Asymmetric Hydrogenation of Amino Ketones Using Chiral $RuCl_2$(diphophine)(1,2-diamine) Complexes

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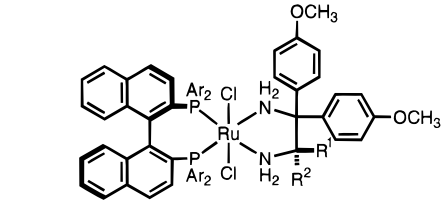
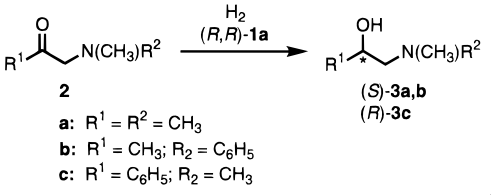
Received March 29, 2000

There are ample examples of asymmetric hydrogenation of functionalized ketones catalyzed by chiral phosphine−Ru and −Rh complexes.[1] The high efficiency of this process is considered to arise from a chelate mechanism involving the ligation of a heteroatom to the metallic center that facilitates hydride delivery from the metal to carbonyl carbon in the chiral template. Enantioselective hydrogenation of amino ketones provides a particularly important tool for synthesis of physiologically active chiral compounds. Unfortunately, most reported procedures used relatively high catalyst loading [substrate to catalyst molar ratio (S/C) = 200−1000 for Rh[2] and 1000 for Ru[3]] and hydrogen pressures as high as 20−100 (Rh) or 100 atm (Ru). A notable exception is Achiwa's MCCP−Rh catalyst hydrogenating 2-diethylaminoacetophenone with an S/C of 100 000 at 20 atm at 50 °C to give the amino alcohol in 96% ee,[4,5] while the reactions of other amino ketones show less satisfactory rates and selectivities.[2d,6] Thus development of practical asymmetric hydrogenation under a mild hydrogen pressure and with a wide scope is highly desirable. The recently devised chiral $RuCl_2$(diphophine)(1,2-diamine) complexes are marvelously effective in differentiating enantiofaces of *unfunctionalized* simple ketones,[7,8] so that various α-, β-, and γ-amino ketones can be asymmetrically hydrogenated at <8 atm and room temperature with an S/C value of 2000−10000, as described below. The diversity of substrates now relies on the capability of the Ru catalysts to effect hydrogenation without nitrogen/Ru coordination.

When a 1.0 M solution of α-dimethylaminoacetone (**2a**) in 2-propanol containing *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen] [(*R*,*R*)-**1a**][7−9] and *t*-C_4H_9OK (ketone:Ru:base molar ratio = 2000:1:16) was stirred under 8 atm of H_2 at 25 °C for 4 h, the amino alcohol (*S*)-**3a** was produced in a 92% ee and 99% yield. Pure *S* amino alcohol was obtained via its crystalline hydrochloride. The diphosphine/diamine Ru catalyst **1a** is much more reactive than the earlier devised diamine-free BINAP−Ru catalysts that require the assistance of heteroatom/Ru interaction and shows an opposite sense of asymmetric induction.[3,11] 2-Dimethylaminoacetophenone (**2c**) was hydrogenated with the same Ru catalyst to give (*R*)-**3c** in 93% ee. The α-amino group in ketonic substrates exerts a directive influence but not through the ligation to the Ru center. The relative enantio-directing effect in this hydrogenation appears to decrease in the order C_6H_5 > $(CH_3)_2NCH_2$ > CH_3. Therefore, in going from acetophenone to the aromatic α-amino ketone **2c** to nonaromatic amino ketone **2a**, the ee value varies from 99%[7b] to 93% (lower selectivity) and −92% (reversed asymmetric sense),[10] respectively.

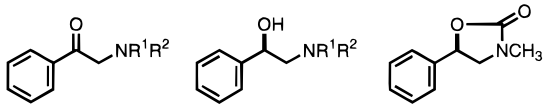


(*R*,*R*)-**1a**: Ar = 3,5-$(CH_3)_2C_6H_3$; R^1 = $(CH_3)_2CH$; R^2 = H
(*R*,*S*)-**1b**: Ar = 3,5-$(CH_3)_2C_6H_3$; R^1 = H; R^2 = $(CH_3)_2CH$



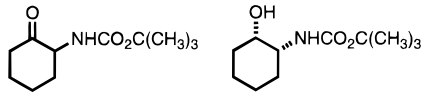
2 (*S*)-**3a,b** (*R*)-**3c**

a: R^1 = R^2 = CH_3
b: R^1 = CH_3; R_2 = C_6H_5
c: R^1 = C_6H_5; R_2 = CH_3



4 (*R*)-**5** (*R*)-**6**

a: R^1 = CH_3CO; R^2 = CH_3
b: R^1 = C_6H_5CO; R^2 = H
c: R^1 = C_6H_5CO; R^2 = CH_3
d: R^1 = CH_3OCO; R^2 = CH_3
e: R^1 = $(CH_3)_3COCO$; R^2 = CH_3



(±)-**7** (*S*,*R*)-**8**

Table 1 illustrates some examples of asymmetric hydrogenation. In the presence of (*R*,*R*)-**1a**, acetophenone derivatives **4a**−**e** possessing an acetamido, benzamido, or alkoxycarbonylamino group at the α position were hydrogenated with a high enantioselectivity, up to 99.8% ee for **5c**. This reaction can be conducted even at 1 atm of H_2. The *tert*-butoxycarbonyl group can be removed from the product under both acidic (HCl in ether) and basic (0.4 M KOH in aqueous C_2H_5OH, 80 °C) conditions. The *N*-methoxycarbonyl analogue **4d** gave the cyclization product (*R*)-**6**[12] in 99% ee, which is easily hydrolyzed to (*R*)-2-methylamino-1-phenylethanol (KOH in aqueous C_2H_5OH, 80 °C). This direction of

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(9) XylBINAP = 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl.[3b] DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine.

(10) In going from 1-phenylethanol to the amino alcohols **5**, the *R*,*S* nomenclature is reversed by the change of atom priority.

(11) High-pressure hydrogenation of **2a** with $RuCl_2$[(*R*)-xylbinap](dmf)$_n$ in methanol (S/C = 500, 50 atm, 25 °C) gave (*R*)-**3a** in 99% ee but with only 44% conversion after 48 h. No reaction took place at 8 atm.

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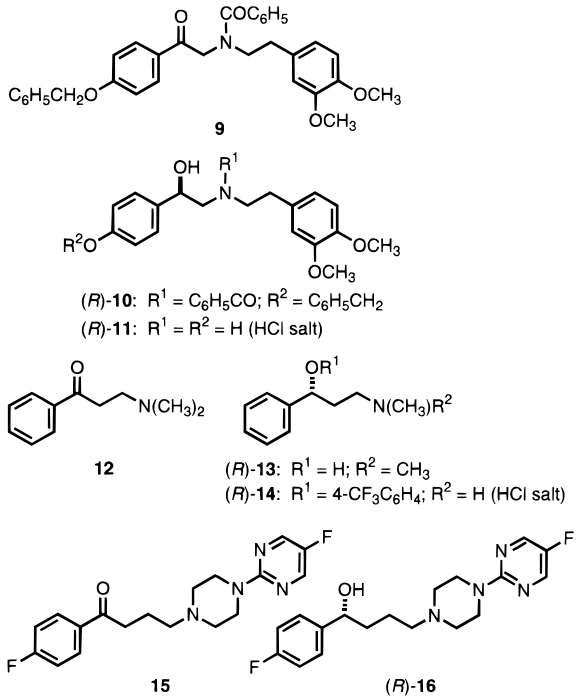
10.1021/ja001098k CCC: $19.00
Published on Web 06/24/2000

Table 1. Asymmetric Hydrogenation of Amino Ketones Catalyzed by Chiral $RuCl_2$(diphosphine)(1,2-diamine) Complexes[a]

ketone	Ru complex	S:C:base[b]	time, h	product structure[c]	product % yield[d]	product % ee[e]
2a	(*R*,*R*)-**1a**	2000:1:16	4	(*S*)-**3a**	99[f]	92[g]
2b	(*R*,*R*)-**1a**	2000:1:20	16	(*S*)-**3b**	93	81
2c	(*R*,*R*)-**1a**	2000:1:20	12	(*R*)-**3c**	90	93
4a	(*R*,*R*)-**1a**	2000:1:20	4	(*R*)-**5a**[h]	87	99
4b	(*R*,*R*)-**1a**	1000:1:20	20	(*R*)-**5b**	92	95
4c	(*R*,*R*)-**1a**	2000:1:16	8	(*R*)-**5c**	96	99.8
4c	(*R*,*R*)-**1a**	250:1:10	11[i]	(*R*)-**5c**	90	94
4d	(*R*,*R*)-**1a**	2000:1:20	14[j]	(*R*)-**6**[h]	98	99
4e	(*R*,*R*)-**1a**	2000:1:16	7	(*R*)-**5e**[h]	94	99
9	(*R*,*R*)-**1a**	2000:1:40	24	(*R*)-**10**	100	97
12	(*S*,*S*)-**1a**[k]	10000:1:10	5	(*R*)-**13**	96[f]	97.5
15	(*S*,*S*)-**1a**	10000:1:200	32	(*R*)-**16**	97	99

[a] Unless otherwise stated, reactions were conducted at 8 atm of H_2 and at 25 °C using a 0.5−1.0 M solution in 2-propanol containing **1a** and *t*-C_4H_9OK. [b] Substrate:catalyst:*t*-C_4H_9OK molar ratio. [c] Absolute configurations were determined by the sign of rotation of the amino alcohols or their derivatives. [d] Isolated yield. [e] Chiral HPLC analysis. [f] ^{1}H-NMR analysis. [g] ^{1}H-NMR analysis using a chiral shift reagent. [h] Absolute configuration was determined by chiral HPLC analysis after conversion to (*R*)-**5c**. [i] At 1 atm of H_2. [j] A 4:1 2-propanol−methanol mixture was used as solvent. [k] (*S*,*S*)-**1a** was treated with *t*-C_4H_9OK at 60 °C for 30 min before addition of **12**.



asymmetric induction is identical with that observed with the dimethylamino compound **2c**. The ketones with a normally strongly coordinative amido group behave as simple aromatic ketones.

The basic, protic reaction conditions rapidly racemize enantiomers of 2-substituted cyclohexanone **7**, allowing dynamic kinetic resolution of the racemate by hydrogenation.[8,13] Thus, the reaction of racemic **7** in a 2-propanol solution containing (*R*,*S*)-**1b** and KOH ([**7**] = 0.2 M, ketone:Ru:base = 300:1:200, 8 atm, 25 °C, 5 h) led to 1,2-cis-configurated (*S*,*R*)-**8** in a 98% yield and 82% ee accompanied by 1% of the trans isomer.[14]

Asymmetric hydrogenation of the α-benzamido ketone **9** presents a convenient way to prepare (*R*)-denopamine [(*R*)-**11**], a β_1-receptor agonist to treat congestive heart failure.[15] The reaction using a 1.0 M solution of **9** in 2-propanol containing (*R*,*R*)-**1a** and *t*-C_4H_9OK (S/C = 2000) at 8 atm produced (*R*)-**10** in 97% ee and in 100% yield. Removal of the amide protector from (*R*)-**10** (KOH in aqueous C_2H_5OH, reflux, 10 h)[16] followed by treatment with HCl, recrystallization (100% ee), and selective removal of the *O*-benzyl group by hydrogenolysis on Pd/C (aqueous 2-propanol, 25 °C, 3 h) afforded (*R*)-**11** in a 94% yield.

This method is extended to the asymmetric hydrogenation of β-amino ketones with an S/C of up to 10 000, allowing for a practical synthesis of the antidepressant (*R*)-fluoxetine [(*R*)-**14**] without the need of any chromatographic techniques.[17,18] A Ru catalyst was first prepared by mixing (*S*,*S*)-**1a** (7.3 mg) and *t*-C_4H_9-OK (60 μL of 1.0 M *t*-C_4H_9OH solution) in 2-propanol (30 mL) at 60 °C for 30 min.[19] Hydrogenation of 3-dimethylaminopropiophenone (**12**) (10.6 g) using this solution (S/C = 10 000, 8 atm, 25 °C, 5 h) gave (*R*)-**13** in 97.5% ee in a 96% yield. The NaH-aided condensation of the alcohol with 4-$ClC_6H_4CF_3$ followed by monodemethylation of the dimethylamino group with α-chloroethyl chloroformate[20] afforded (*R*)-**14**.

The functionalized γ-amino ketone **15** can be converted directly to BMS 181100 [(*R*)-**16**], a potent antipsychotic agent,[21,22] without affecting the aromatic fluoride or 2-amino-5-fluoropyrimidine moiety. Hydrogenation using a 0.5 M solution of **15** in 2-propanol containing (*S*,*S*)-**1a** and *t*-C_4H_9OK was accomplished at 8 atm (S/C = 10 000) to give (*R*)-**16** in 99% ee and 97% yield.

The sense of enantioselection observed with various α-, β-, and γ-amino and protected amino ketones supports the operation of a nonchelate hydrogenation mechanism. This asymmetric method is highly flexible with respect to the substrate's structure and functionality. This hydrogenation can be performed under low pressure (<8 atm) at room temperature with a high S/C ratio and in a reasonably high concentration. This method is applicable to the synthesis of a wide range of pharmaceutically important chiral amino alcohols and their derivatives.[23]

Acknowledgment. This work was financially supported by grants-in-aid from the Ministry of Education, Science, Sports and Culture of Japan (Nos. 07CE2004 and 11440188).

Supporting Information Available: The procedure for the hydrogenation of amino ketones, GC and HPLC behavior, and $[\alpha]_D$ values of products, as well as the procedures for synthesizing (*R*)-denopamine and (*R*)-fluoxetine (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001098K

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