Supplementary Information For:

Asymmetric Hydrogenation of Ketones with Polymer-Supported Chiral 1,2-diphenylethylene-diamine

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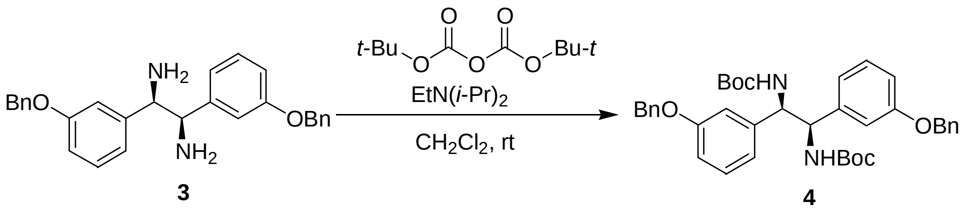
CONTENTS

General:

$[RuCl_2(benzene)]_2$ and ketones, diphosphines, except (*R*)-MeO-BIPHEP which was prepared according to the literature,[1] were obtained from Aldrich or Lancaster. The hydrogenation products were analyzed by a Varian CP-3380 GC equipped with a Chrompack Chirasil-Dex CB (25 m × 0.25 mm) column.

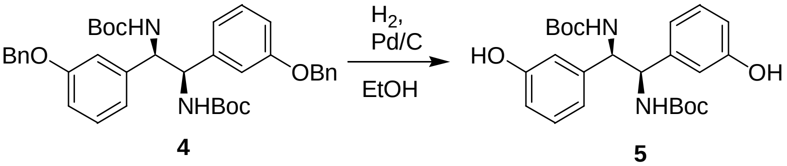
(A) Preparation of Ligand



Synthesis of (***R***,***R***)-N,N-Bis-Boc-1,2-di(3-benzyloxyphenyl)ethane-1,2-diamine (4)

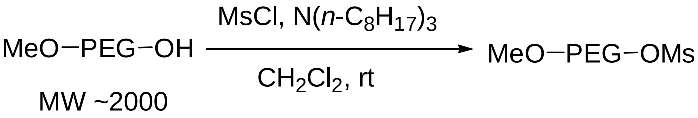
To a solution of (*R*,*R*)-1,2-di(3-benzyloxyphenyl)ethane-1,2-diamine (**3**) (1.32 g, 3.1 mmol) and N,N-diisopropylethylamine (1.21 ml, 7.0 mmol) in CH_2Cl_2 (10 ml) was added di-*tert*-butyl dicarbonate (1.42 g, 6.5 mmol). The reaction mixture was stirred overnight at room temperature. And the mixture was then washed with 1N HCl (5 ml), brine (5 ml). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 4:1) to give the product (1.88 g, 97%) as white solid. $[\alpha]_D^{22}$ = +12.5 (c 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29~7.36 (m, 10H), 7.10 (t, J = 8.0, 2H), 6.78 (dm, J = 8.0, 2H), 6.66 (d, J = 8.0, 2H), 6,65 (s, 2H), 5.50 (br. s, 2H), 4.93 (d, J = 11.6, 2H), 4.88 (d, J = 11.6, 2H), 4.81 (s, 2H), 1.44 (s, 18 H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.79, 140.86, 136.89, 129.49, 128.57, 127.95, 127.47, 120.03, 114.35, 114.05, 79.81, 70.01, 60.48, 28.42. Acc. Mass: Calcd. for $C_{38}H_{44}N_2O_6Na$ (M+Na) 647.3097; Found: 647.3098.

Synthesis of (***R***,***R***)-N,N-Bis-Boc-1,2-di(3-hydroxyphenyl)ethane-1,2-diamine (5):



A suspension of (*R*,*R*)-N,N-Bis-Boc-1,2-di(3-benzyloxyphenyl)ethane-1,2-diamine (**4**) (1.50 g, 2.4 mmol) and 10% Pd-C (50 mg) in EtOAc (10 ml) was stirred for 2 h at room temperature under 10 bar of hydrogen. The reaction mixture was then filtered through a pad of Celite, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane-EtOAc = 1:1) to give the product (1.00 g, 94%) as a white foam. $[\alpha]_D^{22}$ = -22.9 (c 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.97 (s, 4H), 6.55~6.61 (m, 6H), 5.71 (s, 2H), 5.78 (s, 2H), 4.78 (s, 2H), 1.43 (s, 18H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 156.44, 140.94, 130.01, 119.75, 115.37, 114.97, 80.66, 60.81, 28.77. Acc. Mass: Calcd. for $C_{24}H_{32}N_2O_6Na$ (M+Na): 467.2158; found: 467.2170.

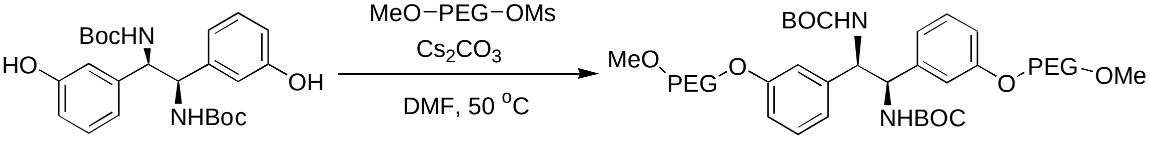
Synthesis of Polyethylene glycol 2000 monomethyl ether mesylate:



$$\underset{\text{MW} \sim 2000}{\text{MeO–PEG–OH}} \xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt}]{\text{MsCl, N}(n\text{-C}_8\text{H}_{17})_3} \text{MeO–PEG–OMs}$$

To a solution of polyethylene glycol 2000 monomethyl ether (20.00 g, 10 mmol) and tri-*n*-octylamine (13.1 ml, 30 mmol) in CH_2Cl_2 (50 ml) was added MsCl (1.55 ml, 20 mmol) at 0 °C. The reaction mixture was stirred for 24 h at room temperature and poured into Et_2O (1000 ml) with stirring. After stirring for 30 min at 0 °C, the precipitate was collected by filtration, washed with Et_2O (5 × 200 ml), and dried in vacuum to give the product (20.50 g) as white solid.

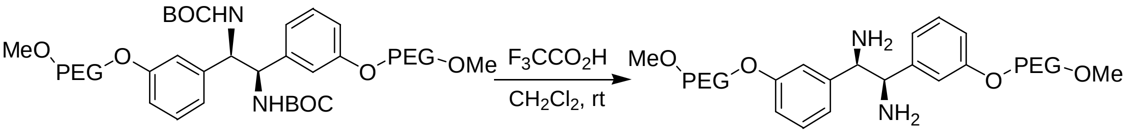
Synthesis of Polymer 6:



5 **6**

A suspension of (*R*,*R*)-N,N-Bis-Boc-1,2-di(3-hydroxyphenyl)ethane-1,2-diamine (**5**) (222 mg, 0.5 mmol), polyethylene glycol 2000 monomethyl ether mesylate (2.00 g, 1.0 mmol) and Cs_2CO_3 (978 mg, 3.0 mmol) in DMF (10 ml) was stirred overnight at 50 °C. Most of DMF were removed under reduced pressure and CH_2Cl_2 (10 ml) was added. The insoluble salts were filtered off, and the filtrate was poured into Et_2O (150 ml) with stirring. After stirring for 30 min at 0 °C, the precipitate was collected by filtration, washed with Et_2O (5 × 20 ml), and dried in vacuum to give the product (2.10 g) as off-white solid.

Synthesis of (*R*,*R*)-Polymer-supported PEG-2:



6 **PEG-2**

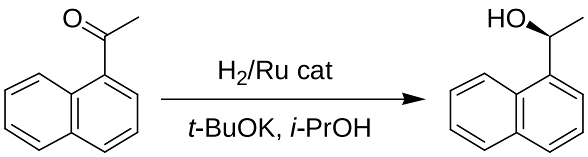
A solution of polymer **6** (2.00 g) in CH_2Cl_2 (5 ml) and CF_3CO_2H (5 ml) was stirred for 4 h at room temperature. Most of solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 ml) and tri-*n*-octylamine (5 ml) was added. The mixture was stirred for 30 min at room temperature and poured into Et_2O (150 ml) with stirring. After stirring for 30 min at 0 °C, the precipitate was collected by filtration, washed with Et_2O (5×20 ml) and dried in vacuum to give the product (1.95 g) as white solid (nitrogen content from elemental analysis: 0.61%).

(B) General Procedure for Preparation of Diphosphine-Ru-Diamine Precatalysts[2]

Method A: Diphosphine (0.055 mmol) and $[(C_6H_6)RuCl_2]_2$ (0.025 mmol) were dissolved in anhydrous and degassed DMF (2 ml) under argon. The mixture was heated to 100 °C for 3-4 hours, then the polymer-supported diamine **2** (0.055 mmol) was added and the reaction was allowed to reach room temperature and stirred for 12-15 hours. The solvent was removed under high vacuum and the residue was used for hydrogenations without further purification.

Method B: Diphosphine (0.055 mmol) and $[(C_6H_6)RuCl_2]_2$ (0.025 mmol) were dissolved in anhydrous and degassed DMF (2 ml) under argon. The reaction was heated to 100 °C for 10-20 minutes and then the solvent removed under high vacuum. The complex obtained was used directly to react with the polymer-supported diamine **2** *in situ* to generate the diphospine-Ru-Diamine precatalyst.

(C) Asymmetric Hydrogenation of Acetonaphthone



Standard procedure at S/C = 2000: An autoclave containing a glass liner was charged with [(Diphosphine)$RuCl_2$((*R*,*R*)-**2**)] (0.0025mmol), *i*-PrOH (3 ml), acetonaphthone (5 mmol) and *t*-BuOK in *i*-PrOH (0.1 M, 0.3 ml, 0.03 mmol) under argon. The reaction mixture was degassed with 10 bar H_2 five times and finally the autoclave was pressurized to 10 bar with H_2. After stirring at room temperature for a certain time, the H_2 was carefully released. The reaction mixture was diluted with Et_2O and passed through a short silica gel column before being subjected to chiral GC analysis (Chirasil Dex CB; carrier gas: helium, 30 psi; injection temperature: 250 °C; column temperature: 150 °C; t_R of (*S*)-1-(1'-naphtyl)ethanol, 7.71 min; t_R of (*R*)-1-(1'-naphtyl)ethanol, 8.88 min).[2,3]

Hydrogenation with [((*S*)-PhanePhos)$RuCl_2$((*R*,*R*)-**2**)] at S/C = 2000: (19.0 mg, 0.0025 mmol), acetonaphthone (0.85 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H_2, r.t., 2 h. (*S*)-1-(1'-naphtyl)ethanol, 98%

conversion, 97% ee.

Hydrogenation with [((*S*)-PhanePhos)RuCl$_2$((*R*,*R*)-**2**)] at S/C = 10000: (19.0 mg, 0.0025 mmol), acetonaphthone (4.25 g, 25 mmol), *i*-PrOH (6.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 1.0 ml, 0.10 mmol), 50 bar H_2, r.t.,10 h. (*S*)-1-(1'-naphtyl)ethanol, 100% conversion, 97% ee.

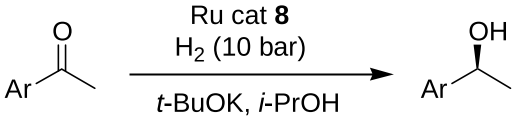
Hydrogenation with [((*R*)-BINAP)RuCl$_2$((*R*,*R*)-**2**)] at S/C = 2000: (19.0 mg, 0.0025 mmol), acetonaphthone (0.85 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H_2, r.t., 4 h. (*S*)-1-(1'-naphtyl)ethanol, 99% conversion, 98% ee.

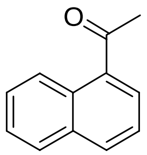
Hydrogenation with [((*R*)-Tol-BINAP)RuCl$_2$((*R*,*R*)-**2**)] at S/C = 2000: (19.0 mg, 0.0025 mmol), acetonaphthone (0.85 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H_2, r.t., 12 h. (*S*)-1-(1'-naphtyl)ethanol, 100% conversion, 91% ee.

Hydrogenation with [((*R*)-**14**)RuCl$_2$((*R*,*R*)-**2**)] at S/C = 2000: [((*R*)-**14**)RuCl$_2$(DMF)$_n$] (2.3 mg, 0.0025 mmol), ((*R*,*R*)-**2**) (16 mg, 0.003 mmol), acetonaphthone (0.85 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H_2, r.t., 12 h. (*S*)-1-(1'-naphtyl)ethanol, 99% conversion, 92% ee.

Hydrogenation with [(**15**)RuCl$_2$((*R*,*R*)-**2**)] at S/C = 2000: [(**15**)RuCl$_2$(DMF)$_n$] (2.2 mg, 0.0025 mmol), ((*R*,*R*)-**2**) (16 mg, 0.003 mmol), acetonaphthone (0.85 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H_2, r.t., 4 h. (*S*)-1-(1'-naphtyl)ethanol, 99% conversion, 61% ee.

(D) Asymmetric Hydrogenation of other ketones





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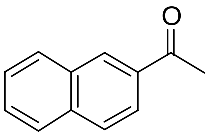

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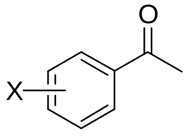
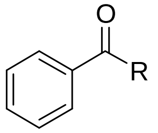


11a: X = *p*-Br
11b: X = *o*-Me
11c: X = *p*-Me
11d: X = *p*-OMe
11e: X = *p*-CF$_3$



12a: R = Me
12b: R = Et

Hydrogenations of other ketones with [((*S*)-PhanePhos)RuCl$_2$((*R*,*R*)-**2**)] were carried out using the same standard procedure as for acetonaphthone. When the reaction completed, the reaction mixture was filtered through a short silica gel column, the filtrate was concentrated and the residue was analyzed by NMR and chiral GC. The stereochemistry of products was assigned by comparing the GC retention time with literature data.

(*S*)-1-(2'-naphtyl)ethanol:[4] [((*S*)-PhanePhos)RuCl$_2$((*R*,*R*)-**2**)] (19.0 mg, 0.0025 mmol), 2-acetonaphthone (0.85 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H$_2$, r.t., 2 h. (*S*)-1-(2'-naphtyl)ethanol, 100% conversion, 96% ee. GC (Chirasil Dex CB); carrier gas: helium, 30 psi; injection temperature: 250 °C; column temperature: 150 °C; 7.11 min (*R*); 7.46 min (*S*).

(*S*)-1-(4'-Bromophenyl)ethanol:[5] [((*S*)-PhanePhos)RuCl$_2$((*R*,*R*)-**2**)] (19.0 mg, 0.0025 mmol), 4-Bromoacetophenone (1.0 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H$_2$, r.t., 2 h. (*S*)-1-(4'-Bromophenyl)ethanol, 99% conversion, 94% ee. GC (Chirasil Dex CB; carrier gas: helium, 30 psi; injection temperature: 250 °C; column temperature: 135 °C; 5.19 min (*R*); 5.56 min (*S*).

(*S*)-1-(2'-Methylphenyl)ethanol:[6] [((*S*)-PhanePhos)RuCl$_2$((*R*,*R*)-**2**)] (19.0 mg, 0.0025 mmol), 2-Methylacetophenone (0.67 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H$_2$, r.t., 4 h. (*S*)-1-(2'-Methylphenyl)ethanol, 100% conversion, 93% ee. GC (Chirasil Dex CB; carrier gas: helium, 30 psi; injection temperature: 250 °C; column temperature: 120 °C; 4.43 min (*R*); 5.42 min (*S*).

(*S*)-1-(4'-Methylphenyl)ethanol:[7] [((*S*)-PhanePhos)RuCl$_2$((*R*,*R*)-**2**)] (19.0 mg, 0.0025 mmol), 4-Methylacetophenone (0.67 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H$_2$, r.t., 4 h. (*S*)-1-(4'-Methylphenyl)ethanol, 100% conversion, 97% ee. GC (Chirasil Dex CB; carrier gas: helium, 30 psi; injection temperature: 250 °C; column temperature: 120 °C; 2.87 min (*R*); 3.14 min (*S*).

(*S*)-1-(4'-Methoxyphenyl)ethanol:[7] [((*S*)-PhanePhos)RuCl$_2$((*R*,*R*)-**2**)] (19.0 mg, 0.0025 mmol), 4-Methoxyacetophenone (0.75 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H$_2$, r.t., 4 h. (*S*)-1-(4'-Methoxyphenyl)ethanol, 100% conversion, 90% ee. GC (Chirasil Dex CB; carrier gas: helium, 30 psi; injection temperature: 250 °C; column temperature: 125 °C; 5.24 min (*R*); 5.45 min (*S*).

(*S*)-1-(4'-Trifluoromethylphenyl)ethanol:[6] [((*S*)-PhanePhos)RuCl$_2$((*R*,*R*)-**2**)] (19.0 mg, 0.0025 mmol), 4-Trifluoromethylacetophenone (0.94 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H$_2$, r.t., 4 h. (*S*)-1-(4'-Trifluoromethylphenyl)ethanol, 99% conversion, 90% ee. GC (Chirasil Dex CB; carrier gas: helium, 30 psi; injection temperature: 250 °C; column temperature: 110 °C; 5.66 min (*R*); 6.86 min (*S*).

(*S*)-1-phenylethanol:[4] [((*S*)-PhanePhos)$RuCl_2$((*R*,*R*)-**2**)] (19.0 mg, 0.0025 mmol), acetophenone (0.60 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H_2, r.t., 4 h. (*S*)-1-phenylethanol, 100% conversion, 94% ee. GC (Chirasil Dex CB; carrier gas: helium, 30 psi; injection temperature: 250 °C; column temperature: 105 °C; 4.92 min (*R*); 5.41 min (*S*).

(*S*)-Phenylpropanol:[4] [((*S*)-PhanePhos)$RuCl_2$((*R*,*R*)-**2**)] (19.0 mg, 0.0025 mmol), phenylpropanone (0.67 g, 5 mmol), *i*-PrOH (3.0 ml), *t*-BuOK in *i*-PrOH (0.1 mmol/ml, 0.3 ml, 0.03 mmol), 10 bar H_2, r.t., 4 h. (*S*)-Phenylpropanol, 100% conversion, 92% ee. GC (Chirasil Dex CB; carrier gas: helium, 30 psi; injection temperature: 250 °C; column temperature: 95 °C; 12.76 min (*R*); 13.14 min (*S*).

The results are also tabulated on page 8.

(E) Catalyst recycle

A mini-autoclave containing a glass liner was charged with [(Diphosphine)$RuCl_2$((*R*,*R*)-**2**)] (0.005 mmol), *i*-PrOH (5 ml), acetonaphthone (0.85 g, 5 mmol) and *t*-BuOK in *i*-PrOH (0.1 M, 0.6 ml, 0.06 mmol) under argon. The reaction mixture was degassed with 9 bar H_2 five times and finally the autoclave was pressurized to 9 bar with H_2. After stirring at room temperature for 3 h, the H_2 was carefully released. After removal of the solvent under vacuum, Et_2O (3 x 10 ml) was added to extract the organic materials. The product was analyzed as in C. To start a new run, a previous degassed *i*-PrOH (5 ml), degassed acetonaphthone (0.85 g, 5 mmol) and *t*-BuOK in *i*-PrOH (0.1 M, 0.6 ml, 0.06 mmol, degassed) were added to the catalyst-containing glass liner under argon. The reaction was repeated under 9 bar H_2 as above. The third run was performed in the same manner as the second one.

References

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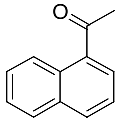
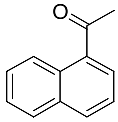
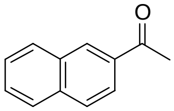
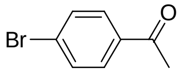
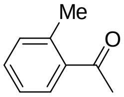
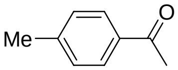
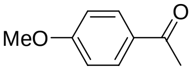
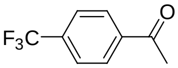
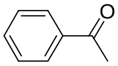
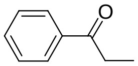
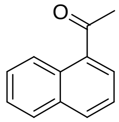
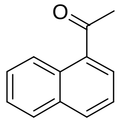
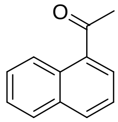
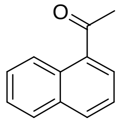
(7) Hayashi, T.; Hirate, S.; Kitayama, K.; Tsuji, H.; Torii, A.; Uozumi, Y. *J. Org. Chem.* **2001**, *66*, 1441.

Ketones	diphosphine	S/C	H_2 (bar)	Time(h)	conv.(%)	e.e.(%)	config
	(*S*)-PhanePhos	2000	10	2	98	97	*S*
	(*S*)-PhanePhos	10000	10	10	100	97	*S*
	(*S*)-PhanePhos	2000	10	2	100	96	*S*
	(*S*)-PhanePhos	2000	10	2	99	94	*S*
	(*S*)-PhanePhos	2000	10	4	100	93	*S*
	(*S*)-PhanePhos	2000	10	4	100	97	*S*
	(*S*)-PhanePhos	2000	10	4	100	90	*S*
	(*S*)-PhanePhos	2000	10	4	99	90	*S*
	(*S*)-PhanePhos	2000	10	2	100	94	*S*
	(*S*)-PhanePhos	2000	10	2	100	92	*S*
	(*R*)-BINAP	2000	10	4	99	98	*S*
	(*R*)-Tol-BINAP	2000	10	12	100	91	*S*
	(*R*)-MeO-BIPHEP	2000	10	12	99	92	*S*
	DPPF	2000	10	4	99	61	*S*