Tetrahedron: *Asymmetry* 19 (2008) 2252–2257

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Chelating 2-azanorbornyl derivatives as effective nitrogen–nitrogen and nitrogen–chalcogen donating ligands in palladium-catalyzed asymmetric allylic alkylation

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ARTICLE INFO

Article history:
Received 1 August 2008
Accepted 24 September 2008
Available online 22 October 2008

ABSTRACT

New chiral 2-azanorbornane derivatives were prepared and used as (N,S)-, (N,Se)-, and (N,N)-donating ligands in a palladium-catalyzed asymmetric allylic alkylation, giving up to 95% ee and 92% yield.

1. Introduction

Over the last few decades, much interest has been focused on chiral ligands, crucial for the catalytic synthesis of enantiomeric products.[1] Some ligands, successful in various, mechanistically different, enantioselective reactions were ascribed to the *privileged ligands* class.[2] Despite the achievements in this field, there still remains much interest in finding new structures and broadening the use of those already known. An important feature of the practically useful ligands is the availability of starting materials for their synthesis. Usually, these are derived from the chiral pool, and thus limited to one enantiomer. However, an increasing number of ligands have recently been prepared using chiral auxiliaries, often available as both enantiomers.

The highly stereoselective aza-Diels–Alder reaction occurs between cyclopentadiene and the Schiff bases formed by optically active 1-phenylethylamine used as an auxiliary. The reaction serves as an effective method for the preparation of bicyclic chiral compounds containing nitrogen donor.[3] The synthesis of 2-azanorbornyl derivative **1** (Fig. 1) and the diverse possibilities of its modification were extensively explored by Andersson et al.[4] Due to their rigidity and steric effects, these ligands were successful in transfer hydrogenation reaction,[4f,h,5] borane reduction of ketones,[6] asymmetric addition of dialkylzinc to imines,[7] allylic oxidation of olefins,[8] and cyclopropanations.[9] Most of these ligands contain nitrogen and oxygen as donor atoms. Among others, (N,N)-coordinating diamine derivatives were used in epoxide rearrangements.[10] Rare examples of (N,S)-ligands were represented by thiazolyl-substituted compounds,[4c] alkyl sulfide derivatives tested in the transfer hydrogenation of acetophenone,[4h] and 2-azanorbornylmethanethiol, which catalyzed the enantioselective addition of diethylzinc to aldehydes.[11]

A variety of chiral ligands containing chalcogen (S,Se)-donors have already been studied in asymmetric catalytic reactions,[12] some of which are very effective.

The successful chelating ligand should accommodate a catalytically active metal in a well-defined coordinating surrounding. One of the strategies applied for the design of new chiral ligand takes advantage of the stereoelectronic differentiation exerted by the application of heterodonating ligands. Thus, in the mechanistically well-understood Tsuji–Trost reaction,[13] in addition to the steric interactions, an attacking nucleophile approaches the Pd-complexed allylic system from the site opposite to the more π-accepting ligand center. Accordingly, in the case of bidentate N(sp^3) and

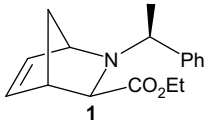

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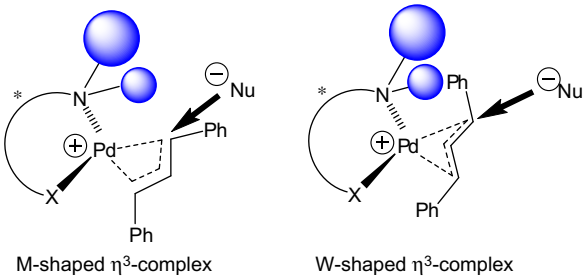
Figure 1.



M-shaped η^3-complex W-shaped η^3-complex

Figure 2.

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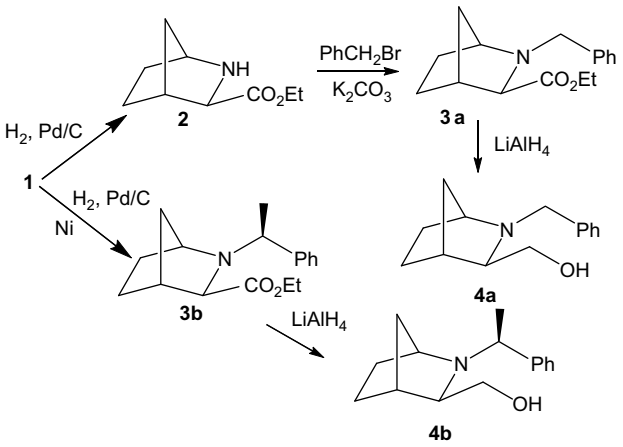
doi:10.1016/j.tetasy.2008.09.025

weakly π-accepting chalcogen atoms, the direction *trans* to chalcogen is generally preferred (Fig. 2).[13]

Within the aim of exploring the preparation and use of chiral organochalcogen compounds, we undertook the synthesis of new sulfur–nitrogen and selenium–nitrogen mixed donor chelate ligands, which were tested in the Tsuji–Trost catalytic reaction.[14] A facile one-step synthesis applicable for the preparation of **1** on a multigram scale[3a,4g] prompted us to use this compound as a readily available starting material for the construction of new chiral ligands. We believe that broadening the scope of reactions where the Andersson's 2-azanorbornyl system can be successfully used, brings this ligand closer to the privileged class.

2. Results and discussion

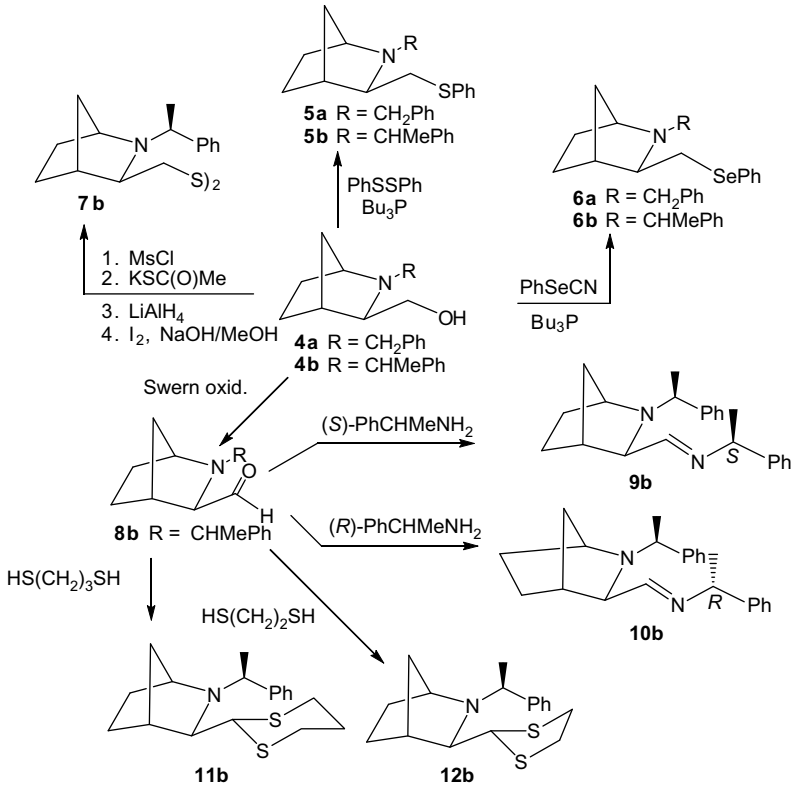
The Aza-Diels–Alder reaction of cyclopentadiene and an iminium ion derived from ethyl glyoxylate and (*S*)-1-phenylethylamine led to ester (1*S*,3*R*,4*R*)-**1**.[4g] The reduction of the double bond and amine deprotection was achieved using H_2 (7 atm) and a 5% Pd–C (20 wt %) catalyst, as described in literature leading to compound **2**.[7a] We observed, however, that when this reaction was conducted in the presence of trace amounts of nickel(II) salts, only the double bond was hydrogenated and the nitrogen atom remained protected, yielding **3b** as a single product in 90% yield. Amine **2** was benzylated to give derivative **3a**; both esters **3a** and **3b** were reduced with $LiAlH_4$ to give the appropriate alcohols **4a** and **4b** (Scheme 1). These compounds served as starting materials for the synthesis of a series of enantiomerically pure ligands containing (N,S)-, (N,Se)- and (N,N)-donors. In N-benzylated series **4a**–**6a**, three stereogenic centers are present in the (1*S*,3*R*,4*R*)-bicyclic fragment, while (*S*)-1-phenylethyl-substituted derivatives **4b**–**12b** have an additional stereogenic carbon atom which can serve as an additional source of asymmetric induction.



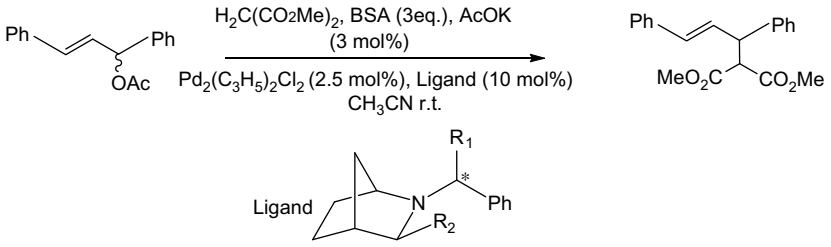
Scheme 1.

We introduced a phenylsulfenyl group into **4a** and **4b** using the Hata reaction.[14,15] Nucleophilic substitution of the hydroxyl group with diphenyldisulfide yielded the corresponding sulfides **5a** (79%) and **5b** (40%). Selenides **6a** and **6b** were prepared according to the Grieco protocol[16] reacting **4a** or **4b** with PhSeCN (yields 71% and 24%, respectively). The disulfide derivative **7b** was prepared from **4b** in a sequence of four reactions: mesylation, followed by reaction with potassium thioacetate, the subsequent reduction of the resulting thioester with $LiAlH_4$ to the corresponding thiol and oxidation with iodine.[11]

Swern oxidation of alcohol **4b** led to (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2,2,1]heptane-3-carbaldehyde **8b**.[7b,10a] Unfortunately, an analogous reaction of **4a** was completely ineffective.



Scheme 2.



Scheme 3.

Even with the use of Dess–Martin reagent the desired aldehyde **8a** could not be obtained.

Aldehyde **8b** was then converted into the Schiff base **9b** using reaction with (*S*)-1-phenylethylamine (yield 56%). The diastereomeric imine **10b** was also prepared when the amine was replaced with its (*R*)-enantiomer. Thus the Schiff bases obtained differed in configuration at one of five stereogenic centers. Dithioacetals **11b** and **12b** were obtained from aldehyde **8b** and ethanedithiol or 1,3-propanedithiol with 81% and 32% yield, respectively. All the performed reactions are shown in Scheme 2.

We tested these new chiral azanorbornane derivatives as ligands in the Pd-catalyzed allylic alkylation (Tsuji–Trost reaction).[13] The results obtained for the model reaction of dimethyl malonate with *rac*-1,3-diphenyl-2-propenyl acetate, using 3 mol % of *N*,*O*-bis(trimethylsilyl)acetamide-potassium acetate as a base, 2.5 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, and 10 mol % chiral ligand in acetonitrile solution (Scheme 3) are shown in Table 1.

As can be seen from Table 1, the product with an (*S*)-configuration was predominant in the reaction mixture. This stereochemical preference can be attributed to the general structure of the bicyclic ligand used. Examination of a simple molecular model often allowed us to predict the configuration of the Tsuji–Trost reaction product. When we took into consideration the key palladium π-allyl complex formed on the *exo* side of bicyclic system, the substrate could be potentially coordinated in either an 'M' or 'W' configuration (Fig. 2). However, one of these possibilities (M-shaped complexes) would bring a pronounced sterical hindrance. Thus, the W-shaped complex should be preferred. Combined with the *trans*-effect, which directs the nucleophile to the position opposite to the X donor, it should lead mainly to the product with an (*S*)-configuration.

Table 1
Pd-Catalyzed alkylation of dimethyl malonate with 1,3-diphenyl-2-propenyl acetate in the presence of N, N-, N, S-, and N, Se-donating ligands

Ligand L*	R_1	R_2	Yield of product (%)	Ee (%)
5a	H	CH_2SPh	95	48 (*S*)
6a	H	CH_2SePh	90	62 (*S*)
5b	Me	CH_2SPh	62	65 (*S*)
6b	Me	CH_2SePh	55	76 (*S*)
9b	Me	(*S*)-C=NCH(Me)Ph	95	90 (*S*)
10b	Me	(*R*)-C=NCH(Me)Ph	86	50 (*S*)
11b	Me	2-Dithiane	94	95 (*S*)
12b	Me	2-Dithiolate	90	48 (*S*)

The observed differences in yield and enantioselectivity between the ligands can be attributed at the first glance to the different natures of donor atoms X. The results obtained for sulfides **5** and selenides **6** show that the selenium derivatives gave slightly lower yields from their sulfur analogues, but higher stereoselectivities were observed for ligands **6**. These observations can be accounted for by the stronger π-accepting properties of the Se donors, as compared to the sulfur atom, which may increase the enantioselectivity due to a more pronounced *trans*-effect. On the other hand, the palladium-Se complex can be less stable, which would decrease the reaction yield.

Compounds **5a** and **6a** can be also confronted with their methylated derivatives **5b** and **6b**. Substitution with methyl group substantially lowers the yield of the catalytic reaction, although with a significant increase in enantioselectivity. As ligands **5a**/**6a** and **5b**/**6b** have identical donor atoms, the difference in their catalytic performance should be due to the increased steric hindrance around the coordinating nitrogen center for the methyl substituted derivatives **5b** and **6b**. An additional stereogenic center present in these ligands provides an additional reason for chiral discrimination.

Disulfide **8b,** the only ligand with a C_2 symmetry, was ineffective in the allylic substitution, thus no Pd-complex was formed.

A remarkable difference is seen in the results obtained for the two Schiff base diastereomers, **9b** and **10b**. Changing the configuration of only one of the five stereogenic centers from (*S*) to (*R*) leads to lower yield and a dramatic decrease of enantioselectivity. The two diastereomers create different chiral environments at the palladium center, which exerts different steric hindrances in the active complex.

A comparison of the stereochemical outcomes observed for dithioacetals **11b** and **12b** shows that much better results were obtained for a six-membered ring derivative. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-(2-dithiane)-2-azabicyclo[2,2,1]heptane **11b** proved to be the best out of all the ligands tested, giving 94% of the (*S*)-product with 95% ee. Tentatively, these results can be connected with an increased strain in the five-membered ring of **12b** which affects the σ-donor/π-acceptor properties of the sulfur center and the possibility of **11b** to adopt a proper conformation during the coordination to palladium.

3. Conclusions

The results obtained for a series of new chiral 2-azanorbornane derivatives show that they can be used as efficient ligands in the Tsuji–Trost reaction. Therefore, this work broadens the field of possible applications of the 2,3-disubstituted 2-azabicyclo[2.2.1]heptanes and serves as an additional proof of the versatility of these compounds-potential members of the *privileged ligands* class.[2]

4. Experimental

4.1. General

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. 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) spectrometer using TMS 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 instrument utilizing electrospray ionization mode. Separations of products by

chromatography were performed on Silica Gel 60 (230–400 mesh) purchased from Fluka. Thin layer chromatography analyses were performed using silica gel 60 precoated plates (Merck).

4.2. Synthesis of (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylic acid ethyl ester 1

This compound was prepared according to the literature procedure via the aza-Diels–Alder reaction of cyclopentadiene with an iminium ion derived from ethyl glyoxylate and (*S*)-1-phenylethylamine.[4g]

4.3. Reduction of Diels–Alder product 1

Ester **1** was hydrogenated in an ethanolic solution using H_2 (7 atm) and 5% Pd–C (20 wt %) catalyst as described in the literature[7a] to give (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid ethyl ester **2**. (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane-3-carboxylic acid ethyl ester **3b** was obtained by reduction of **1** with H_2 (7 atm) and 5% Pd–C in the presence of traces of nickel(II) salt. The characteristics of **3b** was in agreement with the literature data.[7b]

4.4. Synthesis of (1*S*,3*R*,4*R*)-2-benzyl-2-azabicyclo[2.2.1]-heptane-3-carboxylic acid ethyl ester 3a

Benzylation of compound **2** was performed according to a literature procedure.[5a,7a]

4.5. Synthesis of (1*S*,3*R*,4*R*)-2-benzyl-3-hydroxymethyl-2-azabicyclo[2.2.1]heptane 4a and (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-3-hydroxymethyl-2-azabicyclo[2.2.1]heptane 4b

These compounds were obtained by reduction of the appropriate esters **3a** and **3b**, respectively, with $LiAlH_4$ according to the literature procedure.[5a,11]

4.6. Nucleophilic substitution of hydroxyl group in 4a and 4b

4.6.1. Preparation of sulfides

Tributylphosphine (8 mmol, 1.62 g, 1.97 mL) was added by syringe to a solution of alcohol **4a** or **4b** (2 mmol) and diphenyldisulfide (6 mmol, 1.31 g) in dry toluene (6 mL). The mixture was transferred to the ampoule, filled with argon and sealed. This reaction mixture was kept at the oil bath at 80 °C for three days. Diethyl ether (20 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 product **5a** or **5b** was purified by column chromatography using hexane–ethyl acetate (9:1 v/v) as eluent.

4.6.1.1. (1*S*,3*R*,4*R*)-2-Benzyl-3-phenylsulfanylmethyl-2-azabicyclo[2.2.1]heptane 5a. Yield 79%, $[\alpha]_D^{20} = -13.1$ (*c* 1.56, CH_2Cl_2), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.14–1.30 (m, 3H), 1.54–1.60 (m, 1H), 1.70–1.74 (m, 1H), 1.87–1.91 (m, 1H), 2.13–2.18 (m, 1H), 2.33–2.34 (m, 1H), 2.53–2.71 (m, 2H), 3.18 (s, 1H), 3.58 and 3.66 (AB_q, 2* 1H, *J* = 13.06 Hz), 7.08–7.29 (m, 10H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 21.3, 28.1, 34.5, 37.3, 40.2, 54.2, 59.4, 67.4, 124.4, 125.9, 127.2, 127.5, 127.8, 128.1, 135.9, 139.2 ppm. IR (film) 698, 737, 1085, 1155, 1321, 1438, 1480, 1583, 2869, 2957, 3062 cm^{-1}. HRMS (ESI): 310.1653 ([M+H]$^+$); for $(C_{20}H_{24}NS)^+$ M = 310.16296.

4.6.1.2. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-phenylsulfanylmethyl-2-azabicyclo[2.2.1]heptane 5b. Yield 40%, $[\alpha]_D^{20} = -5.1$ (*c* 1.47, CH_2Cl_2), ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.23–1.32 (m, 6H), 1.60–1.66 (m, 1H), 1.75–1.77 (m, 1H), 1.93–1.98 (m, 1H), 2.11–2.14 (m, 1H), 2.20–2.28 (m, 2H), 2.43–2.48 (m, 1H), 3.45 (q, 1H, *J* = 6.42 Hz), 3.64 (br s, 1H), 6.62–6.63 (m, 2H, ArH), 7.04–7.06 (m, 3H, ArH), 7.28–7.36 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 22.9, 23.8, 29.1, 35.3, 37.7, 40.7, 59.9, 61.6, 68.9, 125.4, 127.8, 128.4, 128.7, 128.7, 129.0, 132.4, 136.9 ppm. IR (film) 737, 761, 1163, 1304, 1452, 1480, 1583, 2870, 2969, 3059 cm^{-1}. HRMS (ESI): 324.1653 ([M+H]$^+$); for $(C_{21}H_{26}NS)^+$ M = 324.17862.

4.6.2. Preparation of selenides

At first, PhSeCN (0.15 mL, 1.2 mmol) was added by a syringe to a solution of alcohol **4a** or **4b** (1 mmol) in dry toluene (15 mL) under an argon atmosphere. The mixture was cooled to 0 °C in an ice bath, and tributylphosphine (0.74 mL, 3 mmol) was injected to the stirred solution. The mixture was kept at room temperature for 20 h. After evaporation of the solvent, chloroform (10 mL) was added to the reaction mixture, and then washed with 10% aqueous NaOH, water and brine. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and product **6a** or **6b** was purified by column chromatography with hexane-ethyl acetate (9:1 v/v) as eluent.

4.6.2.1. (1*S*,3*R*,4*R*)-2-Benzyl-3-phenylselenalylmethyl-2-azabicyclo[2.2.1]heptane 6a. Yield 71%, $[\alpha]_D^{20} = -32.5$ (*c* 0.80, CH_2Cl_2), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.21–1.40 (m, 2H), 1.70–1.84 (m, 3H), 2.17–2.21 (m, 1H), 2.45–2.48 (m, 1H), 2.57–2.64 (m, 1H), 2.74–2.79 (m, 1H), 3.10–3.15 (m, 2H), 3.35 and 3.49 (AB_q, 2* 1H, *J* = 13.59 Hz), 7.12–7.44 (m, 10H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 21.2, 28.8, 35.0, 39.1, 46.8, 50.8, 58.8, 59.2, 125.7, 126.0, 127.1, 127.7, 127.9, 130.9, 133.1, 138.3 ppm. ^{77}Se NMR: δ 380.3 ppm. IR (film) 465, 697, 735, 1023, 1071, 1154, 1437, 1453, 1477, 1579, 1867, 2954, 3062 cm^{-1}. HRMS (ESI): 358.1068 ([M+H]$^+$); for $(C_{20}H_{24}NSe)^+$ M = 358.10752.

4.6.2.2. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-phenylselenalylmethyl-2-azabicyclo[2.2.1]heptane 6b. Yield 24%, $[\alpha]_D^{20} = -80.3$ (*c* 0.66, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29–1.32 (d, 3H, *J* = 6.64 Hz), 1.34–1.43 (m, 3H), 1.54–1.58 (m, 1H), 1.70–1.78 (m, 2H), 2.19–2.24 (m, 1H), 2.49–2.54 (m, 1H), 2.67–2.72 (m, 1H), 3.08–3.11 (m, 1H), 3.37 (q, 1H, *J* = 6.65 Hz), 3.60 (t, 1H, *J* = 4.78 Hz) 7.15–7.61 (m, 10H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 21.6, 22.6, 30.1, 36.3, 40.3, 48.4, 50.1, 56.4, 62.4, 126.7, 127.1, 127.4, 128.3, 128.8, 131.6, 132.8, 134.4.ppm. ^{77}Se NMR: δ 382.7 ppm. IR (film) 692, 738, 1437, 1452, 1476, 1578, 2946, 3057 cm^{-1}. HRMS (ESI): 372.1195 ([M+H]$^+$); for $(C_{21}H_{26}NSe)^+$ M = 372.12316.

4.6.3. Synthesis of bis-3-{(1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane}-methyl disulfide 7b

This compound was prepared from alcohol **4b** according to the literature procedure.[11] Mesylation of **4b** followed by the reaction with potassium thioacetate and a subsequent reduction of resulting thioester with $LiAlH_4$ gave (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2,2,1]heptane-3-methanethiol, with the spectral characteristics in agreement with that given in the literature for its enantiomer.[11] Oxidation of this thiol with I_2 in methanolic NaOH solution (20% w/w) gave the appropriate disulfide **7b**.

4.6.4. Bis-3-{(1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane}methyl disulfide 7b

Yield 82%, $[\alpha]_D^{20} = -126.6$ (*c* 0.30, CH_2Cl_2), ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.19–1.34 (m, 5H), 1.61–1.69 (m, 2H), 2.02–2.06 (m, 1H), 2.34–2.40 (m, 1H), 2.47–2.50 (m, 1H), 2.61–2.66 (m, 1H), 3.25–3.32 (m, 1H), 3.44–3.49 (m, 1H), 7.09–7.25 (m, 5 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 21.5, 21.9, 27.0, 35.0, 38.6, 48.5, 53.8, 55.9, 62.3, 126.7, 127.3, 128.3, 145.4 ppm. IR (film) 545, 701, 768,

1135, 1284, 1453, 1491, 2860, 2930, 3024, 3060 cm^{-1}. HRMS (ESI): 493.2712 ($[M+H]^+$); for $(C_{30}H_{41}N_2S_2)^+$ M = 493.27112.

4.7. Oxidation of alcohol 4b and further modifications

Oxidation of **4b** under Swern conditions led to (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane-3-carbaldehyde **8b** as described in the literature.[7b,10a]

4.7.1. Preparation of Schiff base

Aldehyde **8b** (0.10 g, 0.43 mmol) and (*S*)-1-phenylethylamine (0.054 mL, 0.43 mmol) were dissolved in 5 mL of ethanol, and the mixture was left over $MgSO_4$ for 24 h. The solvent was evaporated and the residue was chromatographed on neutral alumina column (hexane–ethyl acetate (5:1 v/v). Compound **10b** was obtained in a similar manner using (*R*)-1-phenylethylamine instead of its enantiomer.

4.7.1.1. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-[(*S*)-1-phenylethylimine]methyl-2-azabicyclo[2.2.1]heptane 9b. Yield 56%, $[\alpha]_D^{20} = -2.5$ (*c* 1.58, CH_2Cl_2), ^1H NMR ($CDCl_3$, 300 MHz): δ 1.20–1.41 (m, 8H), 1.48 (d, 1H, *J* = 6.55 Hz), 1.54–1.59 (m, 2H), 1.71–1.75 (m, 1H), 1.91–1.96 (m, 1H), 2.24–2.27 (m, 1H), 2.62 (d, 1H, *J* = 5.38 Hz), 3.46 (q, 1H, *J* = 6.48 Hz), 3.65 (br s, 1H), 3.80 (q, 1H, *J* = 6.68 Hz), 6.81–7.40 (m, 10H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 21.5, 21.8, 22.7, 28.2, 35.0, 43.1, 57.7, 59.9, 67.4, 70.5, 125.4, 125.7, 126.1, 126.8, 127.0, 127.0, 143.2, 144.1, 166.8 ppm. IR (film) 699, 759, 1370, 1451, 1662, 1687, 2869, 2966, 3027, 3062 cm^{-1}. HRMS (ESI): 333.2293 ($[M+H]^+$); for $(C_{23}H_{29}N_2)^+$ M = 333.2306.

4.7.1.2. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-[(*R*)-1-phenylethylimine]methyl-2-azabicyclo[2.2.1]heptane 10b. Yield 39%, $[\alpha]_D^{20} = +52.9$ (*c* 0.44, CH_2Cl_2), ^1H NMR ($CDCl_3$, 300 MHz): δ 1.16–1.36 (m, 9H), 1.51–1.54 (m, 2H), 1.63–1.66 (m, 1H), 1.92–1.97 (m, 1H), 2.14–2.18 (m, 1H), 2.63 (d, 1H, *J* = 5.64 Hz), 3.49 (q, 1H, *J* = 6.50 Hz), 3.64 (br s, 1H), 3.74 (q, 1H, *J* = 6.62 Hz), 7.02–7.30 (m, 10H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 21.5, 21.8, 22.9, 28.4, 35.1, 43.3, 57.6, 59.9, 67.5, 70.7, 125.3, 125.5, 126.1, 127.2, 127.3, 127.6, 144.2, 144.6, 167.2 ppm. IR (film) 701, 763, 1383, 1451, 1661, 1687, 2869, 2968, 3029, 3061 cm^{-1}. HRMS (ESI): 333.2286 ($[M+H]^+$); for $(C_{23}H_{29}N_2)^+$ M = 333.2306.

4.7.2. Preparation of dithioacetals

To a stirred solution of aldehyde 8**b** (80 mg, 0.35 mmol) and ethanedithiol or 1,3-propanedithiol (0.035 mL, 0.35 mmol) in 5 mL of chloroform 0.1 mL of BF_3·Et2O was added by syringe. A solution was kept over anhydrous sodium sulfate for 24 h. After filtration, the reaction mixture was subsequently washed with water, aqueous NaOH (5%), water and saturated aqueous NaCl and dried with Na_2SO_4. After removal of solvent, the residue was chromatographed on silica column. Elution with chloroform yielded dithioacetal **11b** or **12b**.

4.7.2.1. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-(2-dithiane)-2-azabicyclo[2.2.1]heptane 11b. Yield 81%, $[\alpha]_D^{20} = +18.4$ (*c* 0.68, CH_2Cl_2), ^1H NMR ($CDCl_3$, 300 MHz): δ 1.05–1.07 (m, 1H), 1.15–1.28 (m, 5H), 1.48–1.53 (m, 2H), 1.75–1.81 (m, 2H), 1.88–1.91 (m, 1H), 2.07–2.14 (m, 3H), 2.29–2.30 (m, 1H), 2.40–2.47 (m, 2H), 2.56–2.60 (m, 1H), 3.39 (q, 1H, *J* = 6.54 Hz), 3.59 (br s, 1H), 7.17–7.21 (m, 3H, ArH), 7.33–7.36 (m, 2H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 21.9, 22.6, 26.8, 30.4, 31.5, 31.8, 36.5, 39.9, 54.7, 58.2, 61.4, 72.9, 127.2, 128.0, 128.4, 146.4 ppm. IR (film) 700, 769, 1163, 1299, 1452, 2826, 2870, 2895, 2969, 3025 cm^{-1}. HRMS (ESI): 320.1553 ($[M+H]^+$); for $(C_{18}H_{26}NS_2)^+$ M = 320.15067.

4.7.2.2. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-(2-dithiolate)-2-azabicyclo[2.2.1]heptane 12b. Yield 32%, $[\alpha]_D^{20} = +3.4$ (*c* 0.74, CH_2Cl_2), ^1H NMR ($CDCl_3$, 300 MHz): δ 1.09–1.13 (m, 1H), 1.18–1.35 (m, 4H), 1.50–1.55 (m, 2H), 1.75–1.85 (m, 1H), 2.20–2.26 (m, 2H), 2.36–2.38 (m, 1H), 2.82–2.90 (m, 2H), 2.95–3.02 (m, 2H), 3.37–3.38 (d, 1H, *J* = 3.32 Hz), 3.42 (q, 1H, *J* = 6.56 Hz), 3.58 (br s, 1H), 7.17–7.32 (m, 5 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 21.7, 21.9, 29.3, 35.7, 37.2, 38.5, 56.3, 58.1, 60.4, 72.1, 126.9, 127.3, 127.5, 145.3 ppm. IR (film) 701, 768, 1106, 1163, 1304, 1453, 1492, 1674, 1720, 2869, 2922, 2971, 3026, 3061 cm^{-1}. HRMS (ESI): 306.1309 ($[M+H]^+$); for $(C_{17}H_{24}NS_2)^+$ M = 306.13501.

4.8. Catalytic reactions

The Pd-catalyzed allylic substitution reaction of dimethyl malonate with *rac*-1,3-diphenyl-2-propenyl acetate was performed using 3 mol % of *N*,*O*-bis(trimethylsilyl)acetamide-potassium acetate as a base, 2.5 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, and 10 mol % of the chiral ligand tested in acetonitrile solution. The stereochemical effect of the catalytic reaction was determined by ^1H NMR measurement using $Eu(hfc)_3$ as a chiral shift reagent. The assignment of absolute configuration was based on the specific rotation according to the literature data.[14]

Acknowledgment

We are grateful to the Ministry of Science and Higher Education for financial support (Grant PBZ-KBN-126/T09/2004).

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