ORGANIC LETTERS

2005
Vol. 7, No. 16
3393−3396

Synthesis of a New Chiral *N,N,N*-Tridentate Pyridinebisimidazoline Ligand Library and Its Application in Ru-Catalyzed Asymmetric Epoxidation

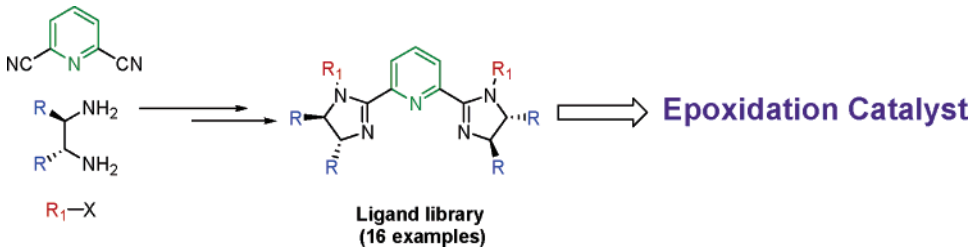
Santosh Bhor, Gopinathan Anilkumar, Man Kin Tse, Markus Klawonn, Christian Döbler, Bianca Bitterlich, Anne Grotevendt, and Matthias Beller*

Leibniz-Institut für Organische Katalyse (IfOK) an der Universität Rostock e.V., Albert-Einstein-Strasse 29A, D-18059 Rostock, Germany

matthias.beller@ifok.uni-rostock.de

Received April 15, 2005

ABSTRACT



A small ligand library of chiral tridentate *N,N,N*-pyridinebisimidazolines have been synthesized for the first time. This new class of ligands can be easily tuned and synthesized on multi g-scale. The usefulness of the ligands is shown in the ruthenium-catalyzed asymmetric epoxidation with hydrogen peroxide as oxidant. Excellent yields (>99%) and good enantioselectivities (up to 71% *ee*) have been obtained for the epoxidation of aromatic olefins.

Transition metal-catalyzed asymmetric reactions offer an efficient and elegant possibility for the synthesis of enantiomerically pure compounds.[1] In general, the choice and synthesis of a suitable chiral controller ligand is the crucial step in the development of a new catalyst for stereoselective reactions. Clearly, a multitude of chiral mono-, bi- and multidentate ligands with P, N, O, and other coordinating atoms are known today and used extensively for all kinds of catalytic reactions. Prominent examples of so-called privileged ligand classes include the salens,[2] bisoxazolines,[3] phosphinooxazolines,[4] tartrate derivatives,[5] and cinchona alkaloids.[6] Nevertheless, there is still an increasing need for new and improved ligands. State-of-the-art chiral ligands[7]

(1) (a) Noyori, R., Ed. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Beller, M.; Bolm, C., Eds. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (c) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis*, Springer: Berlin, 1999.

(2) (a) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 1993; Chapter 4.2. (b) Katsuki, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 287−325. (c) Katsuki, T. *Adv. Synth. Catal*. **2002**, *344*, 131−147.

(3) (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *8*, 1−45. (b) Jorgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thornauge, J. *Acc. Chem. Res*. **1999**, *32*, 605−613.

(4) For a review, see: Helmchen, G.; Pfaltz, A. *Acc. Chem. Res*. **2000**, *33*, 336−345.

(5) (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 1993; Chapter 4.1. (b) Katsuki, T.; Martin, V. S.; *Org. React*. **1996**, *48*, 1−299. (c) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed*. **2001**, *1*, 92−139.

(6) (a) Kolb, H. C.; Van Nieuwenzhe, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483−2547. (b) Beller, M.; Sharpless, K. B. In *Applied Homogeneous Catalysis with Organometallic Compounds*, Vol. 2; Cornils, B.; Herrmann, W. A., Eds.; VCH: Weinheim, 1996; pp 1009−1024. (c) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*, Vol. 2; Beller, M.; Bolm, C., Eds.; VCH: Weinheim, 1998; pp 219−242. (d) Markó, I. E.; Svendsen, J. S. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 713−787. (e) Bolm, C.; Hildebrand, J. P.; Muñiz, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 399−428.

10.1021/ol050821e CCC: $30.25 © 2005 American Chemical Society
Published on Web 07/09/2005

should offer the user a series of advantages: obviously, it should give highly selective and active as well as productive catalysts. In addition, the ligand should be conveniently prepared from mg- to kg-scale, and the synthesis should be economically feasible. Unfortunately, each catalytic reaction needs its own optimized ligand. To find the optimal catalyst for a certain substrate the preparation of ligand libraries with the same basic ligand skeleton should be possible without problems. However, the systematic modification of the structure of new ligands is often difficult and time-consuming.

Herein, we report a new class of chiral ligands, which is simply synthesized and can be easily varied by remote functionalizations to allow for the preparation of ligand libraries in a fast and practical manner.

The starting point of this work was our studies on ruthenium-catalyzed epoxidation of olefins with C_2-symmetric pyridinebisoxazolines (pybox) as the chiral ligand.[8] While synthesizing new pybox ligands, we realized that the preparation of such a ligand library is limited and time-consuming due to the difficulty of functionalizations of the ligand backbone and stepwise formation of the oxazoline moiety.[9]

We thought that introducing a second nitrogen atom in place of oxygen of pyridinebisoxazoline ligands would provide a more flexible ligand scaffold, which might be easily varied by *N*-alkylation, *N*-arylation, and *N*-acylation to tune the reactivity as well as stereoselectivity in catalytic asymmetric reactions (Figure 1).

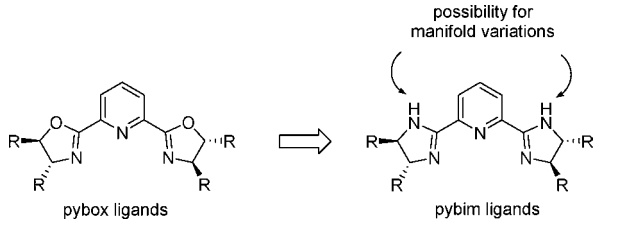


Figure 1. From pybox to pybim ligands.

Despite the importance of pybox ligands for numerous stereoselective reactions,[10] to the best of our knowledge similar chiral *pyridinebisimidazoline* ligands, here abbreviated as *pybim*, have not been synthesized and applied in asymmetric catalysis.

The synthesis of the pybim scaffold is easily done from commercially available 2,6-dicyanopyridine **1** in two steps. Treatment of **1** with a catalytic amount of sodium in anhydrous methanol followed by neutralization with acetic acid and removal of methanol under reduced pressure, afforded the bisimidate **2** as a pale yellow solid in quantitative yield.[11]

Condensation of **2** with chiral diamines such as *R,R*-1,2-diaminocyclohexane and *R,R*-1,2-diphenylethylene-diamine furnished the corresponding *pyridine-bisimidazoline* ligands **3** and **4** in good to excellent yield. The pybims **3** and **4** are stable to air and moisture and offer numerous possibilities for further modification at the amine functionality. Noteworthy, the synthesis of **4** has been performed without problems on 10 *g*-scale.[12]

To demonstrate the usefulness of the concept a small library of 14 pybims was prepared from **3** and **4** (Table 1). Treatment with benzyl bromide in the presence of sodium hydride gave the corresponding ligands **5a** and **6a** in 68% and 65% yields respectively (Table 1, entry 1 and 3).

The reaction of tosyl chloride (Table 1, entry 2 and 4), carbonyl chlorides (Table 1, entry 5−10, and 13) and chloroformates (Table 1, entry 11, 12, and 14) with **3** or **4** gave the corresponding pybim ligands **5b, 6b**−**l** in moderate to very good yield (60 to 97%) by using DMAP in dichloromethane at 0 °C to room temperature.

For the preparation of **6k**, (*S*)-methoxy-α-methyl-2-naphthalene acetyl chloride was prepared by refluxing the corresponding acid in $CHCl_3$ with excess of thionyl chloride (Table 1, entry 13).

With the newly developed ligands in hand, we looked for a suitable test reaction to demonstrate that substitution of imidazoline NH group has a significant influence on catalysis. In principle, pybim-type ligands should be useful for any reaction, which use pybox ligands, e.g., aziridinations, epoxidations, carbene reactions, addition of nucleophiles to carbonyl groups, etc.[10] Among the various catalytic reactions known for pybox ligands asymmetric epoxidations with hydrogen peroxide are among the most challenging methods.[13] Therefore, we decided to study the behavior of the

(7) For a discussion on the "ideal catalyst", see: Gladysz, J. A. *Pure Appl. Chem*. **2001**, *73*, 1319−1324.

(8) (a) Tse, M. K.; Bhor, S.; Klawonn, M.; Döbler, C.; Beller, M. *Tetrahedron Lett*. **2003**, *44*, 7479−7483. (b) Bhor, S.; Tse, M. K. Klawonn, M.; Döbler, C.; Mägerlein, W.; Beller, M. *Adv. Synth. Catal*. **2004**, *346*, 263−267. (c) Klawonn, M.; Tse, M. K.; Bhor, S.; Döbler, C.; Beller, M. *J. Mol. Catal. A* **2004**, *218*, 13−19. (d) Tse, M. K.; Döbler, C.; Bhor, S.; Klawonn, M.; Mägerlein, W.; Hugl, H.; Beller, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5255−5260.

(9) (a) Desimoni, G.; Faita, G.; Quadrrelli, P. *Chem. Rev*. **2003**, *103*, 3119−3154. (b) Nishiyama, H. *Adv. Catal. Proc.* **1997**, *2*, 153−188.

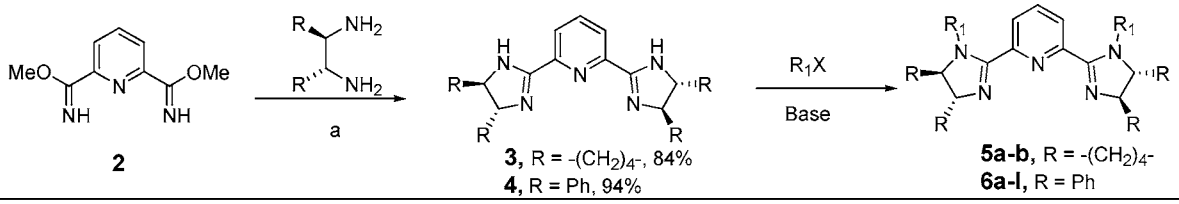
(10) For recent examples of catalysis with pybox derivatives, see: (a) Pfaltz, A. *Acc. Chem. Res*. **1993**, *26*, 339−345. (b) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc*. **1994**, *116*, 2223−2224. (c) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45. (d) Sekar, G.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1998**, *63*, 2961−2967. (e) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res*. **2000**, *33*, 325−335. (f) Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829−1831. (g) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340−1341. (h) Cuervo, D.; Gamasa, M. P.; Gimeno, J. *Chem. Eur. J.* **2004**, *10*, 425−432. (i) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev*. **2003**, *103*, 3119−3154.

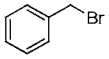
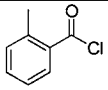
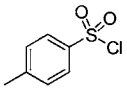
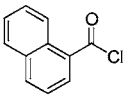
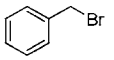
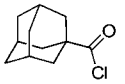
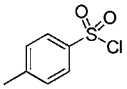
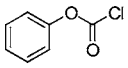
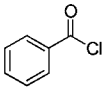
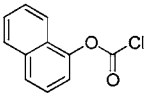
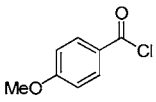
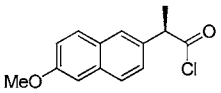
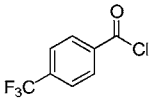
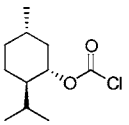
(11) (a) Müller, P.; Bolea, C.; *Helv. Chim. Acta*. **2001**, *84*, 1093−1111. (b) Bastero, A.; Claver, C.; Ruiz, A.; Castillon, S.; Daura, E.; Bo, C.; Zangvando, E. *Chem. Eur. J*. **2004**, *10*, 3747−3760.

(12) A 100 mL pressure tube was charged with bis-imidate **2** (4.55 g, 23.6 mmol), (*R, R*)-1, 2-diphenyl ethylenediamine (10.0 g, 47.1 mmol) and 75 mL of dichloromethane. The resulting mixture was stirred at reflux for 2 days. Then 50 mL of water was added and the phases were separated; the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo to give a light yellow solid, which was purified by crystallization (ether/ethyl acetate) to give **4** in 62% yields (7.6 g, 3.46 mmol).

(13) For reviews of H_2O_2 as epoxidation oxidant see: (a) Grigoropoulou, G.; Clark, J. H.; Elings, J. A. *Green Chem*. **2003**, *5*, 1−7. (b) Lane, B. S.; Burgess, K. *Chem. Rev*. **2003**, *103*, 2457−2473. For a commentary, see: (c) Beller, M. *Adv. Synth. Catal*. **2004**, *346*, 107−108.

Table 1. Synthesis of a Pybim Library



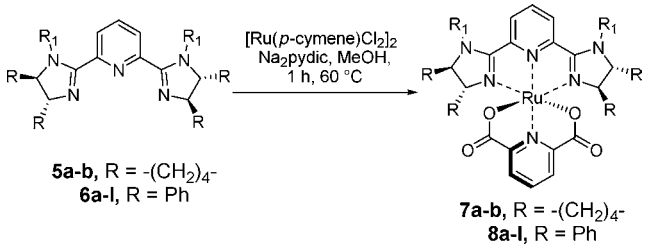
entry	R_1X	ligand	yield (%)	entry	R_1X	ligand	yield (%)
1		**5a**	68[b]	8		**6f**	99[c]
2		**5b**	93[c]	9		**6g**	94[c]
3		**6a**	65[b]	10		**6h**	96[c]
4		**6b**	85[c]	11		**6i**	98[c]
5		**6c**	96[c]	12		**6j**	84[c]
6		**6d**	87[c]	13		**6k**	62[c]
7		**6e**	97[c]	14		**6l**	90[c]

Reagents and conditions: [a] CH_2Cl_2, reflux, 2 d; [b] 2.5 equiv. NaH, THF, 0 °C to room temperature, 4 h; [c] 3.0 equiv. DMAP, CH_2Cl_2, 0 °C to room temperature, 5 h.

new ligands in the ruthenium-catalyzed asymmetric epoxidation[8,14] of stilbene with hydrogen peroxide. For this purpose, the pyridinebisimidazoline ligands **5a**−**b** and **6a**−**l** were transformed into the novel class of Ru(pybim)(pydic) complexes **7a**−**b** and **8a**−**l,** using disodium pyridine-2,6-dicarboxylate and $[Ru(p\text{-cymene})Cl_2]_2$ (Scheme 1).[15] The catalytic reactions were run at room temperature in the presence of 5 mol% of Ru-complex using 3 equiv. of H_2O_2 (30% in water), which was slowly dosed into the reaction mixture.

As shown in Table 2, all the Ru(pybim)(pydic) complexes catalyzed the epoxidation of *trans*-stilbene. It is important to note that the enantioselectivity and reactivity of the catalyst is largely dependent on the respective substituent on the nitrogen of the imidazoline ring (remote functionality) of Ru(pybim)(pydic) complex. This is a clear proof of our concept and by steric and electronic tuning at this position an optimization of the catalyst is possible. Similar effects

Scheme 1. Synthesis of Ru(pybim)(pydic) Complexes



Note: For R_1 substituent see Table 1.

(14) For a review using Ru complexes for epoxidation reactions see: (a) Barf, G. A.; Sheldon, R. A. *J. Mol. Catal.* **1995**, *102*, 23−39. Recent achievements in Ru-based epoxidations with different oxidants, see: (b) End, N.; Pfaltz, A. *Chem. Commun.* **1999**, 589−590. (c) Gross, Z.; Ini, S. *Org. Lett.* **1999**, *1*, 2077−2080. (d) Pezet, F.; Aït-Haddou, H.; Daran, J.-C.; Sadaki, I.; Balavoine, G. G. A. *Chem. Commun.* **2002**, 510−511. Recent examples using Ru salen complexes, see: (e) Takeda, T.; Irie, R.; Shinoda, Y.; Katsuki, T. *Synlett*. **1999**, 1157−1159. (f) Nakata, K.; Takeda, T.; Mihara, J.; Hamada, T.; Irie, R.; Katsuki, T. *Chem. Eur. J.* **2001**, *7*, 3776−3782. (g) Berkessel, A.; Kaiser, P.; Lex, J. *Chem. Eur. J*. **2003**, *9*, 4746−4756.

(15) Nishiyama, H.; Shimada, T.; Itoh, H.; Sugiyama, H.; Motoyama, Y. *Chem. Commun*. **1997**, 1863−1864.

Table 2. Ru(pybim)(pydic)-Catalyzed Asymmetric Epoxidation of *trans*-Stilbene Using H_2O_2 as Oxidant[a]

entry	catalyst	time (h)	conv. (%)	yield (%)[b]	*ee* (%)[c]
1	**7a**	16	85	79	1
2	**7b**	12	100	93	8
3	**8a**	16	90	79	11
4	**8b**	4	77	63	21
5	**8c**	12	100	90	34
6	**8d**	12	100	>99	38
7	**8e**	12	100	78	33
8	**8f**	12	100	>99	52
9	**8 g**	12	100	91	56
10	**8h**	12	100	97	28
11	**8i**	12	100	>99	60
12	**8j**	12	100	>99	71
13	**8k**	12	100	94	69
14	**8l**	12	100	97	71

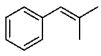
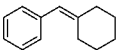
[a] Reaction conditions: In a 25 mL Schlenk tube Ru-complex (0.025 mmol) and *trans*-stilbene (0.5 mmol) were dissolved in *tert*-amyl alcohol (9 mL). Dodecane (GC internal standard, 100 μL) was added. To this mixture a solution of hydrogen peroxide (170 μL, 1.5 mmol) in *tert*-amyl alcohol (830 μL) was added over a period of 12 h by a syringe pump. [b] Determined by comparing with authentic samples on GC-FID. [c] Determined by HPLC and the major enantiomer of *trans*-stilbene oxide had 1*R*,2*R*-configuration.

might be expected for other catalytic reactions which proceed in the presence of pybox ligands, too.

More specifically the Ru(*R*,*R*-cyclohexyl-*N*,*N*′-Bn_2-pybim)(pydic) complex **7a** gave a racemic mixture of *trans*-stilbene oxide (79%) with low reactivity (Table 2, entry 1), while Ru-complexes which were synthesized from *tetra*-phenyl pybim ligands with *N*-benzoyl protection **8a**−**g** led to good to excellent yields (78 → 99%) and significant enantioselectivities (33−56% *ee*) (Table 2, entries 5−9). Best results for the epoxidation of *trans*-stilbene were obtained applying the carbamate-functionalized complexes **8j** and **8l**. Here, the enantioselectivity was increased up to 71% *ee* for *trans*-stilbene oxide (97 → 99% yield) (Table 2, entry 12 and 14). Interestingly, also **8k**, functionalized with the sterically bulky and flexible chiral (*S*)-2-(6-methoxynaphthyl)propionic acid gave 69% *ee* for *trans*-stilbene oxide (Table 2, entry 13).

Next, some preliminary substrate variation was done and catalyst **8l** was applied to different olefins (Table 3). To our delight, mono-, di-, and trisubstituted aromatic olefins gave good to excellent yields (76 → 99%) and moderate to good enantioselectivity (42−68%) (Table 3). Specifically, the result for styrene (Table 3, entry 1) is promising for further development of this type of catalyst since it is one of the most difficult substrates for epoxidation using hydrogen peroxide and often found in the literatures with low yields and enantioselectivity.[16] To the best of our knowledge, the maximum enantioselectivity is only 59% for styrene oxide using hydrogen peroxide as the oxidant.[8d]

Table 3. Catalyst Scope[a]

entry	substrate	conv. (%)[b]	yield (%)[b]	selec. (%)	*ee* (%)[c]
1		100	76	76	42
2		100	82	82	68
3		100	88	88	43
4		100	>99	>99	54

[a] Reaction conditions: In a 25 mL Schlenk tube Ru-catalyst **8l** (0.025 mmol) and substrate (0.5 mmol) were dissolved in *tert*-amyl alcohol (9 mL). Dodecane (GC internal standard, 100 μL) was added. To this mixture a solution of hydrogen peroxide (170 μL, 1.5 mmol) in *tert*-amyl alcohol (830 μL) was added over a period of 12 h by a syringe pump. [b] Determined by comparing with authentic samples on GC-FID. [c] Determined by HPLC.

In summary, we have disclosed a novel class of chiral tridentate, pyridinebisimidazoline ligands (*pybims*). The key building blocks **3** and **4** are conveniently synthesized in two steps from commercially available starting materials. Similar compounds should be available by using other chiral 1,2-diamines.

Ru-complexes derived from most of the new ligands are effective catalysts for asymmetric epoxidation of alkenes with hydrogen peroxide. Advantageously, compared to the well-known pybox ligands systematic modification of the catalyst system is possible due to the presence of the imidazoline NH-groups. As proof of concept it is shown that these remote functionalizations have an important impact on the outcome of catalytic epoxidation reactions.

Acknowledgment. This work has been supported by the State of Mecklenburg−Western Pommerania. We thank Mrs. C. Mewes, Mrs. H. Baudisch, Mrs. A. Lehmann, and Mrs. S. Buchholz (all IfOK) for their excellent technical and analytical support. Dr. H. Hugl and Dr. W. Mägerlein (LANXESS) are thanked for general discussions.

Supporting Information Available: Experimental procedures and characterization of all ligands, complexes and epoxides. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050821E

(16) (a) Stoop, R. M.; Mezzetti, A. *Green Chem.* **1999**, 39−41. (b) Stoop, R. M.; Bachmann, S.; Valentini, M.; Mezzetti, A. *Organometallics* **2000**, *19*, 4117−4126. (b) Bolm, C.; Kadereit, D.; Valacchi, M. *Synlett.* **1997**, 687−688. (c) Bolm, C.; Meyer, N.; Raabe, G.; Weyhermüller, T.; Bothe, E. *Chem. Commun.* **2000**, 2435−2436. (d) Kureshy, R. I.; Khan, N. H.; Abdi, S. H. R.; Patel, S. T.; Jasra, R. V. *Tetrahedron: Asymmetry* **2001**, *12*, 433−437.