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# An improved protocol for the ruthenium(pybox)-catalyzed asymmetric alkene epoxidation

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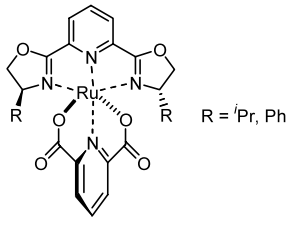
**Abstract**—A considerable rate enhancement in the ruthenium-catalyzed asymmetric epoxidation of olefins in the presence of $PhI(OAc)_2$ is reported. By the addition of $H_2O$, the rate of the reaction was increased by two orders of magnitude. Reactions of both aliphatic and aromatic olefins were realized for the first time and enantioselectivities up to 71% ee were obtained. In addition an in situ generation of ruthenium pybox catalysts for faster screening of oxidation catalysts was also developed.


Chiral non-racemic epoxides are interesting building blocks for fine chemical production and the pharmaceutical industry.[1] Clearly, asymmetric epoxidation of olefins is a powerful way to obtain these compounds. The most important developments of enantioselective oxidation reactions include the titanium-catalyzed epoxidation (Sharpless AE) of allylic alcohols and the manganese–salen-catalyzed epoxidation of unfunctionalized olefins (Jacobsen–Katsuki AE).[1,2] Based on our previous work in asymmetric dihydroxylation reactions,[3] we have been interested recently in developing improved asymmetric epoxidation catalysts. We focused our attention primarily on Ru catalysts because optically active Ru complexes are less well studied compared with Mn–salen type compounds and they tolerate a broader variety of ligand types.[4,5]

Initially we were attracted by Nishiyama's Ru-(pyridinebisoxazoline)(pyridinedicarboxylic acid)-catalyzed asymmetric epoxidation of *trans*-stilbene (Fig. 1, Scheme 1) because of the easy accessibility of pyridinebisoxazoline (pybox) ligands from natural occurring amino acids.[5b]

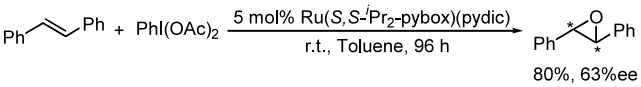
Unfortunately, the previously reported work revealed that this system had several drawbacks such as low reactivity (96 h were needed for full conversion) and the limited scope of the catalyst. So far successful epoxidations have only been achieved using *trans*-stilbene as the substrate.

Our first attempts to increase the reaction rate by doubling the concentration of the oxidizing agent, $PhI(OAc)_2$, resulted in comparable yields but lower enantioselectivity (Table 1, entry 1 and 2). We assumed that the water content present in the reaction mixture reduced the enantioselectivity. However, when carefully dried anhydrous toluene was used as the solvent, the conversion was only 12% after 67 h (Table 1, entry 3)! Surprisingly, when 1 equiv. of $H_2O$ was added to the reaction mixture, the reaction time is reduced to 3.5 h with 70–80% yield and 46% ee (Table 1, entry 4). This suggests that water plays a crucial role in this reaction, possibly due to the enabling of the oxidation of the




Ru(pybox)(pydic)

**Figure 1.** Structure of Ru(pybox)(pyridinedicarboxylic acid).




**Scheme 1.** Nishiyama's epoxidation of *trans*-stilbene.[5b]

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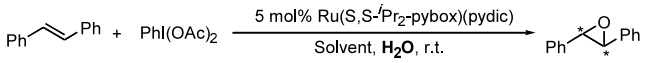
**Table 1.** Effect of solvent and water on the Ru-catalyzed asymmetric epoxidation of *trans*-stilbene using $PhI(OAc)_2$ as the oxidant[a]




| Entry | Ratio[b] | Solvent | Time (h) | Conv.[c] (%) | GC Yield (%) | ee[d] (%) |
|---|---|---|---|---|---|---|
| 1 | 1:3:0 | Toluene | 96 | 97 | 80 | 63[e] |
| 2 | 1:6:0 | Toluene | <63 | 100 | 80 | 53 |
| 3 | 1:6:0 | Anhyd. toluene | 67 | 12 | 11 | n.d.[f] |
| 4 | 1:6:6 | Anhyd. toluene | 3.5 | 100 | 70–80 | 46 |
| 5 | 1:6:3 | Anhyd. toluene | 3 | 100 | 80 | 43–59 |
| 6 | 1:3:3 | Anhyd. toluene | 26 | 100 | 83 | 49 |
| 7 | 1:3:6 | Anhyd. toluene | 5.5 | 82 | 63 | 29 |
| **8** | **1:1:1** | **Anhyd. toluene** | **25** | **55** | **53** | **71** |
| 9 | 1:6:6 | THF/anhyd. toluene 4:6 | 25 | 99 | 25 | n.d.[f] |
| 10 | 1:6:6 | 1,4-Dioxane/anhyd. toluene 4:6 | 2 | 100 | 60 | 59 |
| **11** | **1:6:6** | **$^t$BuOH/anhyd. toluene 4:6** | **1** | **100** | **84** | **57** |

[a] To a solution of Ru(*S*,*S*-$^i$Pr$_2$-pybox)(pydic) (14.2 mg, 0.025 mmol), *trans*-stilbene (90 mg, 0.5 mmol) and ($^n$BuOCH$_2$CH$_2$O)$_2$ or dodecane (100 μL, internal standard) in the appropriate solvent (10 mL) at room temperature, $PhI(OAc)_2$ was added. After stirring for 10 min., $H_2O$ was added. The reaction was then monitored by GC-FID.

[b] Ratio of *trans*-stilbene:$PhI(OAc)_2$:$H_2O$.

[c] Conversion of *trans*-stilbene.

[d] Determined by HPLC, the major enantiomer of *trans*-stilbene oxide had (1*S*,2*S*) configuration.[5b]

[e] Ref. 5b.

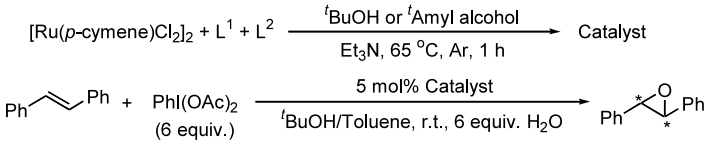
[f] Not determined.

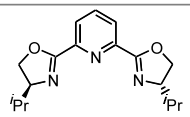
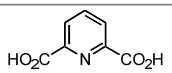
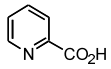
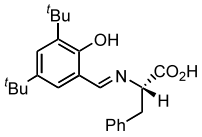
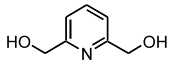
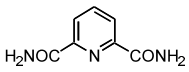
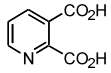
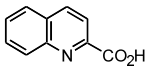
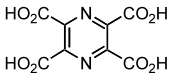
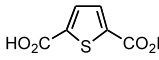
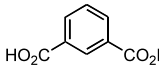
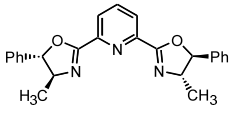
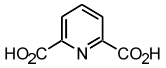
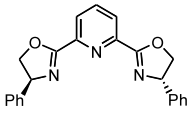
18-electron Ru(*S*,*S*-$^i$Pr$_2$-pybox)(pydic) by ligand dissociation.[6] As shown in Table 1, decreasing the amount of water had an insignificant effect to the reaction when excess oxidizing agent was used (Table 1, entry 5). Moreover, in the presence of an excess amount of water, the reaction ceased and the ee is reduced (Table 1, entries 6 and 7). Hence, a stoichiometric amount of water with respect to oxidant was used. To our delight, the ee of the reaction increased up to 71% at low concentration of $PhI(OAc)_2$ (Table 1, entry 8).

Due to the strong influence of water on the reaction rate and selectivity, the effects of polar co-solvent have been further investigated. We found that a solvent mixture of $^t$BuOH and toluene gave superior results (Table 1, entry 11) compared to toluene. The reaction finished in 1 h with 84% yield and 57% ee, which is approximately 100 times faster than the original system. By using this mixed solvent system, an in situ generation method for the active catalyst was also developed. This procedure is especially important in order to test new chiral pybox ligands and different pyridinedicarboxylate (pydic)-type co-ligands. In general, the Ru catalyst can easily be generated by heating [Ru(*p*-cymene)Cl$_2$]$_2$ with *S*,*S*-$^i$Pr$_2$-pybox, 2,6-pyridinedicarboxylic acid ($H_2$pydic) and $Et_3N$ in $^t$BuOH or $^t$amyl alcohol at 65°C under Ar for 1 h (Table 2). The model reaction of *trans*-stilbene to *trans*-stilbene oxide went well giving 67% yield with 60% ee in 2–3 h (Table 2, entry 1). Next, 3 different commercially available pybox ligands, 6 tri- or tetradentate *N*- or *O*-donating ligands and 27 acid co-ligands have been screened efficiently by this method. Selected results are shown in Table 2. On one hand, successful variations of the structure of the acid co-ligand were relatively limited. Changing the dicarboxylic acid to a mono-acid or scrambling the position of the carboxylic acid groups resulted in the total loss of reactivity and ee (Table 2, entries 2 and 6). The internal nitrogen atom of the co-ligand is also important. Both weakly coordinating thiophene and non-coordinating C–H derivatives manifested to be inferior (Table 2, entries 9 and 10). 2,6-Di(hydroxymethyl)pyridine revealed to be a viable co-ligand candidate, possibly due to the formation of 2,6-pyridinedicarboxylic acid by oxidation (Table 2, entry 4).[7] On the other hand, commercially available 2,6-pyridinebisoxazolines showed very good reactivities (Table 2, entries 1, 11 and 12). Here, the $^i$Pr-substituted pybox gave the best enantioselectivity, while the phenyl-substituted derivative showed the best reactivity. The *trans*-phenyl group α to the oxygen of the oxazoline ring of *S*,*S*-Me$_2$-*S*,*S*-Ph$_2$-pybox induced a minor but reversed enantioselectivity (Table 2, entry 11). Further investigation of chiral ligands was then directed to pybox derivatives containing more bulky aryl groups and also to ligands which contain *cis*-substituents on both 4- and 5-positions of the oxazoline group.

Next, we demonstrated that the Ru(*S*,*S*-$^i$Pr$_2$-pybox)(pydic) catalyst could be also applied to other olefinic substrates (Table 3).[8] These reactions constituted the first examples of ruthenium(pybox)-catalyzed epoxidations other than that of *trans*-stilbene. The highest activity was observed towards 1,2-disubstituted and tri-substituted aromatic alkenes (Table 3, entries 1, 2, 5). For terminal and 1,1-disubstituted aromatic olefins, unspecific decomposition of the catalyst occurred at room temperature and gave low yields of epoxides. However, the reactions of these substrates in $^t$amyl alcohol as the solvent at 0°C gave good yields of the corresponding epoxides (Table 3, entries 3 and 4). Aliphatic olefins also yielded the corresponding epoxide

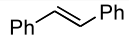
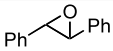
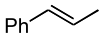
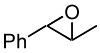
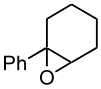
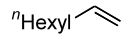
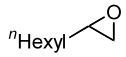
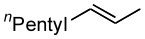
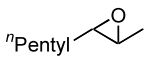
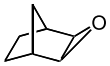
**Table 2.** Influence of ligands on the Ru-catalyzed asymmetric epoxidation of *trans*-stilbene[a)]




| Entry | $L^1$ | $L^2$ | Time (h) | Conv.[a] (%) | GC Yield (%) | *ee* (%)[b] |
|---|---|---|---|---|---|---|
| 1 |  |  | 2-3 | 100 | 67 | 60 |
| 2 | " |  | 21 | 100 | 33 | 0 |
| 3 | " |  | 27 | 84 | 15 | n.d.[c)] |
| 4 | " |  | 4 | 100 | 38 | 47 |
| 5 | " |  | 15 | 100 | 20 | 7 |
| 6 | " |  | 15 | 100 | 47 | 0 |
| 7 | " |  | 24 | 100 | 25 | 9 |
| 8 | " |  | 16 | 100 | 24 | 34 |
| 9 | " |  | 21 | 98 | 13 | n.d.[c)] |
| 10 | " |  | 19 | 98 | 13 | n.d.[c)] |
| 11 |  |  | 16 | 100 | 56 | -5[d)] |
| 12 |  | " | 1 | 100 | 84 | 25 |

[a)][Ru(*p*-cymene)$Cl_2$]$_2$ (7.7 mg, 0.013 mmol) and $L^1$ (0.025 mmol) were stirred in $^t$BuOH (2 mL) under Ar for 15 min. $L^2$ (0.025 mmol) and $Et_3N$ (1.2 equiv. of every acid group) in $^t$BuOH (2 mL) were then added. The whole reaction mixture was then heated at 65 °C for 1 h. After the reaction mixture was cooled to room temperature, anhydrous toluene (6 mL) was added. *trans*-Stilbene (90 mg, 0.5 mmol), ($^n$BuOC$H_2$C$H_2$)$_2$O or dodecane (100 μL, internal standard) and PhI(OAc)$_2$ (966 mg, 3 mmol) were added afterwards. The reaction mixture was stirred at room temperature for 10 min. $H_2O$ (50 μL, 2.8 mmol) was added. The reaction mixture was then stirred at room temperature and monitored by GC-FID. [b)]Determined by HPLC; the major enantiomer of *trans*-stilbene oxide had (1*S*,2*S*) configuration.[5b] [c)]Not determined. [d)] the major enantiomer of *trans*-Stilbene oxide had (1*R*,2*R*) configuration.

**Table 3.** Scope and limitations of the Ru-catalyzed asymmetric epoxidation of olefins[a)]

| Entry | Substrate | Product | Time (h) | Conv. (%) | GC Yield (%) | *ee* (%)[b)] |
|---|---|---|---|---|---|---|
| 1 |  |  | 1 | 100 | 84[c)] | 57 |
| 2 |  |  | 5 | 100 | 86 | 27 |
| 3 |  |  | 45 | 100 | 48[d),e)] | 5 |
| 4 |  |  | 23 | 100 | 73[d),e)] | 11 |
| 5 |  |  | 1 | 100 | 81 | 7 |
| 6 |  |  | 17 | 22 | 15[e)] | n.d.[f)] |
| 7 |  |  | 64 | 91 | 51[e)] | n.d.[f)] |
| 8 |  |  | 38 | 100 | 60[g)] | - |

[a)] Reaction conditions: olefin (0.5 mmol), Ru(*S,S*-$^{i}Pr_2$-pybox)(pydic) (14.2 mg, 0.025 mmol), $PhI(OAc)_2$ (483 mg, 1.5 mmol), ($^{n}BuOCH_2CH_2)_2O$ or dodecane (100 μL, internal standard), $H_2O$ (27 μL, 1.5 mmol), $^{t}BuOH$ (4 mL), toluene (anhydrous, 6 mL), room temperature. [b)]Determined by HPLC. [c)]6 equiv. of $PhI(OAc)_2$ and $H_2O$ were used. [d)]0 °C. [e)]Amyl alcohol (10 mL) was used. [f)]Not determined. [g)]0 °C-r.t.

products in notable amounts in $^{t}$amyl alcohol at room temperature (Table 3, entries 7 and 8). While the reactions gave significant enantioselectivity for *trans*-stilbene (Table 3, entry 1), only poor ee's were found with other olefins.

In summary, a large rate enhancement of the ruthenium(pybox)-catalyzed asymmetric epoxidation of olefins has been demonstrated by adding water. The scope of this epoxidation catalyst was enlarged to terminal, 1,1-disubstituted, trisubstituted and aliphatic olefins.

Further studies towards the mechanism of this reaction and ligand modifications to obtain higher ee's are currently under investigation.

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## References

1. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; (b) *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999.
2. For reviews, see: (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp. 153–158; (b) Jacobsen; E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; pp. 649–693; (c) Katsuki, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp. 287–325; (d) Katsuki, T. *Adv. Synth. Catal.* **2002**, *344*, 131–147.
3. (a) Döbler, C.; Mehltretter, G. M.; Beller, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3026–3028; (b) Döbler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Am. Chem. Soc.* **2000**, *122*, 10289–10297; (c) Döbler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Organomet. Chem.* **2001**, *621*, 70–76; (d) Döbler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M.; Eckert, M.; Militzer, H.-C. *Tetrahedron Lett.* **2001**, *42*, 8447–8449; (e) Sundermeier, U.; Döbler, C.; Mehltretter, G. M.; Baumann, W.; Beller, M. *Chirality* **2003**, *15*, 127–134; (f) Mehltretter, G. M.; Eckert, M.; Bhor, S.; Klawonn, M.; Döbler, C.; Militzer, H.-C.; Beller, M. *Synthesis* **2003**, 295–301.
4. For an excellent review, see: Barf, G. A.; Sheldon, R. A. *J. Mol. Catal.* **1995**, *102*, 23–39.
5. For recent achievements in Ru-based asymmetric epoxidation, see: (a) Kureshy, R. I.; Kahn, N. H.; Abdi, S. H. R.; Bhatt, K. N. *Tetrahedron: Asymmetry* **1993**, *4*, 1693–1701; (b) Nishiyama, H.; Shimada, T.; Itoh, H.; Sugiyama, H.; Motoyama, Y. *Chem. Commun.* **1997**, 1863–1864; (c) End, N.; Pfaltz, A. *Chem. Commun.* **1999**, 589–590; (d) Gross, Z.; Ini, S. *Org. Lett.* **1999**, *1*, 2077–2080 and references therein; (f) Stoop, R. M.; Bachmann, S.; Valentini, M.; Mezzetti, A. *Organometallics* **2000**, *19*, 4117–4126; (e) Pezet, F.; Aït-Haddou, H.; Daran, J.-C.; Sadaki, I.; Balavoine, G. G. A. *Chem. Commun.* **2002**, 510–511.
6. Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299–307.
7. Iwasa, S.; Morita, K.; Tajima, K.; Fakhruddin, A.; Nishiyama, H. *Chem. Lett.* **2002**, 284–285.

8. **General procedure**: In a typical experiment (Table 3, entry 2), *trans*-β-methylstyrene (0.5 mmol), dodecane (100 μL), $PhI(OAc)_2$ (1.5 mmol) and Ru(*S*,*S*-$^i$Pr$_2$-pybox)(pydic)[5b] (5 mol%) were dissolved in anhydrous toluene (6 mL) and $^t$BuOH (4 mL) at room temperature. After 10 min., $H_2O$ (1.5 mmol) was added. The reaction was monitored by GC-FID. *trans*-β-Methylstyrene oxide was identified by comparison with the authentic sample by GC-FID (HP5890 series; column: HP5 (crosslinked 5% PH ME Siloxane, 30 m, 0.25 mm, 0.25 μm). All products were also confirmed by GC–MS and NMR data. After the reaction, the reaction mixture was quenched by saturated $Na_2SO_3$ solution (10 mL) and extracted with $CH_2Cl_2$ (2×10 mL). After removal of solvent under reduced pressure, the products were dissolved in *n*-hexane, filtered and analyzed by HPLC.