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Highly efficient asymmetric transfer hydrogenation of ketones catalyzed by chiral 'roofed' *cis*-diamine–Ru(II) complex

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Abstract—A new type of chiral Ru(II) complex, prepared from a conformationally rigid, sterically bulky 'roofed' *cis*-diamine and $[RuCl_2(benzene)]_2$, functions as an efficient catalyst for the asymmetric transfer hydrogenation of a wide variety of aryl ketones, including sterically bulky ketones, when the reaction is conducted in the presence of $5HCO_2H{\cdot}2NEt_3$.

The asymmetric catalytic transfer hydrogenation of ketones represents a viable method, not only in the laboratory, but also on a commercial scale, because of its ease of handling, lower cost, and safety, compared with the typically used expensive, hazardous, and dangerous reagents such as borane reagents and high-pressure hydrogen gas.[1] Some noteworthy achievements in this area include the preparation of the chiral *trans*-*N*-tosyl-1,2-diphenylethylenediamine–Ru (*p*-cymene) complex **2**, by Noyori et al., which can be used in the presence of 2-propanol or a formic acid-triethylamine azeotrope as a hydrogen donor (Scheme 1).[2]

Focusing on the configuration of 1,2-diamine ligands, a number of *trans*-diamines have been used to obtain the corresponding secondary alcohols in good to excellent yields and enantioselectivities.[3]

cis-1,2-Diaminoindane derivatives, established by Wills et al., represent the only case of a *cis*-diamine–Ru(II) (**4**) catalyzed asymmetric transfer hydrogenation of ketones but the reaction resulted in lower enantioselectivities than Noyori's results (Scheme 1).[4]

We recently developed chiral 'roofed' 2-imidazolidinones, which are conformationally rigid and sterically bulky, from the thermal [4+2] cycloaddition of a simple 5-membered heterocycle, 1,3-dihydro-2-imidazolone, with anthracene followed by optical resolution.[5a] These compounds have proven to be excellent chiral auxiliaries for asymmetric C–C bond formations, including the α-alkylation of carbonyl compounds and the Diels–Alder reaction.[5] The perfect stereoselectivities obtained in these reactions prompted us to apply ring-opened *cis*-diamines to catalytic asymmetric reactions as chiral ligands.

In this paper, we report the 'roofed' *cis*-diamine as an excellent ligand for the Ru(II)-catalyzed asymmetric transfer hydrogenation of ketones, leading to both a high catalytic activity and enantioselectivity.

The 'roofed' *cis*-1,2-diamine **6** was readily obtained from chiral 2-imidazolidinone **5** by hydrolytic ring cleavage with $Ba(OH)_2$ in refluxing ethanol (Scheme 2).

The diamine–ruthenium(II) complexes **7** and **8** were prepared in situ, following Noyori's procedure.[2b,6] We first tested the activity of benzene complex **7** toward acetophenone **1** in the presence of an azeotropic mixture of $5HCO_2H{\cdot}2NEt_3$ as a hydrogen source at 25 °C (Table 1, entry 1). The reaction proceeded smoothly to give the corresponding secondary alcohol **3** in 98% yield and 93% ee. To the contrary, the Ru(II) (*p*-cymene) complex **8** showed a lower reactivity and only a moderate ee value (entry 2).

We also investigated co-solvent effects (Table 1, entries 3–8).[2m,4,7] The reactions proceeded in the presence of CH_2Cl_2, THF, and DMF to give 91–93% ee's, but a slightly longer time was required to complete the reaction. The addition of IPA required a longer reaction

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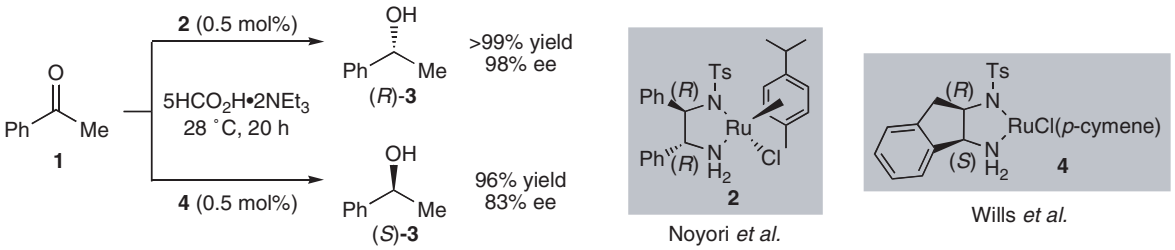
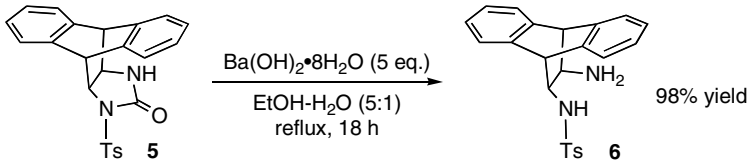
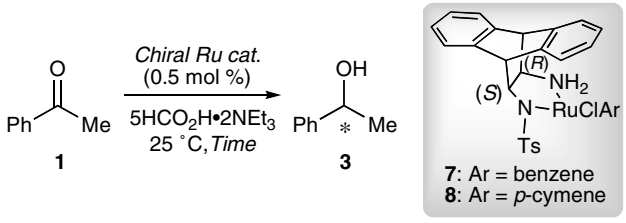


Scheme 1.



Scheme 2.

Table 1. Asymmetric transfer hydrogenation of acetophenone **1** catalyzed by chiral ruthenium(II) complexes (**7**, **8**)



Entry	Catalyst	Co-solvent	Time (h)	Yield (%)[a]	Ee (%)[b]	Configuration[b]
1	**7**	(None)	15	98	93	*S*
2	**8**	(None)	67	53	86	*S*
3	**7**	CH_2Cl_2	19	97	93	*S*
4	**7**	THF	19	91	93	*S*
5	**7**	DMF	19	91	91	*S*
6	**7**	IPA	24	95	94	*S*
7	**7**	DMSO	48	62	90	*S*
8	**7**	H_2O	43	>99	90	*S*

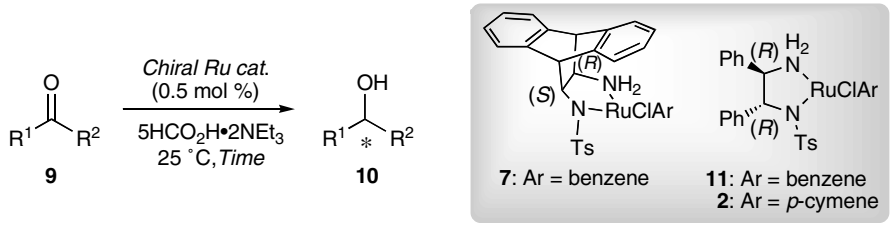
[a] Isolated yields.
[b] Determined by HPLC.

time than standard conditions, but gave 94% ee. DMSO retarded the reaction and only a moderate yield and 90% ee resulted after 48 h. It is interesting to note that the addition of water did not seriously affect either the yield or the enantioselectivity.

Table 2 summarizes the results of some transfer hydrogenation reactions with various ketones **9** in the presence of catalyst **7** and the $5HCO_2H{\cdot}2NEt_3$ azeotrope. Corresponding results using Noyori-type catalysts **11** and **2** are also listed for comparison. In general, the catalytic activity of **7** is superior to Noyori's catalysts **11** and **2**. This is especially true for isobutyrophenone (entries 4–6), 2,2-dimethylpropiophenone (entries 7–9), and 1′-acetonaphthone (entries 14, 15) which are sterically bulky, where **7** showed higher reactivities and enantioselectivities than the others.[8] The cyclic substrate, α-tetralone, was also converted to the corresponding alcohol with the highest enantioselectivity (99% ee) and in a quantitative yield after a 20 h reaction. Another cyclic substrate, β-tetralone, gave an inferior ee value, although the reaction time was quite short. Substitution of the benzene ring with electron-withdrawing or electron-donating groups at the 4′-position (entries 10–13) had only minor effects on the reaction time and ee values. Unfortunately, a dialkylketone such as benzyl ethyl ketone with **7** showed a lower ee value, similar to **11**.

Although the precise structures of the catalyst **7** and the corresponding hydride species are unknown,[9] we speculate the most likely hydride catalyst, depicted in Figure 1. Thus, the hydride has two candidates, **12** and **15**, and **12** looks feasible as an active catalyst because another candidate **15** would be difficult to approach the ketones toward ruthenium hydride because of steric shielding of 'roof' moiety. Arylketones easily approach from the 'non-shielded' side, the site opposite the 'roof' moiety, of the hydride catalyst **12** to subsequently

Table 2. Chiral ruthenium(II) complexes (**2**, **7**, and **11**)—catalyzed asymmetric transfer hydrogenation of various ketones **9**



Entry	R^1	R^2	Catalyst	Time (h)	Yield (%)[a]	ee (%)[b]	Configuration[b]
1	Ph	Me	**7**	15	98	93	*S*
2	Ph	Me	**11**	16	98	96	*R*
3[c]	Ph	Me	**2**	20	>99	98	*R*
4	Ph	*i*-Pr	**7**	24	85	84	*S*
5	Ph	*i*-Pr	**11**	24	12	48	*R*
6[d]	Ph	*i*-Pr	**2**	—	41	83	*R*
7	Ph	*t*-Bu	**7**	24	68	65	*S*
8	Ph	*t*-Bu	**11**	24	6	19	*R*
9[d]	Ph	*t*-Bu	**2**	—	<1	—	—
10	4-ClC_6H_4	Me	**7**	17	>99	89	*S*
11[c]	4-ClC_6H_4	Me	**2**	24	>99	95	*R*
12	4-$MeOC_6H_4$	Me	**7**	24	91	92	*S*
13[c]	4-$MeOC_6H_4$	Me	**2**	60	>99	97	*R*
14	1-Naphthyl	Me	**7**	20	>99	92	*S*
15[c]	1-Naphthyl	Me	**2**	60	93	83	*R*
16	2-Naphthyl	Me	**7**	20	>99	90	*S*
17[c]	2-Naphthyl	Me	**2**	22	>99	96	*R*
18	α-Tetralone		**7**	20	>99	99	*S*
19[c]	α-Tetralone		**2**	48	>99	99	*R*
20	β-Tetralone		**7**	7	>99	66	*S*
21[c]	β-Tetralone		**2**	80	70	82	*R*
22	Bn	Et	**7**	24	92	28	*R*
23	Bn	Et	**11**	24	92	23	*S*

[a] Isolated yields.
[b] Determined by HPLC.
[c] See Ref. 2b.
[d] Reactions at 40 °C; see Ref. 1b.

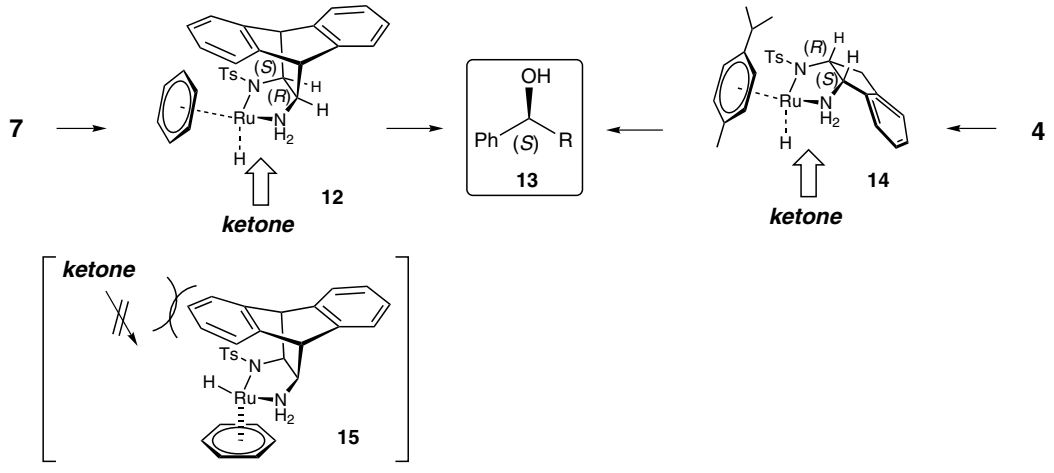


Figure 1.

produce the (*S*)-alcohol **13**. Meanwhile, as reported by Wills',[4,10] the hydride form of **4** appears to be similar to **14** in the production of the (*S*)-alcohol **13**. It is noteworthy that both hydride catalysts **12** and **14**, which

contain *cis*-diamine ligands with opposite configurations, form the (*S*)-alcohol **13**. These characteristics must be caused by the chiral 'roofed' *cis*-1,2-diamine structure, which is both conformationally rigid and sterically congested.

In conclusion, we demonstrate herein that a new type of 'roofed' *cis*-1,2-diamine–Ru (II) complex, which is both conformationally rigid and sterically congested, functions as an excellent catalyst for the asymmetric transfer hydrogenation of ketones. Further studies are currently in progress.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.165.

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6. General procedure for asymmetric transfer hydrogenation of ketone catalyzed by **7**: A mixture of benzeneruthenium (II) chloride dimer (2.5 mg, 0.005 mmol, 0.25 mol%), *N*-tosyl-'roofed' diamine **6** (3.9 mg, 0.01 mmol, 0.5 mol%), and triethylamine (2.8 μL, 0.02 mmol, 1 mol%) in 2-propanol (1 mL) was refluxed for 1 h under an argon atmosphere. After removal of the solvent in vacuo, $5HCO_2H{\cdot}2NEt_3$ azeotrope (1 mL) and ketone (2 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 the purification by flash column chromatography on silica gel to afford the corresponding alcohol. Enantiomeric excess values were determined by chiral HPLC (see supporting information).
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8. Ikariya et al. have reported that the chiral Ru cluster complexes derived from $Ru_3(CO)_{12}$ and chiral diiminophosphine tetradentate ligands effected asymmetric transfer hydrogenation of propiophenone and isobutyrophenone in 2-propanol to form the corresponding chiral alcohols in good to excellent chemical yields and 96% and >99% ee, respectively Zhang, H.; Yaang, C.-B.; Li, Y.-Y.; Donga, Z.-R.; Gao, J.-X.; Nakamura, H.; Murata, K.; Ikariya, T. *Chem. Commun.* **2003**, 142–143.
9. Unfortunately, we have no clear structural data to support our prediction such as X-ray crystallography and a clear NMR spectrum of catalyst **7** or **12**, except for ^1H NMR spectrum of **7** (see supporting information). Further attempts to collect such data are ongoing.
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