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Dibenzothiophene-bis(oxazolines): new sulfur-containing ligands tested in asymmetric palladium-catalyzed allylic substitutions

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Abstract—New asymmetric sulfur-containing ligands based on a dibenzothiophene backbone have been prepared. The chirality was introduced by two oxazoline moieties placed near the sulfur atom. These C_2-symmetric bis(oxazolines) have been successfully tested in asymmetric palladium-catalyzed allylic substitutions leading to up to 77% e.e.

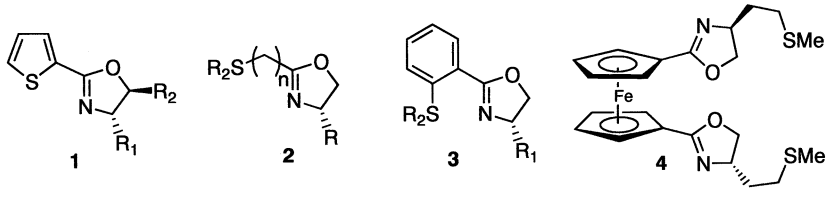
1. Introduction

Chiral sulfur-containing ligands have been successfully used in numerous asymmetric catalytic C–C bond formations,[1] and especially in palladium-catalyzed allylic substitutions.[2] Anderson et al.[3] developed for this purpose sulfur–imine mixed donor chiral ligands which gave up to 94% e.e. Sulfur–pyridine compounds prepared by Chelucci[4] led to 83% e.e. in the same reaction.

Combining the efficiency of oxazolines as ligands in metal-catalyzed reactions[5] and the use of sulfur as an auxiliary donor ligand, Williams prepared various *S*,*N*-ligands (structures **1**[6]–**3**) providing e.e.s of 40–96%.[7] Bryce synthesized chiral oxazolines linked to tetrathiafulvalene[8] towards their use as redox-active ligands, and later improved the activity, the enantioselectivity and the electrochemical stability of this type of complex by the synthesis of chiral ferrocenyl–oxazolines incorporating thioether units (see structure **4**).[9] These systems were successfully tested in palladium-catalyzed allylic substitution reactions (up to 93% e.e.).

We describe the synthesis of new sulfur-containing bis(oxazolines) with dibenzothiophene as backbone, where the sulfur atom is enclosed in a strong π-donor structure. The chirality has been introduced by two oxazoline moieties near the sulfur atom. This skeleton is of particular interest since its aromatic structure allows a great variety of synthetic transformations on various positions of the aromatic rings, according to the procedure used. These C_2-symmetric bis(oxazolines) ligands, DBT-BOx's, offer different possible sites of chelation, by *N*- or *S*-type ligation, and can furthermore afford potential *trans*-chelating tridentate ligands.

During our studies, the publication of a Japanese patent[10] reporting the synthesis of analogous compounds and their use as ligands for the copper-induced cyclopropanation of olefins, prompted us to present here our preliminary results in enantioselective palladium-catalyzed allylic substitution.



Keywords: asymmetric catalysis; dibenzothiophene; bis(oxazolines); palladium; allylic substitutions.

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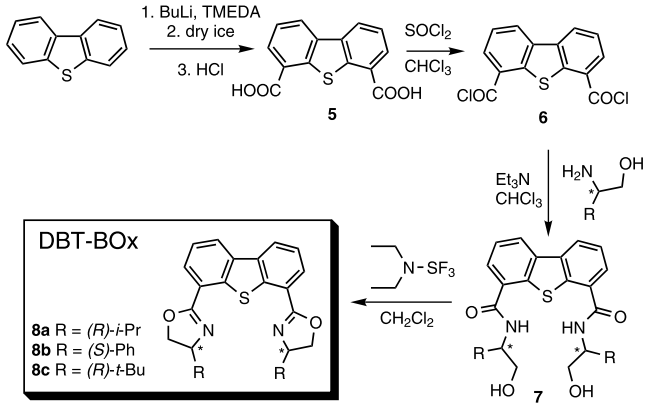
2. Synthesis of 4,6-dibenzothiophenediyl-2,2′-bis(4-alkyloxazolines) (DBT-BOx's)

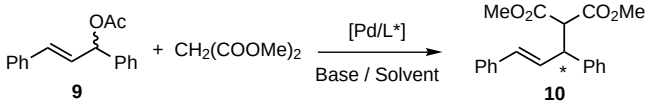
Three different DBT-BOx's have been synthesized following classical synthetic procedures[11] for bis(oxazolines). Commercially available dibenzothiophene was bislithiated[12] and dicarboxylated with dry ice to give 4,6-dibenzothiophenedicarboxylic acid **5** with 88% yield. The corresponding acid chloride **6** was then transformed in amide **7** and cyclization was performed by activation with diethylaminosulfur trifluoride (DAST).[13] DBT-BOx(*i*-Pr) **8a** was thus obtained, by using (*S*)-(+)-2-amino-3-methyl-1-butanol (L-valinol), in 52% yield for the whole process starting from dicarboxylic acid **5**. DBT-BOx(Ph) **8b** was similarly synthesized in 41% yield from (*R*)-(−)-2-phenylglycinol and DBT-BOx(*t*-Bu) **8c** in 37% yield from (*S*)-*tert*-leucinol. These air-stable ligands, easily prepared from commercial amino alcohols, have been fully characterized.†



3. Asymmetric palladium-catalyzed allylic substitution

Allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate **9** with dimethylmalonate was performed under various reaction conditions‡ (see Table 1). This test-reaction allows indeed a facile analysis and comparison of the results due to the symmetry of the substrate. The C_2-symmetric bis(oxazoline) DBT-BOx(*i*-Pr) **8a** was firstly investigated for optimizing reaction conditions. All the tests were performed using a ligand/palladium ratio of 2. The nucleophile was firstly prepared from the reaction between dimethylmalonate and potassium *tert*-butoxide, and $Pd(dba)_2$ was tested as a Pd(0) source. Partial conversion was observed after 70 h reaction in THF at 60°C with 16% e.e. in favour of the (*R*)-(+)-**10** enantiomer (entry 1). A high conversion was observed by using allylpalladiumchloride dimer as palladium precursor, under similar conditions (entry 2). The use of dichloromethane as less coordinating solvent proved however crucial concerning the enantioselectivity of the catalyst (entry 3). An important improvement of the level of enantioselectivity was observed by

Table 1. Allylic substitution of *rac*-**9** in the presence of DBT-BOx ligands



Entry	Ligand	Pd precursor	Base	Solvent	*T* (°C)	*t* (h)	Conversion[a] (% of **10**)	E.e.[b] (% of **10**)
1	**8a**	$Pd(dba)_2$ (5 mol%)	3 equiv. *t*BuOK	THF	60	70	78	16 (*R*)
2	**8a**	$[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2.5 mol%)	3 equiv. *t*BuOK	THF	60	70	95	20 (*R*)
3	**8a**	$[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2.5 mol%)	3 equiv. *t*BuOK	CH_2Cl_2	40	65	95	51 (*R*)
4	**8a**	$[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2.5 mol%)	3 equiv. BSA, 2 mol% KOAc	CH_2Cl_2	40	70	100	77 (*R*)
5	**8b**	$[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2.5 mol%)	3 equiv. BSA, 2 mol% KOAc	CH_2Cl_2	40	120	39	28 (*S*)
6	**8c**	$[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2.5 mol%)	3 equiv. BSA, 2 mol% KOAc	CH_2Cl_2	40	70	50	51 (*R*)

[a] Conversion determined by GC analysis.

[b] E.e. determined by HPLC (Whelk O1) and absolute configuration determined by comparison to literature values.[14]

† *(S,S)-4,6-Dibenzothiophenediyl-2,2′-bis(4-isopropyloxazoline)* (**8a**) (DBTBOx(*i*-Pr)): $[\alpha]_D^{20} = -74.3$ (*c* 2.3, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.27 (dd, 2H, $^3J = 7.8$ Hz, $^4J = 1.0$ Hz), 7.99 (dd, 2H, $^3J = 7.3$ Hz, $^4J = 1.0$ Hz), 7.50 (dd, 2H, $^3J = 7.3$ Hz, $^3J = 7.8$ Hz), 4.51 (m, 2H), 4.19 (m, 4H), 1.84 (m, 2H), 1.17 (d, 6H, $^3J = 6.8$ Hz), 1.03 (d, 6H, $^3J = 6.8$ Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 162.82, 142.44, 136.61, 127.93, 124.57, 124.40, 123.28, 74.16, 71.52, 34.24, 19.79, 19.74; HRMS (ESI) calcd for $C_{24}H_{26}N_2O_2S$ 406.1704, found 406.1715.

‡ *General procedure for the palladium-catalyzed allylic alkylation*: The ligand (10 mol%), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2.5 mol%) and KOAc (2 mol%) were dissolved in dry CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at 40°C for 15 min under an argon atmosphere. BSA (3 equiv.) and dimethyl malonate (3 equiv.) were added, and the resultant solution was stirred at 40°C for 15 min. Whereupon, *rac*-(*E*)-1,3-diphenylprop-2-enyl acetate (50 mg) was added, and the reaction mixture was stirred at 40°C under an argon atmosphere for 3 days. Classical work-up procedure (Et_2O, aq. NH_4Cl) and silica chromatography (cyclohexane/ethyl acetate 9/1) afforded a clear oil (90% yield). The enantiomeric excess was determined by chiral HPLC (Whelk O1, hexane/*i*PrOH 98/2, flow rate 1 mL/min, $\lambda = 254$ nm).

preparing the nucleophile from the reaction of dimethylmalonate and *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[15] using potassium acetate as catalyst. A possible explanation of this effect is that in the presence of the acid scavenger BSA, the catalytic process was initiated by addition of a low amount of potassium acetate: the nucleophile is thus produced portionswise in the reaction mixture. Indeed, the reaction performed under these conditions in dichloromethane allowed the obtention of (*R*)-(+)-**10** with 77% e.e. (entry 4). The use of 3 equiv. of nucleophile led to a total conversion in 3 days (90% isolated yield) in refluxing dichloromethane. The same reaction was also conducted with a ratio L*/Pd = 1 giving the substitution product in a strongly lower yield (18% conversion) but with a similar enantiomeric excess (73% e.e.). An excess of ligand towards palladium (L*/Pd = 4) did not lead to an improved enantioselectivity, compared to entry 4, with however a similar activity. These results suggest that the active catalytic species, formed between one molecule of DBT-BOx per Pd atom, is more rapidly obtained (and stabilized) in the presence of an excess of ligand (at least 2 equiv.). Performing the reaction at room temperature resulted in a drastic loss of activity without improving the selectivity of the catalyst. We have finally checked that the use of $Pd(dba)_2$ as metallic precursor did not improve either the selectivity nor the activity of the substitution in refluxing dichloromethane.

This study indicates that dibenzothiophene-bis(oxazoline) **8a** induces a high level of enantioselectivity in the transformation of *rac*-**9**, when the nucleophile is prepared in refluxing dichloromethane from BSA using the allylpalladiumchloride dimer as catalyst precursor. The structural analogous ligands **8b** and **8c** were tested under these optimized conditions, leading both however to less active and selective catalysts. Ligand **8b** allowed the preparation of (*S*)-(−)-**10** as major isomer (28% e.e., entry 5), whereas **8c** afforded (*R*)-(+)-**10** with 51% e.e. (entry 6).

4. Conclusion

We have synthesized new sulfur containing ligands, DBT-BOx's, that have been successfully used for the asymmetric palladium-catalyzed substitution of the 1,3-diphenylallylsystem. These C_2-symmetric bis(oxazolines) ligands could act as chiral pockets,[16] as proposed by Trost for his highly efficient *N*,*N*′,*P*,*P*′-ligands.[17] We suppose that the steric hindrance generated by the *i*-propyl group represents a good compromise, compared to *t*-butyl or phenyl substituents, for the activity and enantioselectivity of the complex involved in the reaction. Other catalytic enantioselective reactions using DBT-BOx's are currently in progress in our laboratory.

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