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Facile synthesis of C_2-symmetric tridentate bis(thiazoline) and bis(oxazoline) ligands and their application in the enantioselective Henry reaction

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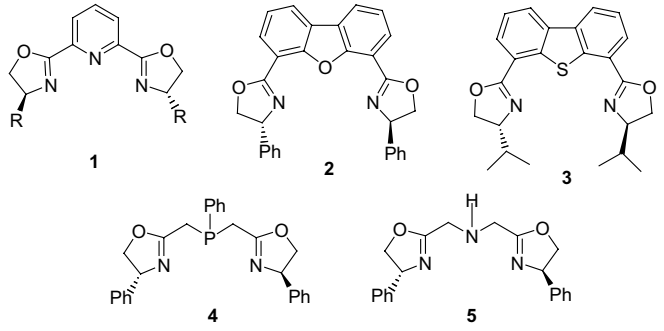
Abstract—A series of novel C_2-symmetric bis(thiazoline) ligands with a diphenylamine backbone as a linkage between two thiazoline rings were synthesized by the use of the simple reagent phosphorus pentasulfide. Their application in the catalytic asymmetric Henry reaction of α-keto esters was investigated with comparison to the corresponding bis(oxazoline) ligands. Cu(II)–bis(oxazoline) complexes furnished moderate enantioselectivities (up to 60% ee), while Cu(II)–bis(thiazoline) complexes gave higher enantioselectivities (up to 70% ee) with neat nitromethane. The enantioselectivity was improved when a halogenated solvent, such as CH_2Cl_2 was used (up to 82% ee), but the yield obtained lower than that in neat reactions.

1. Introduction

In recent years, the C_2-symmetric chiral bis(oxazoline) ligands have proven to be powerful in various catalytic processes, while ligand design is becoming an increasingly important area of synthetic organic chemistry.[1] Among them, tridentate bis(oxazolinyl)-type ligands, supposed to form a deeper chiral concave pocket around the metal centre, have been reported and applied in several asymmetric catalytic reactions. For example, Pybox ligand **1** (Scheme 1) was designed by Nishiyama and used in asymmetric hydrosilylation[2] and cyclopropanation reactions.[3] DBF-Box **2**, DBT-Box **3** and carbazole-Box proved successful in some asymmetric reactions.[4] While these ligands allow only a meridional (*mer*) coordination mode, ligands **4**[5a] and **5**[5b] may allow both *mer* and facial (*fac*) coordination modes. However, tridentate bis(thiazoline) ligands for asymmetric catalytic reactions have seldom been reported.[6] With the replacement of oxygen with sulfur in the oxazoline rings, the different electronic and steric effects may change the chelating behaviour of the heterocycle of bis(thiazoline)



Scheme 1.

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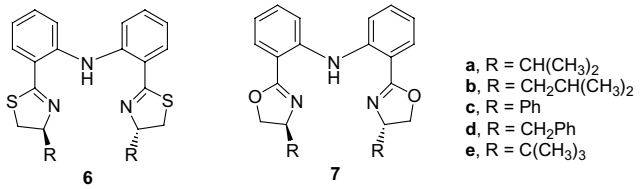


Scheme 2.

towards metals compared with the corresponding bis(oxazoline).

The Henry or nitroaldol reaction is a powerful methodology of carbon–carbon bond formation in organic synthesis and the resulting β-nitro alkanol can go through a range of chemical transformation.[7] Since 1992, asymmetric catalytic Henry reactions have gained particular attention.[8,9] For example, Shibasaki and co-workers have reported that rare-earth-lithium–BINOL complexes can be applied as catalysts for the enantioselective reaction of aldehydes with nitroalkanes.[8a–e] Jørgensen and co-workers reported the catalytic asymmetric Henry reaction of α-keto esters with nitromethane in the presence of chiral catalysts.[8i,j] Trost et al. have recently disclosed a catalytic enantioselective Henry reaction employing a bimetallic zinc complex.[8l,m] Evans et al. recently successfully developed the asymmetric Henry reaction of aldehydes using a bis(oxazoline) complex.[8p] In continuation with our group's research on the design, synthesis and application of bis(oxazoline) and bis(thiazoline) ligands,[10] we herein report the synthesis of a series of new bis(thiazoline) ligands **6** and the comparative study of bis(thiazoline) **6** and bis(oxazoline) **7**[11] (Scheme 2) on Cu(II)-catalyzed asymmetric Henry reaction.

2. Results and discussion

2.1. Preparation of ligands 6 and 7

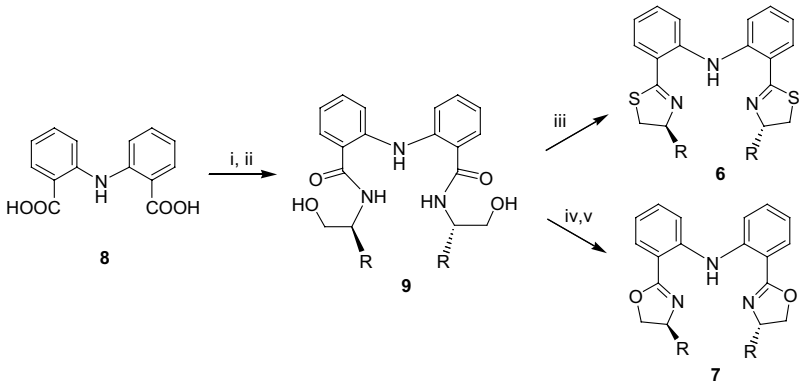
Compounds **6** and **7** were readily prepared from 2,2′-dicarboxyl diphenylamine **8** and enantiomerically pure β-amino alcohols via the corresponding β-hydroxylamides **9** and their mesylates successively as intermediates (Scheme 3). Thus, 2,2′-dicarboxyl diphenylamine **8** was treated with $SOCl_2$ to give the acid dichloride, which was stirred with (*S*)-*tert*-leucinol and triethylamine in dichloromethane (DCM) at room temperature for 4 h to give amide **9e** in 92% yield. Then **9e** was vigorously stirred with phosphorus pentasulfide[10c] in pyridine for 0.5 h and then refluxed for 22 h to give compound **6e** in 57% yield. The bis(thiazolines) **6a**–**d** were synthesized in the same way in 41–61% overall yields from 2,2′-dicarboxyl diphenylamine and the corresponding pure chiral β-amino alcohols.

Although bis(oxazolines) **7** have been synthesized previously, long reaction times (at least one week) and expensive catalysts (Pd precursor and additional ligand) were needed while the highest overall yield obtained 40%.[11] With bis(hydroxyamides) **9** in hand, we preferred to employ them to prepare bis(oxazolines) **7**. Compound **9e** was then treated with methanesulfonyl chloride in the presence of triethylamine in dichloromethane at room temperature to afford the crude dimesylate intermediate, which was refluxed in aqueous-alcoholic sodium hydroxide solution for 3 h to afford compound **7e** in 71% yield. In the same way, bis(oxazolines) **7a**–**d** were prepared in 41–83% overall yields.

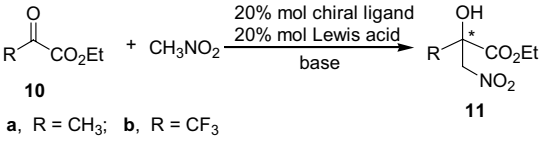
2.2. Asymmetric Henry reaction using ligands 6 and 7

Chiral bis(oxazolines) have been proven to be one of the most efficient chiral ligands for an asymmetric Henry reaction.[8i,j,p] Before investigating the catalytic efficiency of the newly synthesized bis(thiazolines), the corresponding bis(oxazolines) were first examined. The effect of chiral ligands, Lewis acids and bases have been screened for the Henry reaction of ethyl pyruvate **10a** with nitromethane using 20% catalyst loading (Scheme 4).

Initially, Lewis acids were screened[12] with some representative results summarized in Table 1. The combination of different Lewis acids with ligand **7a** was first investigated. Among them, $Cu(OTf)_2$ gave a high yield and good enantioselectivity (Table 1, entry 5). No better results were found with other Lewis acids (Table 1,



Scheme 3. Reagents and conditions: (i) $SOCl_2$, reflux 8 h; (ii) amino alcohol, DCM, Et_3N; (iii) P_2S_5, pyridine, reflux 22 h; (iv) MsCl, DCM, Et_3N; (v) NaOH, CH_3OH–H_2O, reflux 3 h.



Scheme 4.

Table 1. Results for the screening of the reaction conditions for the Henry reaction of ethyl pyruvate **10a** (1 equiv) with nitromethane (64 equiv) in the presence of Et_3N[a]

Entry	Ligand	Lewis acid	Base (%)	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	**7a**	$La(OTf)_3$	20	51	15	*S*
2	**7a**	$Zn(OTf)_2$	20	73	+16	*R*
3	**7a**	$Cu(OAc)_2$	20	75	0	
4	**7a**	$Cu(ClO_4)_2$	20	72	46	*S*
5	**7a**	$Cu(OTf)_2$	20	90	50	*S*
6	**7b**	$Cu(OTf)_2$	20	56	49	*S*
7	**7c**	$Cu(OTf)_2$	20	54	39	*S*
8	**7d**	$Cu(OTf)_2$	20	61	56	*S*
9	**7e**	$Cu(OTf)_2$	20	74	60	*S*
10	**7e**	$Cu(OTf)_2$	40	95	3	*S*
11	**7e**	$Cu(OTf)_2$	10	11	29	*S*

[a] Reaction was performed with 20 mol% complex at room temperature.
[b] Isolated yield by column chromatography.
[c] Determined by HPLC on Daicel Chiracel OB column (hexane/2-propanol 90:10, 1.0 mL/min, t_{major} = 12.2 min, t_{minor} = 14.3 min).
[d] The absolute configurations were established by comparison the sign of optical rotation with that of literature value.[8j]

entries 1–4). In contrast, the $Zn(OTf)_2$ complex gave the major enantiomer opposite to that obtained by the Cu(II) complex. Next, different ligands were screened and of the five chiral bis(oxazoline)–copper(II) catalysts tested for the reaction, ligand **7e** gave the most promising result (Table 1, entry 9). It was found that the conversion and enantioselectivity were dependent upon the amount of base relative to the catalyst. An increase of the amount of Et_3N to 40 mol% relative to the catalyst (20 mol%) gave a higher conversion and an almost racemic product, while a decrease in the amount of Et_3N to 10 mol% resulted in a significant reduction in both conversion and enantioselectivity (Table 1, entries 10 and 11). Other bases such as pyridine, *N*-methylmorpholine and Hünig's base were also tested in the reaction although no better results than Et_3N were obtained.

Since ligand **7a** gave a relatively high yield without a distinct decrease in enantioselectivity and is less cheaper than **7e**, various solvents were first evaluated using ligand **7a** for further improving the enantioselectivity. Reduction of the ratio of $MeNO_2$ to ethyl pyruvate from 64:1 (no solvents) to 10:1 (using 1.5 mL solvents) gave inconsistent results (Table 2). The results indicate that alkyl halides are the best solvent for enantioselectivity. Using $CHCl_3$ (Table 2, entry 4), $ClCH_2CH_2Cl$ (Table 2, entry 5), and CH_2Cl_2 (Table 2, entries 6–8) as solvents in the reaction gave higher enantioselectivity than that without solvents, while other solvents gave the same (Table 2, entry 10) or even worse (Table 2, entries 1–3 and 9) results. Decreasing the temperature did not increase the enantioselectivity significantly (Table 2, entry 7) while the addition of 4 Å molecular sieves (50 mg) caused a lower enantioselectivity (Table 2, entry 8). However, the reaction in all solvents did not proceed completely, with the yield being lower than that in neat reaction. The main side reaction is the self-aldol addition of ethyl pyruvate. The yield of the Henry reaction normally achieved was highest in 16–20 h while longer reaction time afforded more side product. When **7e** was used instead of **7a**, the enantioselectivity did not improve and an even lower enantioselectivity was obtained, this phenomenon is difficult to explain at present.

According to the same procedure in Table 1 in the presence of 20 mol% Et_3N, bis(thiazoline) ligands **6** were examined. Both ethyl pyruvate and ethyl trifluoropyruvate were investigated. For convenience, the obtained results of ligands **6** and **7** are summarized and compared

Table 2. Screening solvents for the Henry reaction of ethyl pyruvate **10a** with nitromethane[a]

Entry	Ligand	Solvent	Temp	Additive	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	**7a**	EtOH	Rt	No	19	27	*S*
2	**7a**	THF	Rt	No	20	42	*S*
3	**7a**	THF	−20 °C	No	11	39	*S*
4	**7a**	$CHCl_3$	Rt	No	22	53	*S*
5	**7a**	$ClCH_2CH_2Cl$	Rt	No	32	76	*S*
6	**7a**	CH_2Cl_2	Rt	No	43	80	*S*
7	**7a**	CH_2Cl_2	−20 °C	No	29	82	*S*
8	**7a**	CH_2Cl_2	Rt	4 Å	30	69	*S*
9	**7a**	Toluene	Rt	No	27	41	*S*
10	**7a**	Cyclohexane	Rt	4 Å	21	50	*S*
11	**7e**	CH_2Cl_2	Rt	No	23	32	*S*
12	**7e**	$ClCH_2Cl_2Cl$	Rt	No	32	19	*S*

[a] Reaction was performed with ethyl pyruvate **10a** (1 equiv) and nitromethane (10 equiv) in solvents (1.5 mL) in the presence of Et_3N (0.2 equiv) and $Cu(OTf)_2$ complex (0.2 equiv).
[b] Isolated yield by column chromatography.
[c] Determined by HPLC on Daicel Chiracel OB column (hexane/2-propane 90:10, 1.0 mL/min, t_{major} = 12.2 min, t_{minor} = 14.3 min).
[d] The direction of specific rotation of major isomer is (−) with the absolute configurations established by comparison of the sign of the specific rotation with that of the literature value.[8j]

Table 3. Enantioselective addition of nitromethane to α-keto esters catalyzed by ligands **6** and **7** in the presence of Et_3N as the base[a]

Entry	α-Keto esters	Ligands	Yield (%)[b] (**11a/11b**)	Ee (%) (**11a**[c]/**11b**[d])	Config.[e]
1	**10a**	**7a/6a**	90/76	50/47	*S*/*S*
2	**10a**	**7b/6b**	56/40	49/8	*S*/*S*
3	**10a**	**7c/6c**	54/30	39/63	*S*/*S*
4	**10a**	**7d/6d**	61/75	56/9	*S*/*S*
5	**10a**	**7e/6e**	74/55	60/70	*S*/*S*
6	**10b**	**7a/6a**	52/88	11/10	*S*/*S*
7	**10b**	**7b/6b**	23/12	6/0	*S*
8	**10b**	**7c/6c**	84/38	23/13	*S*/*S*
9	**10b**	**7e/6e**	66/14	0/0	

[a] Reaction was performed with ethyl pyruvate **10** (1 equiv) and nitromethane (64 equiv) in the presence of Et_3N (0.2 equiv) and a $Cu(OTf)_2$ complex (0.2 equiv).
[b] Isolated yield by column chromatography.
[c] Determined by HPLC on Daicel Chiracel OB column (hexane/2-propane 90:10, 1.0 mL/min, t_{major} = 12.2 min, t_{minor} = 14.3 min).
[d] Determined by HPLC on Daicel Chiracel OJ column (hexane/2-propane 90:10, 0.5 mL/min, t_{major} = 19.8 min, t_{minor} = 21.8 min).
[e] The direction of the specific rotation of major isomer is (−) and the absolute configurations were established by the comparison of the sign of the specific rotation with that of the literature value.[8j]

in Table 3. Normally, the yield of **11b** was lower than **11a**, while the enantioselectivity was inconsistent. The reason is still not clear and is currently under investigation. When ligand **6e** was used instead of **7e**, the enantioselectivity was higher (up to 70% ee) without obvious loss of yield. The similar enantioselectivities and the same absolute configurations of the adducts of **6** and **7** in the catalytic Henry reaction imply the two series of C_2-symmetric ligands may have similar coordinate features in the transition states, although oxazoline and thiazoline ligands showed different enantioface selectivity in the Pd-catalyzed allylic alkylation.[10c] The results in Table 3 also suggest the usefulness of thiazoline ligands, which enabled minor modification of enantioselectivity.

2.3. Crystal structure of bis(thiazoline) 6c

In order to further understand the structural effect of the new bis(thiazoline) ligands on their catalytic activity, the stereostructure of ligand **6c** was determined by X-ray crystal diffraction analysis.[13] Compound **6c** was obtained as air-stable, pale yellow crystals upon slow evaporation of a solution of **6c** in petroleum ether/ethyl acetate (10:1). A perspective view of compound **6c** is shown in Figure 1. The dihedral angle between C1–C2–C3–C4–C5–C6 benzene ring and C16–C17–C18–C19–C20–C21 benzene ring is 53.0°. The two thiazoline rings have a dihedral angle of 27.5°. The two conjugated benzene and thiazoline rings have dihedral angles of 43.4° and 43.1°, respectively. From the crystal structure of **6c**, we can see that the diphenylamine-linked bis(thiazoline) has good tridentate coordination conformation. This conformation of two thiazolines may facilitate the nitrogen atom to coordinate with copper, in contrast, sulfur atom rather than nitrogen atom coordinate with palladium as in our previous report.[10c] The two nitrogen atoms of bis(oxazoline) or bis(thiazoline) may form a

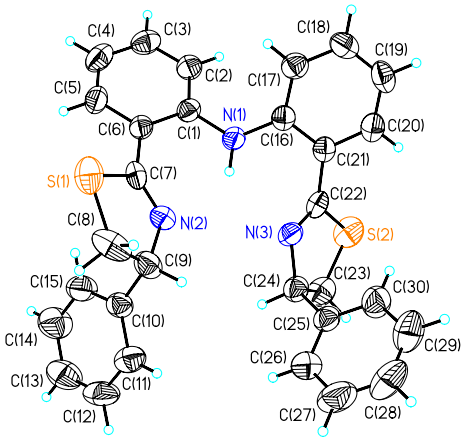


Figure 1. Perspective view of compound **6c**, showing 30% probability ellipsoids.

hydrogen bond with the N–H of the diphenylamine part, and thus the hydrogen bond interaction would affect the coordination configuration. For example, in compound **6c**, there exists two hydrogen bonds, N(1)–HN1···N(2) bond length is 2.16(2) Å, bond angle is 133.9(17)°; N(1)–HN1···N(3) bond length is 2.27(2) Å and bond angle is 125.1(17)°.

Moreover, in order to confirm that in both cases the complexation occurred via the nitrogen atoms, it would be interesting to prepare the corresponding Cu(II) complexes. However, our attempts to get a single crystal of these complexes failed.

2.4. UV spectra

UV spectra were carried out in order to obtain further information about the complexation feature of bis(oxazoline) and bis(thiazoline). It is possible to use spectral methods to investigate the coordination of the ligands with $Cu(OTf)_2$. The UV spectra of bis(oxazoline) **7c**, the **7c**–Cu catalyst, bis(thiazoline) **6c**, and the **6c**–Cu catalyst (the catalyst in molar ratios of 1:1) were determined in CH_2Cl_2 (Figs. 2 and 3). The results showed that the UV spectra of bis(oxazoline) **7c** and bis(thiazoline) **6c** have similar absorption peaks, bis(oxazoline) **7c** with peaks at 232, 293 and 357 nm; bis(thiazoline) **6c** with peaks at 235.5, 300.5 and 371.5 nm. The **7c**–Cu catalyst had new complex peaks at 319.5, 435 nm, whereas the **6c**–Cu catalyst had a similar new peak at 466.5 nm. This implies that bis(oxazoline) and bis(thiazoline) have similar coordination sites with copper and result in a similar tendency of UV peak change.

The above structural and spectral data further support that the same coordination mode of two types of ligands has formed. If the coordination mode is different between bis(thiazoline) and bis(oxazoline) ligands, then the absolute configurations of the Henry adducts should be opposite on the basis of molecular modelling. As the direction of substituents on thiazoline or oxazoline rings in Cu complexes would determine the absolute configuration of the products, the difference in coordination modes should result in a switch of enantioface selection.

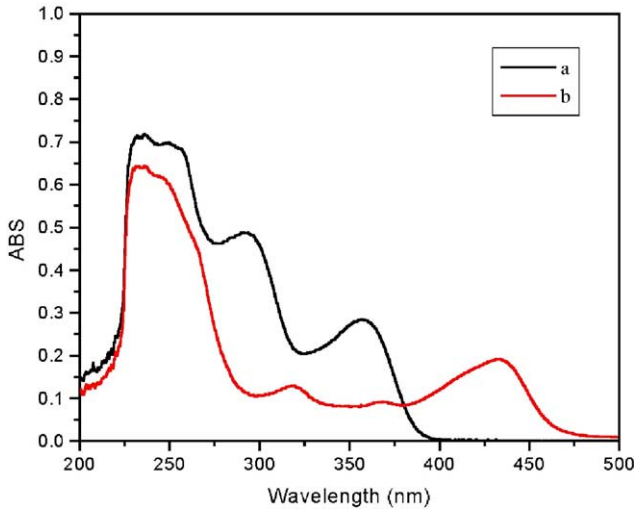


Figure 2. UV spectra of bis(oxazoline) **7c** and **7c**–$Cu(OTf)_2$ complex in CH_2Cl_2 (2.0×10^{-5} mol/L): (a) bis(oxazoline) **7c**, (b) **7c**–$Cu(OTf)_2$ 1:1 complex.

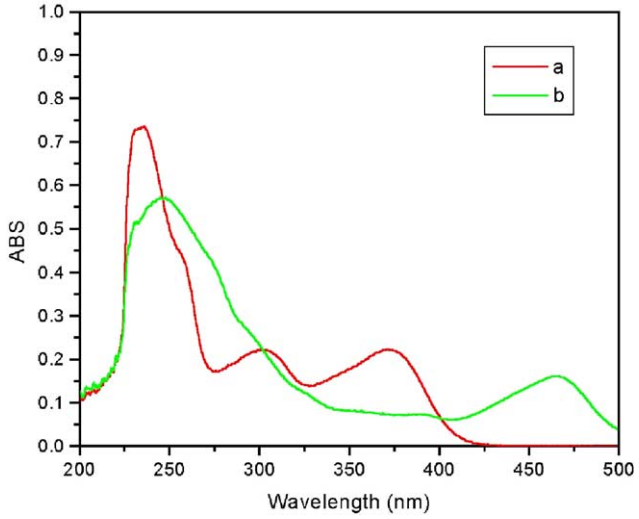


Figure 3. UV spectra of bis(thiazoline) **6c** and **6c**–$Cu(OTf)_2$ complex in CH_2Cl_2 (2.0×10^{-5} mol/L): (a) bis(thiazoline) **6c**, (b) **6c**–$Cu(OTf)_2$ 1:1 complex.

The results in Table 3 clearly suggest that both thiazoline and oxazoline ligands have a similar asymmetric environment. Bis(thiazoline) ligands gave up to 70% ee [(*S*)-adduct], while bis(oxazoline) ligands gave up to 60% ee in the same absolute configurations [(*R*)-adduct]. A difference between 60% ee and 70% ee is quite small and the results imply that a similar chiral space was constructed. Interestingly, our group recently reported[10c] the reversal in absolute configurations in Pd-catalyzed asymmetric allylic alkylation reactions when comparing bis(thiazoline) and bis(oxazoline) ligands. As a result, we think that the coordination mode of thiazoline ligands depends on the metal used. In the case of Pd, our previously reported thiazoline ligands would coordinate through sulfur, but with Cu, the thiazoline ligands synthesized in this paper would coordinate through the nitrogen atom in a similar manner as the oxazoline ligands. This conclusion matches the UV spectra in Cu complexes as both of them have the same tendency. The UV spectra support the idea that both thiazoline ligands and oxazoline ligands should have the same coordination modes in case of current Cu complexes.

3. Conclusion

In conclusion, we have synthesized a series of new C_2-symmetric bis(thiazoline) ligands with a diphenylamine backbone and improved the synthetic method for the corresponding bis(oxazoline) ligands. By the use of bis(hydroxyamides) as synthetic intermediates, these ligands are prepared in good overall yields. The synthetic procedures of tridentate ligands are quite efficient and useful. Comparing results with the two types of C_2-symmetric ligands in the catalytic asymmetric Henry reaction, the bis(oxazoline)–copper(II) complex furnished moderate enantioselectivities (up to 60% ee), while bis(thiazoline) gave slightly better enantioselectivities (up to 70% ee) without an obvious loss in yield. The enantioselectivity was improved when halogenated solvents, such as CH_2Cl_2, $ClCH_2CH_2Cl$, were used (up to 82% ee), although the yield is lower than that obtained in neat reaction. The results herein showed that the corresponding bis(oxazoline) and bis(thiazoline) ligands gave similar enantioselectivities for the asymmetric nitroaldol reaction. Systematic studies comparing the selectivity and reactivity of various tridentate chiral bis(thiazoline) and bis(oxazoline) ligands gave important information in the field of asymmetric catalysis. Further studies are currently in progress in our laboratory in order to expand the application of these tridentate chiral ligands to other asymmetric reactions.

4. Experimental

4.1. General remarks

Melting points were measured on an XT-4 melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Mercury 200, Mercury 300 and Brucker 400 MHz spectrometer with tetramethylsilane serving as the internal standard. Elemental analyses were carried out on an Elementar Vario EL instrument. Infrared spectra were obtained on a Bruker Vector 22 spectrometer. Mass spectra were obtained on APEX II FT-ICRMS (FAB), VG-ZAB-HS (EI) and Thermo Firrnigan LCQ Deca XP Plus (ESI) mass spectrometers. UV spectra were measured on TU-1901 spectrophotometer. Optical rotations were measured on a Perkin–Elmer 341 LC spectrometer. The enantiomeric excesses of 2-hydroxy-2-methyl-3-nitropropanoic acid ethyl ester **11a** were determined by HPLC analysis using a chiral column (Daicel Chiralcel OB; eluent, hexane/isopropyl alcohol 90:10; flow rate, 1.0 mL/min; UV detector, 215 nm). The enantiomeric excesses of 2-hydroxy-2-trifluoromethyl-3-nitropropanoic acid ethyl ester **11b** were determined by HPLC analysis using Chiralcel OJ column. Solvents used were purified and dried by standard procedures.

4.2. General procedure for the synthesis of bis(hydroxyamides) 9a–e

A solution of 2,2′-dicarboxyl diphenylamine **8** (7.0 mmol) and thionyl chloride (10 mL) was refluxed for 4 h. The excess $SOCl_2$ was removed under reduced pressure to afford the diacyl dichloride. The above diacyl dichloride in CH_2Cl_2 (70 mL) was added dropwise to a solution of amino alcohol (14.0 mmol) and Et_3N (4.9 mL, 35.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C and stirred at room temperature for 24 h. The reaction mixture was successively washed with saturated NH_4Cl (aq), HCl (1 M), saturated $NaHCO_3$ (aq) and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography using ethyl acetate as the eluting solvent to afford the bis(hydroxyamide).

4.3. 2,2′-Bis[*N*-(1*S*)-(1-isopropyl-2-hydroxyethyl)carbamoyl]diphenylamine 9a

Yield: 88%, pale yellow solid. Mp: 134–136 °C. $[\alpha]_D^{20} = -104.2$ (*c* 0.81 in $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.40 (s, 1H), 7.65 (dd, $J = 7.8$, 1.3 Hz, 2H), 7.29–7.34 (m, 2H), 7.20 (d, $J = 8.1$ Hz, 2H), 6.98 (t, $J = 7.3$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 3.88–3.92 (m, 2H), 3.68 (t, $J = 4.4$ Hz, 4H), 3.06 (s, 2H), 1.88–1.94 (m, 2H), 0.96 (d, $J = 6.8$ Hz, 6H), 0.94 (d, $J = 6.8$ Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 168.9, 142.0, 131.9, 129.0, 124.1, 121.4, 119.2, 63.0, 57.0, 29.1, 19.5, 19.0. IR (KBr): *v* 3328, 3060, 2933, 2872, 2768, 1668, 1500, 1418, 1320, 1045, 778, 516 cm^{-1}. HRMS (FAB) calcd for $C_{24}H_{34}N_3O_4$ $[M+H]^+$: 428.2544, found: 428.2552.

4.4. 2,2′-Bis[*N*-(1*S*)-(1-isobutyl-2-hydroxyethyl)carbamoyl]diphenylamine 9b

Yield: 87%, pale yellow solid. Mp: 79–81 °C. $[\alpha]_D^{20} = -100.3$ (*c* 0.64 in $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.38 (s, 1H), 7.62 (dd, $J = 7.8$, 1.4 Hz, 2H), 7.29–7.33 (m, 2H), 7.19 (d, $J = 8.1$ Hz, 2H), 6.94–6.98 (m, 2H), 6.75 (d, $J = 8.4$ Hz, 2H), 4.18–4.23 (m, 2H), 6.68–3.71 (m, 2H), 3.50–3.56 (m, 2H), 3.17 (s, 2H), 1.58–1.64 (m, 2H), 1.33–1.49 (m, 4H), 0.92 (d, $J = 3.5$ Hz, 6H), 0.91 (d, $J = 3.5$ Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 168.7, 141.9, 131.9, 128.9, 123.9, 121.3, 119.1, 65.1, 49.9, 40.2, 24.9, 23.0, 22.2. IR (KBr): *v* 3307, 3063, 2954, 2869, 2768, 1651, 1501, 1321, 1163, 1046, 777, 515 cm^{-1}. MS(EI): *m/z* 455 (M^+, 25), 437 (15), 321 (8), 221 (18), 196 (100). HRMS (FAB) calcd for $C_{26}H_{38}N_3O_4$ $[M+H]^+$: 456.2857, found: 456.2864.

4.5. 2,2′-Bis[*N*-(1*S*)-(1-phenyl-2-hydroxyethyl)carbamoyl]diphenylamine 9c

Yield: 88%, pale yellow solid. Mp: 96–98 °C. $[\alpha]_D^{20} = +2.6$ (*c* 0.55 in $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.46 (s, 1H), 7.64 (dd, $J = 7.8$, 1.2 Hz, 2H), 7.50 (d, $J = 7.3$ Hz, 2H), 7.22–7.32 (m, 12H), 7.11 (d, $J = 8.2$ Hz, 2H), 6.95 (t, $J = 7.5$ Hz, 2H), 5.12–5.16 (m, 2H), 3.73 (d, $J = 4.9$ Hz, 4H), 3.84 (s, br, 2H). ^{13}C NMR ($CDCl_3$): δ 168.5, 142.2, 139.2, 132.1, 129.2, 128.6, 127.5, 126.6, 123.7, 121.4, 119.4, 65.5, 55.6. IR (KBr): *v* 3310, 3061, 2934, 2768, 1666, 1417, 1319, 1068, 776, 516 cm^{-1}. HRMS(FAB): calcd for $C_{30}H_{30}N_3O_4$ $[M+H]^+$: 496.2231, found: 496.2224.

4.6. 2,2′-Bis[*N*-(1*S*)-(1-benzyl-2-hydroxyethyl)carbamoyl]diphenylamine 9d

Yield: 74%, pale yellow solid. Mp: 70–72 °C. $[\alpha]_D^{20} = -81.1$ (*c* 0.40 in $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.27 (s, 1H), 7.39 (d, $J = 7.6$ Hz, 2H), 7.24–7.10 (m, 14H), 6.97 (d, $J = 6.7$ Hz, 2H), 6.81 (t, $J = 7.4$ Hz, 2H), 4.30–4.26 (m, 2H), 3.70 (s, br, 2H), 3.60 (dd, $J = 11.2$, 2.5 Hz, 2H), 3.51 (dd, $J = 11.3$, 4.5 Hz, 2H), 2.84 (d, $J = 7.3$ Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 168.6, 141.7, 137.8, 131.7, 129.2, 128.8, 128.4, 126.4, 123.8, 121.0, 118.7, 63.1, 52.8, 36.9. IR (KBr): *v* 3323, 3060, 2934, 2768, 1667, 1417, 1323, 1039, 778, 516 cm^{-1}. ESIMS: calcd for $C_{32}H_{34}N_3O_4$ $[M+H]^+$: 524.2, found: 524.2.

4.7. 2,2′-Bis[*N*-(1*S*)-(1-*tert*-butyl-2-hydroxyethyl)carbamoyl]diphenylamine 9e

Yield: 92%, pale yellow solid. Mp: 94–96 °C. $[\alpha]_D^{20} = -64.9$ (*c* 0.64 in $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.35 (s, 1H), 7.66 (dd, $J = 7.8$, 1.2 Hz, 2H), 7.35–7.30 (m, 2H), 7.18 (d, $J = 8.2$ Hz, 2H), 7.02–6.98 (m, 2H), 6.85 (d, $J = 9.4$ Hz, 2H), 4.03–3.98 (m, 2H), 3.82 (d, $J = 11.4$ Hz, 2H), 3.59 (dd, $J = 11.5$, 7.1 Hz, 2H), 2.91 (s, br, 2H), 0.95 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 169.1, 142.0, 131.9, 129.0, 124.4, 121.4, 119.3, 62.1, 59.1, 34.0, 26.9. IR (KBr): *v* 3409, 3060, 2935, 2768, 1618, 1417, 1319, 1051, 779, 515 cm^{-1}. HRMS $[M+H]^+$ calcd for $C_{26}H_{38}N_3O_4$: 456.2857, found: 456.2862.

4.8. General procedure for the synthesis of bis(thiazoline) ligands 6a–e

To a solution of bis(hydroxyamide) **9** (2.75 mmol) in dry pyridine (25 mL) was added P_2S_5 (11.0 mmol) and the mixture was refluxed for 22 h. Then the reaction mixture was cooled and 20% KOH solution (20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). The organic phase was combined, washed by 2 N HCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude product was purified by silica column chromatography using petroleum ether/ethyl acetate (20:1) as the eluent.

4.9. Bis[2-((4*S*)-4-isopropyl-4,5-dihydrothiazol-2-yl)phenyl]amine 6a

Yield: 54%, pale yellow solid. Mp: 64–66 °C. $[\alpha]_D^{20} = +22.9$ (*c* 0.45 in $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 10.83 (s, 1H), 7.64 (d, $J = 7.9$ Hz, 2H), 7.30–7.23 (m, 4H), 6.95–6.90 (m, 2H), 4.45–4.39 (m, 2H), 3.27 (dd, $J = 10.8$, 8.7 Hz, 2H), 3.00 (dd, $J = 10.6$, 9.6 Hz, 2H), 2.07–1.99 (m, 2H), 1.03 (d, $J = 6.8$ Hz, 6H), 0.96 (d, $J = 6.8$ Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 165.5, 142.4, 131.6, 130.9, 122.4, 120.3, 119.3, 84.1, 34.5, 33.2, 19.8, 19.0. IR (KBr): *v* 3430, 3062, 2956, 2768, 1669, 1448,

1319, 1161, 981, 776, 515 cm^{-1}. MS (70 eV, EI): *m/z* (%) 423 (M^+, 88), 380 (30), 278 (100), 219 (30). Anal. Calcd for $C_{24}H_{29}N_3S_2$: C, 68.04; H, 6.90; N, 9.92. Found: C, 67.85; H, 6.71; N, 9.85.

4.10. Bis[2-((4*S*)-4-isobutyl-4,5-dihydrothiazol-2-yl)phenyl]amine 6b

Yield: 47%, yellow solid. Mp: 134–136 °C. $[\alpha]_D^{20} = +44.7$ (*c* 0.82 in $CHCl_3$). ^1H NMR ($CDCl_3$): δ 10.83 (s, 1H), 7.63 (dd, $J = 7.8$, 1.3 Hz, 2H), 7.29–7.19 (m, 4H), 6.93–6.88 (m, 2H), 4.71–4.63 (m, 2H), 3.34 (dd, $J = 10.7$, 8.2 Hz, 2H), 2.90 (dd, $J = 10.6$, 8.0 Hz, 2H), 1.83–1.73 (m, 4H), 1.47–1.40 (m, 2H), 0.96 (d, $J = 6.2$ Hz, 6H), 0.93 (d, $J = 6.2$ Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 165.2, 142.2, 131.5, 130.8, 122.3, 120.2, 119.2, 76.0, 44.1, 37.5, 25.7, 23.0, 22.5. IR (KBr): *v* 3450, 3250, 3070, 2953, 2866, 2768, 1637, 1512, 1448, 1418, 1319, 1209, 776, 516 cm^{-1}. MS (70 eV, EI): *m/z* (%) 451 (M^+, 40), 394 (8), 278 (18), 219 (25), 149 (12), 97 (34), 57 (100). Anal. Calcd for $C_{26}H_{33}N_3S_2$: C, 69.14; H, 7.36; N, 9.30. Found: C, 68.91; H, 7.36; N, 9.14.

4.11. Bis[2-((4*S*)-4-phenyl-4,5-dihydrothiazol-2-yl)phenyl]amine 6c

Yield: 47%, pale yellow crystal. Mp: 169–171 °C. $[\alpha]_D^{20} = +448.7$ (*c* 0.78 in $CHCl_3$). ^1H NMR ($CDCl_3$): δ 11.35 (s, 1H), 7.67 (dd, $J = 7.8$, 1.4 Hz, 2H), 7.49 (d, $J = 8.3$ Hz, 2H), 7.33–7.17 (m, 12H), 6.97–6.92 (m, 2H), 5.25 (t, $J = 8.9$ Hz, 2H), 3.50 (dd, $J = 10.8$, 8.8 Hz, 2H), 3.04 (dd, $J = 10.8$, 9.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 167.6, 142.14, 142.09, 131.7, 131.0, 128.3, 127.2, 126.5, 121.8, 120.1, 118.7, 80.4, 40.3. IR (KBr): *v* 3250, 3060, 2934, 2768, 1636, 1506, 1449, 1418, 1320, 778, 515 cm^{-1}. MS (70 eV, EI): *m/z* (%) 491 (M^+, 70), 354 (50), 219 (100), 135 (18), 91 (22). Anal. Calcd for $C_{30}H_{25}N_3S_2$: C, 73.29; H, 5.12; N, 8.55. Found: C, 73.05; H, 5.14; N, 8.41.

4.12. Bis[2-((4*S*)-4-benzyl-4,5-dihydrothiazol-2-yl)phenyl]amine 6d

Yield: 82%, pale yellow crystal. Mp: 129–131 °C. $[\alpha]_D^{20} = +97.6$ (*c* 0.96 in $CHCl_3$). ^1H NMR ($CDCl_3$): δ 11.11 (s, 1H), 7.66 (dd, $J = 7.8$, 1.4 Hz, 2H), 7.40 (d, $J = 8.2$ Hz, 2H), 7.32–7.27 (m, 2H), 7.22–7.18 (m, 10H), 6.98–6.93 (m, 2H), 4.93–4.88 (m, 2H), 3.28–3.20 (m, 4H), 3.03 (dd, $J = 11.0$, 6.7 Hz, 2H), 2.84 (dd, $J = 13.6$, 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 166.1, 142.2, 138.4, 131.7, 130.9, 129.3, 128.3, 126.3, 121.9, 120.1, 119.0, 79.0, 40.4, 36.3. IR (KBr): *v* 3254, 3056, 2931, 2856, 2768, 1651, 1505, 1447, 1317, 1214, 1031, 943, 775, 519 cm^{-1}. MS (70 eV, EI): *m/z* (%) 519 (M^+, 70), 428 (65), 278 (100), 219 (10), 117 (12), 91 (25). Anal. Calcd for $C_{32}H_{29}N_3S_2$: C, 73.95; H, 5.62; N, 8.09. Found: C, 73.65; H, 5.85; N, 7.98.

4.13. Bis[2-((4*S*)-4-*tert*-butyl-4,5-dihydrothiazol-2-yl)phenyl]amine 6e

Yield: 57%, pale yellow solid. Mp: 139–141 °C. $[\alpha]_D^{20} = -43.4$ (*c* 0.35 in $CHCl_3$). ^1H NMR ($CDCl_3$): δ 10.73 (s, 1H), 7.68 (dd, $J = 7.9$, 1.2 Hz, 2H), 7.29–7.22 (m, 4H), 6.96–6.91 (m, 2H), 4.32 (dd, $J = 10.6$, 8.8 Hz, 2H), 3.18 (dd, $J = 10.9$, 8.8 Hz, 2H), 3.05 (t, $J = 10.7$ Hz, 2H), 1.00 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 165.6, 142.6, 131.7, 131.0, 122.6, 120.5, 119.5, 87.4, 35.2, 33.0, 26.9. IR (KBr): *v* 3425, 3250, 3059, 2951, 2862, 2768,1637, 1517, 1449, 1321, 1210, 998, 776, 516 cm^{-1}. MS (70 eV, EI): *m/z* (%) 451 (M^+, 48), 394 (75), 278 (100), 219 (8). Anal. Calcd for $C_{26}H_{33}N_3S_2$: C, 69.14; H, 7.36; N, 9.30. Found: C, 69.09, H, 7.13; N, 9.32.

4.14. General procedure for the synthesis of bis(oxazoline) ligands 7a–e

To an ice-cold solution of bis(hydroxyamide) **9** (3.71 mmol) and Et_3N (2.3 mL) in CH_2Cl_2 (30 mL) was added methanesulfonyl chloride (8.2 mmol) via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. Saturated NH_4Cl solution was then poured into the reaction mixture. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the crude bismesylate. The crude bismesylate was dissolved in methanol (7.5 mL) and a solution of 0.3 g NaOH in water (7.5 mL) added to it. The reaction mixture was refluxed for 3 h and cooled to room temperature. The methanol was removed under reduced pressure and the residue extracted with CH_2Cl_2 (3×25mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the crude product, which was purified by column chromatography on silica gel using petroleum ether/ethyl acetate 10:1 as the eluent.

4.15. Bis[2-((4*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl]amine 7a[11]

Yield: 94%, pale yellow crystals. Mp: 114–116 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 10.72 (s, 1H), 7.81 (dd, $J = 7.8$, 1.4 Hz, 2H), 7.40 (d, $J = 7.6$ Hz, 2H), 7.22–7.32 (m, 2H), 6.84–6.93 (m, 2H), 4.36–4.28 (m, 2H), 3.97–4.15 (m, 4H), 1.71–1.84 (m, 2H), 1.01 (d, $J = 6.6$ Hz, 6H), 0.91 (d, $J = 6.8$ Hz, 6H).

4.16. Bis[2-((4*S*)-4-isobutyl-4,5-dihydrooxazol-2-yl)phenyl]amine 7b

Yield: 81%, yellow oil. $[\alpha]_D^{20} = +47.2$ (*c* 1.17 in $CHCl_3$). ^1H NMR ($CDCl_3$): δ 10.67 (s, 1H), 7.80 (d, $J = 7.9$ Hz, 2H), 7.40 (d, $J = 8.3$ Hz, 2H), 7.27–7.23 (m, 2H), 6.87 (t, $J = 7.2$ Hz, 2H), 4.42–4.30 (m, 4H), 3.88 (t, $J = 7.2$ Hz, 2H), 1.83–1.69 (m, 4H), 1.40–1.33 (m, 2H), 0.96 (d, $J = 6.5$ Hz, 6H), 0.94 (d, $J = 6.4$ Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 162.5, 143.0, 131.1, 130.3, 119.7, 118.3, 116.1, 71.9, 65.3, 45.4, 25.4, 22.9, 22.6. IR (KBr): *v* 3225, 3090, 3030, 2955, 2863, 1636, 1577, 1520, 1457, 1361, 1316, 1269, 1223, 1045, 974, 746, 687 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd for $C_{26}H_{33}N_3O_2$: 419.2573, found: 419.2580.

4.17. Bis[2-((4*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)phenyl]amine 7c[11]

Yield: 68%, yellow solid. Mp: 55–56 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.07 (s, 1H), 7.88 (dd, J = 8.0, 1.4 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.12–7.37 (m, 12H), 6.87–6.96 (m, 2H), 5.17 (dd, J = 10.2, 8.2 Hz, 2H), 4.46 (dd, J = 10.2, 8.2 Hz, 2H), 3.98 (t, J = 8.2 Hz, 2H).

4.18. Bis[2-((4*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)phenyl]amine 7d[11]

Yield: 72%, yellow solid. Mp: 35–38 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.91 (s, 1H), 7.81 (dd, J = 7.8, 1.8 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.16–7.34 (m, 12H), 6.90 (ddd, J = 7.8, 7.2, 1.2 Hz, 2H), 4.43–4.52 (m, 2H), 4.2 (dd, J = 9.4, 8.6 Hz, 2H), 3.98 (dd, J = 8.4, 7.4 Hz, 2H), 3.17 (dd, J = 13.6, 5.4 Hz, 2H), 2.72 (dd, J = 13.8, 8.6 Hz, 2H).

4.19. Bis[2-((4*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)phenyl]amine 7e[11]

Yield: 71%, white solid. Mp: 115–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.81 (s, 1H), 7.83 (dd, J = 7.8 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.27 (app t, J = 7.2 Hz, 2H), 6.89 (app t, J = 7.8 Hz, 2H), 4.24 (dd, J = 9.4, 7.8 Hz, 2H), 4.02–4.13 (m, 4H), 0.91 (s, 18H). ^{13}C NMR ($CDCl_3$): 162.4, 143.4, 131.1, 130.4, 119.7, 118.6, 116.2, 76.4, 67.5, 33.9, 25.9.

4.20. General procedure for the catalytic asymmetric Henry reaction

To a round bottom flask, $Cu(OTf)_2$ (0.050 mmol) and the chiral ligand (0.050 mmol) were added. The mixture was stirred under vacuum for 2 h and filled with N_2. Dry freshly distilled $MeNO_2$ (1 mL) was added and the solution stirred for 1 h. Then α-keto ester (0.25 mmol) was added followed by the addition of Et_3N (0.05 mmol). The mixture was stirred for 16 h under N_2 at room temperature. The solvent was removed in vacuo and the residue purified by silica chromatograph (25% AcOEt in petroleum ether) to afford the pure product. Compound **11a** was determined by HPLC on chiral column OB (hexane/2-propanol 90:10, 1.0 mL/min). Compound **11b** was determined by HPLC on chiral column OJ (hexane/2-propanol 90:10, 0.5 mL/min).

4.21. Crystal structure determination of 6c

A colourless crystal with dimensions 0.60 mm × 0.45 mm × 0.20 mm was selected and mounted on a fine-focus sealed tube and used for data collection. The crystallographic measurement was made on a Rigaku RAXIS RAPID IP diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). A total of 20,551 reflections were collected at 293(2) K in the 2θ range from 2.6° to 27.48° using the $\omega - 2\theta$ variable-scan mode. The intensity data obtained were corrected for Lorentz and polarization effects. An empirical absorption correction based on ψ-scan data was applied. The structure was solved by direct methods and successive difference maps (SHELXS 98)[14] and refined by full-matrix least squares on F^2 using all unique data (SHELXL 98).[15] The non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were located theoretically and refined with riding mode position parameters and fixed isotropic thermal parameters. All computations were performed on a FOUNDER FP$^+$ 5-166 586 personal computer.

Compound **6c** $C_{30}H_{35}N_3S_2$, F_W = 491.65, orthorhombic, space group $P2(1)2(1)2(1)$, a = 10.132(2), b = 11.519(2), c = 21.317(4) Å; α = 90°, β = 90°, γ = 90°, V = 2488.0(9) Å^3, Z = 4, $F(000)$ = 1032, Dc = 1.313 Mg/m^3, μ = 0.238 mm^{-1}; index ranges $-13 \leqslant h \leqslant 13$, $-14 \leqslant k \leqslant 14$, $-27 \leqslant l \leqslant 27$; reflections collected/unique, 20,551/3210 (R_{int} = 0.0476); data/restraints/parameters, 3210/0/322; goodness-of-fit on F^2 0.822; final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0320, $wR2$ = 0.0619; R indices (all data), $R1$ = 0.0523, $wR2$ = 0.0656; extinction coefficient 0.0148(7); absolute structure parameter 0.0(2); max. and min. transmission 0.953 and 0.466; max. and mean shift/sigma 0.001 and 0.000; largest diff. peak and hole, 0.177 and −0.187 e Å^{-3}.

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13. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-239470. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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