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The Evaluation of Novel Camphor-derived Pyridyl Ligands as Catalysts in the Asymmetric Diels-Alder Reaction of Cyclopentadiene with 3-Acryloyl-2-oxazolidinone

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ABSTRACT

A series of camphor-derived pyridyl ligands were evaluated in the Diels-Alder reaction of 3-acryloyl-2-oxazolidinone 1 with cyclopentadiene 2. High yields with good *endo:exo* selectivity, but only moderate enantioselectivities (43 % *ee*), were obtained. The structures of the copper (II) complexes of the ligands were calculated using ONIOM density functional theory and the results suggest that chiral induction to the alkene functional group is indeed lacking. This explains the moderate experimental selectivities obtained.

KEYWORDS

Camphor ligands, asymmetric catalysis, Diels-Alder cycloaddition, computational modelling.

1. Introduction

This is the fourth paper in a series of research results from our group in the field of chiral synthesis and catalytic applications. The first paper involved the synthesis of pentacycloundecane oxazolines and the application of the ligands in an asymmetric Diels-Alder reaction.[1] The second paper made use of camphor-derived ligands in the chiral alkylation of aldehydes with diethylzinc[2], while the third utilized these same camphor ligands, as well as two new derivatives, to catalyze the asymmetric Henry reaction.[3]

The Diels-Alder cycloaddition reaction is one of the classic named reactions in organic chemistry.[4] It is widely used in the regio- and stereo-selective construction of six-membered rings.[4–8] The reaction has been the subject of much investigation since it was first reported in 1928.[9] In fact, more than 17 000 papers have been published detailing research into this reaction, half of those in the last decade.[4] The first examples of the asymmetric Diels-Alder reaction were carried out more than 30 years ago in the late 1970s[10] and it has since become an area of intense investigation. The discovery that the reaction is catalyzed by Lewis acids under very mild conditions led to a number of researchers investigating the development of chiral ligands which could complex these Lewis acids, hence leading to asymmetric products from the Diels-Alder reaction.[8] Certain 'benchmark' reactions have emerged as standards for evaluation of chiral ligands as catalysts in the asymmetric Diels-Alder reaction.[11] One such reaction is the addition of 3-acryloyl-2-oxazolidinone **1** to cyclopentadiene **2** (Scheme 1).[11–18]

Camphor-derived complexes have not been widely evaluated as catalysts for this reaction. Only a few examples of camphor-derived ligands appear in the literature as being applied as catalysts in the asymmetric Diels-Alder reaction.[19–21] These ligands have proven to be reasonably successful in terms of selectivity with enantiomeric excesses in the 80 and low 90 % range. Herein we report the evaluation of a series of recently reported[2,3] camphor-derived pyridyl ligands **4**-**9** (Fig. 1) as catalysts in the Diels-Alder reaction of 3-acryloyl-2-oxazolidinone **1** with cyclopentadiene **2**. These molecules are unique in that they represent the only examples of camphor-derived ligands which have pendant donor groups on the C3 position of the camphor alone. All other existing camphor-derived ligands have the donor groups pendant on the C2 position or have one donor group at C2 with the other at C3.[22]

2. Results and Discussion

Ligands **4**–**9** were synthesized according to the procedure outlined in previous studies (Scheme 2).[2,3] The compounds were complexed to a series of metal salts and screened as catalysts in the asymmetric Diels-Alder reaction of 3-acryloyl-2-oxazoli-

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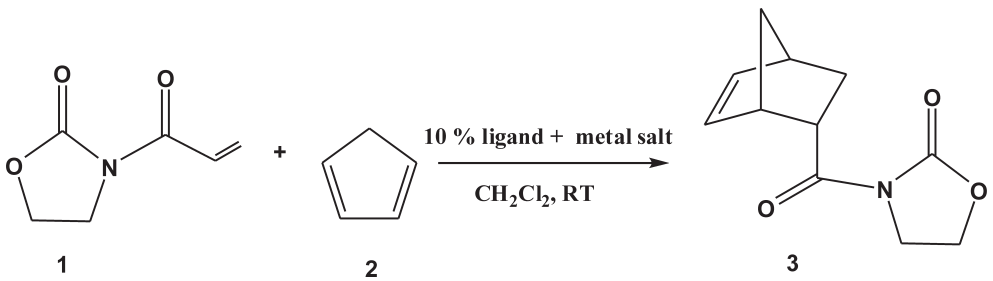


Scheme 1
Diels-Alder reaction of 3-acryloyl-2-oxazolidinone **1** with cyclopentadiene **2**.

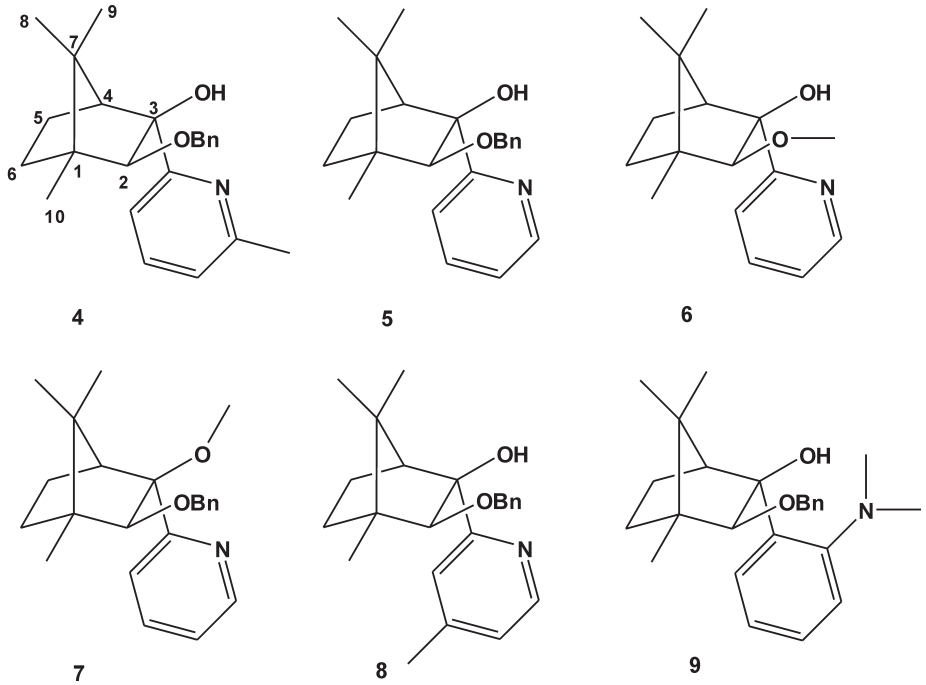


Figure 1 Ligands **4**–**9**.

dinone **1** with cyclopentadiene **2**.

There are four different ways in which the diene **2** can approach the dienophile **1** (Scheme 3). Firstly, the dienophile **1** can either attack from above the plane of the paper and secondly from below the plane of the paper. (*R*)-**3** is formed *via* attack of the diene **2** from above the plane of the paper and (*S*)-**3** is the result of the diene attacking from below the plane of the paper. The chiral catalyst is supposed to limit the formation of one enantiomer over the other.[23] During the reaction of the substrates (**1** and **2**) in the presence of the chiral catalyst, the top side of attack is blocked or hindered to such an extent that *endo*-(*S*)-**3** is almost exclusively observed. Note that in both these cases the diene **2** approaches the dienophile **1** with the CH_2 group pointing away from the carbonyl oxygen of **1**. This is the kinetically preferred approach and leads to what is called the *endo*-product.

The last two possibilities are both the result of the diene **2** attacking the dienophile **1** with the CH_2 group pointing towards the carbonyl carbon of **1**. Again, two products are possible (i.e. attack of the diene from either above or below the plane of the paper). *Exo*-(*S*)-**3** forms when attack is from below the plane of the paper and *exo*-(*R*)-**3** forms when attack occurs from above the plane of the paper. This approach is less kinetically preferred and leads to what is called the *exo*-product.[24]

An equimolar amount of the metal salt was added to a solution of ligand **4** in dichloromethane.[18] The resultant catalyst complex was used to promote the asymmetric Diels-Alder reaction of 3-acryloyl-2-oxazolidinone **1** and cyclopentadiene **2** to yield the cycloadduct **3** as illustrated in Scheme 1. The results for this preliminary screening of the metal salts are summarized in Table 1.

From this initial screening it was determined that $Cu(OTf)_2$ was the most successful metal salt in terms of selectivity, albeit very moderate. Different copper salts were investigated to determine the effect of the counterion on the catalyst in the reaction (Table 2).

OTf emerged as the best counterion and the next step was the screening of the remaining ligands in the hope of obtaining a higher selectivity. The results of this screening process are summarized in Table 3.

From this table it can be seen that ligands **5–9** gave poor selectivity. Only the aniline derivative (**9**) gave any significant selectivity. The only similarity between ligand **4** and ligand **9** is the fact that both of these compounds have sterically hindered *N*-donor atoms. All the other ligands have little or no steric bulk around the nitrogen atom.

In order to determine a possible reason for the observed selectivity obtained for this reaction with these ligands, a computa-

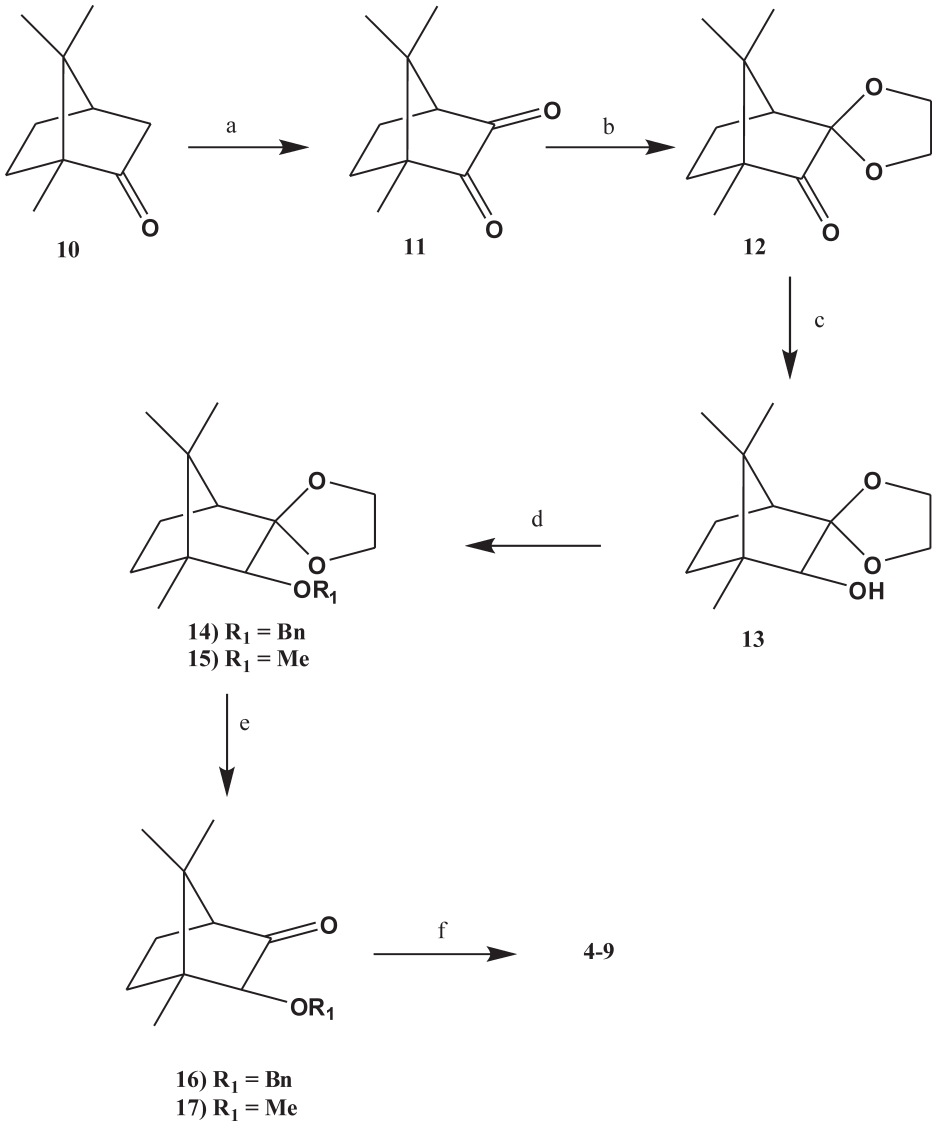
Table 1 Results obtained for the reaction between 3-acryloyl-2-oxazolidinone **1** and cyclopentadiene **2** catalyzed by ligand **4** complexed to various metal salts with CH_2Cl_2 as the solvent at room temperature.

Entry	Metal salt	Time/min	Yield/%	*Endo:exo* [a]	% *(S)-Endo ee* [b]
1	Blank	240	80	96:4	0
2	$Ni(ClO_4)_2$	30	71	83:17	4
3	$Zn(ClO_4)_2$	5	74	81:19	3
4	$Mg(ClO_4)_2$	>30	71	–	0
5	$Mn(ClO_4)_2$	5	61	88:12	3
6	$CoBr_2$	>30	71	–	0
7	ZnI_2	10	83	–	0
8	$MnBr_2$	>30	70	87:13	2
9	$NiBr_2$	>30	75	–	0
11	$FeCl_2$	>30	62	–	0
12	$NiBr_2$	>30	78	–	0
13	$Cu(OTf)_2$	5	55	92:8	43
14	$Sc(OTf)_2$	10	62	86:14	5

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC (Chiralpak IB).

Table 2 Effect of different counterions on the reaction between 3-acryloyl-2-oxazolidinone **1** and cyclopentadiene **2** catalyzed by ligand **4** and Cu with CH_2Cl_2 as the solvent at room temperature.

Metal salt	Time/min	Yield/%	*Endo:exo*	% *(S)-Endo ee*
$Cu(OTf)_2$	5	55	92:8	43
$CuCl_2$	>30	73	–	0
$Cu(ClO_4)_2$	5	74	87:13	23
$Cu(OAc)_2.H_2O$	>30	75	–	0



Scheme 2
The synthetic scheme for ligands 3–6. Key: (**a**) SeO_2, Ac_2O, reflux 16 h, 86 %; (**b**) ethylene glycol, PTSA, benzene, reflux 12 h, 80 %; (**c**) $NaBH_4$, diethyl ether/MeOH (1:1), RT, 2 h, 85 %; (**d**) benzyl bromide or methyl iodide, NaH, dry THF, 12 h, 75 % (14), 95 % (15); (**e**) HCl/THF (1:3), 2 h, 80 %; (**f**) ketone 16 or 17, $CeCl_3$, pyridyllithium or lithioaniline, –78 °C → RT, 12 h.

tional evaluation of the ligand/metal complex with the substrate in two possible orientations was carried out (Fig. 2). The complex was modelled in the square planar arrangement for copper as this is known to be the preferred conformation in the +2 oxidation state. The basis set used for this evaluation is reported in the literature to give accurate estimates of the structure under investigation.[25–27]

The optimized structures revealed some interesting facts about the complex. First, the substrate is likely to complex to the metal preferentially in one orientation, i.e. **18a**. This is determined by considering that the energy of the one orientation (**18a**, Fig. 2) is lower (by 19.2 kJ mol^{-1}) than that of the other (**18b**, Fig. 2) due to steric factors. The observation that **18b** is higher in energy can be practically deduced from the fact that the geometry of the 'square planar' copper ion of **18b** is much more distorted than that of **18a**. This is the result of steric hindrance between the substrate alkene group and the nearby methyl group on the pyridine ring. In **18a** the alkene group is positioned away from the pyridine ring and as a result the square planar geometry around the copper ion is much less distorted out of the plane. Second, the complexed alkene in **18a** (the low energy catalytic complex) is open to attack by cyclopentadiene (see Scheme 3) from both sides (top and bottom), thus resulting in the observed low selectivity.

Table 3 Screening of ligands **5**–**9**.

Entry	Ligand	Time/min	Yield/%	*Endo:exo* [a]	% (S)-Endo ee[b]
1	5	5	81	87:13	4
2	6	5	93	87:13	4
3	7	5	81	80:20	5
4	8	5	80	86:14	5
5	9	5	92	88:12	27

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC (Chiralpak IB).

Several computational studies have been carried out into the selectivity of the Diels-Alder reaction.[28,29] From these it is apparent that for good enantioselectivity to be obtained, one side of the alkene should be completely blocked from attack by cyclopentadiene and the other side should partially block the vertical approach of cyclopentadiene so that the CH_2 group on the

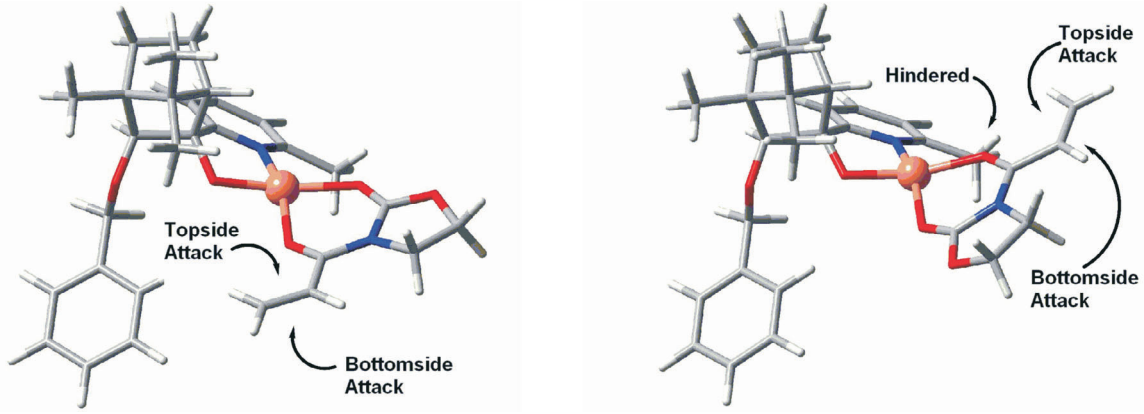


Figure 2 DFT ONIOM optimized model of the ligand/metal complex with substrate in two different conformations, **18a** (**left**) and **18b** (**right**). (Cartesian coordinates of these optimized structures are available as supplementary material.)

cyclopentadiene ring is pointing away due to the partial steric hindrance. Inspection of the 3D structure of **18a** clearly indicates a lack of steric hindrance on either side of the alkene group.

Conclusion

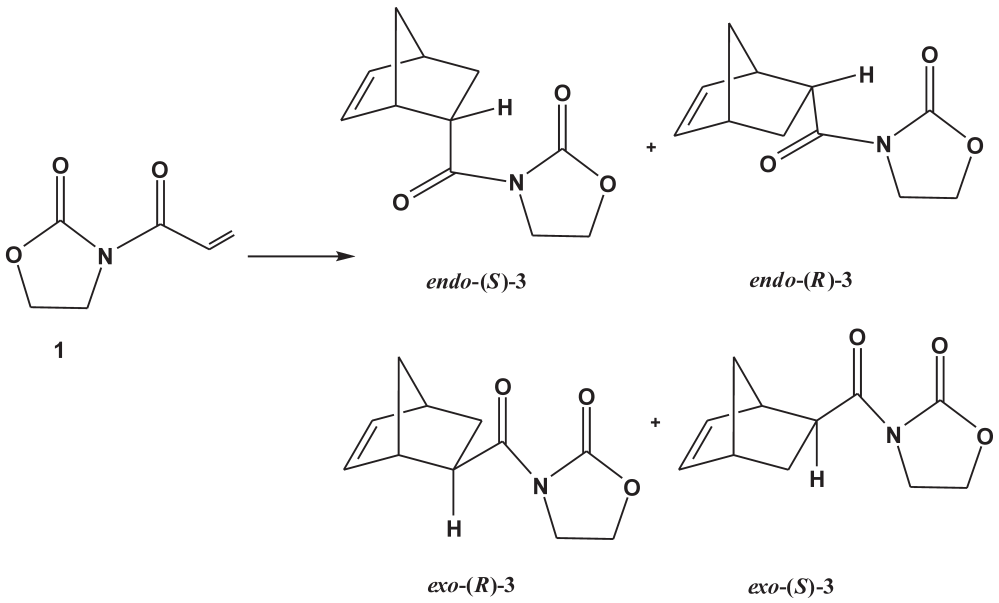
In summary, a series of novel camphor-derived pyridyl and aniline compounds have been screened in the asymmetric Diels-Alder reaction of 3-acryloyl-2-oxazolidinone **1** with cyclopentadiene **2**. The reaction proved to be very sensitive to both ligand and metal salt used, with only the combination of ligand **4** and $Cu(OTf)_2$ giving any significant selectivity. Although the results were only mediocre, the screening of this class of ligands in this reaction was necessary in order to develop an overall picture of how active the compounds are when used in varying catalytic applications. Further studies using computational models could potentially lead to the modification and design of more selective camphor ligands for this application.

Experimental

All NMR spectra were recorded on Bruker (Karlsruhe, Germany) AVANCE III 400 MHz or 600 MHz instruments. All HPLC analysis was carried out on a Shimadzu Prominence (Tokyo, Japan) system using a Diacel Chiralpak IB column with hexane:isopropanol (95:5) as eluent. All solvents were dried using standard procedures prior to use. All reagents were purchased from Fluka or Sigma-Aldrich (St Louis, MO, USA) and used without further purification. Column chromatography was carried out on silica gel 60 particle size 0.063–0.200 mm (230–400 mesh).

General Procedure for the Asymmetric Diels-Alder Reaction of 3-acryloyl-2-oxazolidinone 1 with Cyclopentadiene 2

A mixture of ligand (1 mol eq) and anhydrous metal salt (1 mol eq) in dry CH_2Cl_2 (5 mL) was stirred under dry nitrogen at ambient temperature for 3 h. The resulting complex was used for the Diels-Alder reactions as follows: 3-acryloyl-2-oxazolidinone **1** (50 mg, 0.4 mmol) and freshly distilled cyclopentadiene **2** (0.3 mL, 4.0 mmol) were added. The reaction was performed at room temperature and monitored by TLC. After the completion of the reaction, saturated aqueous ammonium chloride was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and the solvents were removed *in vacuo.* The resulting residue was purified by flash column chromatography (hexane:EtOAc 70:30) to give a mixture of *endo* and *exo* isomers of cycloadduct **3** (60 mg, 85 %). The *endo:exo* ratio was evaluated on the basis of the ^1H NMR spectrum (δ 2.94 ppm and 3.02 ppm) and the enantiomeric excess determined by HPLC with a Daicel Chiralpak IB column



Scheme 3
The four different potential products for the Diels-Alder reaction.

(hexane:*i*PrOH 95:5) flow rate 1 L min^{-1}, *t*(*R*) 24.0 min, *t*(*S*) 22.6 min. Other anhydrous complexes were prepared *in situ* according to a similar procedure by using anhydrous metal halides such as $NiBr_2$, $CaBr_2$, $MnBr_2$, $FeCl_2$, $CoBr_2$, $CuCl_2$ and ZnI_2 and complexation time was 3 h.

3-(Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-2-oxazolidinone 3

Colourless solid; enantiomeric purity was estimated on the basis of HPLC using a chiral column as described above and the *endo:exo* ratio was evaluated on the basis of the ^{1}H NMR spectrum; ^{1}H NMR ($CDCl_3$): δ_H 1.3–1.7 (m, 3H), 1.9–2.1 (m, 1H), 2.94 (m, 1H), 3.31 (m, 1H), 3.8–4.1(m, 3H), 4.40 (t, 2H), 5.88 (dd, 1H), and 6.25 ppm (dd, 1H).

Details of the DFT-optimized Structures

The complexes were optimized using Gaussian 03 utilizing the multilayer ONIOM (UPBEPBE/genecp:B3LYP:UFF) function. For this model the low level incorporated the entire complex, the mid level comprised the entire dienophile substrate, the pyridine moiety as well as the C3 carbon of the camphor skeleton and the attached hydroxyl group. The high level comprised the copper atom. An initial single point energy calculation was carried out in order to provide a starting point for the subsequent high level optimization. For this initial calculation the low level of the ONIOM was optimized using the UFF molecular mechanics force field while the mid and high levels used the 3-21G force field at the HF level of theory. For the high level multistep optimization calculation the low level once again used the UFF molecular mechanics force field, the mid level calculation was carried out using the 6-31+G(d) basis set at the B3LYP level of theory while the high level was carried out using the UPBEPBE/genecp basis set. The copper atom was modelled using the LANL2DZ basis set. The charge on the copper atom was left at +1 with doublet spin multiplicity. The Cartesian coordinates are available as supplementary material. The copper complex is quite rigid and the benzyl side chain was manually rotated to find the lowest energy structure.

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