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Allylic Oxidation Catalyzed by Chiral Dinuclear Copper Complexes

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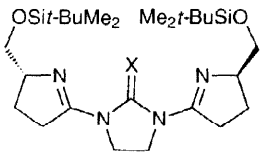
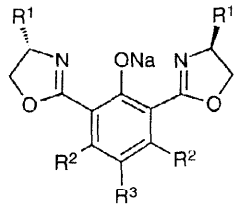
Abstract: Copper(I) complexes prepared *in situ* from $Cu(I)(CH_3CN)_4PF_6$ and several chiral dinucleating ligands have been studied as catalysts for the allylic oxidation of cyclohexene with *tert*-butyl perbenzoate. Cyclohexenyl benzoate was obtained in yields ranging from 30-92% and with enantioselectivities up to 37% ee. Surprisingly, the formation of an imide has also been observed in significant yields.

The development of effective catalysts for the enantioselective oxidation of alkanes and olefins is a particularly challenging goal in asymmetric synthesis. Using mononuclear transition metal complexes as catalysts, numerous highly efficient methods such as the epoxidation of allylic alcohols[1], the epoxidation of olefins by chiral manganese salen catalysts[2] or the dihydroxylation of olefins[3] have been developed and lead to products with excellent enantiomeric purities. There are only few examples known where dinuclear catalytic systems are involved, and the enantiomeric excesses reported so far are below 10% ee.[4] Nevertheless, the application of dinuclear metal complexes as catalysts for oxygenation reactions should be an especially promising approach since such systems are principally able to support multielectron transfers. Apart from reactions which utilize standard oxidants (hydroperoxides, peracids or peresters) dinuclear complexes might also be suitable for the activation of molecular oxygen. For example, methane monoxygenase (MMO) catalyzes the oxidation of methane to methanol and consists of a dinuclear iron complex in the active site.[5] Similar chemistry has been studied with dinuclear Fe(III)-peroxo complexes as catalysts for the oxidation of unfunctionalized hydrocarbons.[6]

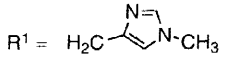


X = O **1a**

S **1b**

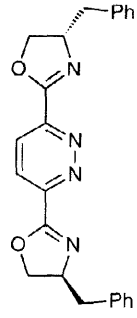


R^1 = *i*-Pr R^2 = H
R^3 = *t*-Bu **2a**



2b

R^2 = CH$_3$ R^3 = H



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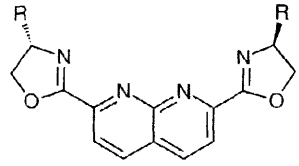
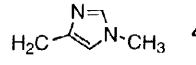


R = Bn **4a**



4b

We recently reported on the synthesis of several dinucleating ligands **1-4** and their coordination properties.[7] In order to find possible applications of these ligands for catalytic enantioselective synthesis we studied first the copper catalyzed allylic oxidation of unfunctionalized cycloalkenes developed by *Kharasch et al.* (*Scheme 1*).[8] Previous mechanistic investigations pointed out, that the reaction presumably proceeds by a radical

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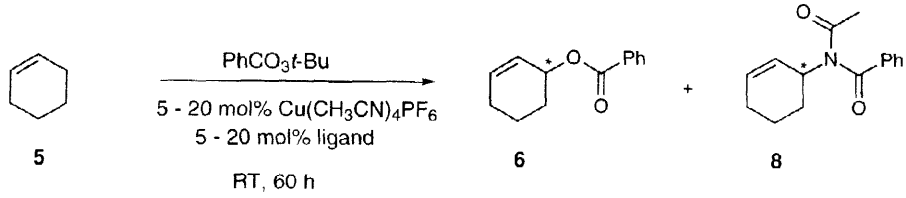
chain mechanism via an intermediate allyl radical.[9] The copper catalyst is suggested to be directly involved in the formation of the allylic C-O bond.[10] Using chiral mononuclear bis- or trisoxazoline-copper complexes[11] or copper-amino acid complexes[4c,12] as catalysts, several groups, including ours, succeeded to perform this reaction enantioselectively with moderate to good optical yields. Copper complex **9** is the only dinuclear catalyst applied to this reaction so far, however, only low enantioselectivities (up to 10% ee) were reported.[4c]



Scheme 1

Table 1: Enantioselective Allylic Oxidation of Cyclohexene with *in situ* Prepared Copper(I) Catalysts

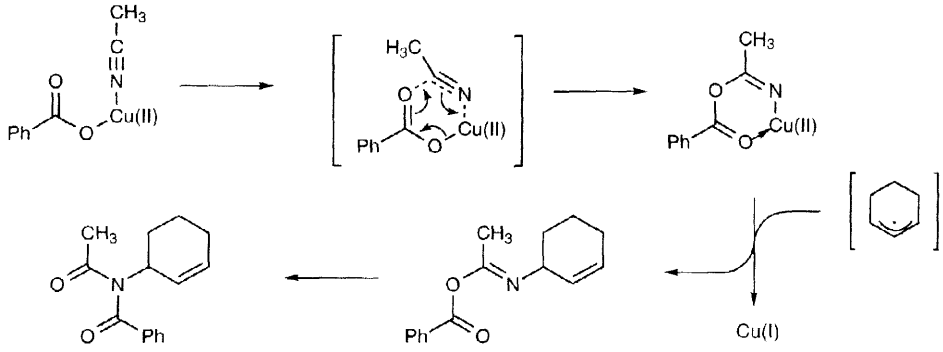
Entry	Ligand	Catalyst [mol%] Lig.	Cu(I)	Time [h]	Conv.[a] [%]	Yield [%][a] Ester **6**	Imide **7**	ee [%] Ester [b]	Imide [c]
1	**1a**	5	10	65	86	82	0	16.8 *(R)*	-
2	**1a**	10	10	65	>99	97	0	8.3 *(R)*	-
3	**1a**	2	3.8	60	95	95	0	8.3 *(R)*	-
4	**1a**	10	19	60	98	88	0	26.3 *(R)*	-
5	**1a**	20	38	60	>99	88	0	32.1 *(R)*	-
6	**1a**	20	10	65	93	92	0	11.8 *(R)*	-
7	**1b**	5	10	65	17	15	0	4.2 *(R)*	-
8	**1b**	6.6	10	65	99	86	0	10.3 *(R)*	-
9	**1b**	10	10	65	83	69	0	4.5 *(R)*	-
10	**2a**	5	10	65	98	77	0	6.6 *(R)*	-
11	**2a**	10	10	65	43	38	0	14.7 *(S)*	-
12	**2a**	20	10	65	4	<1	0	49.3 *(R)*	-
13	**2b**	5	10	60	55	52	0	4.9 *(R)*	-
14	**3**	5	10	65	>99	72	0	5.3 *(R)*	-
15	**3**	10	10	65	99	73	3	0.7 *(S)*	-
16	**3**	20	10	65	>99	70	8	5.9 *(S)*	1.7 *(R)*
17	**4a**	5	10	90	86	36	2	22.5 *(S)*	0.6 *(R)*
18	**4a**	10	10	90	76	32	25	30.2 *(S)*	5.4 *(S)*
19	**4a**	20	10	90	19	2	8	13.2 *(S)*	10.8 *(S)*
20	**4b**	5	10	60	91	56	0	6.3 *(S)*	-
21	**4b**	10	10	60	46	36	0	37.7 *(S)*	-
22	**4b**	20	10	60	10	5	0	10.4 *(S)*	-

a) Determined by GC (tridecane as internal standard) b) Determined by HPLC on a chiral column (Chiracel OJ); determination of the absolute configuration based on ref. (13) c) HPLC (Chiracel OJ).

In our studies we concentrated on the oxidation of cyclohexene in acetonitrile as solvent. The catalyst was prepared *in situ* from $Cu(CH_3CN)_4PF_6$ and the corresponding ligand. Cyclohexene was used in excess and the reaction was run at room temperature for 3 days. A summary of the results is given in *Table 1*. Yield and enantioselectivity were strongly influenced by the copper to ligand ratio suggesting structurally different catalytic active species for different ratios. With ligand **1a** best optical yields were obtained with a ligand to Cu(I) ratio of

1:1.9. Higher enantioselectivities were found with increasing catalyst concentration (up to 32% ee, entry 3-5). Catalysis with complexes of ligand **4a** gave rise to the formation of an additional product in significant yield up to 25% (entry 17-19), though with low ee's. Performing the same reaction on a larger scale yielded this product after column chromatography in 16% yield. Based on the analytical data a structure consistent with imide **8** was assigned. The best enantioselectivities for ester **6** were obtained with a ligand to Cu(I) ratio of 1:1 (30% ee). The same ratio gave also the best ee's (37%) with the N-methylimidazolyl substituted ligand **4b** (entry 20-22). The phenolate ligands **2a** and **2b** showed both lower conversions and enantioselectivities (entry 10-13). The interpretation of these data remains difficult since the nature of the catalyticly involved species is not known.

It is possible that the formation of imide **8** occurs via an alternative route, which presumably involves the insertion of coordinated acetonitrile. Subsequent rearrangement of the initially formed isoimide **7** leads to imide **8** (*Scheme 2*). Acyclic isoimides are known to undergo a O→N-acyl 1,3 shift to afford imides (*Mumm* rearrangement)[15], which are strongly favoured for energetic reasons. *Kawasaki et al.* also reported the formation of a side product in 21% yield using a tris(oxazoline)-copper(II) complex as catalyst and propionitrile as solvent.[11c] However, the assigned structure differs from **8** and is analogous to intermediate **7** with an ethyl rather than a methyl substituent since the reaction was performed in propionitrile.



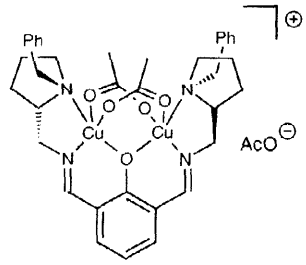
8 **7**

Scheme 2

Nevertheless, the reported chemical shifts of the ^{1}H-NMR spectrum are, with the exception of the ethyl proton signals, identical with the spectrum measured for the side product isolated in our experiment suggesting the same structural framework. On the basis of IR, ^{1}H-NMR and ^{13}C-NMR spectra the proposed assignment is more consistent with imide **8** rather than its isomer **7**. The carbon spectrum of **8** exhibits absorptions at δ = 172 and 175 ppm, whereas the isoimide C=N resonance would be expected at distinct higher field (δ = 157 ppm).[15d] A comparison of the IR carbonyl stretch frequencies found for **8** (1701 and 1656 cm^{-1}) with published values of structurally related imides and isoimides (e.g. imide: $\tilde{\nu}$ = 1696, 1666 cm^{-1}; isoimide: $\tilde{\nu}$ = 1747, 1694 cm^{-1})[15d] additionally supports the assigned structure. Furthermore, the *Mumm* rearrangement of isolated and elusive acyclic isoimides has been observed in many cases and occurs already at room temperature.[15c,d] In fact, the isolation of isoimides of type **7** proved to be successful only with a N-(2,4-dinitrophenyl) substituted derivative,[15b] in which the nucleophilicity of the nitrogen is substantially reduced.

The reaction is generally catalyzed by Cu(II) complexes as well, despite the fact that the catalytic cycle starts with a Cu(I) species. Thermo- or photochemically induced dissociation of the perester produces carbon radicals which are presumably responsible for the initial reduction of the Cu(II) complex.[10] Thus, we

also performed the reaction with 5 mol% of the structurally well characterized Cu(II) complex **10** as catalyst.[7b] Conversion and yield of benzoate were significantly lower (27% and 13% respectively); however, an optical yield of 42% ee *(R)* was obtained. Reduction of the complex *in situ* by 2.5 molar equivalents of phenylhydrazine improved the conversion to 59%, though the yield increased to only 25%, and substantially more benzoic acid was formed. Although the enantioselectivity and catalytic efficiency lag behind the results published with mononuclear systems, significant ee's were induced which exceed the selectivities reported to date for dinuclear systems.



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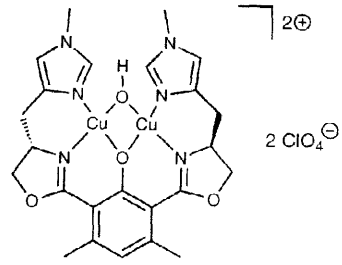

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Further work will be addressed to the isolation and characterization of distinct dinuclear copper complexes as well as the investigation of the solution chemistry of ligands **1–4**. These data will provide important information for the optimization of the reaction conditions and the development of further improved enantioselective dinuclear oxidation catalysts.

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EXPERIMENTAL

General. Quality of solvents and reagents: ethyl acetate, *tert*-butylmethyl ether, MeOH: *Fluka purum*; *i*-propanol, hexane: *Fluka*, for HPLC; acetonitrile: *Fluka puriss.*, distilled from CaH_2; $Cu(CH_3CN)_4PF_6$: *Aldrich* (98%); cyclohexene: *Fluka puriss.*(99.5%); *tert*-butyl-perbenzoate: *Aldrich* (98%). Syntheses of ligands **1-4**: ref. (7a). NMR: δ in ppm *vs.* $SiMe_4$ (^1H, 300 MHz) and $CDCl_3$ (77.0 ppm, ^{13}C, 75 MHz, assignments based on DEPT or APT spectra). MS: selected peaks; *m/z* (%); matrix for FAB-MS: 3-nitrobenzyl alcohol (NBA). IR ($CHCl_3$ or KBr): selected bands in cm^{-1}, br = broad. Optical rotations: Perkin Elmer 141 polarimeter (d = 10 cm, *c* in g/100 ml, $CHCl_3$, 23°C, estimated error ±5%). Flash column chromatography (FC): *Chemie Uetikon C560* silica gel (35–70 μm). *Merck* silica gel 60 F254 visualizing at 254 nm or with 2% $KMnO_4$ solution. All reactions were performed under argon (purity grade 48). All solvents for catalytic reactions were freshly distilled and deaerated *in vacuo* by three freeze/thaw cycles.

Allylic oxidation of cyclohexene with perbenzoic acid *tert*-butyl ester and *in situ* prepared Cu(I) catalysts:

General Procedure. To a solution of the ligand (2-20 mol%, 2.6-26 μmol) in acetonitrile (250 μl) was added the corresponding amount of a $Cu(CH_3CN)_4PF_6$ stock solution in acetonitrile. After stirring for 15

min at r.t. 250 µl of cyclohexene and 25 µl (133 µmol, Fluka pract. ~90%) of *tert*-butyl-perbenzoate were added. The resulting mixture was stirred at r.t. for 3 days and subsequently diluted with hexane up to 5 ml. The mixture was transferred through a Chromafil® disposable filter (pore diameter 0.2 µm) to remove the precepitated catalyst and 1 ml of the clear solution was diluted again with hexane (1:5). The resulting solution was directly used for GC analysis. In order to analyze the product mixture quantitatively, tridecane was used as an internal standard. The response factors were obtained through calibration with a set of solutions with various compositions of analyte and tridecane. Evaluated values: 1.80 (*tert*-butyl perbenzoate), 1.36 (cyclohexenyl benzoate), 1.76 (N-(cyclohexenyl)-acetyl-benzoylimide), 1.49 (benzoic acid). GC-conditions: OV-1701 column, 15m, on column injection, temp. program: 3 min iso 80°C, 80-110°C/40°C min^{-1}; 5 min iso 110°C, 110-200°C/40°C min^{-1}; 10 min iso 200°C (t_R = 3.1 min (benzoic acid), 6.4 min (*tert*-butyl perbenzoate), 10.7 min (cyclohexenyl benzoate), 13.2 min (N-(cyclohexenyl)-acetyl-benzoylimide)). The enantiomeric excess was determined by HPLC (ester: t_R = 23.9 min *(R)*, 26.1 min *(S)*, Chiracel OJ, hexane/*i*-PrOH 1000:1, 0.5 ml/min; imide: t_R = 24.4 min *(S)*, 28.9 min *(R)*, Chiracel OJ, hexane/*i*-PrOH 4:1, 0.5 ml/min; $[\alpha]_D$=–5.2 (c = 0.63, $CHCl_3$, 5.2% ee (*S*)).

Isolation of Products. In order to characterize the products the reaction was also performed on a larger scale:
a) With ligand **4a**: A homogeneous solution of ligand **4a** (23.9 mg, 53 µmol) and $Cu(CH_3CN)_4PF_6$ (19.8 mg, 53 µmol) in 0.5 ml of acetonitrile was stirred for 30 min and then cyclohexene (0.5 ml) and *tert*-butyl-perbenzoate (100 µl) were added. The mixture was stirred for 5 days in a sealed Schlenk-tube at room temperature and then quenched by the addition of aq. 1 M HCl (5 ml). The solution was extracted twice with *tert*-butylmethyl ether (10 ml), the combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (1x18 cm, hexane/EtOAc 99:1) yielding 6.7 mg of ester **6**, 20.4 mg of imide **8** and 29.6 mg of unreacted starting material (perester).
b) With ligand **3**: The reaction was performed as described above, but using ligand **3** (21.1 mg, 53 µmol) and 19.8 mg (53 µmol) of $Cu(CH_3CN)_4PF_6$. Following the same work up procedure yielded 71 mg (34 µmol, 66%) of ester **6** with $[\alpha]_D$ = –4.99 (c=1.32, $CHCl_3$, 2.8% ee).

Cyclohex-2-en-1-yl-benzoate (6) (analytical data identical with data reported in literature[13]): ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.6-2.2 (3 *m*, no baseline sep., $H_2C(4)$, $H_2C(5)$, $H_2C(6)$); 5.51-5.53 (*m*, HC(2)); 5.81-5.87, 5.98-6.03 (2*m*, HC(1), HC(3)); 7.40-7.57 (2 *m*, Ph); 8.05-8.08 (*m*, Ph). HPLC: Chiracel OJ, 0.46x30 cm, hexane/*i*-PrOH 1000:1, 0.5 ml/min, t_R = 23.9 min (*R*), 26.1 min (*S*).
N-((1S)-Cyclohex-2-en-1-yl)-acetyl-benzoylimide (8): ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.56-1.76 (*m*, CH_2); 1.97 (*s*, CH_3); 1.84-2.19 (*m*, CH, CH_2); 5.01-5.09 (*m*, CHN); 5.54-5.59 (*m*, C=CH); 5.78-5.84 (*m*, C=CH); 7.44-7.49 (*m*, Ph); 7.55-7.62 (*m*, Ph); 7.71-7.75 (*m*, Ph). ^{13}C-NMR ($CDCl_3$, 75 MHz): 22.0, 24.3 (CH_2); 26.8 (CH_3); 27.6 (CH_2C=C); 54.9 (NCH); 127.7, 128.8, 129.4 (arom. CH); 133.0 (C=C); 136.5 (arom. C(1)); 172.2 (C=N); 174.8 (C=O). IR ($CHCl_3$): 3032m, 2941m, 2839w, 1701s, 1656s, 1599w, 1449m, 1433w, 1394m, 1371m, 1320m, 1133w, 1025w, 997w, 969w, 923w, 820w, 633w. MS (CI): 246 (1), 245 (12), 244 (73), 202 (5), 181 (26), 165 (10), 164 (100, $[M-C_6H_9+1]^+$), 140 (5), 138 (18), 105 (16), 96 (9). $[\alpha]_D$ = –5.2 (c = 0.63, $CHCl_3$). HPLC: Chiracel OJ, 0.46x30 cm, Hexan/i-PrOH 4:1, t_R(*S*) = 24.4 min, t_R(*R*) = 28.9 min, ee = 5.2% (*S*). R_f = 0.37 (silica, hexane/EtOAc 4:1).
Determination of the Absolute Configuration of 8: A drop of aq. HCl (37%) was added to a solution of imide (–)-**8** in 1 ml MeOH and the mixture was refluxed for 2h. After cooling to room temperature the reaction mixture

was diluted with *tert*-butylmethyl ether and extracted with sat. aq. $NaHCO_3$. The organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallized from diethyl ether to afford (1*S*)-N-cyclohex-2-en-1-yl-benzamide (8.5 mg, 86%) as colorless crystals. The absolute configuration and enantiomeric excess was obtained through comparison of the optical rotation data with published values.[14]
Mp. 107-108°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.59-1.75 (*m*, CH_2); 1.96-2.09 (*m*, CH_2); 4.67-4.72 (*m*, NCH); 5.66-5.72 (*m*, C=CH); 5.89-5.95 (*m*, C=CH); 6.05 (*s*, broad, NH); 7.39-7.52 (*m*, Ph); 7.75-7.79 (*m*, Ph). ^{13}C-NMR ($CDCl_3$, 75 MHz): 19.7, 24.9, 29.5 (CH_2); 45.1 (NCH); 126.8, 127.6, 128.5 (arom CH); 131.3 (C=C); 134.8 (arom. C(1)); 166.7 (C=O). MS (EI): 202 (4), 201 (29, M^+), 122 (11), 106 (7), 105 (100), 80 (9), 77 (37), 51 (9). $[\alpha]_D$ = –5.8 (c = 0.59, $CHCl_3$); (5% ee); Lit.[14]: *(R)*-N-cyclohex-2-en-1-yl-benzamide: $[\alpha]_D$ = +178.6 (c = 3.02, $CHCl_3$, >99.5% ee (GC)). R_f = 0.28 (silica, hexane/EtOAc 4:1).

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