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Chiral dendritic bis(oxazoline) copper(II) complexes as Lewis acid catalysts for enantioselective aldol reactions in aqueous media

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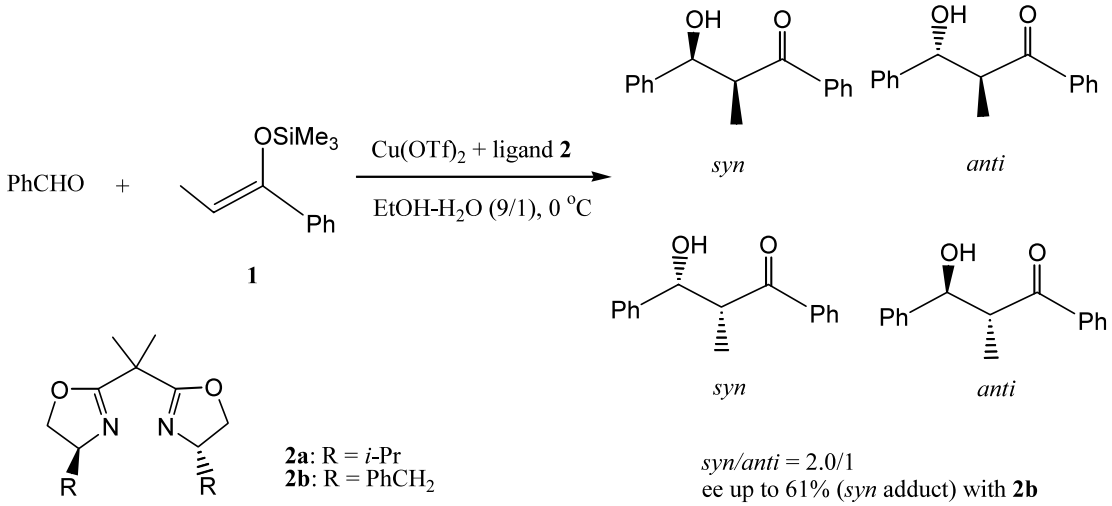
Abstract—A series of copper(II) complexes, with chiral bis(oxazoline) ligands disubstituted at the carbon atom linking the two oxazolines by Fréchet-type polyether dendrimers, have been designed and synthesized. These complexes were used as Lewis acid catalysts in enantioselective aldol reactions in aqueous media. Good yields and moderate enantioselectivities were achieved, which are comparable with those resulting from the corresponding smaller catalysts.

The design and the development of efficient chiral catalysts for enantioselective asymmetric syntheses in aqueous media is one of the most challenging areas of organic chemical research.[1] Chiral Lewis acid-catalyzed enantioselective reactions have attracted much attention in modern organic synthesis.[2] However, these Lewis acids generally must be used under strictly anhydrous reaction conditions because most Lewis acid catalysts are water-labile and are easily decomposed by water. Recently, Kobayashi developed new synthetic methods for Lewis acid-catalyzed reactions in water-containing solvents.[3] For example, the Mukaiyama aldol reaction of benzaldehyde with silyl enol ether **1** was catalyzed by chiral bis(oxazoline) copper(II) complexes in an ethanol–water solution with high yields and moderate to high enantioselectivities (Scheme 1).[3a]



Scheme 1.

Keywords: chiral bis(oxazoline); dendritic catalyst; Mukaiyama aldol reaction; aqueous.

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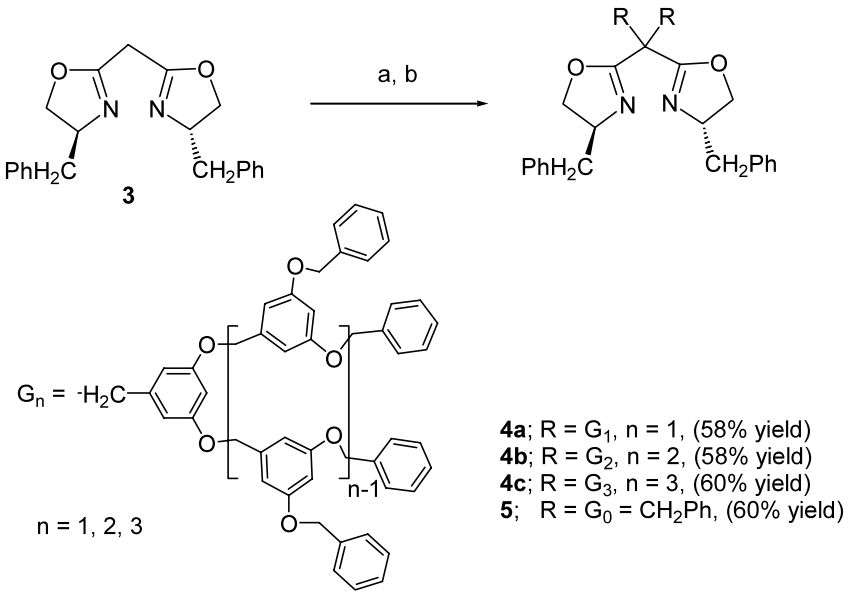
This process, however, still suffered from some problems such as the separation and recycling of the often expensive and toxic chiral catalysts.[4] There is good reason to believe that an aqueous aldol reaction catalyzed by immobilized chiral Lewis acids would offer a 'greener' process.

Chiral bis(oxazoline) ligands have been applied in many enantioselective reactions.[5] Recently, studies of the immobilization of bis(oxazolines) on both soluble and insoluble supports has been of great interest.[6,7] Among the different methods to anchor the homogeneous catalysts, a soluble, polymer-supported catalyst usually achieves higher stereoselectivity and activity because the catalysis can be carried out under homogeneous conditions.[8] After the reaction, the catalyst can be separated and recycled via simple methods such as solvent precipitation. Dendrimers are highly branched macromolecules having precisely defined molecular structures with nanoscale size. Compared with soluble polymer supports, the dendrimer architecture may offer better control of the disposition of the catalytic species in soluble polymer-based catalysts. Therefore, such catalysts may fill the gap between homogeneous and heterogeneous catalysis and combine the advantages of both.[9] In the course of our investigations to develop highly effective chiral dendritic catalysts, we have recently reported several types of chiral dendritic ligands for asymmetric catalysis through the incorporation of BINAP and BINOL into the core of the Fréchet-type dendrimers, respectively.[10] In this paper, we report the synthesis of bis(oxazoline)-centered dendrimers, which are to the best of our knowledge, the first examples of dendrimer-supported chiral bis(oxazoline) ligands.[11] This work is also the first example of aqueous asymmetric aldol reactions catalyzed by polymer-supported chiral catalysts.

Recently, many research groups have been investigating ways to immobilize chiral bis(oxazoline) ligands on organic or inorganic supports where the attachment has been achieved usually at the bridging carbon atom of the bis(oxazoline) skeleton.[7] In our study, bis(oxazoline) **3**[12] was selected as a model ligand. The dendritic substituents were introduced by double alkylations of the methylene bridge of **3** (Scheme 2). Thus, reaction of **3** with methyllithium proceeded smoothly at −55°C in THF, followed by reacting with dendritic benzyl bromide[13] to give dendritic chiral bis(oxazoline) ligands **4a**–**c**. For comparison purposes, the model compound **5** was also synthesized using a similar method. These ligands were purified by column chromatography and characterized by NMR, MS and elemental analyses. All results were in full agreement with the proposed structures.[14] For example, the MALDI TOF MS spectra of **4a**, **4b** and **4c** show the mass ions as 961.2 ($[M+Na]^+$), 1809.3 ($[M+Na]^+$) and 3486.9 ($[M]^+$), respectively.

With these dendritic ligands in hand, catalysts were then obtained by reaction with copper triflate.[15] Because of the architecture of the dendrimer, the catalytically active center is situated at the core of the dendrimer. It is possible to fine-tune the chiral microenvironment by systematically adjusting the size, shape and peripheral functional groups of the dendritic substituents. Reactive substrates are expected to concentrate in the inner areas of the dendrimer, especially in aqueous media, due to a hydrophobic effect. This may help the reactants access the catalytic center. In our study, the catalytic asymmetric aldol reaction of silyl enol ether **1** with benzaldehyde was chosen as model reaction to test the catalytic activity of these chiral dendritic catalysts in aqueous media.



Scheme 2. *Reagents and conditions*: (a) −55°C, MeLi, THF; (b) G_nCH_2Br, reflux, 4 h.

The effect of reaction solvent and temperature on diastereoselectivity, enantioselectivity and chemical yield was firstly evaluated. Considering the insolubility of catalyst substituted with larger dendrimers in ethanol, a mixed solvent system containing water, tetrahydrofuran and ethanol was used. The results are summarized in Table 1.

Model ligand **5** was used to optimize the reaction conditions. As shown in Table 1, catalyst **5**-Cu(II) gave the aldol product in good yield and moderate enantioselectivity in H_2O–EtOH (1:9), both of which are slightly lower than those obtained from **2b**-Cu(II) (entries 1 and 16). When using a mixture of H_2O–THF (1:9) as solvent, in the absence of ethanol, a similar enantioselectivity, albeit in lower yield, was observed (entry 2).

Therefore, a three-component solvent system (H_2O–EtOH–THF) was chosen as the reaction medium. Good yields and moderate enantioselectivities were achieved with different ratios of H_2O/EtOH/THF as solvent (entries 3–7). The highest yield (80%) with 58% ee was obtained when using H_2O:EtOH:THF = 4:9:9 as solvent (entry 7). Increasing the temperature led to a reduction of both enantioselectivity and yield (entry 8).

Based on the optimized reaction conditions, we then tested the asymmetric induction of the dendritic ligands in the same reaction. As shown in Table 1, the catalysts derived from all three dendritic bis(oxazolines) **4a**–**c** were found to be effective. In general, good yields and moderate enantioselectivities were observed, which were comparable to those with **5** and **2b**. It was found that the dendritic substituents, which were assumed to affect the structure of the active center,[9] did not decrease the enantioselectivity or the yield with the increased size. On the contrary, the copper complexes with higher generation ligands (**4b** and **4c**) gave slightly higher enantioselectivities and/or yields. In addition, a simple method for recovery and recycling of the catalyst was tried without further addition of $Cu(OTf)_2$. At the end of the reaction, the catalyst could be separated from the reaction mixtures through precipitation by adding cold methanol. The precipitated catalyst was quantitatively recovered by simple filtration, washed with methanol and used directly in the second run. Unfortunately, the recycled catalyst gave a lower yield and enantioselectivity as compared with the freshly prepared material (entries 13, 14 and 15).

In conclusion, the C_2-symmetric bis(oxazolines) **4a**–**c**, disubstituted with two Fréchet-type polyether dendrimers, showed similar reactivities and enantioselectivities in the asymmetric copper-catalyzed aldol reaction in aqueous media in comparison to the small molecular bis(oxazoline) ligands **5** and **2b**. Further study of this new aspect of dendritic chiral copper(II) bis(oxazoline) catalysis is in progress in our laboratory.

Table 1. Catalytic asymmetric aldol reactions[a] catalyzed by dendritic chiral bis(oxazoline) copper(II) catalysts in aqueous media

Entry	Catalyst	Temp. (°C)	Solvent[b] (v/v)	Yield[c] (%)	*syn*/*anti*[d]	Ee (%)[e,f] (*syn*)
1	**5**-$Cu(OTf)_2$	0	H_2O:EtOH = 1:9	90	1.7/1	50
2	**5**-$Cu(OTf)_2$	0	H_2O:THF = 1:9	38	2.2/1	54
3	**5**-$Cu(OTf)_2$	0	H_2O:EtOH:THF = 1:9:9	74	1.8/1	55
4	**5**-$Cu(OTf)_2$	0	H_2O:EtOH:THF = 1:9:18	72	1.9/1	50
5	**5**-$Cu(OTf)_2$	0	H_2O:EtOH:THF = 1:18:9	68	1.8/1	47
6	**5**-$Cu(OTf)_2$	0	H_2O:EtOH:THF = 2:9:9	75	2.1/1	60
7	**5**-$Cu(OTf)_2$	0	H_2O:EtOH:THF = 4:9:9	80	2.1/1	58
8	**5**-$Cu(OTf)_2$	25	H_2O:EtOH:THF = 2:9:9	48	2.0/1	34
9	**5**-$Cu(OTf)_2$	0	H_2O:EtOH:THF = 2:9:9	74	2.4/1	54
10	**4a**-$Cu(OTf)_2$	0	H_2O:EtOH:THF = 2:9:9	78	2.4/1	60
11	**4b**-$Cu(OTf)_2$	0	H_2O:EtOH:THF = 2:9:9	78	2.2/1	64
12	**4c**-$Cu(OTf)_2$	0	H_2O:EtOH:THF = 2:9:9	81	2.2/1	57
13	**4b**-$Cu(OTf)_2$[g]	0	H_2O:EtOH:THF = 2:9:9	53	1.9/1	32
14	**4b**-$Cu(OTf)_2$[h]	0	H_2O:EtOH:THF = 2:9:9	40	1.8/1	25
15	**4c**-$Cu(OTf)_2$[g,i]	0	H_2O:EtOH:THF = 2:9:9	61	1.7/1	30
16	**2b**-$Cu(OTf)_2$[j]	0	H_2O:EtOH = 1:9	98	2.6/1	61

[a] The configuration of substrate **1** was determined by ^1H NMR analysis (E/Z = <1/>99).
[b] In entries 1–7, the total volume of reaction solvent is 1.5 mL. In entries 8–15, the total volume of reaction solvent is 2.5 mL.
[c] Isolated yield.
[d] The ratio of *syn*/*anti* determined by ^1H NMR analysis.
[e] Determined by HPLC with a Chiracel OD-H column.
[f] Enantiomeric excess of major product diastereomer.
[g] The second run.
[h] The third run.
[i] The reaction time was extended to 36 h.
[j] See Ref. 3a.

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