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Synthetic Methods

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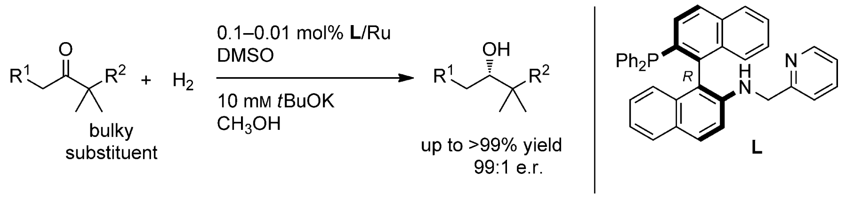
Asymmetric Hydrogenation of *tert*-Alkyl Ketones: DMSO Effect in Unification of Stereoisomeric Ruthenium Complexes



Face off: The ruthenium complexes of a new axially chiral PNN ligand (**L**) are highly efficient in the presence of dimethylsulfoxide (DMSO) for hydrogenation of both functionalized and unfunctionalized *tert*-alkyl ketones. DMSO is thought to narrow down the many possible complex stereoisomers into a single facial **L**/Ru complex, thus enhancing the reactivity, selectivity, and productivity.

Synthetic Methods

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Asymmetric Hydrogenation of *tert*-Alkyl Ketones: DMSO Effect in Unification of Stereoisomeric Ruthenium Complexes**

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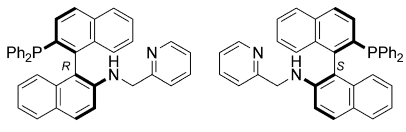
Noyori and co-workers revolutionized asymmetric hydrogenation of functionalized ketones in 1987 through the invention of binap/Ru$(OCOCH_3)_2$/HCl (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl),[1] thereby establishing the leading concept of a soft transition metal/hard Brønsted acid combined catalyst or an intermolecular donor–acceptor bifunctional catalyst (Intermol DACat).[2] Subsequent development of the intramolecular version (Intramol DACat), a binap/Ru/diamine ternary catalyst, expanded the substrate scope to aromatic and sterically bulky unfunctionalized ketones.[3] Complementary use of the two binap/Ru methods covers almost all types of ketonic substrates except for functionalized *tert*-alkyl ketones.[4] The ternary catalyst is thought to lose its Intramol DACat ability when the diamine moiety is replaced with a chelatable functionalized ketone, thereby limiting substrate generality to simple ketones.

With this drawback in mind, we designed the ligand 2′-(diphenylphosphino)-*N*-(pyridine-2-ylmethyl)-[1,1′-binaphthalen]-2-amine (binan-Py-PPh_2; **1**), in which one of the PPh_2

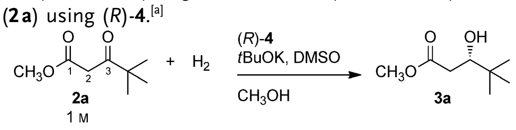


(*R*)-binan-Py-PPh_2 [(*R*)-**1**] (*S*)-binan-Py-PPh_2 [(*S*)-**1**]

groups of binap is replaced with 2-PyCH_2NH, which is an excellent group for C=O hydrogenation.[3c,5] The non-pincer-type ligand, characterized by axial chirality, flexibility, and a linearly arranged $P_{sp^3}N_{sp^2}N_{sp^3}$ system,[6] was prepared in 78% total yield by Staudinger-type reaction/hydrolysis/P=O reduction starting from a known compound, 2′-(diphenylphosphino)-[1,1′-binaphthalen]-2-yl trifluoromethanesulfonate.[7,8]

To evaluate the utility of the ruthenium complex of (*R*)-**1**, [Ru((*R*)-**1**)$(dmso)_3$]$(BF_4)_2$ [(*R*)-**4**], asymmetric hydrogenation of the C3-*t*Bu-substituted β-keto ester **2a** to **3a** was selected as the standard reaction. This reaction is catalyzed neither by the binap/Ru/HCl system nor by the binap/Ru/diamine ternary system. The results are shown in Table 1. The starting conditions of 1 M **2a**, 2 mM (*R*)-**4**, 10 mM *t*BuOK, 100 atm H_2,

Table 1: Asymmetric hydrogenation of methyl 4,4-dimethyl-3-oxopentanoate (**2a**) using (*R*)-**4**.[a]



Entry	(*R*)-**4** [mM]	*t*BuOK [mM]	DMSO [mM]	Yield [%][b]	*S*/*R*[c]
1	2	10	3[d]	22	85:15
2	2	10	100	74	99:1
3	2	10	1400[e]	> 99	99:1
4[f]	1	10	1400[e]	> 99	99:1
5	1	20	1400[e]	> 99	99:1
6[g]	1	20	1400[e]	> 99	1:99
7[h]	0.5	30	1400[e]	> 99	98:2
8[i]	–	10	1400[e]	1	98:2

[a] All of the reactions were carried out in CH_3OH at RT for 24 h under 100 atm H_2 atmosphere unless otherwise specified. [b] Determined by ^1H NMR analysis. [c] Determined by HPLC analysis. [d] Complete removal of DMSO from **4** was impossible. [e] CH_3OH/DMSO = 9:1. [f] 140 atm H_2. [g] (*S*)-**4** was used. [h] 50 °C. [i] [$\{RuCl_2(cod)\}_n$] = [(*R*)-**1**] = 2 mM. cod = cyclo-1,5-octadiene, DMSO = dimethylsulfoxide.

CH_3OH, RT (25–28 °C) for 24 h afforded **3a** with an *S*/*R* enantiomeric ratio (e.r.) of 85:15 in 22% yield (entry 1). Addition of DMSO (100 mM) to this system increased the reactivity by about threefold to give (*S*)-**3a** with 99:1 e.r. (entry 2), and a further increase in the DMSO concentration to 1400 mM led to quantitative conversion of **2a** into (*S*)-**3a** with 99:1 e.r. (entry 3). The concentration of the catalyst (*R*)-**4** could be reduced to 1 mM [substrate/catalyst (S/C) = 1000] either at 140 atm of H_2 (entry 4) or with the concentration of base doubled (20 mM *t*BuOK; entry 5). The enantiomer of the catalyst [(*S*)-**4**] gave (*R*)-**3a** (entry 6). A further decrease in (*R*)-**4** concentration to 0.5 mM (S/C = 2000) required a *t*BuOK concentration of 30 mM for completion of the reaction within 24 hours (entry 7), and with the β-keto ester substrate **2a**, an S/C ratio of 5000 was the limit.[8] The [$\{RuCl_2(cod)\}_n$]/(*R*)-**1** system was not as efficient as (*R*)-**4** even in the presence of DMSO (1400 mM; entry 8). Addition of $P(OCH_3)_3$, CO, $P(CH_3)_3$, $N(C_2H_5)_3$, or pyridine (each 100 mM) instead of DMSO stopped the reaction.[8] CH_3OH was the solvent of choice, and the reactivity in C_2H_5OH decreased at least by one order, although the high enantioselectivity was maintained. Little reaction occurred in *i*PrOH, *t*BuOH, DMSO, THF, CH_2Cl_2, or toluene,[8] and *t*BuOK was the best choice because *t*BuOLi hardly produced **3a**.[8]

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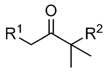
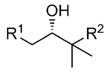
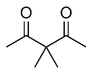
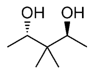
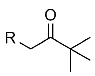
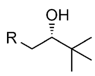
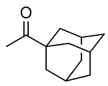
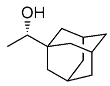
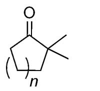
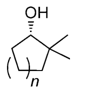
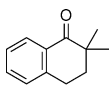
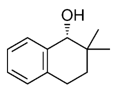
The scope and limitations of the present asymmetric hydrogenation are shown in Table 2. The alkoxycarbonyl group of **2a** can be replaced with an aminocarbonyl, dialkoxyphosphonyl or dimethylamino group (entries 1–4). Introduction of an alkoxycarbonyl or hydroxymethyl group into the *tert*-alkyl part is acceptable (entries 5 and 6). Double hydrogenation of the 1,3-diketone **2g** afforded the corresponding chiral diol **3g** with a high e.r. value by using a meso trick, in which the minor enantiomer of the first hydrogenation is scavenged to the *meso* product at the second stage (entry 7).[1b] Not only functionalized ketones but also unfunctionalized simple *tert*-alkyl ketones can be used as substrates. Pinacolone (**2h**) was quantitatively hydrogenated in the presence of 0.01 mol% of (*R*)-**4** (S/C = 10000) in the same CH_3OH/DMSO solvent system to give (*S*)-**3h** with 98:2 e.r. (entry 8). Various primary alkyl *tert*-butyl ketones (**2i–k**) can be hydrogenated to the secondary alcohols with 99:1 e.r. (entries 9–11). Adamantyl and methyl groups are also tolerated by (*R*)-**4** (entry 12). With α,α-dimethyl cyclic ketones, the enantioselectivity tends to decrease (entries 13–15), and a mesityl group also acts as a bulky substituent, thus giving (*S*)-1-mesitylethanol [(*S*)-2,4,6-$(CH_3)_3C_6H_2CH(OH)CH_3$] with 83:17 e.r. at 50 °C in 95% yield upon isolation.[8] Acetophenone and *tert*-butyl phenyl ketone were not the substrate of choice.[8]

Table 2: Asymmetric hydrogenation of *tert*-alkyl ketones catalyzed by the (*R*)-**4**.[a]

Entry	Substrate	Product	Yield [%][b] (*S*/*R*)[c]
			
1[d]	**2a**: $R^1 = COOCH_3$, $R^2 = CH_3$	**3a**	98 (99:1)
2	**2b**: $R^1 = CON(CH_3)_2$, $R^2 = CH_3$	**3b**	97 (92:8)
3	**2c**: $R^1 = PO(OCH_3)_2$, $R^2 = CH_3$	**3c**	97 (2:98)
4[e]	**2d**: $R^1 = N(CH_3)_2$, $R^2 = CH_3$	**3d**	91 (1:99)
5[f]	**2e**: $R^1 = H$, $R^2 = COOCH_3$	**3e**	97 (96:4)
6	**2f**: $R^1 = H$, $R^2 = CH_2OH$	**3f**	97 (89:11)
			
7[g]	**2g**	**3g**	95 (99:1)[h]
			
8[i]	**2h**: R = H	**3h**	99[j] (98:2)
9	**2i**: $R = CH_2CH_3$	**3i**	97 (99:1)
10	**2j**: $R = n\text{-}C_7H_{15}$	**3j**	99 (99:1)
11	**2k**: $R = CH_2C_6H_5$	**3k**	95 (99:1)
			
12[f]	**2l**	**3l**	99 (99:1)
			
13	**2m**: *n* = 1	**3m**	97 (76:24)
14	**2m**: *n* = 2	**3n**	94 (89:11)
			
15	**2o**	**3o**	97 (5:95)

[a] Conditions unless otherwise specified: [Substrate] = 1 M; [(*R*)-**4**)] = 1 mM; [*t*BuOK] = 10 mM; [DMSO] = 1400 mM; CH_3OH; 100 atm H_2; RT; 24 h. [b] Yield of isolated product. In all cases, the conversion was greater than 99%. [c] Determined by GC or HPLC analysis.[8] [d] [*t*BuOK] = 20 mM. [e] 50 °C. [f] 48 h. [g] 72 h. [h] *dl*/*meso* 91:9, determined by ^1H NMR analysis.[8] [i] [(*R*)-**4**] = 0.01 mM. [j] Determined by GC analysis using mesitylene as an internal standard.[8]

As can be seen from the stereochemical outcomes shown in Table 2, in all cases using the ligand (*R*)-**1**, a hydrogen molecule is formally delivered from the upper side, when the ketone structures are drawn with the larger *tert*-alkyl group on the right and with the smaller substituent on the left. We assume that the present hydrogenation proceeds by a Noyori mechanism (Figure 1).[3b,5a,9,10] Here, the polarized H-Ru···N-

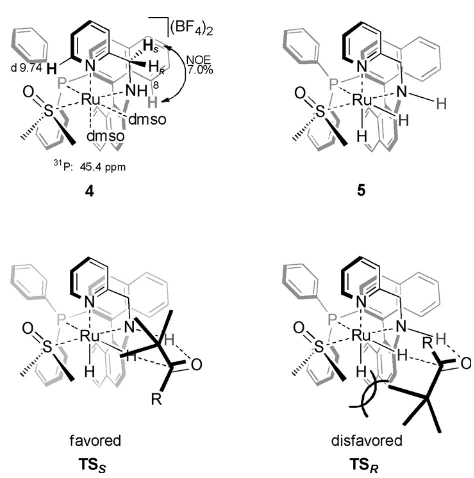


Figure 1. Proposed transition states.

H four-atom system in **5**, generated from **4** probably via a ruthenium amide species, and subsequent heterolytic cleavage of H_2 captures a C=O substrate to give $\mathbf{TS}_S$ or $\mathbf{TS}_R$. The Intramol DACat ability allows quick and simultaneous delivery of hydrogen atoms to N_{sp^3} and Ru to the C=O double bond to give the ruthenium amide species by liberation of the alcoholic product. The hydrogenolysis of the Ru−N bond regenerates **5**. The catalyst (*R*)-**4** was quantitatively generated by treatment with the structurally unambiguous *fac*-[Ru((*R*)-**1**)(C_6H_6)]$(BF_4)_2$[11] in DMSO at 50 °C for 48 hours. The ^1H NMR analysis of (*R*)-**4** in [D_6]DMSO indicates that 1) the three $P_{sp^3}N_{sp^2}N_{sp^3}$ coordinating atoms are arranged in a facial manner (7.0% NOE between C(8)H of the naphthalene ring and NCH_RH_SPy), and 2) the conformation of DMSO trans to N_{sp^3} is fixed by a hydrogen bond between S=O and C(6)H of the pyridine moiety to make O-S···Ru-sp^2N=C6 in the plane (C(6)H of (*R*)-**4**: δ 9.74 versus C(6)H of *fac*-[Ru((*R*)-**1**)(C_6H_6)]$(BF_4)_2$: δ = 9.17).[8] Treatment of (*R*)-**4** with 2 mol amounts of *t*BuOK in 5:1 DMSO/CH_3OH (10 mM) at 25 °C gives a hydride methoxide complex,[12] which may act as a repository for the reactive ruthenium amide or may react directly with H_2 to give **5**.[8] In the transition states $\mathbf{TS}_S$ and $\mathbf{TS}_R$, $\mathbf{TS}_R$ suffers from steric repulsion between the methyl group of a coordinated DMSO and the *tert*-alkyl substituent on C=O, thus leading to the *S* product (R < *t*Bu) via $\mathbf{TS}_S$. This scheme explains the general rule of enantioselection in this asymmetric catalysis (Table 2). Elucidation of the detailed mechanism is ongoing project in our group.

In summary, we have realized the highly enantioselective hydrogenation of both functionalized and unfunctionalized *tert*-alkyl ketones by use of a chiral ruthenium(II) complex of the axially chiral PNN ligand binan-Py-PPh$_2$, thereby solving the problem of the asymmetric hydrogenation of functionalized *tert*-alkyl ketones for the first time. The DMSO effect[13] is important to attain high performance. Combining the flexible $P_{sp^3}N_{sp^2}N_{sp^3}$ tridentate ligand with DMSO unifies the many possible stereoisomeric octahedral ruthenium complexes to one PNN facial and N_{sp^3}/DMSO trans species. Furthermore, a PyC(6)H···O=S(CH$_3$)$_2$ hydrogen bond fixes the conformation of DMSO on ruthenium to control the C=O enantiosurface selection of the ketone substrates. These steric, electronic, and orbital factors are synergistically effected to endow the binan-Py-PPh$_2$/Ru complex with the highly enantioselective Intramol DACat ability. This success hints at the development of even higher performance molecular catalysts.

Experimental Section

The chemicals for hydrogenation were manipulated in a glove box. The catalyst precursor [Ru((*R*)-**1**)(dmso)$_3$](BF$_4$)$_2$ (10 mM in DMSO, 6.32 mL, 63.2 μmol), CH_3OH (35.0 mL), *t*BuOK (100 mM in CH_3OH, 12.6 mL, 1.26 mmol), and methyl 4,4-dimethyl-3-oxopentanoate (**2a**) (10.0 g, 9.35 mL, 63.2 mmol) were added to an inner glass tube containing a Teflon-coated magnetic stirring bar. The tube was then placed in a 250 mL stainless high-pressure autoclave. After closing the autoclave, the hydrogenation apparatus was taken out from the glove box and connected to an H_2 cylinder. After three displacements of air in the introductory pipe by H_2 gas, a pressure of 10 atm of H_2 gas was introduced and carefully released. This fill–release cycle was replaced three times; the autoclave was then pressurized to 100 atm with H_2. The solution was vigorously stirred for 24 h at RT. After careful release of the H_2 gas, the resulting yellow-to-reddish solution was concentrated under a reduced pressure (ca. 260 mmHg) to give a crude reaction mixture containing DMSO (25.0 g). This was passed through a short silica gel column (6 cm$\phi \times$ 20 cm; 250 g; eluent: 2:1 *n*-hexane/Et$_2$O). The filtrate was concentrated to give (*S*)-methyl 3-hydroxy-4,4-dimethylpentanoate (**3a**) (9.92 g, 98% yield) with a 99:1 *S*/*R* e.r. as a colorless oil ($[\alpha]_D^{25} = -35.7$ ($c = 2.7$, C_2H_5OH)).

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[11] The structure was determined by X-ray crystallographic analysis.[8]

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