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(Phosphino-oxazoline)copper(II) Complexes as Chiral Catalysts for Enantioselective Diels-Alder Reactions[‡]

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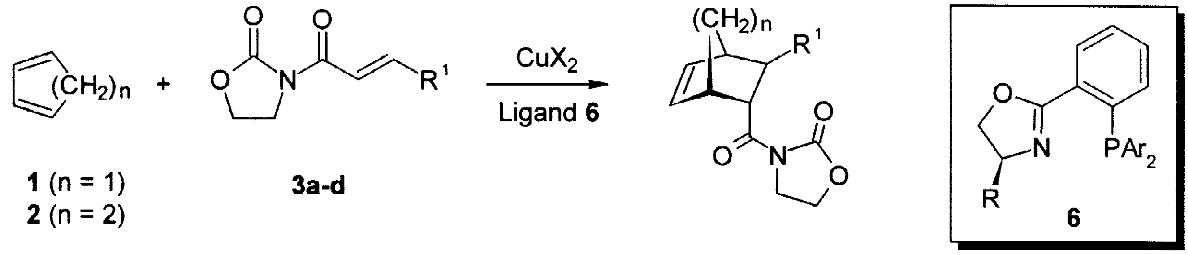
Abstract: (Phosphino-oxazoline)copper(II) complexes with bulky aryl groups at phosphorus were found to be excellent catalysts for Diels-Alder additions of 3-acryloyl-1,3-oxazolidin-2-one. Diels-Alder reactions with a range of substrates were investigated. Enantioselectivities of up to 97 % ee were achieved. © 1997 Elsevier Science Ltd. All rights reserved.

Evans and coworkers discovered that Cu(II) complexes of C_2-symmetric bisoxazolines (BOX) and of pyridyl-bisoxazolines (PYBOX) are effective chiral Lewis acid catalysts for Diels-Alder[1] and Mukaiyama aldol reactions.[2,3] Earlier, corresponding complexes of Mg(II) and Fe(III) were used as catalysts for Diels-Alder reactions.[4] A general problem associated with these complexes is their fairly weak Lewis acidity and, therefore, low catalytic activity. A phosphorus σ-donor/π-acceptor ligand is expected to display enhanced Lewis acidity compared to a N-donor ligand. This observation induced us to probe phosphino-oxazolines as ligands. As result we are able to report the first application of chiral (phosphino-oxazoline)Cu(II) complexes as catalysts in the Diels-Alder reaction of substituted N-acylamide dienophiles (Scheme 1).

Scheme 1



3a, 4a, 5a R^1 = H
3b, 4b R^1 = Me
3c, 4c R^1 = Ph
3d, 4d R^1 = COOEt

4a-d (n = 1)
5a (n = 2)

The catalyst was prepared by treatment of $Cu(OTf)_2$ with ligand **6**[5] [molar ratio of **6** : Cu(II) = 1.1] at rt in dry solvent for 1 h under an inert atmosphere. The resulting colored solution (deep green to dark brown, depending on the ligand) of the catalyst (0.1-10 mol % relative to **3**) was cooled and 1 equiv of dienophile and 5 equiv of freshly distilled diene were added. Cycloadducts were isolated by chromatography and analyzed for *endo-exo* ratio by ^{1}H NMR or HPLC and enantiomeric excess by either HPLC or GLC on chiral phases. Results are summarized in Table 1.

Enantioselectivity was found to depend strongly on the size of both the substituent R and the P-Ar group of the ligand (entries 1-7). With the smallest ligand **6a** (R = Me, Ar = Ph) enantioselectivity was low (37 % ee, entry 1). However, enantioselectivities increased with the steric bulk of the substituent R (entries 2, 3) and the aryl substituents at phosphorus (Ar = mesityl, 1-naphthyl, entries 4, 6). The best result (97 % ee, entry 6) in this

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[‡] Dedicated to Prof. Dieter Seebach on the occasion of his 60th birthday.

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series was obtained with ligand **6f**. In comparison to the bis(oxazoline)copper(II) complexes employed by Evans (reaction time of 18 h at -78 °C for the reaction of **1** with **3a**[1a] and of 48 h at 25 °C for the reaction of **2** with **3a**[1b]) the catalysts prepared from Cu(OTf)$_2$ and the ligands **6e** and **6f**, with naphthyl substituents, showed much higher activity (entries 5, 6, 16). With ligand **6g** unexpected results were obtained (entry 7) in that *endo-exo* selectivity was reversed[6] (28:72) and an *endo* adduct with opposite absolute configuration (2*R*) was formed. This result is probably due to the enormous steric bulk of the dianthrylphosphino group which perhaps causes a distortion of the planar towards a tetrahedral coordination arrangement.[2b,4b-c]

A variety of solvents were probed; the best results were obtained with CH$_2$Cl$_2$ and EtNO$_2$.[7] In general, reactions were significantly faster in EtNO$_2$ than in CH$_2$Cl$_2$ as is demonstrated for complexes of ligands **6c** and **6f** by Figure 1. However, enantioselectivity was slightly higher in CH$_2$Cl$_2$ than in EtNO$_2$. The plot also illustrates that the very bulky ligand **6f** gives rise to the most active catalyst.

Table 1. Diels-Alder reactions of N-acylamides **3a-d**.

No.	Diene	Dienophile	Ligand				X	Solvent	Temp. [°C]	Time [h]	Yield[b] [%]	*endo-exo*[c] ratio	ee [%][d] (config.)
				R	Ar[a]	mol %							
1	**1**	**3a**	**6a**	Me	Ph	10	OTf	EtNO$_2$[e]	-78	40	86	93:7	37 (2*S*)
2	**1**	**3a**	**6b**	*i*Pr	Ph	10	OTf	EtNO$_2$[f]	-78	22	84	92:8	54 (2*S*)
3	**1**	**3a**	**6c**	*t*Bu	Ph	10	OTf	CH$_2$Cl$_2$	-78	15	86	95:5	82 (2*S*)
4	**1**	**3a**	**6d**	*t*Bu	Mesityl	10	OTf	CH$_2$Cl$_2$	-78	40	91	96:4	92 (2*S*)
5	**1**	**3a**	**6e**	*t*Bu	2-Naph	10	OTf	CH$_2$Cl$_2$	-78	3	96	92:8	75 (2*S*)
6	**1**	**3a**	**6f**	*t*Bu	1-Naph	10	OTf	CH$_2$Cl$_2$	-78	2.5	92	94:6	**97** (2*S*)
7	**1**	**3a**	**6g**	*t*Bu	1-Anth	10	OTf	CH$_2$Cl$_2$	-78	20	95	**28:72**	92[g]
8	**1**	**3a**	**6f**	*t*Bu	1-Naph	10	OTf	EtNO$_2$	-78	1	94	94:6	93 (2*S*)
9	**1**	**3a**	**6f**	*t*Bu	1-Naph	1	OTf	EtNO$_2$	-78	44	86	95:5	92 (2*S*)
10	**1**	**3a**	**6f**	*t*Bu	1-Naph	10	OTf	CH$_2$Cl$_2$	-20	0.5	94	89:11	89 (2*S*)
11	**1**	**3a**	**6f**	*t*Bu	1-Naph	1	OTf	CH$_2$Cl$_2$	-20	0.5	92	88:12	88 (2*S*)
12	**1**	**3a**	**6f**	*t*Bu	1-Naph	0.1	OTf	CH$_2$Cl$_2$	-20	5	89	89:11	81 (2*S*)
13	**1**	**3b**	**6f**	*t*Bu	1-Naph	10	OTf	CH$_2$Cl$_2$	-20	42	98	88:12	86 (2*S*)
14	**1**	**3c**	**6f**	*t*Bu	1-Naph	10	OTf	EtNO$_2$	RT	64	74	**40:60**	85[h]
15	**1**	**3d**	**6f**	*t*Bu	1-Naph	10	OTf	CH$_2$Cl$_2$	-40	4	95	60:40	75 (3*R*)[i]
16	**2**	**3a**	**6f**	*t*Bu	1-Naph	10	OTf	CH$_2$Cl$_2$	RT	4.5	87	>98:2	72 (2*S*)
17	**2**	**3a**	**6f**	*t*Bu	1-Naph	10	OTf	CH$_2$Cl$_2$	0	48	82	>98:2	79 (2*S*)
18	**1**	**3a**	**6f**	*t*Bu	1-Naph	10	SbF$_6$	CH$_2$Cl$_2$	-78	1.5	92	95:5	88 (2*S*)
19	**1**	**3a**	**6f**	*t*Bu	1-Naph	10	SbF$_6$	EtNO$_2$	-78	1.5	91	93:7	30 (2*S*)
20	**2**	**3a**	**6f**	*t*Bu	1-Naph	10	SbF$_6$	CH$_2$Cl$_2$	0	40	61[k]	>98:2	79 (2*S*)
21	**2**	**3a**	**6f**	*t*Bu	1-Naph	10	SbF$_6$	EtNO$_2$	0	15	96	>98:2	55 (2*S*)

[a] Naph = Naphthyl, Anth = Anthryl. [b] Yields of isolated cycloadducts. [c] *Endo-exo* ratios were determined by ^{1}H NMR or HPLC. [d] Ee of *endo* isomers, determined as follows (**x** and **n** refer to *exo* and *endo* isomers, respectively): HPLC using a Daicel ODH column, **4a**: hexane/isopropanol 9:1, **4ax**: t_r = 39.5 min, 41.0 min, (-)-(2*S*)-**4an**: t_r = 42.9 min, (+)-(2*R*)-**4an**: t_r = 47.3 min; **4b**: hexane/ethanol 95:5, **4bx**: t_r = 36.9 min, 38.0 min, (-)-(2*S*)-**4bn**: t_r = 40.6 min, (+)-(2*R*)-**4bn**: t_r = 44.2 min; **4c** after conversion of the cycloadducts with (-)-(*S*)-1-phenylethylamine to the corresponding diastereomeric amides (ref. 9): hexane/isopropanol 85:15, *exo*-amides: t_r = 12.6 min (major isomer), 16.8 min, *endo*-amides: t_r = 20.7 min, 23.9 min]; GLC [**4dn** after conversion to the corresponding iodolactone (ref. 10), γ-cyclodextrin, FS Lipodex E (Macherey-Nagel), temp. 180 °C: (-)-(1*S*)-iodolactone: t_r = 28.4 min, (+)-(1*S*)-iodolactone: t_r = 30.1 min; **5an** after conversion to the corresponding iodolactone, permethyl-β-cyclodextrin-B-236-M-19 (Chrompack), temp. 160 °C: (+)-(1*S*)-iodolactone: t_r = 39.5 min, (-)-(1*S*)-iodolactone: t_r = 41.8 min]. Absolute configurations were determined by comparison with literature data (ref. 1, 8). [e] In CH$_2$Cl$_2$ the reaction was very slow at -78 °C. [f] In CH$_2$Cl$_2$: 43 % ee, *endo-exo* ratio: 85:15. [g] Ee of the *exo* product; ee of the *endo* product: 71 % ee (**2*R***). [h] Ee of the *exo* product; ee of the *endo* product: 32 % ee. [i] Note that reversal of the descriptor is a consequence of CIP priorities. [k] 30 % of the starting material were recovered.

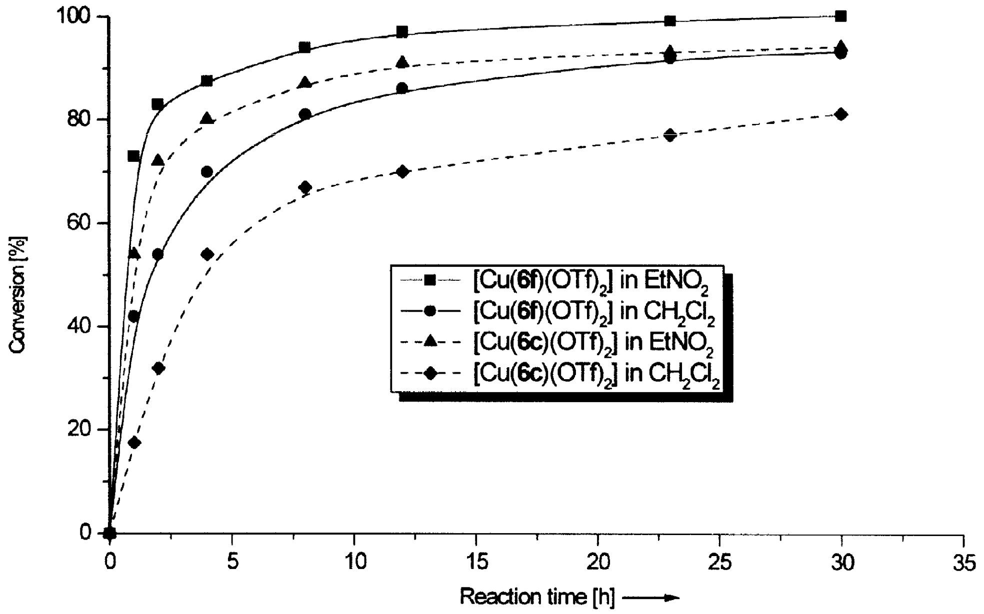

Figure 1. Influence of the ionization capacity of the solvent and the steric bulk of the ligand on the rate of the Diels-Alder reaction of cyclohexadiene with dienophile **3a** [5 °C, c(**3a**) = 0.3 mol/l, 10 mol % of catalyst].

In order to further test the efficiency of the best ligand (**6f**), experiments were carried out with less than 10 mol % of catalyst. Only 1 mol % in EtNO$_2$ at -78 °C furnished complete conversion in 44 h without decrease of enantioselectivity (92 % ee, entries 8, 9). At -20 °C the reaction proceeded even with 0.1 mol % of catalyst within 5 h, however, with lower enantioselectivity (81 % ee, entry 12).

The scope of the reaction was assessed by reactions of dienophiles **3b**-**3d** with cyclopentadiene. The N-crotonoyl-oxazolidinone **3b** reacted at -20 °C with good enantioselectivity (86 % ee, entry 13), while the N-cinnamoyl-oxazolidinone **3c** underwent the reaction with reversed *endo-exo* selectivity (*endo-exo* ratio = 40:60, entry 14) and good *exo* (85 % ee) and low *endo* enantioselectivity (32 % ee). Enantiomeric excess of **4c** was determined by HPLC using a Daicel ODH column after conversion of the cycloadducts with (-)-(*S*)-1-phenylethylamine to the corresponding diastereomeric amides.[9] Finally, the N-fumaroyl-oxazolidinone **3d** afforded the cycloadduct **4d** (entry 15) with moderate *endo-exo* selectivity (60:40) and good enantioselectivity (75 % ee). The enantiomeric excess of **4d** was determined *via* the corresponding iodolactone.[10]

It was recently reported for Diels-Alder reactions catalyzed by Cu(II) complexes of bisoxazolines that with SbF$_6^-$ as counter ion particularly high enantioselectivity and reactivity are obtained.[1b] Accordingly, we compared catalysts with SbF$_6^-$ and triflate counter ion (entries 18-21). Slightly lower enantioselection (88 % ee, entry 18), compared to that with the corresponding triflate (entry 6), was obtained in the reaction of acrylimide **3a** with cyclopentadiene in CH$_2$Cl$_2$ in the presence of 10 mol % of the complex [Cu(**6f**)(SbF$_6$)$_2$][11]. However, in the more polar solvent EtNO$_2$ the SbF$_6^-$ salt induced a low degree of enantioselectivity (30 % ee, entry 19). Similar results were obtained for the reaction of **3a** with cyclohexadiene (entries 17, 20, 21).

The steric course of these reactions can be rationalized by assuming a square-planar phosphino-oxazoline-Cu(II)-dienophile complex as intermediate, similar to that proposed by Evans[1a] for bis(oxazoline)Cu(II) complexes (cf. Figure 2). Other than with C$_2$-symmetric bis(oxazoline) ligands, there are two possible isomeric square-planar phosphino-oxazoline complexes (**A**, **B**). In isomer **A**, the attack of the diene at the *endo*-*Re*-face of the acryloyl group, leading to the observed (2*S*)-cycloadduct, is favoured. In complex **B** the *Si*-face of the acryloyl moiety is expected to be better accessible. On the basis of this model, the higher enantioselectivity induced by ligands with bulky aryl substituents at phosphorus (1-naphthyl, mesityl) can be explained by increased interaction between an aryl group and the dienophile (model **B**) which disfavours isomer **B**.

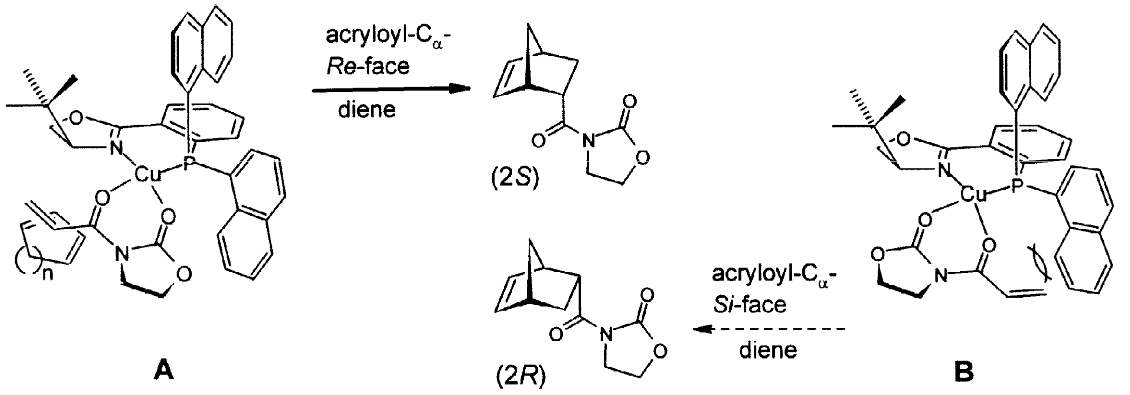

Figure 2. Proposal concerning the steric course of the cycloaddition *via* a square planar Cu(II) complex.

In conclusion, we have found that Cu(II) complexes of chiral phosphino-oxazolines can be useful chiral Lewis acids in enantioselective Diels-Alder reactions. Thus, the range of successful applications[12] of these remarkable ligands is once more extended.

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