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Asymmetric Hydrogenation of *tert*-Alkyl Ketones

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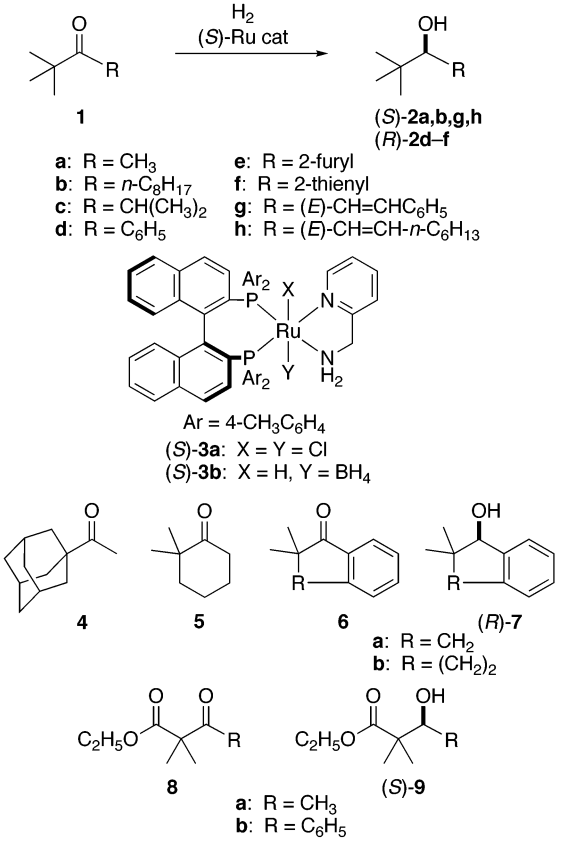
No practical methods exist for asymmetric hydrogenation of *tert*-alkyl ketones, despite tremendous efforts made to date.[1] Chiral RuX_2(binap)(1,2-diamine)[2] complexes (X = anionic ligand) with[3,4] or without[5,6] a strong base allow rapid, enantioselective hydrogenation of various simple, unfunctionalized ketones, where 2-propanol is the solvent of choice. However, for an obvious steric reason, *tert*-alkyl ketones are feebly reactive in this hydrogenation. For example, *trans*-$RuCl_2$[(*S*)-tolbinap][(*S*,*S*)-dpen][2] hydrogenated pinacolone (**1a**) in 2-propanol at 9 atm to produce (*S*)-**2a** in only 20% yield and 14% ee ([**1a**] = 1.04 M, [$KOC(CH_3)_3$] = 21.2 mM, **1a**:Ru:base = 2000:1:20, 25 °C, 24 h). With *trans*-$RuCl_2$[(*S*)-tolbinap](bipy)[2] under similar conditions, no hydrogenation took place. We here report that this problem can be overcome by replacement of the symmetrical 1,2-diamine or bipyridine ligand by an unsymmetrical NH_2/pyridine hybrid ligand, α-picolylamine (PICA), and also by the use of ethanol rather than 2-propanol as solvent.[7] The new BINAP/PICA-based Ru catalyst system allows for practical asymmetric hydrogenation of a wide range of *tert*-alkyl ketones.

$RuCl_2$[(*S*)-tolbinap](pica) [(*S*)-**3a**] was conveniently synthesized by treatment of oligomeric $RuCl_2$[(*S*)-tolbinap](dmf)$_n$[8] with 1.2 equiv of commercial PICA in CH_2Cl_2 at 25 °C for 2 h (see Supporting Information). Five diastereomers are possible for this pale orange octahedral Ru complex, and in fact, the $^{31}P\{^1H\}$ NMR spectrum (benzene-d_6, 22 °C) showed two major AB quartets at 42.2 and 45.9 ppm with J_{P-P} = 35.6 Hz (30%) and 44.7 and 48.2 ppm with J_{P-P} = 36.0 Hz (20%) together with three minor quartets (total 50%). The content of the most dominant diastereomer was increased to >90% by heating at 80 °C for 30 min in toluene. However, we used the diastereomeric mixture as a precatalyst since the variable diastereomeric ratio did not affect the catalytic efficiency and enantioselectivity. Reaction of (*S*)-**3a** with 16 equiv of $NaBH_4$ in a 1:1 ethanol/benzene mixture afforded RuH(η^1-BH_4)-[(*S*)-tolbinap](pica) [(*S*)-**3b**] as a pale yellow powder showing $^{31}P\{^1H\}$ NMR signals (benzene-d_6, 22 °C) at 71.6 and 74.2 ppm with J_{P-P} = 41.4 Hz (AB) and a hydride resonance at δ −13.82 (dd, J_{H-P} = 23.9 Hz).[9]

The chiral Ru complex **3** effects asymmetric hydrogenation of various *tert*-butyl ketones with a high substrate/catalyst (S/C) ratio under mild conditions. Thus, when an ethanol solution of **1a** (the simplest aliphatic *tert*-butyl ketone) (21.1 g, 5 M) containing (*S*)-**3a** (2.0 mg, S/C = 100 000) and $KOC(CH_3)_3$ (83.0 mg in HOC-$(CH_3)_3$, 20 mM) was stirred under 20 atm of H_2 in a 100 mL glass autoclave with a plastic cover at 25 °C for 24 h, (*S*)-**2a** was obtained quantitatively in 98% ee. The reaction proceeded even under atmospheric pressure of hydrogen with the same enantioselectivity. Phosphazene bases (metal-free, strong organic bases)[6] could also be used in place of $KOC(CH_3)_3$ (Table 1). Hydrogenation of **1a** in ethanol with the H/BH_4 complex (*S*)-**3b** (S/C = 2000, 4 atm, 25 °C, 5 h) proceeded without added base to afford (*S*)-**2a** in 97% ee and 100% yield. Some other examples are given in Table 1. Reaction of an analogous ketone **1b** with (*R*)-**3a** gave (*R*)-**2b** in 97% ee. Hydrogenation of pivalophenone (**1d**) (the simplest aromatic *tert*-butyl ketone) catalyzed by (*S*)-**3a** in ethanol (ketone: **3**:base = 2000:1:18, [$KOC(CH_3)_3$] = 20 mM, 5 atm, 25 °C, 12 h) gave (*R*)-**2d** in 100% yield and 97% ee. This method can be used for reaction of heteroaromatic *tert*-butyl ketones. Hydrogenation of **1e** and **1f** with (*S*)-**3a** gave (*R*)-**2e** and (*R*)-**2f** in high enantiomeric excess, where the furan or thiophene ring remained unaffected.[4d] This hydrogenation is carbonyl-selective. Reaction of the olefinic *tert*-butyl ketone **1g** with (*S*)-**3a** quantitatively afforded the allylic alcohol (*S*)-**2g** in 97% ee without saturation of the olefinic linkage.[3−5,10] The aliphatic enone **1h** was converted to (*R*)-**2h** in 98% ee by using (*R*)-**3a**. The alkenyl groups behaved similarly to aromatic and heteroaromatic rings in enantioface selection.



In the presence of (*S*)- or (*R*)-**3a** and a base in ethanol, 1-adamantyl ketone **4**, cyclic *tert*-alkyl ketone **5**, and aromatic cyclic

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Table 1. Asymmetric Hydrogenation of *tert*-Alkyl Ketones[a]

ketone	catalyst	S/C[b]	H_2,atm	time, h	Alcohol % yield[c]	Alcohol % ee[d]	Alcohol config.[e]
1a	(*S*)-**3a**	2000	5	5	100	97	*S*
1a	(*R*)-**3a**	2000	1	9	100	98	*R*
1a	(*S*)-**3a**	2000[f]	4	5	100	97	*S*
1a[g]	(*S*)-**3a**	100000	20	24	100	98	*S*
1a	(*S*)-**3b**	2000[h]	4	5	100	97	*S*
1b	(*R*)-**3a**	2300	5	5	100	97	R[i]
1c	(*S*)-**3a**	2020	8	24	<5	nd[j]	nd[j]
1d	(*S*)-**3a**	2000	5	12	100	97	*R*
1e[k]	(*S*)-**3a**	2400	8	5	99	97	*R*[i]
1f	(*S*)-**3a**	2100	8	5	100	98	*R*[i]
1g	(*S*)-**3a**	2050	5	5	100	97	S[i]
1h[l]	(*R*)-**3a**	2040	8	5	99.6[l]	98[m]	*R*[i,m]
4	(*S*)-**3a**	2000	5	5	100	98	*S*[n]
5[o]	(*S*)-**3a**	2250	8	5	95	84	*S*[p]
6a	(*R*)-**3a**	2050	8	20	99.6	90	*S*
6b	(*R*)-**3a**	2400	8	5	100	98	*S*
8a	(*S*)-**3a**	2000	5	5	100	97	*S*
8b	(*S*)-**3a**	2000	5	5	100	82	*S*

[a] Unless otherwise stated, reactions were conducted at 25−27 °C using a 0.26−0.93 M ketone solution in ethanol containing **3** (0.10−0.53 mM) and $KOC(CH_3)_3$ (20−28 mM). [b] Substrate/catalyst molar ratio. [c] GC or ^1H NMR analysis. [d] Chiral GC or HPLC analysis. [e] Determined by the sign of rotation. [f] A phosphazene base, 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)phosphoranylidenamino]-2′,4′-catenadi(phosphazene), was used in place of $KOC(CH_3)_3$. [g] Reaction using 21.1 g of **1a** (5 M) with **3a** (0.05 mM) in 15 mL of ethanol. [h] No additional base. [i] See Supporting Information. [j] Not determined. [k] Purity was 93%. [l] A 5:1 *E*/*Z* mixture. [m] Data of the *E* allylic alcohol. [n] (*S*)-1-(1-Adamantyl)ethanol. [o] Purity was 92%. [p] (*S*)-2,2-Dimethylcyclohexanol.

tert-alkyl ketones **6** were hydrogenated to the corresponding chiral alcohols in good to excellent enantiomeric excess. The reaction exhibited a consistent and predictable asymmetric induction. The chiral alcohol obtained from **7a** is an intermediate for the synthesis of a herbicide.[11] Highly hindered β-keto esters **8** behave as simple *tert*-alkyl ketones. The BINAP/PICA−Ru complex is much more reactive than the PICA-free BINAP−Ru complex, which hydrogenates β-keto esters via a chelate mechanism.[12,13] Thus, reaction of the methyl and phenyl ketones **8a** and **8b** catalyzed by (*S*)-**3a** gave the expected chiral hydroxy esters (*S*)-**9a** and (*S*)-**9b** in 97 and 82% ee, respectively.

Under optimum conditions, aliphatic, olefinic, and aromatic *tert*-alkyl ketones are hydrogenated with equally high enantioselectivity and the same mode of face selection.[14] Thus, the asymmetric bias results primarily from the difference in steric bulk of the two substituents flanking the carbonyl function. Reaction parameters, together with catalyst structures, must be carefully selected. Alcoholic solvents influence both catalytic activity and enantioselectivity.[3,4,6] In fact, ethanol was found to be the best solvent for this asymmetric hydrogenation. Hydrogenation of **1a** in conventional 2-propanol containing (*S*)-**3a** (S/C = 2000, $[KOC(CH_3)_3]$ = 20 mM, 9 atm, 12 h) gave (*S*)-**2a** quantitatively but in only 36% ee (cf. 98% ee in ethanol). Use of *tert*-butyl alcohol even reversed the asymmetric sense to give (*R*)-**2a** in 68% ee and 100% yield. Although no hydrogenation took place in pure methanol, the reaction in a methanol (>30%)/*tert*-butyl alcohol (>3:7) mixture gave (*S*)-**2a** quantitatively in 97−99% ee. Reaction of **1a** with (*S*)-**3a** in (*R*)-1-phenylethanol (S/C = 2000, $[KOC(CH_3)_3]$ = 22 mM, 4 atm, 6 h) formed (*S*)-**2a** in 76% ee, but, notably, the hydrogenation in the *S* alcohol was 1.5 times slower and less stereoselective to give (*S*)-**2a** in 39% ee.[15] The stereochemical outcome is interpreted in terms of a metal−ligand bifunctional mechanism[6] involving an 18e *cis*-RuH(OR)[(*S*)-tolbinap](pica) complex(es) as dominant reactive species. The higher activity in comparison to the conventional BINAP/1,2-diamine complexes is ascribed to the functional/structural characteristics of PICA. The bidentate ligand has a functional NH_2 group[6] and an unfunctional flat, small-sized pyridine ring that mitigates the nonbonded repulsion with the *tert*-butyl group of an approaching ketone. Notably, the BINAP/PICA−Ru catalyst is suitable only for reaction of *tert*-alkyl ketones. Hydrogenation of acetophenone with (*S*)-**3a** gave (*R*)-1-phenylethanol in 100% yield, but with only 54% ee (ethanol) or 14% ee (2-propanol).

In summary, the newly devised BINAP/PICA−Ru complex **3**, with or without a strong base, depending on the anionic ligand, efficiently catalyzes asymmetric hydrogenation of sterically congested *tert*-alkyl ketones to chiral *tert*-alkyl carbinols in high enantiomeric purity. Aliphatic, aromatic, heteroaromatic, and olefinic ketones, as well as certain cyclic ketones, can be employed. The reaction proceeded smoothly under mild conditions (1−20 atm, room temperature) with an S/C ratio as high as 100 000.

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Supporting Information Available: Preparative methods and properties of chiral Ru complexes **3**, synthesis and procedures for asymmetric hydrogenation of the *tert*-alkyl ketones, NMR, GC, and HPLC behavior of products, together with $[\alpha]_D$ values and absolute-configuration determination (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. TolBINAP = 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl. DPEN = 1,2-diphenylethylenediamine. Bipy = 2,2′-bipyridine.

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(13) Hydrogenation of methyl 2,2-dimethyl-3-oxobutanoate in methanol with $RuBr_2$[(*S*)-binap] under hard conditions (S/C = 200, 100 atm, 50 °C, 68 h) gave the *S* hydroxy ester in 96% ee and 100% yield. See: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 2.

(14) Due to the group priority in nomenclature, (*S*)-**2a**,**b**,**g**,**h** and (*R*)-**2d**−**f** have the same β configuration.

(15) In hydrogenation of acetophenone with *trans*-RuH(η^1-BH_4)[(*R*)-tolbinap]-[(*R*)-dpen], the nature of alcoholic solvents affects the reaction rate but not the extent of enantioselection.[6] *trans*-RuH_2(tolbinap)(dpen) among other coexisting RuH species has been considered to be the reacting species. Enantioselectivity in hydrogenation of **1a** and **1d** catalyzed by *trans*-$RuCl_2$[(*S*)-tolbinap][(*S*,*S*)-dpen] was considerably enhanced by use of ethanol in place of 2-propanol [(*S*)-**2a** in 14−82% ee and (*R*)-**2d** in 61−97% ee, respectively], albeit with moderate rate enhancement.

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