The influence of ligand bite angle on the enantioselectivity of copper(II)-catalysed Diels–Alder reactions

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Novel spirobis(oxazolines) provide excellent levels of stereocontrol in copper-catalysed Diels–Alder reactions; the larger the ligand bite angle the higher the enantioselection (up to 98.4% ee).

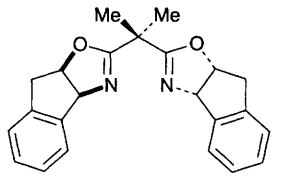
One of the key features of transition metal-catalysed processes is the ability to control the regio- and stereo-chemical outcome of a reaction by variation of the steric and electronic nature of the ligand. Some of the most important examples of 'ligand tuning' are evident in asymmetric catalysis where ligands can have a profound influence on the enantiomeric excess of the product.[1] Bis(oxazolines) have recently been used by Evans[2] and others[3] in a wide range of transition metal-catalysed processes, but to our knowledge a systematic study of the role of ligand bite angle in this area has not been reported. Herein, we describe the synthesis of spirobis(oxazolines) **2a–d**, and show a direct correlation between the size of the ligand bite angle and enantioselectivity in asymmetric Diels–Alder reactions.

Recently we reported that the ligand **1** can be used in the copper(II)-catalysed two-point binding asymmetric Diels–Alder reaction of acrylimide **3** and cyclopentadiene to give the product **4** in 82.5% ee at −50 °C and 95.0% ee at −75 °C (Scheme 1).[4] We were intrigued to determine what role the ligand bite angle θ had on the enantio- and diastereo-selectivity of this reaction. To establish the influence of ligand bite angle θ, a series of spirobis(oxazoline) ligands **2a–d** were prepared that have different Φ, and hence, ligand bite angles.

The ligands **2a–d** were synthesized in two steps from the readily available 1*S*,2*R*-amino indanol **5** (Scheme 2). Condensation with diethylmalonimidate **6** at reflux in 1,2-dichloroethane on a 0.2 mol scale gave the pivotal bis(oxazoline) **7** which was isolated in 72% yield by direct crystallization. Treatment of a mixture of **7** (1 equiv.), TMEDA (2 equiv.), and diisopropylamine (1 equiv.) with butyllithium (2 equiv.) at −65 to −20 °C, followed by addition of the appropriate diiodoalkane (1.1 equiv.) (−65 °C to room temp.) led to formation of the spirobis(oxazolines) **2a–d**, which were isolated by crystallization in 50–70% yield.‡§ By using iodomethane as the electrophile the dimethyl ligand **1**, which has been previously prepared *via* a Ritter-type reaction of indandiol,[5] was also obtained in 62% yield. Hence, this alkylation strategy has the flexibility to provide a wide variety of bis(oxazoline) ligands.

Computational methods were used to determine the value of Φ for the *uncomplexed* spirobis(oxazolines) **2a–d** and the dimethyl ligand **1**. Conformations were generated for each bis(oxazoline) using a distance geometry program, JG. All of the conformations were energy minimized using a distance-dependent dielectric constant and the MM2X forcefield implemented in the molecular mechanics program OPTIMOL.[6] The angles Φ from the minimizations are shown in Table 1.¶

The spirobis(oxazoline) ligands **2a–d** were utilized in the Cu(OTf)$_2$-catalysed two-point binding Diels–Alder reaction of acrylimide **3** and cyclopentadiene at −50 °C. The enantio- and diastereo-selectivities were determined by supercritical fluid chromatography (SFC) and the results of this study are shown in Table 1. In all cases the reactions proceeded at qualitatively similar rates. The use of innocent counter ions (SbF_6^-) in this reaction has been reported to give increased turnover numbers.[2] This was indeed the case and identical enantioselectivities were obtained (**2a**, 96.0% ee); however, the reaction proceeded with diminished diastereoselectivity (*endo*:*exo* 26:1). When the reaction was performed at −70 °C the ee increased to 98.4% ee for ligand **2a** with either triflate (*endo*:*exo*, 96:1) or hexafluoroantimonate (*endo*:*exo*, 59:1) as counterions. Significantly substitution of the dimethyl moiety in ligand **1** (Φ = 104.7 °)—the most commonly used architectural feature of the bis(oxazoline) scaffolds—to a cyclopropyl in ligand **2a** caused a dramatic increase in enantioselectivity from 82.5 to 96.3% ee



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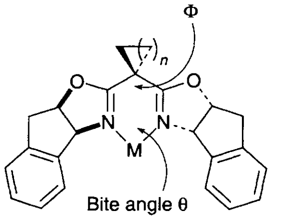
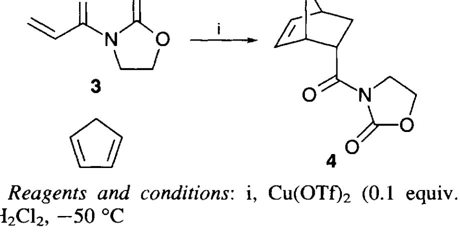
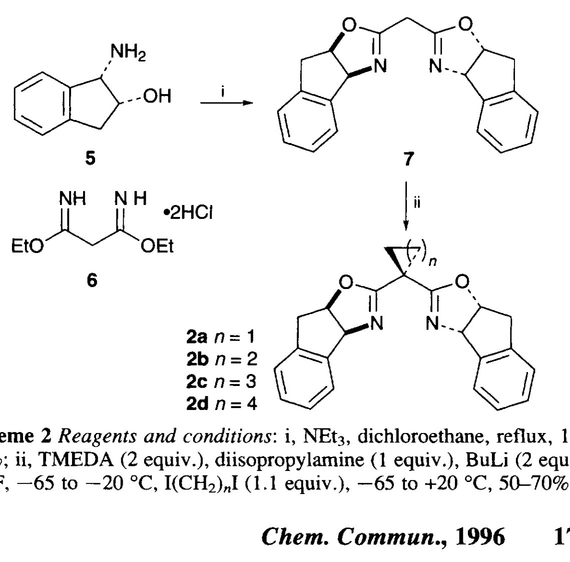


2a–d, *n* = 1–4



Scheme 1 *Reagents and conditions*: i, Cu(OTf)$_2$ (0.1 equiv.), **1** (0.11 equiv.), CH_2Cl_2, −50 °C



Scheme 2 *Reagents and conditions*: i, NEt$_3$, dichloroethane, reflux, 12 h, 72%; ii, TMEDA (2 equiv.), diisopropylamine (1 equiv.), BuLi (2 equiv.), THF, −65 to −20 °C, I(CH$_2$)$_n$I (1.1 equiv.), −65 to +20 °C, 50–70%

at −50 °C. This new ligand **2a** now provides synthetically useful selectivities at these relatively moderate temperatures.

A clear trend has emerged from this study. The larger the value of Φ in **2a–d**—and hence the ligand bite angle θ—the higher the observed enantioselectivity. A similar correlation of ligand bite angle θ and enantioselectivity has been reported by Trost in palladium-catalysed allylic alkylation reactions.[7] The orientation of the C_8–H bond in aminoindanol-derived auxiliaries has been shown to have a significant effect on the diastereoselectivity of Diels-Alder reactions.[8] Similarly, the orientation of this C_8–H proton in the 'chiral-pocket' of the copper-complex may play an important role in this class of ligands. Alternatively, the larger value of Φ may promote a change in coordination away from an idealized square-planar geometry at the copper(II)-centre. Preliminary UV–VIS data suggests that the bis(oxazoline)–Cu(II) complexes have similar molar absorbances and position of absorption bands ($\Delta_o \sim 15\,000$ cm^{-1}) and hence formation constants. However, discussion of actual coordination structure of the complexes will have to be postponed until further experimental and computational data is available.[9]

Table 1 Reaction of acrylimide **3** and cyclopentadiene in CH_2Cl_2 at −50 °C in the presence 10% $Cu(OTf)_2$ and 11% ligand

Ligand	Φ(°)	% ee *endo* (*S*)[a]	*endo* : *exo*[a]
2a	110.6	96.3	44 : 1
2b	108.0	92.0	38 : 1
2c	105.8	89.5	37 : 1
2d	103.7	83.0	26 : 1
1	104.7	82.5	49 : 1

[a] Sense of induction, % ee, and *endo* : *exo* selectivity were determined by SFC on a Chiracel OD-H column. In all cases the yield was >90% (ref. 5).

Footnotes

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[‡] All reactions were performed with reagents and solvents as received from commercial sources. All compounds gave satisfactory spectral and analytical data.

[§] For **2a** 1,2-dibromoethane gave a 35% yield.

[¶] Address questions regarding the calculations to Dr Laurie Castonguay.

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