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Highly Efficient and Highly Enantioselective Asymmetric Hydrogenation of Ketones with TunesPhos/1,2-Diamine−Ruthenium(II) Complexes

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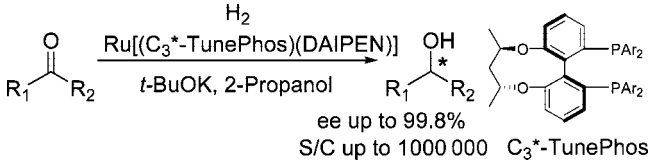
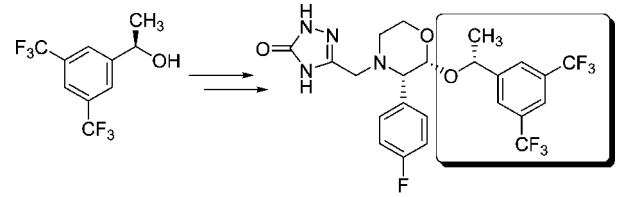


The TunePhos/diamine−Ru(II) complex combined with *t*-BuOK in 2-propanol effectively catalyzes enantioselective hydrogenation of a wide range of simple ketones including aromatic, heteroaromatic, α,β-unsaturated, and cyclopropyl ketones, affording high reactivity (up to 1 000 000 TON) and excellent enantioselectivities (>99% ee for 13 examples).

Catalytic enantioselective hydrogenation of prochiral ketones has been a powerful method to prepare enantiomerically pure secondary alcohols, which are key structural elements in a large number of pharmaceutical products.[1] For example, (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol is a key intermediate in the synthesis of the neurokinin 1 (NK_1) receptor antagonist Emend (Aprepitant; Scheme 1).[2] This FDA-approved drug is for prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV).

The milestone discoveries have been done by Noyori and co-workers, who developed the BINAP−ruthenium−diamine complexes as a highly effective catalyst system for asymmetric hydrogenation of ketones.[3] Prompted by this fundamental study,

SCHEME 1. Structure of Aprepitant



Emend (Aprepitant)

a few analogue ligands, such as PhanePhos,[4] P-Phos,[5] and SDP ligand,[6] were developed and proved to be effective for the ruthenium-catalyzed asymmetric hydrogenation. However, development of more efficient catalyst systems comprised of more readily accessible ligands of high enantioselectivity for practical applications[7] is still of significant importance for chemists.[8]

Despite the great success that has been achieved, asymmetric hydrogenation of ketones has not gained the same amount of attention in practical applications as in academia. The main obstacles include the use of a high level of metal catalysts, which not only dramatically increases the cost but also raises serious issues of heavy metal contamination. Thus it is necessary to develop and demonstrate such catalytic systems that remain effective even at an extremely low level without compromising the selectivity. Herein, we would like to report our achievements in the preparation of a wide variety of chiral alcohols in ideal-approaching enantioselectivities (>99% ee for 13 examples) with only a ppm level of C_3*-TunePhos/diamine−Ru(II) catalysts (TON up to 1 000 000).

Recently, we have developed a practical and convenient synthetic route to prepare a series of air-stable modular C_3-Tunephos-type chiral diphosphine ligands (C_3*-TunePhos),[9] which have been demonstrated earlier to be highly effective in the hydrogenation *N*-substituted allylphthalimides and α-keto esters.[9c] These ligands were designed to achieve superior enantioselectivities for asymmetric hydrogenations utilizing their highly modular nature. To illustrate potential utilities of Tune-

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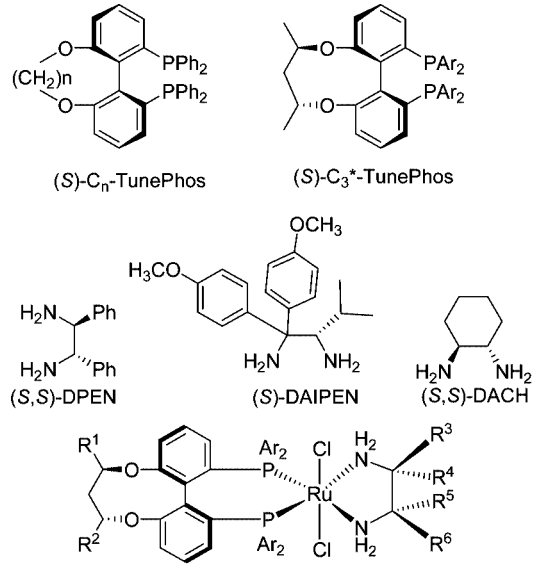


(*S*),(*S*,*S*)-**1a**: Ar = C_6H_5; R^1 = R^2 = H; diamine = (*S*,*S*)-DPEN;
(*S*),(*S*,*S*)-**1b**: Ar = C_6H_5; R^1 = R^2 = CH_3; diamine = (*S*,*S*)-DPEN;
(*S*),(*S*,*S*)-**1c**: Ar =4-MeC_6H_4; R^1 = R^2 = CH_3; diamine = (*S*,*S*)-DPEN;
(*S*),(*S*,*S*)-**1d**: Ar =3,5-$Me_2C_6H_3$; R^1 = R^2 = CH_3; diamine = (*S*,*S*)-DPEN;
(*S*),(*S*,*S*)-**1e**: Ar = 3,5-$Me_2C_6H_3$; R^1 = R^2 = CH_3; diamine = (*S*,*S*)-DACH;
(*S*),(*S*)-**1f**: Ar = 3,5-$Me_2C_6H_3$; R^1 = R^2 = CH_3; diamine = (*S*,*S*)-DAIPEN;

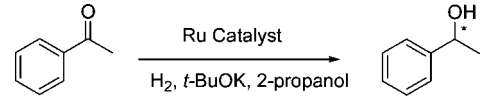
FIGURE 1. TunePhos and C_3-TunePhos/1,2-diamine−Ru(II) catalysts.

Phos ligands, we envisioned that application of these ligands in a diphosphine−ruthenium−diamine system for reduction of simple ketones is a natural choice (Figure 1).

By employing Noyori's protocol,[3a] the diphosphine ligands were reacted with [Ru(benzene)Cl_2]$_2$ in DMF and this was followed by addition of diamine. The resulting diphosphine−ruthenium−diamine complexes were used as the precatalyst directly in the hydrogenation reactions without any further purification. We initiated our studies by screening catalysts **1a**−**f** in the hydrogenation of acetophenone. Under the conditions of room temperature (20−22 °C), 50 atm of H_2, 2-propanol as the solvent, and *t*-BuOK as the base (substrate/base = 220), (*S*)-C_3-TunePhos and DPEN (DPEN = 1,2-diphenyl ethylenediamine) were utilized to distinguish the matching/mismatching stereochemical elements between the two chiral components in this catalyst system. From the results in entries 1 and 2 in Table 1, it can be derived that the (*S*,*S*) isomer of DPEN should be the matching partner with (*S*)-C_3-TunePhos. Thereafter when switching to the modular (*S*)-C_3*-TunePhos, the highest enantioselectivity 98.0% ee was achieved by applying precatalyst (*S*),(*S*,*S*)-**1d** (Table 1, entry 6) when assessing the effect from aryl substituents in the phosphine moiety. On the other hand, when the chiral diamine was further replaced by DACH (*trans*-1,2-diaminocyclohexane), the ee value decreased to 91.2% (Table 1, entry 7). The best combination was not discovered until DAIPEN (1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine) was introduced to serve as the diamine partner, where 99.8% ee was achieved (Table 1, entry 9) with a turnover number (TON) of 10 000. It is noteworthy that this best combination is consistent with Noyori's finding with the Xyl-BINAP−Ru^{II}−DAIPEN system.[3b]

The high catalytic capability of the catalyst (*S*),(*S*)-**1f** was further explored at even lower catalyst loading (0.001%) and milder conditions (10 atm of H_2). The acetophenone substrate was smoothly hydrogenated within 12 h, without any ee value

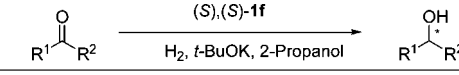
TABLE 1. Screening of TunePhos−Ru(II) Precatalyst for the Hydrogenation of Acetophenone[a]



entry	catalyst	S/C[b]	*t* (h)	conv (%)[c]	ee % (config)[d]
1	(*S*),(*S*,*S*)-**1a**	10 000	2	<99.9	83.3(*R*)
2	(*S*),(*R*,*R*)-**1a**	10 000	2	<99.9	24.3(*S*)
3	(*S*),(*S*,*S*)-**1b**	10 000	2	<99.9	83.0(*R*)
4	(*S*),(*S*,*S*)-**1c**	10 000	2	<99.9	79.5(*R*)
5	(*S*),(*R*,*R*)-**1d**	10 000	2	<99.9	72.1(*R*)
6	(*S*),(*S*,*S*)-**1d**	10 000	2	<99.9	98.0(*R*)
7	(*S*),(*S*,*S*)-**1e**	10 000	2	<99.9	91.2(*R*)
8	(*S*),(*S*)-**1f**	10 000	2	>99.9	99.8(*R*)

[a] Reactions were performed with 2−2.5 M solutions of acetophenone in 2-propanol with added *t*-BuOK (base/Ru = 220/1) at 20−22 °C and 50 atm initial hydrogen pressure. [b] Substrate-to-catalyst molar ratio. [c] Determined by GC analysis. [d] The ee was determined by chiral GC analysis. The absolute configuration was determined by comparison of the retention times with literature data.

TABLE 2. Asymmetric Hydrogenation of Ketones[a]



entry	R^1	R^2	S/C[b]	*t* (h)	conv (%)[c]	ee % (config)[d]
1	C_6H_5	CH_3	10 000	4	>99.9	99.8(*R*)
2	C_6H_5	CH_3	100 000	12	>99.9	99.8(*R*)
3[e]	C_6H_5	CH_3	500 000	24	97.0	99.2(*R*)
4[f]	C_6H_5	CH_3	1 000 000	48	94.5	98.0(*R*)
5	C_6H_5	C_2H_5	10 000	8	>99.9	99.8(*R*)
6	*m*-$CH_3C_6H_4$	CH_3	10 000	4	>99.9	99.7(*R*)
7	*m*-$CH_3OC_6H_4$	CH_3	10 000	4	>99.9	99.6(*R*)
8	*m*-ClC_6H_4	CH_3	10 000	4	>99.9	99.5(*R*)
9	*p*-$CH_3C_6H_4$	CH_3	10 000	4	>99.9	99.6(*R*)
10	*p*-$CH_3OC_6H_4$	CH_3	10 000	4	>99.9	99.6(*R*)
11	*p*-ClC_6H_4	CH_3	10 000	4	>99.9	99.6(*R*)
12	*p*-FC_6H_4	CH_3	10 000	4	>99.9	99.3(*R*)
13	3,5-$(CF_3)_2C_6H_3$	CH_3	10 000	4	>99.9	99.6(*R*)
14	2-furyl	CH_3	10 000	4	>99.9	99.6(*R*)
15	2-thienyl	CH_3	10 000	4	>99.9	99.7(*R*)
16	2-naphthyl	CH_3	10 000	4	>99.9	99.7(*R*)
17	1-naphthyl	CH_3	10 000	4	>99.9	97.0(*R*)
18	*o*-$CH_3C_6H_4$	CH_3	10 000	4	>99.9	97.5(*R*)
19	cyclopropyl	CH_3	10 000	4	>99.9	97.9(*R*)
20	*trans*-PhCH=CH	CH_3	10 000	4	>99.9	97.4(*R*)
21	C_6H_5	cyclopropyl	10 000	8	>99.9	93.2(*R*)

[a] Unless otherwise noted, reactions were performed with 2−2.5 M solutions of acetophenone in 2-propanol with added *t*-BuOK (base/Ru = 220/1) at 20−22 °C and 10 atm initial hydrogen pressure. [b] Substrate-to-catalyst molar ratio. [c] Determined by GC. [d] The ee were determined by Chiral GC analysis. The absolute configuration was determined by comparison of the retention times with literature data. [e] Initial hydrogen pressure was 50 atm. [f] Precatalyst (*S*),(*S*,*S*)-**1d** was used and initial hydrogen pressure was 50 atm.

erosion (99.8% ee) (Table 2, entry 2). Furthermore, when TON was increased to 500 000, this highly active catalyst can still retain over 99% ee enantioselectivity within 24 h under 50 atm of H_2 pressure (Table 2, entry 3). To test the maximum catalytic reactivity, in an illustrative extreme example of high TON (TON = 1 000 000), the catalyst reached 94.5% conversion with 98.0% ee (Table 2, entry 4). These results indicate that this ruthenium catalyst is practically useful to prepare a variety of chiral alcohols under mild operational pressure.[10,3a]

(10) Noyori et al. reported hydrogenation of acetophenone of 2 400 000 TON within 48 h giving 80% ee, under reaction conditions of 45 atm of H_2 at 30 °C. See ref 3a.

To explore the synthetic utility of this catalyst, we have surveyed the substrate scope. A systematic study of the general efficiency included different acetophenone-derived substrates bearing different substituent groups on the phenyl ring, heteroaromatic ketones, and some aliphatic ketones. Good conversions were observed for all substrates, with ee values ranging from 93.2% to 99.8%. The catalyst showed high tolerance of the various substituent groups on the meta and para positions bearing different electronic properties (Table 2, entries 6 to 16). Substrates containing electron-donating groups, such as a methyl group or a methoxy group, and substrates containing electron-withdrawing groups, such as a Cl group or a F group, were hydrogenated successfully at 0.01% catalyst loading within 4 h under 10 atm of H_2 pressure, all giving >99% ee. Meanwhile, heteroaromatic ketones, 2-acetofuran and 2-acetothiophene, were also equally converted to corresponding alcohol products with >99% ee. The hydrogenation of some alkyl ketones, for example, cyclopropyl methyl ketone, also proceeded efficiently (97.9% ee, entry 19). In another example, under the mild conditions, hydrogenation of *trans*-4-phenyl-3-butenone afforded the product quantitatively in 97.4% ee, highly selectively reducing the ketone without reduction of the C=C bond (entry 20). It noteworthy that the result (99.6% ee) in Table 2, entry 13 justified the potential utility of this Ru−C_3*-TunePhos complex in the practical synthesis of Emend (Aprepitant).

In conclusion, we have developed a highly efficient catalyst system for practical asymmetric hydrogenations of a wide range of unfunctionalized ketones. Its nature of extremely high reactivity and enantioselectivity, broad substrate scope, and mild reaction conditions enables practical application for production of enantiomerically enriched alcohols. Further modification of the linker length in the ligands to improve the enantioselectivity for more substrates is underway and will be reported in due course.

Experimental Section

General Procedure for Preparation of C_3*-TunesPhos−Ru(II)−Diamine Precatalysts. C_3*-TunePhos (0.105 mmol) and $[Ru(benzene)Cl_2]_2$ (0.05 mmol) were dissolved in anhydrous degassed DMF (6 mL) under nitrogen protection. The reaction was heated to 100 °C for 0.5−1 h, followed by addition of (*S*)-1,1-bis(4-methoxyphenyl)-3-methylbutane-1,2-diamine ((*S*)-DAIPEN) (0.105 mmol) at room temperature and stirring for 0.5−1 h. The solvent was removed under high vacuum.

General Hydrogenation Procedure. The precatalyst (0.0025 mmol) was dissolved in degassed 2-propanol (8 mL) in a 20-mL vial, and distributed equally among ten vials. A solution of *t*-BuOK (1 mol/L, 0.114 mL, 0.114 mmol) and substrate (2.5 mmol) were added via syringe. The resulting mixture was transferred into an autoclave, and the autoclave was purged with H_2 (3 × 10 atm) and charged with H_2 (10 atm). After stirring at room temperature for 4 h, the H_2 was carefully released. The reaction solution was purified by a silica gel column to give the corresponding hydrogenation product, which was then directly analyzed by chiral GC to determine the enantiomeric excess. The hydrogenation products were also characterized by ^{1}H NMR (Table 2, entry 1, (*R*)-1-phenylethanol; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, J = 6.4 Hz, 3H), 2.02 (br, 1H), 4.88 (q, J = 6.4 Hz, 1H), 7.25−7.29 (m, 1H), 7.29−7.39 (m, 4H)).

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Supporting Information Available: Complete description of catalyst preparation, asymmetric hydrogenation, and product characterization together with photocopies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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