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Application of Indane-derived C_2-Symmetric Bis(oxazolines) in Two-point Binding Asymmetric Diels-Alder Reactions

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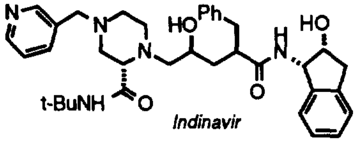
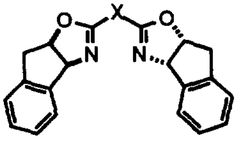
Summary: Bis(oxazolines) 1 - 5 were examined in copper(II)-catalyzed asymmetric Diels-Alder reactions of acrylimide 6 and cyclopentadiene. Highly enantioselective reactions were attained with ligand 1 (up to 95% e.e.) as well as good endo selectivity (39:1) in the $Cu(SbF_6)_2$-catalyzed process.

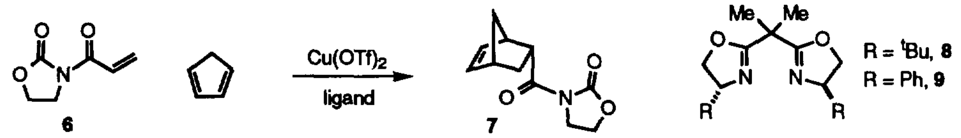
Chiral 2,2'-bis(oxazoline)alkanes and 2-oxazolines have recently been used as ligands in a wide range of transition-metal catalyzed processes.[1] We recently reported[2] a novel approach for the construction of indane-derived C_2-symmetric bis(oxazolines) **1**- **5** by expanding upon the Ritter-type reaction[3] developed for the synthesis of the orally active HIV protease inhibitor *Indinavir*.[4]





X = CMe_2, **1**
X = $(CH_2)_2$, **2**
X = $(CH_2)_3$, **3**
X = 1,2-C_6H_4, **4**
X = 1,3-C_6H_4, **5**

In this paper, we wish to describe our preliminary results using these ligands in asymmetric Diels-Alder reactions. As our model reaction, we chose to use the reaction of the two-point binding dienophile **6** in a copper(II)-catalyzed reaction with cyclopentadiene (Scheme). Evans has extensively studied this reaction using copper(II) catalysts and demonstrated that the bis(oxazoline) **8** derived from *tert*-leucinol gave extremely high levels of stereocontrol (97% e.e.; 96% d.e.; - 78 °C).[5] However, the ligand **9** derived from phenylglycinol gives low levels of selectivity (30% e.e.; - 50 °C).[6] We were intrigued to see how these new indane-derived ligands would perform in the Diels-Alder reaction since we have recently shown that indane-derived chiral auxiliaries allow for excellent stereocontrol in the Diels-Alder reaction.[7]



Scheme

To compare the selectivity of the ligands **1-5**, we chose to investigate the reaction at - 50 °C. The diastero- and enantioselectivity were determined by Supercritical Fluid Chromatography (SFC) and the results are displayed in the Table. It was gratifying to note that, in contrast to the phenylglycinol derived ligand **9**, the conformationally constrained indane-derived ligand **1** gave enhanced levels of selectivity. *Furthermore, by performing the reaction at -65 °C the reaction proceeded with 92% e.e. and endo/exo selectivity of 130:1.* Ligands **2** and **3** with larger bite size and greater flexibility gave disappointing results as did the 1,3-dibenzo ligand **5**. The 1,2-benzo ligand **4**, which is more rigid, behaved quite differently. Surprisingly, the endo adduct *R*-**7** was obtained in 73% e.e. which is the opposite sense of induction observed with ligands **1** and **8**.

During the course of this work, Evans published an improved procedure utilizing innocent counter ions which resulted in much higher turnover numbers.[8] Similar results were obtained with ligand **1** in the $Cu(SbF_6)_2$ system— 92% e.e. at -65 °C. At -75 °C the adduct *S*-**7** was obtained in 92% yield *with 95% e.e. and endo/exo selectivity of 39:1* (10 mol%, 3 h). The latter result is particularly significant since the $Cu(SbF_6)_2$ catalyst generally gives rise to diminished diastereoselectivity.

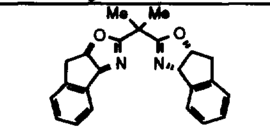
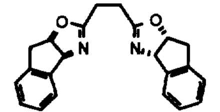
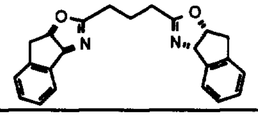
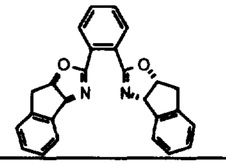
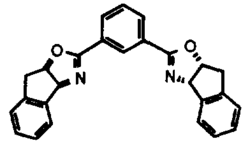
entry	ligand	% e.e.^{a}	endo: exo^a
1	1 	82 (S) 92 (S)^b	50: 1 130:1^b
2	2 	13 (R)	8: 1
3	3 	6 (R)	29: 1
4	4 	73 (R)	22: 1
5	5 	41 (S)	12: 1

Table: Reaction of acrylimide 6 and cyclopentadiene with 10 mol% Cu(OTf)$_2$ and 11 mol% ligand at -50 °C in CH_2Cl_2. a) Determined by SFC (300 bar, 1ml/min, 12% modifier (3% MeOH in hexane) on a HP G1205A instrument using a Chiracel OD-H column. R_t:*endo S 24.65, R 32.99: exo R 28.19, S 26.99*. The sense of induction is based on correlation with the 4*S*-*tert*-butyl ligand 8.[5] b) Run at - 65 °C.

In summary, we have described the use of indane-derived bis(oxazolines) in asymmetric Diels-Alder reactions and demonstrated that highly selective reactions occur in the presence of the ligand **1**. Not only does this ligand provide high levels of enantioselectivity but it also retains high levels of diastereo-control in the copper(II)-hexafluoroantimonate catalyzed Diels-Alder reaction.

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