Pure & Appl. Chem., Vol. 62, No. 6, pp. 1135–1138, 1990.
Printed in Great Britain.

New chiral ruthenium complexes for asymmetric catalytic hydrogenations

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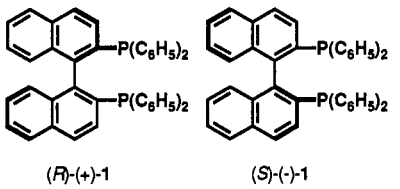
Abstract: New mononuclear complexes, $Ru(OCOR)_2(binap)$, and cationic $[RuX(binap)(arene)]Y$, have been prepared and characterized. These complexes and their derivatives are highly efficient catalysts for asymmetric hydrogenation of enamides, alkyl- and aryl-substituted acrylic acids, β,γ-unsaturated carboxylic acids, allylic and homoallylic alcohols, and a variety of functionalized ketones such as β-keto esters, α-amino ketones, *etc.*

INTRODUCTION

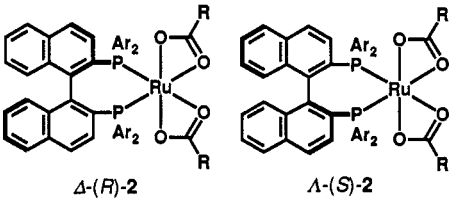
Homogeneous asymmetric hydrogenation of olefins and ketones catalyzed by chiral transition metal complexes provides a powerful means for preparing optically active organic compounds. We have developed chiral diphosphine ligand BINAP (**1**) [BINAP = bis(diphenylphosphino)-1,1'-binaphthyl] (refs. 1—4) and showed that BINAP—Rh(I) complexes are highly efficient catalysts for asymmetric hydrogenation of α-acylaminoacrylic acids (refs. 1, 2) and asymmetric conversion of prochiral allylamines into enamines (ref. 5). Recently, we have found that Ru(II) complexes of BINAP and its derivatives are highly efficient catalysts for asymmetric hydrogenation of various olefinic and ketonic substrates.

SYNTHESIS OF NEW MONONUCLEAR BINAP–Ru(II) DICARBOXYLATE COMPLEXES

Mononuclear ruthenium complexes, $Ru(OCOR)_2(binap)$ (**2**), have been prepared in 71—87% yields by the treatment of $[RuCl_2(cod)]_n$ with (*R*)- or (*S*)-BINAP (or its derivatives) and triethylamine in toluene and then with sodium carboxylate in *tert*-butyl alcohol (ref. 6). The molecular structure of Λ-(*S*)-**2b** has been determined by *X*-ray crystallography (Fig. 1), which revealed interesting structural features of these complexes (ref. 6). The central Ru(II) atom has a distorted octahedron coordination geometry involving two phosphorus atoms of BINAP and four oxygen atoms of pivalate ligands.



(*R*)-(+)-**1** [(*R*)-BINAP] (*S*)-(-)-**1** [(*S*)-BINAP]



Δ-(*R*)-**2** Λ-(*S*)-**2**

a, R = CH_3; Ar = C_6H_5
b, R = $C(CH_3)_3$; Ar = C_6H_5
c, R = CH_3, Ar = *p*-$CH_3C_6H_4$

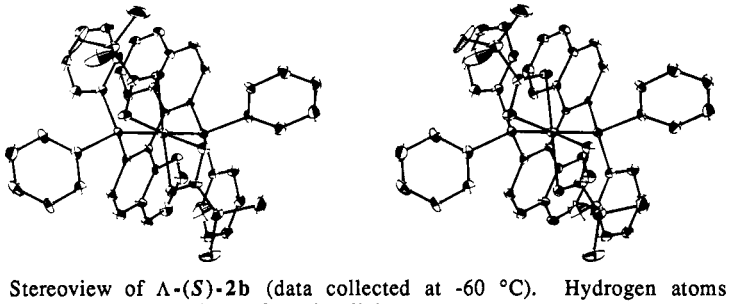
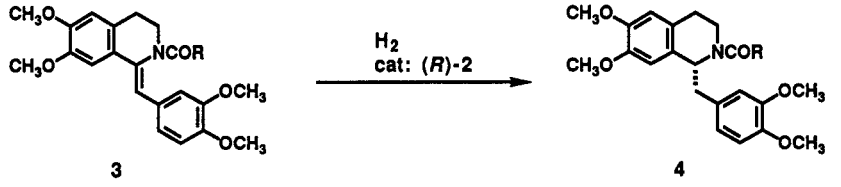


Fig. 1. Stereoview of Λ-(*S*)-**2b** (data collected at -60 °C). Hydrogen atoms of the *tert*-butyl groups were omitted for simplicity.

ASYMMETRIC HYDROGENATION BY USE OF BINAP–Ru(II) DICARBOXYLATE COMPLEXES

Asymmetric hydrogenation of *N*-acyl-1-alkylidenetetrahydroisoquinolines

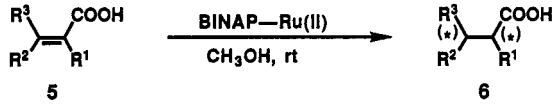
The hydrogenation of the *Z*-enamide substrates **3** in the presence of 0.5—1.0 mol% of (*R*)-**2** in a mixture of ethanol and dichloromethane (H_2 4 atm, room temp.) leads **4** having 1*R* configuration in 96—100% *ee* (ref. 7). The *E*- isomer of **3** is inert to such catalytic conditions. This method possesses wide applicability and has been successfully applied to asymmetric synthesis of morphines, benzomorphans, and morphinans (ref. 8).



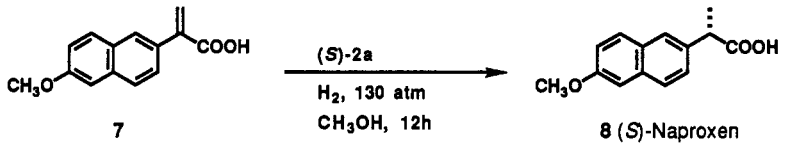
3 R = H, CH_3, C_6H_5, *etc.* **4**

Asymmetric hydrogenation of substituted acrylic acids

We have found that the ruthenium(II) complexes **2** are highly efficient catalysts for asymmetric hydrogenation of acrylic acids **5** having only carboxylic acid functionality whose hydrogenation in high enantioselectivity has been rarely attained using any of the catalyst systems designed so far (refs. 9, 10). The optimum reaction conditions are highly dependent on the structures of the olefinic substrates. The synthetic significance of this asymmetric catalysis is obvious. For instance, (*S*)-naproxen (**8**), a useful antiinflammatory agent, was prepared by hydrogenation of **7** with (*S*)-**2a** as catalyst in 92% yield and in 97% *ee*. Certain β,γ-unsaturated carboxylic acids were also hydrogenated in 81—88% *ee*.



5 **6**

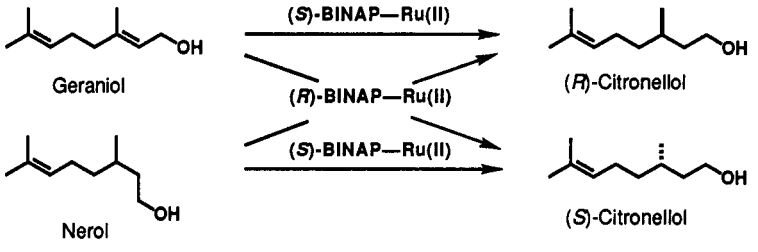


7 **8** (*S*)-Naproxen

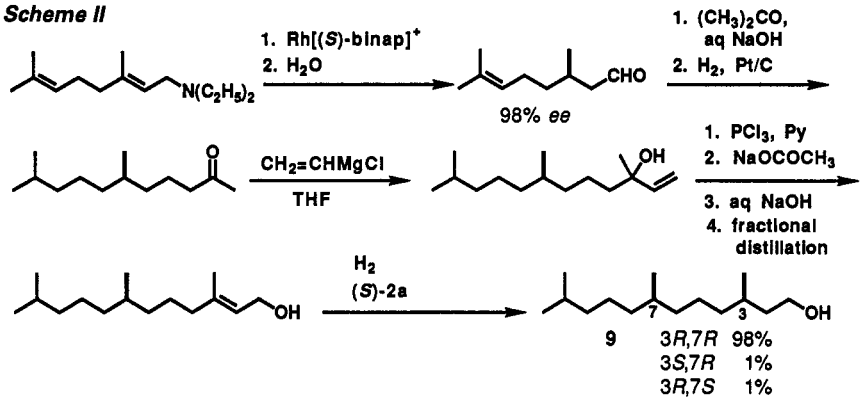
Asymmetric hydrogenation of allylic and homoallylic alcohols

The complexes **2** catalyze efficiently enantioselective hydrogenation of prochiral allylic and homoallylic alcohols (ref. 11). Geraniol and nerol are hydrogenated in methanol under H_2 (30—100 atm) at room temperature to give citronellol in nearly quantitative yield and with 96—99% *ee* (Scheme I). The present work marks the first example of the high enantioselection with simple prochiral olefinic alcohols. This homogeneous catalysis has been successfully applied to the synthesis of (3*R*,7*R*)-3,7,11-trimethyldodecanol (**9**), a versatile intermediate for synthesis of α-tocopherol (vitamin E) (Scheme II). The kinetic resolution of racemic allylic alcohols has also been carried out in high *de* (ref. 12).

Scheme I



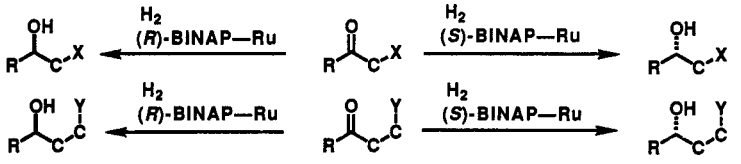
Scheme II



Asymmetric synthesis of β-functionalized ketones

β-Functionalized secondary alcohols are an extremely important class of compounds for the synthesis of physiologically active compounds. The C=O bond of α-aminoacetone derivatives can be easily reduced in high *ee* by the use of complex **2**, while reduction of other functionalized ketones are hardly attained. In the presence of the BINAP—Ru(II) complexes derived from **2** and two equiv of HX (X = Cl, Br, or I), however, a wide range of functionalized ketones are hydrogenated in high enantioselectivities (refs. 13, 14). The hydrogenation proceeds smoothly in alcohols at room temperature with initial hydrogen pressure of 40—100 atm. Various functionalities including dialkylamino, hydroxyl, alkoxyl, siloxyl, keto, alkoxycarbonyl, alkylthiocarbonyl, dialkylaminocarbonyl, carboxyl, *etc.*, can act as efficient directing functional groups (Scheme III).

Scheme III

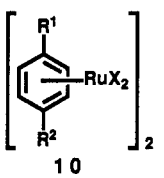


X, Y = O, N, Br, *etc*; C = sp^2 or nonstereogenic sp^3 carbon

SYNTHESIS OF NEW CATIONIC BINAP–Ru(II) COMPLEXES AND USE IN ASYMMETRIC HYDROGENATIONS

Synthesis of BINAP–Ru(II)–arene complexes

Mononuclear cationic complex **11a** was prepared in 90% yield by the treatment of $[RuCl_2(C_6H_6)]_2$ (**10a**) with one equivalent of (*S*)-BINAP in an 8:1 mixture of ethanol and benzene at 50—55 °C for 40 min. Complex **11b** was synthesized in 94% yield from $[RuBr_2(C_6H_6)]_2$ (**10b**) and (*S*)-BINAP (ref. 15). A similar reaction of $[RuI_2(C_6H_6)]_2$ (**10c**) with (*S*)-BINAP afforded rather unstable **11c**, which is prone to lose benzene ligand in solution. Chloride ion of **11a** could be replaced by BF_4^- or $B(C_6H_5)_4^-$ by the treatment with $AgBF_4$ in dichloromethane or $NaB(C_6H_5)_4$ in methanol. The *p*-cymene complexes **11d** and **11e**, prepared by the reaction of $[RuCl_2(p\text{-cymene})]_2$ (**10d**) or $[RuBr_2(p\text{-cymene})]_2$ (**10e**) with (*S*)-BINAP in 94% and 97% yields, respectively, are more stable than the corresponding benzene complexes **11a—c**, and even iodide complex **11f** could be isolated in pure form in 94% yield by the reaction of $[RuI_2(p\text{-cymene})]_2$ (**10f**) in 4:1 mixture of ethanol and dichloromethane.



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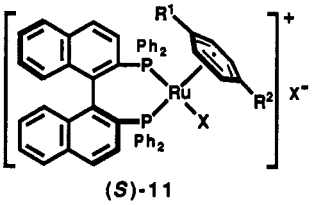
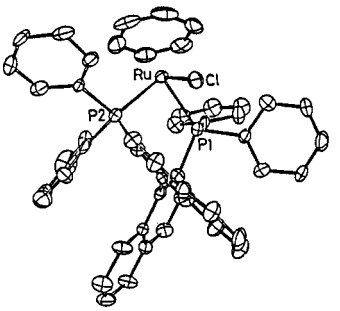


(*S*)-**11**

a: X = Cl,	$R^1 = R^2 = H$	90% yield
b: X = Br,	$R^1 = R^2 = H$	94%
c: X = I,	$R^1 = R^2 = H$	—
d: X = Cl,	$R^1 = CH_3$, $R^2 = CH(CH_3)_2$	94%
e: X = Br,	$R^1 = CH_3$, $R^2 = CH(CH_3)_2$	97%
f: X = I,	$R^1 = CH_3$, $R^2 = CH(CH_3)_2$	94%

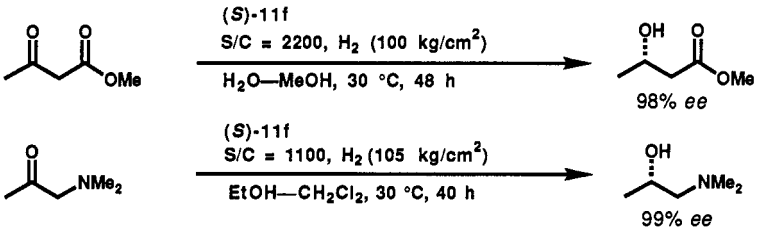
An *ORTEP* drawing of the complex [RuCl((*S*)-binap)(benzene)]BF_4 determined by *X*-ray crystallography is shown in Fig. 2. One of the characteristic features is the dihedral angle between two naphthyl planes. The value of 75.7(2)° for complex [RuCl((*S*)-binap)(benzene)]BF_4 is comparable to that of 74.4° for [Rh((*R*)-binap)(nbd)]ClO_4 and much larger than the value of 65.6° found for **2b**.



Ru—P1	2.379(3) Å
Ru—P2	2.334(3)
Ru—Cl	2.393(4)
Ru—C_6H_6	1.770
P1—Ru—P2	91.4(1)°
P1—Ru—Cl	89.1(1)
P2—Ru—Cl	84.9(1)
P1—Ru—C_6H_6	126.3
P2—Ru—C_6H_6	129.8
Cl—Ru—C_6H_6	122.5

Fig. 2. *ORTEP* view of [RuCl((*S*)-binap)(benzene)]BF_4.

Thus, the complexes **11** can be prepared in high yields and in high purity. Moreover we found that the arene ligands are easily liberated under the catalytic conditions to afford coordinatively unsaturated species which exhibit sufficient catalytic activity and selectivity in the hydrogenation of number of unsaturated substrates. Methyl 3-oxobutanoate was hydrogenated in the presence of (*S*)-**11** under hydrogen (95—100 kg/cm^2) in methanol or dichloromethane to give methyl (*S*)-3-hydroxybutyrate in 97—99% *ee*. Aminoketone was also hydrogenated by **11f** to give the corresponding alcohol in 99% *ee*. Geraniol was hydrogenated in the presence of **11f** to (*R*)-citronellol in 96% *ee*. (*E*)-2-Methyl-2-butenoic acid and 2-(6-methoxy-2-naphthyl)propenoic acid were converted to (*S*)-2-methylbutanoic acid and (*S*)-naproxen (**8**) in up to 89% and 96% *ee*, respectively.



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