Chiral phenyl-bis(oxazoline) as an efficient auxiliary for asymmetric catalysis*

Hisao Nishiyama‡, Jun-ichi Ito, Takushi Shiomi, Toru Hashimoto, Takeshi Miyakawa, and Megumi Kitase

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan

Abstract: A new class of phenyl-bis(oxazoline) auxiliaries was readily prepared from isophthaloyl chloride and appropriate β-amino alcohols, and the derived rhodium complexes underwent new cyclization reactions at the metal center and exhibited high catalytic efficiency for asymmetric conjugate reduction of α,β-unsaturated carbonyl compounds and reductive aldol reactions of aldehydes and ketones.

Keywords: asymmetric catalysis; rhodium; oxazoline; reduction; C–H bond activation.

INTRODUCTION

The synthesis of organic auxiliaries for transition-metal complexes is a very important subject in the field of organometallic chemistry and organic synthesis, including molecular catalysis and asymmetric synthesis, because the auxiliaries are able to provide appropriate stereochemical and electronic circumstances around active metal centers as indispensable partners. We have developed the heterocyclic oxazoline skeleton, 4,5-dihydro-1,3-oxazole, as a modular unit of multidentate auxiliaries, because of its efficient substituent diversity at 4- and 5-carbon atoms using a variety of β-amino alcohols. In 1989, we first reported pyridine-bis(oxazoline) (abbreviated as pybox) as a tridentate N,N,N-type oxazoline-based ligand for asymmetric catalysis (Fig. 1) [1,2]. Despite its tridentate nature, dissociation of pybox from metals was observed. Therefore, we designed a new ligand, phenyl-bis(oxazoline) (abbreviated as phebox), which has bis(oxazoline) and phenyl groups to make C_2-symmetric and meridional configuration with a central covalent bond to metal atom [3,4]. Here, we introduce the chemistry of phebox and its rhodium complexes related to organometallic chemistry and asymmetric catalysis.

![Fig. 1 Phebox and pybox.](image)


‡Corresponding author
SYNTHESIS OF PHEBOX AND ITS RHODIUM COMPLEXES

A precursor for phebox is bis(oxazolinyl)benzene 1, which can be readily prepared with isophthaloyl chloride in two steps, amide formation with a chiral β-amino alcohol followed by oxazoline formation with methanesulfonyl chloride (Scheme 1). Then, the reaction with rhodium chloride in methanol or rhodium-cyclooctene complex in chloroform via C–H bond activation provides Rh-phebox-aqua complex 2, which can be converted to the corresponding acetate complex 3 by treatment with silver acetate [5].

When we used 4,5-dimethylbenzene derivative 4 prepared from 4,6-dimethylphthalic acid, we could improve the yield for complex formation by C–H bond activation (Scheme 2) [6]. We assumed that undesirable C–H bond activation at the 4- or 6-positions could be suppressed by blocking with the two methyl groups to increase the yield of the C–H activation at the central carbon atom.

Treatment of the Rh-complex 6 with triethylamine in the presence of CH₂Cl₂ and ClCH₂CO₂Me furnished the ClCH₂-complex 7 and the MeOCOCH₂-complex 8, respectively (Scheme 3) [7]. Triethylamine acted as a reducing agent to form a Rh(I) species, which was captured with organic halides to form the corresponding products 7 and 8 by oxidative addition reactions. When HNi-Pr₂ was used in place of Et₃N, a new complex 9 with a five-membered rhodaazacyclopentene skeleton was isolated in 50 % yield, and its structure was determined by X-ray analysis. On the basis of experiments with CD₂Cl₂, the carbon atom derived from dichloromethane was incorporated into the α-position to the rhodium atom. Therefore, we proposed the mechanism as follows: (1) reduction of the complex 6

© 2008 IUPAC, Pure and Applied Chemistry 80, 743–749
with HNi-Pr₂, (2) oxidative addition of CH₂Cl₂, (3) formation of the intermediate imine-complex A, (4) tautomerization to the enamine-complex B, (5) intramolecular C–C bond-forming cyclization. In terms of intramolecular cyclization on metals, we have already reported the N,O-hetero-carbene complex of Rh-phebox prepared from the corresponding isonitrile complex and related reactions [8].

When we adopted the acetate complex 10, we found that the corresponding phenyl-rhodium complex 11 was formed by a C–H bond activation reaction with benzene (Scheme 4) [9]. The reactions with o- and m-xylene were also carried out at 140 °C to furnish the corresponding xylyl complexes, respectively. We think that the acetate group on rhodium atom plays an important role as an internal base.

© 2008 IUPAC, Pure and Applied Chemistry 80, 743–749
complex 10 also reacted with phenylacetylene at 60 °C to give phenylacetylide complex 12 in 72 % [10]. In addition, the acetate complexes exhibited catalytic activity for cross-coupling of phenylacetylene and dimethyl acetylenedicarboxylate to form enyne derivatives [10].

ASYMMETRIC CONJUGATE REDUCTION

We found that the Rh-phebox complex catalyzed hydrosilylation reactions of styrene derivatives with several hydrosilanes followed by oxidation to give optically active secondary alcohols in over 90 % ee [11]. We extended the hydrosilylation reaction to conjugate reduction with α,β-unsaturated esters and ketones (Scheme 5) [5,12]. Treatment of the unsaturated ester 13 with 1 mol % of Rh-phebox-acetate complex 3 and (EtO)2MeSiH at 60 °C gave rise to conjugate reduction furnishing the saturated ester 14 in 96 % yield with 96 % ee. A variety of esters was subjected to the asymmetric conjugate reduction to give high enantioselectivity up to 98 %. In general, conjugate reduction of α,β-unsaturated ketones may suffer from 1,2-reduction to give secondary alcohols. However, the choice of hydrosilane can solve the problem to give the saturated ketones exclusively [5]. The ketone 15 was reduced in 96 % yield with 92 % ee with (EtO)2MeSiH. The isopropyl group at the β-position provided products with the highest enantioselectivity.

![Scheme 5 Asymmetric conjugate reduction of α,β-unsaturated esters and ketones.](image_url)

In the case of α,β-unsaturated aldehydes, cinnamaldehyde could be exclusively reduced to give the dihydrocinnamaldehyde under the same conditions as that for ketones. However, when we adopted β-methyl cinnamaldehyde for asymmetric reduction, we obtained the 1,4-reduction product in 50 % yield with 91 % ee accompanied with the 1,2-reduction product in 47 % yield [13].

© 2008 IUPAC, Pure and Applied Chemistry 80, 743–749
ASYMMETRIC REDUCTIVE ALDOL REACTION

The reductive aldol reaction is a very important method for preparation of \( \beta \)-hydroxylcarbonyl compounds with \( \alpha,\beta \)-unsaturated carbonyl ones and carbonyl ones as acceptors catalyzed by transition-metal catalysts [14]. As we have demonstrated, the conjugate reduction of \( \alpha,\beta \)-unsaturated esters with chiral Rh-phebox catalysts in the presence of hydrosilanes, we expected the possibility to trap intermediate Rh-enolate species with aldehydes. The reaction of benzaldehyde (1 equiv) and tert-butyl acrylate (1.5 equiv) was carried out at 50 °C using 1 mol % of Rh-phebox acetate complex 3 and (EtO)\(_2\)MeSiH to form the corresponding aldol product 17 in 91 %. Unexpectedly, we found anti-diestereoselectivity (anti: syn = 95:5) and high enantioselectivity, 91 % ee for the anti-product (Scheme 6) [15]. When PhMe\(_2\)SiH was used a hydride source, the highest ee of 95 % for anti-17 was obtained. Furthermore, the scope of these reactions was examined on other substrates, which also gave products with high ee. The acetate catalyst derived from 3,5-dimethyl complex 5 also furnished almost similar activity to give 98 % yield, 95:5 of anti:syn, and 95 % ee for anti-17 [6].

![Scheme 6 Asymmetric reductive aldol reaction of acrylate and aldehydes.](image)

When trimethylsilyl acrylate was adopted as an enolate source, the corresponding carboxylic acid was directly obtained after acid hydrolysis [16]. The reaction of 1-naphthaldehyde gave high enantioselectivity, up to 97 %, for anti-18, even with 0.1 mol % of catalyst loading (Scheme 7).

![Scheme 7 Asymmetric reductive aldol reaction of trimethylsilyl acrylate.](image)

The utilization of ketones as acceptors in the aldol reaction, leading to \( \beta \)-tertiary alcohols, constitutes a challenge. Under the standard conditions outlined in Scheme 5, the reductive aldol reaction of acetone and ethyl cinnamate was carried out, and resulted in low chemical yields. After several trials, we found optimum conditions to achieve good to excellent yields of 83 % with 97 % ee with MePh\(_2\)SiH (Scheme 8) [17]. The reactions with substituted cinnamates and several ketones were demonstrated to attain 96–98 % ee.

© 2008 IUPAC, Pure and Applied Chemistry 80, 743–749
Judging from the absolute configuration of 19, the si-face of the hypothetical Rh-enolate may attack the coordinated acetone moiety via a cyclic transition state (Scheme 9).

**CONCLUSIONS**

We have demonstrated organometallic and asymmetric catalytic chemistry of the rhodium complexes with phebox auxiliaries, which have flourished as a credible partner for metal atoms to make stable complexes and has showed high efficiency of diastereoselectivity and enantioselectivity.

**ACKNOWLEDGMENTS**

This work was financially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and from the Japan Society for the Promotion of Science. H.N. is supported by the Mitsubishi Foundation and the Daiko Foundation.

**REFERENCES**


