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General Asymmetric Hydrogenation of α-Branched Aromatic Ketones Catalyzed by TolBINAP/DMAPEN−Ruthenium(II) Complex

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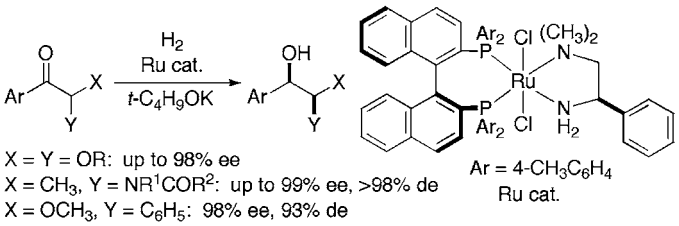
ABSTRACT



A catalyst system consisting of $RuCl_2$[(*S*)-tolbinap][(*R*)-dmapen] and *t*-C_4H_9OK in 2-propanol effects asymmetric hydrogenation of arylglyoxal dialkylacetals to give the α-hydroxy acetals in up to 98% ee. Hydrogenation of racemic α-amidopropiophenones under dynamic kinetic resolution predominantly gives the syn alcohols in up to 99% ee and >98% de, while the reaction of racemic bezoin methyl ether gives the anti alcohols in excellent stereoselectivity.

Asymmetric hydrogenation of functionalized ketones is a key technology providing synthetically useful chiral functionalized alcohols.[1] A variety of Ru and Rh catalysts modified by chiral phosphine ligands have been synthesized for this important transformation.[1,2] However, to our knowledge, no efficient homogeneous catalyst exists for enantioselective hydrogenation of arylglyoxal dialkylacetals to the chiral α-hydroxy acetals, which can be converted to the chiral α-hydroxy carbonyl compounds, 1,2-diols, β-amino alcohols, and aldol derivatives.[3,4] Heterogeneous reaction of phenylglyoxal diethylacetal (**2a**) and the dimethylacetal in the presence of Pt/Al_2O_3 catalysts modified by cinchonidine derivatives is the only example, although the optical yield was less than 90%.[3,5] We also tried asymmetric hydrogenation of **2a** with $RuCl_2$[(*R*)-xylbinap][(*R*)-daipen][6] and *t*-C_4H_9-

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(6) TolBINAP = 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl. XylBINAP = 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl. DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine.

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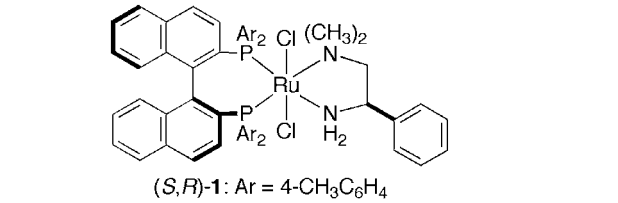
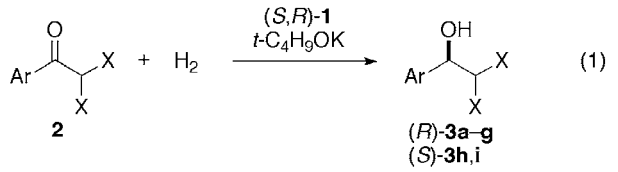
OK in 2-propanol, which shows excellent activity and enantioselectivity for hydrogenation of a variety of simple aromatic, heteroaromatic, and α,β-unsaturated ketones.[7,8] To our regret, the (*R*)-α-hydroxy acetal [(*R*)-**3a**] was obtained in only 37% enantiomeric excess (ee).[8] We here report that this difficult problem is solved by the use of 2-dimethylamino-1-phenylethylamine (DMAPEN), an *N*,*N*-dimethylethylenediamine ligand, instead of conventional ethylenediamine ligands with no *N*-substituent.[9,10] Thus, the newly devised $RuCl_2$(tolbinap)(dmapen)[6]−*t*-C_4H_9OK catalyst system promotes hydrogenation of α-keto acetals with a substrate-to-catalyst (S/C) molar ratio as high as 5000 to give the chiral α-hydroxy acetals in up to 98% ee. Moreover, hydrogenation of racemic α-heterosubstituted ketones affords the β-substituted alcohols with excellent enantio- and diastereoselectivity via dynamic kinetic resolution.[8,11]

(*R*)-DMAPEN was easily synthesized from commercially available (*R*)-2-phenylglycinol according to the method described in the literature.[12] $RuCl_2$[(*S*)-tolbinap][(*R*)-dmapen] [(*S*,*R*)-**1**] (Scheme 1) was prepared in 86% isolated yield by

Scheme 1





a: Ar = C_6H_5, X = OC_2H_5
b: Ar = C_6H_5, X–X = $O(CH_2)_3O$
c: Ar = 2-$CH_3C_6H_4$, X = OC_2H_5
d: Ar = 4-$CH_3C_6H_4$, X = OC_2H_5
e: Ar = 4-$CH_3OC_6H_4$, X = OC_2H_5
f: Ar = 4-ClC_6H_4, X = OC_2H_5
g: Ar = 2-naphthyl, X = OC_2H_5
h: Ar = C_6H_5, X = CH_3
i: Ar = 4-FC_6H_5, X–X = $(CH_2)_2NBoc(CH_2)_2$

treatment of $RuCl_2$[(*S*)-tolbinap](dmf)$_n$ (oligomeric form)[13] and 1.0 equiv of (*R*)-DMAPEN in DMF at 25 °C for 3 h (see the Supporting Information). The $^{31}P\{^1H\}$ NMR spectrum ($CDCl_3$ at 25 °C) showed a set of doublets at 36.6 and 51.4 ppm with J_{P-P} = 38.5 Hz, suggesting that this complex exists as a single diastereomer in solution phase.[14]

The chiral Ru catalyst **1** efficiently promotes asymmetric hydrogenation of a series of arylglyoxal dialkyl acetals **2a**−**g** with a high S/C ratio (Scheme 1, eq 1). When a 0.7 M solution of **2a** (580 mg) in 2-propanol containing the (*S*)-TolBINAP/(*R*)-DMAPEN−Ru complex [(*S*,*R*)-**1**] (1.4 mg, S/C = 2000) and *t*-C_4H_9OK (13.0 mg) was stirred under 8 atm of H_2 in a glass autoclave at 30 °C for 18 h, the α-hydroxy acetal (*R*)-**3a** was produced in 96% ee quantitatively (Table 1). The reaction with an S/C of 5000 smoothly

Table 1. Asymmetric Hydrogenation of Arylglyoxal Dialkyl Acetals, Aryl *sec*-Alkyl Ketones, and Racemic α-Heterosubstituted Ketones[a]

				alcohol			
ketone no.	S/C[b]	H_2 (atm)	time (h)	yield[c] (%)	dr[d,e]	ee[e] (%)	config[f]
2a	2000	8	18	95		96	*R*
2a[g]	5000	50	22	98		96	*R*
2a	500	1.5	9	94		96	*R*
2b	1000	8	24	97		93	*R*
2c	1000	8	18	96		92	*R*[h]
2d	1000	8	4	95		96	*R*[h]
2e	1000	8	5	96		98	*R*[h]
2f	1000	8	4	95		92	*R*[h]
2g	1000	8	24	91		97	*R*[h]
2h	2000	8	10	94		95	*S*
2i	400	8	7	98		>99	*S*[h]
4a	500	8	9	90	>99:1	98[i]	1*R*,2*R*[h]
4b	1000	8	64	92	96:4	99[i]	1*R*,2*R*[h]
6	1000	8	18	95	3:97	98[j]	1*R*,2*S*[h]

[a] Unless otherwise stated, reactions were conducted at 25−30 °C using a 0.3−1.4 M ketone solution in 2-propanol containing (*S*,*R*)-**1** (0.25−0.73 mM) and *t*-C_4H_9OK (20 mM). Conversion was >95% in all cases. [b] Substrate/catalyst molar ratio. [c] Isolated yield. [d] Syn/anti diastereomeric ratio. [e] Chiral HPLC analysis. [f] Determined by the sign of rotation. [g] Reaction using 2.21 g of **2a** (1.5 M). [h] See the Supporting Information. [i] Data for the syn diastereomer. [j] Data for the anti diastereomer.

proceeded under 50 atm of H_2. Complete conversion was attained even under 1.5 atm of H_2 at an S/C of 500. The hydrogen pressure did not affect the enantioselectivity. The substrate with a cyclic acetal **2b** was also hydrogenated in high optical yield. A high level of enantioselectivity was achieved in the reaction of 2′- and 4′-CH_3-substituted ketones, **2c** and **2d**. Reaction of ketone **2e** with an electron-donating

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(14) The configuration of (*S*,*R*)-**1** is not determined yet. However, we assume that it has a *trans*-dichloro geometry according to the structures of eleven known *trans*-$RuCl_2$(diphosphine)(1,2-diamine) complexes. See: Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703−1707, and reference 7.

CH_3O group at the 4′ position achieved excellent enantioselectivity of 98%, while substitution of an electron-attracting Cl function (**2f**) slightly reduced the stereoselectivity. The reaction of 2-naphthyl ketone **2g** afforded (*R*)-**3g** in 97% ee with the same sense of enantioselection. Interestingly, the Ru complex (*S*,*R*)-**1** also effects asymmetric hydrogenation of unfunctionalized aryl *sec*-alkyl ketones. Thus, isobutyrophenone (**2h**) was smoothly converted to (*S*)-**3h** in 95% ee. The degree and sense of enantioselection were the same as those in the reaction of α-keto acetals **2a**−**g** with the same *S*,*R* catalyst,[15] indicating that the TolBINAP/DMAPEN−Ru catalyst recognizes dialkoxymethyl moiety as a just *sec*-alkyl group. This characteristic markedly differs from that of the former (*S*)-XylBINAP/(*S*)-DAIPEN−Ru catalyst, with which hydrogenation of **2a** and **2h** gave (*S*)-**3a** and (*R*)-**3h** in 37% ee and 99% ee, respectively.[7,8] Hydrogenation of **2i** in the presence of (*S*,*R*)-**1** afforded (*S*)-**3i** in >99% ee, which is an intermediate for the synthesis of a non-narcotic analgesic and muscle relaxant agent.[16]

A practical procedure for enantio- and diastereoselective synthesis of 1-aryl-2-aminoalkanols[17] is highly desired because of their pharmacological[18] and synthetic[19] utility. Asymmetric hydrogenation of the corresponding racemic α-amino ketones via dynamic kinetic resolution with in-situ mutation of the α stereogenic center is a straightforward method, yielding a single stereoisomer of products.[1,8,11] Despite the synthetic utility of this reaction, no efficient catalyst has been reported. The TolBINAP/DMAPEN−Ru catalyst showed excellent performance on both enantio- and diastereoselectivity in hydrogenation of racemic α-amido ketones (±)-**4** (Scheme 2, eq 2). When racemic 2-(benzoylmethylamino)propiophenone [(±)-**4a**] was hydrogenated with (*S*,*R*)-**1** in a basic 2-propanol ([**4a**] = 0.4 M, [*t*-C_4H_9OK] = 33 mM, ketone/Ru/base = 500:1:45, 30 °C, 8 atm H_2, 9 h), the (1*R*,2*R*)-amido alcohol, (1*R*,2*R*)-**5a**, was produced in 98% ee with a perfect syn-selectivity (Table 1). The excellent diastereoselectivity clearly shows that the TolBINAP/DMAPEN−Ru catalyst acts as a bulky metalhydride according to the Felkin−Anh model.[20] Removal of the amide protector from (1*R*,2*R*)-**5a** (NaOH, C_2H_5OH aq, reflux, 12 h) gave (−)-pseudoephedrine, a widely used nasal decongestant[18] as well as a useful chiral auxiliary in synthetic organic chemistry.[19] In the same manner, racemic 2-(pivaloylamino)propiophenone [(±)-**4b**] was converted to (1*R*,2*R*)-**5b** in 99% ee (syn/anti = 96.4:3.6) by hydrogenation with (*S*,*R*)-**1**. It is noteworthy that hydrogenation of racemic bezoin methyl ether [(±)-**6**] with (*S*,*R*)-**1** selectively afforded the anti (anti:syn = 96.6:3.4) alcohol (1*R*,2*S*)-**7** in 98% ee (Scheme 2, eq 3, and Table 1). This is the first example of anti-selective asymmetric hydrogenation of α-alkoxy ketones under dynamic kinetic resolution.[21] The exclusive anti-selectivity suggests that the TolBINAP/DMAPEN−Ru catalyst differentiates between the α-CH_3O group and the α-phenyl ring purely by the size and not by the electronegativity.[20,22]

In conclusion, the newly devised TolBINAP/DMAPEN−Ru complex **1** in a base containing 2-propanol efficiently catalyzes asymmetric hydrogenation of arylglyoxal dialkylacetals to chiral α-hydroxy acetals in excellent enantiomeric excess. Simple aryl *sec*-alkyl ketones are also hydrogenated with excellent enantioselectivity. Hydrogenation of racemic α-amidopropiophenones via dynamic kinetic resolution selectively gives the *syn*-α-amido alcohols in excellent ee by precise control of two contiguous stereocenters. High *anti*- and enantioselectivity are also achieved in the hydrogenation of racemic bezoin methyl ether. Thus, the TolBINAP/DMAPEN−Ru catalyst provides the most general procedure for asymmetric hydrogenation of aromatic ketones with α-branched carbon moieties, that is, CHR_2, $CH(OR)_2$, $CH(R^1)NR^2COR^3$, and $CH(R^1)OR^2$.

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Supporting Information Available: Preparative methods and properties of chiral Ru complex **1**, synthesis and procedures for asymmetric hydrogenation of α-branched ketones, NMR, GC, and HPLC behavior of products, together with $[\alpha]_D$ values and the absolute configuration determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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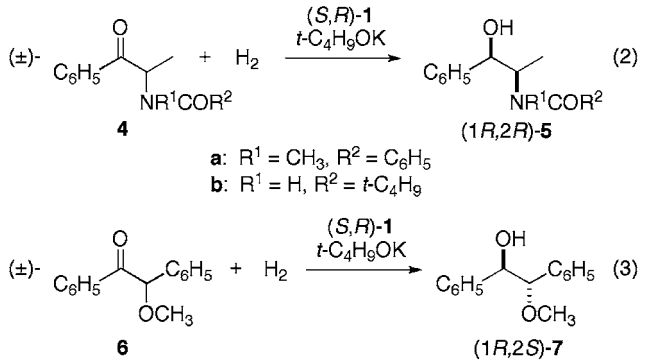
Scheme 2



(15) (*R*)-**3a** and (*S*)-**3h** are both β alcohols in equation 1.

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(22) Reduction of **6** with potassium tri-*sec*-butyl borohydride (K-Selectride), a bulky and non-chelation reducing agent, in ether at −78 °C predominantly afforded *anti*-**7**. See: Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021−2024.