Experimental Section

Typical procedure for an iodine–magnesium exchange reaction: Preparation of **3l**: A solution of ethyl 4-iodobenzoate (552 mg, 2 mmol) in THF (20 mL) was cooled to −40 °C, and *i*Pr_2Mg (2.3 mL, 1.06 mmol) in *tert*-butyl methyl ether was added. After 1 h at −40 °C, benzaldehyde (233 mg, 2.2 mmol) was added. After stirring for 3 h, the reaction mixture was worked up as usual to give a crude yellow oil, which was purified by flash chromatography (pentane/ether, 80/20) to give 460 mg of pure **3l** (90% yield).

Typical procedure for an iodine–magnesium exchange reaction on the solid phase: Preparation of **5a**: Wang resin (100 mg) charged with 4-iodobenzoic acid (70 μmol) was dried for 2 h under vacuum (0.1 Torr) at 50 °C. After cooling to room temperature under an inert atmosphere, the resin was allowed to swell for 10 min in THF (2 mL). The heterogeneous mixture was cooled to −35 °C, and a solution of *i*PrMgBr (0.70 mL, 0.51 mmol, 0.73 M) in THF was added. After stirring for 15 min, a solution of CuCN · 2 LiCl (0.70 mL, 0.7 mmol, 1.0 M) was added, followed, after a further 15 min, by allyl bromide (0.30 mL, 50 equiv). After stirring for 40 min, the reaction mixture was filtered, and the resin was successively washed with DMF, MeOH, and CH_2Cl_2 (six cycles) and treated with CF_3CO_2H (4 mL of $CF_3CO_2H/CH_2Cl_2/H_2O$, 9/1/1) for 20 min. After filtration and evaporation of the volatile materials under high vacuum, **5a** (10.8 mg, 95% yield) was isolated as a white solid. The HPLC purity was 98% (RP-18, MeCN/H_2O, 0.1% CF_3CO_2H; UV detection at 254 nm).

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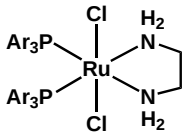
trans-[$RuCl_2$(phosphane)$_2$(1,2-diamine)] and Chiral *trans*-[$RuCl_2$(diphosphane)(1,2-diamine): Shelf-Stable Precatalysts for the Rapid, Productive, and Stereoselective Hydrogenation of Ketones**

Henri Doucet, Takeshi Ohkuma, Kunihiko Murata, Tohru Yokozawa, Masami Kozawa, Eiji Katayama, Anthony F. England, Takao Ikariya, and Ryoji Noyori*

We recently discovered that a system comprising [$RuCl_2$(phosphane)$_n$], 1,2-diamine, and an inorganic base is an excellent catalyst for the hydrogenation of simple ketones in 2-propanol, at high substrate/catalyst molar ratios (S/C) under mild conditions.[1] In addition to other features, this reaction is characterized by high diastereo-, enantio-, and C=O/C=C selectivity. However, the concentration of the catalytic species generated in situ remains unknown. Because the quantities of the metallic and organic components used are extremely small, it is possible that the intermolecular reactions may be incomplete. Furthermore, the catalytically active metal complexes may not be the only complexes formed. We speculated that the use of a pure, stable phosphane/diamine complex would significantly increase the catalytic efficiency. We describe here procedures for the preparation of Ru^{II} complexes with phosphane and diamine ligands from commercial or other readily available materials. As expected, these complexes proved to be exceedingly efficient hydrogenation precatalysts. The reaction rate and productivity were two orders of magnitude higher than those obtained from the complexes generated in situ.

Achiral Ru type **1** complexes with triarylphosphane, ethylenediamine, and chloro ligands were prepared by the addition of two equivalents of ethylenediamine to [$RuCl_2$(phosphane)$_3$][2] in CH_2Cl_2 at 25 °C. The mixture was stirred for three hours (method A). Type **2** chiral complexes were most



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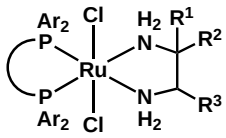

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conveniently obtained by treatment of oligomeric [$RuCl_2$(diphosphane)$(dmf)_n$][3] with 1.1 equivalents of a diamine[4] in dmf at 25 °C for three hours (method B). In place of [$RuCl_2$(binap)$(dmf)_n$], [$NH_2(C_2H_5)_2$][{RuCl(binap)}$_2(\mu$-Cl$)_3$][5] and [RuCl(binap)(η^6-arene)]Cl[6] can also be used (abbreviations are given in Figure 1). The desired mixed-ligand complex can also be obtained by the reaction of [Ru{η^3-$CH_2C(CH_3)CH_2$}$_2$(diphosphane)][7] in acetone with two equivalents of methanolic HCl, followed by treatment of the resulting [$RuCl_2$(diphosphane)]$_n$ with one equivalent of a diamine in DMF at 25 °C for three hours (method C). This procedure, though somewhat tedious, provides a general route to the preformed complexes. The diphosphane/diamine Ru complexes thus prepared[8] are listed in Table 1. These complexes are soluble in many common organic solvents. The *p*-tolylphosphane and TolBINAP[9] complexes are more soluble than the triphenylphosphane and BINAP analogues. The isolated Ru complexes are fairly air- and moisture-stable and can be stored in an ordinary vial for a long period, preferably under an argon atmosphere.

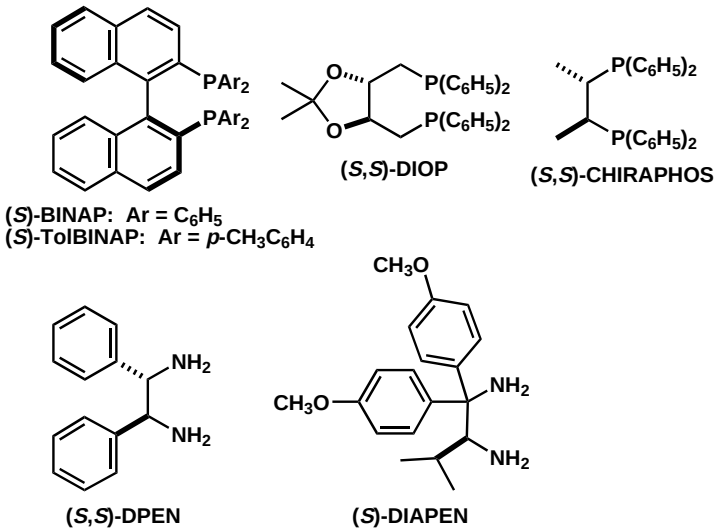

Figure 1. Chiral diphosphanes and diamines

All the complexes in Table 1 have *trans*-dichloro geometries. Single-crystal X-ray analysis[10] of (*R*),(*R*,*R*)-**2d** indicated a distorted octahedral geometry of the Ru center that approaches C_2 symmetry, in which both the TolBINAP and DPEN chelate ligands are coordinated in a λ fashion (Figure 2a). In the diastereomer, (*R*),(*S*,*S*)-**2e**, the TolBINAP ligand forms a λ seven-membered structure, while the DPEN ligand assumes a five-membered ring structure with a δ conformation (Figure 2b).

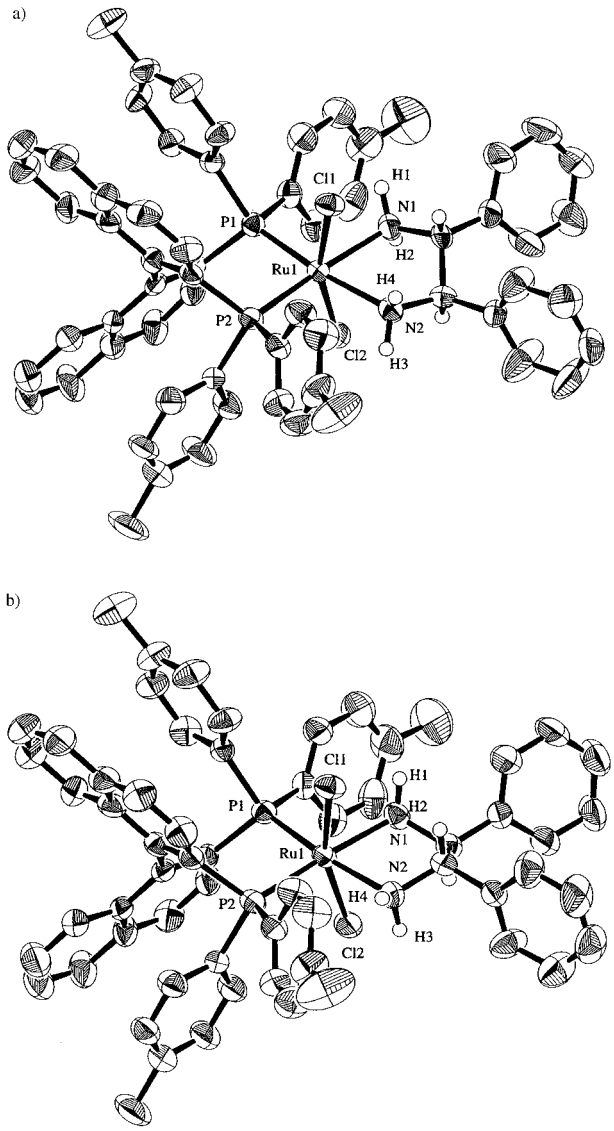

Figure 2. ORTEP diagrams of the structures of (*R*),(*R*,*R*)-**2d** (a) and (*R*),(*S*,*S*)-**2e** (b). All hydrogen atoms except for the amino and methine protons of DPEN have been omitted for clarity. Selected distances [Å] and bond angles [°]: (*R*),(*R*,*R*)-**2d**; Ru–Cl1 2.421(2), Ru–Cl2 2.420(2), Ru–P1 2.282(3), Ru–P2 2.273(2), Ru–N1 2.196(7), Ru–N2 2.183(7), Cl1–(H4)N2 2.74, Cl2–(H2)N1 2.77; Cl1-Ru-Cl2 162.96(8), P1-Ru-P2 92.22(8), N1-Ru-N2 77.7(2). (*R*),(*S*,*S*)-**2e**; Ru–Cl1 2.408(2), Ru–Cl2 2.426(2), Ru–P1 2.276(2), Ru–P2 2.296(2), Ru–N1 2.141(5), Ru–N2 2.189(6), Cl1–(H1)N1 2.70, Cl2–(H3)N2 2.70; Cl1-Ru-Cl2 163.23(6), P1-Ru-P2 91.50(7), N1-Ru-N2 78.0(2).

Table 1. Synthesis and properties of the Ru complexes **1** and **2**.

Complex	formula[a]	Method	Decomp [°C][b]	δ (^{31}P)[c]
1a	[(*OC*-6-13)-$RuCl_2${$P(C_6H_5)_3$}$_2$(en)]	A	176	45.5 (s)
1b	[(*OC*-6-13)-$RuCl_2${$P(p$-$CH_3C_6H_4)_3$}$_2$(en)]	A	185	44.3 (s)
(*R*),(*R*,*R*)-**2a**	[(*OC*-6-13)-$RuCl_2${(*R*)-binap}{(*R*,*R*)-dpen}]	B	235	47.4 (s)
(*R*),(*S*,*S*)-**2b**	[(*OC*-6-13)-$RuCl_2${(*R*)-binap}{(*S*,*S*)-dpen}]	B	242	46.9 (s)
(*S*),(*S*)-**2c**	[(*OC*-6-13)-$RuCl_2${(*S*)-binap}{(*S*)-daipen}]	B	183	47.9 (d), 48.9 (d)[d]
(*R*),(*R*,*R*)-**2d**	[(*OC*-6-13)-$RuCl_2${(*R*)-tolbinap}{(*R*,*R*)-dpen}]	B	209	46.2 (s)
(*R*),(*S*,*S*)-**2e**	[(*OC*-6-13)-$RuCl_2${(*R*)-tolbinap}{(*S*,*S*)-dpen}]	B	234	45.5 (s)
(*S*),(*S*)-**2f**	[(*OC*-6-13)-$RuCl_2${(*S*)-tolbinap}{(*S*)-daipen}]	B	173	45.9 (d), 47.6 (d)[e]
(*S*,*S*),(*R*,*R*)-**2g**	[(*OC*-6-13)-$RuCl_2${(*S*,*S*)-diop}{(*R*,*R*)-dpen}]	B	226	38.9 (s)
(*S*,*S*),(*S*,*S*)-**2h**	[(*OC*-6-13)-$RuCl_2${(*S*,*S*)-chiraphos}{(*S*,*S*)-dpen}]	C	204	79.1 (s)

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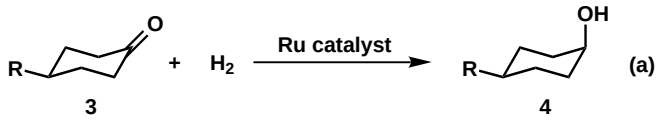
In these stereoisomers, the two phenyl substituents of the N,N-ligated five-membered ring are oriented in the equatorial direction, and the flexible $P(p\text{-}H_3CC_6H_4)_2$ moieties adopt similar spatial arrangements. The Cl–HN distances (2.7–2.8 Å) are rather short due to intramolecular hydrogen bonding (expected van der Waals separation, 3.0 Å). ^1H and ^{31}P NMR analysis of these compounds show that they exist as a single conformer in C_6D_6.

The isolated Ru complexes are among the most reactive (pre)catalysts for homogeneous hydrogenation so far reported.[11] When cyclohexanone (**3a**) was hydrogenated in 2-propanol (2.1 M) in the presence of **1b** and $(CH_3)_3COK$ (ketone:**1b**:base = 100000:1:450) at 10 atm H_2 and 60 °C for two hours, cyclohexanol (**4a**) was produced in 96% yield [Eq. (a)]. The reaction was extremely rapid with an initial

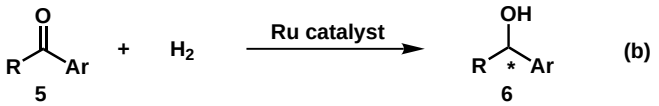


3 4

a: R = H b: R = $(CH_3)_3C$ c: R = C_6H_5

turnover frequency (TOF) of 563000 h^{-1} or 156 s^{-1}.[11, 12] Hydrogenation of 4-*tert*-butylcyclohexanone (**3b**) in the presence of **1b** and $(CH_3)_3COK$ (50000:1:250) at 10 atm and 60 °C, proceeded with a TOF of 178000 h^{-1} (49 s^{-1}), and produced the *cis* alcohol **4b** with a *cis/trans* stereoselectivity of 97/3. The 4-phenyl derivative **3c** was produced with a *cis/trans* selectivity of 96/4.[1c]

Rapid, highly productive asymmetric hydrogenation of ketones can be achieved with chiral precatalysts. When a mixture of acetophenone (**5a**) (601 g), (*S*),(*S*,*S*)-**2d** (2.2 mg), and $(CH_3)_3COK$ (5.6 g) in 2-propanol (1.5 L) was stirred under H_2 (45 atm) at 30 °C for 48 h, (*R*)-1-phenylethanol ((*R*)-**6a**) was obtained with 80% *ee* and in 100% yield (94% (577 g) after distillation). The turnover number (TON) was 2400000, while the TOF at 30% conversion was 228000 h^{-1} (63 s^{-1}).[11, 12] Hydrogenation of 1′-acetonaphthone (**5g**) in 2-propanol in the presence of (*R*),(*R*,*R*)-**2d** and $(CH_3)_3COK$ ([ketone] = 2.1 M, ketone:**2d**:base = 50000:1:200) at 10 atm H_2 and 80 °C proceeded with an initial TOF of 259000 h^{-1} (72 s^{-1}), and after one hour afforded (*S*)-1-(1-naphthyl)ethanol ((*S*)-**6g**) with 91% *ee* in 93% yield.[13] As exemplified in Table 2, high level enantioselectivity was obtained with various ring-substituted acetophenones, including the *o*-bromo and -methoxy derivatives **5c** and **5d**, and higher



5 6

a: R = CH_3, Ar = C_6H_5 f: R = CH_3, Ar = *p*-*i*$C_4H_9C_6H_4$

b: R = CH_3, Ar = *o*-$CH_3C_6H_4$ g: R = CH_3, Ar = 1-naphthyl

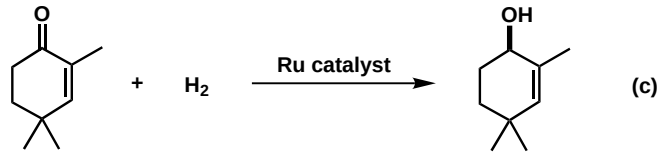
c: R = CH_3, Ar = *o*-BrC_6H_4 h: R = C_2H_5, Ar = *p*-$CH_3OC_6H_4$

d: R = CH_3, Ar = *o*-$CH_3OC_6H_4$ i: R = *n*-C_3H_7, Ar = C_6H_5

e: R = CH_3, Ar = *p*-$C_2H_5C_6H_4$ j: R = *cyclo*-C_6H_{11}, Ar = C_6H_5

analogues of acetophenone, with an S/C as high as 100000 [Eq. (b)].[14, 15] The degree of enantioselectivity and the absolute configuration of the products are the same as those obtained with the complexes generated in situ.

Asymmetric hydrogenation of 2,4,4-trimethyl-2-cyclohexenone (**7**) with (*S*),(*R*,*R*)-**2e** acts on the carbonyl group only and gave (*R*)-2,4,4-trimethyl-2-cyclohexenol ((*R*)-**8**) with 94% *ee* and in 100% yield [Eq. (c)]. The chiral alcohol **8** is an intermediate in the synthesis of various carotenoid-derived bioactive terpenes and odorants.[16]



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This new hydrogenation procedure is clean, mild, and efficient, and offers a very practical method of chiral alcohol synthesis.

Table 2. Ruthenium-catalyzed asymmetric hydrogenation of ketones.[a]

Ketone	Precatalyst	S/C[b]	Conditions			Alcohol product	
			H_2 [atm]	*t* [h]	Yield [%][c]	*ee* [%][c]	Config.[d]
5a	(*S*),(*S*,*S*)-**2d**	2400000[e]	45	48	100	80	*R*
5b	(*S*),(*S*)-**2f**	100000	10	48	94	99	*R*
5c	(*R*),(*R*)-**2f**	10000	10	6	100	98	*S*
5d	(*S*),(*S*)-**2f**	2000	4	10	98	82	*R*
5e	(*R*),(*R*)-**2f**	10000	10	21	100	97	*S*
5f	(*R*),(*R*,*R*)-**2d**	100000	10	48	99	96	*S*
5f	(*S*),(*S*,*S*)-**2d**	800	1	24	98	94	*R*
5g	(*S*),(*S*,*S*)-**2d**	100000	10	40	99.5	98	*R*
5g	(*R*),(*R*,*R*)-**2d**	50000	10	1[f]	93	91	*S*
5h	(*R*),(*R*)-**2f**	10000	10	14	100	95	*S*
5i	(*S*),(*S*)-**2f**	100000	10	48	87	94	*R*
5j	(*S*),(*S*)-**2f**	100000	10	48	98	92	*R*
7	(*S*),(*R*,*R*)-**2e**	10000	10	48	100	94	*R*

[a] Reactions were conducted at 24–30 °C with a 2.1–2.4 M solution of substrate (25 mmol) in 2-propanol in the presence of $(CH_3)_3COK$ (ketone:base = 220:1). [b] Substrate/catalyst molar ratio. [c] Determined by GC or HPLC analysis of the chiral phase. [d] Determined by sign of rotation. [e] Reaction with 601 g **5a** (ketone:$(CH_3)_3COK$ = 100:1) [f] at 80 °C.

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Experimental Section

1a[8] (method A): $[RuCl_2\{P(C_6H_5)_3\}_3]$ (1.11 g, 1.16 mmol) was placed in a 50-mL Schlenk flask filled with argon. CH_2Cl_2 (10 mL) and $NH_2(CH_2)_2NH_2$ (0.15 mL, 2.2 mmol) were then added. The mixture was degassed and stirred under argon at 25 °C for 3 h. After removal of turbidity by filtration, the filtrate was concentrated to about 5 mL, *n*-hexane (20 mL) was added, and a light brown powder was obtained. The supernatant was removed and the resulting solid was dried under reduced pressure (1 Torr) to give analytically pure **1a** (0.55 g, 63% yield). ^{1}H NMR (400 MHz, C_6D_6, 25 °C, TMS): $\delta = 2.1$ (m, 4H; CH_2), 2.8 (m, 4H; NH_2), 6.8–8.0 (m, 30H; aromatic H).

1b (method A): A light brown solid was obtained from CH_2Cl_2:ether (1:3) (79%). ^{1}H NMR: $\delta = 2.00$ (s, 18H, CH_3), 2.2 (m, 4H, CH_2), 2.9 (m, 4H, NH_2), 6.86 (d, 12H, $J = 7.5$ Hz, *o*-aromatic H), 7.9 (m, 12H, *m*-aromatic H).

(*R*),(*R*,*R*)-**2a** (method B): $[RuCl_2(C_6H_6)]_2$ (129 mg, 0.258 mmol) and (*R*)-BINAP (341 mg, 0.55 mmol) were placed in a 50-mL Schlenk flask. After the air in the flask was replaced with argon, DMF (9 mL) was added, the mixture was degassed and stirred under argon at 100 °C for 10 min to form a reddish brown solution. After the solution was cooled to 25 °C, [14] (*R*,*R*)-DPEN (117 mg, 0.55 mmol) was added and the mixture was stirred for 3 h. The solvent was removed under reduced pressure (1 Torr). The residue was dissolved in CH_2Cl_2 (10 mL) and turbidity was removed by filtration. The filtrate was concentrated to about 1 mL, then ether (10 mL) was added and a light brown powder was obtained. The supernatant was removed and the resulting solid was dried under reduced pressure to give (*R*),(*R*,*R*)-**2a** (0.34 g, 66% yield). ^{1}H NMR: $\delta = 3.3$ (m, 2H, N*H*H), 3.45 (m, 2H, NH*H*), 4.55 (m, 2H, NH_2CH), 6.3–8.8 (m, 42H, aromatic H).

(*R*),(*S*,*S*)-**2b** (method B): A light brown solid was obtained from CH_2Cl_2:ether (1:12) (62%). ^{1}H NMR: $\delta = 3.0$ (m, 2H, N*H*H), 4.4 (m, 2H, NH*H*), 4.65 (m, 2H, NH_2CH), 6.3–8.8 (m, 42H, aromatic H).

(*S*),(*S*)-**2c** (method B): A cream yellow solid was obtained from CH_2Cl_2:ether (1:10) (50%). ^{1}H NMR $\delta = -0.12$ (d, 3H, $J = 6.8$ Hz, CH_3CHCH_3), 0.54 (d, 3H, $J = 6.8$ Hz, CH_3CHCH_3), 1.7 (m, 1H, $(CH_3)_2CH$), 2.75 (m, 1H, N*H*H((CH$_3$)$_2$CH)CH), 3.05 (m, 1H, NH*H*((CH$_3$)$_2$CH)CH), 3.12 (s, 3H, CH_3O), 3.31 (s, 3H, CH_3O), 3.8 (m, 1H, N*H*H(*p*-$CH_3OC_6H_4)_2$C), 4.40 (m, 1H, NH*H*(*p*-$CH_3OC_6H_4)_2$C), 5.05 (m, 1H, NH_2CH), 6.2–8.4 (m, 40H, aromatic H).

(*R*),(*R*,*R*)-**2d**: A light brown solid was obtained from CH_2Cl_2:ether (1:5) (58%). ^{1}H NMR: $\delta = 1.70$ (s, 6H, CH_3), 1.87 (s, 6H, CH_3), 3.3 (m, 2H, N*H*H), 3.5 (m, 2H, NH*H*), 4.55 (m, 2H, NH_2CH), 6.55–8.8 (m, 38H, aromatic H).

(*R*),(*S*,*S*)-**2e**: A light brown solid was obtained from CH_2Cl_2:ether (1:5) (51%). ^{1}H NMR: $\delta = 1.70$ (s, 6H, CH_3), 1.81 (s, 6H, CH_3), 3.05 (m, 2H, N*H*H), 4.4 (m, 2H, NH*H*), 4.7 (m, 2H, NH_2CH), 6.3–8.8 (m, 38H, aromatic H).

(*S*),(*S*)-**2f**: A cream yellow solid was obtained from CH_2Cl_2:ether (1:14) (60%). ^{1}H NMR: $\delta = -0.08$ (d, 3H, $J = 6.8$ Hz, $CH_3(CH_3)CH$), 0.67 (d, 3H, $J = 6.8$ Hz, $CH_3(CH_3)CH$), 1.66 (s, 3H, *p*-$CH_3C_6H_4P$), 1.70 (s, 3H, *p*-$CH_3C_6H_4P$), 1.72 (m, 1H, $(CH_3)_2CH$), 1.99 (s, 3H, *p*-$CH_3C_6H_4P$), 2.00 (s, 3H, *p*-$CH_3C_6H_4P$), 2.9 (m, 1H, N*H*H((CH$_3$)$_2$CH)CH), 3.1 (m, 1H, NH*H*((CH$_3$)$_2$CH)CH), 3.18 (s, 3H, CH_3O), 3.40 (s, 3H, CH_3O), 3.8 (m, 1H, N*H*H(*p*-$CH_3OC_6H_4)_2$C), 4.4 (m, 1H, NH*H*(*p*-$CH_3OC_6H_4)_2$C), 5.15 (m, 1H, NH_2CH), 6.2–8.8 (m, 36H, aromatic H).

(*S*,*S*),(*R*,*R*)-**2g**: Conditions: $[RuCl_2(C_6H_6)]_2$ (248 mg, 0.495 mmol), (*S*,*S*)-DIOP (504 mg, 1.01 mmol), DMF (10 mL), 100 °C, 2 h, and (*R*,*R*)-DPEN (220 mg, 1.03 mmol), 25 °C, 3 h.[14] Isolation: removal of DMF (1 Torr, 25 °C→50 °C), extraction with CH_2Cl_2 (20 mL), and crystallization (CH_2Cl_2:ether, 1:14, 45 mL), to give a light brown solid (530 mg, 61% yield). ^{1}H NMR: $\delta = 1.43$ (s, 6H, CH_3), 3.25–3.70 (m, 6H, CH_2P and N*H*H), 3.95–4.15 (m, 2H, NH*H*), 4.55 (m, 2H, NH_2CH), 4.73 (m, 2H, CHO), 6.5–8.2 (m, 30H, aromatic H).

(*S*,*S*),(*S*,*S*)-**2h** (method C): $[Ru\{\eta^3\text{-}CH_2C(CH_3)CH_2\}_2\{(S,S)\text{-chiraphos}\}]$ (2.13 g, 3.0 mmol)[7] was placed in a 150-mL Schlenk flask filled with argon. Acetone (50 mL) and HCl in CH_3OH (2.27 M, 3.2 mL, 7.3 mmol) were added and the mixture was stirred at 25 °C for 2 h. The turbidity was removed by filtration, and the solvent was evaporated under reduced pressure (1 Torr). Then dmf (20 mL) and (*S*,*S*)-dpen (632 mg, 3.0 mmol) were added to the residue. The mixture was degassed and stirred under argon for 3 h. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL). The turbidity was removed by filtration and the filtrate was concentrated to about 2 mL. Ether (10 mL) was then added and the turbidity was again removed by filtration. Ether (10 mL) was again added to the filtrate and a light brown powder precipitated. The supernatant was removed and the resulting solid was dried to give (*S*,*S*),(*S*,*S*)-**2h** (1.90 g, 78%). ^{1}H NMR: $\delta = 0.95$ (d, 6H, $J = 4.3$ Hz, CH_3), 2.77 (m, 2H, CH_3CH), 3.84 (m, 2H, N*H*H), 4.05 (m, 2H, NH*H*), 4.69 (m, 2H, NH_2CH), 6.7–8.1 (m, 30H, aromatic H).

Hydrogenation of cyclohexanone: (**3a**):[14] Conversions were determined by gas chromatography (HP-INNOVAX (30 m), 100 °C, He (55 kPa), 9.2 min (**3a**), 12.8 min (**4a**)). Correlations between reaction time (min) and TON were as follows: (5, 12330), (10, 59280), (15, 68980), (20, 76150), (120, 96130). **4b**: cis/trans = 97/3; GC: HP-INNOVAX, 130 °C, 17.4 min (*cis*), 20.1 min (*trans*). **4c**: cis/trans = 96/4; GC: HP-INNOVAX, 190 °C, 28.6 min (*cis*), 30.4 min (*trans*).

Asymmetric hydrogenation:[14] (*S*),(*S*,*S*)-**2d** (22 mg) was dissolved in degassed 2-propanol (20 mL), which was used as the catalyst stock solution. Ketone **5a** (601 g), 2-propanol (1.5 L), $(CH_3)_3COK$ (5.6 g), and an aliquot of the catalyst solution (2.0 mL, 0.002 mmol) (molar ratio ketone:Ru:base = 2400000:1:24000) were placed in a 10 L stainless steel autoclave. The mixture was degassed and hydrogen was introduced to a pressure of 45 atm. The mixture was vigorously stirred at 30 °C for 48 h. The yield was determined by GC to be 100%. GC: Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), 115 °C, He (50 kPa), 26.7 min ((*R*)-**6a**), 28.7 min ((*S*)-**6a**), 17.8 min (**5a**). After the solvent was removed under reduced pressure, the residue was passed through a silica gel column (300 g, ethyl acetate) and then distilled (99 °C, 15 Torr) to give (*R*)-**6a** (577 g, 94%, 80% *ee*).[1a] $[\alpha]_D^{24} = +38.1$ ($c = 1.02$, CH_2Cl_2).[1a, 17]

Hydrogenation of **5g** at 80 °C: (*S*)-**6g**, 91% *ee*; GC: Chirasil-DEX CB (25 m), 150 °C, He (50 kPa), 46.8 min ((*R*)-**6g**), 42.3 min ((*S*)-**6g**), 19.1 min (**5g**). Correlations between reaction time (min) and TON were as follows: (5, 7815), (10, 29360), (15, 37870), (60, 46350).

(*R*)-**6b**: $[\alpha]_D^{24} = +52.8$ (neat);[1a, 18] 99% *ee*; Chirasil-DEX CB, 125 °C, 17.1 min ((*R*)-**6b**), 20.0 min ((*S*)-**6b**).

(*S*)-**6c**: $[\alpha]_D^{24} = -60.5$ ($c = 0.57$, CH_2Cl_2);[19] 98% *ee*; Chirasil-DEX CB, 150 °C, 13.0 min ((*R*)-**6c**), 16.2 min ((*S*)-**6c**).

(*R*)-**6d**: $[\alpha]_D^{24} = +59.1$ ($c = 1.10$, toluene);[20] 82% *ee*; Chirasil-DEX CB, 130 °C, 20.7 min ((*R*)- **6d**), 23.5 min ((*S*)-**6d**).

(*S*)-**6e**: $[\alpha]_D^{24} = -48.2$ ($c = 1.12$, $CHCl_3$);[21] 97% *ee*; Chirasil-DEX CB, 110 °C, 43.3 min ((*R*)-**6e**), 47.2 min ((*S*)-**6e**).

(*S*)-**6f**: $[\alpha]_D^{25} = -35.5$ (neat);[22] 96% *ee*; Chirasil-DEX CB, 130 °C, 30.1 min ((*R*)-**6f**), 33.4 min ((*S*)-**6f**).

(*R*)-**6g**: $[\alpha]_D^{25} = +77.0$ ($c = 1.02$, ether);[1a, 23] 98% *ee*.

(*S*)-**6h**: $[\alpha]_D^{22} = -36.1$ ($c = 5.10$, benzene);[24] 95% *ee*; Chirasil-DEX CB, 140 °C, 23.7 min ((*R*)-**6h**), 22.9 min ((*S*)-**6h**).

(*R*)-**6i**: $[\alpha]_D^{23} = +36.7$ ($c = 1.40$, CH_3OH);[25] 94% *ee*; HPLC: CHIRALCEL OB (Daicel, 250 mm), 2-propanol:hexane (1:9), 30 °C, 254 nm, 0.5 mL min^{-1}, 11.2 min ((*R*)-**6i**), 9.4 min ((*S*)-**6i**).

(*R*)-**6j**: $[\alpha]_D^{22} = +26.8$ ($c = 3.29$, benzene);[26] 92% *ee*; Chirasil-DEX CB, 110 °C, 64.6 min ((*R*)-**6j**), 66.6 min ((*S*)-**6j**).

(*R*)-**8**: $[\alpha]_D^{23} = +87.9$ ($c = 1.00$, CH_3OH);[1d, 16a] 94% *ee*; Chirasil-DEX CB, 90 °C, 49.1 min ((*R*)-**8**), 46.4 min ((*S*)-**8**).

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[10] X-ray crystallographic analysis was performed with a Rigaku AFC diffractometer (graphite monochromator, $Mo_{K\alpha}$ radiation). The structures were solved with PATTY and DIRDIF 94. (*R*),(*R*,*R*)-**2d**: $C_{62}H_{56}Cl_2N_2P_2Ru$, $M_r = 1063.06$, orange crystal, $0.1 \times 0.1 \times 0.1$ mm, monoclinic, space group *C*2 (no. 5), $a = 24.50(1)$, $b = 20.533(9)$, $c = 24.80(1)$ Å $\beta = 119.20(3)^\circ$, $V = 10908(10)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.294$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 4.84$ m^{-1}, $T = 296$ K. 9880 reflections were independent and unique, and 6220 with $I > 3.00\sigma(I)$ ($2\theta_{max} = 50^\circ$) were used for the solution of the structure. All hydrogen atoms were calculated from ideal geometries, fixed, and included in the calculation of the structural factor. $R = 0.034$, $Rw = 0.034$. (*R*),(*S*,*S*)-**2e**: $C_{62}H_{56}Cl_2N_2P_2Ru$, $M_r = 1063.06$, orange crystal, $0.1 \times 0.1 \times 0.2$ mm, monoclinic, space group *C*2 (no. 5), $a = 24.74(2)$, $b = 20.49(1)$, $c = 25.04(1)$ Å $\beta = 120.79(4)^\circ$, $V = 10908(11)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.294$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 4.84$ m^{-1}, $T = 296$ K. 12862 reflections were independent and unique, and 7807 with $I > 3.00\sigma(I)$ ($2\theta_{max} = 55^\circ$) were used for the solution of the structure. All hydrogen atoms were calculated from ideal geometries, fixed, and included in the calculation of the structural factor. $R = 0.034$, $Rw = 0.033$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101399. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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[12] The turnover number (TON) is the number of moles of product per mole of catalyst. The turnover frequency (TOF) is the TON per hour or second.
[13] Reaction with the diastereomeric isomer (*R*),(*S*,*S*)-**2e**, either preformed or formed in situ, gave the *S* alcohol in 15 ± 2%.
[14] Various alkaline bases, such as KOH, $(CH_3)_2CHOK$, $(CH_3)_2CHONa$, $(CH_3)_3COK$, and K_2CO_3 can be used as cocatalysts. For reactions with a high S/C, acidic impurities should be carefully removed from substrates and solvents.
[15] Reaction of $[RuCl_2\{(S)\text{-TolBINAP}\}(dmf)_n]$ and (*S*,*S*)-DPEN in DMF at 50 °C (method B) gave a mixture of (*S*),(*S*,*S*)-**2d** and its *cis* isomer (^{31}P NMR, $\delta = 50.2$ (d, $J = 38.0$ Hz), 57.0 (d, $J = 38.0$ Hz)). Hydrogenation of **5g** with the *cis* isomer showed comparable reactivity to (*S*),(*S*,*S*)-**2d**, to give (*R*)-**6g** with 97% *ee*.
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Parallel Synthesis of Sialyl Lewis X Mimetics on a Solid Phase: Access to a Library of Fucopeptides**

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In response to injury or inflammation the damaged tissue releases cytokines, which trigger the expression of P-selectin followed by E-selectin on the endothelium. The initial recognition of the tetrasaccharide sialyl Lewis X (sLe^x) of the terminal unit of surface glycoconjugates by the selectins leads to leukocyte "rolling" followed by protein – protein interactions (integrins CD 11/18, ICAM-1 ligand) and extravasation of leukocytes into the endothelium.[1] Thus, blocking the sLe^x/selectin interactions at an early stage of the inflammatory cascade, especially the P-selectin/ligand interactions, has been considered to be an effective way of treating acute and perhaps chronic inflammatory diseases.[2]

Although sLe^x is being clinically evaluated for the treatment of reperfusion injury, it must be administered by injection at high doses, as it binds the selectins weakly and is orally inactive and unstable in the blood. However, the structure of sLe^x has served as a useful guide for designing simpler and better low molecular weight compounds as

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