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Design and Synthesis of the First Spiro Bis(isoxazoline) Derivatives as Asymmetric Ligands

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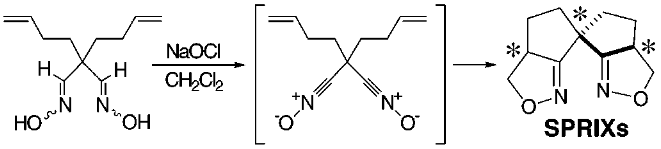
ABSTRACT



A chiral bis(isoxazoline) ligand (SPRIX) containing a rigid spiro skeleton was designed and synthesized via a double intramolecular nitrile oxide cycloaddition. The optically pure SPRIX greatly accelerated the $Cu(acac)_2$-catalyzed asymmetric reaction of diisopropylzinc with cyclohexenone to give the Michael adduct with 49% ee. This is the first example of the use of an isoxazoline ligand for a transition metal-catalyzed reaction. The X-ray crystallographic analysis of the hexacoordinated copper complex of SPRIX confirmed the ligand character.

In recent years isoxazolines have become important compounds in organic synthesis because of their utility as synthetic intermediates for functionalized building blocks.[1] Although the isoxazoline ring has a rigid five-membered ring containing two heteroatoms (nitrogen and oxygen) which serve as Lewis bases, to the best of our knowledge, no study of isoxazolines as ligands for organic reactions has been reported.[2,3] Isoxazolines seemed promising as ligands for transition metal-promoted reactions for several reasons. The ab initio calculations indicated that an isoxazoline could coordinate to metals as shown in Figure 1.[4] The extent and shape of the nitrogen p-orbital of an isoxazoline were similar to that of an oxazoline[5] and we also expected that optically active isoxazoline derivatives would act as ligands for asymmetric synthesis.

We have designed novel bis(isoxazoline) compounds containing a spiro backbone (SPRIXs) (Figure 2).[6] SPRIXs

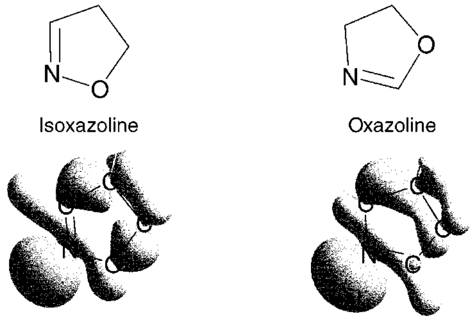


Figure 1. The next HOMO orbitals of isoxazoline and oxazoline.

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(1) (a) Sainsbury, M. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.: Pergamon Press: Oxford, 1991; Vol. 8, pp 646−648. (b) Curran, D. P. *Advances in Cycloaddition*; Curran, D. P., Ed.: JAI Press: Greenwich, CT, 1988; Vol. 1, pp 129−189. (c) Padwa, A.; Schoffstall, A. M. *Advances in Cycloaddition*; Curran, D. P., Ed.: JAI Press: Greenwich, CT, 1988; Vol. 2, pp 28−46. (d) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410−416.

(2) Acidic ligands bearing isoxazoline moiety: (a) Deshmukh, B. K.; Kharat, R. B. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 584−587. (b) Athappan, P. R.; Shanthi, P.; Natarajan, C. *Indian J. Chem., Sect. A* **1995**, *34A*, 648−651. (c) Lampeka, R.; Mihan, S.; Beck, W. *Z. Naturforsh., B: Chem. Sci.* **1996**, *51*, 581−587. (d) Raghuwanshi, P. B.; Doshi, A. G.; Narwade, M. L. *J. Indian. Chem. Soc.* **1996**, *73*, 21−24 and references therein.

(3) Example of chelation control of reaction passway by acylisoxazoline: (a) Wade, P. A.; Price, D. T.; Carroll, P. J.; Dailey, W. P. *J. Org. Chem.* **1990**, *55*, 3051−3056. (b) Curran, D. P.; Zhang, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2613−2625. (c) Kamimura, A.; Yoshihara, K.; Marumo, S.; Yamamoto, A.; Nishiguchi, T.; Kakehi, A.; Hori, K. *J. Org. Chem.* **1992**, *57*, 5403−5413.

10.1021/ol9902881 CCC: $18.00

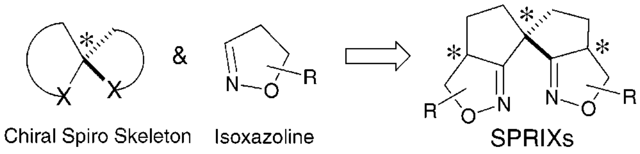


Figure 2. Design of spiro bis(isoxazoline) ligands (SPRIXs).

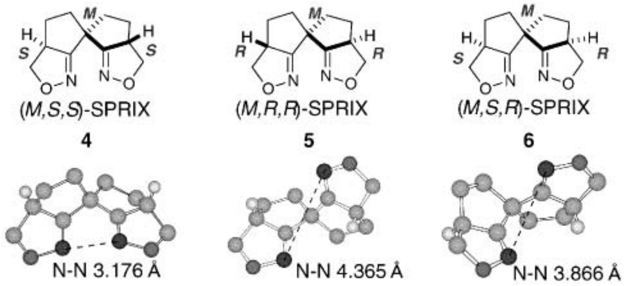


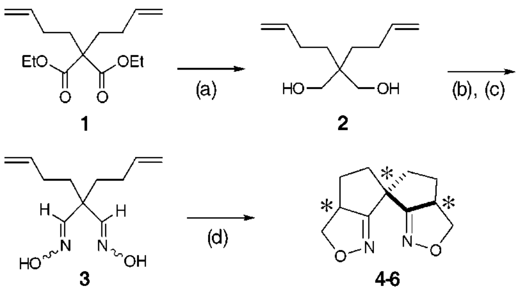
Figure 3. X-ray structures and N−N distances in SPRIXs.

would be efficiently prepared by means of double intramolecular nitrile oxide cycloaddition, which constructs four rings and a spiro backbone in one step. Recently, spiro compounds have been investigated as possible chiral ligands for catalytic asymmetric reactions.[7] The rigid spiro backbone could reduce the conformational obscurity in the transition state in metal-catalyzed reactions, and such compounds containing the spiro backbone seem to make up a new group of chiral ligands. In this paper, we report the first synthesis, characterization, and application of chiral bis(isoxazoline) compounds as a novel class of asymmetric ligands.

The synthesis of SPRIX is shown in Scheme 1. Diethyl dibut-3-enylmalonate (**1**)[8] was reduced with $LiAlH_4$ to afford the diol product **2**. After the oxidation of **2**, the resulting dialdehyde was directly used in the next dioxime formation step. The dioxime **3** was prepared as a single isomer in 87% yield from **2**. All the possible diastereomers of SPRIXs **4**−**6** were easily synthesized via double intramolecular nitrile oxide cycloaddition from **3** in 74% yield (**4** = 36%, **5** = 13%, and **6** = 25%). These SPRIXs could be prepared in multigram quantities. All ligands are stable to air and moisture at room temperature, and stable even under acidic, basic, and oxidative conditions.[9] After the separation of each diastereomer using silica gel column chromatography, we obtained single crystals for each diastereomer. The structures of **4**−**6** were unequivocally determined by X-ray crystallographic analyses as shown in Figure 3.[10] (*M,S,S*)-SPRIX **4** has the shortest distance (3.17 Å) and the smallest torsion angle (45.6°) between the two nitrogens. Enantiomerically pure **4**−**6** were easily obtained by separation with chiral stationary phase column chromatography.[11]

The coordination ability of **4**−**6** to transition metals was briefly examined by mixing SPRIXs with metal salts such as $Cu(OTf)_2$, CuOTf, $CoCl_2$, $NiCl_2$, and $Pd(OAc)_2$ in organic solvents such as MeOH, EtOH, CH_2Cl_2, or toluene. In all cases, the mixture of SPRIX and metal ions showed characteristic color changes. These results indicate a spontaneous and tight metal complex formation with SPRIX. Using optically pure SPRIX **4** and Cu salts, we were able to obtain preliminary results regarding the application of SPRIX as a chiral ligand. The reaction of diisopropylzinc with cyclohexenone was greatly accelerated with a catalytic amount of **4**−$Cu(acac)_2$ complex (the mixing ratio of **4**:Cu = 1.2:1.0) to give the michael adduct in 79% yield with 49% ee (Scheme 2).[12,13] This is the first reported use of an isoxazoline ligand in asymmetric synthesis.

Scheme 1. Synthesis of the Spiro Bis(isoxazoline) Ligands (SPRIXs)[a]



[a] (a) $LiAlH_4$, THF: 94%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (c) $NH_2OH{-}HCl$, Py; 87% (2 steps); (d) NaOCl, CH_2Cl_2; 74% (**4** = 36%, **5** = 13%, **6** = 25%).

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(4) Ab initio calculations were carried out at the HF/6-31G level with Gaussian 94. Frish, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Callacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, Revision D.4; Gaussian, Inc.: Pittsburgh, PA, 1995.

(5) Review of the chiral bis(oxazoline) ligands: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.

(6) SPRIX is an abbreviation of *spiro* bis(*isoxazoline*).

(7) Recent remarkable chiral spiro ligands for asymmetric reactions: (a) Srivastava, N.; Mital, A.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1992**, 493−494. (b) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng, J. *J. Am. Chem. Soc.* **1997**, *119*, 9570−9571.

(8) Bien, S.; Ovadia, D. *J. Org. Chem.* **1974**, *39*, 2258−2260.

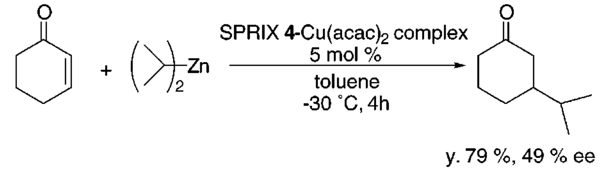
(9) Acidic conditions: MeOH−aqueous 1 N HCl solution (1:1) at room temperature overnight. Basic conditions: MeOH−aqueous 1 N NaOH solution (1:1) at room temperature overnight. Oxidative conditions: MeOH−35% aqueous H_2O_2 (1:1) at room temperature overnight.

(10) All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. (1) Crystal data for **4** : monoclinic; space group *C*2/*c*; $a = 10.860(3)$ Å, $b = 10.154(2)$ Å, $c = 10.865(3)$ Å; $\beta = 121.57(1)°$; $V = 1020.7(5)$ Å^3, $Z = 4$; Mo Kα radiation (−75 °C); $R = 0.041$, $R_w = 0.041$. (2) Crystal data for **5**: orthorhombic; space group *Pccn*; $a = 8.786(2)$ Å, $b = 10.351(2)$ Å, $c = 11.001(2)$ Å; $V = 1000.4(6)$ Å^3, $Z = 4$; Mo Kα radiation (−75 °C); $R = 0.080$, $R_w = 0.078$. (3) Crystal data for **6**: orthorhombic; space group $P2_12_12_1$; $a = 10.461(2)$ Å, $b = 11.285(2)$ Å, $c = 8.660(1)$ Å; $V = 1022.3(3)$ Å^3, $Z = 4$; Mo Kα radiation (−75 °C); $R = 0.097$, $R_w = 0.070$.

(11) DAICEL CHIRALPAK AD (ϕ 2 cm × 25 cm). HPLC conditions: **4** (EtOH 3.0 mL/min, 21 min, 29 min); **5** (EtOH 4.5 mL/min, 30 min, 66 min); **6** (EtOH 3.0 mL/min, 33 min, 39 min).

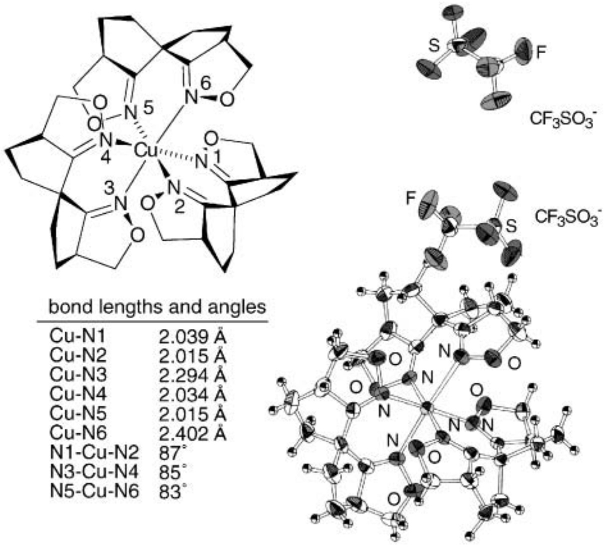
(12) After completion of the reaction, chiral **4** was recovered.

Scheme 2. Asymmetric Catalytic Michael Reaction of Diisopropylzinc Using Cu−SPRIX Complex



This result stimulated us to carry out further experiments to obtain structural information of the SPRIX−Cu complex. Fortunately, single crystals grew from an ethanol solution of the chiral **4**−Cu(OTf)$_2$ complex.[14−16] Surprisingly, X-ray crystallographic analysis showed three molecules of **4** coordinated to a Cu(II) cation.[17] This hexacoordinated copper complex illustrated for us that **4** has the bidentate interaction with copper. Selected bond lengths and angles are listed in Figure 4. The four nitrogens and Cu are coplanar, and the lengths of these four N−Cu bonds are about 2.0 Å. The two *trans* N−Cu bonds were longer than the other N−Cu bonds. In addition, we succeeded in determining the absolute configuration of **4** by X-ray crystallographic analysis of this copper-containing complex. Although we cannot comment on the structure of the active catalyst for the Michael reaction in solution, the information obtained from this complex should be useful in the design of other novel ligands containing an isoxazoline unit.

In conclusion, the first chiral spiro bis(isoxazoline) ligands (SPRIXs) have been prepared, characterized, and shown to act as chiral ligands for asymmetric synthesis. The strong ligand-acceleration ability is very promising for further studies of other catalytic asymmetric reactions. For the construction of more effective asymmetric environments, introduction of aryl and/or alkyl substituents to isoxazoline rings of SPRIXs is also in progress. Moreover, from the isoxazoline rings in SPRIX, several different kinds of transformations are possible, resulting in efficient chiral spiro ligands such as γ-amino alcohol and/or β-hydroxy ketone.



bond lengths and angles	
Cu-N1	2.039 Å
Cu-N2	2.015 Å
Cu-N3	2.294 Å
Cu-N4	2.034 Å
Cu-N5	2.015 Å
Cu-N6	2.402 Å
N1-Cu-N2	87˚
N3-Cu-N4	85˚
N5-Cu-N6	83˚

Figure 4. A hexacoordinated Cu complex of (*M*,*S*,*S*)-SPRIX.

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Supporting Information Available: Detailed experimental procedures, ab initio calculations, and ^{1}H and ^{13}C NMR, IR, and mass spectral data for the products. X-ray crystallographic analyses data for **4**−**6** and Cu complex of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] Enantiomeric excess was determined by ^{13}C NMR spectroscopy after derivatization with 1,2-diphenylethylenediamine. Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431−2434.

[14] The reaction of diethylzinc with cyclohexenone was also accelerated with a catalytic amount (5 mol %) of SPRIX (**4**, **5**, or **6**)−Cu(OTf)$_2$ complex (the mixing ratio of SPRIX:Cu = 1.2:1.0) at −50 °C to give the Michael adduct (88% yield with 10% ee, 41% yield with 15% ee, and 79% yield with 42% ee, respectively.)

[15] The enantiomeric excesses of Michael adduct were not largely affected by the ligand/Cu ratio from 1/1 to 3.3/1.

[16] We were not able to obtain a single crystal of the **4**−Cu(acac)$_2$ complex.

[17] Crystal data for **4**−Cu(OTf)$_2$ complex: monoclinic; space group $P2_1$; $a = 7.493(3)$ Å, $b = 13.001(4)$ Å, $c = 20.876(2)$ Å; $\beta = 95.77(2)°$; $V = 2023.3(10)$ Å^3, $Z = 4$; Mo Kα radiation (−75 °C); $R = 0.049$, $R_w = 0.050$.