Asymmetric Hydrogenation of Alkenyl, Cyclopropyl, and Aryl Ketones. $RuCl_2$(xylbinap)(1,2-diamine) as a Precatalyst Exhibiting a Wide Scope

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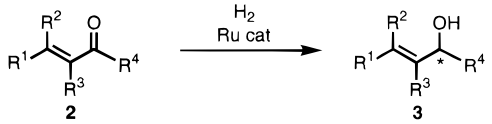
trans-$RuCl_2$(phosphine)$_2$(1,2-diamine), when coupled with a strong base in 2-propanol, acts as the most reactive catalyst for homogeneous hydrogenation of ketones.[1] Use of a chiral diphosphine and diamine ligand allows a rapid, productive, and enantioselective hydrogenation of simple ketones having no second heteroatom functionality. The asymmetric hydrogenation of certain aromatic ketones has achieved a TON (mols of product per mol of catalyst) as high as 2 400 000 and a TOF (TON sec^{-1}) of 72.[1] Furthermore, this reaction, unlike conventional hydrogenations, proceeds selectively at a C═O bond leaving coexisting C═C linkages intact.[2] However, no single asymmetric catalyst can be universal, since there exist a structurally diverse array of ketones. To secure high enantioselection, a proper catalyst as well as appropriate reaction conditions must be selected, depending on the properties of substrates. This hydrogenation system can flexibly cope with diverse situations by modifying catalyst structures and reaction parameters. Although the original BINAP/DPEN-based catalysts[3] had a limited scope for substrates displaying sufficiently high enantioselectivity,[1,2,4] we have now found that the use of XylBINAP[5] as a chiral diphosphine increases the enantioselectivity for many substrates and that the structures of chiral 1,2-diamines fine-tune the extent of the selectivity. This new system not only enhances the enantioselectivity of the known asymmetric hydrogenation but also expands the synthetic scope to a great extent.

Chiral allylic alcohols are important not only for their own sake but also in connection with the Claisen technology.[6] However, the enantioselective hydrogenation of simple α,β-unsaturated ketones (eq 1) has remained difficult[2,7−9] because of the conformational flexibility of the substrates as well as the high

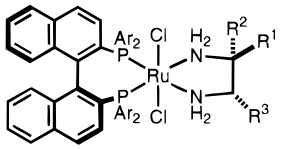


(1)

2 **3**

a: $R^1 = C_6H_5$; $R^2 = R^3 = H$; $R^4 = CH_3$
b: $R^1 = C_6H_5$; $R^2 = R^3 = H$; $R^4 = (CH_3)_2CH$
c: $R^1 = n\text{-}C_5H_{11}$; $R^2 = R^3 = H$; $R^4 = CH_3$
d: $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = (CH_3)_2CHCH_2$
e: $R^1 = R^2 = R^4 = CH_3$; $R^3 = H$
f: R^1–$R^3 = (CH_2)_4$; $R^2 = H$; $R^4 = CH_3$
g: R^1–$R^3 = (CH_2)_5$; $R^2 = H$; $R^4 = CH_3$
h: R^1–$R^3 = (CH_2)_3$; $R^2 = R^4 = CH_3$

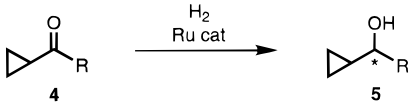
sensitivity to basic conditions. Now the combined use of *trans*-$RuCl_2$(xylbinap)(1,2-diamine) (**1**) (1,2-diamine = DAIPEN,[3] *trans*-cyclohexane-1,2-diamine, DPEN[3]) and K_2CO_3, a weak base cocatalyst in place of conventional KOH or $KOC(CH_3)_3$,[1,2,4] has solved this long-standing problem. The hydrogenation of benzalacetone (**2a**) (100 g) in 2-propanol (150 mL) containing (*S*,*S*)-**1a**



(*S*,*S*)-**1a**: Ar = 3,5-$(CH_3)_2C_6H_3$; $R^1 = R^2$ = 4-$CH_3OC_6H_4$; $R^3 = (CH_3)_2CH$
(*S*,*SS*)-**1b**: Ar = 3,5-$(CH_3)_2C_6H_3$; R^1–$R^3 = (CH_2)_4$; $R^2 = H$
(*S*,*SS*)-**1c**: Ar = 3,5-$(CH_3)_2C_6H_3$; $R^1 = R^3 = C_6H_5$; $R^2 = H$

(8.3 mg) and K_2CO_3 (9.4 g) (substrate/catalyst (S/C) = 100000, 2.7 M solution) at 80 atm (or 10 atm with S/C = 10000) and 30 °C for 43 h afforded quantitatively (*R*)-**3a** in 97% ee (cf. 65% ee (Ir)[7] and 70% ee (Ru)[2] in earlier works). No trace of C═C reduction products were detected, despite the eminent catalytic activity of diamine-free BINAP−Ru complexes for hydrogenation of the C═C unit of allylic alcohols.[10] Highly base-sensitive 3-nonen-2-one (**2c**) (0.1 M solution) was equally converted to **3c** with 97% ee. Hydrogenation of the enone **2d** catalyzed with (*R*,*R*)-**1a** gave (*S*)-**3d** with 90% ee, a key building block for preparation of a vitamin E side chain.[11] As listed in Table 1, flexible enones with various substitution patterns were hydrogenated to allylic alcohols in high enantiomeric purity.

Hydrogenation of cyclopropyl methyl ketone (**4a**) in the presence of (*S*,*S*)-**1a** and $KOC(CH_3)_3$ gave (*R*)-**5a** in 95% ee without cleavage of the three-membered ring (eq 2) (Table 1). In



(2)

4 **5**

a: $R = CH_3$ **b**: $R = C_6H_5$

comparison, cyclohexyl methyl ketone formed an *R* alcohol in

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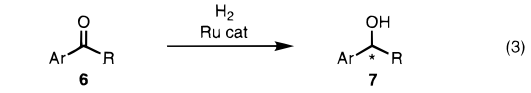
Table 1. Asymmetric Hydrogenation of Alkenyl and Cyclopropyl Ketones[a]

ketone	Ru complex	S/C[b]	conditions H_2, atm	conditions time, h	alcohol product % yield[c]	alcohol product % ee[d]	alcohol product config[e]
2a	(*S,S*)-**1a**[f]	100 000	80	43	100	97	*R*
2a	(*S,S*)-**1a**	10 000	10	15	100	96	*R*
2a	(*R,RR*)-**1b**	2 000	10	15	100	91	*S*
2b	(*S,S*)-**1a**	2 000	8	20	100	86	*R*[g]
2c[h]	(*S,S*)-**1a**	2 000	8	15	98	97	*R*[g]
2d	(*R,R*)-**1a**	2 000	10	37	100	90[i]	*S*
2e	(*S,SS*)-**1c**	10 000	8	16	100	93	*R*
2f	(*S,S*)-**1a**[j]	10 000	10	16	99	100	*R*
2g	(*S,S*)-**1a**[j]	2 000	8	7	99.9	99	*R*[g]
2h	(*S,S*)-**1a**[j]	13 000	10	15	100	99	*R*[g]
β-ionone	(*S,S*)-**1a**	10 000	8	22	99	94	*R*
4a	(*S,S*)-**1a**[j]	11 000	10	12	96	95	*R*
4b	(*S,S*)-**1a**[j]	2 000	8	14	99.7	96	*R*

[a] Reactions were conducted at 28−30 °C using a 1.0−2.7 M solution in 2-propanol containing **1** and K_2CO_3 (Ru:base = 1:8−40). [b] Substrate/catalyst molar ratio. [c] Determined by GC or ^{1}H NMR. No saturation of the olefinic function. [d] Determined by chiral GC or HPLC. [e] Determined by sign of rotation. [f] Ru:base = 1:10 000. [g] Determined by CD spectrum of its 4-bromobenzoate. [h] Reaction in a 0.1 M solution of **2c**. [i] HPLC analysis of the 1-naphthoate. [j] $KOC(CH_3)_3$ as base (Ru:base = 1:8−40).

85% ee.[12] Cyclopropyl phenyl ketone (**4b**) was hydrogenated with an equally high enantioselectivity (96% ee) and with an opposite sense of asymmetric induction.

Furthermore, a great improvement in enantioselectivity was seen in the hydrogenation of aromatic ketones. For example, when acetophenone (**6a**) was hydrogenated at 8 atm at 28 °C in 2-propanol containing (*S,S*)-**1a** and $KOC(CH_3)_3$ with S/C = 100 000, (*R*)-**7a** was produced in 99% ee in 97% yield. The ee value is far superior to the 87% obtainable with the parent BINAP- or TolBINAP-based complex.[1,3,4a] Now with the use of the XylBINAP/DAIPEN Ru complex **1a**, various 2′-, 3′-, and 4′-substituted acetophenones have been hydrogenated with consistently high stereoselectivity (eq 3).[12,13] Table 2 lists the reactions



(3)

6

a: Ar = C_6H_5; R = CH_3
b: Ar = 3-$CH_3C_6H_4$; R = CH_3
c: Ar = 2-FC_6H_4; R = CH_3
d: Ar = 4-ClC_6H_4; R = C_2H_5
e: Ar = 4-BrC_6H_4; R = CH_3
f: Ar = 4-IC_6H_4; R = CH_3

7

g: Ar = 4-$CF_3C_6H_4$; R = CH_3
h: Ar = 4-$CH_3OC_6H_4$; R = CH_3
i: Ar = 4-$[(CH_3)_2CHOCO]C_6H_4$; R = CH_3
j: Ar = 4-$NO_2C_6H_4$; R = CH_3
k: Ar = 4-$NH_2C_6H_4$; R = CH_3

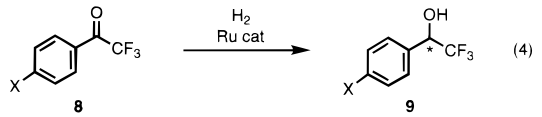
of only new and very difficult substrates which earlier were hydrogenated in <90% optical yield.[14] This hydrogenation is tolerant of many ring substituents including F, Cl, Br, I, CF_3, OCH_3, $COOCH(CH_3)_2$, NO_2, and NH_2. The electronic effects of para and meta substitutents on ee values are relatively small.

Table 2. Asymmetric Hydrogenation of Aromatic Ketones[a]

ketone	Ru complex	S/C[b]	conditions H_2, atm	conditions time, h	alcohol product % yield[c]	alcohol product % ee[d]	alcohol product config[e]
6a	(*S,S*)-**1a**	100 000[f]	8	60	97	99	*R*
6a	(*R,RR*)-**1c**	2 000	4	2	98	99	*S*
6b	(*S,S*)-**1a**	10 000	10	48	98	100	*R*
6c	(*S,S*)-**1a**	2 000	8	13	100	97	*R*
6c	(*R,RR*)-**1c**	2 000	4	3	100	96	*S*
6d	(*S,S*)-**1a**	20 000[f]	8	16	99.9	99	*R*
6e	(*S,S*)-**1a**	20 000[f]	8	5	99.9	99.6	*R*
6e	(*S,S*)-**1a**	500	1	3	99.7	99.6	*R*
6f	(*S,S*)-**1a**	2 000	8[g]	4	99.7	99	*R*[h]
6g	(*S,S*)-**1a**	10 000	10	20	100	99.6	*R*
6h	(*S,S*)-**1a**	2 000	10	1	100	100	*R*
6i	(*S,S*)-**1a**	2 000	8	3	100	99	*R*[i]
6j	(*S,S*)-**1a**	2 000	8	15	100	99.8	*R*
6k	(*S,S*)-**1a**	2 000	8	4	100	99	*R*
8a	(*S,S*)-**1a**	11 000	10	16	100	96	*S*
8b	(*S,S*)-**1a**	2 000	8	4	100	94	*S*
8c	(*S,S*)-**1a**	2 000	8	4	100	94	*S*
8d	(*S,S*)-**1a**	2 000	8	4	100	96	*S*

[a] Reactions were conducted at 26−30 °C using a 1.0−2.7 M solution in 2-propanol containing **1** and $KOC(CH_3)_3$ (Ru:base = 1:8−40). [b] Substrate/catalyst molar ratio. [c] Determined by GC or ^{1}H NMR. [d] Determined by chiral GC or HPLC. [e] Determined by sign of rotation. [f] Ru:base = 1:400. [g] Reaction in 5:1 2-propanol−toluene. [h] Converted to 1-phenylethanol. [i] Determined by conversion to ethyl 4-(1-hydroxyethyl)benzoate.

Higher analogues of acetophenone are also usable as substrates. Furthermore, 2,2,2-trifluoroacetophenone and its various derivatives **8** were hydrogenated in high yield and high enantioselectivity by the XylBINAP/DAIPEN complex **1a** (eq 4).[9,15] Some examples



(4)

8 **9**

a: X = H **b**: X = Cl **c**: X = Br **d**: X = CH_3O

are given in Table 2.

Thus, the combined use of (*S*)-XylBINAP and an (*S*)-diamine (or *R* and *R*) resulted in a superior stereoselectivity with a slight decrease in rate (1.3 times with **6a**) in comparison to analogous reactions catalyzed by the original BINAP- or TolBINAP-based complexes, although the latter systems remain better for certain substrates.[16] This practical asymmetric hydrogenation with a very wide scope will greatly facilitate the synthesis of biologically active compounds and functional materials.

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Supporting Information Available: Preparative methods and properties of **1**, procedures for asymmetric hydrogenation of ketones, GC behavior and $[\alpha]_D$ values of chiral alcohols, and examples of hydrogenation of other ketones (15 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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