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

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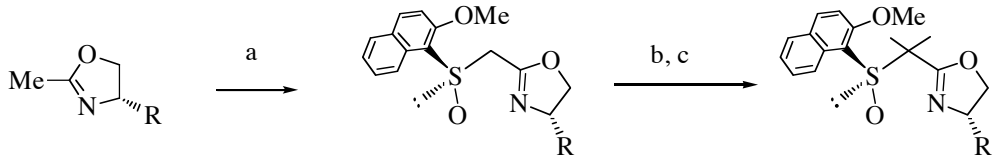
Abstract—New chiral sulfoxides bearing a chiral 1,3-oxazoline ring were prepared and used as chiral ligands in copper(Ⅱ)-catalyzed Diels-Alder reactions. The copper(Ⅱ)-catalyzed cycloaddition reactions using the new chiral ligands were carried out at –78℃ to afford adducts with rather high (up to 75 %) 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]



(*S*)-**1a** R = *t*-Bu
b = Ph
c = Bn

(*R*s,*S*)-**2a** R = *t*-Bu
b = Ph
c = Bn

(*S*s,*S*)-**3a** R = *t*-Bu
b = Ph
c = Bn

a) LDA, (-)-menthyl (S)-2-methoxynaphthalenesulfinate, -78°C, 12 h. b) LDA, MeI, -78°C-rt, 6 h. c) KHMDS, MeI, 0°C-rt, 2 h.

Scheme 1

Chiral sulfoxide ligands ((*S*s,*S*)-**3a-c**) were prepared *via* chiral 1,3-oxazolines ((*S*)-**1a-c**) derived from readily available optically active α-amino acids, as follows. Sulfinylation of the chiral 1,3-oxazolines ((*S*)-**1a-c**) with (-)-menthyl (*S*)-2-methoxynaphthalenesulfinate[7] was carried out in THF at –78℃ using LDA as a base to give (*R*s,*S*)-**2a-c**. Methylation of the sulfoxides ((*R*s,*S*)-**2a-c**) with methyl iodide (LDA, THF, at –78℃—room temperature) followed by the reaction with methyl iodide using potassium hexamethyldisilazide (KHMDS) as a base at –78℃—room temperature, affording (*S*s,*S*)-**3a-c** (Scheme 1).[8]

4

R = *t*-Bu, Ph, Bn

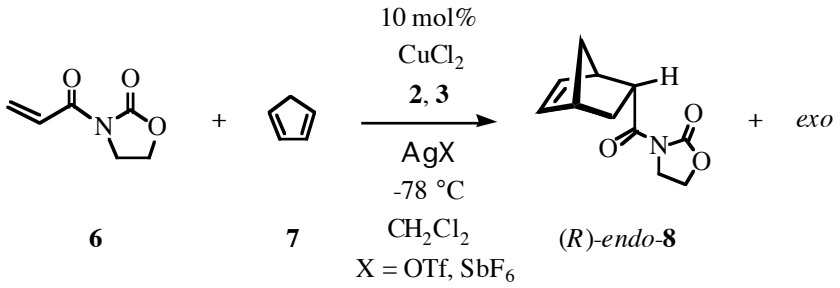
5

R = *t*-Bu, Ph, Bn
X = OTf, SbF_6

Scheme 2

Chiral Copper(Ⅱ)—oxazoline-sulfoxide complexes (**4**) were prepared by the reaction of (*S*s,*S*)-**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 (**6**) with a diene (**7**) in the presence of 10 mol % of a catalyst (**4**) at –78℃ 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 (**4**), we have investigated various counterion effects in the above reactions. Thus, a copper(Ⅱ)—oxazoline-sulfoxide catalyst (**5**) (X= OTf) with triflate counterion was prepared by treatment of **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℃, 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}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 lebel 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 trifrate 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,*S*)-**2a**) with a trifrate counterion catalyzed the reaction to afford (*R*)-*endo*-**8** with 51% ee, while the use of the catalysts ((*R*s,*S*)-[(**2b**,**c**)-Cu(SbF_6)$_2$]) 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,*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,*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,*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**	*endo* / *exo* [b)] of **8**	e.e. (%) of (*R*)-*endo* -**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 CH_2Cl_2 at -78 °C for 8 h in the presence of copper complexes CuX_2 (X = ClO_4 or SbF_6) (0.1 equiv.), which were prepared by reacting ligands (**2**) or (**3**) (0.1 equiv.) with $CuCl_2$ at rt in CH_2Cl_2 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 ^{1}H-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 trifrate 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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