

HETEROCYCLES, Vol. 78, No. 3, 2009, pp. 617 - 622. © The Japan Institute of Heterocyclic Chemistry
Received, 29th September, 2008, Accepted, 4th November, 2008, Published online, 5th November, 2008
DOI: 10.3987/COM-08-11563

A CHIRAL “ROOFED” *cis*-DIAMINE-Ru(II) COMPLEX: AN EFFICIENT CATALYST FOR ASYMMETRIC TRANSFER HYDROGENATION OF KETIMINES

Hirofumi Matsunaga,^a Kyoko Nakanishi,^a Makoto Nakajima,^a Takehisa Kunieda,^b and Tadao Ishizuka^{a*}

^aFaculty of Medical and Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan

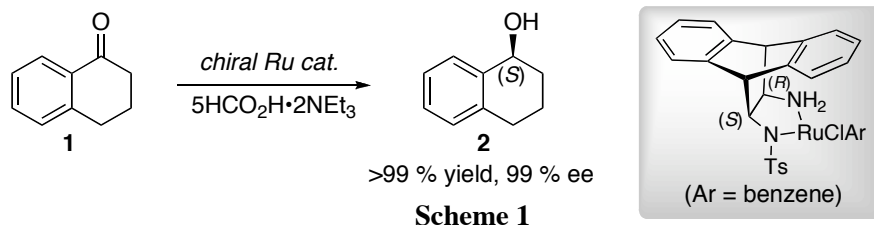
^bFaculty of Pharmaceutical Sciences, Sojo University, 4-22-1 Ikeda, Kumamoto 860-0082, Japan

Abstract – Highly enantioselective transfer hydrogenation of ketimines to the corresponding chiral amines was achieved with the chiral Ru(II) complex, prepared from the conformationally rigid and sterically bulky “roofed” *cis*-1,2-diamine.

Optically active amines are very important building blocks for biologically active molecules, pharmaceuticals, and agrochemicals. Among the numerous methods currently available for the preparation of enantiomerically pure amines, catalytic enantioselective reduction of ketimines is one of the most important methods,¹ as it is used to accomplish chiral ligand-transition metal complex-catalyzed high-pressure hydrogenations,² hydrosilylations³ or transfer hydrogenations⁴, and chiral organic compound-catalyzed hydrosilylations.⁵ However, compared with the reduction of ketones using a similar procedure, the number of highly effective methods currently available for the reduction of ketimines is limited. Therefore, the study of versatile and/or highly enantioselective reduction of ketimines remains challenging.

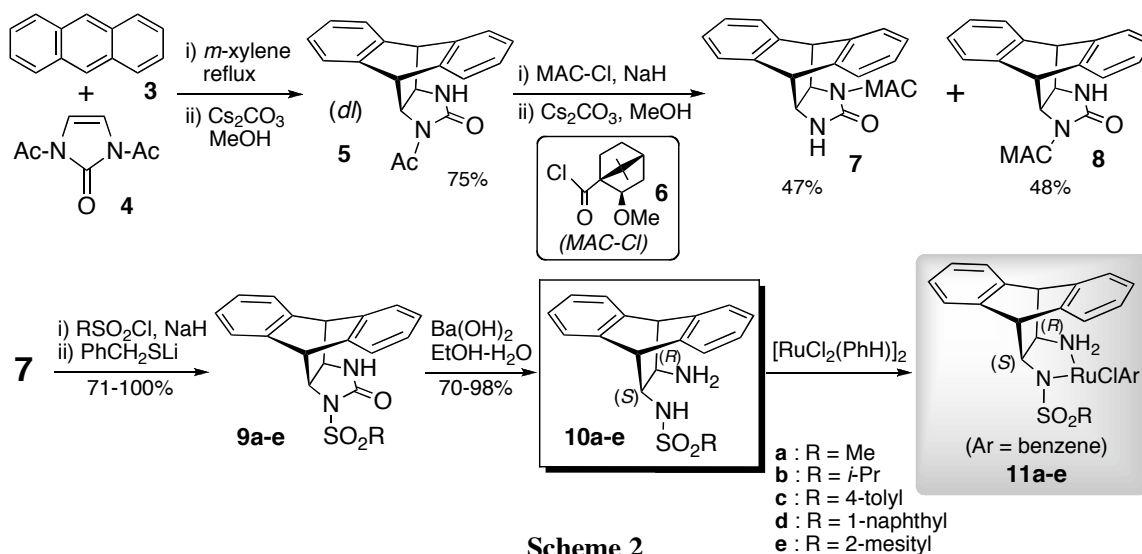
We previously demonstrated that chiral “roofed” *cis*-1,2-diamine, which is conformationally rigid and sterically bulky, was easily derived from chiral “roofed” 2-imidazolidinone. Moreover, *cis*-1,2-diamine was an excellent ligand for the Ru(II)-catalyzed asymmetric transfer hydrogenation of a wide variety of arylketones, including sterically bulky ketones, resulting in high catalytic activity and enantioselectivity

(Scheme 1).⁶ These positive results encouraged us to apply this system to the catalytic asymmetric reduction of ketimines.



In this paper, we describe a highly effective asymmetric transfer hydrogenation of ketimines catalyzed by the “roofed” *cis*-1,2-diamine-Ru(II) complex in the presence of 5HCO₂H·2NEt₃.

Five types of “roofed” *cis*-1,2-diamines **10a-e** were readily prepared by *N'*-sulfonylation of the optically pure *N*-((1*S*)-2-*exo*-methoxy-1-apocamphanecarbonyl (abbreviated as MAC))-2-imidazolidinone (**7**, **8**), obtained from the thermal [4+2] cycloaddition of 1,3-dihydro-2-imidazolone (**4**), with anthracene (**3**) and successive optical resolution, followed by removal of the MAC group and hydrolytic ring cleavage with Ba(OH)₂ (Scheme 2).^{6,7}



The “roofed” *cis*-1,2-diamine-ruthenium(II) complexes (**11a-e**) were easily prepared by mixing the 1,2-diamines (**10a-e**) with [RuCl₂(benzene)]₂ *in situ*, according to the method of Noyori.^{8,9}

Initially, we examined the catalytic efficiency of the *N*-tosyl complex **11c** toward α-tetralone-derived ketimine **13** in the presence of an azeotropic mixture of 5HCO₂H·2NEt₃ as a hydrogen source at 25 °C. This reaction was completed in 6 hours to give the corresponding chiral amine in 91% yield and 81% ee (Table 1, entry 1). We also tested the co-solvent effects with ketimine **13**. Although the reaction times were longer and the chemical yields slightly diminished, enantioselectivity was enhanced in the presence of CH₂Cl₂.¹⁰ Similar reactions were performed in the presence of a typical

1,2-diphenylethylenediamine-Ru(II) (*p*-cymene) complex (**12**)^{4a,8} to give results inferior to those obtained using catalyst **11c** (Table 1, entries 3, 4).

We also tested the substituent effect of a sulfonyl group on the “roofed” *cis*-1,2-diamine ligand for the asymmetric reduction of ketimine **13** (Table 1, entries 2, 5-8). Higher enantioselectivities resulted with catalysts **11b**, **11c** and **11d** (entries 2, 6 and 7). Therefore, additional trials of the asymmetric reduction of ketimine **14a** in the presence of catalysts **11b-d** were performed and, intriguingly, the *N*-isopropylsulfonylated catalyst **11b** showed superior catalytic activity and enantioselectivity (entries 9-11).

Table 1. Asymmetric hydrogen transfer reduction of ketimines catalyzed by chiral Ru(II) complex.

Entry	Imine	Cat.	Yield ^{a)} (%)	ee ^{b)} (%)	Entry	Imine	Cat.	Yield ^{a)} (%)	ee ^{b)} (%)
1 ^{c)}		11c	91	81 (<i>S</i>)	5		11a	78	43 (<i>S</i>)
2		11c	83	88 (<i>S</i>)	6		11b	78	90 (<i>S</i>)
3 ^{c)}		12	68	77 (<i>R</i>)	7		11d	71	89 (<i>S</i>)
4		12	73	76 (<i>R</i>)	8		11e	41	64 (<i>S</i>)
a) Isolated yields. b) Determined by chiral HPLC. For absolute configuration, see ref 11. c) In the absence of CH ₂ Cl ₂ .					9		11b	78	77 (<i>S</i>)
					10		11c	61	71 (<i>S</i>)
					11		11d	56	63 (<i>S</i>)

Table 2 summarizes the results of the transfer hydrogenation reaction with various ketimines **14a-i** in the presence of catalyst **11b** and the 5HCO₂H·2NEt₃ azeotrope in CH₂Cl₂. *Para*-substituted acetophenone-derived ketimines **14a-e** showed good to excellent chemical yields and ee values of 74-77%. The electronic nature of the *para*-substituent did not affect the enantioselectivity. Propiophenone-derived ketimines **14f** showed higher reactivity than acetophenone-derived ketimines with slightly lower ee values. The greater the bulky of the R² group of the ketimines (entries 7 and 8), the lower the observed reactivities and enantioselectivities. Cyclic imine **14i** gave inferior enantioselectivity, but a relatively short reaction time.

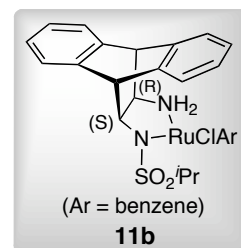
Apparently, the enantioselectivities were correlated with the *E/Z* ratios of the imines measured using ¹H NMR. Thus, higher *E*-containing ketimines, such as **13** (*E* only), and acetophenone-derived ketimines **14a-e** gave good to excellent enantioselectivities, but higher *Z*-containing ketimines such as **14g-i** showed poor ee values.

Although the precise structure of the catalyst **11** and the corresponding hydride species are unknown, we speculate the most likely hydride catalyst **16**, depicted in Figure 1. Thus, the *re*-face of ketimines easily

approach from the less-hindered side, which is opposite the “roof” moiety, of the ruthenium hydride **16** to create the (*S*)-amine **17**. The clear discrimination between “shielding” and “non-shielding” site by minimum steric hindrance make the chiral ruthenium complex **16** a highly reactive and selective catalyst. The “roofed” *cis*-1,2-diamine structure, which is both conformationally rigid and sterically bulky, creates an ideal space for asymmetric transfer hydrogenation.

Table 2. Chiral Ru(II) complex **11b** -catalyzed asymmetric transfer hydrogenation of various ketimines **14a-i**.

Entry	Imine	R ¹	R ²	<i>E</i> / <i>Z</i> ^{a)}	Time (h)	Yield ^{b)} (%)	ee ^{c)} (%)
1	14a	H	Me	15 / 1	24	78	77 (<i>S</i>)
2	14b	MeO	Me	20 / 1	18	91	74 (<i>S</i>)
3	14c	Me	Me	15 / 1	24	79	75 (-) ^{d,e)}
4	14d	Cl	Me	20 / 1	24	71	74 (<i>S</i>)
5	14e	NO ₂	Me	29 / 1	12	92	75 (-) ^{d,e)}
6	14f	H	Et	2 / 1	6	85	69 (-) ^{d,e)}
7	14g	H	<i>i</i> -Pr	1 / 24	24	63	51 (<i>S</i>)
8	14h	H	<i>t</i> -Bu	<i>Z</i> only	48	13	1 ^{d)}
9	14i			<i>Z</i> only	1.5	83	36 (<i>S</i>)



a) Measured by ¹H NMR (300 or 400 MHz).
b) Isolated yields.
c) Determined by chiral HPLC. For absolute configurations, see ref 11.
d) Absolute configurations were not determined.
e) The signs of optical rotation of the isolated products are shown.

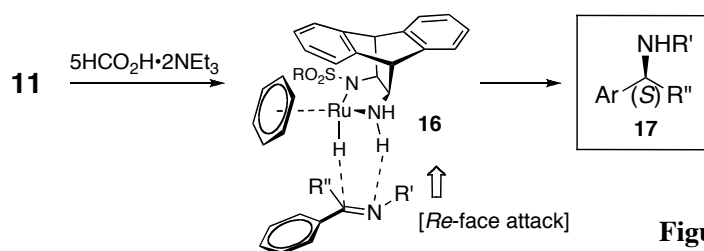


Figure 1

In conclusion, we demonstrated that the “roofed” *cis*-1,2-diamine-Ru(II) complex, which is both conformationally rigid and sterically bulky, is an excellent catalyst for asymmetric transfer hydrogenation of ketimines. Additional studies are now in progress.

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 9. General procedure for asymmetric transfer hydrogenation of ketimines catalyzed by **11**: A mixture of benzeruthenium (II) chloride dimer (1.25 mg, 0.0025 mmol, 0.25 mol%), *N*-sulfonylated-“roofed” diamine **10** (0.005 mmol, 0.5 mol%) and triethylamine (1.4 μ L, 0.01 mmol, 1 mol%) in 2-propanol (1 mL) was refluxed for 1 h under an argon atmosphere (formation of catalyst **11**). After removal of the solvent *in vacuo*, 5HCO₂H•2NEt₃ azeotrope (0.5 mL), CH₂Cl₂ (1.5 mL) and ketimine (1 mmol) were successively added and the mixture was stirred at 25 °C. The reaction was monitored by TLC until substantial completion. After the addition of satd. NaHCO₃ aq. (5 mL), the product was extracted (EtOAc, 20 mL $\times$ 3), washed (brine, 10 mL $\times$ 3), dried (anhyd. Na₂SO₄) and evaporated *in vacuo*, followed by purification using flash column chromatography on silica gel to afford the corresponding amine. Enantiomeric excess values were determined by chiral HPLC.
 10. Other type of co-solvents were also examined (toluene, THF, MeCN, DMF, DMSO and IPA) and CH₂Cl₂ gave the optimal result.
 11. Absolute configurations of the chiral amines were determined by comparing the sign of optical

rotation of the isolated products to the literature data, see: ref 4a (reduced product of **13**, **15a** and **15i**); C. Lensink and J. G. de Vries, *Tetrahedron: Asymmetry*, 1992, **3**, 235 (**15b** and **15d**); S. D. Bull, S. G. Davies, P. M. Kelly, M. Gianotti, and A. D. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3106 (**15b**); J. L. Stymiest, G. Dutheuil, A. Mahmood, and V. K. Aggarwal, *Angew. Chem. Int. Ed.*, 2007, **46**, 7491 (**15g**).