Ruthenium-Catalyzed Asymmetric Alkene Epoxidation with *tert*-Butyl Hydroperoxide as Oxidant

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Abstract: A ruthenium-catalyzed asymmetric epoxidation of various olefins using *tert*-butyl hydroperoxide (TBHP) as the oxidant is reported. By applying ruthenium(pyridinebisoxazoline)-(pyridinedicarboxylate) complexes **1** [Ru(pybox)(pydic), **1**] as catalysts, aromatic and aliphatic olefins yielded the corresponding epoxides at room temperature in good to excellent yields and enantioselectivities up to 65% ee. Slow addition of the stoichiometric oxidant significantly improved the yield and the chemoselectivity of the reaction.

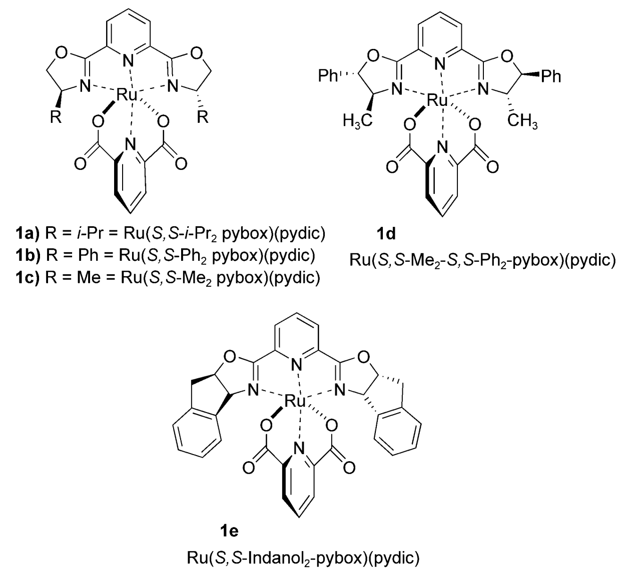
Keywords: asymmetric catalysis; *tert*-butyl hydroperoxide; epoxidation; homogeneous catalysis; N,O ligands; ruthenium

Introduction

Chiral epoxides are versatile building blocks for syntheses of numerous natural products and biological active substances.[1] Among the various possibilities for their preparation, asymmetric catalysis constitutes an elegant and efficient tool for the synthesis of enantiomerically pure epoxides. In the past transition metal complexes based on titanium[2] and manganese[3] have been used most successfully as catalysts for the enantioselective epoxidation of olefins. In spite of extensive research efforts up-to-date, the development of a general, highly selective epoxidation method is still one of the major goals in asymmetric catalysis.

For some time we have been involved in the development of improved procedures for asymmetric dihydroxylation reactions.[4] More recently, we set out to develop new catalytic asymmetric methods for the synthesis of epoxides.[5] We focused our attention initially on optically active ruthenium catalysts,[6,7] which are less well studied compared with manganese salen complexes.[8] As a starting point of our investigations we chose Nishiyama's ruthenium-(pyridinebisoxazoline)(pyridinedicarboxylate) complex [Ru(pybox)(pydic)], which catalyzes the epoxidation of *trans*-stilbene with approximately 70% ee.[6b] Unfortunately this system has also several drawbacks such as the low reactivity (96 h were needed for full conversion) and the limited scope of the catalyst. We were able to solve these problems by adding a defined amount of water to the reaction mixture,[5] however the use of $PhI(OAc)_2$ as the stoichiometric oxidant remained as a major disadvantage. Therefore we were interested in the behavior of ruthenium(pyridinebisoxazoline)(pyridinedicarboxylate) complexes **1** (Figure 1) in the presence of more practical oxidants such as alkyl peroxides.

To utilize *tert*-butyl hydroperoxide (TBHP) is significantly advantageous compared with $PhI(OAc)_2$ with



1a) R = *i*-Pr = Ru(*S,S*-*i*-Pr_2 pybox)(pydic)
1b) R = Ph = Ru(*S,S*-Ph_2 pybox)(pydic)
1c) R = Me = Ru(*S,S*-Me_2 pybox)(pydic)

1d
Ru(*S,S*-Me_2-*S,S*-Ph_2-pybox)(pydic)

1e
Ru(*S,S*-$Indanol_2$-pybox)(pydic)

Figure 1. Structure of ruthenium(pyridinebisoxazoline)(pyridinedicarboxylate).

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regards to the percentage of active oxygen, the nature of the by-product, environmentally friendliness and price. Here, we report the asymmetric catalytic epoxidations of various olefins in the presence of **1** using TBHP as the final oxidant.

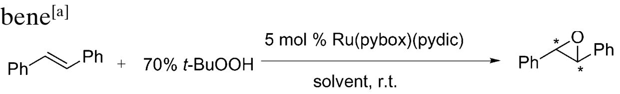
Results and Discussion

By comparing the UV-VIS spectra of the reaction of **1a** and $PhI(OAc)_2$ with that of **1a** and TBHP, it appeared that the same oxidized ruthenium species is formed. Hence, the usage of *tert*-butyl hydroperoxide should be possible as a stoichiometric oxidant for this reaction. Firstly, we examined the epoxidation of *trans*-stilbene with TBHP (70% in water) in the presence of 5 mol % of **1a** at room temperature using previously optimized reaction conditions (Table 1, entry 1).[5,6b]

To our delight, it was indeed possible to obtain a significant amount of *trans*-stilbene epoxide, albeit with low ee (28%).[6b] By varying the amount of the oxidant (Table 1, entries 1–3), it became clear that a major amount of TBHP is destroyed during the course of the reaction by the catalyst. Hence, an excess of oxidant was necessary for full conversion. However, in the presence of 6 equivalents of TBHP the oxidation of the co-solvent toluene to benzaldehyde was observed as side reaction. Applying *tert*-amyl alcohol or *tert*-butanol as the solvent gave a cleaner reaction with good yield (up to 86%) and chemoselectivity of the epoxide (Table 1, entries 4–6). Apart from **1a**, Ru(*S,S*-Ph_2-pybox)(pydic) **1b**, Ru(*S,S*-Me_2-pybox)(pydic) **1c**, Ru(*S,S*-Me_2-*S,S*-ph_2-pybox)(pydic) **1d** and Ru(*S,S*-$Indanol_2$-pybox)(pydic) **1e** were also used as the catalysts (Table 1, entries 9, 10, 11 and 13). All ruthenium catalysts were directly prepared from the corresponding pybox ligand and $[Ru(p\text{-cymene})Cl_2]_2$. In case of **1c** and **1e** the ligand was synthesized according to previously described procedures.[9,10] The best epoxide yield (97%) and enantioselectivity (60%; 1*S*,2*S*-*trans*-stilbene oxide as the major enantiomer) were obtained using **1b** as the catalyst. Interestingly, the *trans*-phenyl group alpha to the oxygen of the oxazoline ring of **1d** induced a reversed enantioselectivity (Table 1, entry 13).

In addition to the catalyst, the concentration of the oxidant and the solvent have major influences on the

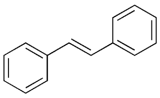
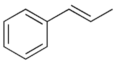
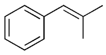
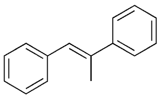
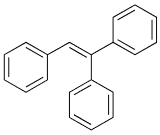
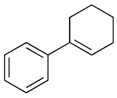
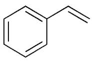
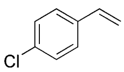
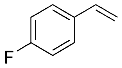
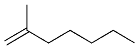
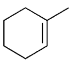
Table 1. Epoxidation of *trans*-stilbene[a]



Entry	Oxidant [equiv.]	Catalyst	Solvent	Conversion [%]	Yield [%][c]	ee [%][d]
1	1.5[b]	**1a**	toluene/*tert*-amyl alcohol	30	27	28
2	3[b]	**1a**	toluene/*tert*-amyl alcohol	91	86	25
3	6[b]	**1a**	toluene/*tert*-amyl alcohol	100	72	17
4	6[b]	**1a**	*tert*-amyl alcohol	100	86	17
5	6[b]	**1b**	*tert*-amyl alcohol	100	85	24
6	6[b]	**1b**	*tert*-BuOH	100	77	42
7	3	**1b**	*tert*-amyl alcohol	100	91	55
8	3	**1a**	*tert*-BuOH	100	80	28
9	3	**1c**	*tert*-BuOH	100	88[g]	44
10	3	**1e**	*tert*-BuOH	100	84[h]	38
11	3	**1b**	*tert*-BuOH	100	93	59
12	1.5	**1b**	*tert*-BuOH	100	97	60
13	3	**1d**	*tert*-BuOH	100	88	– 39[e]
14	3	**1b**	isopropanol	91	71	59
15	3	**1b**	acetonitrile	100	84	23
16	3	**1b**	3,7-dimethyl-3-octanol	100	88	57
17	3	**1b**	THF	18	15	n.d.[f]
18	3	**1b**	isobutyl methyl ketone	99	90	29
19	3	**1b**	CH_2Cl_2	76	45	17

[a] Reaction condition: 0.5 mmol substrate, solvent (10 mL), TBHP added over a period of 12 h, room temperature.
[b] TBHP added in one portion.
[c] GC yield.
[d] Determined by HPLC, the major enantiomer was *S,S*-*trans*-stilbene oxide.
[e] *R,R*-*trans*-Stilbene oxide was the major enantiomer.
[f] Not determined.
[g] Reaction time 14 h.
[h] Reaction time 16 h.

Table 2. Scope and limitations of the Ru-catalyzed asymmetric epoxidation of olefins.[a]

Entry	Olefin	Time [h]	Conversion [%]	Epoxide yield [%][b]	ee [%][c]
1		12	100	97	60
2		12	100	90	51
3		12	100	95	65
4		12	100	93	22
5		12	100	90	8
6		12	100	88	10
7		36	100	56	30
8		36	100	48	34
9		36	91	54	34
10		24	84	80	n.d.[d]
11		12	100	70	n.d.[d]

[a] Reaction condition: 0.5 mmol olefin, 5 mol % Ru(*S,S*-Ph_2-pybox)(pydic), *tert*-BuOH (10 mL), 1.5 equivs. TBHP added over a period of 12 h, room temperature.

[b] GC yield.

[c] Determined by HPLC.

[d] Not determined.

epoxide yield and the enantioselectivity. The best enantioselectivities are observed at low concentration of the oxidant in *tert*-butanol. The negative influence of a larger excess of oxidant on the enantioselectivity is explained by the increased amount of water in the reaction mixture.[5] Variation of the solvent (Table 1, entries 7, 11, 14–19) showed that alcohols were best suited as the reaction medium. Isobutyl methyl ketone and acetonitrile gave good yields, but low ees. Besides, dichloromethane and THF led to both low yield and ee.

All reactions shown in Table 1 were run with 5 mol % of Ru catalyst. In addition we also performed reactions with lower catalyst concentration. In the presence of 2.5 and 1.0 mol % Ru catalyst 95% and 79% yield of epoxide (54% and 49% ee) were obtained after 15 and 36 h respectively.

The "best" catalyst **1b** was then applied to other olefins, too. As shown in Table 2 different aromatic and aliphatic olefins reacted with *tert*-butyl hydroperoxide in moderate to very good yields (48–97%) under mild conditions (room temperature). The catalyst showed the best reactivity towards 1,2-disubstituted and trisubstituted aromatic olefins (Table 2, entries 1–6). Styrene and substituted styrenes were obtained in significantly lower yields (48–56%) due to unspecified side-reactions of the olefin. These substrates also needed longer reaction time in order to get completed (Table 2, entries 7–9). In addition to aromatic olefins, we tested also aliphatic olefins, e.g., 1-methylcyclohexene and 2-methyl-1-heptene. The corresponding epoxides were obtained in 70% and 80% yield respectively (Table 2, entries 10, 11). Moderate enantioselectivities (50–65% ee) were observed with 1-phenyl-2-methylpropene, stilbene and β-methylstyrene. Styrene and substituted styrenes gave mediocre ees (30–34%).

Conclusion

In summary, we showed that Ru(pybox)(pydic) complexes can be used as general catalysts for the epoxidation of olefins with TBHP in good to excellent yield (up to 97%) with reasonable ees (up to 65%) under mild reaction conditions (room temperature). Compared with previously known reactions using $PhI(OAc)_2$ as the stoichiometric oxidant, this procedure represented a significant improvement with regard to practicability and generality. Further studies towards improvements of the enantioselectivities by varying pybox ligands are currently in progress.

Experimental Section

General information

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer (^{1}H: 400.1 MHz, ^{13}C 100.6 MHz). Chemical shifts (δ) are given in ppm and refer to the residual solvent as the internal standard. Gas chromatography was performed on a Hewlett Packard HP 6890 chromatograph with a HP5 column (5% phenyl methyl siloxane, 30 m, 250 µm, 0.25 µm). Mass spectra were recorded on an AMD 402/3 mass spectrometer. High-performance liquid chromatography was carried out using a Hewlett Packard HP 1090 liquid chromatograph equipped with a DAD. Enantiomeric excess values were determined by HPLC. Chemicals and solvents were purchased from Fluka and Aldrich and used as received.

Synthesis of the Ruthenium Complexes

To a solution of the corresponding pybox ligand (0.34 mmol) and $[Ru(p\text{-cymene})Cl_2]_2$ (104 mg, 0.17 mmol) in MeOH (2 mL), disodium pyridine-2,6-dicarboxylate, Na_2pydic, (72 mg, 0.34 mmol) in MeOH/H_2O 1:1 (2 mL) was added under Ar. The whole reaction mixture was heated to 65 °C for 1 h. After cooling to room temperature the mixture was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (30 mL). The deep orange organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The reaction mixture was then purified by silica gel column chromatography (70–230 mesh), using CH_2Cl_2/MeOH (100:2 to 100:5). After removal of solvent under reduced pressure, the products can be crystallized from CH_2Cl_2/*n*-hexane.

Ru(*S,S*-*i*-Pr₂-pybox)(pydic) (1a):[6b] $R_f = 0.33$ (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.30 (2H, d, *J* = 7.7 Hz), 8.08 (1H, t, *J* = 7.7 Hz), 7.85 (2H, d, *J* = 7.8 Hz), 7.61 (1H, t, *J* = 7.8 Hz), 4.64–4.68 (2H, unresolved dd), 4.56–4.60 (2H, unresolved dd), 3.66–3.71 (2H, m), 1.03–1.10 (2H, m), 0.59 (6H, d, *J* = 7.2 Hz), 0.44 (6H, d, *J* = 6.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.5, 166.5, 150.9, 147.1, 134.7, 127.0, 126.6, 123.8, 71.0, 68.9, 18.8, 13.8; FAB-MS: *m/z* = 568 (M^+); UV-VIS (CH_2Cl_2): λ_{max} (log ε) = 382 (3.56), 480 nm (4.30).

Ru(*S,S*-Ph₂-pybox)(pydic) (1b):[6b] $R_f = 0.08$ (CH_2Cl_2/MeOH, 100:5); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.95 (2H, d, *J* = 7.7 Hz), 7.65 (1H, t, *J* = 7.7 Hz), 7.54 (3H, m), 7.12–7.16 (2H, m), 7.02–7.05 (4H, m), 6.68 (4H, d, *J* = 6.8 Hz), 5.15–5.21 (2H, m), 4.59–4.68 (4H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.1, 167,4, 149.2, 147.1, 136.0, 135.6, 133.7, 129.1, 128.6, 127.3, 125.9, 124.0, 78.5, 67.8; FAB-MS: *m/z* = 636 (M^+); UV-VIS (CH_2Cl_2): λ_{max} (log ε) = 375 (3.36), 484 nm (4.47); anal. calcd. for $C_{30}H_{22}N_4O_6Ru \cdot 0.5\ CH_2Cl_2$ (%): C 54.03, H 3.42, N 8.26; found: C 54.37, H 3.79, N 8.50.

Ru(*S,S*-Me₂-pybox)(pydic) (1c): $R_f = 0.07$ (CH_2Cl_2/MeOH, 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.30 (2H, d, *J* = 7.7 Hz), 8.08 (1H, t, *J* = 7.7 Hz), 7.83 (2H, t, *J* = 7.7 Hz), 7.60 (1H, t, *J* = 7.7 Hz), 4.87–4.92 (2H, unresolved dd), 3.77–3.86 (2H, m), 0.74 (6H, d, *J* = 6.6 Hz); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 171.45, 166.61, 150.97, 147.27, 134.75, 127.03, 126.65, 123.64, 59.96, 33.81, 18.88; FAB-MS: *m/z* = 512 (M^+); UV-VIS (CH_2Cl_2): λ_{max} (log ε) = 381 (3.57), 480 nm (4.30); HRMS (ESI+): *m/z* calcd. for $C_{20}H_{19}N_4O_6{}^{102}Ru + H^+$: 513.03380; found: 513.03479.

Ru(*S,S*-Me₂-*S,S*-Ph₂-pybox)(pydic) (1d): $R_f = 0.16$ (CH_2Cl_2/MeOH, 100:5); ^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 8.23 (2H, d, *J* = 7.5 Hz), 8.08 (1H, t, *J* = 7.5 Hz), 8.00 (2H, d, *J* = 7.9 Hz), 7.69 (1H, t, *J* = 7.9 Hz), 7.38–7.41 (6H, m), 7.33–7.37 (4H, m), 5.51 (2H, d, *J* = 9.7 Hz), 3.75 (2H, dd, *J* = 9.7, 6.7 Hz), 0.84 (6H, d, *J* = 6.7 Hz); ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ = 171.3, 166.5, 151.3, 147.4, 136.7, 135.8, 135.1, 129.1, 126.9, 126.5, 124.1, 92.5, 68.1, 18.2; FAB-MS: *m/z* = 664 (M^+); UV-VIS (CH_2Cl_2): λ_{max} (log ε) = 382 (3.81), 482 nm (4.53); analysis calcd. (%) for $C_{32}H_{26}N_4O_6Ru$: C 57.91, H 3.95, N 8.44; found: C 57.86, H 3.84, N 8.27.

Ru(*S,S*-indanol₂-pybox)(pydic) (1e): $R_f = 0.11$ (CH_2Cl_2/MeOH, 100:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (2H, d, *J* = 7.7 Hz), 8.31 (1H, t, *J* = 7.7 Hz), 7.86 (2H, d, *J* = 7.7 Hz), 7.59 (1H, t, *J* = 7.7 Hz), 7.12–7.18 (4H, m), 7.00–7.03 (2H, m), 5.95 (2H, d, *J* = 7.7 Hz), 5.83–5.87 (2H, m), 4.99 (2H, d, *J* = 8.1 Hz), 3.50 (2H, dd, *J* = 7.3, 18.2 Hz), 3.37 (2H, dd, *J* = 2.2, 18.2 Hz); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 192.67, 171.33, 152.14, 147.36, 139.22, 136.75, 135.08, 129.70, 127.87, 127.47, 125.27, 124.22, 125.11, 116.45, 87.71, 78.60, 73.68; FAB-MS: *m/z* = 660 (M^+); UV-VIS (CH_2Cl_2): λ_{max} (log ε) = 383 (3.62), 484 nm (4.39); HRMS (ESI+): *m/z* calcd. for $C_{36}H_{23}N_4O_6{}^{102}Ru$: 661.06538; found: 661.06610.

General Procedure for the Catalytic Reactions

All prepared oxiranes are known compounds.[11] The preparation of *trans*-stilbene oxide is shown as a typical example of the catalytic reactions.

Preparation of *trans*-Stilbene Oxide (Table 1 and Table 2, entry 1)

In a 25-mL Schlenk tube, substrate (0.5 mmol) and Ru (*S,S*-Ph₂-pybox)(pydic) (15.9 mg, 0.025 mmol) were dissolved in *tert*-butanol (9 mL). Then dodecane (100 µL) was added as an internal standard for GC and a solution of TBHP (103 µL, 0.75 mmol, 1.5 equivs.) in *tert*-butanol (1 mL) was added over a period of 12 h by a syringe pump. After completion of the reaction (monitored by GC-FID), the mixture was quenched with saturated Na_2SO_3 solution (~10 mL), extracted with dichloromethane (10 mL × 2) and washed with water

($\sim$20 mL). The combined organic layers were dried over $MgSO_4$ and analyzed by HPLC. The epoxide was further purified by silica gel column chromatography (70–230 mesh), saturated with triethylamine ($\sim$3%), and *n*-hexane/ethyl acetate (100:1) as the eluent.

***trans*-Stilbene oxide:** Colorless solid; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 7.24-7.31$ (10H, m), 3.87 (2H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 137.1$, 128.6, 128.6, 125.5, 62.8; EIMS (70 eV): $m/z = 196$ (M^+); HPLC (Chiralcel AD-114; hexane/EtOH, 99:1, flow rate 1.0 mL/min): $t_R = 7.12$ min, 16.63 min.

2,2-Dimethyl-3-phenyloxirane (Table 2, entry 3): Colorless oil; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 7.37-7.27$ (5H, m), 3.88 (1H, s), 1.09 (3H, s), 1.49 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 137.0$, 128.4, 127.8, 126.8, 61.6, 25.2, 18.4; EIMS (70 eV): $m/z = 148$ (M^+); HPLC (Chiralcel AD-114; hexane/EtOH, 99:1, flow rate 0.5 mL/min): $t_R = 9.25$ min, 10.25 min.

***trans*-α-Methylstilbene oxide (Table 2, entry 4):** White solid; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 7.30-7.46$ (10H, m), 3.96 (1H, s), 1.64 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta =$ 142.8, 136.3, 129.2, 128.6, 127.9, 126.9, 125.5, 67.5, 63.5, 17.1; EIMS (70 eV): $m/z = 210$ (M^+); HPLC (Whelk 01 (*R,R*); hexane/EtOH, 99:1, flow rate 0.6 mL/min): $t_R = 5.33$ min, 5.97 min.

(4-Chlorophenyl)-oxirane (Table 2, entry 8): Colorless oil; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 7.12-7.26$ (4H, m), 3.76 (1H, dd, $J = 4.0, 2.6$ Hz), 3.07 (1H, dd, $J = 5.6, 4.0$ Hz), 2.68 (1H, dd, $J = 5.6, 2.6$ Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 136.3$, 134.1, 128.8, 127, 51.9, 51.4; EIMS (70 eV): $m/z = 156$ [$(M+2)^+$], 154 (M^+); HPLC (Chiralcel OB-H; hexane, flow rate 1.0 mL/min): $t_R = 14.88$ min, 17.61 min.

1,2-Epoxy-1-methylcyclohexane (Table 2, entry 11). Colorless oil; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 2.87$ (1H, br s), 1.82–1.78 (2H, m), 1.59 (2H, m), 1.36–1.31 (2H, m), 1.22 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 59.6$, 57.8, 29.9, 25.0, 22.7, 20.1, 19.7; EIMS (70 eV): $m/z = 112$ ($[M]^+$).

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