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Chiral pyrrolidine thioethers: effective nitrogen–sulfur donating ligands in palladium-catalyzed asymmetric allylic alkylations

Renata Siedlecka, Elżbieta Wojaczyńska and Jacek Skarżewski*

Institute of Organic Chemistry, Biochemistry and Biotechnology, Wrocław University of Technology, 50-370 Wrocław, Poland

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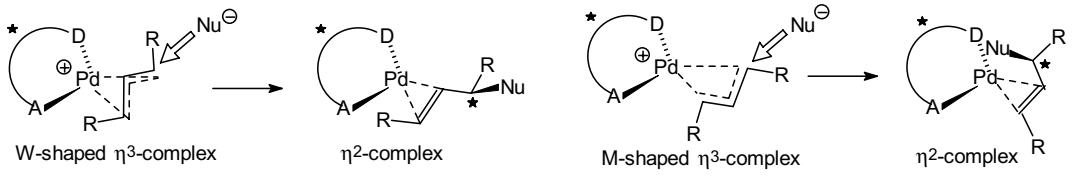
Abstract—Enantiomeric cyclic, five-membered alcohols and *vic*-diols were converted into the corresponding mono- and bis(arylsulfanyl) derivatives with complete inversion of configuration at one or both stereogenic centers. The thus obtained chiral thioethers were tested in the Pd-catalyzed allylic alkylation of dimethyl malonate with *rac*-1,3-diphenyl-2-propenyl acetate. The purely S,S-donating C_2-symmetric chiral ligands showed poor to moderate enantioselectivity (up to 42%), while 1-alkyl-3,4-bis(arylthio)pyrrolidines afforded much higher results, 81–89% ee. When chiral pyrrolidine mono-thioethers were applied the observed enantioselectivity improved further to 86–90% ee. These results suggest that the pyrrolidine thioethers served as the N(sp^3),S-donating chiral ligands. Examination of molecular models showed that the sense of stereoinduction, namely (*R*)-product from with (3*R*)-1-benzyl-3-(arylthio)pyrrolidine is in agreement with the nucleophilic attack being directed at the allylic carbon located *trans* to the sulfur atom in the intermediate η^3-allylpalladium complex.

1. Introduction

Asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic chemistry.[1] Within this field palladium-catalyzed allylic nucleophilic substitution is one of the most important tools for the enantioselective formation of carbon–carbon and carbon–heteroatom bonds.[2] The reaction mechanism is well understood and the process has already found numerous applications in the synthesis of natural products.[3] The reaction enantioselectivity is determined by the steric and stereoelectronic properties of the chiral ligand coordinated to the palladium atom. The ligand must provide an effective chiral environment at the reacting face of the π-allyl unit, the face opposite to the metal. Because of this highly demanding requirement, the reaction remains a useful platform for testing new ligands for transition-metal catalyzed processes.

In the rational design of chiral ligands two general concepts have led to the most effective structures.[4] The first one relies on the reduction of the number of possible diastereomeric transition states, which are attained using homodonating ligands with C_2-symmetry.[5] In this case, stereodifferentiation comes from purely steric interactions that raise the energy of some structures, while at the same time making the others prevalent. This idea was exploited fruitfully in the title reaction by the use of P,P- and N,N-donating ligands.[6] The second strategy takes advantage of the stereoelectronic differentiation exerted by the application of heterodonating



Scheme 1.

* Corresponding author. Fax: +71-328-4064; e-mail: jacek.skarzewski@pwr.wroc.pl

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ligands. Thus, due to the *trans*-effect,[7] an attacking nucleophile should approach the allylic system from the site opposite to the more π-accepting ligand center. (Scheme 1).

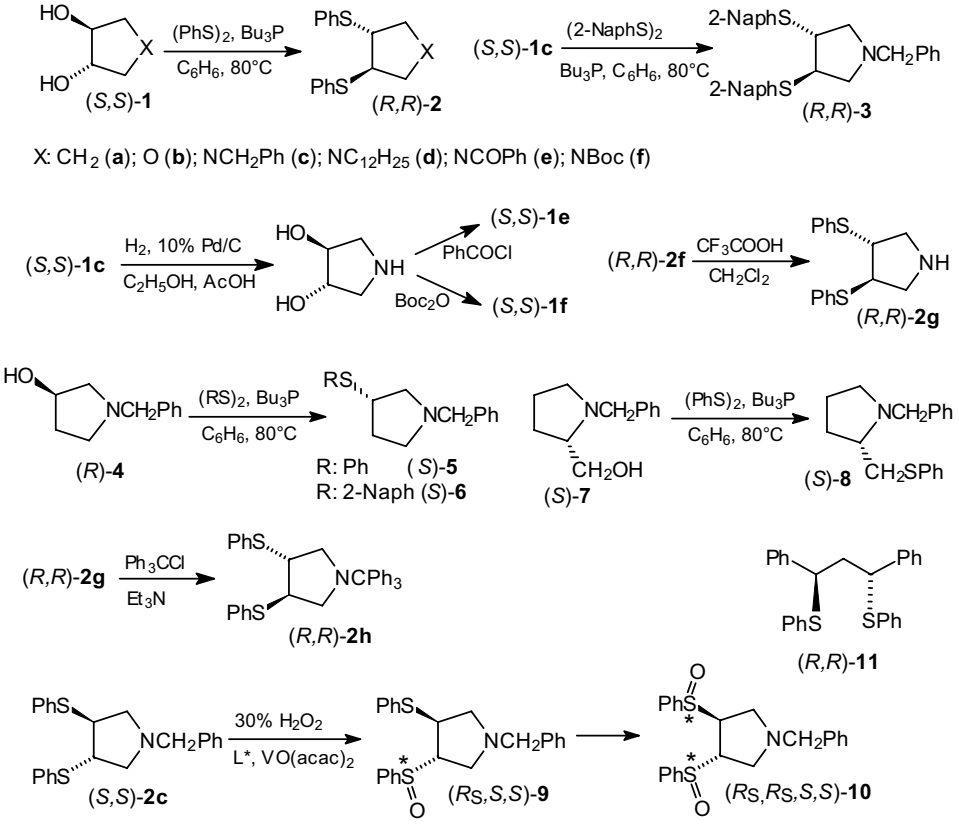
Accordingly P,N-, P,S-, and N,S-bidentate ligands have been applied successfully in the Pd-catalyzed allylic substitutions and their electronic effects were considered as the main cause of enantioselectivity.[8] Nonetheless, even for these ligands the stereochemical outcome of the reaction was often influenced by purely steric effects. Recently various C_2-symmetric chiral S,S-donating ligands were derived from tartaric acid and examined in the Pd-catalyzed allylic alkylation.[9] Dithioethers formed from 2,3-isopropylidenethreitol (the sulfur analogues of DIOP) showed low activities and poor enantioselectivities (up to 42%). However, it was discovered that (3*R*,4*R*)-1-benzyl-3,4-bis(phenylsulfanyl)pyrrolidine efficiently catalyzed the alkylation and, in spite of the formation of four diastereomeric complex species, gave 81% ee.[9] This unexpectedly high enantioselectivity was ascribed to the chiral backbone rigidity of the S,S-donating ligand.[9,10b] Since we have recently developed easy enantioselective syntheses of the corresponding dithioethers,[11] we could investigate a collection of similar ligands. Herein we present our results that provide an explanation of the sense of the enantioselectivity and the ligand complexation mode different from the current interpretation offered.[9,10b] We also report new highly selective chiral N,S-ligands, readily available in both enantiomeric forms.

2. Results and discussion

2.1. Ligands synthesis

Homochiral 1,2-bis(phenylsulfanyl)cyclopentane and its heterocyclic analogues **2a**–**f** and **3** were synthesized directly from the readily available enantiomeric diols **1** via double substitution occurring with the inversion of configuration at both stereogenic centers. To achieve this, the hydroxy groups were activated as the oxophosphonium salts generated from tributylphosphine oxidized with diphenyl disulfide. Under the reaction conditions these intermediates underwent S_N2 reactions with the generated thiophenolate anion, thus bringing about the desired conversion of diols into bis-thiophenyl ethers (the Hata reaction).[12] We applied the Hata reaction in a sealed tube according to our published protocol[13] and that simple procedure gave the required products in good to reasonable yields (Scheme 2).

The antipodes of **1** were also converted to the respective *ent*-**2** and *ent*-**3**. The complete stereospecificity of the reaction on homochiral substrates was confirmed by the absence (NMR, GC) of any *meso*-disubstituted product. Moreover, under Hata reaction conditions commercially available (*S*)- and (*R*)-1-benzyl-3-hydroxypyrrolidine **4** were easily converted into (*R*)- and (*S*)-1-benzyl-3-phenylsulfanylpyrrolidine **5**, respectively and also (*S*)-1-benzyl-2-pyrrolidinemethanol **7** was smoothly changed into the thioether **8**. As described in the literature hydrogenolysis of the *N*-benzyl group in **1c**[14] allowed



Scheme 2.

subsequent N-acylation to give the diols **1e** and **1f**, which, in turn, were submitted to the Hata reaction. A standard deprotection of the *N*-Boc function[15] in **2f** furnished (3*R*,4*R*)-3,4-bis(phenylsulfanyl)pyrrolidine **2g**. This compound was smoothly transformed into the corresponding *N*-trityl derivative **2h** using the recently developed procedure.[16] Finally, (*S*,*S*)-**2c** was oxidized with 30% H_2O_2 in the presence of catalytic L-*N*-(3-phenyl-5-nitrosalicylidene)valinol and $VO(acac)_2$.[17] The sulfoxidation gave the corresponding mono- (R_S,*S*,*S*)-**9** (45%, 80% de) and bis-sulfoxide (R_S,R_S,*S*,*S*)-**10** (40%, 64% de) isolated as the pure diastereomeric products. The absolute configuration of the introduced phenylsulfinyl group was ascribed according to the sign of the Cotton effects (CE) observed in their CD spectra. It is well established that for the (*R*)-configuration of this inherently chiral chromophore the primary UV band (235–255 nm, log ε ca. 3.6) demonstrates a positive CE of $\Delta\varepsilon$ ca. 20 and the shorter wavelength band (ca. 220 nm) shows a negative CE of similar strength.[18]

The CD spectra obtained for **9** and **10** fitted to this pattern strictly (Fig. 1) Moreover, the C_2-symmetric bis(sulfide) derivative (*R*,*R*)-**11** was available from our earlier work.[11]

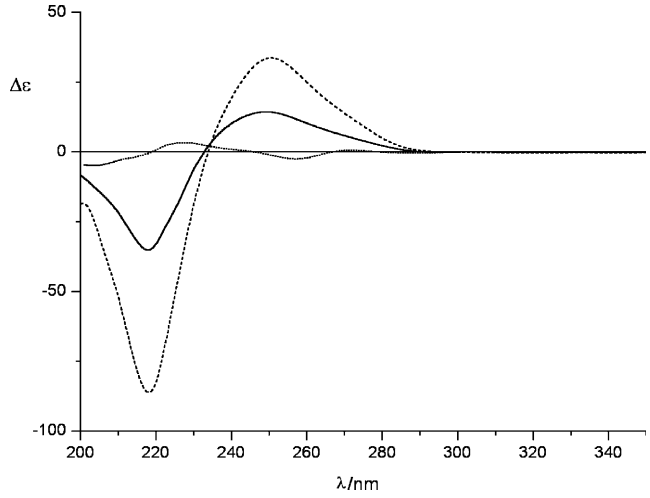


Figure 1. CD spectra of (*S*,*S*)-**2c** (···), (R_S,*S*,*S*)-**9** (—), and (R_S,R_S,*S*,*S*)-**10** (- - -) in acetonitrile solution in 10^{-4} M concentration range.

2.2. Asymmetric allylic alkylation

With the above mentioned set of chiral sulfides in hand we examined their effectiveness in the Pd-catalyzed allylic alkylation. As a model reaction we studied the alkylation of dimethyl malonate with *rac*-1,3-diphenyl-2-propenyl acetate, using *N*,*O*-bis(trimethylsilyl)acetamide (BSA)–potassium acetate (3 mol%) as the base, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) as the palladium pre-catalyst and the respective sulfide as the chiral ligand (10 mol%). The reaction was carried out in methylene dichloride at 25 °C for 3–10 days. In the absence of the ligand no product could be detected after the same time (Scheme 3).

Firstly, the ligands, which we consider being purely S,S-donating were tested and the results obtained are presented in Table 1. It can be clearly seen that these derivatives show relatively low to moderate activity and selectivity and the results are similar to those previously reported for the other C_2-symmetric bis-thioethers.[9,10b]

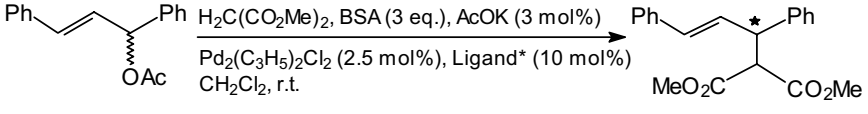
Table 1. Pd-catalyzed alkylation of dimethyl malonate with 1,3-diphenyl-2-propenyl acetate in the presence of C_2-symmetric S,S-donating ligands

Entry	Ligand	Reaction time (d)	Yield (%)	Ee (%)	Configuration of product
1	(*R*,*R*)-**2a**	3	68	42	(−)-(*S*)
2	(*R*,*R*)-**2b**	8	42	20	(−)-(*S*)
3	(*R*,*R*)-**2e**	3	71	15	(−)-(*S*)
4	(*R*,*R*)-**2f**	3	40	18	(−)-(*S*)
5	(*R*,*R*)-**11**	10	82	36	(+)-(*R*)

Then, we turned to 1-alkyl-3,4-bis(arylthio)pyrrolidines and the results are shown in Table 2. Generally, the enantioselectivities are much higher than the previous ones. Thus, for (*R*,*R*)-**2c**[9] the reported high yield and enantioselectivity were reproduced and its *N*-dodecyl **2d**

Table 2. Pd-catalyzed alkylation of dimethyl malonate with 1,3-diphenyl-2-propenyl acetate in the presence of C_2-symmetric 1-alkyl-3,4-bis(phenylthio)pyrrolidines

Entry	Ligand	Reaction time (d)	Yield (%)	Ee (%)	Configuration of product
1	(*R*,*R*)-**2c**	3	88	81[9]	(−)-(*S*)
2	(*S*,*S*)-**2c**	3	46	85	(+)-(*R*)
3	(*S*,*S*)-**2c**	8	77	86	(+)-(*R*)
4	40% Ee (*S*,*S*)-**2c**	3	47	30	(+)-(*R*)
5	40% Ee (*R*,*R*)-**2c**	3	58	33	(−)-(*S*)
6	(*R*,*R*)-**2d**	3	75	87	(−)-(*S*)
7	(*S*,*S*)-**2d**	3	64	89	(+)-(*R*)
8	(*R*,*R*)-**2g**	3	70	49	(−)-(*S*)
9	(*R*,*R*)-**2h**	8	61	39	(−)-(*S*)
10	(*R*,*R*)-**3**	3	82	82	(−)-(*S*)
11	(*S*,*S*)-**3**	3	81	90	(+)-(*R*)



Scheme 3.

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

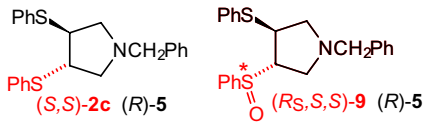
Entry	Ligand	Reaction time (d)	Yield (%)	Ee (%)	Configuration of product
1	(*S*)-**5**	3	75	90	(−)-(*S*)
2	(*R*)-**5**	3	73	90	(+)-(*R*)
3	(*R*)-**5**[a]	8	78	90	(+)-(*R*)
4	(*S*)-**6**	8	78	87	(−)-(*S*)
5	(*R*)-**6**	8	79	86	(+)-(*R*)
6	(R_S,*S*,*S*)-**9**	8	71	88	(+)-(*R*)
7	(R_S,R_S,*S*,*S*)-**10**	8	<5		
8	(*S*)-**8**	3	78	79	(+)-(*R*)

[a] Half of the usual catalyst amount was used.

and bis(2-naphthylsulfanyl) **3** analogues were found to perform even better. Two derivatives with a very large (Tr) and the smallest (H) substituent at the pyrrolidine nitrogen (**2g** and **2h**) were the only exceptions from this tendency. Moreover, the ligands of (*R*,*R*)-configuration gave the allylic alkylation product of (*S*)-configuration and their enantiomers afforded the (*R*)-product. Interestingly, the (*R*,*R*)-ligands seemed to be more active with only slightly less enantioselectivity than their enantiomers (cf. Table 2, entries: 1 vs 2, 6 vs 7, 10 vs 11). Nonetheless, no meaningful nonlinear effects were detected (entries 4 and 5) and the cause for the small differences observed remains obscure. Additionally, the substrate recovered after the reaction did not show any enantioenrichment.

Simple inspection of a molecular model for C_2-symmetric 1-benzyl-3,4-bis(phenylsulfanyl)pyrrolidine **2c** revealed that essentially this derivative can operate as both an S,S- and/or an S,N-donating ligand. The literature data did not prove its solely S,S-donating character,[9] so, in order to examine the second possibility we used the corresponding ligands having within their structure only one arylsulfanyl group. Thus, both enantiomers of 1-benzyl-3-(arylsulfanyl)pyrrolidine (**5** and **6**) were used in the same allylic alkylation and the respective results are presented in Table 3 (entries 1–5). We obtained higher activity and enantioselectivity than with the corresponding bis-thioethers. Even half of the normal catalyst/ligand loading did not decrease the ee value. Here, the (*S*)-ligand gave the alkylation product of (*S*)-configuration and the application of its enantiomer resulted in the formation of the (*R*)-product.

The stereochemical outcomes of the reaction with both types of ligands, mono- and bis-thioethers are in full agreement. Mono-thioether, for example, (*R*)-**5** can be regarded as a catalytically active part of the structure of bis-thioether (*S*,*S*)-**2c** and their absolute configuration descriptor change results from the CIP rules.



Since the phenylsulfinyl functionality can act as S- or O-donating group and the chiral C_2-symmetric S,S-bidentate complex of the bis-sulfoxide with palladium is known and moderately active in asymmetric allylic alkylation,[19] we also tested the catalytic performance of the respective bis-sulfoxide (R_S,R_S,*S*,*S*)-**10** and monosulfoxide (R_S,*S*,*S*)-**9**. The first derivative was almost completely inactive, while the second one gave the (*R*)-alkylation product in 88% ee. Remarkably the last result lies between 86% ee for (*S*,*S*)-**2c** and 90% ee for (*R*)-**5**. All these facts made us believe that the examined mono- and bis-thioethers of pyrrolidine operate mainly as the sp^3-nitrogen and sulfur-donating ligands. This conclusion can be additionally supported by the result obtained using the other mono-thioether of pyrrolidine **8** (Table 3, entry 8). Although the previous works on the N,S-heterodonating ligands in the Pd-catalyzed allylic alkylation concerned mainly those of N(sp^2), S-type, a recent precedent involved the use of chiral N(sp^3),S-donating ligands derived from ephedrine and pseudoephedrine.[20] The stereochemical outcome of that reaction was plausibly accounted for by both *trans* to sulfur and *trans* to nitrogen nucleophilic attack.[20b]

2.3. Stereochemical models

The generally accepted reaction mechanism[2] involves the formation of the intermediate Pd^+(chiral ligand)(η^3-*trans*-1,3-diphenylpropenyl). The symmetrical π-allyl system can be complexed in an M or W-configuration. Each of the complexes, after nucleophilic attack rearranges into two possible Pd^0(chiral ligand)(η^2-olefin) complexes leading to the enantiomeric substituted products (Scheme 1). If A denotes a π-accepting, σ-donating ligand center and D is only a σ-donating center, the nucleophilic attack can be expected to occur from the *trans* to A direction. On the other hand, the favorable site of this nucleophilic addition should be that which corresponds to the release of more steric strain when coming from η^3- to η^2-complex. Generally, thioether ligands are considered rather poor σ-donors and weakly π-accepting ligands and their *trans* influence within the coordination sphere is regarded to be higher than that of amines.[21] With all these features in mind, we examined the molecular models representing all the possible intermediates formed in the reaction catalyzed by (*S*,*S*)-**2c** and (*R*)-**5**. It seems that for the S,S-donating (*S*,*S*)-**2c** both M and W-η^3-complexes, for example (Fig. 2, **A**), are of similar energy and in both cases the nucleophilic attack at any of the prochiral centers releases only little and similar steric strain when coming to the corresponding η^2-complexes. Thus, this model barely explains the high enantioselectivity observed for **2c**. On the other hand, this reaction mode is perhaps operating for the purely S,S-donating ligands, which give poor to moderate enantioselectivities.

Contrary to this, for the N,S-donating (*S*,*S*)-**2c** the M-shaped allylic system is clearly favored (**B**) and the nucleophilic addition should preferentially occur *trans* to S leading to the *R*-configuration in the product. Similarly, for (*R*)-**5** the M-shaped η^3-allylic complex (**C**) seems to be privileged over its W-shaped isomer (**E**),

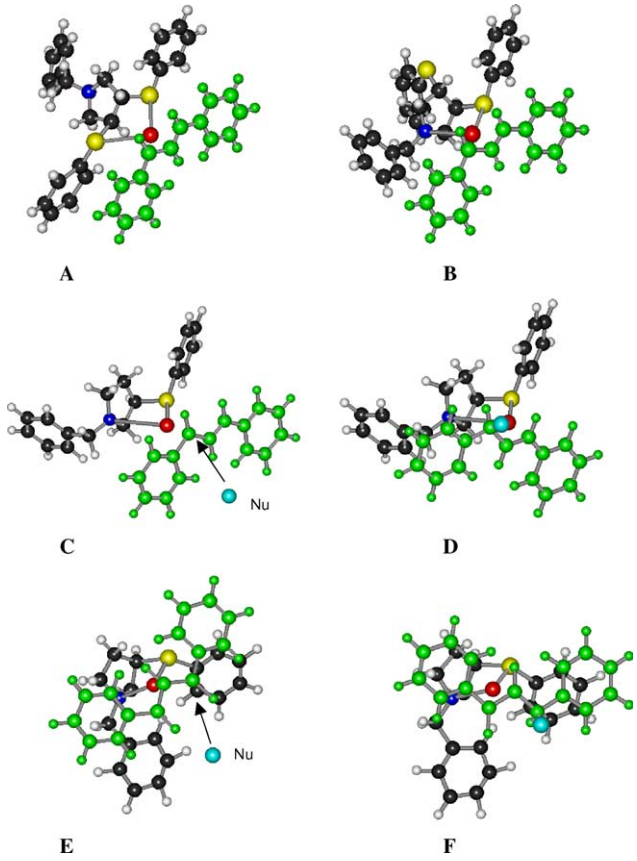


Figure 2. Selected molecular models of the intermediate complexes (see, the text).

which also differs in configuration at the sulfur atom. Moreover, again the nucleophilic attack on the M-isomer leading to the (*R*)-product releases the steric strains (**D**). The respective attack on the W-form produces the overcrowded η^2-complex (**F**) and this route can be excluded on this basis. Summarizingly, the attack preferentially takes place at the carbon located *trans* to the sulfur atom in the M-shaped complex (**B**, **C**), thus giving the (*R*)-enantiomer of product. This suggests that both factors, steric and stereoelectronic are responsible for the enantioselectivity. The role of the second effect can be additionally supported by the fact that replacement of phenylsulfanyl groups in **2c** by isopropylsulfanyl functions,[9] with the more σ-donor and less π-accepting character of the sulfur-donating center, resulted in a substantial decrease of enantioselectivity (from 81% to 30% ee).[9] Interestingly, it is an opposite effect to that observed for the chiral N(sp^3),S-donating ligands derived from ephedrine and pseudoephedrine. There the highest ee was observed for the *tert*-butylthioether (89% ee), and arylthioethers were much inferior (15% ee) and consequently both types of nucleophilic attack (*trans* to S and *trans* to N) were postulated.[20] Finally, it is noteworthy that the diminished enantioselectivity of **2c** versus **5** can be explained by the parallel participation of the S,S-along with the S,N-complexing species in the former case. This interpretation is in line with the observation of four different Pd^+(**2c**)(allyl) complexes in the respective ^{1}H NMR spectrum.[9]

3. Conclusions

In conclusion, chiral pyrrolidine arylthioethers are effective catalysts in the Pd-catalyzed asymmetric alkylation operating as the N(sp^3),S-donating chiral ligands. The models show that the sense of stereoinduction is in agreement with the nucleophilic attack directed at the allylic carbon located *trans* to the sulfur atom in the intermediate complex.

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. UV and CD spectra were recorded for CH_3CN solutions using a Hewlett-Packard 8452 diode array spectrophotometer and a JASCO J 600 spectropolarimeter, respectively. Observed rotations at 589 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. GC–MS analyses were determined on a Hewlett-Packard 5890 II gas chromatograph (25 m capillary column) with a Hewlett-Packard mass spectrometer 5971 A operating on the electron impact mode (70 eV). Separations of products by chromatography were performed on silica gel 60 (230–400 mesh) purchased from Merck. Thin layer chromatography analyses were performed using silica gel 60 precoated plates (Merck).

4.2. Ligand synthesis

4.2.1. General procedure for the preparation of mono- and bis(sulfides). A solution of diol (0.8 mmol), ArSSAr (4.8 mmol) and Bu_3P (1.59 mL, 6.4 mmol) in dry benzene (5 mL) was placed under argon in a reaction ampoule. For mono-alcohols amounts of the reagents were halved. The sealed tube was heated at 80 °C for 3 days. Thereafter the cooled mixture was diluted with ether (20 mL), washed with 2 M NaOH, brine, and dried over anhyd Na_2SO_4. After evaporation, the crude product was purified by chromatography on silica gel. Selected data for the obtained products **2a**–**d** were reported before.[11]

4.2.2. (+)-(3*R*,4*R*)-1-Benzoyl-3,4-bis(phenylsulfanyl)pyrrolidine 2e. Yield 67%. Mp = 131–133 °C. $[\alpha]_D^{20} = +84.2$ (*c* 0.76, CH_2Cl_2, >95% ee). ^{1}H NMR ($CDCl_3$): 3.45 (d, 1H, $J = 11.7$ Hz), 3.56 (d, 1H, $J = 4.5$ Hz), 3.67–3.77 (m, 2H), 4.12–4.15 (m, 1H), 4.29–4.33 (m, 1H), 7.14–7.23 (m, 10H, ArH), 7.37–7.43 (m, 3H, ArH), 7.49–7.51 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$): 49.7, 50.4, 51.5, 53.0, 127.6, 128.2, 128.3, 128.8, 129.7, 130.6, 132.6, 132.9, 136.7, 170.3; IR (KBr): 3047, 2948, 1625, 1427, 1250, 741, 690. Anal. Calcd for $C_{23}H_{21}NOS_2$ (M = 391.551):

C, 70.55; H, 5.41; N, 3.58; S, 16.38. Found: C, 70.78; H, 5.58; N, 3.36; S, 16.35.

4.2.3. (+)-(3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3,4-bis(phenylsulfanyl)pyrrolidine 2f. Yield 79%. Mp = 97–99 °C. $[\alpha]_D^{20} = +50.0$ (*c* 0.90, CH_2Cl_2, >95% ee). ^1H NMR ($CDCl_3$): 1.48 (s, 9H, $OC(CH_3)_3$), 3.41–3.52 (m, 2H), 3.58–3.60 (m, 2H), 3.92–4.02 (m, 2H), 7.17–7.35 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): 28.9, 49.9, 51.0, 80.3, 128.1, 129.6, 132.6, 133.8, 154.7; IR (KBr): 3067, 2977, 2876, 1698, 1402, 1154, 1117, 739, 690. $R_f = 0.44$ (*n*-hexane–ethyl acetate 90:10). Anal. Calcd for $C_{21}H_{25}NO_2S_2$ (M = 387.561): C, 65.08; H, 6.50; N, 3.61; S, 16.55. Found: C, 65.38; H, 6.33; N, 3.70; S 16.72.

The BOC protecting group was removed according to the literature procedure.[15]

4.2.4. (+)-(3*R*,4*R*)-3,4-Bis(phenylsulfanyl)pyrrolidine 2g. Yield 90%. $[\alpha]_D^{20} = +40.0$ (*c* 0.68, CH_2Cl_2, >95% ee). ^1H NMR ($CDCl_3$): 2.96 (dd, 2H, $J_1 = 12.7$ Hz, $J_2 = 3.2$ Hz), 3.49–3.52 (m, 2H), 3.56–3.58 (m, 2H), 3.69 (br s, 1H, NH), 7.22–7.27 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): 52.4, 52.5, 127.8, 129.6, 132.1, 134.4; IR (film): 3058, 2876, 1727, 1683, 1481, 1210, 1142, 741. GC–MS (EI, 70 eV): 274 (53% $(PhS)_2C_3H_4NH_2^+$), 161 (100%, $PhSNC_3H_2^+$), 109 (54%, PhS^+).

4.2.5. Preparation of *N*-tritylpyrrolidine. Triethylamine (100 mg, 1 mmol) was added in one portion to a solution of trityl chloride (95 mg, 0.34 mmol) and (+)-(3*R*,4*R*)-3,4-bis(phenylsulfanyl)pyrrolidine (90 mg, 0.31 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for about 20 h at room temperature and the reaction was monitored by TLC. Dichloromethane (10 mL) was then added and the solution was washed with water (10 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by chromatography on silica gel.

4.2.6. (+)-(3*R*,4*R*)-1-Trityl-3,4-bis-(phenylsulfanyl)pyrrolidine 2h. Yield 84%. Mp = 98–100 °C (CH_2Cl_2–hexane). $[\alpha]_D^{20} = +41.6$ (*c* 0.48, CH_2Cl_2, >95% ee). ^1H NMR ($CDCl_3$): 2.53 (dd, 2H, $J_1 = 10.4$ Hz, $J_2 = 3.9$ Hz), 2.93 (dd, 2H, $J_1 = 9.9$ Hz, $J_2 = 5.9$ Hz), 3.55–3.60 (m, 2H), 7.19–7.34 (m, 19H, ArH), 7.55–7.59 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$): 51.3, 52.4, 73.9, 126.3, 126.8, 127.5, 129.0, 129.3, 131.1, 135.6, 142.1; IR (KBr): 3446, 2929, 1728, 1583, 1481, 1438, 1023, 740. $R_f = 0.73$ (*n*-hexane–ethyl acetate 9:1).

4.2.7. (+)-(*R*)-1-Benzyl-3-phenylsulfanylpyrrolidine 5. Yield 84%. $[\alpha]_D^{20} = +21.1$ (*c* 1.04, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.74–1.78 (m, 1H, H4), 2.25–2.29 (m, 1H, H4), 2.39 (dd, 1H, $J_1 = 9.9$ Hz, $J_2 = 6.2$ Hz, H2), 2.51–2.56 (m, 1H, H5), 2.61–2.65 (m, 1H, H5), 3.01 (dd, 1H, $J_1 = 9.9$ Hz, $J_2 = 7.3$ Hz, H2), 3.53 and 3.60 (AB_q, 2H, $J = 12.9$ Hz, CH_2Ph), 3.67–3.73 (m, 1H, H3), 7.10–7.81 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): 32.8, 43.5, 53.6, 60.5, 61.2, 126.5, 127.4, 128.7, 129.2, 129.3, 130.1, 137.1, 139.2; IR (film): 3060, 3027, 2959, 2792, 1584, 1480, 1439, 1145, 738, 699. GC–MS (EI, 70 eV): 269 (2% M^+), 159 (47% $M^+ - PhSH$), 91 (100%, $PhCH_2^+$). $R_f = 0.27$ (*n*-hexane–ethyl acetate 9:1). Anal. Calcd for $C_{17}H_{19}NS$ (M = 269.322): C, 75.80; H, 7.11; N, 5.19; S, 11.88. Found: C, 75.50; H, 7.34; N, 4.82; S, 12.14.

4.2.8. (−)-(*S*)-1-Benzyl-3-phenylsulfanylpyrrolidine 5. Yield 90%. $[\alpha]_D^{20} = -20.0$ (*c* 1.26, CH_2Cl_2).

4.2.9. (+)-(*R*)-1-Benzyl-3-(2-naphthylsulfanyl)pyrrolidine 6. Yield 90%. Mp = 37–38 °C. $[\alpha]_D^{20} = +36.1$ (*c* 1.08, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.87–1.92 (m, 1H, H4), 2.38–2.42 (m, 1H, H4), 2.54 (dd, 1H, $J_1 = 9.8$ Hz, $J_2 = 6.2$ Hz, H2), 2.63–2.67 (m, 1H, H5), 2.67–2.74 (m, 1H, H5), 3.13 (dd, 1H, $J_1 = 9.5$ Hz, $J_2 = 7.7$ Hz, H2), 3.62 and 3.69 (AB_q, 2H, $J = 12.9$ Hz, CH_2Ph), 3.89–3.92 (m, 1H, H3), 7.17–7.78 (m, 12H, ArH); ^{13}C NMR ($CDCl_3$): 32.8, 43.4, 53.6, 60.5, 61.2, 126.1, 126.9, 127.5, 127.6, 127.9, 128.1, 128.2, 128.7, 128.8, 129.2, 132.2, 134.2, 134.7, 139.1; IR (film): 3054, 2959, 2792, 1625, 1589, 1500, 1453, 1133, 812, 743. $R_f = 0.35$ (*n*-hexane–ethyl acetate 3:1). Anal. Calcd for $C_{21}H_{21}NS$ (M = 319.378): C, 78.96; H, 6.62; N, 4.38; S, 10.01. Found: C, 78.70; H, 6.68; N, 4.22; S, 9.70.

4.2.10. (−)-(*S*)-1-Benzyl-3-(2-naphthylsulfanyl)pyrrolidine 6. Yield 90%. $[\alpha]_D^{20} = -34.9$ (*c* 1.06, CH_2Cl_2).

4.2.11. (+)-(3*R*,4*R*)-1-Benzyl-3,4-bis(2-naphthylsulfanyl)pyrrolidine 3. Yield 88%. Mp = 98–100 °C (CH_2Cl_2–hexane). $[\alpha]_D^{20} = +108$ (*c* 0.78, CH_2Cl_2, >95% ee). ^1H NMR ($CDCl_3$): 2.73 (dd, 2H, $J_1 = 10.3$ Hz, $J_2 = 3.9$ Hz), 3.21–3.31 (m, 2H), 3.65 and 3.79 (AB_q, 2H, $J = 13.7$ Hz), 3.79–3.83 (m, 2H), 6.98–7.74 (m, 19H, ArH); ^{13}C NMR ($CDCl_3$): 52.6, 59.7, 60.0, 126.4, 126.9, 127.5, 127.7, 128.0, 128.7, 128.8, 128.9, 129.1, 130.3, 132.5, 132.9, 134.0, 138.8; IR (KBr): 3050, 2961, 1727, 1271, 1130, 819, 740. $R_f = 0.45$ (*n*-hexane–ethyl acetate 9:1). Anal. Calcd for $C_{31}H_{27}NS_2$ (M = 477.685): C, 77.95; H, 5.70; S, 13.43. Found: C, 78.30; H, 5.71; S, 13.50.

4.2.12. (−)-(*S*)-1-Benzyl-2-(phenylsulfanylmethyl)pyrrolidine 8. Yield 81%. $[\alpha]_D^{20} = -67.5$ (*c* 1.20, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.66–1.68 (m, 1H, H_3), 1.71–1.77 (m, 2H, H_3, H_4), 1.99–2.02 (m, 1H, H_4), 2.15–2.23 (m, 1H, H_5), 2.75–2.76 (m, 1H, H_2), 2.89–2.94 (m, 2H, H_5, CH_2S), 3.14–3.17 (m, 1H, CH_2S) 3.33 and 3.99 (AB_q, 2H, $J_{AB} = 13.0$ Hz, CH_2Ph), 7.10–7.30 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): 23.0, 30.9, 39.0, 54.9, 59.3, 63.2, 126.0, 127.3, 128.6, 129.2, 129.3, 129.3, 137.7, 139.9; IR (film): 3060, 2964, 2791, 1584, 1480, 1026, 738, 698. GC–MS (EI, 70 eV): 283 (0.03%, M^+), 160 (86% $M^+ - PhSCH_3$), 91 (100%, $PhCH_2^+$). $R_f = 0.38$ (*n*-hexane–ethyl acetate 85:15). Anal. Calcd for $C_{18}H_{21}NS$

(M = 283.432): C, 76.28; H, 7.47; N, 4.94; S, 11.31. Found: C, 76.50; H, 7.33; N, 4.95; S, 11.53.

Diastereoselective sulfoxidation of (+)-(3*S*,4*S*)-1-benzyl-3,4-bis(phenylsulfanyl)pyrrolidine **2c** was performed according to the earlier described procedure.[17] The products were isolated by chromatography and purified by recrystallization from the *n*-hexane–dichloromethane mixture.

4.2.13. (+)-(3*S*,4*S*,R_S)-1-Benzyl-3-(phenylsulfinyl)-4-(phenylsulfanyl)pyrrolidine 9. Yield 40%. Mp = 106–107 °C (CH_2Cl_2–hexane). $[\alpha]_D^{20} = +34.6$ (*c* 0.52, CH_2Cl_2, >95% ee). ^{1}H NMR ($CDCl_3$): 2.64–2.71 (m, 2H), 3.04–3.24 (m, 3H), 3.60 and 3.70 (AB_q, 2H, $J = 13.1$ Hz), 3.76–3.82 (m, 1H), 7.23–7.32 (m, 10H, ArH), 7.44–7.48 (m, 3H, ArH), 7.52–7.56 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$): 45.8, 50.8, 59.2, 60.8, 69.1, 124.6, 127.2, 127.7, 128.4, 128.6, 129.2, 129.3, 131.4, 132.2, 133.9, 138.0, 142.2; IR (KBr): 3436, 2794, 1438, 1033, 748, 690; UV (CH_3CN): $\lambda \cong 210$ nm (sh), $\lambda = 250$ nm ($\varepsilon = 10{,}200$); $R_f = 0.56$ (*n*-hexane–ethyl acetate 1:1).

4.2.14. (+)-(3*S*,4*S*,R_S,R_S)-1-Benzyl-3,4-bis(phenylsulfinyl)pyrrolidine 10. Yield 40%. Mp = 156–158 °C (CH_2Cl_2–hexane). $[\alpha]_D^{20} = +56.0$ (*c* 0.36, CH_2Cl_2, >95% ee). ^{1}H NMR ($CDCl_3$): 2.59 (dd, 2H, $J_1 = 10.3$ Hz, $J_2 = 6.7$ Hz), 3.12 (dd, 2H, $J_1 = 10.4$ Hz, $J_2 = 4.7$ Hz), 3.35–3.41 (m, 2H), 3.69 (s, 2H, CH_2Ph), 7.21–7.31 (m, 5H, ArH), 7.45–7.54 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): 51.3, 58.9, 63.2, 124.7, 127.3, 128.4, 128.5, 129.5, 131.8, 137.8, 141.6; IR (KBr): 3434, 2797, 1493, 1442, 1085, 1036, 746; UV (CH_3CN): $\lambda \cong 210$ nm (sh), $\lambda = 254$ nm ($\varepsilon = 10{,}700$); $R_f = 0.22$ (*n*-hexane–ethyl acetate 1:1).

4.2.15. Preparation of 1-acyl-3,4-dihydroxypyrrolidines. 3,4-Dihydroxypyrrolidine acetate[14] (1.0 g, 6.1 mmol) and 4.6 g of anhydrous K_2CO_3 were placed into 7 mL of the chloroform–methanol mixture (1:1 v/v). Benzoyl chloride (0.85 mL, 7.3 mmol, 1.2 equiv) was added dropwise to the stirred, cooled solution. The resultant mixture was stirred overnight and then evaporated to dryness. The solid residue was extracted continuously with diethyl ether and after removal of solvent the crude product was recrystallized from ethyl acetate. 1-*tert*-Butoxycarbonyl-3,4-dihydroxypyrrolidine was obtained in an analogous manner using di(*tert*-butyl) dicarbonate instead of benzoyl chloride.

4.2.16. (−)-(3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3,4-dihydroxypyrrolidine 1f. Yield 79%. Mp = 163–164 °C. $[\alpha]_D^{20} = -19.1$ (*c* 1.02, CH_3OH, >95% ee). ^{1}H NMR ($CDCl_3$): 1.38 (s, 9H, $OC(CH_3)_3$), 1.80 (br s, 2H, OH), 3.24 (d, 1H, $J = 11.4$ Hz), 3.31 (d, 1H, 11.4 Hz), 3.50–3.58 (m, 2H), 4.25 (br s, 2H); ^{13}C NMR ($CDCl_3$–CD_3OD 2:1): 28.2, 51.2, 51.7, 74.3, 74.9, 79.9, 155.5; IR (KBr): 3407, 2917, 1621, 1471, 1077. $R_f = 0.44$ (*n*-hexane–ethyl acetate 90:10).

4.2.17. (−)-(3*S*,4*S*)-1-Benzoyl-3,4-dihydroxypyrrolidine 1e. Yield 86%. Mp = 131–133 °C. $[\alpha]_D^{20} = -86.0$ (*c* 0.78, CH_3OH, >95% ee). ^{1}H NMR ($CDCl_3$): 2.15 (br s, 1H, OH), 2.29 (br s, 1H, OH), 3.32 (d, 1H, $J = 11.7$ Hz), 3.58 (d, 1H, $J = 13.6$ Hz), 3.74–3.76 (m, 1H), 3.88–3.91 (m, 1H), 4.10 (s, 1H), 4.20 (s, 1H), 7.29–7.48 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$–CD_3OD 2:1): 52.2, 54.9, 73.8, 75.0, 127.1, 128.5, 130.4, 136.2, 171.3; IR (KBr): 3395, 2921, 1611, 1564, 1454, 1077, 988, 695.

4.3. Catalytic reaction procedure

A solution of the allylpalladium chloride dimer (4 mg, 0.01 mmol) and ligand (0.04 mmol) in dry dichloromethane (1.0 mL) was stirred under argon atmosphere at room temperature for 15 min before a solution of *rac*-1,3-diphenyl-2-propenyl acetate (100 mg, 0.4 mmol) in dichloromethane (1.5 mL) was added. The resulting yellow solution was treated successively with dimethyl malonate (0.137 mL, 1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (0.296 mL, 1.2 mmol) and anhydrous potassium acetate (1.2 mg, 0.012 mmol). The reaction was carried out at room temperature for 3–10 days (monitored by TLC). The reaction mixture was diluted with ether (10 mL) and quenched with the satd NH_4Cl solution. The separated organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The product was purified by column chromatography (hexane–ethyl acetate 3:1). The enantiomeric excess was determined by ^{1}H NMR using Eu(hfc)$_3$ (0.5 equiv) as a chiral shift reagent. Under these conditions the chemical shift difference observed for one of the diastereotopic ester methyl groups was ca. 11 Hz [downfield for the dextrorotatory (*R*)-enantiomer]. The assignment of absolute configuration was based on the specific rotation according to the literature data.[22]

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