

## Asymmetric hydrogenation via architectural and functional molecular engineering\*

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**Abstract:** RuCl<sub>2</sub>(phosphine)<sub>2</sub>(1,2-diamine) complexes, coupled with an alkaline base in 2-propanol, allows for preferential hydrogenation of a C=O function over coexisting conjugated or nonconjugated C=C linkages, a nitro group, halogen atoms, and various heterocycles. The functional group selectivity is based on the novel metal–ligand bifunctional mechanism. The use of appropriate chiral diphosphines and diamines results in rapid and productive asymmetric hydrogenation of a range of aromatic, hetero-aromatic, and olefinic ketones. The versatility of this method is manifested by the asymmetric synthesis of various biologically significant chiral compounds.

### INTRODUCTION

Asymmetric hydrogenation is a core technology in fine chemical synthesis, particularly for pharmaceuticals, agrochemicals, flavors, and fragrances which require a high degree of stereochemical precision [1]. Earlier we developed BINAP–Ru chemistry that allows efficient asymmetric hydrogenation of *functionalized* olefins and ketones which is now widely practiced in research and also industry [1,2]. Its efficiency comes from a chelate mechanism involving the simultaneous ligation of a heteroatom and unsaturated group to the Ru center. Such interaction facilitates hydride delivery from the metal to the unsaturated bond in the highly organized chiral metal template. Notably, methyl 3-oxobutyrate is hydrogenated even *in aqueous acetone* containing RuCl<sub>2</sub>[(*R*)-binap](dmf)<sub>*n*</sub> to give methyl (*R*)-3-hydroxybutyrate in 97% ee. Unfunctionalized ketones including acetone, the simplest ketone, are almost inert to this Ru-catalyzed hydrogenation. Thus, development of practical asymmetric hydrogenation of unfunctionalized ketones with a wide scope is highly desirable.

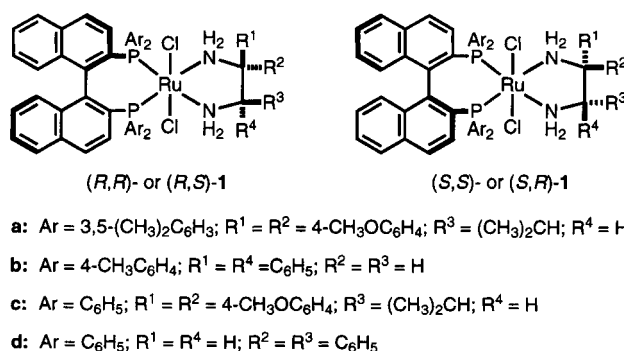
### RAPID, PRODUCTIVE, AND CHEMO- AND STEREOSELECTIVE HYDROGENATION OF KETONES

A high turnover number (TON) and turnover frequency (TOF) can be obtained only by designing suitable molecular catalysts and reaction conditions. We focused on the use of the chemical characteristics of primary amines as protic neutral ligands for obtaining high catalytic activity. This is distinct from the conventional strategy that utilizes electronic and steric properties of aprotic neutral ligands or anionic ligands. Thus, RuCl<sub>2</sub>(phosphine)<sub>2</sub>(1,2-diamine) complexes act as excellent precatalysts for homogeneous hydrogenation of simple ketones that lack any functionality capable of interacting with the Ru center [3–5]. The reaction proceeds smoothly at room temperature at 1–8 atm in 2-propanol containing an alkaline base such as KOH, KOC(CH<sub>3</sub>)<sub>3</sub>, or NaOCH(CH<sub>3</sub>)<sub>2</sub> (Ru:base < 1:2). Most notably, the Ru complexes allow for preferential saturation of a C=O function over a coexisting C=C linkage [6,7]. This

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hydrogenation tolerates many substituents including F, Cl, Br, I, CF<sub>3</sub>, OCH<sub>3</sub>, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, COOCH(CH<sub>3</sub>)<sub>2</sub>, NO<sub>2</sub>, NH<sub>2</sub>, and NRCOR [7] as well as various electron-rich and -deficient heterocycles [8]. Furthermore, stereoselectivity is readily controlled by the electronic and steric properties (bulkiness and chirality) of the ligands as well as the reaction conditions. Diastereoselectivities obtained in the hydrogenation of cyclic and acyclic ketones with the standard (C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>P/NH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub> ligand combination compare well with those of the best conventional hydride reductions [9]. The use of appropriate chiral diphosphines, particularly BINAPs, and chiral diamines results in rapid and productive asymmetric hydrogenation of a range of aromatic [5,7,10,11] and hetero-aromatic ketones [8] with a consistently high enantioselectivity. In certain cases, the TOF approaches 259 000 h<sup>-1</sup> or 72 s<sup>-1</sup> [5]. The complexes of type **1** serve as air-stable precatalysts, whereas the complexes *in situ* formed from “RuCl<sub>2</sub>(phosphine)<sub>2</sub>S<sub>2</sub>” and 1,2-diamines exhibit a very similar selectivity, albeit with a lower reactivity [10] (Scheme 1). Cyclic and acyclic α,β-unsaturated ketones can be converted to chiral allylic alcohols of high enantiomeric purity [6,7,12,13]. Hydrogenation of certain configurationally labile ketones allows for dynamic kinetic discrimination of diastereomers, epimers, and enantiomers [9]. Prior to this work, no general catalysts that effect selective ketone hydrogenation have existed.

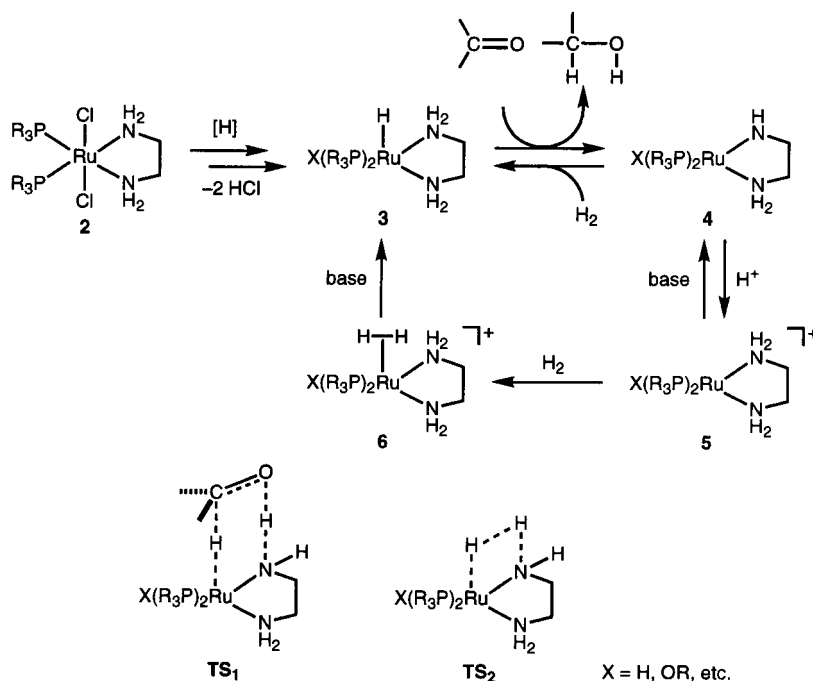


Scheme 1

## MECHANISTIC MODEL

The catalytic hydrogenation generally involves a metal hydride species, MH (M = metallic species), which is formed by base-aided heterolysis or bimetallic homolysis of H<sub>2</sub>, or a metal dihydride, MH<sub>2</sub>, which is generated by oxidative addition of H<sub>2</sub> to M. Hydrogenation of carbonyl compounds has been conceived to occur via a 2 + 2 reaction of a substrate–MH (or MH<sub>2</sub>) π complex forming metal alkoxides. However, we consider that this hydrogenation promoted by the phosphine/diamine Ru complexes occurs via a nonclassical metal–ligand bifunctional mechanism (Scheme 2) [14]. The presence of an NH<sub>2</sub> end in the diamine auxiliary is crucial for the catalytic activity. First, the mixed-ligand RuCl<sub>2</sub> complex **2** is converted to the RuHX complex **3** (X = H or OR) with the aid of 2 equiv of alkaline base and a hydride source, H<sub>2</sub> and partly 2-propanol. The catalytic cycle involves two ground-state components, **3** and its dihydro complex **4**, that are linked by transition states **TS**<sub>1</sub> and **TS**<sub>2</sub>. The NH<sub>2</sub> proton in **3** plays a key role in hydrogen delivery to ketones, while the amide nitrogen in **4** cleaves H<sub>2</sub>. In both steps, the Ru centers and the ligands directly cooperate in the bond-breaking and bond-forming processes. Although several diastereomers are possible for the octahedral reducing species **3**, the hydride and two nitrogen atoms must have a *fac* relationship. The 18-electron Ru hydride **3** reacts with a ketonic substrate via a six-membered, pericyclic transition state **TS**<sub>1</sub>, giving the 16-electron complex **4** and an alcoholic product. The hydrogenative reactivity of coordinatively saturated **3** originates from the charge-alternating H<sup>δ-</sup>–Ru<sup>δ+</sup>–N<sup>δ-</sup>–H<sup>δ+</sup> arrangement which fits well with the C<sup>δ+</sup>=O<sup>δ-</sup> dipole. Thus, the hydride on Ru possesses sufficient nucleophilicity, while the NH moiety exhibits a hydrogen-bonding ability to activate the carbonyl function. The 16-electron complex **4** actually resonates with the 18-electron complex with a Ru=N bond through electron release from the nitrogen to the electron-deficient Ru atom.

Because of the unique  $\text{Ru}^{\delta+}-\text{N}^{\delta-}$  dipolar bond, **4** splits  $\text{H}_2$  in a heterolytic fashion via **TS<sub>2</sub>** to restore the Ru hydride **3**. Alternatively, **3** may be regenerated from **4** and  $\text{H}_2$  by way of **5** and **6** by action of protic medium and base. Unlike current putative pathways, this mechanism does not require the interaction of a carbonyl moiety to the metallic center. Neither a ketone/Ru complex nor a Ru alkoxide is involved in this mechanism. The alcohol forms directly from the ketone. The outer sphere reaction is the major reason for the high rate. This nonclassical mechanistic model also explains the uncommon functional selectivity for the C=O group. When the chiral “molecular surface” of the Ru hydride recognizes the difference of ketone enantiofaces, asymmetric hydrogenation is achievable. This is different from the earlier BINAP–Ru chemistry [1] where the enantioface differentiation is made within the chiral “metal template” with the assistance of heteroatom/metal coordination. This mechanism corroborates our recent experimental and theoretical studies on a related catalytic reaction [14].



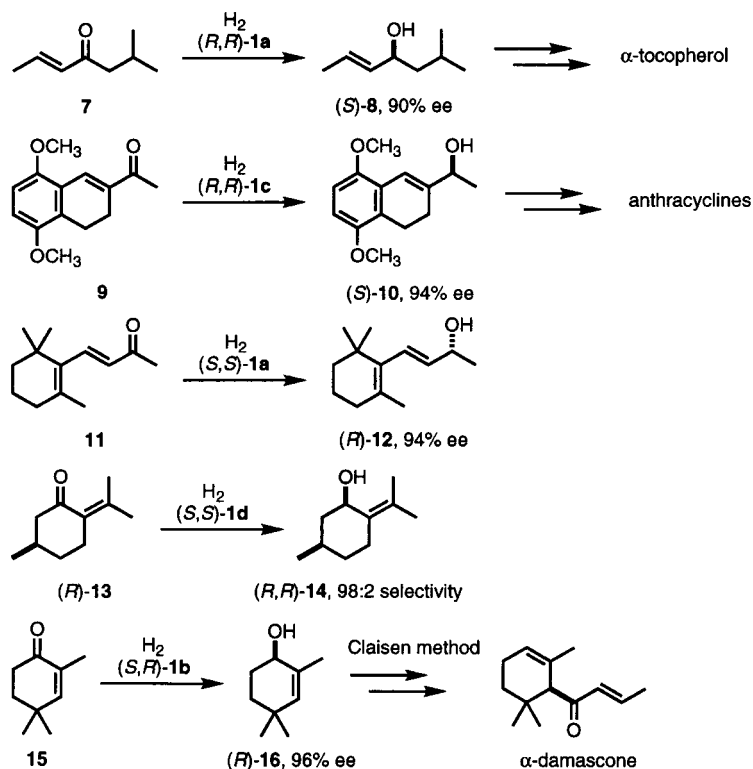
Scheme 2

## SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

This asymmetric hydrogenation method shows promise for the practical synthesis of a wide variety of chiral alcohols. The wide scope relies largely on the capability of the Ru catalysts to promote hydrogenation without heteroatom/Ru coordination [3]. Its versatility has been demonstrated by the asymmetric synthesis of various biologically significant chiral compounds.

This hydrogenation presents the first example of general and efficient asymmetric hydrogenation of  $\alpha,\beta$ -unsaturated ketones to chiral allylic alcohols of high enantiomeric purity. Reaction of the enone **7** catalyzed with the chiral Ru complex (*R,R*)-**1a** and  $\text{K}_2\text{CO}_3$  in 2-propanol [substrate to catalyst molar ratio (*S/C*) = 2000, 10 atm] gave (*S*)-**8** with 90% ee, a key building block for preparation of an  $\alpha$ -tocopherol side chain [7] (Scheme 3). Similarly, hydrogenation of **9** with (*R,R*)-**1c** and KOH allows asymmetric synthesis of (*S*)-**10**, a key intermediate for anthracycline antibiotics [6].  $\beta$ -Ionone (**11**), a dienone, is convertible to **12** in 94% ee by selective hydrogenation of the keto group [7]. In the presence of (*S,S*)-**1d**, (*R*)-pulegone (**13**), a chiral *s-cis* enone, was hydrogenated to (*R,R*)-**14** with a 98:2 diastereos-

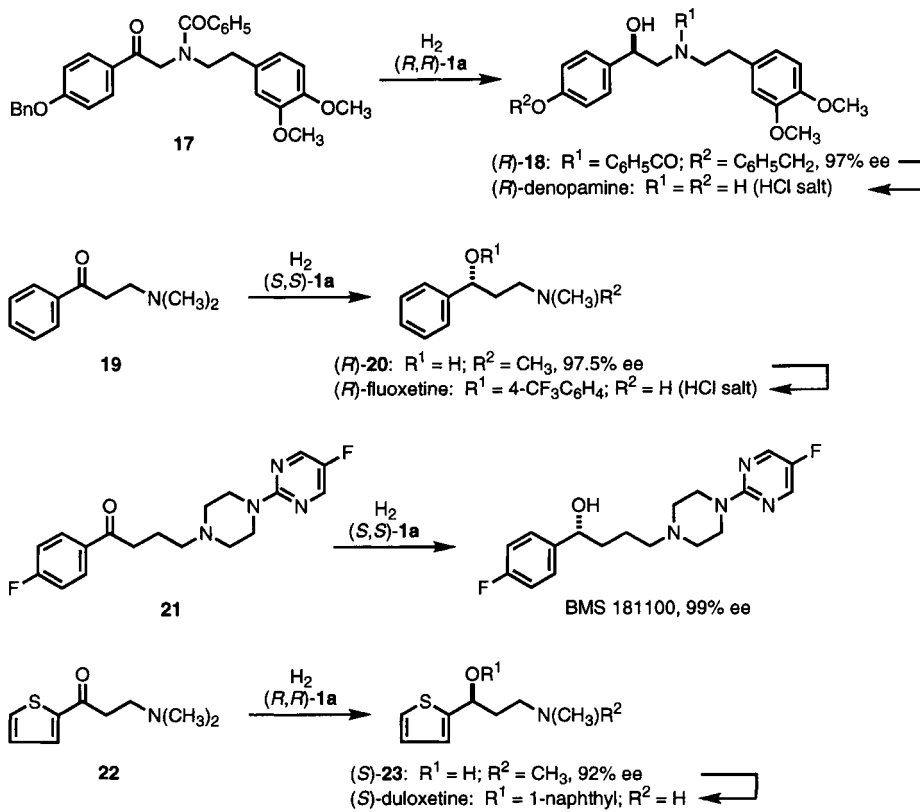
electivity [12]. When the substituted 2-cyclohexenone **15** was hydrogenated in the presence of (*S,R*)-**1b** and  $\text{KOC}(\text{CH}_3)_3$  ( $S/C = 10\,000$ , 10 atm), the  $\text{C}=\text{O}$  group was selectively hydrogenated to give (*R*)-**16** with up to 96% ee [5,12,13]. This chiral alcohol, combined with the Claisen reaction, can be converted to a series of carotenoid-derived odorants and other bioactive terpenes including  $\alpha$ -damascone [15]. The *R* and *S* alcohols with enantiomeric excess as high as 95% can be obtained even with a racemic TolBINAP– $\text{RuCl}_2$  complex in the presence of (*R,R*)- or (*S,S*)-1,2-diphenylethylenediamine ( $\text{Ru}:\text{diamine} = 1:1$ ) via asymmetric activation [13].



Scheme 3

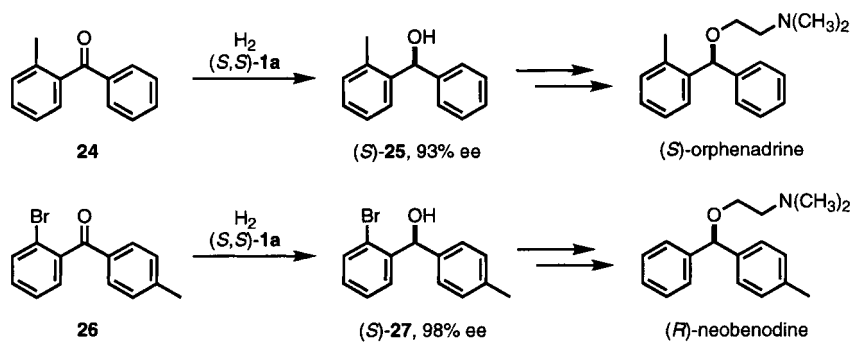
The chiral diphosphine/diamine Ru complexes **1** effect enantioselective hydrogenation of certain amino ketones via a non-chelate mechanism without nitrogen/Ru interaction [16]. The reaction accomplished at 8 atm is much faster than hydrogenation with the diamine-free BINAP–Ru catalyst that proceeds via a chelate mechanism [1]. Hydrogenation of the  $\alpha$ -benzamidoalkyl aryl ketone **17** ( $S/C = 2000$ , 8 atm) to (*R*)-**18** has been utilized for the synthesis of (*R*)-denopamine, a  $\beta_1$ -receptor agonist (Scheme 4). Extension of the substrate to  $\beta$ -amino ketone **19** ( $S/C = 10\,000$ , 8 atm), giving (*R*)-**20**, results in an easy synthesis of the antidepressant (*R*)-fluoxetine. Hydrogenation of the highly functionalized  $\gamma$ -amino ketone **21** ( $S/C = 10\,000$ , 8 atm) provides direct access to the antipsychotic BMS 181100 in 99% ee. The aromatic fluoride and 2-amino-5-fluoropyrimidine moieties were left intact. Hydrogenation of the 2-thienyl ketone **22** possessing a  $\beta$ -dimethylamino group with (*R,R*)-**1a** took place without affecting the thiophene ring to afford (*S*)-**23** in 92% ee, which serves as an intermediate for the synthesis of (*S*)-duloxetine, a potent inhibitor of serotonin and norepinephrine uptake carriers [8].

Enantioselective hydrogenation of the ortho-methylated ketone **24** catalyzed by (*S,S*)-**1a** ( $S/C = 2000$ , 8 atm), giving (*S*)-**25** in 93% ee, has been used as a key step in the synthesis of



Scheme 4

(*S*)-orphenadrine, an anticholinergic and antihistaminic agent [11] (Scheme 5). As expected, simple meta- and para-substituted benzophenones were hydrogenated with moderate enantioselectivity. However, highly selective hydrogenation of **26** to (*S*)-**27** was achievable by utilizing a bromine at the ortho position as an enantiodirective, functional substitute [11]. This allows for asymmetric synthesis of the antihistaminic (*R*)-nebenodine.



Scheme 5

## ACKNOWLEDGMENTS

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