer of **12a**; 95% yield, 90% *ee*).

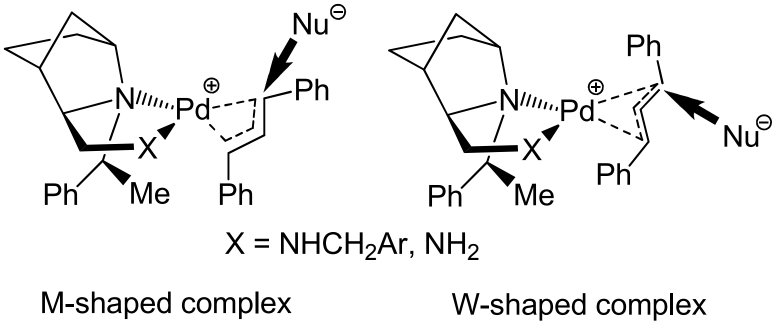


Figure 3. Transition states of palladium-catalyzed Trost-Tsuji reaction with the 2-azanorbornane ligands **18** and **20a-20d**.

Conclusions

A series of new heterocyclic chiral pyrrolidine derivatives was obtained by the Hata reaction, and 2-azanorbornane-based imines and secondary amines were prepared from the respective amine and aldehyde precursors. The new enantiopure ligands were applied in the asymmetric induction in AAA (Tsuji-Trost) reaction between dimethyl malonate and a racemic 1,3-diphenyl-2-propenyl acetate, and they led to generally high yields and up to 82% *ee*. Our studies extended the family of N,N- and N,S-donating heterocyclic and bicyclic compounds which may find further application in asymmetric synthesis.

Experimental Section

General. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker CPX (^{1}H, 300 MHz) or a Bruker Avance (^{1}H, 500 MHz or ^{1}H, 600 MHz) spectrometers using solvent residual peak as an internal standard. Optical rotations were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. High resolution mass spectra were recorded using a microTOF-Q and WATERS LCT Premier XE instruments utilizing electrospray ionization mode. Separations of products by chromatography were performed on silica gel 60 (230-400 mesh) purchased from Merck. Thin layer chromatography was carried out using silica gel 60 precoated plates (Merck). HPLC analyses were performed on Chiracel OD-H or Chiralpak AD-H chiral columns (flow rate of 1.0 mL/min).

Preparation of sulfides 14a-14c and bissulfides 13a, 13b.[3-5] Tributylphosphine (4.0 mmol, 0.84 g, 0.98 mL) was added by syringe to a solution of (*S*)-1-benzylpyrrolidin-3-ol **8** (1.0 mmol, 0.18 g) and diaryldisulfide (3.0 mmol) in dry toluene (3 mL). The mixture was transferred to an ampoule, filled with argon and sealed. This reaction mixture was kept in an oil bath at 80 °C for three days. Diethyl ether (10 mL) was added to the cooled solution, the organic layer was washed with 10% aqueous NaOH, water and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the obtained product was purified by column chromatography using hexane-ethyl acetate (9:1 v/v) as eluent.

For the preparation of bissulfides **13a**, **13b** from diol **6a**, the amounts of diaryldisulfide and tributylphosphine were doubled (6.0 and 8.0 equivalents, respectively).

(+)-(3*R*,4*R*)-1-Benzyl-3,4-bis[(2-pyridyl)thio]pyrrolidine (**13a**). Yellow oil (0.29 g, 76%). $[\alpha]_D^{20}$ +93 (*c* 0.80, CH_2Cl_2). R$_f$ 0.53 (*n*-hexane-ethyl acetate, 3:1). IR (film, ν_{max}, cm^{-1}): 3063, 3043, 2957, 2793, 2731, 1724, 1578, 1556, 1453, 1415, 1281, 1124, 985, 757, 727, 699. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.74-2.79 (2H, dd, *J*$_1$ 9.0 Hz; *J*$_2$ 4.2 Hz); 3.37-3.43 (2H, m), 3.70 and 3.79 (2H, AB system, *J* 13.2 Hz), 4.17-4.37 (2H, m), 6.94-6.95 (2H, m), 7.17-7.45 (9H, m), 8.31-8.34 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 47.1, 59.6, 60.8, 119.5, 122.3, 127.0, 128.3, 128.7, 135.9, 138.5, 149.4, 158.9. HRMS (ESI-TOF) calcd for (M+H) $C_{21}H_{22}N_3S_2$: 380.1255; found 380.1247 (2.1 ppm).

(+)-(3*R*,4*R*)-1-Benzyl-bis[(1-phenyl-1*H*-tetrazol-5-yl)thio]pyrrolidine (**13b**). Yellow oil (0.14 g, 28%). $[\alpha]_D^{20}$ +10 (*c* 1.46, CH_2Cl_2). R$_f$ 0.35 (*n*-hexane-ethyl acetate, 3:1). IR (film, ν_{max}, cm^{-1}): 3063, 2959, 2930, 2871, 2809, 1730, 1596, 1498, 1423, 1343, 1092, 760, 690. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.87 (1H, dd, *J*$_1$ 10.5 Hz, *J*$_2$ 5.4 Hz), 2.97 (1H, dd, *J*$_1$ 9.8 Hz, *J*$_2$ 6.4 Hz), 3.28 (1H, dd, *J*$_1$ 9.7 Hz, *J*$_2$ 8.1 Hz), 3.44 (1H, dd, *J*$_1$ 10.3 Hz, *J*$_2$ 8.0 Hz), 3.66 and 3.72 (2H, AB system, *J* 13.0 Hz), 4.89-4.92 (1H, m), 5.54-5.58 (1H, m), 7.39-7.51 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.0, 49.9, 59.2, 59.5, 63.9, 124.4, 124.8, 125.0, 125.2, 129.6, 129.7, 130.1, 130.2, 130.3, 130.8, 130.9, 153.4, 164.3. HRMS (ESI-TOF) calcd for (M+H) $C_{25}H_{24}N_9S_2$: 514.1595; found 514.1599 (-0.8 ppm).

(–)-(3*R*)-1-Benzyl-3-[(2-pyridyl)thio]pyrrolidine (**14a**). Yellow oil (0.24 g, 89%). $[\alpha]_D^{20}$ –58 (*c* 1.00, CH_2Cl_2). R$_f$ 0.40 (*n*-hexane-ethyl acetate, 1:1). IR (film, ν_{max}, cm^{-1}): 3062, 3027, 2962, 2791, 2733, 1578, 1556, 1453, 1414, 1280, 1126, 757, 699. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.84-1.92 (1H, m), 2.44-2.54 (1H, m), 2.57-2.62 (1H, dd, *J*$_1$ 10.0 Hz; *J*$_2$ 5.8 Hz), 2.67-2.73 (2H, m), 3.18-3.24 (1H, dd, *J*$_1$ 10.0 Hz; *J*$_2$ 7.6 Hz), 3.65 and 3.72 (2H, AB system, *J* 12.9 Hz), 4.26-4.32 (1H, m), 6.94-6.99 (1H, m), 7.14-7.18 (1H, m), 7.25-7.36 (5H, m), 7.44-7.49 (1H, m), 8.40-8.43 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 32.5, 40.6, 53.7, 60.5, 61.4, 119.7, 122.4, 127.4, 128.7, 129.2, 136.2, 139.2, 149.9, 160.2. HRMS (ESI-TOF) calcd for (M+H) $C_{16}H_{19}N_2S$ 271.1269; found 271.1275 (-2.2 ppm).

(–)-(3*R*)-1-Benzyl-[(1-phenyl-1*H*-tetrazol-5-yl)thio]pyrrolidine (**14b**). Yellow oil (0.30 g, 90%). $[\alpha]_D^{20}$ –3 (*c* 1.12, CH_2Cl_2). R$_f$ 0.43 (*n*-hexane-ethyl acetate, 1:1). IR (film, ν_{max}, cm^{-1}): 3062, 3028, 2964, 2796, 1597, 1499, 1386, 1090, 761, 697. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.89-1.91 (1H, m), 2.53-2.59 (2H, m), 2.72-2.79 (2H, m), 3.09-

3.15 (1H, dd, J_1 10.5 Hz, J_2 6.9 Hz), 3.63 and 3.69 (2H, AB system, *J* 12.9 Hz), 4.38-4.42 (1H, m), 7.26-7.53 (5H, m), 7.54-7.57 (5H, m). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 32.3, 43.9, 52.9, 59.7, 60.8, 123.8, 124.7, 127.2, 128.4, 128.8, 129.8, 130.1, 138.4, 154.5. HRMS (ESI-TOF) calcd for (M+H) $C_{18}H_{20}N_5S$ 338.1439; found 338.1446 (-2.1 ppm).

(–)-(3*R*)-1-Benzyl-3-[(2-aminophenyl)thio]pyrrolidine (**14c**). Yellow oil (0.20 g, 71%). $[\alpha]_D^{20}$ –46 (*c* 1.00, CH$_2$Cl$_2$). R$_f$ 0.32 (*n*-hexane-ethyl acetate, 1:1). IR (film, $\nu_{max,}$ cm^{-1}): 3452, 3356, 3062, 3026, 2960, 2793, 1733, 1606, 1478, 1447, 1307, 1250, 1141, 759, 699. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 1.73-1.78 (1H, m), 2.09-2.16 (1H, m), 2.44-2.47 (1H, m), 2.54-2.56 (1H, m), 2.57-2.61 (1H, m), 2.78-2.81 (1H, dd, J_1 9.0 Hz, J_2 7.8 Hz), 3.45-3.54 (1H, m), 3.60 and 3.73 (2H, AB system, *J* 12.8 Hz), 4.26 (2H, bs, NH$_2$), 6.57-6.62 (2H, m), 7.01-7.03 (1H, m), 7.17-7.29 (6H, m). ^{13}C NMR (125 MHz, CDCl$_3$): δ_C 32.4, 44.7, 53.7, 60.6, 61.1, 115.3, 118.3, 118.8, 127.4, 128.7, 129.2, 130.3, 136.7, 139.3, 149.0. HRMS (ESI-TOF) calcd for (M+H) $C_{17}H_{21}N_2S$ 285.1425, found: 285.1420 (1.8 ppm).

Preparation of imines 15, 17, 19a-19e and amines 20a-20e. Amine **14c** (0.076 g, 0.26 mmol) and benzaldehyde (0.028 g, 0.26 mmol) were dissolved in dry dichloromethane (5 mL). Anhydrous sodium sulfate was then added and the reaction mixture was stirred for 48 h at room temperature. The reaction mixture was filtered and dichloromethane was evaporated under vacuum. Water (5 ml) was added to the residue, which was then extracted with diethyl ether (3 x 10 ml). The combined organic layers were dried over Na$_2$SO$_4$, filtered and evaporated. A quick chromatography through a short silica column yielded imine **15**.

Schiff base **17** was prepared in a similar manner using (*R*)-(-)-1-benzyl-3-aminopyrrolidine **16** (0.12 g, 0.66 mmol) and aldehyde (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-3-al[10-12] **11** (0.15 g, 0.66 mmol).

Imines **19a-19e** were obtained analogously from (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-3-aminemethyl-2-azabicyclo[2.2.1]heptane **18** (prepared from **11** as described previously;[14] 0.12 g, 0.50 mmol) and the respective aldehydes (0.5 mmol). Due to their instability, the crude product obtained after filtration and evaporation of solvent was dissolved in 8 mL of methanol. Sodium borohydride (0.028 g, 0.75 mmol, 1.5 eq.) was added in one portion, the solution was stirred for 2 hours and evaporated. The residue was chromatographed on silica gel column. Chloroform eluted alcohol (a side-product coming from reduction of unreacted aldehyde), and chloroform-methanol mixture (95/5 v/v) eluted amines **20**.

(+)-(3*S*)-(*E*)-1-Benzyl-3-[(2-*N*-benzylideneaminephenyl)thio]pyrrolidine (**15**). Yellow oil, (0.031 g, 32%), $[\alpha]_D^{20}$ +32 (*c* 0.62, CH$_2$Cl$_2$). IR (film, $\nu_{max,}$ cm^{-1}): 3060, 2959, 2792, 1702, 1626, 1575, 1494, 1463, 1453, 1191, 1073, 761, 692. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 1.86-1.93 (1H, m), 2.38-2.45 (1H, m), 2.48-2.54 (1H, m), 2.56-2.64 (1H, m), 2.71-2.76 (1H, m), 3.17-3.23 (1H, dd, J_1 9.8 Hz, J_2 7.4 Hz), 3.62 and 3.68 (2H, AB system, *J* 12.8 Hz), 3.85-3.88 (1H, m), 6.96-6.99 (1H, m), 7.16-7.19 (2H, m), 7.24-7.28 (2H, m), 7.29-7.32 (4H, m), 7.46-7.51 (3H, m), 7.92-7.98 (2H, m), 8.39 (1H, s). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 32.9, 41.3, 53.7, 60.6, 61.2, 118.4, 126.5, 126.7, 127.4, 127.9, 128,7, 129.2, 129.2, 129.5, 131.9, 132.9, 136.6, 139.2, 150.5, 160.5. HRMS (ESI-TOF) calcd for (M+H) $C_{24}H_{25}N_2S$: 373.1738; found 373.1733 (1.3 ppm). R$_f$ 0.56 (*t*-BuOMe: CHCl$_3$ 3:1).

(+)-(*E*)-1-benzyl-*N*-{[(1*S*,3*R*,4*R*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[2.2.1]heptan-3-yl]methylene}pyrrolidin-3-amine (**17**). Yellow oil (0.23 g, 89%). $[\alpha]_D^{20}$ +14 (*c* 0.57, CH$_2$Cl$_2$), IR (film, $\nu_{max,}$ cm^{-1}): 3288, 2966, 2869, 2793, 1662, 1453, 1133, 700. ^{1}H NMR (600 MHz, CDCl$_3$): δ_H 1.02-1.08 (1H, m), 1.26 (1H, d, *J* 9.6 Hz), 1.32 (3H, d, *J* 6.5 Hz), 1.36-1.44 (2H, m), 1.56-1.76 (3H, m), 1.94-2.01 (1H, m), 2.12-2.17 (2H, m), 2.40 (1H, q, *J* 8.5 Hz), 2.58 (1H, d, *J* 6.2 Hz), 2.62-2.67 (1H, m), 2.71-2.76 (1H, m), 3.24-3.30 (1H, m), 3.51 (1H, q, *J* 6.5 Hz), 3.53 and 3.59 (2H, AB system, *J* 12.0 Hz), 3.68 (1H, s), 6.93 (1H, d, *J* 6.2 Hz), 7.11 (1H, tt, J_1 7.3 Hz, J_2 1.4 Hz), 7.18 (2H, t, *J* 7.6 Hz), 7.20-7.32 (7H, m, ArH). ^{13}C NMR (150 MHz, CDCl$_3$): δ_C 22.5, 22.8, 29.5, 32.5, 36.0, 43.8, 53.4, 58.5, 60.4, 60.5, 60.8, 67.7, 71.6, 127.0, 127.1, 128.06, 128.13, 128.2, 129.0, 138.7, 145.5, 167.4. HRMS (ESI-TOF) calcd for (M+H) $C_{22}H_{29}N_2OS$: 388.2753; found 388.2746 (1.3 ppm).

(–)-(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-(benzylaminomethyl)-2-azabicyclo[2.2.1]heptane (**20a**). Yellow oil (0.14 g, 90%). $[\alpha]_{\mathrm{D}}^{20}$ –13 (*c* 1.96, CH_2Cl_2), IR (film, ν_{max}, cm^{-1}): 3298, 2969, 1453, 1165, 1305, 743, 705. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 1.23-1.42 (4H, m), 1.36 (3H, d, *J* 6.6 Hz), 1.59-1.67 (1H, m), 1.72-1.77 (1H, m), 1.78-1.83 (1H, m), 1.88-2.02 (2H, m), 2.10-2.14 (1H, m), 2.21-2.23 (1H, m), 3.25 and 3.30 (2H, AB system, *J* 10.8 Hz), 3.48 (1H, q, *J* 6.6 Hz), 3.65 (1H, s), 7.09 (2H, d, *J* 6.6 Hz), 7.19-7.40 (8H, m). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 22.3, 22.4, 29.3, 35.6, 41.2, 54.1, 54.6, 58.8, 61.3, 69.2, 126.6, 127.4, 128.0, 128.1, 128.2, 128.3, 140.6, 145.9. HRMS (ESI-TOF) calcd for (M+H) $C_{22}H_{29}N_2$: 321.2331; found 321.2326 (1.6 ppm).

(–)-(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-{[(4-chlorophenyl)methylamino]methyl}-2-azabicyclo[2.2.1]heptane (**20b**). Yellow oil (0.16 g, 90%). $[\alpha]_{\mathrm{D}}^{20}$ –14 (*c* 2.00, CH_2Cl_2), IR (film, ν_{max}, cm^{-1}): 3296, 2968, 2869, 1491, 1454, 1360, 1165, 1108, 806, 762, 701. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 1.22-1.37 (3H, m), 1.30 (3H, d, *J* 6.6 Hz), 1.50-1.67 (3H, m), 1.72-1.85 (2H, m), 1.92-1.98 (1H, m), 2.02-2.05 (1H, m), 2.15-2.17 (1H, m), 3.24 (2H, s), 3.44 (1H, q, *J* 6.6 Hz), 3.60 (1H, s), 6.99 (2H, d, *J* 8.4 Hz), 7.18-7.33 (7H, m). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 22.3, 22.4, 29.3, 35.6, 41.2, 53.2, 54.4, 58.7, 61.2, 69.2, 127.3, 128.10, 128.11, 128.4, 129.3, 132.2, 139.1, 146.1. HRMS (ESI-TOF) calcd for (M+H) $C_{22}H_{28}ClN_2$: 355.1941; found 355.1924 (4.8 ppm).

(–)-(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-{[(4-fluorophenyl)methylamino]methyl}-2-azabicyclo[2.2.1]heptane (**20c**). Yellow oil (0.15 g, 89%). $[\alpha]_{\mathrm{D}}^{20}$ –14 (*c* 1.28, CH_2Cl_2), IR (film, ν_{max}, cm^{-1}): 3297, 2969, 2869, 1689, 1603, 1509, 1454, 1306, 1221, 825, 701. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 1.22-1.40 (4H, m), 1.33 (3H, d, *J* 6.5 Hz), 1.60-1.69 (2H, m), 1.76-1.78 (1H, m), 1.84-1.89 (1H, m), 1.94-2.00 (1H, m), 2.07-2.09 (1H, m), 2.18-2.20 (1H, m), 3.23 and 3.26 (2H, AB system, *J* 12.8 Hz), 3.46 (1H, q, *J* 6.5 Hz), 3.62 (1H, s), 6.90-6.93 (2H, t, *J* 6.6 Hz), 7.02-7.05 (2H, m), 7.19-7.26 (3H, m), 7.32-7.34 (2H, m).^{13}C NMR (75 MHz, CDCl$_3$): δ_C 22.29, 22.33, 29.2, 35.6, 41.2, 53.1, 54.2, 58.8, 61.3, 69.1, 115.0 (d, *J* 20.1 Hz), 127.3, 128.16, 128.17, 129.5 (d, *J* 80.0 Hz), 135.8, 145.8, 161.8 (d, *J* 242.5 Hz). HRMS (ESI-TOF) calcd for (M+H) $C_{22}H_{28}FN_2$: 339.2237; found 339.2225 (3.5 ppm).

(–)-(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-[(1-naphthylmethylamino)methyl]-2-azabicyclo[2.2.1]heptane (**20d**). Yellow oil (0.17 g, 90%); $[\alpha]_{\mathrm{D}}^{20}$ –10 (*c* 0.42, CH_2Cl_2), IR (film, ν_{max}, cm^{-1}): 3441, 2030, 1642, 1358, 1213, 1165, 1049, 736. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 1.23-1.42 (4H, m), 1.35 (3H, d, *J* 6.5 Hz), 1.62-1.66 (1H, m), 1.76-1.82 (2H, m), 2.00-2.07 (2H, m), 2.12-2.14 (1H, m), 2.20-2.22 (1H, m), 3.48 (1H, q, *J* 6.5 Hz), 3.62 (1H, s), 3.67 and 3.76 (2H, AB system, *J* 13.4 Hz), 7.09-7.18 (1H, m), 7.20-7.24 (3H, m), 7.34-7.38 (3H, m), 7.46-7.53 (2H, m), 7.73 (1H, d, *J* 8.0 Hz), 7.84-7.89 (2H, m). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 22.3, 22.4, 29.2, 35.6, 41.2, 51.6, 55.1, 58.6, 61.2, 69.2, 123.7, 125.37, 125.43, 125.6, 125.8, 127.2, 127.4, 128.0, 128.2, 128.6, 131.7, 133.8; 136.3, 146.1. HRMS (ESI-TOF) calcd for (M+H) $C_{26}H_{31}N_2$: 371.2487; found 371.2471 (4.3 ppm).

(–)-(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-[(2-pyridylmethylamino)methyl]-2-azabicyclo[2.2.1]heptane (**20e**). Yellow oil (0.14 g, 85%). $[\alpha]_{\mathrm{D}}^{20}$ –17 (*c* 1.26, CH_2Cl_2), IR (film, ν_{max}, cm^{-1}): 3333, 2967, 2870, 1668, 1592, 1449, 1307, 1165, 756, 703. ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 1.25-1.45 (4H, m), 1.39 (3H, d, *J* 6.5 Hz), 1.62-1.76 (2H, m), 1.83-1.87 (1H, m), 1.94-2.01 (2H, m), 2.18-2.23 (1H, m), 2.31 (1H, d, *J* 3.9 Hz), 3.36 and 3.49 (2H, AB system, *J* 14.5 Hz), 3.52 (1H, q, *J* 6.4 Hz), 3.72 (1H, s), 7.03-7.39 (7H, m), 7.57 (1H, td, J_1 9.4 Hz, J_2 1.8 Hz), 8.47-8.49 (1H, m). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 22.0, 22.2, 29.1, 35.5, 40.7, 53.4; 54.7; 59.4, 61.5, 69.1, 121.9, 122.1, 127.7, 128.3, 128.4, 136.4, 144.8, 149.1, 159.1. HRMS (ESI-TOF) calcd for (M+H) $C_{21}H_{27}N_3$: 322.2283; found 322.2294 (-3.4 ppm).

General procedure for AAA (Trost-Tsuji) reaction. The solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3.7 mg, 0.010 mmol) and chiral ligand (0.040 mmol, 10 mol%) in acetonitrile (1.0 mL) was stirred under argon atmosphere at room temperature for 15 min. To this mixture the solution of *rac*-1,3-diphenyl-2-propenyl acetate (0.40 mmol, 0.10 g) in CH_3CN (1.5 mL) was added followed by dimethyl malonate (0.14 mL, 1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 0.30 mL, 1.2 mmol) and anhydrous potassium acetate (1.0 mg, 0.010 mmol). The solution was stirred at room temperature. The reaction was monitored by TLC. After three days the solution was evaporated and the residue was purified by column chromatography (*n*-hexane: ethyl acetate, 5:1 v/v). Products were analyzed by ^{1}H NMR, and the enantiomeric excess was determined using chiral HPLC (Chiracel AD-H column, *n*-hexane/*i*PrOH 95: 5, flow rate 1.0 mL/min, λ 225 nm, t(*R*) 20.7 min, t(*S*) 33.3 min).

Acknowledgements

This work was financed by a statutory activity subsidy from the Polish Ministry of Science and Higher Education for the Faculty of Chemistry of Wrocław University of Science and Technology.

Supplementary Material

Table of ^{1}H and ^{13}C chemical shifts of the aliphatic parts of compounds **17** and **20a-e**.

References

1. Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213-7256 and references cited therein. http://dx.doi.org/10.1016/j.tet.2006.05.024
2. Zhang, S.; Wang, W. in *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L. Ed.; Viley-VCH, Weinheim 2011, pp. 409-445.
3. Skarżewski, J.; Gupta, A.; Wojaczyńska, E.; Siedlecka, R. *Synlett* **2003**, 1615-1618. http://dx.doi.org/10.1055/s-2003-41015
4. Siedlecka, R.; Wojaczyńska, E.; Skarżewski, J. *Tetrahedron: Asymmetry* **2004**, *15*, 1437-1444. http://dx.doi.org/10.1016/j.tetasy.2004.03.015
5. Hata, T.; Sekine, M. *Chem. Lett.* **1974**, 837-838. http://dx.doi.org/10.1246/cl.1974.837
6. Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2944. http://dx.doi.org/10.1021/cr020027w
7. Wojaczyńska, E.; Skarżewski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 593-597. http://dx.doi.org/10.1016/j.tetasy.2008.02.001
8. Wojaczyńska, E.; Wojaczyński, J.; Kleniewska, K.; Dorsz, M.; Olszewski, T. K. *Org. Biomol. Chem.* **2015**, 13, 6116-6148 and references cited therein. http://dx.doi.org/10.1039/C5OB00173K
9. Okuyama, Y.; Nakano, H.; Hongo, H. *Tetrahedron: Asymmetry* **2000**, *11*, 1193–1198. http://dx.doi.org/10.1016/S0957-4166(00)00049-5
10. Wojaczyńska, E.; Skarżewski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 2252-2257. http://dx.doi.org/10.1016/j.tetasy.2008.09.025
11. Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc*. **1998**, *120*, 10760-10761. http://dx.doi.org/10.1021/ja982381a
12. Brandt, P.; Hedberg, C.; Lawonn, K.; Pinho, P.; Andersson, P. G. *Chem. Eur. J.* **1999**, *5*, 1692-1699. http://dx.doi.org/10.1002/(SICI)1521-3765(19990604)5:6<1692::AID-CHEM1692>3.0.CO;2-M
13. Olszewski, T. K.; Wojaczyńska, E.; Wieczorek, R.; Bąkowicz, J. *Tetrahedron: Asymmetry* **2015**, *26*, 601-607. http://dx.doi.org/10.1016/j.tetasy.2015.04.012

14. Kamińska, K.; Wojaczyńska, E.; Wietrzyk, J.; Turlej, E.; Błażejczyk, A. *Tetrahedron: Asymmetry* **2016**, *27*, 753-758.
http://dx.doi.org/10.1016/j.tetasy.2016.06.009