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

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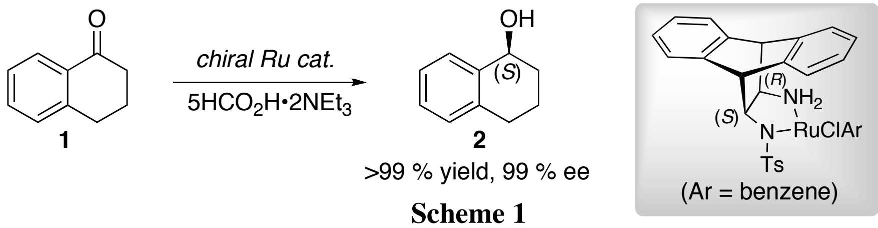
Abstract – Highly enantioselective transfer hydrogenation of ketimines to the corresponding chiral amines was achieved with the chiral Ru(II) complex, prepared from the conformationally rigid and sterically bulky "roofed" *cis*-1,2-diamine.

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] hydrosilylations[3] or transfer hydrogenations[4], 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

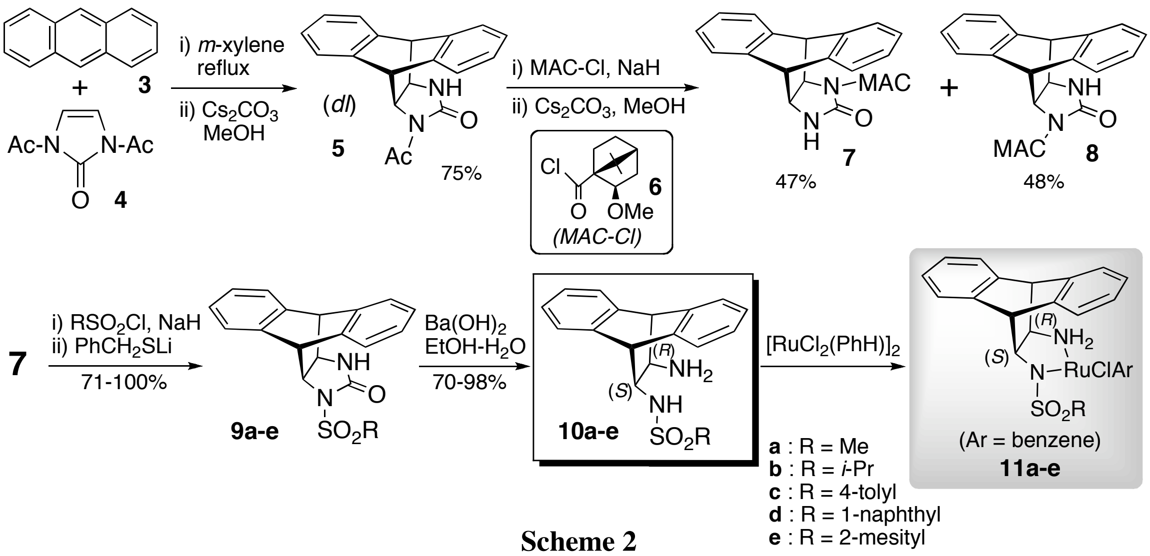
(Scheme 1).[6] These positive results encouraged us to apply this system to the catalytic asymmetric reduction of ketimines.



Scheme 1

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 $5HCO_2H•2NEt_3$.

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]



Scheme 2

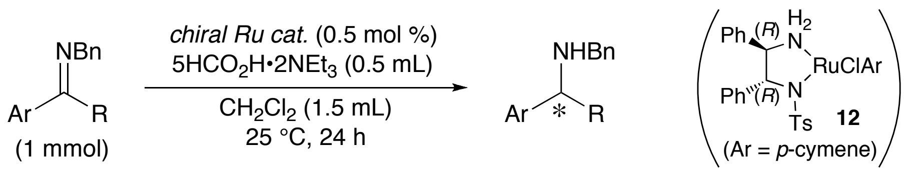
The "roofed" *cis*-1,2-diamine-ruthenium(II) complexes (**11a-e**) were easily prepared by mixing the 1,2-diamines (**10a-e**) with $[RuCl_2(benzene)]_2$ *in situ*, according to the method of Noyori.[8,9]

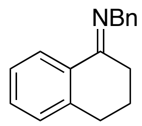
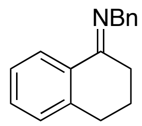
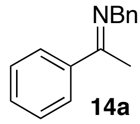
Initially, we examined the catalytic efficiency of the *N*-tosyl complex **11c** toward α-tetralone-derived ketimine **13** in the presence of an azeotropic mixture of $5HCO_2H•2NEt_3$ as a hydrogen source at 25 °C. This reaction was completed in 6 hours to give the corresponding chiral amine in 91% 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 CH_2Cl_2.[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)] (%)
1[c)]		**11c**	91	81 (*S*)
2		**11c**	83	88 (*S*)
3[c)]		**12**	68	77 (*R*)
4	**13**	**12**	73	76 (*R*)
5		**11a**	78	43 (*S*)
6		**11b**	78	90 (*S*)
7		**11d**	71	89 (*S*)
8	**13**	**11e**	41	64 (*S*)
9		**11b**	78	77 (*S*)
10		**11c**	61	71 (*S*)
11	**14a**	**11d**	56	63 (*S*)

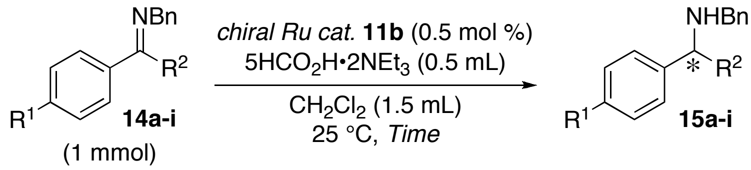
a) Isolated yields.
b) Determined by chiral HPLC. For absolute configuration, see ref 11.
c) In the absence of CH_2Cl_2.

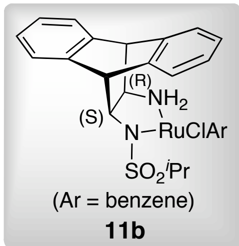
Table 2 summarizes the results of the transfer hydrogenation reaction with various ketimines **14a-i** in the presence of catalyst **11b** and the $5HCO_2H•2NEt_3$ azeotrope in CH_2Cl_2. *Para*-substituted acetophenone-derived ketimines **14a-e** showed good to excellent chemical yields and ee values 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 R^2 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.

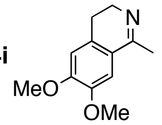
Apparently, the enantioselectivities were correlated with the *E*/*Z* ratios of the imines measured using ^1H NMR. Thus, higher *E*-containing ketimines, such as **13** (*E* only), and acetophenone-derived ketimines **14a-e** gave good to excellent enantioselectivities, but higher *Z*-containing ketimines 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	*E* / *Z* [a)]	Time (h)	Yield[b)] (%)	ee[c)] (%)
1	**14a**	H	Me	15 / 1	24	78	77 (*S*)
2	**14b**	MeO	Me	20 / 1	18	91	74 (*S*)
3	**14c**	Me	Me	15 / 1	24	79	75 (-)[d,e)]
4	**14d**	Cl	Me	20 / 1	24	71	74 (*S*)
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*-Pr	1 / 24	24	63	51 (*S*)
8	**14h**	H	*t*-Bu	*Z* only	48	13	1[d)]
9	**14i**			*Z* only	1.5	83	36 (*S*)

a) Measured by ^{1}H 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.

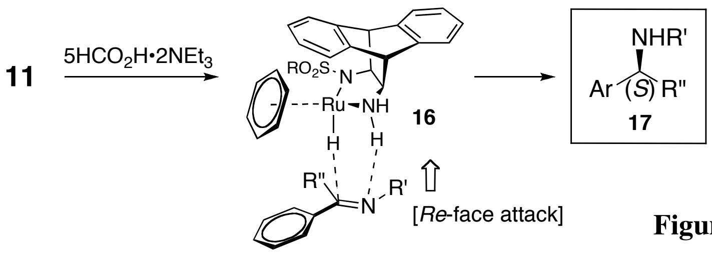


Figure 1

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 benzeneruthenium (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 μL, 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*, $5HCO_2H{\bullet}2NEt_3$ azeotrope (0.5 mL), CH_2Cl_2 (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. $NaHCO_3$ aq. (5 mL), the product was extracted (EtOAc, 20 mL × 3), washed (brine, 10 mL × 3), dried (anhyd. Na_2SO_4) 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 CH_2Cl_2 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 (reducted 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**).