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A multivalent PyBox asterisk ligand

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ABSTRACT

A discrete multivalent PyBox ligand was investigated. An efficient synthesis and the properties of **1** are reported (UV–visible, cyclic voltammetry, NMR, MALDI-Tof). It incorporates a sulfur-rich persulfurated benzene core which was compatible with a metal-catalyzed reaction in spite of donating and oxidizable sulfur atoms. Metal-catalysis with a persulfurated aromatic ligand was demonstrated for the first time in a model reaction: the Rh-enantioselective hydrosilylation of acetophenone. The interesting features were the reactivity and the enantiocatalytic behavior while varying the metal content. This work promotes new thoughts toward chiral supramolecular assemblies or metal nanoparticles stabilized with chiral multivalent ligands.

Homogeneous asymmetric catalysts are essential tools for modulating regio-, enantio-, and stereoselectivity of a reaction by regulating the kinetics. Most of them contain one metal center bound to one chiral ligand.[1] However, multimetallic dendritic asymmetric catalysts with several active sites appeared in the last decade.[2] It encouraged the design of new multivalent dendritic-type ligands, which are not only important in catalysis, but also in chiral supramolecular assemblies and in nanosciences (for instance, for stabilizing chiral nanoparticles).

Following this trend and the development of persulfurated aromatic compounds,[3] we designed and characterized a discrete mutivalent PyBox asterisk ligand **1** and a reference PyBox model **2**. The investigation of multivalency in PyBox chemistry is a central concept in this work. It correlates well with recent uses of PyBox ligands in numerous stereoselective reactions:[4] aldol condensation,[5] cyclopropanation,[6] Diels–Alder,[7] hydrosilylation of ketones,[8] alkene epoxidation,[9] 1,3-dipolar cycloaddition,[10] ene,[11] Negishi couplings,[12] cyanation,[13] and Friedel-Crafts,[14] etc.

Among some concepts to test, the variation of the metal loading would be of interest for modulating the stereoselectivity. Other features involve the behavior of a sulfur-rich ligand on the binding affinity to a metal center by possible secondary soft–soft interactions.[15] In this regard, persulfurated aromatic compounds were never used as a ligand in a transition metal-catalyzed reaction,[3a] where multiple sulfur donor sites could challenge the enantiocatalytic process with a thiophilic and an oxidizable transition metal (such as Rh). Knowing that electronic effects often govern the catalytic behavior of PyBox ligands, UV–visible and cyclic voltammetry studies were undertaken. Preliminary enantiocatalytic tests were investigated with ligands **1** and **2** in a model asymmetric reaction: the enantioselective hydrosilylation of ketones (Fig. 1).

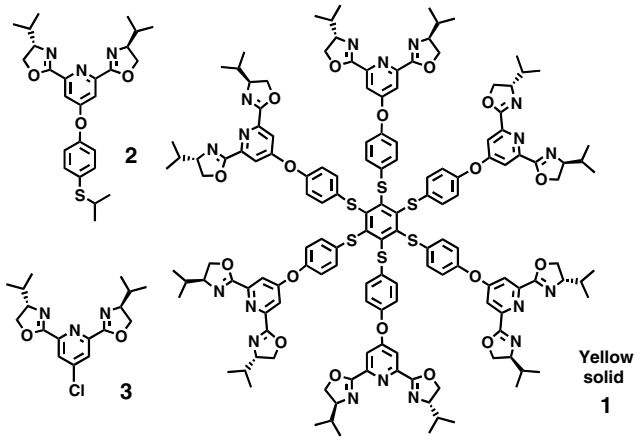

Figure 1. Multivalent asterisk **1** and model Pybox ligands **2**,**3**.

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The synthesis of PyBox asterisk **1** started from the high-yielding preparation of hexakis(4-methoxyphenylthio)benzene **5** from sodium *p*-methoxy-benzenethiolate with hexachlorobenzene (95% yield).[16] It was followed by a deprotection with BBr_3 to afford **4** in a 86% yield.[17] After preparing 4-chloro-PyBox **3**,[8d] the key-step couplings of this last compound to hexakis(4-hydroxyphenylthio)benzene **4** smoothly proceeded at 80 °C in anhydrous DMSO with Cs_2CO_3 to efficiently provide **1** in an optimized 94% yield (average yield per coupling: 99%), without the need for a purification by column chromatography (Scheme 1).[18] Repeated washings by stirring in EtOH and filtration ensure a good purity which was ascertained by ^1H NMR (600 MHz), ^{13}C NMR, and elemental analysis. A complete substitution was consistent with the NMR data, to the elemental analysis and to the MALDI-TOF MS spectra, which indicated a prominent protonated ion at *m*/*z* 2618.4, consistent with the expected monoisotopic dendrimer (Mcalcd: 2617.03 *m*/*z*). The facile cleavage of a thioether bond at the core led to some fragment ion products at *m*/*z* 2192.5 and 1767.8, corresponding to the consecutive losses of one and two PyBox chains. This proposal was further substantiated in separate post-source decay experiments where these cleavage products were readily observed as metastable ions.

We next turned our attention to the synthesis of **2**[19] as a model ligand for evaluating the kinetics and the electronic contribution of the sulfur-donating substituent. 4-(Isopropylthio)phenol was prepared from the alkylation of 4-methoxythiophenol with 2-bromopropane, followed by a deprotection with BBr_3. 4-ChloroPyBox **3** then reacted with 4-(isopropylthio)phenol in anhydrous DMSO in the presence of Cs_2CO_3 at 80 °C (74% yield).

Because the electronic contribution could strongly modulate the reactivity of a PyBox ligand, UV–visible studies were undertaken on **1** in order to qualitatively evaluate a possible electronic delocalization between the asterisk core and the arms (Fig. 2). After a comparison of the UV–visible absorption spectra of **3** and **4**, the spectra of **1** indicated a more or less separate electronic contribution similar to **3** (λ_{max} = 290 and 305 nm) and **4** (λ_{max} = 305 and 340 nm). UV–visible spectra of **3** and **4** were consistent with previous data for a pyridine ring and for hexakis(phenylthio) benzene, respectively. In a nut shell, the electronic contribution of the persulfurated benzene core to the PyBox ligand was negligible, which is in agreement with the similar catalytic reactivity of the asterisk **1** and its model ligand **2** (vide infra).

Cyclic voltammetry studies (DMF, nBu_4NPF_6) indicated a reduction potential below −1.7 V (vs SCE), in agreement with published data on similar systems (such as hexakis(*p*-methoxyphenylthio) benzene at −1.69 V vs SCE).[16]

As shown in Scheme 1, the Rh-precatalysts were prepared by heating asterisk **1** at 80 °C in EtOH/DMSO (1:1, v/v) in the presence of $RhCl_3$ until disappearance of the metal salt (about three days for ensuring completion), originally seen as a black suspension. The excellent yields of the precatalysts were in the range of 95–99% after purification by column chromatography over silica gel.[8d] The stoichiometry of $RhCl_3$/asterisk **1** was varied from a molar ratio of 2:1 up to 6:1. As a model ligand, **2** was also coordinated to $RhCl_3$ using a similar procedure.

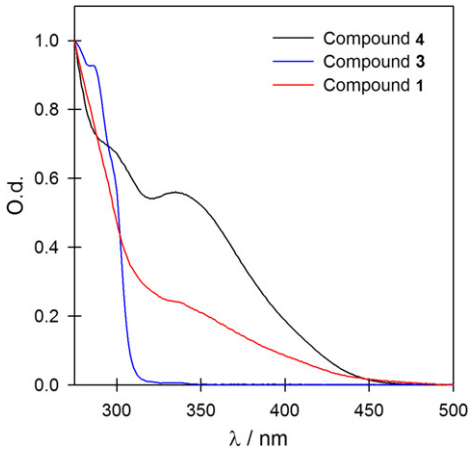
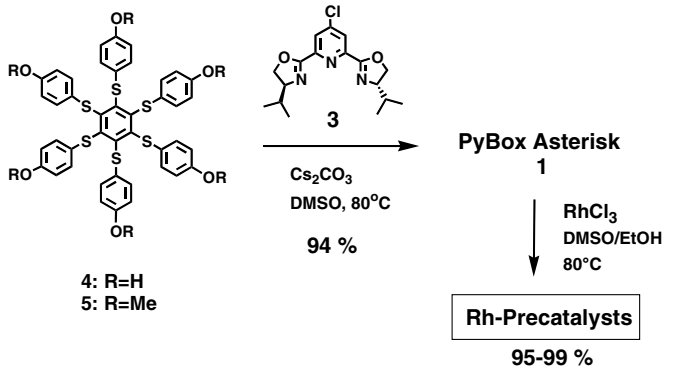


Figure 2. UV–visible absorption spectra of **1**, **3**, and **4** in DMF (10^{-4} M).

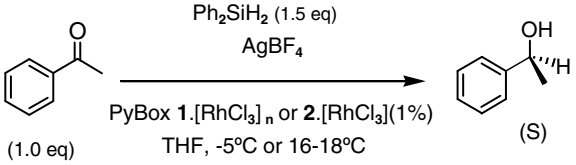
Some catalytic studies were then performed using the experimental conditions of Nishiyama et al.[8d] with its most stable catalytic system having an oxygenated 4-substituted PyBox ligand (Scheme 2).

The hydrosilylation of acetophenone was achieved with various sulfurated precatalysts (Scheme 2, Table 1). To our knowledge, those results with sulfurated PyBox ligands are among the early ones in the literature. Yields varied from 40% to 70% with only 1% molar ratio of precatalyst/substrate in spite of numerous coordinating sulfur groups. For having some reproducible data, it was necessary to freshly distill Ph_2SiH_2. The kinetic data qualitatively showed that the reaction rates suddenly increased at a threshold temperature of 16–18 °C with sulfur-containing ligands **1** and **2**, whereas 4-chloroPyBox **3** was already reactive at −5 °C (Table 1, entry 2; albeit with a moderate yield on a small scale, compared to the literature data.[8d] An electron-donating group at the *para* position of the pyridine ligand is known to deactivate those reactions.[8d] However, a donating sulfur group in ligand **2** only partially repressed the catalytic activities (Table 1, entry 1, 70% yield, 74% ee, 1 mol% $RhCl_3$) when compared to other donating ligands substituted by OMe or NMe_2 groups.[8d] Interestingly, only 1% of the polysulfurated precatalyst with PyBox asterisk ligand **1** could provide a yield close to 60% (Table 1, entry 5) in spite of so many soft metal-coordinating divalent sulfur atoms.

In Figure 3, a linear relation was found between the molar ratio of $RhCl_3$/PyBox asterisk **1** and the % ee. The best enantioselectivity was observed at a low Rh content (excess of PyBox groups) as it was observed by others.[8d] A projected 1:1 ratio would provide the highest enantiopurity at about 75% ee. (as for model [**2**]·[$RhCl_3$]). If the rhodium content increases, the free sites of PyBox decrease and it could probably negatively affect the results



Scheme 1. Synthesis of PyBox asterisk **1** and Rh-precatalysts.



Scheme 2. Model reaction under study, reagents and conditions.

Table 1
Asymmetric Rh-hydrosilylation of acetophenone with PyBox ligands **1**, **2**, and **3**

Entry	Precatalyst (mol %)	Acetophenone (mmol)	Ph_2SiH_2 (mmol)	Molar ratio Ph_2SiH_2/aceto	Silver salt (mol %)	Temperature (0 °C)	Time (h)	Yield (%)	% ee[a]
1	**2**·$RhCl_3$ (1%)	0.85	1.34	1.58	$AgBF_4$ (2%)	18	20	70	74
2	**3**·$RhCl_3$ (1%)	1.83	2.93	1.60	$AgBF_4$ (2%)	−5	3	50	86
3	**1**·$[RhCl_3]_6$ (1%)	0.28	0.44	1.57	$AgBF_4$ (12%)	18	22	47	0
4	**1**·$[RhCl_3]_5$ (1%)	0.55	0.87	1.58	$AgBF_4$ (10%)	18	24	40	15
5	**1**·$[RhCl_3]_4$ (1%)	0.29	0.46	1.59	$AgBF_4$ (8%)	18	72	59	32
6	**1**·$[RhCl_3]_3$ (1%)	0.61	1.05	1.72	$AgBF_4$ (6%)	18	24	47	46
7	**1**·$[RhCl_3]_2$ (1%)	0.33	0.52	1.58	$AgBF_4$ (4%)	18	24	50	60
8	**1**·$[RhCl_3]_2$ (5%)	0.26	0.42	1.62	$AgBF_4$ (20%)	18	24	58	59
9	$RhCl_3$ (1% blank test)	0.96	1.52	1.58	$AgBF_4$ (2%)	18	24	68	0

Isolated yields; all reactions were run in anhydrous THF (dry over Na/benzophenone) with a typical acetophenone concentration of 0.750–1.4 M.
[a] Determined by ^1H NMR of the Moscher ester and confirmed by HPLC analysis (Daicel Chiralcel OD 25 cm × 4.6 mm, hexane/EtOH/diethylamine (94.9:5.01:0.1), detection at 254 nm).

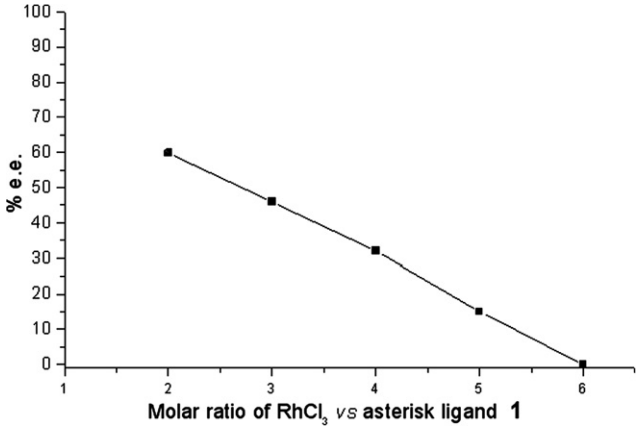


Figure 3. Modulation of the enantioselectivity according to the Rh content in PyBox asterisk ligand **1**.

by leaching the metal out of the coordination sphere. A blank experiment without PyBox **1** (Table 1, entry 9) indicated an important competing non stereoselective hydrosilylation, which might be responsible for the decrease of enantioselectivity. Additionally, a metal coordination of PyBox usually modifies the skewed polyaromatic conformation to a planar one. In this case, it could possibly change the topology of the whole multisite catalyst and hence its catalytic behavior. The linear relation rules out a multivalent or a cooperative effect of the PyBox ligands in our case.

In summary, we demonstrated an efficient synthesis of a discrete multivalent PyBox asterisk **1** obtained from an easy purification. The key step comprised six consecutive couplings of 4-chloro-PyBox **3** to **4** in a 94% yield. The characterization and the electronic properties of **1** were determined by NMR, MALDI-Tof MS, UV–visible, cyclic voltammetry, and elemental analysis. The catalytic behavior of sulfurated PyBox ligands **1** and **2** indicated that single or multiple divalent sulfur donating ligands did not repress so much the catalyst activity. The first transition metal-catalyzed reaction with a persulfurated aromatic compound was shown. Even if the chosen enantioselective reaction did not allow us to fully appreciate a multivalent effect of **1**, some fundamental questions were raised concerning the modulation of the catalyst activity according to its metal content. Additionally, ligand **1** opens the door to other multivalent ligands with various metal and lanthanide salts. The effects of multivalency and multiple sulfur donor ligands were not previously investigated in PyBox chemistry but it could lead to other interesting chiral organometallic supramolecular architectures, to stabilized chiral metallic nanoparticles or to some metal sensors, with UV–visible or electrochemical detection.

Acknowledgments

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References and notes

1. (a) Some reviews: Chan, A. S.; Hayashi, T. *Tetrahedron: Asymmetry* **2006**, *17*, 479–724.; (b) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269–279; (c) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296.
2. Some reviews: (a) Caminade, A.-M.; Servin, P.; Laurent, R.; Majoral, J.-P. *Chem. Soc. Rev.* **2008**, *37*, 56–67; (b) Méry, D.; Astruc, D. *Coord. Chem. Rev.* **2006**, *250*, 1965–1979; (c) Berger, A.; Gebbink, R. J. M. K.; van Koten, G. *Top. Organomet. Chem.* **2006**, *20*, 1–38; (d) *Multimetallic Catalysts in Organic Chemistry*; Shibasaki, M., Yamamoto, Y., Eds.; Wiley: Weinheim, 2004; p 310.
3. (a) Gingras, M.; Raimundo, J.-M.; Chabre, Y. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1686–1712; (b) Gingras, M.; Pinchart, A.; Dallaire, C.; Mallah, T.; Levillain, E. *Chem. Eur. J.* **2004**, *10*, 2895–2904.
4. Some reviews: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335; (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45.
5. (a) Jankowska, J.; Mlynarski, J. *J. Org. Chem.* **2006**, *71*, 1317–1321; (b) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669–685.
6. (a) Alfonso, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 458–461; (b) Allais, F.; Angelaud, R.; Camuzat-Dedenis, B.; Julienne, K.; Landais, Y. *Eur. J. Org. Chem.* **2003**, 1069–1073; (c) Davies, I. W.; Gerena, L.; Cai, D.; Larsen, R. D.; T.R.Verhoeven, ; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 1145–1148.
7. (a) Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M. *Chem. Eur. J.* **2007**, *13*, 9478–9485; (b) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162–10163.
8. (a) Inamoto, T.; Itoh, T.; Yamanoi, Y.; Narui, R.; Yoshida, K. *Tetrahedron: Asymmetry* **2006**, *17*, 560–565; (b) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798–800; (c) Nishiyama, H.; Yamaguchi, S.; Park, S.-B.; Itoh, K. *Tetrahedron: Asymmetry* **1992**, *3*, 1029–1034; (d) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306–4309.
9. (a) Ginotra, S. K.; Singh, V. K. *Tetrahedron* **2006**, *62*, 3573–3581; (b) Tse, M. K.; Döbler, C.; Bhor, S.; Klawonn, M.; Mägerlein, W.; Hugl, H.; Beller, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5255–5260; (c) Nishiyama, H.; Shimada, T.; Itoh, H.; Sugiyama, H.; Motoyama, Y. *Chem. Commun.* **1997**, 1863–1864.
10. (a) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227–232; (b) Iwasa, S.; Maeda, H.; Nishiyama, K.; Tsushima, S.; Tsukamoto, Y.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 8281–8287.
11. Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8006–8007.
12. (a) Gong, H.; Sinisi, R.; Gagne, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 1908–1909; (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483 and references cited therein.
13. (a) Aspinall, H. C.; Bickley, J. F.; Greeves, N.; Kelly, R. V.; Smith, P. M. *Organometallics* **2005**, *24*, 3458–3467; (b) Jönsson, C.; Lundgren, S.; Haswell, S. J.; Moberg, C. *Tetrahedron* **2004**, *60*, 10515–10520; (c) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928–9929.

14. Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041.
15. (a) Masdeu-Bulto, A. M.; Dieguez, M.; Martin, E.; Gomez, M. *Coord. Chem. Rev.* **2003**, *242*, 159–201; (b) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534–3543.
16. Brand, H.; Gingras, M.; Lehn, J.-M.; Tucker, J. H. R. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1303–1307.
17. (a) Menger, F. M.; Azov, V. A. *J. Am. Chem. Soc.* **2002**, *124*, 11159–11166; (b) Lowe, J. N.; Fulton, D. A.; Chiu, S.-H.; Elizarov, A. M.; Cantrill, S. J.; Rowan, S. J.; Stoddard, J. F. *J. Org. Chem.* **2004**, *69*, 4390–4402.
18. *Selected data for PyBox* **1**. Yellow solid. UV–visible (10^{-4} M, DMF): λ_{max} 300 (shoulder), 340 nm. $[\alpha]_D^{23}$ −33.5 (*c* 0.60, $CHCl_3$). R_f = 0.60 (SiO_2, $CHCl_3$/MeOH, 85:15). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 12H, H_{pyr}), 7.08 and 6.97 (A_2B_2, 24H, J_{app} = 8.4 Hz, H atom), 4.47 (t_{app}, 12H, J_{app} = 8.7 Hz), 4.17 (t_{app}, 12H, J_{app} = 8.7 Hz), 4.06 (m, 12H), 1.81 (m, 12H), 1.00 (d, 36H, *J* = 6.6 Hz), 0.88 (d, 36H, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 19.2, 32.8, 71.0, 73.0, 114.0, 124.4, 130.7, 134.0, 147.6, 149.0, 152.8, 161.9, 165.2. MALDI-Tof MS: *m*/*z* = 2618.4 ($M+H^+$), Mcalcd: *m*/*z* = 2617.03 (M^+). Anal. Calcd for $C_{144}H_{156}N_{18}O_{18}S_6$: C, 66.03; H, 6.00. Found C, 65.51; H, 6.15.
19. *Selected data for PyBox ligand* **2**. White solid. $[\alpha]_D^{23}$ +48.4 (*c* 1.0, $CDCl_3$). R_f = 0.57 (SiO_2, AcOEt).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 2H, H pyr), 7.47 and 7.04 (A_2B_2, J_{app} = 8.4 Hz, 4H, H arom), 4.51 (t_{app}, 2H, J_{app} = 8.7 Hz), 4.20 (t_{app}, 2H, J_{app} = 8.7 Hz), 4.10 (m, 2H), 3.36 (sept, 1H, *J* = 6.6 Hz), 1.84 (m, 2H), 1.31 (d, 6H, *J* = 6.7 Hz,), 1.02 (d, 6H, *J* = 6.6 Hz), 0.91 (d, 6H, *J* = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 19.1, 23.1, 32.8, 38.8, 71.05, 72.9, 114.0, 121.0, 132.6, 134.3, 148.9, 152.8, 161.9, 165.4. MS *m*/*e* 467 ($M^{+\cdot}$, 83%), 424 ($M^{+\cdot}$-*i*Pr, 100), 396 (43). HRMS (70 eV, EI): calcd for $C_{26}H_{33}N_3O_3S$ ($M^{+\cdot}$) 467. 2242. Found 467.2247. Anal. Calcd for $C_{26}H_{33}N_3O_3S$: C, 66.78; H, 7.11. Found: C, 66.82; H, 7.03.