New Ligand Concepts for Cerium-Catalyzed Asymmetric α-Hydroxylation

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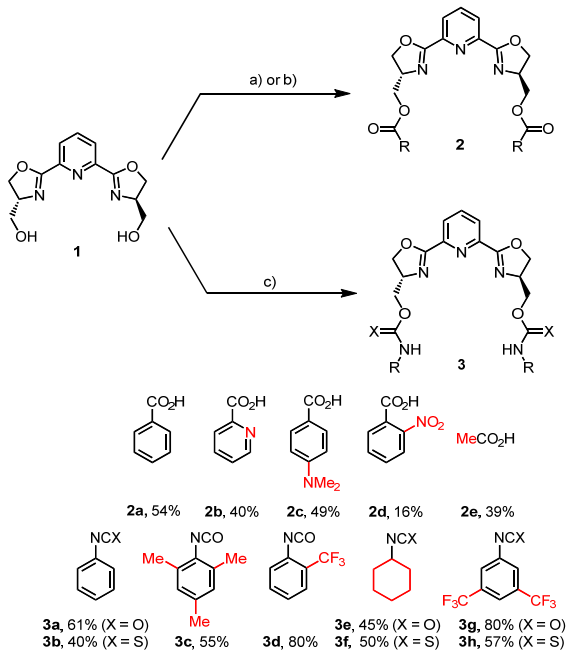
Pyridylbisoxazoline (PyBOX) scaffolds are investigated as ligand motifs for cerium-catalyzed asymmetric α-hydroxylation. Herein we report on the functionalization of (4-hydroxymethyl)pyridylbisoxazoline by esterification with carboxylic acids (five compounds) or with iso(thio)cyanates to furnish (thio)carbamates (eight compounds). In a model reaction, up to 84% *ee* was achieved.

Introduction

The cerium catalyzed α-hydroxylation of β-oxoesters in the presence of molecular oxygen is known in its racemic version since a couple of years.[1] As a further extension of this method, an asymmetric version should be developed. However, it is a challenge to find an appropriate polydentate ligand, because the β-dicarbonyl motif is actually a high attractive binding site for cerium ions and also the proposed radical reaction mechanism keeps it difficult. There is a high demand on synthesizing a ligand which can bind cerium ions more effectively and gain higher enantioselectivities. We suggested to increase the number of available donor functions to achieve higher binding constants of the ligand.

Preparation of Various Ligands

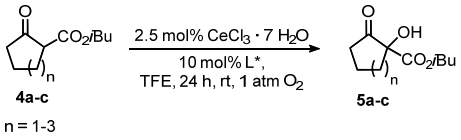
(4-Hydroxymethyl)pyridylbisoxazoline **1** is prepared according to Nishyama et al.[2] In the next step platform compound **1** can be converted by esterification to the corresponding products **2** with up to 54% yield after flash chromatography. The problem for this type of reaction is the insufficient solubility of compound **1** in nearly every common solvent. The second type of ligands **3** can be prepared with iso(thio)cyanates to give (thio)carbamates in good yields up to 80%.



Scheme 1. Synthesis of bisoxazoline type ligands **2** and **3**. (a) carboxylic acid chloride, KOH (40%), DCM/H_2O (4:1), rt, 24 h or (b) carboxylic acid chloride, *t*BuOK, DCM, rt, 24 h. (c) iso(thio)cyanate, KOH (40%), DCM/H_2O (2:1), rt, 24 h.

Screening

For examination of the potential of the ligand library in asymmetric catalysis, it is tested in the already known hydroxylation of cyclic β-oxoesters with cerium salts.[3] Previous to this screening the optimal reaction conditions were examined in another screening and trifluoroethanol (TFE) was found to be the best solvent to give the highest enantiomeric excesses.



Scheme 2. Model reaction for ligand screening.

As shown in Table 1, the carbamates give better results than the esters and the unfunctionalized compounds **3a** and **3e** give the best results so far. Very promising results shows the sulfur containing ligand **3b** with a high enantiomeric excess but still low conversion.

Table 1. Experimental results.

ligand L*	*ee*/% (conv./%)[a]		
	n = 1	n = 2	n = 3
2a	21 (100)	34 (100)	21 (100)
2b	–4 (100)	12 (100)	6 (100)
2c	0 (100)	0 (100)	0 (100)
2d	0 (100)	0 (100)	0 (100)
2e	–7 (100)	0 (100)	5 (100)
3a	26 (100)	36 (100)	23 (100)
3b	**–84 (20)**	0 (2)	–
3c	14 (95)	0 (90)	–
3d	5 (100)	3 (100)	2 (100)
3e	36 (100)	46 (100)	25 (100)
3f	–	–	–
3g	20 (100)	8 (100)	5 (100)
3h	–10 (60)	–	–

[a] Enantiomeric excess was determined by GLC on a chiral phase.

Conclusion

A new class of ligands based on (4-hydroxymethyl)pyridyl-bisoxazoline as a platform was developed and a ligand library of 13 compounds was synthesized. Application of the synthesized pyridylbisoxazolines in the cerium catalyzed α-hydroxylation of β-oxoesters showed an improved enantioselectivity up to 84% *ee*, especially for the sulfur containing ligand **3b**. Although the conversion in this case is low. It is still hard to find the right residue which combines high enantioselectivity with high conversion. But we could show within the optimizing process the potential of the bisoxazoline ligand system. Along the way we need further improvement of the ligand backbone and we are looking forward to find the best functionality for high enantioselectivity and high yields.

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[2] S. Iwasa, H. Nakamura. H. Nishiyama, *Heterocycles* **2000**, *52*, 939–944.
[3] a) M. Schulz, J. Christoffers, *Eur. J. Org. Chem*. **2013**, 7624–7630; b) M. Schulz, J. Christoffers, *Synthesis* **2014**, *46*, 81–86.