

**CATIONIC COPPER(II)–OXAZOLINE-SULFOXIDE CATALYSTS:
APPLICATION TO ASYMMETRIC DIELS-ALDER REACTIONS**

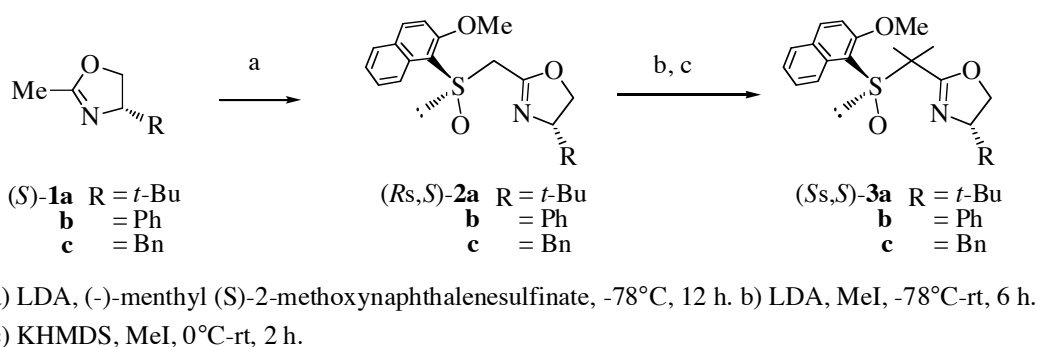
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Abstract—New chiral sulfoxides bearing a chiral 1,3-oxazoline ring were prepared and used as chiral ligands in copper(II)-catalyzed Diels-Alder reactions. The copper(II)-catalyzed cycloaddition reactions using the new chiral ligands were carried out at -78°C to afford adducts with rather high (up to 75 %) enantiomeric excess. Introduction of a counterion (triflate or hexafluoroantimonate) into the catalysts represented higher degree of asymmetric induction; namely, the more cationic copper(II)-oxazoline sulfoxide catalysts improved the enantioselectivity in the cycloaddition reaction.

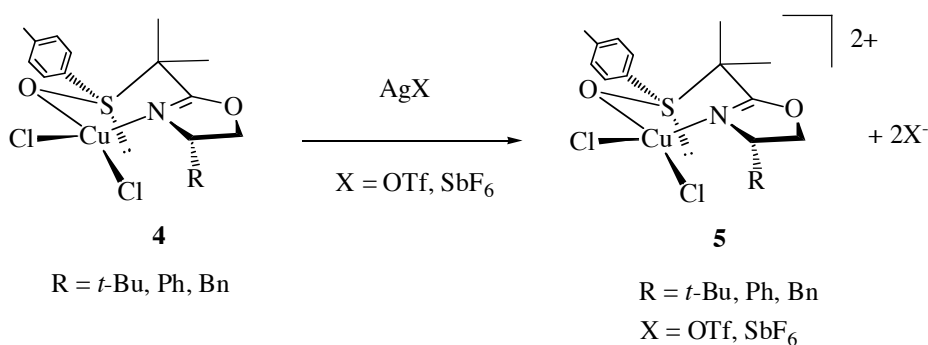
An asymmetric Diels-Alder reaction is one of the most powerful and versatile methods for the creation of six-membered rings in organic synthesis.¹ Catalytic enantioselective processes with chiral Lewis acid-derived catalysts significantly extended the scope and utility of this reaction.^{2,3} In the design of chiral Lewis acidic catalysts, the choice of a matched chiral ligand for the reactions is seriously crucial for the achievement of the superior *endo/exo* selectivity as well as the *endo* enantioselectivity.⁴ Hitherto we have developed a number of chiral sulfoxide ligands in transition metal-catalyzed asymmetric reactions, in which palladium-catalyzed asymmetric allylic alkylations with them were exemplified.⁵

We wish to communicate herein the synthesis of O-N type ligands (**2** and **3**) containing both chiral sulfoxide bearing a bulky aryl group (2-methoxy-1-naphthyl) and 1,3-oxazoline functions, and their application as the chiral ligands in copper(II)-catalyzed enantioselective Diels-Alder reactions.⁶



Scheme 1

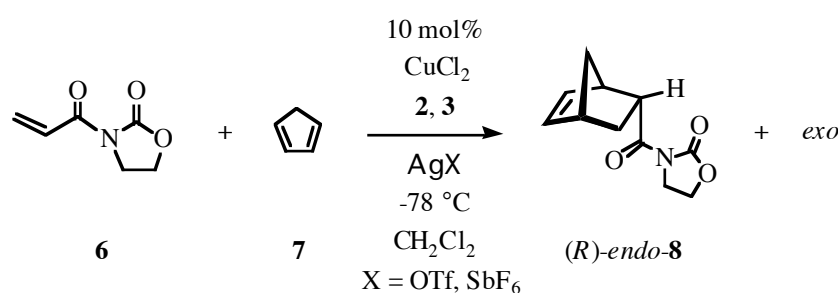
Chiral sulfoxide ligands ($(S_s,S)\text{-3a-c}$) were prepared *via* chiral 1,3-oxazolines ($(S)\text{-1a-c}$) derived from readily available optically active α -amino acids, as follows. Sulfinylation of the chiral 1,3-oxazolines ($(S)\text{-1a-c}$) with (-)-menthyl (*S*)-2-methoxynaphthalenesulfinate⁷ was carried out in THF at -78°C using LDA as a base to give $(R_s,S)\text{-2a-c}$. Methylation of the sulfoxides ($(R_s,S)\text{-2a-c}$) with methyl iodide (LDA, THF, at -78°C – room temperature) followed by the reaction with methyl iodide using potassium hexamethyldisilazide (KHMDS) as a base at -78°C – room temperature, affording $(S_s,S)\text{-3a-c}$ (Scheme 1).⁸



Scheme 2

Chiral Copper(II)–oxazoline-sulfoxide complexes ($\mathbf{4}$) were prepared by the reaction of $(S_s,S)\text{-3a-c}$ (1 equiv.) with commercially available CuCl_2 (1 equiv.) in CH_2Cl_2 at room temperature for 4 h. Initial attempts of a catalytic Diels-Alder reaction of a dienophile ($\mathbf{6}$) with a diene ($\mathbf{7}$) in the presence of 10 mol % of a catalyst ($\mathbf{4}$) at -78°C for 48 h resulted in a very sluggish result in low (below 10 %) yields with practically almost no enantioselectivity (<5% ee).⁹ For increasing the reactivity of the catalyst ($\mathbf{4}$), we have investigated various counterion effects in the above reactions. Thus, a copper(II)–oxazoline-sulfoxide catalyst ($\mathbf{5}$) (X= OTf) with triflate counterion was prepared by treatment of $\mathbf{4}$ (1 equiv.) with AgOTf (2 equiv.) in anhydrous CH_2Cl_2 at room temperature for 2 h under argon atmosphere (Scheme 2). The resulting catalyst

(10 mol%) suspended was cooled to -78°C , and **6** (1 equiv.) was added followed by addition of freshly distilled cyclopentadiene (**7**) (5 equiv.). The reaction mixture was stirred at the temperature for 8 h to provide a Diels-Alder cycloadduct (**8**) in 80 % yield after purification by column chromatography over silica gel (Table 1, Entry 7). The stereochemistry of the cycloadduct (**8**) resulted was determined by $^1\text{H-NMR}$ and HPLC analysis as shown in Table 1.¹⁰ It indicates that the reaction proceeded with high *endo* selectivity (*endo/exo* 82/18) and moderate enantioselectivity (43% ee). The various counterion effects using other ligands in the Diels-Alder reactions are summarized in Table 1.



Scheme 3

The level of the enantioselectivity observed depended on the steric bulk of both the substituents on the 1,3-oxazolines and the counterions (X) employed, or the combination of both the steric factors. The Table 1 indicates that the enantioselectivity of the reactions was increasing in an order of **2c,3c**>**2a,3a**>**2b,3b** upon using triflate as a counterion, whereas **2c,3c**>**2b,3b**>**2a,3a** with a hexafluoroantimonate counterion. The copper(II)-complex derived from the chiral ligand ((*R*,*S*)-**2a**) with a triflate counterion catalyzed the reaction to afford (*R*)-*endo*-**8** with 51% ee, while the use of the catalysts ((*R*,*S*)-[(**2b,c**)-Cu(SbF₆)₂]) with phenyl and benzyl groups provided higher enantioselectivity of (*R*)-*endo*-**8** (64 and 75% ee, respectively).

The anchored effects by dimethyl substituents in the ligands were studied with cupric catalysts using sulfoxide ligands ((*S*,*S*)-**3a-c**). Interestingly, the chiral ligands **2a-c** without anchored substituents provided higher enantioselectivity than the ligands **3a-c** anchored by dimethyl groups, as listed in Table 1, except for entry 11. Similar effects of the counterion and the substituents on the 1,3-oxazolines were observed. The use of (*S*,*S*)-**3b** with hexafluoroantimonate provided (*R*)-*endo*-**8** with moderate enantioselectivity (52% ee, Entry 10). The highest enantioselectivity (75% ee) of (*R*)-*endo*-**8** was obtained with (*S*,*S*)-**2c** as a chiral ligand using hexafluoroantimonate as a counterion.

Table 1. Studies on the Cu (II)-Catalyzed Asymmetric Diels-Alder Reactions of **6** with **7** Using Chiral Ligands (**2**) and (**3**)^{a)}

Entry	Ligand	Counterion X	Yield (%) of 8	<i>endo</i> / <i>exo</i> ^{b)} of 8	e.e. (%) of (<i>R</i>)- <i>endo</i> - 8 ^{c)}
1	2a	OTf	92	83 / 17	51
2	2a	SbF ₆	92	92 / 8	48
3	2b	OTf	86	82 / 18	41
4	2b	SbF ₆	82	88 / 12	64
5	2c	OTf	83	90 / 10	59
6	2c	SbF ₆	83	89 / 11	75
7	3a	OTf	80	82 / 18	43
8	3a	SbF ₆	81	91 / 9	29
9	3b	OTf	91	81 / 19	36
10	3b	SbF ₆	94	89 / 11	52
11	3c	OTf	75	84 / 16	74
12	3c	SbF ₆	80	92 / 8	63

a) The reactions of **6** with **7** (5.0 equiv.) were carried out in CH₂Cl₂ at -78 °C for 8 h in the presence of copper complexes CuX₂ (X = ClO₄ or SbF₆) (0.1 equiv.), which were prepared by reacting ligands (**2**) or (**3**) (0.1 equiv.) with CuCl₂ at rt in CH₂Cl₂ for 4 h, followed by treatment with the corresponding silver salts (AgX) (0.2 equiv.).

b) The *endo/exo* ratios of the product were determined by ¹H-NMR spectrometry.

c) The enantiomeric excess (ee) was determined by HPLC analysis with chiral column OD.

In conclusion, the usefulness of chiral copper(II)—oxazoline-sulfoxide complexes as chiral catalysts and their counterion effects in enantioselective Diels-Alder reactions are now reported. Introduction of triflate and antimonate as a counterion into the catalyst represented a highly effective catalytic system for enantioselective Diels-Alder reactions. The degree of the asymmetric induction was dependent on the steric bulk of the substituents at the chiral centers on the 1,3-oxazolines.

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